Bipolar Disorder

Best Practices in Screening, Diagnosis and Treatment

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I have no financial interests to disclose.

I have no involvement with any pharmaceutical companies.
At the end of this lecture, participants will be able to:

1. Compare two screening tools for bipolar disorder: the Mood Disorders Questionnaire and CIDI Bipolar Screening Tool

2. Examine evidence supporting various pharmacologic treatments in each stage of bipolar disorder

3. Differentiate evidence for efficacy of medications for bipolar disorder based on type of mood episode being treated or prevented
Mnemonic for Symptoms of Mania

- **D**: Distractibility
- **I**: Indiscretion
- **G**: Grandiosity
- **F**: Flight of ideas
- **A**: Activity increase
- **S**: Sleep deficit
- **T**: Talkativeness

Adapted from Lewis, et al. An Overview of Primary Care Assessment and Management of Bipolar Disorder. JAOA Supp6 Vol 104 No 6 June 2004
DSM 5 Criteria for Manic Episode

Criteria

A = A distinct period of elevated or irritable mood, or elevated energy or activity level lasting 1 week
B = 3 of the DIGFAST symptoms (4 if A was irritable mood):
   - Distractibility, Indiscretions, Grandiosity, FOI, increased Activity,
   - decreased need for Sleep, Talkative
C = Marked impairment requiring hospitalization to prevent harm or psychotic features
D = Not attributable to substance use, medications, or a medical condition
DSM 5 Criteria for Hypomaniac Episode

Criteria

A = A distinct period of elevated or irritable mood, or elevated energy or activity level lasting at least 4 days for hypomania

B = 3 of the DIGFAST symptoms (4 if mood is irritable)

C = Unequivocal change in functioning

D = Mood and functioning change observable by others

E = No need for hospitalization, no psychotic symptoms

F = Not attributable to substance use, medications, or medical condition
Mood Instability: Not Only in Bipolar Disorder

- Substance Use Disorders
- Major Depressive Disorder with Irritability
- Adjustment disorder with mixed disturbance of emotions and conduct
- Personality disorder (Borderline, Antisocial)
- Post-Traumatic Stress Disorder
- Anxiety disorders
- Psychosis
- Dementia
- Medication Effects (steroids, hormones, stimulants, drugs of abuse, dopamine antagonists, etc.)
- Non-Psychiatric Medical Condition (thyroid d/o, pregnancy, neurologic d/o, delirium/infection, rheum d/o, etc.)
One Year Prevalence Data: Bipolar Spectrum Disorders - World Mental Health Survey

* Bipolar disorder type 1 – 0.4%
  * h/o full blown mania

* Bipolar disorder type 2 – 0.3%
  * h/o hypomania and major depressive episode

* Subthreshold bipolar symptoms – 0.8%
  * Poorly defined group, not well studied

* Total of all bipolar illnesses – just 1.5%
One Year Prevalence Data:
SAMHSA’s Mental Health Surveillance Study 2008-2012

* Bipolar disorder type 1: 0.4%
* Major depressive disorder: 6.0%
* Dysthymic disorder: 1.7%
* Alcohol use disorder: 6.4%
* Illicit drug use disorder: 3.0%
National Comorbidity Survey Replication Data on Lifetime Prevalence:

* Borderline Personality Disorder: 5.9%

* Bipolar disorder: 1.4%
  (types 1 & 2 combined)
Emotional dysregulation and impulsive aggressive behaviors are common reactions for those with borderline personality features when stressors overwhelm their coping skills.

- Irritability, racing thoughts, poor sleep, and anger outbursts can be symptoms of depression, anxiety symptoms, or mania/hypomania.

- The episodes of mood dysregulation in borderline personality disorder usually last 1-2 days, whereas untreated mania/hypomania tends to persist for weeks.

- A diagnosis of bipolar disorder may be held onto tightly related to external locus of control and function of the diagnosis in interpersonal relationships.
Borderline Personality Disorder Treatments

- Psychotherapy, DBT
- Medications have a clear role in treating co-morbid depression, anxiety, PTSD
  - Antidepressants; adjunctive mood stabilizers and antipsychotics
- Controversies exist over targeting core BPD symptoms with medications, but some studies suggest reduction in targets like affective dysregulation and impulsive behaviors
  - Mood stabilizers: valproate, lamotrigine, topiramate
  - Antipsychotics: aripiprazole, olanzapine, haloperidol, and quetiapine

Mood Disorder Questionnaire (MDQ)

* Patient self administered
* Takes 5 minutes to complete
* Positive screening requires:
  * Question 1: YES response to 7 or more of the 13 items
  * Question 2: YES response
  * Question 3: “Moderate” or “Serious Problem” response
## MDQ (Mood Disorder Questionnaire)

1. Has there ever been a period of time when you were not your usual self and...
   - ...you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble? [Yes] [No]
   - ...you were so irritable that you shouted at people or started fights or arguments? [Yes] [No]
   - ...you felt much more self-confident than usual? [Yes] [No]
   - ...you got much less sleep than usual and found you didn’t really miss it? [Yes] [No]
   - ...you were much more talkative or spoke much faster than usual? [Yes] [No]
   - ...thoughts raced through your head or you couldn’t slow your mind down? [Yes] [No]
   - ...you were so easily distracted by things around you that you had trouble concentrating or staying on track? [Yes] [No]
   - ...you had much more energy than usual? [Yes] [No]
   - ...you were much more active or did many more things than usual? [Yes] [No]
   - ...you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night? [Yes] [No]
   - ...you were much more interested in sex than usual? [Yes] [No]
...thoughts raced through your head or you couldn't slow your mind down?

...you were so easily distracted by things around you that you had trouble concentrating or staying on track?

...you had much more energy than usual?

...you were much more active or did many more things than usual?

...you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night?

...you were much more interested in sex than usual?

...you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?

...spending money got you or your family into trouble?

2. If you checked YES to more than one of the above, have several of these ever happened during the same period of time?

3. How much of a problem did any of these cause you—like being unable to work; having family, money or legal troubles; getting into arguments or fights? Please circle one response only.

   No Problem    Minor Problem    Moderate Problem    Serious Problem

4. Have any of your blood relatives (i.e. children, siblings, parents, grandparents, aunts, uncles) had manic-depressive illness or bipolar disorder?

5. Has a health professional ever told you that you have manic-depressive illness or bipolar disorder?
Mood Disorder Questionnaire (MDQ): A Flawed Screening Tool for Bipolar Disorder

* Early validation studies looked good
  * Done in outpatient clinic with mostly mood disorders
  * Sensitivity of 0.73 and specificity of 0.90 in initial studies
* Later studies showed sensitivities as low as 28% in the general population (prone to miss bipolar 2 and NOS)
* Many false positives actually identifying cases of:
  * Borderline Personality Disorder
  * PTSD
  * Substance Use Disorders
  * Eating Disorders
Is there a Better Screening Tool for Bipolar Disorder?

CIDI Toolkit for Bipolar Screening:
WHO’s Composite International Diagnostic Interview (CIDI) Bipolar Screening

* Sensitivity of CIDI: 67-96%
  * MDQ’s sensitivity per various studies: 28-73%

* Fewer false positives
  * Excellent concordance with the diagnostic gold standard, the Structured Clinical Interview for DSM Disorders

* Quick – The 12 Questions take about three minutes
WHO’s Composite International Diagnostic Interview (CIDI) Bipolar Screening

* “Criterion A” Stem questions:
  * Question 1: Euphoria Stem
  * Question 2: Irritability Stem
    * Yes to either → You go on . . .
    * No to both → Stop. Negative screen for bipolar disorder.

* “Criterion B” Screening question
  * No response → Stop. Negative screen for bipolar disorder.
  * Yes to either → You go on . . .

* “Criterion B” Symptom questions
  * Q1: Euphoria Stem → max score will be 9
  * Q2: Irritability Stem → max score will be 8
    * Don’t count the irritability stem question, which is also the first of the 9 symptom questions.
“Some people have periods lasting several days when they feel much more excited and full of energy than usual. Their minds go too fast. They talk a lot. They are very restless or unable to sit still and they sometimes do things that are unusual for them, such as driving too fast or spending too much money.

Have you ever had a period like this lasting several days or longer?”

* If no → ask the Question 2: the Irritability Stem

* If yes → Go to the criterion B screening question.
“Have you ever had a period lasting several days or longer when most of the time you were so irritable or grouchy that you either started arguments, shouted at people or hit people?”

* If no (to both 1 and 2) → Stop. Negative for bipolar disorder.
* If yes (to either 1 or 2) → Go on to ask the criterion B screening question.
“People who have episodes like this often have changes in their thinking and behavior at the same time, like being more talkative, needing very little sleep, being very restless, going on buying sprees, and behaving in many ways they would normally think inappropriate.

Did you ever have any of these changes during your episodes of being excited and full of energy or very irritable or grouchy?”

* If no ➔ Stop. Negative screen for bipolar.
* If yes ➔ Go on the Criterion B Symptom Questions.
Criterion B Symptom Questions

Think of an episode when you had the largest number of changes like these at the same time. During that episode, which of the following changes did you experience?

1. Were you so irritable that you either started arguments, shouted at people, or hit people?
   
   This first symptom question is asked only if the euphoria stem question (#1 above) is endorsed

2. Did you become so restless or fidgety that you paced up and down or couldn’t stand still?

3. Did you do anything else that wasn’t usual for you—like talking about things you would normally keep private, or acting in ways that you would usually find embarrassing?

4. Did you try to do things that were impossible to do, like taking on large amounts of work?

5. Did you constantly keep changing your plans or activities?

6. Did you find it hard to keep your mind on what you were doing?

7. Did your thoughts seem to jump from one thing to another or race through your head so fast you couldn’t keep track of them?

8. Did you sleep far less than usual and still not get tired or sleepy?

9. Did you spend so much more money than usual that it caused you to have financial trouble?
Positive Predictive Values (PPVs) will vary in different settings as the prevalence of bipolar disorder varies.

- Estimates below give a general idea of how likely a patient is to have true bipolar disorder.
- Higher percentages (PPVs) when your population has higher rates of bipolar disorder, as in MH clinics.

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<tr>
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<th>Questions with Positive Endorsement</th>
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<td>9 questions</td>
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<tr>
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Positive Predictive Values in sub-populations for CIDI-based Screening Scales

<table>
<thead>
<tr>
<th>Number of Questions Endorsed</th>
<th>For respondents who have seen a primary care physician at least 12 times in the year before the interview</th>
<th>For respondents who have seen a primary care physician at least once in the year before the interview</th>
<th>For respondents who have received specialty mental health treatment in the year before the interview.</th>
</tr>
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<tbody>
<tr>
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<td>PPV = 0.0</td>
<td>PPV = 0.2</td>
<td>PPV = 0.0</td>
</tr>
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<tr>
<td>3 Questions = Y</td>
<td>PPV = 3.6</td>
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</tr>
<tr>
<td>5 Questions = Y</td>
<td>PPV = 17.0</td>
<td>PPV = 20.8</td>
<td>PPV = 39.0</td>
</tr>
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<td>6 Questions = Y</td>
<td>PPV = 33.4</td>
<td>PPV = 37.2</td>
<td>PPV = 39.0</td>
</tr>
<tr>
<td>7 Questions = Y</td>
<td>PPV = 52.6</td>
<td>PPV = 50.2</td>
<td>PPV = 55.2</td>
</tr>
<tr>
<td>8 Questions = Y</td>
<td>PPV = 54.9</td>
<td>PPV = 53.7</td>
<td>PPV = 71.0</td>
</tr>
<tr>
<td>9 Questions = Y</td>
<td><strong>PPV = 100.0</strong>)</td>
<td><strong>PPV = 84.3</strong>)</td>
<td><strong>PPV = 88.2</strong>)</td>
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<tr>
<td>AUC = .865</td>
<td>AUC = .854</td>
<td>AUC = .800</td>
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CIDI Bipolar Screening Tool: Interpretation of Scores

• Positive Predictive Values (PPVs) will vary in different settings as the prevalence of bipolar disorder varies.
  • Estimates below give a general idea of how likely a patient is to have true bipolar disorder
  • Higher percentages (PPVs) when your population has higher rates of bipolar disorder

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Four Jobs for “Mood Stabilizers”:

1) Treat acute mania or hypomania
2) Treat acute bipolar depression
3) Prevent recurrence of mania or hypomania
4) Prevent recurrence of bipolar depression
Treatment of Mania

* Mood stabilizers and antipsychotics
  * Hospital: Antipsychotics often first, because faster onset
  * Severe mania: Antipsychotic + Mood Stabilizer
  * Milder cases: Lithium or Depakote alone may suffice

* Stop agents that drive mania
  * Antidepressants – TCAs & SNRIs > SSRIs & bupropion
  * Buspirone, Stimulants, Steroids, Light boxes

* Promote sleep
  * Consider sedating meds at bedtime
  * Consider short course of benzo
Anti-manic Treatments: Rankings for Efficacy and Tolerability

Green area (Best):
HAL = haloperidol*
RIS = risperidone
OLZ = olanzapine
QTP = quetiapine

*Note: haloperidol is not FDA approved for any phase of bipolar disorder, but ample evidence supports its use.
Anti-manic Treatments: Rankings for Efficacy and Tolerability

Lighter Red Areas:
ARI = aripiprazole
LIT = lithium
CBZ = carbamazepine
VAL = valproate
ASE = asenapine
ZIP = ziprasidone

Anti-manic Treatments: Rankings for Efficacy and Tolerability

Dark Red Area:
LAM = lamotrigine
TOP = topiramate
GBT = gabapentin
PBO = placebo

These are not effective for treatment of mania.

Diagnosis of Bipolar Depression

* Simple answer:
  * Major depressive episode + history of mania/hypomania

* Real world:
  * Often lack clear diagnosis from interview alone
  * Often have some degree of suspicion for hypomania/mania and lingering diagnostic questions
Bipolar vs. Unipolar Depression

* Symptoms More Common in Bipolar Depression:
  * Mood lability
  * Hypersomnia
  * Hyperphagia
  * Psychomotor retardation, Leaden paralysis
  * Pathologic guilt
  * Psychotic features (AH, paranoia, delusions)
  * Longer speech latencies
Bipolar vs. Unipolar Depression

* Additional clues from history:
  * Family history of bipolar disorder, schizophrenia, or schizoaffective disorder
  * Onset of depression under 25 years of age
  * Many episodes with abrupt onset and ending
  * Poor antidepressant response
    * Due to having no effect
    * Or due to worsening of illness
      * Possibly leading to mood lability, irritability, inability to sleep, suicidality
Antidepressant Effects in Bipolar Depression (STEP-BD)

* **STEP-BD**
  * Published in 2007
  * 26 week long study

* **366 bipolar patients**
  * All patients on mood stabilizers (Li / VPA)
  * Randomized to paroxetine, bupropion, or placebo

* **Outcomes:**
  1) Depression recovery
  2) Rates of manic switching
Antidepressant Effects in Bipolar Depression (STEP-BD)

* Rates of manic switching
  * No significant difference between groups
  * Paroxetine and bupropion groups did not show higher switch rates
    * Risks with SNRIs and TCAs have been shown to be higher in other studies

* Rates of recovery from depression
  * No significant difference between groups

* Bottom lines:
  * Some antidepressants are probably safe when taken with an Anti-manic agent
  * But they probably won’t help depression
Antidepressant Effects in Bipolar Depression (STEP-BD)

* Some antidepressants (SSRIs & bupropion) are probably safe when taken with an Anti-manic agent in bipolar disorder’s depressed phase

* But antidepressants are unlikely to help bipolar depression

* Potential roles
  * For treating anxiety or other comorbid conditions
  * When both unipolar and bipolar depression remain in your differential diagnosis
**Bipolar Depression Treatment: FDA Approved Treatments**

* Olanzapine/fluoxetine combo pill (2003)  
  * NNT = 4  
  * NNH (>7% weight gain) = 6, 7

* Quetiapine (2006, XR in 2008)  
  * NNT = 6  
  * NNH (somnolence/sedation) = 3, 5  
  * NNH (dizziness) = 12  
  * NNH (>7% weight gain) = 16  
  * NNH (EPS) = 19

* Lurasidone (2013)  
  * NNT = 5  
  * NNH (akathisia) = 12, 15  
  * NNH (EPS) = 16  
  * NNH (>7% weight gain) = 58

Neither olanzapine or fluoxetine alone was found effective.

Quetiapine’s effectiveness in bipolar disorder begins at doses of 300mg/day. Titrate up to mitigate orthostatic and sedating side effects.

Lurasidone must be taken with food for adequate absorption.

Citrome, L. Treatment of bipolar depression: Making sensible decisions. CNS Spectrums (2014). (both are Pharma funded studies)
Bipolar Depression Treatment: Not FDA-Approved & Not supported by the evidence

- **Olanzapine** (2 studies, 8 and 6 weeks long)
  - NNT = 12 and 11
  - NNH (>7% weight gain) = 6 and 5

- **Antidepressants** (paroxetine, bupropion and pooled antidepressants studied)
  - NNT = 29
  - NNH (mood switch) = 200

- **Lamotrigine**
  - NNT = 12
  - NNH (sedation/somnolence) = 37
  - NNH (benign rash) = 44

Lithium for Bipolar Depression:
Not FDA approved, yet a First-Line Recommendation

* Lithium is an orphan drug
  * It lacks the industry and financial backing needed for more studies and to get through the FDA approval process

* Most studies on lithium were done in the 1970s, when unipolar and bipolar depression were not well separated groups.

* Modern pharma studies have used lithium as an active comparator at suspiciously low doses where the average lithium level was on 0.6.
If psychotic, use an antipsychotic

First line:
* Lithium (level 0.8-1.2)

Second line:
* Quetiapine
* Lamotrigine
* Lurasidone

Third line (very limited evidence):
* Valproate
* Combo of those above
* Add antidepressant to adequate antimanic agent.
  * Choose one with low risk of mood switching → SSRI or bupropion

http://www.psychopharm.mobi/
Evidence base
- Few long-term studies published, only 15 included in 2010 review

FDA-approved monotherapies:
- Lithium
- Lamotrigine
- Olanzapine
- Aripiprazole
- Quetiapine
- Risperidone LAI (long acting injectable)

FDA-approved adjunctive therapy:
- ziprasidone as added to lithium or valproate
**Bipolar Maintenance Treatment**

* Goals of treatment in maintenance phase:
  1. Prevent recurrence of mania/hypomania
  2. Prevent recurrence of depression

* Do the FDA-approved drugs for bipolar disorder maintenance phase prevent both?
Bipolar Maintenance Treatment:

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<tr>
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<tr>
<td>Valproate (not FDA approved for bipolar maintenance phase)</td>
<td>NS (22)</td>
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Bipolar Maintenance Treatment: Lamotrigine Monotherapy

* Lamotrigine monotherapy is inadequate for bipolar type 1
  * Prevention of mania is essential in bipolar type 1
  * Lamotrigine does not prevent mania

* Bipolar type 2
  * Lamotrigine monotherapy may be adequate
    * Be cautious about addition of agents that promote mania (antidepressants, steroids, stimulants, light box therapy, etc.)
### Bipolar Maintenance Treatment:

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# Bipolar Maintenance Treatment: Prevention of Mania and Depression

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<tr>
<td>Valproate (not FDA approved)</td>
<td>NS (22)</td>
<td>NS (11)</td>
<td>7</td>
</tr>
</tbody>
</table>

Lithium has the Best Evidence for Long-term Relapse Prevention

* **Benefits of lithium:**
  * Reduced risk of manic relapses by 38%
  * Reduced risk of depressive relapses by 28%
  * Reduced risk of suicide by 50%

* **Risks:**
  * Low therapeutic index
    * Drug interactions with diuretics, ACEI, ARBs and NSAIDs can be serious
  * Monitoring for lithium levels, renal and thyroid function, and parathyroid issues necessary

* **Benefits > Risks:**
  * Bipolar experts and studies promote lithium as a safe and underutilized treatment in bipolar disorder

Relapse Prevention in Bipolar Disorder: Psychosocial treatments

* Psychoeducation
* Early intervention plans for warning signs of a mood episode beginning
* Stabilize sleep and wake rhythms, sleep hygiene
* Coping with illness, stigma, and interpersonal relationships
* Enhancing medication compliance
* Maintaining family and social supports
Mood instability is a common issue, and bipolar disorder is only one of the many possible causes.

The WHO’s Composite Index Diagnostic Interview for bipolar disorder is reliable and easy to use screening tool that may reduce trends towards over-diagnosis.

Most treatments for bipolar disorder do not have evidence for treating each phase of the illness effectively.

Considering the 4 roles for medications in bipolar disorder provides a useful schema to approach treatment options for any individual patient.