Recognition, Detection, and Management of Bipolar Disorder

Anne Holmes, Ph.D.
Assistant Professor
Department of Psychiatry and Behavioral Health
The Ohio State University Wexner Medical Center

MedNet21
Center for Continuing Medical Education

The Ohio State University
Wexner Medical Center

Learning Objectives

- Understand the importance of early detection of bipolar disorder
- Recognize symptoms of bipolar disorder
- Summarize evidence-based treatments for bipolar disorder

Why should I learn about bipolar disorder if I'm not a psychiatrist?

Why should I learn about bipolar disorder if I'm not a psychiatrist?

- Will you treat individuals with this illness?
  - Common disorder (>1% of the population)
  - High rates of medical comorbidity
- Will you prescribe anti-depressants?
  - Antidepressants typically don't work for bipolar depression
  - Antidepressants may trigger mania/exacerbate cycling in individuals with bipolar disorder (especially BP I disorder)

Global Disease Burden

- BD has a worldwide prevalence of about 2%, with subclinical variants affecting another 2% of the population.
- BD is among the top 10 leading causes of disability-adjusted life years in young adults.
- People with BD die on average 10 years earlier, and the lifetime risk of suicide is estimated to be at least 20 times that of the general population.

Knezevic & Nedic. *Eur Rev Med Pharmacol Sci* 2013;17:1542-5.
Altamura et al. *J Affect Disord* 2015;182:70-5.

Global Disease Burden

- The risk of recurrence increases with the number of previous episodes.
- The number of previous episodes is associated with:
  - Increased duration and symptomatic severity of subsequent episodes
  - Decreased response to treatment
  - Increased risk of dementia in the long-term

Yatham et al. 2019

Challenges of Diagnosis

- 69% of individuals with BD were initially misdiagnosed, receiving an average of 3.5 incorrect diagnoses before accurate identification of BD.
- In primary care settings, the misdiagnosis rate is reported to be even higher, with BD being missed in 78% of patients.
- The delay from the onset of symptoms to an accurate diagnosis can range from 5 to 8 years, with even longer delays observed in cases of bipolar II disorder.

Hirschfeld RM, et al. J Am Board Fam Pract. 2005;18(4):233-239. Hirschfeld RM, et al. Am J Manag Care. 2005;11(3 Suppl):S85-S90. Dilsaver SC. J Affect Disord. 2011;129(1-3):79-83. Leboyer M, et al. J Clin Psychiatry. 2010;71(12):1689-1695. Hirschfeld RM, et al. J Clin Psychiatry. 2003;64(2):161-174. Baldessarini RJ, et al. Bipolar Disord. 2007;9(4):386-393.

Challenges of Diagnosis

- Up to 69% of persons with bipolar disorder are misdiagnosed initially, most often as Major Depressive Disorder (MDD).
- Schizophrenia and other psychotic disorders are the initial diagnosis in 30% of patients with BD.
- Other misdiagnoses include borderline personality disorder, substance use disorder, and ADHD.

DSM 5 Criteria for Major Depressive, Bipolar I, and Bipolar II Disorder

- **Major Depressive Disorder:** One or more Major Depressive Episodes (MDEs)
- **Bipolar I Disorder:** One or more Manic Episodes, usually accompanied by MDEs
- **Bipolar II Disorder:** One or more Hypomanic Episodes and one or more MDEs

Manic Episode

Criterion A: Distinct elevated (irritable) mood and increased energy/activity- 1 week (most of the day; nearly every day)

Criterion B: Three (four*) or more of the following are present and represent a noticeable change from usual behavior: grandiosity, more talkative, decreased need for sleep, distractibility, flight of ideas, increased activity, excessive engagement in risky activities

May be accompanied by psychotic symptoms

Marked impairment

Not substance induced

*if irritable mood only

Hypomanic Episode

Criterion A: Distinct elevated (irritable) mood and increased energy/activity- 4 consecutive days (most of the day; nearly every day)

Criterion B: Three (four*) or more of the following are present and represent a noticeable change from usual behavior: **grandiosity, more talkative, decreased need for sleep, distractibility, flight of ideas, increased activity, excessive engagement in risky activities**

NO psychotic symptoms or hospitalization

Observable by others

Change in functioning (may be better!) but does NOT cause marked impairment

Not substance induced

*if irritable mood only

Criteria	Mania (more severe)	Hypomania (less severe)
Minimum time-frame for diagnosis	1 week	4 days
Mood elevation/irritability and increased energy	Yes	Yes
No. of additional symptoms for diagnosis	At least 3	At least 3
• Grandiosity	Yes	Yes
• Decreased need for sleep	Yes	Yes
• More talkative	Yes	Yes
• Flight of ideas	Yes	Yes
• Distractibility	Yes	Yes
• Increased goal-directed activity	Yes	Yes
• Risky behaviour	Yes	Yes
Marked impairment of social/occupational functioning	Yes	No
Psychotic features	Yes	No
May require hospitalization	Yes	No

Major Depressive Episode

Criterion A: Depressed mood or loss of interest - 2 weeks

Criterion B: Five or more of the following: **Depressed mood, Psychomotor agitation or retardation, Loss of interest, Fatigue or low energy, Change in weight, Feelings of worthlessness/guilt, Poor concentration, Suicidal thoughts, Insomnia or hypersomnia**

May be accompanied by psychotic symptoms

Marked impairment

Not substance induced

Bipolar I Disorder: one or more **Manic Episode**, usually accompanied by **Major Depressive Episodes**

Bipolar II Disorder: one or more **Hypomanic Episode** and one or more **Major Depressive Episode**

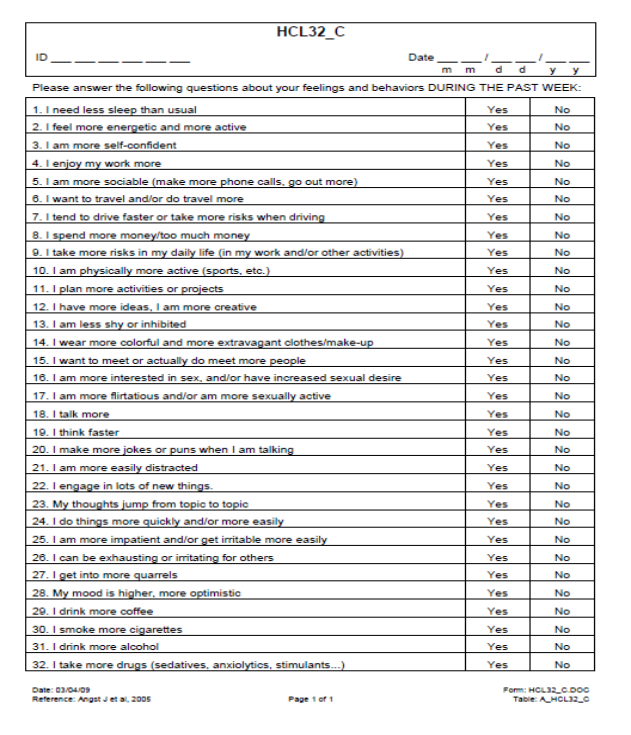
Screening for bipolar disorder

A positive screen is a flag for a more detailed assessment/referral. Screening has poor sensitivity and specificity.

Rapid Mood Screener (RMS)

Item		Response	
1.	Have there been at least 6 different periods of time (at least 2 weeks) when you felt deeply depressed?	Yes	No
2.	Did you have problems with depression before the age of 18?	Yes	No
3.	Have you ever had to stop or change your antidepressant because it made you highly irritable or hyper?	Yes	No
4.	Have you ever had a period of at least 1 week during which you were more talkative than normal with thoughts racing in your head?	Yes	No
5.	Have you ever had a period of at least 1 week during which you felt any of the following: unusually happy; unusually outgoing; or unusually energetic?	Yes	No
6.	Have you ever had a period of at least 1 week during which you needed much less sleep than usual?	Yes	No

Hypomania Checklist (HCL-32)



HCL32_C

ID ___ ___ ___ ___ ___ ___ Date ___ ___ / ___ ___ / ___ ___ (m m d d y y)

Please answer the following questions about your feelings and behaviors DURING THE PAST WEEK:

1. I need less sleep than usual	Yes	No
2. I feel more energetic and more active	Yes	No
3. I am more self-confident	Yes	No
4. I enjoy my work more	Yes	No
5. I am more sociable (make more phone calls, go out more)	Yes	No
6. I want to travel and/or do travel more	Yes	No
7. I tend to drive faster or take more risks when driving	Yes	No
8. I spend more money/too much money	Yes	No
9. I take more risks in my daily life (in my work and/or other activities)	Yes	No
10. I am physically more active (sports, etc.)	Yes	No
11. I plan more activities or projects	Yes	No
12. I have more ideas, I am more creative	Yes	No
13. I am less shy or inhibited	Yes	No
14. I wear more colorful and more extravagant clothes/make-up	Yes	No
15. I want to meet or actually do meet more people	Yes	No
16. I am more interested in sex, and/or have increased sexual desire	Yes	No
17. I am more flirtatious and/or am more sexually active	Yes	No
18. I talk more	Yes	No
19. I think faster	Yes	No
20. I make more jokes or puns when I am talking	Yes	No
21. I am more easily distracted	Yes	No
22. I engage in lots of new things.	Yes	No
23. My thoughts jump from topic to topic	Yes	No
24. I do things more quickly and/or more easily	Yes	No
25. I am more impatient and/or get irritable more easily	Yes	No
26. I can be exhausting or irritating for others	Yes	No
27. I get into more quarrels	Yes	No
28. My mood is higher, more optimistic	Yes	No
29. I drink more coffee	Yes	No
30. I smoke more cigarettes	Yes	No
31. I drink more alcohol	Yes	No
32. I take more drugs (sedatives, anxiolytics, stimulants...)	Yes	No

Date: 03/04/09
Reference: Angst J et al, 2005
Page 1 of 1
Form: HCL32_C.DOC
Table: A_HCL32_C

Clues to Avoid Misdiagnosis

- Family History
  - Higher rates of psychiatric illness and positive for bipolar disorder; h/o suicide
- Course of Illness
  - Onset before age 25 and high number of recurrent episodes
  - Abrupt onset and end of depressive episode; postpartum
  - Atypical depressive symptoms
  - Psychosis during depression
- Treatment Response
  - Suboptimal outcome with antidepressants
  - Antidepressant-induced hypomania, irritability, agitation
- Associated Features
  - Chaotic relationships/job environments
  - Substance use

Sachs GS, et al. *N Engl J Med*. 2007;356(17):1711-1722. Valentí M, et al. *J Clin Psychiatry*. 2012;73(2):e271-e276. Glauser TA, et al. *Postgrad Med*. 2013;125(1):144-153. Pacchiarotti I, et al. *Am J Psychiatry*. 2013;170(11):1249-1262.

Goals of Treatment for Bipolar Disorder

- Treat acute mania
- Treat acute depression
- Treat of mixed or rapid cycling states
- Prevent mood episodes
  - Maintain stability
  - Manage subsyndromal symptom flurries

Psychotherapy for Bipolar Disorder

- Compared to medication alone:
  - Remission 3 months earlier
  - 1.5 x more likely to stay well
- In BP2:
  - Interpersonal & Social Rhythm Therapy (IPSRT) as a monotherapy

Evidence-supported psychotherapies

- Cognitive Behavioral Therapy (CBT)
- Interpersonal and Social Rhythm Therapy (IPSRT)
- Family-Focused Therapy (FFT)

Bipolar-Specific Therapeutic Strategies

- Sleep-wake cycle regulation
- Daily rhythms regulation
- Communication training
- Mood monitoring
- Relapse prevention planning
- Illness psychoeducation
- Medication adherence support

Bipolar Disorder

Shamsun Nahar, MD
Assistant Professor - Clinical
Department of Psychiatry
Division of General Psychiatry
The Ohio State University Wexner Medical Center

MedNet21
Center for Continuing Medical Education

The Ohio State University
Wexner Medical Center

Bipolar Spectrum Disorders ?

- "Not quite bipolar": rapid but unsustained response to antidepressants, unstable mood without defined mania or hypomania. Can benefit from addition of mood stabilizers.
- Hyperthermic temperaments ?: over confidence, impulsive, grandiose, lack of inhibition, above normal mood. Increased risk of mood disorder later in life.
- Patients with protracted or recurrent hypomania without depression, may later develop Bipolar II
- Major depression with cyclothymia, described as "moody", may worsen with antidepressants monotherapy

Bipolar Spectrum Disorders ? (continued)

- Antidepressants induced mania or hypomania: not good candidate for antidepressant monotherapy
- Agitated depression, early onset with frequent episodes with SI, family history of Bipolar DO

Determine level of care

- Evaluate safety.
- Careful assessment of the patient's risk for suicide is critical;
- The overwhelming majority of suicide attempts are associated with depressive episodes or depressive features during mixed episodes. Ask every patient about suicidal ideation, intention to act on these ideas, and extent of plans or preparation for suicide.
- Collect collateral information from family members or others.
- Assess for access to means of committing suicide (e.g., medications, firearms) and the lethality of these means.

Determine level of care (continued)

- Assess for factors associated with increased risk, such as agitation, pervasive insomnia, impulsiveness, or other psychiatric comorbidity such as substance abuse, psychosis (especially with command hallucinations), or personality disorder.
- **Consider hospitalization for patients who:**
  - pose a serious threat of harm to themselves or others,
  - are severely ill and lack adequate social support outside a hospital setting or demonstrate significantly impaired judgment,
  - have complicating psychiatric or general medical conditions

Treatment

- Medications
- Psychotherapy
- Goals of Psychiatric Management include being able to:
  - Establish and maintain a therapeutic alliance.
  - Monitor the patient's psychiatric status.
  - Provide education regarding bipolar disorder.
  - Enhance treatment adherence.
  - Promote regular patterns of activity and sleep.
  - Anticipate stressors.
  - Identify new episodes early.
  - Minimize functional impairments.

Medications

- Remains main form of treatment for most patients
- Different ways to think about how to chose the appropriate medication.
- Important to identify the degree of mania and depression history and understand difference between Bipolar I (with mania history) and Bipolar II disorders (hypomania and MDD history).
- There are other forms of possible Bipolar Spectrum Disorders to consider.
- Primary Goal of treatment: prevention of mania or prevention of depression

Mood Stabilizers

- Since Bipolar is a Mood Disorder, treatment is use of mood stabilizer
- What is Mood stabilizer? Medication controlling mania and depression and preventing mania and depression.
- Closest to ideal Mood stabilizer is Lithium.
- Several but not all anticonvulsants used as mood stabilizers
- Antipsychotic medications, primarily atypical ones can be used alone or in combination with mood stabilizers

Acute Mania or Mixed state

- For severe mania or mixed episodes, initiate lithium in combination with an antipsychotic or valproate in combination with an antipsychotic.
- For less ill patients, monotherapy with lithium, valproate, or an antipsychotic such as olanzapine may be sufficient.
- Short-term adjunctive treatment with a benzodiazepine may also be helpful.
- For mixed episodes, valproate may be preferred over lithium.
- Atypical antipsychotics are preferred over typical antipsychotics because of their generally more tolerable side effect profile (most current evidence supports the use of olanzapine and risperidone)
- Antidepressants should be tapered and discontinued if possible.

Acute Depression

- For patients not yet in treatment for bipolar disorder, initiate either lithium or lamotrigine, Quetiapine, Lurasidone, Cariprazine, Lumateperone, Olanzapine/Fluoxetine combination.
- As an alternative, especially for more severely ill patients, consider initiating treatment with both lithium and an antidepressant simultaneously (although supporting data are limited).
- Antidepressant monotherapy is not recommended.
- Consider ECT for - patients with life-threatening inanition, suicidality, or psychosis or - severe depression during pregnancy.

Maintenance Treatment

- *Goals of Treatment* :
- Prevent relapse and recurrence.
- Reduce subthreshold symptoms.
- Reduce suicide risk.
- Reduce cycling frequency or milder degrees of mood instability.
- Improve overall function.

Maintenance treatment (continued)

- *Recommended options*:
- Treatment options with the best empirical support include lithium or valproate.
- If one of the above medications led to remission from the most recent depressive or manic episode, it generally should be continued.
- Maintenance ECT may also be considered for patients who respond to ECT during an acute episode.
- Treatment selection should be guided by illness severity, associated features such as rapid cycling or psychosis, and, where possible, patient preference

Lithium

- Has been in use for more than 50 years.
- Exact mechanism of action of Lithium ion is unclear
- Includes second messenger system such as phosphatidyl Inositol system, modulating G proteins and regulation of gene expression for growth factors and neuronal plasticity. Enhances GAB activity, reduces DA and CNS adrenergic activities.
- Indications includes acute mania, mixed episodes and maintenance phase of Bipolar DO to prevent mania. Can also prevent depression in known Bipolar disorder.
- Less known benefits are ant suicidal property and theoretically inhibits phosphorylation of tau protein.

Lithium (continued)

- Lithium dosing: Can be started at 300 mg bid and adjusted based on steady state blood level obtained after 5 days, trough level between 0.6 to 1.2 mEq/L. Level is considered toxic above 1.5, showing a narrow therapeutic index.
- Monitoring: initially after 5 days and after each dose titration and steady state achievement. Every 3-6 months during maintaining phase. Check renal function and thyroid function every 6 months.
- Side effects: Common side effects are fatigue, dry mouth, nausea/vomiting/diarrhea, fine tremor, polyuria, polydypsia, weight gain, cognitive problems, impaired coordination, gastrointestinal distress, hair loss, benign leukocytosis, acne, and edema.
- System based Adverse reaction: acute and chronic renal function impairment, hypothyroidism, hyperparathyroidism, AV block, unmask Brugada syndrome, benign leukocytosis.

Lithium Toxicity and teratogenicity

- Reason for toxicity: dehydration of any cause, sodium depletion, decreased clearance
- NSAIDs use with Lithium can cause increased Lithium reabsorption
- ACE inhibitors or ARBs can cause compensatory Lithium reabsorption due to sodium depletion
- Thiazide and overuse of loop diuretics can cause increased Lithium level
- Mild to moderate toxicity (Serum level 1.5-2.0): hand tremor, polyuria and increased thirst, diarrhea, vomiting, drowsiness, decreased coordination
- Moderately severe toxicity (Serum level 2.0-2.5): blurred vision, ataxia, tinnitus, EKG changes
- Severe toxicity (serum level 3.0 or greater): delirium, seizure, coma

Lithium Toxicity and teratogenicity (continued)

- Treatment: Hemodialysis at serum level of 2.5 or above, esp with severe cardiac and neurological s/s. .
- Forced diuresis not recommended due to dehydration causing increased Lithium level
- Supportive care including adequate hydration at serum Lithium level <2.5.
- Permanent neurotoxicity can occur in acute or chronic toxicity
- Teratogenicity: Ebstein's anomaly with use in first trimester use

Valproic Acid or Sodium Valproate

- Possible mechanisms of action: Inhibition of voltage sensitive Sodium channels leading to enhancing inhibitory actions of GABA, indirectly blocking Glutamate actions and modulating Calcium channels.
- Has anti kindling properties, prevents rapid cycling
- Primarily used for acute mania and prevention of mania, not much benefit on depression
- Monitoring : Serum level of 50-150 is therapeutic but >125 can have more adverse effects
- Side effects/Adverse reaction: tremor, sedation, weight gain, hair loss, nausea, thrombocytopenia, hyperammonemia, hepatitis, pancreatitis; rarely Stephens-Johnson syndrome and DRESS, increased SI

Valproic Acid or Sodium Valproate (continued)

- Teratogenicity: neural tube defect in first trimester use, not recommended for child-bearing age without appropriate birth control
- Drug interactions: Lamotragine and Carbapenam antibiotics reduces level, Lamotragine level increased significantly with concomitant VPA use.
- Phenytoin may double VPA clearance
- Increased effect of Warfarin with VPA use.

Carbamazepine

- First anticonvulsant to show efficacy in treating mania.
- Mechanism of action appears to come from blocking voltage sensitive sodium channels. Blocks calcium influx through NMDA glutamate receptors, decreases presynaptic glutamate release.
- Approved for treatment of acute mania and prevention of mania
- Monitoring: serum level does not correlate with control of bipolar s/s. For epilepsy, serum level 4-12 mcg/ml recommended. CBC with diff, LFTs, pregnancy tests in women of childbearing age.
- Higher dose may be required later due to autoinduction, usually not after 5 weeks of dose stabilization.
- Side effects/adverse reactions : rash (7%), SJS/DRESS, sedation, dizziness, nausea/vomiting, constipation, dry mouth, ataxia, hyponatremia, bone marrow suppression, osteomalacia/osteoporosis and low Vit D, SIADH, withdrawal seizure.

Carbamazepine (continued)

- Grapefruit may increase concentration
- Toxicity: nystagmus and ataxia above serum level of 12, seizure and coma above serum level of 40.
- Teratogenicity: Neural tube defect, reduced serum concentration of hormonal birth control and alternative birth control is recommended.

Carbamazepine drug Interactions

- Induces CYP450 3A4 and 1A2: reducing serum concentration of substrates
- Decrease effectiveness: Antiretrovirals, anticoagulants (warfarin), hormonal birth controls, antipsychotic, Benzodiazepines, antidepressants, etc.

Lamotragine

- Recommended as first line agent for Bipolar depression
- Most likely acts on blocking voltage sensitive Sodium channels, very similar to Carbamazepine but not as potent. Also, reduce the release of glutamate which can be unique in action for Bipolar depression.
- Well tolerated but requires slow titration to avoid rare but life-threatening Stevens-Johnson Syndrome.
- Side Effects : benign rash, SJS/DRESS, dizziness, sedation, diplopia, rare agranulocytosis, delayed hypersensitive reaction, aseptic meningitis, nausea/vomiting, diarrhea.
- No need for monitoring of blood level
- Drug interactions: Estrogen can cause decreased level, VPA can increase level by 50%

Antipsychotic Medications

- Antidepressants actions: not every atypical antipsychotics have antidepressant property. Primarily partial agonist of 5HT1A and antagonism of 5HT1B/2C, 5HT3/7. SNRI and Alpha-2 antagonism.
- Antimanic actions: D2 antagonism and partial agonism, 5HT2A antagonism.
- Second generation antipsychotics are better tolerated
- Acute mania: consider Olanzapine, Risperidone, Paliperidone, Aripiprazole, Ziprasidone, Clozapine (treatment resistant mania), Asenapine. With or without mood stabilizers.
- Depressive or mixed episodes: Consider Aripiprazole, Lurasidone, Brexipiprazole, Lumateperone, Cariprazine, Quetiapine.

Antipsychotics

- Details of each medication not discussed due to time limits.
- Common side effects: Parkinsonian s/s, Tardive dyskinesia, acute dystonia, sedation, hyperprolactinemia, QTc prolongation, metabolic syndrome, risks of NMS, lowering seizure threshold, leukopenia and agranulocytosis, anticholinergic s/s, etc.
- Benefits over mood stabilizers: therapeutic levels not indicated besides Clozapine, safer in pregnancy than some mood stabilizers, some available in LAI form for better compliance.

Other Medications

- Benzodiazepines: acute mania, catatonia (high dose)
- Medications ineffective: Topiramate, Oxcarbazepine, Gabapentin, Levetiracetam, Pregabalin.