Bipolar Disorder

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Case Presentation

- The office receives a call from your patient Sally's sister, sharing concerns about changes in Sally's behavior recently
- Sally's sister was called by security at the local mall yesterday because she "caused a disturbance"
- She was hyperactive, running between stores, and intrusively proclaiming that she would pay for everyone's purchases.
- She was talking loudly and rapidly, made sexually provocative comments to men in the store, as well as religiously themed statements about acting for "the Glory of God."
- When confronted by store employees about her behavior, she claimed to own all the stores in the mall. Mall security was called after she became more escalated, and she eventually slapped a security officer, saying he was "a demon sent by Satan"
- Her sister said Sally had recently returned from an out-of-town business trip, and had not slept in several days. She suspects Sally forgot to take her medication with her on the trip.

Objectives

- Background
- Bipolar I criteria
- Bipolar II criteria
- Co-morbidities
- Differential Diagnosis
- Work-up
- Treatment

What is Bipolar Disorder?

- Mood disorder characterized by episodes of mania as well as episodes of depression
- More heritable than depression or anxiety
- May be mistaken for a variety of other medical and psychiatric conditions
- May be comorbid with, or worsened by, substance use

Who has bipolar disorder?

- Carrie Fisher
- Florence Nightingale
- Jane Pauley
- Sinead O'Connor
- Maria Bamford
- Mariah Carey
- Catherine Zeta-Jones
- Vincent van Gogh
- Rosemary Clooney
- Robert Downey, Jr
- Patty Duke
- Virginia Woolf
- Selena Gomez
- Linda Hamilton
- Beethoven
- Winston Churchill

Epidemiology of Bipolar Disorder

- US Lifetime prevalence (varies by source)
  - Bipolar I 0.6 -2%
  - Bipolar II 0.4 - 1%
- 1:1 male:female
- Risk factors
  - Family history of bipolar disorder or unipolar depression
  - Family history of psychotic illness
  - Advanced paternal age
  - Early trauma/childhood physical or sexual abuse
  - History of substance abuse

Bipolar I Disorder: Mania

- A manic episode is required to diagnose bipolar I disorder
- A distinct period of persistent, abnormally elevated or irritable mood accompanied by abnormal and persistent, increase in goal-directed activity or energy
- Lasts >7 days (or any number if hospitalization is required)
- 3 or more of the following (4, if mood is irritable)
  - Decreased need for sleep
  - Distractibility
  - Grandiosity/inflated self-esteem
  - Flight of ideas
  - Pressured speech
  - Increased goal-directed activity
  - Reckless behavior

Elevated/Expansive Mood

- Elevated
  - Increased happiness, confidence, optimism
  - Feelings of well-being, enthusiasm, success
  - "Walking on sunshine"
- Expansive
  - Extreme or unrestrained emotional expression
  - Excessively superior, over-valuation of self or significance to the world
  - May dress or act flamboyantly

Irritability

- Increased tendency to experience negative emotional states
  - Anger
  - Annoyance
  - Frustration
- Often includes a sense that the feelings or reactions are in some way disproportionate or difficult to justify
- Despite this, the emotions and responses feel difficult to control

Grandiosity

- Excess belief in the individual's specialness or importance
- Belief in having exceptional mental/physical fitness or talent, wealth, power, influence/affiliation, aristocratic ancestry
- May dismiss or try to outshine accomplishments of others
- Belief that the rules don't apply to them
- At a lower intensity, may appear to be self-centeredness or arrogance
- When more intense, can become delusional
  - Supernatural powers
  - Hyperreligiosity "Mission from God"

Decreased Need for Sleep

- Sleeping only a few hours a night or not at all
- Sleeplessness can persist for several days
- Refreshed, full of energy on awakening even after a brief sleep
- Progressive and ongoing sleep disruption intensifies other symptoms of mania and prolongs recovery
- Voluntarily decreased sleep (cramming for an exam, etc) may also precipitate mania in patients with known bipolar diagnosis

Increased Goal-directed Behaviors

- Excess house-cleaning
- Increased hours at work, making business plans, etc
- More time engaging in crafts or artistic activities
- Intense social activities, "fun times" with friends or family
- Perception of being "more effective" or "more productive" may limit insight into behavior being abnormal

Reckless/Impulsive Behaviors

- Inability to limit impulses leads to dangerous and risky actions
- Examples:
  - Gambling
  - Impulse buys/shopping sprees
  - Unwise investments
  - Sexually provocative behaviors/promiscuity
  - Substance use
- Poor impulse control increases risk of agitation or aggression
- Impacts of these persist long after episode remission
  - Physical, financial, personal difficulties

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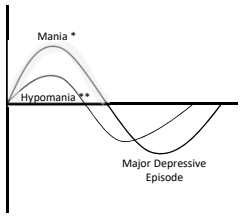
Bipolar II Disorder

- Present or past episode of hypomania and present or past *major depressive episode* are required to meet criteria for bipolar II disorder
- Hypomanic episode:
  - A distinct period of persistent, abnormally elevated or irritable mood accompanied by abnormal and persistent, increase in goal-directed activity or energy
  - Lasts > 4 days (distinct change, observable by others)
  - 3 or more of the following (4, if mood is irritable)
    - Decreased need for sleep
    - Distractibility
    - Grandiosity/inflated self-esteem
    - Flight of ideas
    - Pressured speech
    - Increased goal-directed activity
    - Reckless behavior
- True manic episode excludes this diagnosis

Major Depressive Episode of Bipolar Disorder

- Low mood, sadness, emptiness
- Loss of interest, pleasure, and enjoyment
- Weight loss or gain
- Insomnia or hypersomnia
- Agitation or sluggishness in motor behavior
- Fatigue or loss energy
- Feelings of worthlessness or excessive guilt
- Difficulty thinking and concentrating
- Recurrent thoughts of death/suicide

Bipolar I Disorder

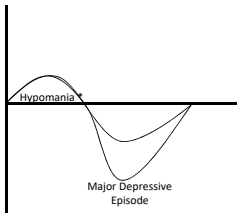


Those with bipolar I disorder may have a history of manic, hypomanic, or major depressive episodes

* Severe enough to produce marked impairment

** Not severe enough to produce marked impairment

Bipolar II Disorder



Those with bipolar II disorder have a history of hypomanic or major depressive episodes

* Not severe enough to produce marked impairment

Course and Prognosis of Bipolar Disorder

- Life-long, chronic illness
- Mean age of onset typically in early 20s
  - First episode after age 40 is rare
  - 20% begin during adolescence
- 46th out of 291 causes of world-wide disability, per the WHO
  - Greater impact than breast cancer, Alzheimer disease
- 18th leading cause of disability in the United States

"Manic Depression"

- These are *depressive* illnesses
- Three times more days spent depressed than manic in bipolar disorders
- 30% will attempt suicide in their lifetime
  - 10-15 % die by suicide
  - Rate of suicide 12 – 15x that of general population
- While euphoric mania is a classic feature of BD, mixed states including agitated depression or dysphoric mania are more common
- Manic episodes predominate in youth, but depressive episodes predominate in later years

Psychiatric Comorbidity & Bipolar Disorder

- Substance use
  - Alcohol: 60% of patients with bipolar 1 and 50% of patients with bipolar II meet criteria for alcohol use disorder
  - Associated with higher risk of hospitalization and more severe course of illness
- ADHD
  - 9-21% comorbidity
- Anxiety disorders (75% of patients)
- OCD, Eating Disorders

Medical Comorbidity & Bipolar Disorder

- Cardiovascular Disease
- Diabetes
- Obesity
- Pain
- Migraines
- Interplay between medical and mental health
  - Psychotropic medications carry metabolic risks
  - Psychiatric illness interferes with routine medical care
  - Stigma impacts medical care as well

Differential Diagnosis

- Medication-induced (antidepressants, stimulants, steroids, others)
- Oppositional defiant disorder (in children)
- Infectious causes (ex. neurosyphilis, HIV)
- Substance-induced/substance intoxication
- Hypo- or hyperthyroid disorder
- SLE
- Cushing Syndrome
- Other psychiatric disorders (PTSD, schizophrenia, anxiety disorders, personality disorders)

Clinical Presentation in Primary Care

- Initial presentation is typically a depressive episode
- Diagnosis may be delayed, as there may be a series of depressive episodes prior to hypomania/mania
  - One survey of bipolar patients showed 35% described a 10 year delay in diagnosis from first seeking treatment
- Metabolic syndrome and migraines are more common than in the general population.

Assessment

- Medical history
- Psychiatric history
- Mental status examination
- Physical examination
- Basic lab work up: Chem, CBC, TSH, UDS
- Given extensive DDx, consider other labs:
  - EEG, MRI, fasting glucose/HgbA1c (also for potential treatment options), calcium, VDRL/HIV, ESR/CRP/ANA, Cr/BUN (lithium)

Psychiatric History of Depressed Patient

- Previous major depressive episodes
- Symptoms of hypomania or mania?
- Impulsivity/risk taking behavior?
- Hospitalizations?
- Psychosis?
- Lethality
- Family history
- May involve talking with family/collateral, as patients may not recall previous mood episodes or have limited insight into their illness

Mood Disorder Questionnaire (MDQ)

An imperfect tool!

- 15 item screen for lifetime history of mania/hypomania
- Sensitivity ~65%
- Specificity ~ 80%

APPENDIX 1. The Mood Disorder Questionnaire

		YES	NO
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?	☐	☐
	...you were so irritable that you shouted at people or started fights or arguments?	☐	☐
	...you felt much more self-confident than usual?	☐	☐
	...you got much less sleep than usual and found you didn't really miss it?	☐	☐
	...you were much more talkative or spoke faster than usual?	☐	☐
	...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? *Please circle one response only.*	YES	NO
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	

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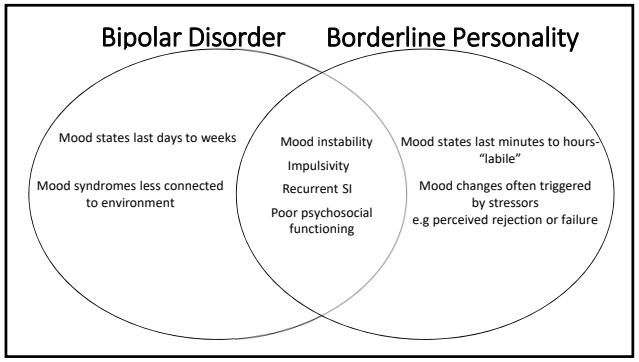
Case Presentation

- A woman presents to the office for mental health treatment. She reports frequent "mood swings," irritability, and has been in more conflict with her family.
- She describes moments of good mood and feeling "on top of the world," interspersed with moments of deep sadness. Her mood can change dramatically throughout the day.
- She reports last week she had a day of feeling "great" and dyed her hair a new color on a whim, which she now regrets.
- In the office she speaks intensely and rapidly, and notes previous doctors have never understood her well.

Is this Bipolar Disorder?

- Yes…!
  - Elevated mood
  - Irritability
  - Impulsivity
  - Rapid speech
- …or is it?
  - Mood state is not sustained
  - No indication of sleep disruption
  - No grandiosity



Treatment of Bipolar Disorder

- Three phases
  - Acute mania
  - Acute bipolar depression
  - Maintenance
- Medications are selected according to the phase of illness

Treating acute mania (FDA-approved)

- Mood stabilizers
  - Lithium, valproate, carbamazepine
- Second Generation (SGA)/Atypical Antipsychotics
  - Olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole, asenapine, and cariprazine
- Lithium or valproate with SGA
  - Except ziprasidone and cariprazine, which are approved only as monotherapy
- First-generation antipsychotic (chlorpromazine)

Treating bipolar depression (FDA-approved)

- Bipolar I
  - Olanzapine-fluoxetine combination pill
  - Quetiapine
  - Lurasidone
  - Cariprazine
- Bipolar II
  - Quetiapine
- Off-label (tolerability advantage over SGAs, less robust evidence of efficacy)
  - Antidepressants (in combination with mood stabilizer)
  - Lamotrigine
  - Modafinil/Armodafinil

Antidepressants for Bipolar Depression?

- Use of antidepressants in bipolar depression is controversial
  - Weak/equivocal evidence regarding efficacy
  - Risk of affective switch/treatment-emergent mania in unopposed antidepressant treatment
- Some evidence suggests antidepressant use may be safe in the depressed phase of bipolar disorder; must optimize mood stabilizer to prevent mania
- Bupropion appears to have lowest risk of manic switch; TCAs and venlafaxine have highest risk

Maintenance treatment

- Goals for treatment
  - Reduce residual symptoms; delay/prevent recurrence of mood episodes; improve functioning
- Recurrent mood episodes diminish efficacy of future treatments
- Recommend long-term maintenance therapies in all patients
- Maintenance treatment reduces suicide risk
  - Lithium has strongest data for prevention of suicide

Maintenance Treatments

- FDA-Approved medications
  - Lithium, lamotrigine, olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole
  - Lamotrigine is only approved for maintenance phase
- 1st line treatment
  - Continue agent that was successful in treating acute mood episode
- 2nd line treatment, *if unable to tolerate 1st line (side effect burden, etc)*
  - Lithium
  - Valproate
  - Quetiapine
  - Lamotrigine

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Lithium Pearls

- Renally excreted, low volume of distribution
  - Dehydration increases concentration; urine should be light yellow to clear
- Goal levels vary per treatment phase, generally 0.6-1
- Narrow therapeutic window, toxicity >1.5
- Immediate release and extended release formulations

Lithium Pearls

- Monitoring includes lithium levels (12 h post-dose), BUN/Cr, TSH, serum electrolytes with Ca+, CBC with diff, pregnancy status, EKG
- May lead to increased lithium levels
  - ACEIs/ARBs
  - NSAIDs
  - Diuretics
  - Dehydration, renal disease, low Na+ diet

Valproic Acid Pearls

- Hepatically excreted
- Goal levels 50-120, but optimal level not clearly established
- Wide therapeutic window, and may be loaded in acute phase of treatment
- Immediate release, delayed release, and extended release formulations
- Monitoring includes VPA level (12 h post-dose), LFTs, CBC with platelets, pregnancy status
  - Consider ammonia level in encephalopathy; may be elevated without LFT abnormalities
- Significant interaction with lamotrigine as well as other AEDs

Second Generation Antipsychotics

- Hepatically metabolized
- No commonly accepted therapeutic levels
- Risk of metabolic syndrome and movement abnormalities
  - qTc prolongation associated with some antipsychotics
- Monitoring includes lipid panel, HgbA1C, fasting blood glucose, waist circumference, weight, blood pressure, EKG
- Abnormal Involuntary Movement Scale (AIMS) exam should be performed every 6 months to detect movement disorders (tardive dyskinesia)

Pregnancy and Bipolar Disorder

- Carefully weigh risks and benefits of regimen change during pregnancy
  - 50% risk of mood episode within only two weeks if meds are stopped suddenly
  - Stable mood in pregnancy leads to better outcomes for mom and baby
- Teratogenicity
  - Valproic acid may cause neural tube defects
  - Lithium increase risk of Ebstein's anomaly
- As pts are more likely to be depressed, may consider lamotrigine
- Quetiapine has lowest placental permeability; lurasidone was considered category B
- Consider ECT if symptoms are severe.
- Other considerations: psychotherapy, stress reduction, exercise

Indications for inpatient treatment

- Mania
  - Presence of severe agitation or violence that puts the life of the patient or others at risk
  - Nonresponse to combination of first-line agents
- Depression
  - Presence of suicidal behavior
  - Presence of severe agitation or violence that puts the life of the patient or others at risk
  - Refusal to eat or severe malnutrition
  - Catatonia
  - Nonresponse to combination of first-line agents

Other Interventions

- Electroconvulsive therapy (ECT)
- Repetitive Transcranial Magnetic Stimulation (rTMS)
- Ketamine infusion
- Psychotherapy

Summary

- Bipolar I Disorder is characterized by manic episodes, *but more time is spent in depression*.
- Bipolar II Disorder features hypomanic episodes and is not severe enough to cause marked impairment.
- Expect psychiatric and medical co-morbidities
- Great imitator - *consider wide differential diagnosis*.
- Be careful of antidepressant alone (affective switch) - use with a mood stabilizer

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