BIPOLAR DISORDERS

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Week 2

Educational Objectives:

1. Understand the importance of recognizing bipolar disorders in primary care
2. List the diagnostic criteria for bipolar disorders
3. Describe the indications for and side effects of lithium

CASE ONE:

Mr. G is a 29-year-old man who comes to clinic to establish care at the urging of his fiancée. He reports feeling anxious and irritable, feelings which have worsened since losing his job about a week ago. He had been working as a store clerk but was fired for poor performance including arriving late, missing work, and discrepant cash register counts. For the past two or three weeks he has been staying up late and going out drinking with friends nightly, sometimes staying up all night. He has been fighting with his fiancée, mostly over money. She is upset because he has been spending money on alcohol and restaurants, even though he just lost his job.

His history is notable for ADHD, diagnosed in his early teen years, and a prior psychiatric hospitalization in his early 20s for suicidal ideation. At the time, he was drinking heavily and feeling depressed. He may have been prescribed medications, but he is not sure what they were, and he did not take them for long. After his hospitalization, he did not have consistent care for several years until age 26, when he again experienced depressive symptoms. He was treated by a primary care doctor with bupropion for about a year and a half and he felt it helped him. He stopped taking it eventually when he felt improved. He has had no further hospitalizations. Currently he takes no psychiatric medications and is not seeing any other providers for mental health.

Questions:

1. **What is the differential diagnosis for this patient?**
   This patient describes symptoms characterized by irritability, decreased need for sleep, and an increase in energy/goal-directed behavior (specifically socializing with friends). In addition, he has been using substances (alcohol, marijuana). His past medical history is notable for ADHD, periods of depression, and a history of suicidality. Given this constellation of symptoms and behaviors, the differential diagnosis for this patient includes bipolar I disorder, bipolar II disorder, cyclothymia, major depressive disorder, substance-induced mood disorder, generalized anxiety disorder, and potentially others.

Distinguishing bipolar disorders from other psychiatric disorders can be challenging because of many overlapping symptoms. However, it is critical to consider the diagnosis of bipolar I or II in any patient presenting with symptoms of depression or anxiety, in part because treating bipolar disorders with antidepressant monotherapy is contraindicated. SSRIs, SNRIs, tricyclic antidepressants, and MAOIs can precipitate manic episodes. Therefore, considering and ruling out bipolar disorders is critical when initiating one of these agents. In addition, the medications that are most effective in treating bipolar disorders are distinct from those used to treat unipolar depression or anxiety. Lastly, recognizing this diagnosis is important because bipolar disorders are associated with a higher risk of self-harm.

2. **What are the diagnostic criteria for bipolar disorders and what clinical features help distinguish them from other psychiatric diseases?**
Bipolar disorders are characterized by a period of mania or hypomania. During manic episodes, people experience a period of elevated, expansive, or irritable mood, in conjunction with an increase in energy or goal-directed activity. Hypomanic episodes are similar to manic episodes, but may be shorter and do not impair function, cause psychosis, or lead to hospitalization. The DSM V diagnostic criteria for bipolar I requires at least one episode of mania that is not explained by another medical condition or substance use (described in more detail below). Depressive symptoms are common in bipolar I and II but are not required for diagnosis.

Definition of a manic episode (APA, 2013):

- "A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently goal-directed behavior or energy, lasting at least one 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
    - More talkative than usual
    - Flight of ideas or subjective experience that thoughts are racing
    - Distractibility
    - 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 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 direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or 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."

In addition to the DSM V criteria, there are number of other features of a patient's history that may raise suspicion a bipolar disorder (Marzani, 2021):

- Bipolar disorders have a heritable component, and a family history of bipolar disorder may suggest the diagnosis.
- Suicidal behavior is relatively prevalent among people with bipolar disorder, and suicide attempts, particularly at a younger age, should raise concern for the diagnosis. About one-third of people with a bipolar disorder will attempt suicide during their lifetimes and about 7% will complete suicide.
- History of other comorbid psychiatric disorders such as substance use disorders and ADHD
- History of recurrent job loss, multiple divorces, substantial legal or financial trouble

3. **What further history might you gather?**
   Additional history should include asking specifically about symptoms of mania included in the DSM V definition. In addition, primary care doctors should also assess for other psychiatric symptoms such as auditory or visual hallucinations, delusions, suicidal thoughts, or thoughts of harming others. Hallucinations may suggest psychosis rather than mania. Thoughts of self-harm or harm to others are important to assess as they can lead to specific actions (safety evaluation/risk assessment, hospitalization, etc.). A detailed substance use history is important to a distinguish substance-induced mood disorder from a manic episode. Substance use and bipolar disorders can co-occur, but making a diagnosis of a bipolar disorder in the setting of substance use is challenging given overlapping symptoms and therefore often requires expert consultation. Lastly, it is important to evaluate for medical conditions that might cause similar symptoms such as neurologic conditions (e.g., dementias), metabolic conditions (hyperthyroidism, hypercalcemia), infections (neurosyphilis, other CNS infections), or medication-induced mania (steroids, antidepressants, especially TCAs, SNRIs, or MAOIs). There is no established battery of tests that should be completed to rule out a medical mimic, but a careful history and physical exam may suggest one of these other etiologies.

CASE ONE CONTINUED:

> **Mr. G denies any auditory or visual hallucinations and does not have suicidal thoughts. On exam, you note pressured speech, flight of ideas, and restlessness. On physical exam, his heart rate is 96, blood pressure 125/83, respiratory rate 16. Temperature is normal. HEENT exam notable for normal thyroid exam. Normal cardiac, pulmonary, and abdominal exams. Neurologic exam is normal.**

4. **Based on his history and exam, do you think he has a bipolar disorder? What are the next steps in management?**

This patient likely meets criteria for an acute manic episode: he has had a persistently elevated/irritable mood with increased energy/goal directed behavior. In addition, he has decreased need for sleep, flight of ideas, psychomotor agitation, and is engaging in behavior with the potential for painful consequences (spending large amounts of money after losing his job). Most patients who have an acute manic episode (or suspected acute manic episode if it is not possible to distinguish from other disorders immediately) are treated in the inpatient setting. This allows for thorough assessment, rapid administration and titration of medications, and regularization of sleep/wake cycles, and can help keep patients from self-harm while they may be most impulsive. If it is uncertain whether to recommend hospitalization, urgent psychiatric consultation can be helpful.

Medications used to treat acute manic episodes include mood stabilizers (lithium, lamotrigine, valproic acid, carbamazepine) and antipsychotics (risperidone, olanzapine, quetiapine). Choice of initial therapy depends on acuity of symptoms, comorbidities such as presence of chronic kidney disease and metabolic syndrome. Once the acute manic episode has abated, maintenance treatment often includes mood stabilizers (especially lithium and lamotrigine). Antipsychotics like quetiapine can also be used longer term, although metabolic effects must be considered (Carvalho, 2020).

Depressive symptoms occur in more than half of patients with bipolar disorders. For patients with a bipolar disorder who experience depressive symptoms, antipsychotics such as quetiapine and lurasidone can be used, or the combination of olanzapine and fluoxetine. Nonpharmacologic therapies such as electroconvulsive therapy and cognitive behavioral therapy can also have a role (Carvalho, 2020).

In patients who have a history of bipolar disorder, but who are not experiencing an acute manic episode, the primary care physician can play a key role. Most patients are managed or comanaged by a psychiatrist. However, the primary care physician can play an important part in the patient's care in the following ways:

- Recognizing the diagnosis of a bipolar disorder
- Ruling out medical mimics
- Avoiding medications that can worsen symptoms

- Coordinating care when symptoms change or worsen or when comorbid conditions such as substance use arise
- Recognizing common side effects and toxicities of medications

CASE TWO:

In clinic you are seeing Ms. S, a 49-year-old woman with a history of well-controlled bipolar disorder treated with lithium, as well as diabetes and hypertension. Her blood pressure medications are amlodipine and hydrochlorothiazide. Today in clinic, her blood pressure is 165/96. She notes polyuria and polydipsia.

5. **What are the signs and symptoms of lithium toxicity?**
Lithium is a commonly used, effective medication for the treatment of bipolar disorder. Primary care providers must be aware of common medication interactions and side effects. Lithium toxicities can occur acutely, due to a supratherapeutic dose, or chronically, from long-term effects at a therapeutic dose.

Acute lithium toxicity can occur as a result of intentional overdose or because of changes in lithium elimination, such as acute kidney injury from another illness. Acute lithium toxicity often presents with GI symptoms such as nausea and vomiting. Neurologic symptoms can be delayed and may include sluggishness, ataxia, confusion, tremors, hyperreflexia, nystagmus, seizures, and delirium/encephalopathy (Perrone, 2022). Consider lithium toxicity in any patient with lithium exposure (or access to lithium) who has new neurologic symptoms. When acute lithium toxicity is suspected, a lithium level can confirm the diagnosis, although lithium levels corelate poorly with severity of symptoms. Patients with lithium toxicity require hospitalization, and treatments range from holding lithium to gut decontamination with polyethylene glycol to dialysis for severe cases.

Long-term sequalae of lithium use include development of nephrogenic diabetes insipidus (arginine vasopressin resistance). This often manifests with polyuria and polydipsia and dilute urine. Patients who have access to free water may be able to compensate and may not develop hypernatremia. Long-term neurologic effects are also well-described and include a fine tremor, cerebellar dysfunction, and extrapyramidal symptoms. Chronic lithium use can also cause a variety of other metabolic abnormalities including chronic interstitial nephritis, hypo- and hyperthyroidism, and hypercalcemia (due to hyperparathyroidism) (McKnight, 2012). Electrolytes, renal function, and thyroid function should be assessed about every six months. Lithium is also relatively contraindicated in pregnancy.

In this case, serum electrolytes are indicated to evaluate sodium, calcium, and glucose. A urinalysis can identify dilute urine in the absence of hyperglycemia, suggesting diabetes

insipidus. A lithium level is useful for identifying acute toxicity and for long-term therapy monitoring.

CASE TWO CONTINUED:

You note that the patient's blood pressure is elevated.

6. **What are general considerations for blood pressure management in patients who take lithium?**
   Lithium is a monovalent cation much like sodium and potassium. As such, many antihypertensives can alter lithium levels. Thiazide diuretics and ACE inhibitors raise lithium levels while potassium sparing diuretics and SGLT-2 inhibitors can lower levels. Calcium channel blockers and loop diuretics have variable effects. None of these medications is contraindicated, but initiating and titrating medications requires monitoring of the lithium level. In this case, checking lithium levels before prescribing a new antihypertensive would be indicated. Once a second medication is started, monitoring lithium levels in coordination with the prescriber (often the patient's psychiatrist) is recommended.

Primary Reference:

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Additional References:

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3. Carvalho AF, Firth J, Vieta E. Bipolar Disorder. N Engl J Med. 2020 Jul;383(1):58–66.
4. McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium Toxicity Profile: A Systematic Review and Meta-Analysis. The Lancet. 2012; 379(9817): 721-8.

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Knowledge Questions:

1. **A 45-year-old woman presents to clinic for evaluation of poor sleep. She reports that for the last few weeks she has had difficulty initiating sleep. She feels restless and anxious at night. She has a history of periods of depressed mood, anhedonia, and changes in sleep, appetite, and energy level. She has a history of alcohol use and reports periods of heavy drinking in the past, at least four drinks per day, but recently has cut back. She had a suicide attempt at age 16. What would you do next?**

    a. Start citalopram 10 mg daily
    b. Start zolpidem 10 mg at night
    c. Obtain additional history, including the specific timeline of alcohol use and inquiring about manic symptoms
    d. Start melatonin 5 mg nightly

2. **A 38-year-old man with bipolar I disorder comes to you for an urgent visit. Some members of his household recently had gastroenteritis and he has been feeling ill. He describes nausea, vomiting, and diarrhea. He takes lithium 600 mg twice daily, a dose he has been on for the past five years with stable manic symptoms. His vital signs and neurologic exam are normal. What do you do next?**

    a. Stop lithium and have the patient follow up with his psychiatrist as scheduled in two weeks
    b. Check lithium level, renal function, and electrolytes at today's visit
    c. Reduce lithium to 300 mg twice daily
    d. Symptomatic management alone with oral rehydration and antiemetics

3. **Which of the following statements is false?**

    a. The diagnosis of bipolar I disorder requires at least one manic episode lasting at least one week that is disabling in nature and at least one depressive episode in a patient's lifetime.
    b. People with bipolar disorders are at elevated risk of suicide compared to the general population.
    c. Bipolar disorders commonly co-occur with other psychiatric conditions such as substance use disorders.
    d. Some antidepressants such as SSRIs can be used in bipolar disorders in specific circumstances such as in combination with antipsychotic medications

Answers:

1. **c** *The reason for this patient's sleep disturbance is not evident from the information given. The differential diagnosis includes a range of mood disorders (major depressive disorder, anxiety disorders, bipolar disorders), as well as substance-induced etiologies (e.g., alcohol use or withdrawal). More history is needed. Starting citalopram (among other SSRIs) would be appropriate for the treatment of major depressive disorder or generalized anxiety disorder but is not advised until mania is ruled out. Sedative-hypnotic sleep agents should be used with caution and should not be considered until other causes of sleep disturbance are ruled out. There is not strong evidence for the effectiveness of melatonin for insomnia in general, and in this case, additional information about the patient's sleep disturbance is needed before suggesting a treatment.*
2. **b** *This patient likely has acute viral gastroenteritis, given his history of close contacts with similar symptoms. Dehydration in people who take lithium can precipitate lithium toxicity (which also often presents with gastrointestinal symptoms). In people who take lithium who present with nausea and vomiting, considering lithium toxicity is critical. If laboratory evaluation is readily available, checking lithium levels and renal function is an important next step to assess for toxicity. Stopping lithium (choice A) would be appropriate if it is not possible to check lithium levels immediately and toxicity is suspected. However, if acute toxicity is suspected, patients should be directed to the emergency room, rather than later follow up. Reducing lithium or symptomatic management alone would not be appropriate without more information.*
3. **a** *The diagnosis of bipolar disorders requires only the presence of a manic or hypomanic episode. The presence of depressive symptoms is common but not necessary for the diagnosis of bipolar I or II.*