An Update on the Diagnosis and Treatment of Bipolar Disorder, Part 1: Mania

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This article reviews DSM-5 changes to symptom criteria for bipolar disorder. The primary focus is on the diagnosis and treatment of mania and hypomania.

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ACTIVITY GOAL
This article reviews DSM-5 changes to symptom criteria for bipolar disorder. The primary focus is on the diagnosis and treatment of mania and hypomania.

LEARNING OBJECTIVES
At the end of this CE activity, participants should be able to:
• Understand the various bipolar specifiers
• Identify bipolar diagnostic categories
• Identify FDA-approved indications for pharmacologic management of bipolar mania
• Distinguish which intervention (pharmacotherapy or psychotherapy) is best for each patient

TARGET AUDIENCE
This continuing medical education activity is intended for psychiatrists, psychologists, primary care physicians, physician assistants, nurse practitioners, and other health care professionals who seek to improve their care for patients with mental health disorders.

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Philip G. Janicak, MD, reports that he has received grant support from, and is on the speakers bureau for, Neuronetics Inc, Sunovion, and Ortho-McNeil/Janssen; he is also a consultant for Neuronetics Inc.
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Schizoaffective disorder is distinguished from acute mania with psychosis by a period of psychotic hallucinations and fixed delusions. While similar symptoms may occur in both disorders, schizophrenia more commonly presents with mania and requires careful attention to the patient’s psychiatric history to help clarify the diagnosis. Often substantial symptomatic overlap. Acute schizophrenia can mimic a more severe episode of bipolar disorder can be difficult to distinguish from other psychiatric conditions because there is no period of normal mood that last more than 2 months. These mood disturbances should never present in bipolar II patients, and hospitalization is a specific exclusion criterion. Per DSM-5, if either mania or hypomania presents with at least 3 criteria for a depressive episode, they would warrant a mixed specifier designation as well. Clarifying whether there has been a manic or hypomanic episode may be difficult. This is in part because patients may not consider hypomania or mild mania to be problematic. Clinicians need to carefully explore for possible past episodes, using collateral sources of information whenever possible. Screening instruments such as the Mood Disorders Questionnaire and the prospective Life Chart Method are also helpful. Cyclothymic disorder is characterized by at least 2 years (1 year in children and adolescents) of periodic hypomanic and depressive symptoms that are distinct from each other. Neither mood phase, however, ever meets the full criteria for a hypomanic or depressive episode. During this time, there are no periods of normal mood that last more than 2 months. These mood disturbances should also lead to problems in social or occupational functioning.

**Differential diagnosis**

Bipolar disorder can be difficult to distinguish from other psychiatric conditions because there is often substantial symptomatic overlap. Acute schizophrenia can mimic a more severe episode of mania and requires careful attention to the patient’s psychiatric history to help clarify the diagnosis. While similar symptoms may occur in both disorders, schizophrenia more commonly presents with hallucinations and fixed delusions.

Schizoaffective disorder is distinguished from acute mania with psychosis by a period of psychotic...
symptoms that lasts at least 2 weeks in the absence of significant mood symptoms. Over the long-term course of schizoaffective disorder, however, there should be a substantial proportion of time (> 50%) when mood symptoms are present.

MDD and bipolar depression are often clinically indistinguishable. MDD, however, involves only depressive episodes, whereas bipolar depression requires a history of mania or hypomania. Obtaining a thorough personal and family history, including premorbid functioning, may help clarify the diagnosis.

Other disorders (eg, ADHD, conduct disorder, stimulant use) may also include certain symptoms of hypomania or mania and, to further complicate the diagnosis, often occur as comorbidities with bipolar disorder. Various substances, medications, and medical conditions can mimic the symptoms of bipolar disorder and have their own specific diagnostic categories. For example, manic or hypomanic symptoms due to the effects of cocaine would not be given a bipolar diagnosis unless the symptoms persisted well after the drug’s effects subsided.

**Table 3** lists and briefly describes DSM-5 categories for bipolar disorder.

**Management of bipolar mania and hypomania**

**Treatment recommendations**

Several reviews, professional guidelines, pragmatic studies, and treatment algorithms serve as the basis for our suggested treatment approaches. The strategies recommended in these publications are based primarily on the strength of evidence from placebo- and/or active comparator-controlled trials involving various medications or psychotherapeutic approaches. In some cases, however, there is a lack of such data and information of lesser strength forms the basis for recommendations. In particular, guidelines for the management of certain patient subgroups (eg, rapid cyclers) are often based on results from fewer and less well-controlled trials. One additional caveat is that the preponderance of evidence derived from controlled trials is industry sponsored.

**Emergency interventions**

Manic patients who present with severe agitation or aggression may require immediate pharmacologic intervention to prevent harm to themselves and others. Second-generation antipsychotics are generally preferred over first-generation (typical) agents because of their lower short-term adverse effect burden. Benzodiazepines may also be used as adjuncts to quickly calm an agitated patient, to reduce the amount of antipsychotic required, or to prevent withdrawal symptoms when alcohol or other substances are involved.

When possible, oral formulations should be offered initially and acute parenteral formulations reserved for those unwilling or unable to tolerate oral therapy. Alternatively, the combination of lower doses of haloperidol (eg, 2 to 5 mg) and lorazepam (eg, 2 mg) may be used either orally or parenterally. A recent study indicated that successful remission of postpartum psychotic mania may require combined treatment with lithium, an antipsychotic, and a benzodiazepine. In more emergent situations such as manic delirium, ECT can be life-saving.

**Stabilization strategies**

Once the safety of the patient and others is assured, attention turns to resolution of an acute episode (Figure). If the patient is currently taking an antidepressant, it should be discontinued (preferably by taper rather than by abrupt cessation) to prevent persistent manic symptoms and a greater risk for relapse. Most published strategies to manage acute, mild to moderate manic or mixed episodes (and to a lesser extent hypomania) recommend lithium, valproate, or a second-generation antipsychotic as first-line monotherapies. Of note, recent evidence supports lithium’s potential neuroprotective properties and lower non-suicide mortality risk compared with anticonvulsants. In patients with more severe symptoms, associated psychosis, or schizoaffective disorder, a second-generation antipsychotic alone or in combination with other mood stabilizers plus a benzodiazepine are usually recommended (eg, lithium or valproate plus an antipsychotic). Second-generation antipsychotics are usually preferred to first-generation antipsychotics to minimize adverse effects, particularly neuromotor; or to lithium, valproate, or carbamazepine during pregnancy. With insufficient benefit, clozapine as monotherapy or augmentation therapy may also be an alternative. Finally, ECT alone or combined with an atypical antipsychotic can control episodes of psychotic mania and severe refractory episodes, and constitutes a safer alternative during pregnancy.

Lithium and valproate appear to be comparably effective in treating pure manic episodes, while valproate may be more effective for mixed or rapid cycling presentations. Carbamazepine with or without an antipsychotic is usually recommended as second-line therapy because it is limited by its adverse effect profile and the risk of significant interactions with other psychotropic and nonpsychotropic medications. In this context, oxcarbazepine—a structurally similar analog of...
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Lithium is contraindicated in patients with significant renal impairment, dehydration, and low sodium levels, because these states increase the likelihood of acute toxicity. Lithium should also be avoided in patients with significant cardiovascular disease because of its impact on the heart's conduction. Its half-life in a healthy adult is about 24 hours, and steady-state serum levels generally fall between 900 and 1900 mg daily to achieve a target serum concentration of 0.8 to 1.2 mEq/L. If dose adjustments are made, a lithium trough (10 to 12 hours after the last dose) level should be drawn 5 to 7 days after the change to properly reflect the new steady-state concentration. If symptoms are not adequately controlled with medication(s) and psychotherapy, maintenance ECT may be continued after a successful acute treatment course at the lowest possible frequency, if symptoms are not adequately controlled with medication(s) and psychotherapy. Maintenance treatment should be continued for at least 6 to 12 months after complete remission of a manic episode before assessing the need for ongoing treatment. Given the high relapse rates with discontinuation, however, it is generally recommended that maintenance therapy continue indefinitely. If lithium is discontinued, it should be done by a slow taper over several weeks to decrease the risk of relapse.

Pharmacotherapy
Lithium
While lithium’s exact mechanism of action is unknown, its ability to modulate various aspects of brain chemistry is consistent with many current models of the pathogenesis of bipolar disorder. Lithium exerts multiple biochemical effects at a variety of targets owing to its relatively simple nature. Because of its similarity to other cations (eg, Na⁺, K⁺, Ca²⁺, Mg²⁺), lithium can alter ion channels and pumps in cell membranes. It is also implicated in the modulation of neurotransmitters and neuropeptides such as lithium-induced decreases in beta-adrenergic receptor number, beta-adrenergic activity through inhibition of thyroid hormone, dopamine receptor supersensitivity, and glutamate-mediated calcium signaling; and increases in serotonin release.

In addition, lithium interacts with G-protein and second messenger systems leading to downstream effects on DNA transcription, which may serve to explain its long-term therapeutic effects. Neuroprotective properties such as increasing neuronal viability in the context of glutamate cytotoxicity and the expression of brain-derived neurotrophic factor are also associated with sustained lithium treatment.

Lithium is rapidly absorbed in the gastrointestinal tract, is not protein bound, and distributes throughout total body water with peak serum concentrations at 1 to 2 hours after administration (4 to 5 hours for slow-release preparations). It has no metabolites and is almost entirely excreted by the kidneys. Its typical half-life in a healthy adult is about 24 hours, and steady-state serum levels are usually achieved in 4 to 5 days. Lithium is usually started at 300 mg, 2 or 3 times daily, and gradually increased 300 to 600 mg every 1 to 5 days based on response to treatment, blood levels, and tolerability. Optimal dosing generally falls between 900 and 1900 mg daily to achieve a target serum concentration of 0.8 to 1.2 mEq/L. If dose adjustments are made, a lithium trough (10 to 12 hours after the last dose) level should be drawn 5 to 7 days after the change to properly reflect the new steady-state concentration. Lithium is contraindicated in patients with significant renal impairment, dehydration, and low sodium levels, because these states increase the likelihood of acute toxicity. Lithium should also be avoided in patients with significant cardiovascular disease because of its impact on the heart’s conductive properties.
Lithium is associated with a number of adverse effects even at therapeutic levels. Nausea is most commonly managed by encouraging food intake with each dose or the use of extended-release formulations. Tremor, which can also be an early sign of toxicity, may be managed by dividing doses and avoiding exacerbating factors such as anxiety, stress, and caffeine. Weight gain, loose stools, and cognitive impairment can also occur and may require dose adjustment. Renal function should be assessed once or twice a year because lithium may cause impairment with long-term use. Lithium also affects the thyroid and parathyroid glands, reducing thyroid hormone release and increasing parathyroid hormone activity.

In the context of pregnancy, lithium is listed as a category D drug owing to the risk of cardiac defects such as Ebstein's anomaly. During pregnancy (particularly the first trimester), the developing fetus should be closely monitored for cardiac defects. Doses will need adjustment, particularly near parturition and postpartum because of changes in metabolism and fluid volumes. When neonates are breastfed while their mother is taking lithium, they should be assessed for lethargy, as well as growth and feeding problems.

Valproate

As with lithium, the mechanism of action for valproate as a mood stabilizer is not fully understood. Two actions that may be relevant include blockade of voltage-dependent sodium ion receptor channels and enhancement of gamma-aminobutyric acid activity by increasing its synthesis and release.

Valproate is well absorbed with greater than 80% bioavailability after oral administration and may be administered after meals because food delays absorption, lessening adverse effects. It is highly protein bound and remains mainly in the extracellular fluid. Peak serum levels occur between 1 and 4 hours after administration, and half-life ranges between 6 and 16 hours. Valproate is metabolized by the liver and excreted through the kidneys.

Valproate is usually started at a dose of 250 mg, 2 or 3 times daily, and titrated every few days until a dose of 1500 to 2500 mg/d is reached. Valproate can also be orally loaded at 20 to 30 mg/kg daily to more rapidly achieve therapeutic levels. Optimal therapeutic plasma levels of valproate generally fall between 50 and 125 µg/mL and should be checked 2 to 5 days after a dose increase, 12 hours after the last dose.

Valproate can cause nausea, vomiting, hair loss, easy bruising, and tremor. Valproate-associated weight gain and insulin resistance can lead to metabolic syndrome. More rarely, it may cause liver toxicity, elevations in ammonium levels, pancreatitis, thrombocytopenia, and coagulation problems. It is contraindicated in persons with liver disease and those with mitochondrial disorders. Liver function tests should be performed before starting treatment and repeated during the first few months if indicated.

In the context of pregnancy, valproate is listed as a category D drug because of a 9% risk of development of major malformations. Women of child-bearing age should use adequate contraceptive methods while taking valproate and should receive folic acid. If pregnancy does occur, the patient should be switched to an alternative treatment and the fetus monitored for cardiac anomalies. Valproate also carries an increased risk of polycystic ovary syndrome, which is particularly relevant in women of childbearing age.

Carbamazepine

The hypothetical mechanism of action of carbamazepine in bipolar disorder may relate to its binding of sodium ion channels, enhancing the inactivated state and blocking the propagation of rapid action potentials. It is absorbed slowly, with peak serum levels occurring 6 to 8 hours after administration and a bioavailability of 85%, and is metabolized in the liver by cytochrome P450 (CYP450) 3A4. Its half-life during the initial stages of treatment ranges from 25 to 65 hours, but may decrease to 12 to 17 hours after several weeks owing to autoinduction. For this reason, serum levels should be measured at 3, 6, and 9 weeks after starting treatment.

Oxcarbazepine is usually fully absorbed and not affected by food with peak serum concentrations achieved 4 to 6 hours after administration and a half-life of 8 to 12 hours. Oxcarbazepine also undergoes hepatic metabolism but is less likely to induce liver enzymes than carbamazepine. Carbamazepine is usually started at an oral dose of 400 to 600 mg daily with dose increases of 200 mg every 3 to 5 days until a clinical effect is achieved or adverse effects become intolerable. Although target serum levels for patients with epilepsy typically range from 4 to 12 µg/mL, clinical response and tolerability should take priority over levels in those with bipolar disorder. Starting doses of oxcarbazepine are generally 300 to 600 mg daily, which can be increased by up to 600 mg per day weekly with a range of 300 to 3000 mg daily.
Common adverse effects of carbamazepine include nausea, vomiting, headache, diarrhea, hyponatremia (possibly higher risk with oxcarbazepine), rash, pruritus, fluid retention, and low testosterone in males. More serious effects include Stevens-Johnson syndrome, agranulocytosis, and aplastic anemia, which often present within the first few months of treatment. Carbamazepine can lead to multiple clinically relevant drug interactions, primarily through CYP450 3A4 induction. Pharmacogenetic testing (eg, HLA-B*1502, HLA-A*31:01) can prevent carbamazepine-induced hypersensitivity reactions (ie, Stevens-Johnson syndrome) in certain ethnic groups (eg, Han Chinese, Europeans).

In the context of pregnancy, carbamazepine is labeled as a category D drug owing to an increased risk of spina bifida, craniofacial defects, cardiovascular malformations, developmental delays, and hypospadias. Women of childbearing age should use adequate contraceptive methods while taking carbamazepine and should receive folic acid. While carbamazepine enters the breast milk as its active metabolite and is detected in the serum of breastfed infants, it is generally thought to be safe. However, mothers are encouraged to discontinue breastfeeding if the neonate begins to experience related adverse events (eg, transient hepatic dysfunction).

Oxcarbazepine is a category C drug found to cause adverse effects in animal studies, but with no specific malformations identified in humans. It is also transferred to newborns in small amounts through breast milk.

Antipsychotics

First-generation antipsychotics preceded the availability of lithium in the US by almost 20 years and were the mainstay of medication treatment for bipolar disorder during this period. Indeed, chlorpromazine still has an FDA-approved indication for this disorder. With the advent of lithium, however, the primary role of antipsychotics was to serve as adjunctive therapy for more severe episodes. With extended experience, lithium was found insufficiently effective and/or poorly tolerated in a substantial proportion of patients with bipolar disorder. This ushered in a series of studies with anticonvulsant agents and second-generation antipsychotics to ascertain their potential as alternative mood stabilizers. Theories on the mechanism of action of second-generation antipsychotics focus on their multiple neuroreceptor effects, particularly related to the dopamine and serotonin systems.

A series of controlled trials considered olanzapine as either monotherapy or adjunctive therapy for bipolar disorder, particularly for acute mania. The consistently positive results with olanzapine led to studies with other second-generation antipsychotics. While the most common adverse effects of antipsychotics include neuromotor, sedative, hormonal, and metabolic complications, they vary substantially among the different agents. For example, haloperidol and risperidone can increase the risk of acute extrapyramidal side effects and hyperprolactinemia, while agents such as olanzapine and quetiapine may be more likely to cause sedation, weight gain, and related cardiometabolic effects. Table 4 lists the agents approved by the FDA for acute and maintenance treatment of mania and hypomania; phases of the illness for which antipsychotics have approved indication(s) as either monotherapy or adjunctive therapy; their usual dosing ranges; and other clinically relevant considerations.

Conclusion

The defining characteristic of bipolar disorder is the presence of mania or hypomania. Bipolar I disorder is primarily distinguished from bipolar II disorder by meeting the criteria for a full manic episode. Conversely, bipolar II disorder must meet criteria for both a hypomanic and a depressed episode. Cyclothymic disorder consists of more chronic mood disturbances that do not meet the full criteria for hypomania, mania, or depression.

Treatment approaches depend on the illness phase and symptom severity. Mania, hypomania, and mixed episodes can be managed initially with 1 of 3 strategies: lithium, valproate, or a second-generation antipsychotic either as monotherapy or in various combinations. Short-term use of antipsychotics and/or benzodiazepines may also address associated symptoms (eg, agitation, psychosis, drug or alcohol withdrawal) during an acute exacerbation. Successful maintenance strategies usually require a combination of pharmacologic and psychotherapeutic approaches customized to meet the needs of a given patient.

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Table 1 – Bipolar specifiers

Table 2 – Mania and hypomania diagnostic criteria

Figure. Treatment Strategy for Acute Mania
Table 3 – Bipolar diagnostic categories

Table 4 – FDA-approved indications for pharmacologic management of bip...

Disclosures:
Dr Janicak is Director of the Transcranial Magnetic Stimulation Center at Edward/Elmhurst Healthcare and is on the faculty of the department of psychiatry and behavioral sciences at Northwestern University Feinberg School of Medicine in Chicago; Dr Esposito is a First-Year Resident at the Delaware Psychiatric Center in New Castle, Del.

References:


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