THE OREGON STATE DRUG REVIEW©
AN EVIDENCE BASED DRUG THERAPY RESOURCE http://pharmacy.oregonstate.edu/drug-policy/newsletter

March 2021 Volume 11, Issue 3

Bipolar Disorder: Resources for Primary Care Providers

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Mental illnesses are common conditions in the United States, and affect nearly 20% of the adult population.[1] Bipolar disorder affects 2.8% of adults yearly, and there is a 4.4% lifetime risk.[2] It occurs equally among adult men and women, and is slightly more common in adolescent girls than boys. Prevalence is highest in adults 18 to 29 years old and adolescents 17 to 18 years old.[2] Bipolar disorder has one of the highest rates of severe impairment of the mood disorders, over 80% of adults and nearly 90% of adolescents.[2] Individuals with bipolar disorder are at high suicide risk, and have the second highest suicide rate within 90 days of hospital discharge for patients with a psychiatric diagnosis.[3]

Bipolar disorder is characterized by distinct mood episodes which include shifts in mood, energy, activity levels, concentration, and functional capacity.[4] These episodes are distinctly differently from a patient's normal behavior and function at baseline. There are multiple types of bipolar disorder described in the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5), but patients are primarily categorized as bipolar I and bipolar II.[5] Bipolar I is characterized by having a manic episode, with or without a depressive episode, while bipolar II is characterized by depressive and hypomanic episodes without presence of manic episodes. The Mental Health Clinical Advisory Group (MHCAG), as part of the Oregon Health Authority (OHA) has recently completed publication of several care guides to assist clinicians with the diagnosis and care of individuals with bipolar disorder.[3,6-12] This newsletter will focus on the content of these care guides.

Differential Diagnosis

Several psychiatric conditions have overlapping symptoms with the depressive, hypomanic, and manic episodes seen in patients with bipolar disorder. Patients with bipolar disorder may be more likely to seek treatment when experiencing depression so it is also important to ask about symptoms of mania.[3] Hypomania may present before or after either manic or major depressive episodes.[3] Before diagnosis of bipolar disorder, other conditions which may present with symptoms of mania or hypomania should be considered and ruled out. Examples of other diagnoses to consider include schizoaffective disorder, schizophrenia, delusional disorder and, in the pediatric population, disruptive mood dysregulation disorder (DMDD).[9,13]

Differential diagnosis is further complicated by other mental health conditions that can present with an irritable mood. These include: depressive episodes, borderline personality disorder, post-traumatic stress disorder (PTSD), and attention-deficit/hyperactivity disorder (ADHD). A patient may have more than one of these conditions simultaneously, and substance intoxication or withdrawal can also mimic any of these states.[11] Co-occurring substance use disorders are common in patients with bipolar disorder. Delusions and hallucinations, racing thoughts, euphoria/elated mood, and grandiosity are key hallmark symptoms of mania that distinguish it from the other disorders.[11] **Table 1** differentiates mania from hypomania, with full symptom list available through MHCAG resources.[11]

Table 1: Differentiation of Mania and Hypomania[11]

Feature	Mania (Bipolar I)	Hypomania (Bipolar II)	NOT Bipolar Disorder
Energy/Activity	**Increased**	**Increased**	**Unchanged**
Number of associated symptoms*	3+ 4+ if mood only irritable	3+ 4+ if mood only irritable	< 3
Length of persistent symptoms	7+ days	4+ days	< 4 days **or** continuously for months or years
Psychotic symptoms	Maybe	No	
Change in function	Yes	Yes	
Functionally impairing	Yes	No	

*Symptoms of mania include: Inflated self-esteem, decreased sleep need, more talkative, flight of ideas/racing thoughts, distractibility, increased goal directed activity or psychomotor agitation, excessive involvement in activities with potential painful consequences. Symptoms present within episodes and differ from baseline.

Pharmacologic Therapy

Medication therapy during all phases of the disorder is a mainstay of bipolar treatment.[3] Initial treatment can vary depending on the patient's current symptoms at presentation (either manic or depressive symptoms). Those with severe disease, posing a safety risk to themselves or others, should be strongly considered for emergency department referral and/or inpatient treatment.[6,7]

Acute Mania

First-line therapy for mania should generally include lithium or quetiapine.[7] If a patient remains symptomatic despite first-line treatment, combination therapy should be considered. If combination therapy is ineffective, then generally patients should be switched to monotherapy with an alternative second generation antipsychotic in **Table 2**.[7]

Acute Depression

In addition to lithium and quetiapine, lamotrigine is recommended as first-line monotherapy treatment for patients presenting with bipolar depression.[6] Aripiprazole and monotherapy antidepressants should *never* be prescribed in acute bipolar depression. Both strategies are ineffective and antidepressants may trigger a manic or mixed episode.[6] If a patient with bipolar depression remains symptomatic despite first-line monotherapy, consider an alternative monotherapy or combination therapy in **Table 2**.[6]

Detailed treatment flowcharts[6,7] and side effect tables[12] are available from MHCAG to guide therapy decisions. All therapy should be tailored to individual patient's needs, with specific consideration for side effects, patient preference, symptom severity, and bipolar illness history. Maintenance therapy, usually with continuation of the pharmacotherapy used for stabilization, may continue for years or lifelong if tolerated and effective. Laboratory monitoring of serum levels (e.g. lithium and divalproex) and side effects should be more frequent in the first 6 months, then generally every 6 to 12 when stable and without new interacting medications.[6,7,12,14,15] Remember to include ammonia levels in patients on divalproex, particularly in those who appear to present with symptoms consistent with worsening depression.[14,16]

Consider consulting with specialists at the Oregon Psychiatric Access Line (OPAL) for patients with severe symptoms after initial combination therapy, or who remain symptomatic after 1 or 2 second-line treatments.[6,7] OPAL is a peer support resource available to primary care medical providers in Oregon and provides child and adult psychiatric phone consultations at no cost to clinicians.

Table 2. MHCAG Bipolar Medication Therapy Recommendations[6,7]

Acute Bipolar Mania		
1st Line Monotherapy	**1st line Combo therapy**	**2nd Line therapy**
Lithium **Quetiapine** **Temporary* lorazepam (anxiety or insomnia), olanzapine (agitation)**	Quetiapine+Lithium Quetiapine+Divalproex	Aripiprazole Asenapine Cariprazine Risperidone Ziprasidone
AVOID lamotrigine		
Acute Bipolar Depression		
1st Line Monotherapy	**2nd Line Monotherapy or Combo therapy**	
Lamotrigine **Lithium** **Quetiapine**	Cariprazine Divalproex Lurasidone	Lamotrigine+other bipolar tx med Lurasidone+Lithium Lurasidone+Divalproex Olanzapine+Fluoxetine SSRI+other bipolar tx med Bupropion+other bipolar tx med
AVOID Aripiprazole and antidepressant monotherapy		

Abbreviations: SSRI = selective serotonin reuptake inhibitor; tx = treatment.
*Generally limited to a few days and reserved for inpatient use

Certain patient populations, specifically women of childbearing potential, adolescents, and elderly patients require additional care with medication selection. Valproic acid and carbamazepine (CBZ) are contraindicated in pregnancy and use in women of childbearing potential should be avoided without effective birth control (BC) methods. Hormonal BC effectiveness is also reduced by CBZ. Hormonal BC may also lower the serum concentrations of lamotrigine and valproic acid; both should be monitored. Other first- and second-line treatments require caution or have insufficient safety data during pregnancy.[8] Young people may be more susceptible to metabolic side effects, and the lowest dose possible should always be used. Diagnosis is difficult in this population and should be confirmed before medication initiation.[8] Geriatric patients may see changes in their disease as they age, with more frequent, but less intense cycles. Be wary of polypharmacy and age-related changes in volume of distribution and metabolism, and increasing risk of cardiovascular disease with atypical antipsychotic use. If able, reduce doses or aim for the lower end of goal serum concentrations and monitor for age-related cognitive impairment.[8]

Co-occurring anxiety, ADHD, and substance use add complexity to bipolar treatment. If possible, use non-pharmacologic therapy to treat anxiety. If concurrent medication therapy is required, selective serotonin reuptake inhibitors (SSRIs) are likely safer than serotonin-norepinephrine reuptake inhibitors (SNRIs).[8] Tricyclic antidepressants (TCAs) should be considered contraindicated in bipolar disorder, as they have the highest risk of inducing mania.[3,8] Similarly, stimulants also confer risk of mania. If non-pharmacologic treatments are ineffective for ADHD, use the lowest effective stimulant dose, or consider atomoxetine or bupropion. These may have a lower risk of conversion to mania.[8] Clonidine or guanfacine may be other options for some patients. Substance use symptoms can mimic mania and depression, and increase a patient's risk of suicide.[3,8] If possible, clarify if symptoms of bipolar disorder were present during periods of sobriety and attempt to minimize substance-medication interactions.[8]

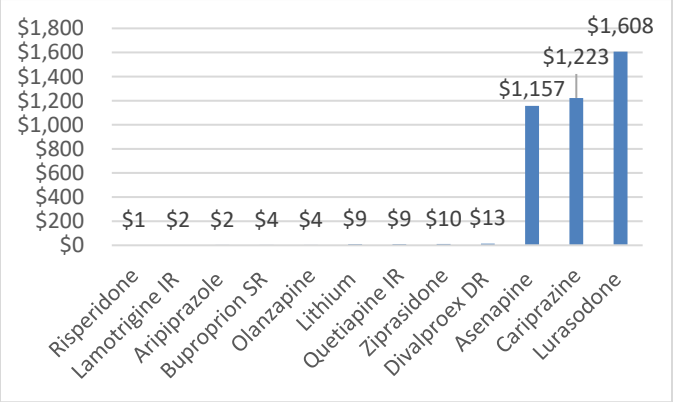
Non-pharmacological Therapy

In addition to pharmacologic therapy, psychosocial treatment, psychoeducation for the patient and patient supports, a regular sleep-wake cycle, and appropriately managing stress are key aspects of treatment for bipolar disorder. Certain psychotherapies, such as Interpersonal and Social Rhythm therapy in Bipolar I are considered evidence based and can reduce likelihood of recurrence.[17] Psychosocial needs should always be reassessed when breakthrough symptoms and lack of treatment effect are present.[3,6,7]

Comparative Costs

There are many medication options available to choose from, with generic products representing the best value. **Figure 1** illustrates the dramatic difference in 30-day supply average actual acquisition cost (AAAC) for various agents recommended in the treatment of bipolar disorder. Additionally, many brand name antipsychotic agents are priced the same for all strengths across the dosage spectrum ("flat-priced"). For those products, use of a single tablet to administer the total daily dose can result in significant medication savings compared to administration of multiple tablets to achieve the same daily dose (e.g. 40 mg, one tab Qday vs 20 mg, two tabs Qday).

Figure 1. Comparative Bipolar Monthly Cost for Select Agents



*Prices based on Myers and Stauffer Average Actual Acquisition Cost (AAAC) March 2, 2021. Available at:
https://www.mslc.com/uploadedFiles/Oregon/AACArchive/OHA%20Generic%20Web%20Listing_20210302_State.pdf
https://www.mslc.com/uploadedFiles/Oregon/AACArchive/OHA%20Brand%20Web%20Listing_20210302_State.pdf

Resources

Uncontrolled bipolar disorder causes severe impairment to the vast majority of patients with this condition. It also carries a high suicide risk. MHCAG resources[18] to assist on the diagnosis and treatment of this disorder can be found at: https://www.oregon.gov/oha/HPA/DSI-Pharmacy/Pages/MHCAG-Recommendations.aspxOPAL specialists are available to prescribing providers Monday-Friday 9am to 5pm at 503-346-1000.

- Many factors should be considered when choosing therapy for patients with acute bipolar depression or mania.
- Resources and specialists are available for patients with difficult to treat disease.
- Giving medications as the fewest number of daily tablets may decrease costs and increase adherence to therapy.

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