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BIPOLAR DISORDER IN PRIMARY CARE: DIAGNOSIS AND MANAGEMENT

Introduction

Primary care physicians play an important role in supporting and providing medical care for individuals with bipolar disorder. This includes correctly identifying bipolar disorder in those presenting with depressive symptoms to primary care settings or seeking psychiatric consultation and advise as needed; initiating treatment for depressive and hypomanic episodes; assessing risk for suicide or aggressive behaviour; referring to emergency services as needed; and providing maintenance care and monitoring for those with an established diagnosis with collaborative or as needed consultative support from psychiatric colleagues. The objective of this article is to provide up-to-date information to aid primary care physicians in achieving the above objectives related to diagnosing and managing patients with bipolar disorder.

What is bipolar disorder?

Bipolar disorder is a type of a mood disorder that includes various subtypes such as bipolar I disorder, bipolar 2 disorder, cyclothymic disorder and bipolar spectrum disorders (categorized in DSM-5 as “other specified or unspecified bipolar and related disorders”). Bipolar disorder affects approximately 2.4% of the population.¹

Mania is the defining feature of bipolar I disorder. While major depressive episodes (MDE) are common and pose the greatest disease burden for individuals with bipolar I disorder, their occurrence is not required for diagnosis of this condition. Conversely, a diagnosis of bipolar 2 disorder requires occurrence of at least one major depressive episode, in addition to at least one hypomanic episode. Patients who present with hypomanic symptoms with or without depressive symptoms but do not meet the criteria for bipolar I or bipolar 2 disorder are assigned a diagnosis of cyclothymic disorder or other specified or unspecified bipolar disorder depending on the severity and duration of the symptoms. The clinical implications of the latter diagnoses remain uncertain at this point as few proven specific treatments exist for managing patients with these conditions.

Table 1 itemizes the DSM-5 criteria for a manic episode and a MDE.² In addition to experiencing a minimum number of symptoms most of the day and nearly every day for at least 1 week in case of a manic episode, and 2 weeks for a MDE, these symptoms must be associated with significant impairment in functioning, and unrelated

to the effects of a substance or a medical condition. While the requirement of a minimum number of symptoms is the same for a hypomanic episode as the manic episode, these symptoms must be present for only 4 consecutive days for a hypomanic episode, while 7 days is required for a manic episode unless the patient was hospitalized for such symptoms. In addition, hypomanic episodes are never associated with psychosis nor marked impairment in functioning, although alteration in functioning is often present. Approximately one-third of hypo/manic and depressive episodes in patients with bipolar disorder present with a mixed features specifier.³ Hypo/manic episodes with a mixed features specifier are less likely to respond to lithium, while depressive episodes with mixed features pose a greater risk of hypo/manic switch with antidepressant treatment.

Screening and diagnostic techniques for bipolar disorder

Patients presenting with depressive symptoms should be screened for previous hypo/manic episodes. A diagnosis of major depressive disorder (MDD) should only be made after excluding bipolar disorder. The rationale for this is that patients with bipolar disorder typically seek help for depressive symptoms and may not volunteer information concerning previous manic symptoms. Therefore, without systematic inquiry about previous manic symptoms, such patients can easily be misdiagnosed with MDD.

Asking patients who are seeking help for depressive symptoms to complete a mood disorders questionnaire (MDQ) may trigger their memory about previous manic symptoms; those who endorse any symptoms can be probed in greater detail to verify the occurrence of previous episodes. The MDQ is a screening tool and must not be used as an instrument to confirm diagnosis.

Family physicians may have limited time to screen patients; it is therefore important to ask screening questions that are sensitive in eliciting previous hypo/manic symptoms in those presenting with depressive symptoms. These include, “Has there been a period when you felt you had more energy than usual?” “Has there ever been a period when you had too many thoughts rapidly going through your head or when you had too many ideas that you thought were great?”; “Have you ever had a period when you felt you could function with less sleep than usual or you had a lot of energy even though

Criteria: Manic Episode	Criteria: Major Depressive Episode (MDE)
<p>A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently goal-directed behavior or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).</p> <p>B. During the period of mood disturbance and increased energy or activity, 3 or more of the following symptoms (4 if the mood is only irritable) are present to a significant degree and represent noticeable change from usual behaviour</p>	<p>A. Five (or more) of the following symptoms have been present during the same 2 week period and represent a change from previous functioning: at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure</p> <p>A1 Depressed mood—indicated by subjective report or observation by others (in children and adolescents, can be irritable mood).</p>
<p>1. Inflated self-esteem or grandiosity</p>	<p>A2 Loss of interest or pleasure in almost all activities—indicated by subjective report or observation by others.</p>
<p>2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep)</p>	<p>A3 Significant (more than 5% in a month) unintentional weight loss/gain or decrease/increase in appetite (in children, failure to make expected weight gains).</p>
<p>3. More talkative than usual or pressure to keep talking</p>	<p>A4 Sleep disturbance (insomnia or hypersomnia).</p>
<p>4. Flight of ideas or subjective experience that thoughts are racing</p>	<p>A5 Psychomotor changes (agitation or retardation) severe enough to be observable by others.</p>
<p>5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.</p>	<p>A6 Tiredness, fatigue, or low energy, or decreased efficiency with which routine tasks are completed.</p>
<p>6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation</p>	<p>A7 A sense of worthlessness or excessive, inappropriate, or delusional guilt (not merely self-reproach or guilt about being sick).</p>
<p>7. 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).</p>	<p>A8 Impaired ability to think, concentrate, or make decisions—indicated by subjective report or observation by others.</p>
<p>C. 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.</p>	<p>A9 Recurrent thoughts of death (not just fear of dying), suicidal ideation, or suicide attempts.</p>
<p>D. 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.</p> <p>Note: A full manic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a manic episode and therefore a bipolar I diagnosis.</p>	<p>B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning;</p> <p>C. The episode is not due to the direct physiological effects of a substance or a medical condition</p>

Table 1. DSM-5 criteria for a manic episode and MDE²

Bipolar Disorder and Substance Induced Bipolar symptoms		Bipolar Disorder and Borderline Personality		Bipolar Disorder and ADHD	
Bipolar Disorder	Substance Induced Bipolar symptoms	Bipolar Disorder	Borderline Personality	Bipolar Disorder	ADHD
<ul style="list-style-type: none"> • Cocaine and amphetamine use more common • Use of substances is episodic • Mood problems in the absence of substance use • Hypomania/mania symptoms present • Family history of bipolar or other mood disorders 	<ul style="list-style-type: none"> • Polysubstance use more common • Use of substances is continuous, dictated by access • Periods of substance use without any mood problems • Clear hypo/manic symptoms usually absent • Family history of externalising and anxiety disorders 	<ul style="list-style-type: none"> • Biphasic mood dysregulation • Mood symptoms meet threshold criteria for MDD • Reasonable functioning during euthymic periods • Family history of bipolar disorder 	<ul style="list-style-type: none"> • Mood dysregulation in the depressive spectrum • Mood symptoms often do not reach threshold for MDD • Dysfunction persists even in euthymic periods • Family history of deprivation and abuse 	<ul style="list-style-type: none"> • Onset of clear-cut symptoms after age 12 years • Onset with dysthymia or depression • Symptoms are typically episodic • Family history of mood disorders • Variable or negative response to stimulants • Good Response to mood stabilizers 	<ul style="list-style-type: none"> • Onset of clear-cut symptoms before age 12 years • Onset of hyper or disruptive behaviour • Symptoms are continuous • Family history of disruptive disorders • Good response to stimulants • Variable or no response to mood stabilizers

Table 2. Differential diagnosis of bipolar disorder, particularly in youth; courtesy of Lakshmi N. Yatham, MBBS, FRCPC, MRCPsych (UK), MBA (Exec)

you were sleeping fewer hours than usual?" If a patient endorses any of these, further probing questions should be asked about other symptoms to verify if the patient has had a discrete period of a minimum of 4 to 7 days when they had sufficient number of symptoms to meet the DSM-5 criteria for a hypomanic or manic episode.

It is important to consider substance induced bipolar disorder, borderline personality disorder, and attention deficit hyperactivity disorder (ADHD) in the differential diagnoses, especially in younger patients presenting with mood fluctuations, hyperactivity and erratic behavior.

Table 2 describes specific features that are helpful in differentiating between various conditions.

In a patient presenting with a depressive episode, does absence of a previous hypo/manic episode automatically exclude bipolar disorder?

It is important to bear in mind that if screening for previous history does not reveal hypo/manic episodes, does not necessarily mean that the patient has MDD. This is due to the fact that the majority (approximately 70%)

of patients with bipolar disorder present with depression as the first mood episode⁴ and may experience several depressive episodes as a part of the course of the illness before manifesting the first manic or hypomanic episode. In such patients, the presence of features such as family history of bipolar disorder; reverse vegetative symptoms such as sleeping too much or eating too much with carbohydrate craving; psychotic symptoms; post-partum onset or younger age at onset; episodic anxiety symptoms; or poor response or agitation with antidepressant medication, may suggest that the depressive episode is more likely part of a bipolar-related disorder than unipolar MDD.⁵ This distinction has treatment implications as such patients may be at higher risk of hypo/manic switch with conventional antidepressant therapy. Therefore, if antidepressants are offered, patients should be counselled about these risks and advised to self-monitor for emergence of hypo/manic symptoms and seek help urgently. In addition, patients should be offered the choice of utilizing treatments with proven effectiveness for both bipolar depression and MDD, such as quetiapine.

Role of primary care physicians in the management of bipolar disorder

When to refer

Patients with bipolar disorder are at significantly increased risk of suicide, particularly during depressive episodes or when mood episodes are associated with mixed features.⁶ Therefore, every patient with bipolar depression must be assessed for suicide risk and if there are concerns for patient safety, they should be referred to hospital emergency departments (EDs) for further evaluation and possible admission for in-patient care. Similarly, while patients with hypomanic or mild manic episode can be managed on an out-patient basis, the majority of patients with an acute manic episode, particularly those with psychotic symptoms or aggressive behaviour, will require in-patient care for stabilization. They may need to be referred to the hospital ED under the Mental Health Act if they refuse to seek help on a voluntary basis. If needed, atypical antipsychotics such as quetiapine (50 mg to 300 mg), olanzapine (5 to 10 mg), aripiprazole (10 to 15 mg sublingually) or risperidone (2 mg) can be administered in primary care offices to control agitation and calm the patient in order to facilitate assessment and referral to the ED for further evaluation and treatment.

Both psychiatric and substance use comorbidities are common in individuals with bipolar disorder. These frequently present diagnostic challenges which may warrant referral to a psychiatric consultation for diagnostic clarification. Other situations that might warrant referral include seeking advice on treatment options for: 1. Patients who are not responding to adequate trials with recommended first- and second-line agents; 2. Young women with bipolar disorder who are planning pregnancy; and 3. Patients who experience syndromal or sub-syndromal symptoms despite receiving maintenance therapy.

Treatment options for managing bipolar disorder

Several treatment strategies are available for managing patients with bipolar disorder.^{7,8,9} These are described in **Table 3**. These recommendations are excerpted from the Canadian Network for Mood and Anxiety Treatments/ International Society for Bipolar Disorders Guidelines; the list has been modified to incorporate recent evidence that has emerged since the publication of these guidelines.

These recommendations are organized in a hierarchical fashion taking into account the evidence for the efficacy of an agent for the phase being treated; the efficacy of the agent for other phases of bipolar disorder; and the

adverse event profile of agents.⁷ The treatment algorithm for bipolar depression above indicates that quetiapine should be initiated prior to considering cariprazine. The rationale for this is that both quetiapine and cariprazine have demonstrated efficacy for the treatment of acute bipolar depression and acute mania; however, quetiapine has also demonstrated efficacy in preventing both mania and depression, but no data are available for cariprazine. Therefore, the management guidance is that treatment listed higher in the hierarchy for each phase should be initiated prior to progressing to the next treatment. The exceptions to this are: If specific clinical features of the mood episode; patient preference regarding the adverse event profile of a particular medication; or previous patient or family history of response or non-response to medications dictate alternative choices. Thus, if a patient is presenting for support with a bipolar depressive episode, quetiapine should be initiated prior to considering cariprazine or other treatment options listed in the hierarchy below.

The adverse events profile of psychotropic medications include: metabolic syndrome; effects on kidney, liver, thyroid and heart rhythm; hence, a medical review of systems, and laboratory evaluation that includes routine blood counts, liver function tests, thyroid-stimulating hormone, fasting blood sugar, lipid profile, blood urea nitrogen and estimated glomerular filtration rate should be performed before commencing treatment. Patients should be counselled regarding the adverse event profile of medications and the importance of treatment adherence prior to prescribing medications. Medical trials should be initiated utilizing adequate doses of each agent. In the absence of even a 20% improvement following a 2-week trial, the reasons for lack of response, which may include poor treatment adherence, ineffectiveness of the agent, comorbidities or contribution of other factors, must be explored. If a trial with a second agent also fails to elicit response, it might be reasonable to seek a second opinion from psychiatric consultation.

If lithium or divalproex is used for managing bipolar disorder, serum levels should be measured following approximately 5 days of reaching the target dose in order to monitor trough serum levels. Typically these are measured at approximately 12 hours following the last dose. Lithium levels should be maintained at between 0.6 and 1 mE/L, and valproate levels at between 350-700 mMol/L. If the levels fall outside this range, the doses should be adjusted accordingly. Valproate should be avoided in younger women because of the risk of polycystic ovary syndrome and higher teratogenic risk. If patients are receiving maintenance treatment with mood

Acute Bipolar Depression	Acute Manic Episode	Maintenance Treatment
First Line <ul style="list-style-type: none"> • Quetiapine • Cariprazine • Lurasidone + lithium or divalproex • Lithium • Lamotrigine • Lurasidone • Lumateperone • Lamotrigine adjunctive therapy 	First Line <ul style="list-style-type: none"> • Lithium • Quetiapine with or without MS • Divalproex • Asenapine with or without MS • Aripiprazole with or without MS • Paliperidone (>6 mg) • Risperidone with or without MS • Cariprazine 	First Line <ul style="list-style-type: none"> • Lithium • Quetiapine with or without MS • Divalproex • Lamotrigine • Asenapine • Aripiprazole with or without MS • Aripiprazole once- monthly
Second Line <ul style="list-style-type: none"> • Divalproex • SSRI/bupropion adjunctive therapy • ECT • Olanzapine + fluoxetine combination 	Second Line <ul style="list-style-type: none"> • Olanzapine • Carbamazepine • Olanzapine with MS • Lithium plus divalproex • Ziprasidone • Haloperidol • ECT 	Second Line <ul style="list-style-type: none"> • Olanzapine • Risperidone long-acting injectable with or without MS • Carbamazepine • Paliperidone (>6 mg) • Lurasidone with MS • Ziprasidone with MS

Table 3. First- and second-line treatments for mania, depression; maintenance treatment of bipolar disorders ; courtesy of Lakshmi N. Yatham, MBBS, FRCPC, MRCPsych (UK), MBA (Exec)

stabilizers, they should be asked routinely about adverse events including weight gain, polyuria and polydipsia, cold intolerance, and hair loss during follow-up visits. Serum levels should be monitored at approximately 6- 12-month intervals, along with additional laboratory assessments as appropriate. If lamotrigine is used, patients must be counselled on the risk of skin rash and Steven Johnson syndrome, and must be asked to routinely monitor for skin rash and report if they notice the occurrence of this. If atypical antipsychotics are used for acute or maintenance treatment of bipolar disorder, serum level monitoring is not required. However, patients must be monitored for the emergence of adverse events related to the specific tolerability profile of each of the agents. Psychoeducation is effective in reducing relapse in patients with bipolar disorder, and patients may be referred to psychoeducation groups if they are available.

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