Identification and optimal management of bipolar disorder (BD) can be a challenging proposition. Distinguishing the symptoms of the depressed phase of the disorder from those of unipolar major depression represents perhaps the most significant obstacle to diagnosis. Furthermore, comorbidities with anxiety disorders, substance-use disorders and Attention Deficit Hyperactivity Disorder (ADHD) may further hinder a correct diagnosis of a bipolar mood disorder.

This review (Part 1 in a series of two articles) briefly outlines the epidemiology and natural history of BD. It then explores in some depth the most effective ways to distinguish between the various presentations of mood, anxiety and somatic symptoms, to help differentiate between BD and unipolar depression. Part 2 of the review (later in this issue) includes a discussion of treatment options for patients diagnosed with BD.

**Epidemiology and Natural History of Bipolar Disorder**

Epidemiologic data from a variety of sources suggest that BD is more common than once believed. Data from Canada (published in 1988), suggested a prevalence of 0.5%. American data indicate that lifetime prevalence rates of bipolar I disorder, bipolar II disorder and sub-threshold BD are 1.0%, 1.1% and 2.4%, respectively. Overall, the prognosis associated with BD can be further improved upon; this is a disorder characterized by frequent recurrences. In fact, studies published by Judd et al in 2002 and 2003 showed that after having been diagnosed, followed prospectively and treated, patients with BD spent half of their lives being symptomatic (Figure 1).

Comorbidities are very common among patients with BD. Anxiety disorders are the most common psychiatric comorbidities, present in at least 93% of BD patients. Perhaps the most menacing non-psychiatric comorbidities include metabolic syndrome and cardiovascular disease, for which bipolar patients are at higher risk compared to the general population. Specifically, the authors of the 2009 Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) Collaborative guidelines list obesity, type 2 diabetes, cardiovascular disease, migraine, hepatitis C, HIV, dementia, lower back pain, chronic obstructive pulmonary disease, asthma and allergies as non-psychiatric conditions seen at elevated rates in patients with BD.

Overall, the prognosis associated with bipolar disorder can be further improved upon; this is a disorder characterized by frequent recurrences.
medications) met criteria for metabolic syndrome and 7% had type 2 diabetes.

A recent American study showed that people with BD were more than twice as likely to have hypertension compared to controls and were approximately five times more likely to have cardiovascular disease.¹⁷

**Diagnosis of Bipolar Disorder**

**Distinguishing between BD and unipolar depression.** The natural history of BD can include a range of symptoms, from full mania or depression to complete euthymia. In between, patients may experience subsyndromal depressive symptoms or hypomania. As shown in Figure 2, most patients with BD (especially bipolar II) spend more time with depressive symptoms than with manic symptoms.¹⁸ Also, a patient experiencing manic or hypomanic symptoms is much less likely to seek medical attention than one who is experiencing depression.¹⁹ As such, it is particularly important for clinicians to be able to distinguish between unipolar depression and bipolar depression. Unipolar and bipolar depression can appear identical and therefore, when seeing a patient with depression at any one point in time, it can be impossible to tell the difference and determine an effective approach to treatment without a longitudinal history. Collateral information from loved ones is also imperative to reveal hypomanic episodes that patients might consider to be euthymic reprieves from depression. Patients presenting with depressive symptoms are often diagnosed with unipolar depression, without proper consideration given to the possibility of a BD diagnosis. Statistics from the U.S. have shown that as many as two thirds of patients with BD are initially misdiagnosed.¹ While the most frequent misdiagnosis (~60% of misdiagnoses) is unipolar depression, patients with BD are also often misdiagnosed as having an anxiety disorder, schizophrenia, schizoaffective disorder, a personality disorder or substance abuse. Furthermore, in as many as one third of BD patients, arriving at the correct diagnosis can take up to a decade or longer.¹,²⁰

**FIGURE 1.**

Proportion of Time Patients with Bipolar Disorder Spend in Affective Symptom Categories¹³,¹⁴

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Asymptomatic</th>
<th>Depressed</th>
<th>Manic/hypomanic</th>
<th>Cycling/mixed affective symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>146 bipolar I patients</td>
<td>32%</td>
<td>53%</td>
<td>9%</td>
<td>6%</td>
</tr>
<tr>
<td>followed weekly for 12.8 years</td>
<td>(NIMH Collaborative Depression Study)¹³</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>86 bipolar II patients</td>
<td>50%</td>
<td>46%</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>interviewed every 6-12 months</td>
<td>for 13.4 years¹⁴</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FIGURE 2.**

Natural History of Bipolar Disorder¹⁸

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euthymia</td>
<td>Mania</td>
</tr>
<tr>
<td>Hypomania</td>
<td>Subsyndromal depression</td>
</tr>
<tr>
<td>Depression</td>
<td>Depression</td>
</tr>
</tbody>
</table>

Asymptomatic
Depressed
Manic/hypomanic
Cycling/mixed affective symptoms
### Table 1.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Bipolar Depression</th>
<th>Unipolar Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of BD</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Family history of unipolar MDD</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Age of onset</td>
<td>Teens and 20s</td>
<td>Older than 30 years</td>
</tr>
<tr>
<td>Sex Ratio</td>
<td>Equal (for BPI) F:M = 2:1 (for BP II)</td>
<td>F:M = 2:1</td>
</tr>
<tr>
<td>Substance abuse</td>
<td>High</td>
<td>Moderate</td>
</tr>
<tr>
<td>Seasonality</td>
<td>Common</td>
<td>Occasional</td>
</tr>
<tr>
<td>Postpartum episodes</td>
<td>More common</td>
<td>Less common</td>
</tr>
<tr>
<td>Episode onset</td>
<td>Often abrupt</td>
<td>More subtle</td>
</tr>
<tr>
<td>Episode frequency</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Atypical features when depressed</td>
<td>More common</td>
<td>Less common</td>
</tr>
<tr>
<td>Rapid on/off pattern</td>
<td>Typical</td>
<td>Unusual</td>
</tr>
<tr>
<td>Brief major depressive episodes (&lt; 3 months)</td>
<td>More common</td>
<td>Less common</td>
</tr>
<tr>
<td>Psychotic features under age 35 years</td>
<td>More common</td>
<td>Less common</td>
</tr>
<tr>
<td>Psychomotor activity</td>
<td>Retardation &gt; agitation</td>
<td>Agitation &gt; retardation</td>
</tr>
<tr>
<td>Sleep</td>
<td>Hypersomnia &gt; insomnia</td>
<td>Insomnia &gt; hypersomnia</td>
</tr>
<tr>
<td>Treatment-refractory depression</td>
<td>More common</td>
<td>Less common</td>
</tr>
<tr>
<td>Short-lived antidepressant efficacy</td>
<td>More common</td>
<td>Less common</td>
</tr>
<tr>
<td>Risk for antidepressant-induced mania or hypomania</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Mixed features (hypomanic symptoms while depressed)</td>
<td>Predictive</td>
<td>Rare</td>
</tr>
<tr>
<td>Comorbid anxiety</td>
<td>Very common (90%)</td>
<td>Common (60%)</td>
</tr>
<tr>
<td>History of legal problems</td>
<td>More common</td>
<td>Less common</td>
</tr>
<tr>
<td>Feelings of people being unfriendly</td>
<td>More common</td>
<td>Less common</td>
</tr>
<tr>
<td>Irritability and anger</td>
<td>More common</td>
<td>Less common</td>
</tr>
<tr>
<td>Medical comorbidities (migraine, asthma, chronic fatigue, chronic bronchitis, hypertension, gastric ulcer)</td>
<td>More common</td>
<td>Less common</td>
</tr>
</tbody>
</table>
Making the distinction between unipolar and bipolar depression can be challenging. Simply keeping the possibility of BD in mind is an important first step for physicians facing a patient with depressive symptomatology. Moving forward, there is additional information from which one can draw to help distinguish BD from unipolar depression.

There are a number of features that can suggest a diagnosis of BD rather than unipolar depression (Table 1). The 2009 CANMAT/ISBD guidelines focus on the presence of atypical depressive symptoms (e.g., hypersomnia, hyperphagia, weight gain and leaden paralysis which refers to extreme body fatigue), psychomotor disturbance, psychotic features and a positive family history of BD.

Careful history taking can uncover some of these features. With respect to the actual symptoms, hypersomnia, hypomania, hyperphagia and marked weight gain are particularly suggestive of the possibility of a bipolar depression. Patients should also be asked whether they’ve experienced episodes with increased energy and decreased need for sleep, racing thoughts, irritability, distractability, sexual disinhibition and depersonalization/derealization (outside of panic attacks). If the patient has a history of prior treated depression, one should ask about the response to pharmacotherapy. Patients with BD who are treated with antidepressants sometimes experience an overly rapid response to treatment or a paradoxical, persistent worsening of mood and anxiety symptoms. In my clinical practice, on more than a dozen occasions, in patients who turned out to have BD, I have seen otherwise law-abiding citizens develop kleptomania after being prescribed antidepressants. Other impulse-control disorders I have commonly seen comorbid with BD include pathological gambling, trichotillomania and skin picking. Another trend I have encountered

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**Differentiating Between Bipolar Subtypes: Case Presentation 1**

**Mr. Y: 31-year-old man, CEO of own computer business**

January 2007: “Constant high” for approximately two months: grandiosity (belief he was an aristocrat), very high energy with decreased need for sleep, talking rapidly, euphoric mood, uncharacteristic spending of thousands of dollars and giving away possessions (e.g., motorcycle).

March 2007: After two months of pure euphoria, became irritable and angry while at the same time euphoric (i.e., mixed state referred to as dysphoric mania).

May 2007: While overseas diagnosed with major depressive episode (MDE), unipolar type
  – Treated with bupropion, no effect.

July 2007: On return to Canada diagnosed with Bipolar I when saw psychiatrist in ER
  – Switched to olanzapine 15 mg HS; subsequent hypersomnia, weight gain (10 kg in one month).
  – Switched to valproate 1500 mg HS & lamotrigine 200 mg AM & HS beginning with 25 mg HS and dose increased by 25 mg every two weeks; depression resolved slowly over three months.

September 2007 – January 2009: Euthymic while taking valproate and lamotrigine, then patient discontinued his medications because he “felt well.”

July – October 2010: “High,” similar to index episode in January 2007; uncharacteristic spending, significant weight loss; again developed mixed state.

October 2010: Hospitalized with mixed episode and psychosis believing he was the prophet Mohammed. Started on valproate 1500 mg HS and aripiprazole 10 mg AM to treat the mixed state and psychosis; psychosis resolved after dose increased to 15 mg one week later and patient was euthymic three weeks after admission. Euthymia maintained until present.

These characteristics are indicative of a diagnosis of bipolar I disorder (history of at least one mania or dysphoric mania–this patient had both); while high he was psychotic, had marked impairment in insight and judgment and required hospitalization, any of which automatically means the patient is beyond hypomania (i.e., manic).

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repeatedly in my clinical practice (not noted in the literature) has been marked weight gain (20-30 kg) with SSRIs and SNRIs, particularly in my bipolar II patients as compared to the typical 4-6 kg seen in unipolar patients after they have been taking an antidepressant for six months or longer. I have also observed a tendency towards little to no improvement of panic attacks, agitation and insomnia during depressive/mixed states in bipolar II patients with high doses of benzodiazepines (e.g., 12 mg of clonazepam, which is the equivalent of 48 mg of lorazepam). Insomnia that does not respond to high doses of zopiclone, trazodone and sedating tricyclics often responds well to low doses of sedating second-generation (atypical) antipsychotics (e.g., olanzapine 2.5-5 mg, quetiapine 25-50 mg).

Working in a tertiary care anxiety disorders clinic for more than 15 years, I noted that the greater the number of anxiety disorders for which a patient met criteria (especially OCD, social anxiety disorder and panic disorder), the greater the likelihood that they had bipolar disorder. In an as yet unpublished analysis (Kjernisted and Chartier) of Ontario Health Survey data, if a patient screened positive for three or more anxiety disorders, the odds ratio for having bipolar disorder was 71. In bipolar patients, anxiety symptoms often cycle with the depressive episodes, becoming significantly less during euthymia or hypomania. Functional impairment, suicide risk and prognosis are worse for bipolar patients with substantial anxiety symptoms or comorbid anxiety disorders.

Obtaining a focused longitudinal history of symptoms from the patient and loved ones, including the classic features of mania and hypomania, is essential in making the distinction between BD and unipolar depression. One useful self-report screening tool is the Mood Disorder Questionnaire (MDQ), which consists of a checklist of manic/hypomanic symptoms derived from DSM-IV and clinical experience. If a clinician suspects bipolarity it is helpful to refer the patient to the website psycheducation.org authored by Dr. James Phelps. This website provides access to another self-report screening tool, the “Mood Check,” which assesses for symptoms of depression as well as hypomania or mania. Dr. Phelps has written an excellent book, “Why Am I Still Depressed? Recognizing and Managing the Ups and Downs of Bipolar II and Soft Bipolar Disorder.” In order to educate my patients about bipolar disorder I ask them to read this book. Many of my patients, even those with “softer” forms of bipolarity, who would meet criteria for Bipolar NOS (e.g., hypomaniacs less than four days duration or cycling below the euthymic line) will often say to me, “this book was written about me,” helping me to be more certain about the diagnosis.

**Diagnosing the particular type of BD.** To further complicate matters, there are different subtypes of BD that have been identified. Making a diagnosis of one of these particular BD subtypes is important, as the clinical practice guidelines make different treatment recommendations for each subtype. Bipolar I disorder (in one paper referred to as “Cade’s Disease,” describing the grandiose, euphoric patient, without any mixed features, who responds well to lithium as John Cade had discovered in Australia in 1949) is the classic presentation, in which patients have a history of fully manic and fully depressed states. Patients with bipolar II disorder have experienced at least one episode of major depression and have experienced at least one four-day hypomanic episode but no overt mania (see case presentation sidebar, Mrs. X). There has been some debate as to whether bipolar II is a legitimately distinct diagnosis, but expert consensus has determined that it is. Bipolar II appears to be familial and if someone has had hypomaniacs and meets criteria for bipolar II for more than five years, according to Akiskal, they are unlikely to ever have a full-blown mania and thus be diagnosed as bipolar I. Cyclothymic disorder is characterized by a history of fluctuations between hypomanic symptoms and depressive symptoms that are not
Making the distinction between unipolar and bipolar depression can be challenging. Simply keeping the possibility of BD in mind is an important first step for physicians facing a patient with depressive symptomatology.

Features are suggestive of bipolar II disorder (history of major depression and at least one hypomania lasting four or more days).

Mrs. X: 55-year-old woman with 15-year history of fibromyalgia

- At age 14, had significant anxiety and feelings of impending doom.
- In her 20s and 30s, experienced several miscarriages, with periods of major depression following each.
- Gave birth to three children by C-section; each followed by post-partum depression.
- History of panic attacks following birth of second son; persistent agoraphobic avoidance.
- Increase in "mood swings" beginning in her mid-20s
  - Periods of depression with hypersomnia, anergia, hyperphagia, weight gain, "heavy limbs," increased anxiety, increased fibromyalgia pain, weeping. Variable duration (< 1 week to a few months); marked premenstrual irritability.
  - Short (~3-4 day) "high" periods, approximately every three months: joyful mood, decreased need to sleep (3-5 hours) with ongoing increased energy, increase in activity, including cleaning, shopping; increased libido with flirtatiousness; reprieve from anxiety and pain; no significant loss of insight or judgement; no psychotic symptoms and no need to be hospitalized because of her "high" mood.
- Comorbidities: Fibromyalgia and chronic fatigue syndrome, migraines (treated with nabilone), asthma, hypothyroidism and type 2 diabetes.
- History of opioid dependence: has attended Narcotics Anonymous meetings.
- Family history:
  - Mother with lupus, fibromyalgia, obsessive-compulsive disorder (OCD), possible bipolar disorder (never diagnosed).
  - Three younger sisters, all with history of depression.
  - Oldest son has OCD.
- Mood stabilized with lamotrigine 200 mg bid and quetiapine XR 300 mg taken 3 hours before bedtime, and optimization of her thyroid hormone dosing; mood stabilization associated with marked improvement in her anxiety symptoms, migraines, fibromyalgia and chronic fatigue.

Features are suggestive of bipolar II disorder (history of major depression and at least one hypomania lasting four or more days).
disorder and obsessive-compulsive disorder are particularly common among people with BD. In childhood BD, anxiety disorders, attention deficit disorder, conduct disorder, oppositional-defiant disorder and enuresis are common comorbidities. Stigma, particularly in children and adolescents, may also interfere with the ability to make the diagnosis of BD.

Conclusions
BD is a highly variable disorder with a high risk of relapse and recurrence. There is an increased risk of having numerous medical disorders and significant comorbidity with other psychiatric disorders including anxiety disorders (OCD most common according to the National Comorbidity Survey Replication [NCS-R], followed by social anxiety then panic disorder), eating disorders and substance-use disorders. Diagnosis can be difficult, as most patients with BD only seek medical attention in the depressed phase of their illness. Bipolar depression is often atypical in nature with hypersomnia, hyperphagia, weight gain, leaden fatigue, interpersonal sensitivity and significant anxiety. This though is impossible to distinguish from atypical unipolar depression. Comprehensive longitudinal history taking, and collateral history from loved ones, with the aid of structured symptom checklists, can help to reveal other clues to the diagnosis, which is of utmost importance to determine proper treatment.

References