

Bipolar Disorder for Family Physicians *Part 1: Diagnosis*

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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.¹ 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.²

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.⁴⁻¹¹ Data from Canada (published in 1988), suggested a prevalence of 0.5%.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.¹² 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).^{13,14}

Comorbidities are very common among patients with BD. Anxiety disorders are the most common psychiatric comorbidities, present in at least 93% of BD patients.¹⁶ Perhaps the most menacing non-psychiatric comorbidities include metabolic syndrome and cardiovascular disease, for which bipolar patients are at higher risk

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compared to the general population.^{3,17} Specifically, the authors of the 2009 Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) Collaborative guidelines³ 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. Of particular note, data have emerged since the previous (2007) CANMAT guidelines were published to further support reports of high rates of metabolic syndrome in patients with BD. One analysis showed that up to 30% of 60 consecutive patients (all but seven being treated with antipsychotic

FIGURE 1.

Proportion of Time Patients with Bipolar Disorder Spend in Affective Symptom Categories^{13,14}

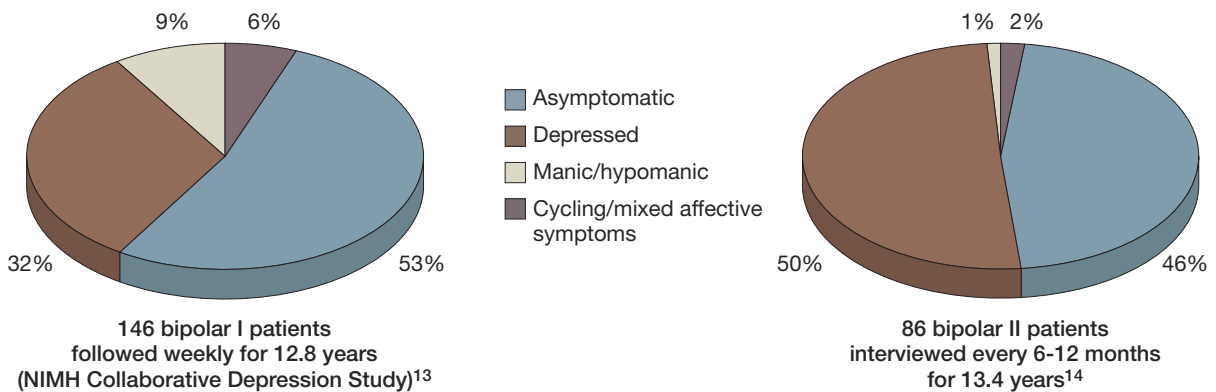
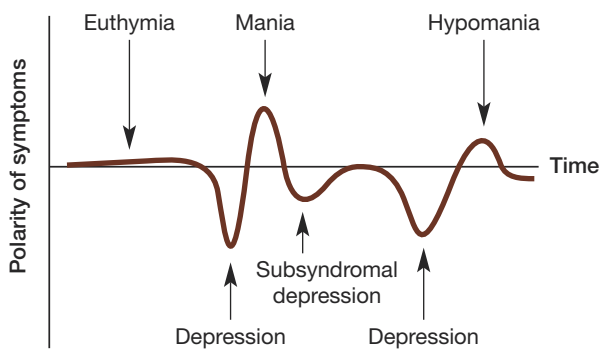


FIGURE 2.

Natural History of Bipolar Disorder¹⁸



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}

TABLE 1.

Clues in Differentiating Bipolar Depression from Unipolar Depression²¹

Characteristic	Bipolar Depression	Unipolar Depression
Family history of BD	High	Low
Family history of unipolar MDD	High	High
Age of onset	Teens and 20s	Older than 30 years
Sex Ratio	Equal (for BPI) F:M = 2:1 (for BP II)	F:M = 2:1
Substance abuse	High	Moderate
Seasonality	Common	Occasional
Postpartum episodes	More common	Less common
Episode onset	Often abrupt	More subtle
Episode frequency	High	Low
Atypical features when depressed	More common	Less common
Rapid on/off pattern	Typical	Unusual
Brief major depressive episodes (< 3 months)	More common	Less common
Psychotic features under age 35 years	More common	Less common
Psychomotor activity	Retardation > agitation	Agitation > retardation
Sleep	Hypersomnia > insomnia	Insomnia > hypersomnia
Treatment-refractory depression	More common	Less common
Short-lived antidepressant efficacy	More common	Less common
Risk for antidepressant-induced mania or hypomania	High	Low
Mixed features (hypomanic symptoms while depressed)	Predictive	Rare
Comorbid anxiety	Very common (90%)	Common (60%)
History of legal problems	More common	Less common
Feelings of people being unfriendly	More common	Less common
Irritability and anger	More common	Less common
Medical comorbidities (migraine, asthma, chronic fatigue, chronic bronchitis, hypertension, gastric ulcer)	More common	Less common

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 hypersomnolence, 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).

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).²¹ The 2009 CANMAT/ISBD guidelines³ focus on the presence of

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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, hypersomnolence, anergia, 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, distractibility, 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

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 hypo/mania. 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.¹⁸ 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.^{22,23} 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., hypomanias 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 1949²⁴) 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.²⁵ Bipolar II appears to be familial and if someone has had hypomanias and meets

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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

Differentiating Between Bipolar Subtypes: Case Presentation 2

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).

sufficient to qualify as an episode of major depression. Cyclothymic disorder and other subtypes of BD are more difficult to diagnose than the relatively straightforward bipolar I and II, and attempts have been made to characterize these. For these "softer," less classic presentations, the concept of "Bipolar Spectrum Disorder" has been proposed, for which suggested diagnostic criteria have been published.^{24,26} There is also a validated tool, the Bipolar Spectrum Diagnostic Scale (BSDS), which has been shown to be highly sensitive and specific for bipolar


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spectrum illness.²⁷ The BSDS uses a descriptive narrative that captures subtle features of bipolar illness; patients are asked to what extent the story corresponds with their own experiences on a sentence-by-sentence basis. The "Mood Check" noted above was derived from the BSDS.

Comorbidities. The presence of a psychiatric comorbidity can mask the diagnosis of BD. It is important for clinicians to realize this, as there is significant co-existence of other psychiatric conditions with BD. Evidence from Evans (2000) suggests that symptom overlap with other disorders (e.g., schizophrenia and unipolar depression), comorbid conditions (including the anxiety disorders, eating disorders and substance-use disorders) and neurocognitive dysfunction (which often interferes with patients' insight into their illness and the ability to recognize their own manic symptoms) may all contribute to misdiagnosis of BD.² Anxiety disorders, including panic disorder with agoraphobia, social anxiety

disorder and obsessive-compulsive disorder are particularly common among people with BD.²⁸ In childhood BD, anxiety disorders, attention deficit disorder, conduct disorder, oppositional-defiant disorder and enuresis are common comorbidities.²⁹ 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 disorder³⁰), 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. 

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References

- Hirschfeld RM, Lewis L, Vornik LA. Perceptions and impact of bipolar disorder: how far have we really come? Results of the national depressive and manic-depressive association 2000 survey of individuals with bipolar disorder. *J Clin Psychiatry* 2003; 64(2):161-74.
- Evans DL. Bipolar disorder: diagnostic challenges and treatment considerations. *J Clin Psychiatry* 2000; 61 Supp 13:26-31.
- Yatham LN, Kennedy SH, Schaffer A, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. *Bipolar Disorders* 2009; 11:225-55.
- Regier DA, Shapiro S, Kessler LG, et al. Epidemiology and health service resource allocation policy for alcohol, drug abuse, and mental disorders. *Public Health Rep* 1984; 99(5):483-92.
- Bland RC, Orn H, Newman SC. Lifetime prevalence of psychiatric disorders in Edmonton. *Acta Psychiatr Scand Suppl* 1988; 338:24-32.
- Heun R, Maier W. Morbid risks for major disorders and frequencies of personality disorders among spouses of psychiatric inpatients and controls. *Compr Psychiatry* 1993; 34(2):137-43.
- Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry* 1994; 51(1):8-19.
- Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity, and course. *J Am Acad Child Adolesc Psychiatry* 1995; 34(4):454-63.
- Weissman MM, Bland R, Joyce PR, et al. Sex differences in rates of depression: cross-national perspectives. *J Affect Disord* 1993; 29(2-3):77-84.
- Szádóczy E, Papp Z, Vitrai J, et al. The prevalence of major depressive and bipolar disorders in Hungary. Results from a national epidemiologic survey. *J Affect Disord* 1998; 50(2-3):153-62.
- Angst J. The emerging epidemiology of hypomania and bipolar II disorder. *J Affect Disord* 1998; 50:143-51.
- Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry* 2007; 64:543-52.
- Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry* 2002; 59(6):530-7.
- Judd LL, Akiskal HS, Schettler PJ, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. *Arch Gen Psychiatry* 2003; 60(3):261-9.
- Angst J, Sellaro R. Historical perspectives and natural history of bipolar disorder. *Biol Psychiatry* 2000; 48(6):445-57.
- Coryell W, Solomon DA, Fiedorowicz JG, et al. Anxiety and outcome in bipolar disorder. *Am J Psychiatry* 2009; 166(11):1238-43.
- Goldstein BI, Fagioliini A, Houck P, et al. Cardiovascular disease and hypertension among adults with bipolar I disorder in the United States. *Bipolar Disord* 2009; 11(6):657-62.
- Muzina DJ, Colangelo E, Manning JS, et al. Differentiating bipolar disorder from depression in primary care. *Cleve Clin J Med* 2007; 74(2):89, 92, 95-9.
- Suppes T, Leverich GS, Keck PE, et al. The Stanley Foundation Bipolar Treatment Outcome Network. II. Demographics and illness characteristics of the first 261 patients. *J Affect Disord* 2001; 67:45-59.
- Lish JD, Dime-Meenan S, Whybrow PC, et al. The National Depressive and Manic-depressive Association (DMDA) survey of bipolar members. *J Affect Disord* 1994; 31:281-94.
- Muzina DJ, Kemp DE, McIntyre RS. Differentiating bipolar disorders from major depressive disorders: treatment implications. *Ann Clin Psychiatry* 2007; 19(4):305-12.
- Hirschfeld RM, Calabrese JR, Weissman MM, et al. Screening for bipolar disorder in the community. *J Clin Psychiatry* 2003; 64:53-9.
- Hirschfeld RM, Williams JB, Spitzer RL, et al. Development and validation of a screening instrument for bipolar spectrum disorder: The Mood Disorder Questionnaire. *Am J Psychiatry* 2000; 157:1873-5.
- Ghaemi SN, Ko JY, Goodwin FK. "Cade's disease" and beyond: misdiagnosis, antidepressant use, and a proposed definition for bipolar spectrum disorder. *Can J Psychiatry* 2002; 47(2):125-34.
- Vieta E, Suppes T. Bipolar II disorder: arguments for and against a distinct diagnostic entity. *Bipolar Disord* 2008; 10(1 Pt 2):163-78.
- Ghaemi SN, Ko JY, Goodwin FK. The bipolar spectrum and the antidepressant view of the world. *J Psychiatr Pract* 2001; 7(5):287-97.
- Ghaemi SN, Miller CJ, Berv DA, et al. Sensitivity and specificity of a new bipolar spectrum diagnostic scale. *J Affect Dis* 2005; 84: 273-7.
- Angst J, Gamma A, Endrass J, et al. Obsessive-compulsive syndromes and disorders: significance of comorbidity with bipolar and anxiety syndromes. *Eur Arch Psychiatry Clin Neurosci* 2005; 255(1):65-71.
- Henin A, Biederman J, Mick E, et al. Childhood antecedent disorders to bipolar disorder in adults: a controlled study. *J Affect Disord* 2007; 99(1-3):51-7.
- Kessler RC, Chiu WT, Demler O, et al. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005; 62(6):617-27.