Review Article

Subthreshold bipolarity: diagnostic issues and challenges

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Background: Research suggests that current diagnostic criteria for bipolar disorders may fail to include milder, but clinically significant, bipolar syndromes and that a substantial percentage of these conditions are diagnosed, by default, as unipolar major depression. Accordingly, a number of researchers have argued for the upcoming 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) to better account for subsyndromal hypomanic presentations.

Methods: The present paper is a critical review of research on subthreshold bipolarity, and an assessment of some of the challenges that researchers and clinicians might face if the DSM-5 were designed to systematically document subsyndromal hypomanic presentations.

Results: Individuals with major depressive disorder (MDD) who display subsyndromal hypomanic features, not concurrent with a major depressive episode, have a more severe course compared to individuals with MDD and no hypomanic features, and more closely resemble individuals with bipolar disorder on a number of clinical validators.

Conclusion: There are clinical and scientific reasons for systematically documenting subsyndromal hypomanic presentations in the assessment and diagnosis of mood disorders. However, these benefits are balanced with important challenges, including (i) the difficulty in reliably identifying subsyndromal hypomanic presentations, (ii) operationalizing subthreshold bipolarity, (iii) differentiating subthreshold bipolarity from borderline personality disorder, (iv) the risk of over-diagnosing bipolar spectrum disorders, and (v) uncertainties about optimal interventions for subthreshold bipolarity.

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Introduction

The World Health Organization (WHO) ranks bipolar disorder as one of the top 10 causes of disability in the world (1). Bipolar disorder is associated with significant work impairment, high rates of divorce, and substance abuse, and leads to suicide attempts in almost one out of every five diagnosed individuals (2–5). Individuals with bipolar disorder also have higher rates of metabolic syndromes and risk factors for cardiovascular disease (e.g., obesity, hyperglycemia, hypertension, and type 2 diabetes) than the general population (6), and have a 10-year earlier mortality rate (7). Accordingly, it is important to have precise and comprehensive diagnostic criteria to reliably identify individuals with, and at risk for, bipolar disorders.

A growing number of researchers, however, have argued that current diagnostic criteria for bipolar disorders do not address milder, albeit clinically significant, bipolar syndromes. Moreover, a

substantial percentage of these conditions, according to some researchers, are diagnosed by default as unipolar major depression (8–19). For the purpose of the present review, we consider the bipolar spectrum to be the continuum from psychotic mania through other expressions of bipolar I disorder, to bipolar II disorder, to soft, subsyndromal manifestations of hypo/mania.

Benazzi and Akiskal (13) and Benazzi (12) reported that approximately 50% of outpatients with major depressive disorder (MDD) were classified as being in the bipolar spectrum when the strict Structured Clinical Interview for DSM-IV (SCID) criteria for a history of hypomania, not necessarily concurrent with a major depressive episode (MDE), were broadened to include those reporting fewer than the criterion number of symptoms. Further reports that approximately 40–50% of individuals with MDD display a lifetime history of hypomanic features, again not necessarily concurrent with an MDE, come from studies by Angst et al. (10), Akiskal and Mallya (20), Benazzi (21), Cassano et al. (22), and Hantouche et al. (23). Furthermore, compared to MDD with no history of hypomanic features, individuals with MDD and a history of hypomanic features (not concurrent with an MDE) are reported to have more general impairment (11, 24, 25) and are more likely to convert to a bipolar I diagnosis over time (19).

The current focus on revising the Diagnostic and Statistical Manual of Mental Disorders in preparation for the publication of the 5th edition (DSM-5) in May 2013 provides an opportunity to reflect on the optimal diagnostic criteria for the bipolar spectrum disorders. Considering the aforementioned clinical and epidemiological data, a number of researchers have argued for DSM-5 to better account for hypomanic features that do not satisfy current criteria for the full syndrome (8, 9, 11, 12, 14, 16, 18–20, 22, 25, 26). We agree with this argument, particularly in light of growing evidence that major mood disorders form a spectrum from MDD without bipolar features via bipolar subgroups to pure mania (11, 25). However, we also argue that modifying DSM-5 to more systematically document subsyndromal hypomanic states raises a number of challenges and complexities. For example, what are the pharmacological treatment implications for individuals with MDD who have a history of hypomanic symptoms that do not meet the criteria for mania or hypomania? Should such individuals be prescribed an antipsychotic or mood stabilizer as opposed to an antidepressant as a prophylactic treatment to prevent a worsening of course along the bipolar spectrum? Several groups have concerns with such a treatment approach given the nature of the side effects associated with antipsychotic medications and mood stabilizers (27–31) [It is important to note, however, that lithium is used by some to treat affective disorders more generally, given its antisuicidal properties (32, 33)]. Moreover, there is still debate as to whether antidepressants may be a risk factor for so-called 'switching' into hypo/manic episodes and/or cycle acceleration among individuals with bipolar I or II disorder (34–36); however, to the best of our knowledge, this question has yet to be examined in individuals with subsyndromal hypomanic presentations. Further, how do we balance the tension between reliably classifying meaningful subsyndromal hypomanic presentations against the risk of over-diagnosing bipolar spectrum disorders given the severity of, and potential stigma attached to, these diagnoses?

The purpose of the present report is threefold. First, we review the literature on the prevalence of both bipolar spectrum disorders and subthreshold hypomania. Second, we outline the clinical and scientific utility of expanding the mood disorder criteria in the DSM-5 to better account for subsyndromal hypomanic presentations as proposed by several researchers. Third, we directly address a number of challenges and complexities that researchers and clinicians face in diagnosing, classifying, and treating subthreshold bipolarity.

Before we proceed, it is important to briefly address two issues. First, the present report focuses only on subthreshold bipolarity in adults. The accurate and timely diagnosis of pediatric bipolar disorder is an issue of critical importance that is, however, beyond the scope of the present review.

Second, with respect to terminology, researchers have examined subsyndromal hypomanic presentations from two different perspectives. The first focuses on a history of hypomanic presentations that are not necessarily concurrent with an MDE; that is, hypomanic presentations that occur outside the context of a depressive episode. The second perspective examines subsyndromal hypomanic presentations that are *concurrent* with an MDE, commonly referred to as mixed depressive episodes. The present report focuses exclusively on adult individuals with a history of MDD who display subsyndromal hypomanic features that are not concurrent with an MDE.

Prevalence and the bipolar spectrum

The DSM-IV–text revised (DSM-IV-TR) (37) defines the bipolar spectrum disorders as encompassing three diagnoses: cyclothymia, bipolar II

disorder, and bipolar I disorder. All three diagnoses are characterized by hypomanic/manic and depressive symptoms (except for instances of pure mania), but differ in severity level, with bipolar I disorder being the most severe and cyclothymia the least severe. Cyclothymia is diagnosed as the presence of erratic depressive and hypomanic periods, in the absence of a history of a full MDE. Bipolar II disorder is diagnosed when there is a history of at least one MDE and one hypomanic episode, but no history of a manic episode. Bipolar I disorder is diagnosed when there is a history of at least one manic or mixed episode, as currently defined. A diagnosis of bipolar disorder not otherwise specified (NOS) is reserved for individuals who display bipolar symptomatology that does not meet criteria for any of these three bipolar diagnoses.

Epidemiological studies relying on DSM criteria have consistently reported lifetime prevalence rates for bipolar I disorder between 0.0% and 1.7% (38, 39) and bipolar II disorder between 0.5% and 1.9% (40, 41). There is growing evidence, however, that major mood disorders form a spectrum from MDD to pure mania via bipolar subgroups (11, 25). This spectrum embraces mania, hypomania, recurrent brief hypomania, sporadic brief hypomania, and cyclothymia (9). Although researchers have addressed this spectrum using different terminology, there is growing appreciation of the importance of identifying and diagnosing subsyndromal hypomanic presentations among individuals with MDD (8, 11, 17). It is argued that the current diagnostic criteria for bipolar disorder fail to include milder, but clinically significant, bipolar syndromes and that a significant percentage of these conditions are diagnosed, by default, as unipolar major depression (9, 11, 19, 42). Accordingly, researchers have begun conducting epidemiological studies that give particular attention to the prevalence of subsyndromal hypomania.

As indicated above, these studies suggest that approximately 40–50% of individuals with MDD display lifetime subsyndromal hypo/manic features when the strict DSM-IV criteria for hypomania are broadened (10, 20–23). For example, a recent study by Angst and colleagues (11) examined the prevalence and clinical correlates of MDD with subsyndromal hypomanic features, not concurrent with an MDE, versus MDD with no history of hypomanic features in the National Comorbidity Survey Replication (NCS-R), a nationally representative household survey of the US population. Subsyndromal hypomania was operationalized as: (i) the presence of at least one of two screening questions for hypomania (e.g.,

"some people have periods lasting several days or longer when they feel much more excited and full of energy than usual")[1], and (ii) a failure to meet the full DSM-IV diagnostic criteria for hypomania. The authors reported that nearly 40% of MDD cases experienced subsyndromal hypomania outside the context of an MDE, noting that their "findings demonstrate heterogeneity of major depressive disorders and support the validity of a wider spectrum of bipolar disorders" (11, p. 1194). Zimmerman et al. (19) used data from the prospective, longitudinal Early Developmental Stages of Psychopathology (EDSP) study to examine how many cases previously classified as DSM-IV MDD would be reclassified as being in the bipolar spectrum by broadening the criteria for mania/hypomania. Subsyndromal hypomania was defined as at least a four-day period (not concurrent with an MDE) with (i) elated/expansive mood that created troubles or was noticed by others as a change in functioning, but DSM-IV criterion B (meeting the required minimum number of symptoms) was not fulfilled, or with (ii) unusually irritable mood expressed as starting arguments, or shouting at or hitting people plus the presence of at least three symptoms, but criterion D (symptoms are observable by others) was not met. In line with Angst et al. (11), the authors reported that among the 488 respondents with MDD, 40% had subsyndromal hypomanic features at some point during their lifetime and 60% had no history of subsyndromal hypomanic features. A study by Benazzi (43) interviewed 111 remitted outpatients with prior depression for a history of lifetime hypomania and hypomanic symptoms with the Structured Clinical Interview for DSM-IV–clinician version. All past hypomanic symptoms (especially overactivity) were assessed and subsyndromal hypomania was defined as at least a two-day period of overactivity (increased goal-directed activity) plus at least two other hypomanic symptoms. He reported that a history of subsyndromal hypomania, not concurrent with an MDE, was present in 39% of the MDD sample.

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[1]The two screening questions used by Angst and colleagues (11) to assess for subsyndromal hypomania were (i) "Some people have periods lasting several days or longer when they feel much more excited and full of energy than usual. Their minds go fast. They talk a lot. They are very restless or unable to sit still and they sometimes do things that are unusual for them, such as driving too fast or spending too much money. Have you ever had a period like this lasting several days or longer?"; (ii) "Have you ever had a period lasting several days or longer when most of the time you were so irritable that you either started arguments, shouted at people, or hit people?".

As reported by Angst et al. (10), a stepwise broadening of the criteria for hypomania allocated almost half of the participants with MDD to a broadly defined bipolar spectrum group.

Researchers have argued that the substantial percentage of individuals with MDD who display subsyndromal hypomanic features poses a challenge to the categorical perspective taken in the current DSM in which unipolar depression and bipolar disorder are viewed as separate disease processes. It is argued that data, instead, support a continuum from pure MDD to bipolar I disorder (9, 14, 16, 17, 43–45). This spectrum perspective allows for a broader range of symptoms and the possibility that there is not a clear distinction between the two mood disorder categories. In line with this perspective is research indicating a strong genetic relationship between unipolar depression and bipolar disorder (46) and the fact that common genetic variations increase susceptibility for the entire affective spectrum (47–49). The idea, however, that unipolar depression and bipolar disorder are on a spectrum of severity is not a new concept. Indeed it was first endorsed by Kraepelin (50) when he created the rubric of 'manic-depressive insanity' that for him spanned the continuum from the mildest affective disturbance to the most extreme psychosis. Goodwin and Jamison (4) also supported a bipolar spectrum that included MDD plus what they refer to as bipolar signs (early onset, many recurrences, atypical depression, bipolar family history, and antidepressant-associated switching) (51, 52).

Researchers have also addressed how broadening the spectrum of what is considered diagnosable hypomania would affect the prevalence rates for both MDD and bipolar disorder. Zimmerman and colleagues (19) reported that the cumulative incidence of 23.2% for DSM-IV MDD would drop to 13.9% if cases with subsyndromal hypomanic features (9.3%), not concurrent with an MDE, were deducted. Correspondingly, the rate of a lifetime bipolar spectrum diagnosis would increase to 13.7%, thus being equal to the rate of MDD with no history of subsyndromal hypomanic features. This is consistent with data from the epidemiologic studies of Angst et al. (10) which showed a lifetime prevalence of 11.0% for a softly defined bipolar spectrum diagnosis versus 11.4% for MDD with no history of subsyndromal hypomanic features, and from clinical investigations (13).

It is apparent that modifying the DSM-5 to systematically document subthreshold bipolarity could generate prevalence rates for bipolar spectrum disorders that are quite different from those reported in previous epidemiological research which adhered to earlier versions of the DSM (38–41). As we examine later, this would likely generate challenges for both researchers and clinicians around issues of medication management and the stigma often associated with a bipolar spectrum diagnosis. However, prior to addressing these challenges, we first examine the validity and clinical impact of subsyndromal hypomania, not concurrent with an MDE, which are important to consider in the cost–benefit analysis of whether to modify DSM-5 to account for subthreshold bipolar features.

Validators of subthreshold bipolarity

Growing evidence indicates that individuals with MDD who report subsyndromal hypomania, outside the context of an MDE, more closely resemble individuals with bipolar disorder on a number of clinical validators, as compared to individuals with MDD and no history of subsyndromal hypomania (see Table 1 for the cohort and definition of subthreshold hypomania for studies of clinical validators of subthreshold bipolarity). Relative to those with MDD and no history of hypomanic symptoms, individuals with subsyndromal hypomania, outside the context of an MDE, have increased comorbidity with impulse control and substance disorders (9–11, 19, 53), and experience more episodes (11) (see Table 2 for an overview of clinical validators of bipolarity for individuals with MDD and subsyndromal hypomanic features versus MDD and no history of subsyndromal hypomanic features). The comorbidity between MDD and alcohol use disorders becomes non-significant after exclusion of individuals with subsyndromal hypomania (19, 54). Data with respect to comorbidity with anxiety disorders are more inconsistent, however. Three studies reported that the presence of subsyndromal hypomania, not concurrent with an MDE, was associated with elevated rates of comorbid anxiety (9, 11, 19), while two studies did not find this effect (10, 53). Lastly, a 10-year prospective longitudinal study reported that individuals with MDD who had subsyndromal hypomania, not concurrent with an MDE, were more likely to convert to a DSM-IV bipolar spectrum diagnosis as compared to individuals with pure depression (19). The authors reported that, in most cases, this conversion was to bipolar I disorder.

Family and genetic studies also provide support for the validity of subthreshold bipolarity. Cassano and colleagues (22) reported that individuals with MDD who had hypomanic personality traits (e.g., uninhibited, stimulus-seeking, promiscuous, vigorous, full of plans, overconfident, self-assured, and

Table 1. Cohort and definition of subthreshold hypomania for studies of clinical validators of subthreshold bipolarity

Study	Cohort	Definition of subthreshold hypomania/bipolar disorder
Akiskal et al., 1995 (53)	National Institute of Mental Health (NIMH) Collaborative Depression Study (USA; N = 559)	Individuals with MDD who converted to bipolar II disorder
Angst et al., 2010 (11)	National Comorbidity Survey Replication (USA; N = 5,692)	Presence of at least one of the screening questions for mania on the Composite International Diagnostic Interview (CIDI) and three or more symptoms
Angst, 1998 (9)	Zurich Cohort Study (Zurich, Switzerland; N = 591)	Met DSM-IV symptomatic criteria for hypomania but only lasted 1–3 days
Angst et al., 2003 (10)	Zurich Cohort Study (Zurich, Switzerland; N = 591)	'Hypomanic symptoms only'; did not have consequences and not required to meet duration or number of symptoms criteria
Benazzi & Akiskal, 2008 (15)	Outpatient psychiatry private practice (Italy; N = 560)	Early onset (before age 21) MDD
Cassano et al., 1992 (22)	Collaborative initiative between Institute of Clinical Psychiatry at the University of Pisa, Italy and the Section of Affective Disorders at the University of Tennessee, (USA; N = 687)	MDE with pre-existing hyperthymic temperament. A hyperthymic temperament was defined as 5 of the following: (i) irritable, cheerful, overoptimistic, or exuberant; (ii) naïve, overconfident, self-assured, boastful, bombastic, or grandiose; (iii) full of plans, imprudent, or carried away by restless impulses; (iv) over talkative; (v) warm, people-seeking, or extroverted; (vi) over-involved and meddlesome; (vii) uninhibited, stimulus seeking, or promiscuous
Lewinsohn et al., 2002 (24)	Oregon Adolescent Depression Project (USA; N = 1,709)	Criterion A hypo/manic symptom plus one or more other hypo/manic symptoms, but never meeting criteria for the full bipolar diagnosis
Merikangas et al., 2007 (25)	National Comorbidity Survey Replication (USA; N = 9,282)	Any of the following: (i) recurrent subthreshold hypomania (≥ 2 criterion B symptoms and all other criteria for hypomania) in the presence of intercurrent MDE; (ii) recurrent (> 2 episodes) hypomania in the absence of recurrent MDE with or without subthreshold MDE; (iii) recurrent subthreshold hypomania in the absence of intercurrent MDE with or without subthreshold MDE. The number of required symptoms for a determination of subthreshold hypomania was confined to two criterion B symptoms
Zimmerman et al., 2009 (19)	Early Development Stages of Psychopathology study (Munich, Germany; N = 2,210)	At least a 4-day period with the following: (i) noticeable elated or expansive mood but minimum number of symptoms criterion not fulfilled, or (ii) unusually irritable mood, at least three symptoms, but observable by others criterion not fulfilled

MDD = major depressive disorder; MDE = major depressive episode.

Table 2. Clinical validators of bipolarity for individuals with major depressive disorder (MDD) with subsyndromal hypomanic features versus MDD and no history of subsyndromal hypomanic features[a,b]

Study	Increased impairment	Increased suicidality	BD family history	Increased criminality	Increased conversion to BD	Increased comorbid anxiety	Increased comorbid substance/ alcohol	Younger age of onset
Akiskal et al., 1995 (53)	+					−	+	+
Angst et al., 2010 (11)	−	−	+			+	+	+
Angst, 1998 (9)		−	+			+	+	
Angst et al., 2003 (10)		−	+	−		−	+	+[c]
Benazzi & Akiskal, 2008 (15)			+					+
Cassano et al., 1992 (22)		−	+					−
Lewinsohn et al., 2002 (24)	+							
Zimmerman et al., 2009 (19)		−	+	+	+	+	+	−

A blank cell indicates that the study did not compare groups on that particular validator. BD = bipolar disorder; + = MDD with subsyndromal hypomanic features greater than MDD and no subsyndromal hypomanic features; − = no difference between MDD with subsyndromal hypomanic features and MDD with no subsyndromal hypomanic features.
[a]There were notable differences in methodology, statistical analyses, and definition of subthreshold hypomanic features across the reported studies. The present table reflects our best attempt to synthesize and summarize the literature.
[b]Subsyndromal hypomanic features occur outside the context of a major depressive episode.
[c]Contrast is at the trend level.

grandiose) had rates of familial bipolarity significantly higher than individuals with MDD without these temperamental qualities. Zimmerman et al. (19) reported familial data demonstrating increased rates of parental mania among respondents with subthreshold bipolarity, but not among individuals with MDD and no history of subsyndromal hypomania. Akiskal and colleagues (8) noted that displaying subsyndromal hypomania places an individual in a genetic cohort more in line with bipolar disorder than unipolar depression. Angst et al. (9, 10) and Musetti et al. (55) provide additional evidence that family members of individuals with subthreshold bipolarity display greater rates of bipolar disorder.

Finally, research indicates that an early age at onset of first MDE (before 21 years) may be an important validator of bipolar risk status (8, 11). Benazzi and Akiskal (15) reported that early age at onset was the only variable that identified a MDD subgroup significantly associated with all bipolar validators. The authors noted that the odds of an individual with MDD having bipolar disorder were three times higher if he or she had an early onset. Furthermore, an early age at onset of first MDE has been shown to predict conversion from MDD to syndromal bipolar disorder (bipolar I and II) (56–58). Three additional studies reported that MDD with subsyndromal hypomanic features was associated with an earlier age of onset of a first MDE compared to MDD and no history of subsyndromal hypomanic features (10, 11, 53). These studies, however, need to be considered in light of two studies that found no differences in age of onset for MDD with and without subsyndromal hypomanic features (19, 22).

Researchers have also compared individuals with MDD and subsyndromal hypomania, outside the context of an MDE, to individuals with syndromal bipolar disorder (e.g., bipolar II disorder) on clinical validators of bipolarity (see Table 3). Much of this research provides support for the spectrum or dimensional model of bipolarity, documenting a direct association between the severity of the bipolar diagnosis and indicators of clinical validity, including number of episodes, chronicity, symptom severity, and impairment (9, 59). For example, Merikangas and colleagues (25) reported that the proportion of individuals with work impairment increased from 19.8% for subthreshold bipolar disorder to 47.5% for bipolar II to 62.3% for bipolar I, and the estimated average number of lifetime episodes was 32.0 for subthreshold bipolar disorder, 63.6 for bipolar II, and 77.6 for bipolar I. Likewise, Zimmerman et al. (19) noted that with increasing severity of the manic component, rates for diverse validators increased (alcohol use disorders and parental mania) or decreased (harm avoidance), accordingly. Benazzi and Akiskal (15) demonstrated a dose–response relationship between the number of bipolar validators and bipolar family history, suggesting that a clustering of bipolar markers increases the genetic vulnerability to bipolarity among those with MDD. These data, however, need to be interpreted in the context of other work indicating comparable profiles on clinical validators across the bipolar spectrum. For example, a number of studies report equivalent rates of comorbidity for substance/alcohol abuse and anxiety disorders in individuals with subsyndromal versus syndromal bipolar disorder (9, 10, 24, 25). Furthermore, in at least one

Table 3. Clinical validators of bipolarity for individuals with syndromal hypomania (e.g., bipolar II disorder) versus major depressive disorder (MDD) with subsyndromal hypomanic features[a,b]

Study	Increased impairment	Increased suicidality	BD family history	Increased criminality	Increased comorbid anxiety	Increased comorbid substance/alcohol	Younger age of onset
Angst et al., 2010 (11)	+	−	−		+	−	+
Angst, 1998 (9)		−	+		−	−	
Angst et al., 2003 (10)		−	−	−	−	−	−
Benazzi & Akiskal, 2008 (15)			−				
Cassano et al., 1992 (22)		+	−				+
Lewinsohn et al., 2002 (24)	+	+			−	−	
Merikangas et al., 2007 (25)	+				+	−	+
Zimmerman et al., 2009 (19)		+	+	+	+	+	

A blank cell indicates that the study did not compare groups on that particular validator. BD = bipolar disorder; + = threshold hypomania (e.g., bipolar II disorder) greater than MDD with subsyndromal hypomanic features; − = no difference between threshold hypomania (e.g., bipolar II disorder) and MDD with subsyndromal hypomanic features.
[a]There were notable differences in methodology, statistical analyses, and definition of both threshold and subthreshold hypomanic features across the reported studies. The present table reflects our best attempt to synthesize and summarize the literature.
[b]Subsyndromal hypomanic features occur outside the context of a major depressive episode.

review, individuals with bipolar I or II disorder were found to have comparable rates of suicide attempts (60), and individuals with bipolar II disorder, relative to those with bipolar I disorder, may experience a more chronic course and a lower likelihood of returning to premorbid levels of functioning between episodes (61). Thus, although bipolar disorder is organized along a spectrum of severity, milder or 'softer' forms of bipolar disorder are clearly associated with substantial impairment that typically exceeds that observed in individuals with no evidence of bipolarity.

Clinical and scientific importance of diagnosing subthreshold bipolarity

Considering the epidemiological and clinical data, a number of researchers have called on the DSM-5 to better account for subsyndromal hypomanic presentations (8–14, 16, 18–20, 22, 25, 26). In line with this perspective, we next put forth four arguments supporting the need to take subthreshold bipolarity into consideration in the diagnosis, treatment, and scientific investigation of mood disorders. We then follow these arguments with an analysis of challenges and complexities that clinicians and researchers would likely face if the DSM-5 were to be structured to account for subthreshold bipolarity.

The first argument for documenting subsyndromal hypomanic presentations is that, as discussed in the previous section, they are clinically significant and associated with role impairment. Data from the NCS-R indicate that 45.9% of individuals with subthreshold bipolar disorder reported severe role impairment associated with subthreshold hypomania, and an even higher percentage (78.8%) reported severe role impairment from MDEs in the context of subthreshold bipolar disorder (25). Moreover, individuals with MDD who display subsyndromal hypomania outside the context of an MDE have a more severe and pernicious course as compared to individuals with MDD and no hypomanic features, including greater likelihood of converting to a bipolar diagnosis (19), higher rates of comorbid psychiatric illness (10, 11, 19, 25), and more depressive episodes (11).

Second, systematically assessing for subsyndromal hypomania may help remedy an important related concern: the fact that threshold bipolar disorder (bipolar I or II disorder) is either frequently misdiagnosed, or there is a lengthy time period from the point of illness onset to correct diagnosis. Delays ranging from 6 to 10 years or longer have been reported before bipolar I or II

disorder are correctly diagnosed and appropriately treated (51, 52). Hirschfeld et al. (62) reported data from the National Depressive and Manic Depressive Association survey indicating that 69% of respondents with bipolar disorder I or II disorder were initially misdiagnosed, with the most frequent diagnosis being unipolar depression (60%). Those who were misdiagnosed consulted a mean of four physicians prior to receiving the correct diagnosis and over one-third waited 10 years or more before receiving an accurate diagnosis. In a follow-up study, Hirschfeld and colleagues (63) screened adult patients diagnosed with MDD for bipolar I or II disorder. Twenty-one percent of the patients with MDD screened positive for bipolar disorder, and nearly two-thirds of those who screened positive had never received a diagnosis of bipolar disorder. Ghaemi et al. (51) reported that 40% of consecutively admitted patients with DSM-IV bipolar I disorder were previously misdiagnosed with MDD. An average period of 7.5 ± 9.8 years elapsed in this group before the correct bipolar diagnosis was made. In a follow-up study, Ghaemi et al. (52) reported that bipolar disorder I, II, or NOS was misdiagnosed as unipolar depression in 37% of patients who first saw a mental health professional after their initial hypo/manic episode.

Converging factors contribute to the frequent mis- and under-diagnosis of bipolar disorder. For example, the significant impairment associated with bipolar depression (64) results in individuals with bipolar disorder being more likely to present for treatment when depressed, increasing the likelihood of an inaccurate diagnosis of unipolar depression (26). However, researchers have proposed that another important factor in the frequent misdiagnosis of bipolar disorder may be the narrow diagnostic criteria in the current nosology, and the fact that clinicians and physicians do not systematically assess for subthreshold bipolarity (11, 16). As proposed by Cassano et al. (16, p. 319), "attention should be devoted to mild symptomatic manifestations of a manic diathesis, even if such manifestations may sometimes enhance quality of life". This attention may be critical in differentiating individuals with 'pure' depression from those with subthreshold bipolar presentations. However, it may also be important for increasing the accuracy with which we identify threshold bipolar disorder, type I or II. By assessing only the most obvious signs of type I mania (e.g., hospitalization due to mania, and psychotic features), researchers and clinicians may fail to identify important signs and symptoms of the larger bipolar spectrum, particularly those that the patient views as ego-syntonic, and increase the risk of misdiagnosing

individuals with bipolar disorder as having MDD. It could be argued, therefore, that systematically assessing for and documenting subsyndromal hypomanic features may help remedy this situation.

It is important to mention that while there is significant evidence for the under-diagnosis of bipolar disorder, there is a parallel literature documenting the fact that under certain circumstances bipolar disorder may also be overdiagosed (65–70). This literature, however, is not arguing that the possible overdiagnosis of bipolar disorder is attributable to an increased awareness of the importance of assessing for and documenting subthreshold bipolarity, but rather a tendency to attribute symptoms of other disorders such as borderline personality disorder to the bipolar spectrum. We address this issue in detail below.

Third, it is argued that the assessment and management of subthreshold bipolar features are in line with a prevention-oriented treatment model for bipolar disorder. A goal of mental health treatment is not only to effectively manage an illness once it has emerged, but ideally prevent its emergence or re-emergence. Prevention strategies, however, require accurate assessment of the early signs of an illness. Expanding the diagnostic criteria for mood disorders in order to systematically document the presence or absence of subthreshold bipolar features in MDD may help facilitate clinicians' identifying at-risk individuals and ideally employing strategies in order to prevent the onset of threshold bipolar disorder.

Finally, documenting subthreshold bipolarity in individuals with MDD has important implications for research on mood disorders. The recent research agenda for the DSM-5 has emphasized the need to apply basic and clinical neuroscience findings to develop a framework for identifying biomarkers that reflect pathophysiological processes to facilitate earlier and more accurate diagnoses of psychiatric disorders (71–73). A difficulty in examining biomarkers, however, is that many illnesses are characterized by notable diagnostic heterogeneity (74) that introduces uncontrolled variance into analyses. This is clearly the case in MDD where, as documented above, upwards of 40% of individuals with MDD display subsyndromal bipolarity. This subgroup is likely characterized by different pathophysiological processes than individuals with 'pure' depression, given family and genetic studies indicating they more closely resemble individuals with bipolar disorder (9, 10, 19, 22, 55). Systematically assessing for subthreshold bipolarity in individuals with MDD may therefore assist researchers in generating more homogenous groups of mood disorder patients for neuroimaging and biomarker based research.

Challenges and complexities associated with diagnosing, classifying, and managing subthreshold bipolarity

Having discussed the prevalence and validity of subthreshold bipolarity, we now turn our attention to some of the challenges and complexities associated with the assessment, diagnosis, and management of subthreshold bipolarity and, where supported by research, put forth suggestions for addressing them.

Reliably identifying subthreshold bipolar features

The first challenge is the difficulty in reliably assessing and identifying subsyndromal hypomania (16). Several factors that contribute to this difficulty are the fact that both syndromal and subsyndromal hypomania: (i) are often not associated with stress or suffering and thus not a cause for pursuing treatment, (ii) are often ego-syntonic and associated with heightened confidence and productivity, (iii) may not be noticed by family members, and (iv) may be misinterpreted as a personality disorder (16). Taking these factors into consideration, researchers and clinicians have proposed a number of recommendations for better identifying and diagnosing hypomanic features, which we review below.

Overactivity as a stem criterion for hypomania diagnosis. The first recommendation is to focus the probing for history of hypomania at least as much on changes in goal-directed activity and energy as on mood changes, as this has been shown to reduce the under-diagnosis of hypomania (14). Benazzi (43) reported that in a sample of remitted outpatients with a history of depression, overactivity was the most common and easiest to identify symptom of hypomania. Moreover, overactivity was found to be as important as mood change for the diagnosis of hypomania on the basis of clinical, family history, and psychometric findings (10, 13). Overactivity is typically better remembered than mood change by patients and key informants (13), and is more closely linked to bipolar validators such as bipolar family history (10). Accordingly, a number of researchers have argued that one way to address the difficulty in identifying subsyndromal hypomania is to balance the currently central diagnostic importance placed on the mood criterion with more emphasis on the hypomanic symptoms of overactivity and excessive goal-directed

behavior (10, 11, 14, 16, 43). These researchers propose that overactivity should be included as a stem criterion for the diagnosis of hypomania (11, 14, 43), especially given that periods of elevated activity are easier for patients to remember, and increase the sensitivity with which clinicians can identify subsyndromal hypomania (14, 43).

Reduce duration requirement for hypomania. The minimum duration required for a diagnosis of hypomania has changed significantly over the years. It was two days in the Research Diagnostic Criteria (75), not specified in DSM-III or DSM-III-R, and is currently four days in DSM-IV. However, the current four-day cut-off is not data-based (76), and, according to some researchers, may unnecessarily narrow the range of bipolar spectrum disorders diagnosable in clinical and epidemiological studies (8). By contrast, a cut-off of two days is supported by data (8–10, 42, 53, 56, 77, 78). Angst et al. (10) reported that hypomanic episodes of 1–3 days were of comparable clinical significance as episodes having a four-day minimum criterion. Moreover, a large clinical study on individuals with bipolar II disorder that used a definition of hypomanic duration of two days found that these individuals had a rate of bipolar family history statistically indistinguishable from that of individuals with bipolar I disorder, both of which were higher than that of individuals with MDDs. Accordingly, a number of researchers have argued that the DSM-5 duration criteria for hypomanic episodes should be reduced to better reflect the data and to better capture subsyndromal hypomanic features (8, 10, 14, 43).

Depression features may inform diagnosis of hypomania. An individual's depression history may yield important information about their risk status for bipolar spectrum disorder and thus may serve as a cue for clinicians and researchers to probe more thoroughly for a history of subthreshold bipolarity. As reported earlier, the odds of an individual with MDD having bipolar disorder are three times higher if they had an early onset of depression (age less than 21 years) (8, 11, 15). Research also suggests that the depressive episodes of individuals with, and at risk for, bipolar disorder may be more likely to be characterized by atypical features. According to DSM-IV, atypical depression is characterized by symptoms such as mood reactivity, hypersomnia, hyperphagia, leaden paralysis, and rejection sensitivity. Atypical depression is associated with greater functional impairment and more chronic dysphoria (79). Importantly, atypical features of MDD have been found to be a useful clinical marker of bipolar risk status (10, 21). Perugi et al. (18) reported that 72% of individuals whose depression was characterized by atypical features met criteria for bipolar II disorder or subthreshold bipolarity, and nearly 60% had cyclothymic temperaments. Benazzi (12) reported that individuals with MDD who were reclassified as having bipolar II disorder had a depression history characterized by early onset and atypical features. An earlier study by Ebert et al. (80) showed a progression of atypical depression to bipolar spectrum disorders: however, this progression only reached a statistical trend in a more recent study by Angst and colleagues (10). Assessing for atypical depressive symptoms and age of onset of first depressive episode may help clinicians and researchers more accurately identify which individuals with MDD are at heightened risk for conversion to a bipolar diagnosis. We are not advocating that atypical depressive symptoms or an early age of depression onset be included in the diagnostic criteria for the bipolar spectrum disorders. We are suggesting, however, that they may indicate a heightened risk for a bipolar spectrum diagnosis and, when present, clinicians and researchers may benefit from initiating a more comprehensive assessment for hypo/manic symptoms.

Operationalizing subthreshold bipolarity

Recognition of the full spectrum of bipolar disorders is dependent on the identification of the most appropriate definitions for these subthreshold conditions. The concept of a spectrum of bipolar disorders was stimulated by Dunner et al. (81), who distinguished between bipolar I and bipolar II disorders. Angst (82) extended this logic, drawing a distinction between hypomania (m), cyclothymia (md), mania plus major depression (MD), and major depression and hypomania (Dm). Akiskal and colleagues have described a 'soft' bipolar spectrum and proposed broadening bipolar II criteria, as well as creating a third bipolar category, to more fully acknowledge cyclothymic and hyperthymic states, family history of bipolar disorder, temperament, and hypomanic episodes which occur during pharmacotherapy (8, 77, 83). A consequence of these diverse definitions, however, is that many studies have operationalized subthreshold bipolarity using very different diagnostic criteria. With respect to the criteria for subsyndromal hypomania that is not concurrent with an MDE, some studies have reduced the number of symptoms required to obtain a diagnosis (11, 19, 25, 43), others the number of days or whether

change in function was obligatory (9–11, 14, 19), and others have emphasized overactivity, as opposed to change in mood, as a Criterion A symptom (10, 43).

An important direction for future research is to directly compare the validity and utility of different definitions of, and criteria for, subthreshold bipolarity in order to identify optimal diagnostic criteria. Angst and colleagues (10, 84) have proposed a diagnostic system for subsyndromal hypomania not concurrent with an MDE that is well defined, testable, and receiving preliminary empirical support across different patient samples and research groups. This proposal involves: (i) overactivity plus at least two to three of the seven DSM-IV hypomanic symptoms, (ii) a duration ≥ 1 day, and (iii) a change in functioning that is noticeable to others. Benazzi (14) reported that when using Angst's proposed criteria of overactivity plus 3 out of 7 symptoms, hypomania was not over-diagnosed. Comparisons between DSM-IV hypomania and Angst's criteria for hypomania showed that there were no significant differences on age, gender, symptom structure of hypomania, number of episodes, episode duration, and episode level of functioning. Thus, Angst's criteria may be a useful launching pad for research on the optimal diagnostic criteria for subthreshold hypomania. However, as noted by Angst himself (10, p. 134), "minimum duration, stem criteria, and the number of signs and symptoms are three areas requiring a good deal more systematic investigation" in the study of how to optimally identify and define hypomania.

Differentiating subthreshold bipolarity from borderline personality disorder

A challenge that both clinicians and researchers often face is determining whether the affective instability an individual presents is an expression of bipolar disorder, borderline personality disorder (BPD), or both (8, 69, 85). Bipolar disorder and BPD share a number of phenomenological features including affective lability, difficulty controlling anger and irritability, impulsivity, suicidality, and notable social impairment (67, 69, 85–89). Furthermore, the high frequency of inter-episode residual symptoms in bipolar disorder increases the similarities between BPD and bipolar disorder, making it difficult to distinguish the two disorders both cross-sectionally and longitudinally (86). Indeed, certain researchers have proposed that the two disorders might share a cyclothymic temperament (90). These similarities frequently result in BPD being misdiagnosed as bipolar

disorder. Using data from the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project, Ruggero and colleagues (67) reported that nearly 40% of patients diagnosed with BPD were at some point misdiagnosed as having bipolar disorder, as compared to only 10% of patients without BPD. Furthermore, the likelihood of being misdiagnosed with bipolar disorder increased with the number of BPD criteria a patient met. The misdiagnosis of BPD and bipolar disorder has important treatment implications given data suggesting the medications used to treat bipolar disorder may not be effective for BPD, and vice versa (91), although Reich et al. (92) and Nickel et al. (93) present data suggesting that mood stabilizers may ameliorate the symptoms of both bipolar disorder and BPD.

While there are exceptions (8, 20, 43), the majority of research on the prevalence and validators of subthreshold bipolarity has not systematically examined or controlled for borderline personality features, nor excluded individuals with BPD. The importance of this fact is highlighted by three themes. First, research suggests that the relationship and comorbidity between bipolar disorder and BPD become stronger for milder forms of the bipolar spectrum. In studies of individuals with bipolar II disorder, between 12% and 23% had comorbid BPD (94–96), and 22% of individuals with cyclothymia reported having comorbid BPD (97). Deltito and colleagues (98) reported that depending on the level of bipolar disorder from the most severe (mania) to the most 'soft' (bipolar family history), between 13% and 81% of BPD patients showed signs of bipolarity. This suggests that the relationship between BPD and milder forms of the bipolar spectrum, such as cyclothymia and MDD with subsyndromal hypomanic features, may be particularly strong, emphasizing the need for sophisticated differential diagnosis. Second, researchers highlight that individuals with softer expressions of bipolar disorder may also be frequently misdiagnosed as having BPD (8, 99). Thus, where Ruggero and colleagues (67) argue that individuals with BPD are frequently misdiagnosed as having bipolar disorder, researchers such as Akiskal and colleagues (8, 99) argue that that this misdiagnosis may go both ways, particularly as it pertains to softer expressions of bipolarity such as bipolar II, cyclothymia, and MDD with subsyndromal hypomanic features. Third, many of the clinical validators (e.g., substance use, suicidality, and early onset) that distinguish individuals with MDD and subsyndromal hypomanic features from MDD with no history of subsyndromal hypomania have also been found to distinguish between

depressed patients with and without BPD (88, 100–102). The one exception is that family members of individuals with BPD do not show elevated rates of bipolar disorder, highlighting the fact that despite their phenomenological similarities, bipolar disorder and BPD appear to be genetically distinct (88).

It will be important for future research on both the prevalence and validators of subthreshold bipolarity to examine and take into consideration co-occurring BPD and borderline features. Other disorders that are often difficult to differentiate from bipolar disorder and prone to misdiagnosis include substance use disorders, posttraumatic stress disorder (PTSD), and lifetime impulse control disorders (70, 103). Clinically and scientifically validating subthreshold bipolarity will be difficult if its symptoms are frequently confused as BPD or other conditions such as PTSD. Moreover, diagnosing bipolar disorder when it is not present and thus unnecessarily starting pharmacological treatment for bipolar disorder can have negative implications given medications used to treat the illness may have negative side effects (28–31). The misdiagnosis of BPD as bipolar disorder, and vice versa, may also prevent an individual from receiving treatment that targets their actual illness (67).

An important direction for future research will be to identify clinical characteristics and symptom profiles that may aid the differential diagnosis of subthreshold bipolarity from BPD and other psychiatric disorders. Preliminary research indicates that bipolar disorder and BPD may be characterized by different profiles of elevated affect and elation. In contrast to bipolar disorder, BPD moods rarely include elation and are more likely to shift from euthymia to anger (89, 104, 105). Future research is needed to operationalize these differences and test their clinical and diagnostic utility.

Classifying subthreshold bipolarity

Identifying the optimal diagnostic criteria for subsyndromal hypomania and differentiating it from disorders such as BPD is an important first step in accurately accounting for subthreshold bipolarity. The second step is determining how best to classify MDD with subsyndromal hypomania. That is, if we conceptualize a continuum from pure unipolar to bipolar I disorder, where do we set the categorical cut point for a bipolar diagnosis? The key message from research reviewed in the present report is that approximately 40–50% of individuals with MDD display some hypomanic features, and these individuals have greater impairment, and a more severe and pernicious course than individuals with MDD and no subsyndromal hypomanic features. However, classifying 40–50% of individuals with MDD as having a bipolar spectrum diagnosis raises some legitimate concerns. There is both a qualitative and quantitative difference between bipolar I disorder, characterized by a history of multiple hospitalizations during psychotic manic episodes, and MDD with subsyndromal hypomania. Although revisions to diagnostic criteria could make it clear that subsyndromal hypomania is a milder expression of the bipolar spectrum, classifying MDD with subsyndromal hypomania as a bipolar spectrum diagnosis runs the risk of being more stigmatizing than unipolar depression. A growing body of research documents the stigma associated with a diagnosis of bipolar disorder and the negative consequences that this diagnosis may generate (106). Research has shown that employers, mental health workers, and prospective landlords all endorsed devaluing statements about or discriminated against individuals with a psychiatric disorder (107). Individuals with bipolar disorder who report concerns about stigma show greater social impairment and social isolation (107, 108), and reduced self-esteem (109). Researchers have suggested that to avoid discrimination and rejection, people with psychiatric illnesses such as bipolar disorder may limit their social interaction to individuals who are similarly stigmatized or aware of and accepting of the stigma (110). Social isolation has also been demonstrated in caregivers of individuals with bipolar disorder (108). However, two caveats are as follows. First, to the best of our knowledge, research has not directly compared the stigma associated with a bipolar spectrum diagnosis to the stigma of unipolar depression, and thus it is unclear what incremental increase in stigma would occur if MDD with subsyndromal hypomanic features was categorized as a bipolar spectrum disorder. Second, research suggests that stigma is typically associated with behavioral factors identifying individuals as *different* during symptomatic periods (108). Given that any impairment or change in behavior associated with subsyndromal hypomania will be significantly less than that experienced during a manic episode, it seems probable that the stigma associated with MDD and subsyndromal hypomanic features would also be significantly less than that associated with a bipolar I diagnosis. That said, classifying MDD with subsyndromal hypomanic features in the bipolar spectrum does represent an increase in the severity of the diagnosis and it will be important for clinicians and researchers to try to mitigate any increase in stigma.

A second legitimate concern in classifying individuals with MDD and subsyndromal hypomania as having a bipolar spectrum diagnosis is that it could increase the risk of inappropriate treatment, particularly with antipsychotic medications and mood stabilizers, both of which may have notable side effects (28–31) and carry their own stigma (111). We will address this issue in detail in the next section on treatment recommendations.

A final concern in classifying MDD with subsyndromal hypomania in the bipolar spectrum is that it could increase insurance premium rates for individuals with subthreshold bipolarity or elevate the chance of individuals being denied insurance coverage. To date, research has not systematically examined the effect of having a bipolar spectrum diagnosis on insurance rates/coverage or legal issues. The research most directly related to this topic suggests that individuals incorrectly diagnosed as having bipolar disorder were actually more likely to obtain disability payments (65). Future research is warranted to examine the effect of diagnostic status on insurance and legal related issues, not simply to document the issue, but to minimize any negative insurance and litigation-related consequences of having a bipolar spectrum diagnosis.

These concerns, however, are balanced with the literature reviewed in the present paper documenting not only the presence of subsyndromal hypomania in those with MDD, but also its clinical importance on a number of validators. Thus, while the aforementioned concerns are of critical importance, we argue that the weight of evidence highlights the importance of systematically assessing for subthreshold bipolarity. A very important challenge for the field will be to find a way to balance the need to diagnose and treat subsyndromal hypomanic features in MDD with the importance of minimizing stigma and the risk of providing inappropriate treatment. We also propose that, within the DSM, MDD with multiple episodes of subsyndromal hypomanic features, not concurrent with an MDE, will likely best be classified within the context of what is currently referred to as bipolar disorder NOS, but may eventually be called bipolar disorder not elsewhere classified (NEC) when the DSM-5 is published. What is less clear is how an individual with a single brief episode of subsyndromal hypomania should be classified. Future research is needed to address this issue.

Of note, bipolar disorder NOS, as it is currently defined in DSM-IV-TR, is quite vague, defined "as disorders with bipolar features that do not meet criteria for any specific bipolar disorder." This leaves open the possibility that symptom profiles with very different degrees of severity and impairment are given the same diagnostic label. Accordingly, we propose that if subthreshold bipolarity is diagnosed within the context of bipolar disorder NOS or NEC, it will be helpful to have a mechanism within the bipolar disorder NOS or NEC classification indicating the presence versus absence of MDD with subsyndromal hypomania. This will have two advantages. First, it will provide a more precise description for clinicians and researchers of the clinical profile of the patient and make it clear that the reason behind the bipolar NOS or NEC diagnosis is the presence of MDD with subsyndromal hypomanic features. Second, it will highlight the fact that the patient with MDD and subsyndromal hypomanic features displays a mild form of bipolarity, ideally minimizing stigma-related issues.

Treatment recommendations

Regardless of where subsyndromal hypomanic presentations are eventually classified in the DSM-5, the act of classifying them has important clinical implications. In this next section we briefly address these implications, as well as complexities, regarding the pharmacological management of patients who report subsyndromal hypomania.

Currently an individual with MDD and subsyndromal hypomania (either concurrent or not concurrent with an MDE) will likely have a treatment plan that exclusively targets his or her depressive symptoms (26). This is to be expected given that our current diagnostic criteria do not highlight the clinical importance of subsyndromal hypomania and it is likely depression for which the patient has sought treatment. However, as indicated above, subsyndromal hypomania is of clinical importance, and likely important to address in treatment. At the psychosocial level, we argue that individuals with MDD and subsyndromal hypomania may benefit from psychotherapeutic interventions that involve psychoeducation about bipolar spectrum disorders and that are designed to address hypomania. Currently, there are four psychosocial interventions for bipolar disorder that have shown promise as an adjunct to pharmacotherapy: Cognitive Behavioral Therapy (CBT) (112, 113) modified for bipolar disorder, group (114) and individual (115) psychoeducational interventions, Family-focused Treatment (FFT) (116), and Inter-personal Social Rhythm Therapy (IPSRT) (117). Growing evidence highlights the efficacy of these interventions, as indicated in a meta-analysis (118) that reported a significant reduction in relapse

rates (~40%) for individuals with bipolar disorder engaged in psychosocial treatment.

Modifying psychosocial interventions for bipolar disorder to be appropriate for addressing subsyndromal hypomania may have two important implications. First, it may help individuals manage the greater impairment associated with these presentations. As indicated, subsyndromal hypomania in and of itself is often associated with notable impairment, and helping people identify and manage these symptoms may reduce this impairment. Second, psychosocial interventions for bipolar disorder could be employed as a prophylactic treatment to reduce the risk that an individual with subsyndromal hypomania will develop a full-blown hypo/manic episode and convert to a more severe bipolar I or II diagnosis. For example, patients could be educated on the early warning signs—or prodromes—of hypo/mania and taught cognitive-behavioral strategies to counteract such manic tendencies. Drawing from psychoeducational and FFT techniques (119), patients and their family members could be educated on the types of life events shown to trigger hypo/manic episodes and the communication patterns among family systems (i.e., criticism, hostility, and/or emotional over-involvement) that have been associated with a more severe course. Drawing from IPSRT, individuals could be taught strategies for maintaining consistent social and circadian rhythms and educated on the role that disruptions to these rhythms can have on the course of bipolar disorder (120). Thus, with slight modifications, existing psychosocial interventions for bipolar disorder could have important implications for managing the course and severity of subthreshold bipolarity.

Where there appears to be a clear role for psychosocial interventions for managing subthreshold bipolarity, the pharmacological implications are more complex. One potential argument is that individuals with MDD and subsyndromal hypomania should be treated with mood-stabilizing agents, as opposed to antidepressant monotherapy. This argument is based on (i) the idea that antidepressants may be a risk factor for 'switching' into hypo/manic episodes and/or cycle acceleration among individuals with bipolar I or II disorder and (ii) the logic that mood stabilizers may serve as a prophylactic treatment for conversion to a more severe bipolar diagnosis. We disagree with this argument for two reasons. First, at the present time, there is still controversy regarding the extent to which antidepressant treatment precipitates hypo/manic episodes and/or cycle acceleration even among those

diagnosed with bipolar I or II disorder. On this topic, Kukopulos et al. (121) first described an association between antidepressant use and a new or worsening rapid-cycling course of illness in those with bipolar disorder. In a follow-up study, Altshuler and colleagues (122), using retrospective data, found that 35% of patients with bipolar disorder experienced a manic episode judged to be attributable to antidepressants. Further evidence that about one-quarter to one-third of individuals with bipolar I or II disorder may be susceptible to antidepressant-induced manias and cycle acceleration come from work by Ghaemi et al. (52, 123), Goldberg et al. (124), and Truman et al. (125). Countering these findings, however, is research by Carlson and colleagues (34) who report that switching from depression to mania was not associated with antidepressant treatment in a sample with severe bipolar disorder. Sachs and colleagues (35), using data from the multisite Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), also reported that standard antidepressant medication was not associated with increased risk of treatment-emergent affective switch. A review by Visser and colleagues (36) summarizes additional research indicating no strong evidence that antidepressant use in bipolar disorder increases risk for hypo/manic episodes.

Second, to the best of our knowledge, research has not systematically examined whether individuals with MDD and subsyndromal hypomania have a different or adverse response to antidepressant treatment as compared to individuals with MDD and no hypomanic features. Furthermore, and again to the best of our knowledge, researchers have yet to examine whether mood stabilizers or the currently popular atypical antipsychotic medications are more or less effective in managing either depression or subsyndromal hypomania features in individuals with subthreshold bipolarity, or whether they might serve as a prophylactic treatment against conversion to bipolar I or II disorder. Thus, at this time, and irrespective of the debate on the appropriateness of antidepressants for managing bipolar I or II disorders, there appears to be no clinical or scientific basis for suggesting that individuals with MDD and subsyndromal hypomania should be treated with mood-stabilizing agents or antipsychotic medications. This is particularly relevant given the heightened side effects and toxicity associated with these compounds (28–31). However, we emphasize "at this time," as this is fundamentally an empirical question, and future research is needed to examine this issue.

Summary

The research reviewed in the present report indicates that approximately 40–50% of individuals with MDD display lifetime subsyndromal hypo/manic presentations that are not necessarily concurrent with an MDE (10, 11, 19–23). Moreover, these individuals have a more severe and pernicious course compared to individuals with MDD and no hypomanic features, and more closely resemble individuals with bipolar disorder on a number of clinical validators of bipolarity (8–11, 15, 19, 22, 24, 53–56). Accordingly, a number of researchers have argued for the upcoming 5th edition of the DSM to better account for subsyndromal hypomanic features (8, 9, 11, 12, 14, 16, 18–20, 22, 25, 26). As indicated, we agree with this argument. Accounting for subsyndromal hypomania: (i) is important given the clinical significance of subsyndromal hypomania (10, 11, 19, 25), (ii) may facilitate the more accurate and timely diagnosis of syndromal bipolar spectrum disorders (11, 16), (iii) is in line with a prevention-oriented treatment model for bipolar disorder, and (iv) may generate more homogenous groups for neuroimaging and biomarker based research (9, 10, 19, 22, 55).

However, these potential benefits are balanced by a number of challenges and complexities that need to be seriously considered in modifying the diagnostic criteria to account for subthreshold bipolarity. We argue that a central challenge is minimizing the risk of over-diagnosing bipolar spectrum disorders. As indicated, the diagnosis of bipolar disorder is one that should only be made when clearly appropriate. The risk in classifying individuals with MDD and subsyndromal hypomania as having a bipolar spectrum diagnosis is that it could increase false positives in the diagnosis of the disorder. It will be important for the field to consider strategies for minimizing stigma and the risk of providing inappropriate treatment.

Finally, the implications of modifying the DSM to account for subsyndromal hypomania are unclear when it comes to the pharmacotherapy of such conditions. As indicated: (i) there is still controversy regarding the extent to which antidepressant treatment precipitates hypo/manic episodes in bipolar disorder (34–36, 52, 121–125), and (ii), to the best of our knowledge, researchers have yet to examine whether mood stabilizers are effective in managing subthreshold bipolarity. We argue that, at this point in time, there is no empirical support for the claim that individuals with MDD and subsyndromal hypomanic features should be treated with a mood stabilizer or the atypical antipsychotic medications currently being used to treat syndromal level bipolar disorders. Future research is needed to address this issue.

Acknowledgements

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