

## **DSM-5 and ICD-11 criteria for bipolar disorder: Implications for the prevalence of bipolar disorder and validity of the diagnosis - A narrative review from the ECNP bipolar disorders network**

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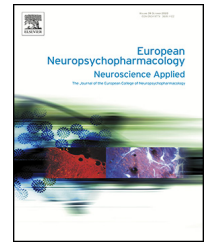
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## REVIEW

# DSM-5 and ICD-11 criteria for bipolar disorder: Implications for the prevalence of bipolar disorder and validity of the diagnosis - A narrative review from the ECNP bipolar disorders network

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## KEYWORDS

Bipolar disorder; DSM-5; ICD-11; Validity of diagnosis; Diagnostic delay; Delayed early intervention

## Abstract

This narrative review summarizes and discusses the implications of the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 and the upcoming International Classification of Diseases (ICD)-11 classification systems on the prevalence of bipolar disorder and on the validity of the DSM-5 diagnosis of bipolar disorder according to the Robin and Guze criteria of diagnostic validity. Here we review and discuss current data on the prevalence of bipolar disorder diagnosed according to DSM-5 versus DSM-IV, and data on characteristics of bipolar disorder in the two diagnostic systems in relation to extended Robin and Guze criteria: 1) clinical presentation, 2) associations with para-clinical data such as brain imaging and blood-based biomarkers, 3) delimitation from other disorders, 4) associations with family history / genetics, 5) prognosis and long-term follow-up, and 6) treatment effects. The review highlights that few studies have investigated consequences for the prevalence of the diagnosis of bipolar disorder and for the validity of the diagnosis. Findings from these studies suggest a substantial decrease in the point prevalence of a diagnosis of bipolar with DSM-5 compared with DSM-IV, ranging from 30-50%, but a smaller decrease in the prevalence during lifetime, corresponding to a 6% reduction. It is concluded that it is likely that the use of DSM-5 and ICD-11 will result in diagnostic delay and delayed early intervention in bipolar disorder. Finally, we recommend areas for future research.

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## 1. Introduction

Sine qua none, mood abnormalities characterize mood disorders. Accordingly, in DSM-IV (American Psychiatric Association, 1994) and ICD-10 (World Health Organization, 1992) elevated, expansive or irritable mood is required as the only cardinal symptom (criterion A) for a hypomanic/manic episode. In 2013 DSM-5 was published requiring increased energy or activity as a criterion A alongside mood disturbances to diagnose hypomania/mania (American Psychiatric Association, 2013). The intention with the modification of criterion A was to improve specificity of the diagnosis of hypomania/mania, and consequently of bipolar disorder (Calabrese et al., 2017). The International Classification of Diseases (ICD) will likely follow in the footsteps of the DSM definitions. The latest online released version of the ICD-11, like DSM-5, includes increased energy or activity as criterion A alongside mood abnormalities (Angst et al., 2020; Reed et al., 2019; Severus and Bauer, 2020). These changes made in the classification system have consequences both for clinical practice as well as for research. The present narrative review summarizes and discusses the implications of the DSM-5 and the upcoming ICD-11 diagnostic criteria for bipolar disorder in relation to 1) the prevalence of bipolar disorder and 2) the validity of the diagnosis of bipolar disorder according to extended Robin and Guze criteria of diagnostic validity (Robins and Guze, 1970). We would query the clinical or epidemiological usefulness of substantial changes in diagnostic criteria that are inadequately justified by reliable advances in clinical or mechanistic understanding of the disorder. Hence, this review will not address all the changes introduced in DSM-5 as compared to DSM-IV regarding affective disorders, which include creating an independent chapter for bipolar disorders, accepting antidepressant-induced manic or hypomanic switch as part of the condition under certain circumstances (Valentí et al., 2012), and re-defining mixed states as a specifier rather than an episode subtype (Pacchiarotti et al., 2020). Moreover, this review does not constitute a totally alternative proposal for the diagnostic classification of bipolar disorders (Ghaemi et al., 2008), and potential additions to forthcoming versions of DSM-5, such as the inclusion of new specifiers (predominant polarity, early onset, cognitive impairment, and others) (Pallaskorpi et al., 2019; Vieta, 2014) are not discussed.

## 2. Results

### 2.1. Background for changes from DSM-IV to DSM-5 diagnosis of bipolar disorder

Initially when Kraepelin described mania and depression, he identified three core domains - mood, cognition and motor activity - without ascribing primacy to any of these three domains (Fredskild et al., 2019). It was only later with the appearance of the DSM that mood was highlighted as the most important domain (Fredskild et al., 2019). The modification of the criterion A in DSM-5, requiring the presence of increased energy or activity for the diagnosis of mania and hypomania and, therefore, for the diagnosis of bipolar

disorders, was likely based on the data from the BRIDGE study (Angst et al., 2011), which showed that increased activity was one of the most common symptoms in individuals with bipolar disorder. Kraepelin's original description included change in motor activation as a core domain of mania and depression together with changes in mood and cognition. This seminal observation has been complemented by a few longitudinal data showing that episode forecasting highly relies on changes in energy levels as an important predictor of recurrences of episodes (Ortiz et al., 2018). Further, increased activation levels have been found to predict bipolar disorder diagnosis in a sample of first psychotic episodes (Arrasate et al., 2014). A systematic review of factor analytic studies provide fairly consistent evidence that mood and activation represent a distinct dimension of bipolar disorder and possibly of the construct structure of BD - especially BD-I - is more often characterized by an activation factor than a mood factor (Scott et al., 2017). The reasons why the DSM project originally omitted a motor criterion as part of the A criterion are unclear and a few studies have now investigated the impact of the modification to DSM-5 criterion A for the diagnosis of hypomanic/manic episodes.

### 2.2. The prevalence of bipolar disorder according to DSM-5 versus DSM-IV or ICD-10 criteria

The modified DSM-5 criteria impact the prevalence of hypomanic/manic episodes. The STEP-BD study (Machado-Vieira et al., 2017) found that applying DSM-5 criteria reduced the identified number of hypomanic/manic episodes by 48% compared with DSM-IV criterion A. Fredskild et al. (2019) found a 34% reduction in the number of individuals with bipolar disorder experiencing a hypomanic/manic episode during follow up when DSM-5 criterion A was applied. Notably the two mentioned studies included also populations with bipolar disorder with a more chronic course. An ongoing longitudinal study of 387 patients with bipolar disorder newly diagnosed with ICD-10 reported a reduction of 60% in the prevalence of hypomania/mania at the first visit and reduction of 50% in the number of subjects who experience a hypomanic/manic visit during follow-up when applying DSM-5 criteria (Fredskild et al., 2020). In the two latter studies including patients with an ICD-10 bipolar diagnosis, the probability of a patient receiving a DSM-5 diagnosis of bipolar disorder increased with the number of clinical visits (Fredskild et al., 2019, 2020). Further, empirical data show that DSM-5 capture fewer hypomanic/manic episodes with irritable mood than the DSM-IV because irritable mood is less often associated with increased energy/activity in contrast to elevated mood (Fredskild et al., 2020) and so will not meet the DSM-5 A criterion.

Differences between DSM-IV and DSM-5 are smaller regarding the lifetime prevalence of bipolar disorder. The U.K. Bipolar Disorder Research Network (BDRN) study (Gordon-Smith et al., 2017) found that up to 94% of patients with a lifetime diagnosis of DSM-IV bipolar disorder also met lifetime DSM-5 criteria for bipolar disorder. Similarly, re-analyses of data from the Zurich cohort showed a small reduction in the lifetime diagnosis of bipolar disorder with ICD-11 compared with ICD-10 (from 31 to 29 patients, corresponding to 6%) (Angst et al., 2020). These findings are intu-

itively reliable because the broad population of newly diagnosed patients are more heterogeneous by nature with fewer patients fulfilling the narrower DSM-5 criteria for bipolar disorder than among patients with more progressed and chronic disorders.

Together, studies report a substantial decrease in the number of patients that fulfill the new criteria for bipolar disorder. Patients with an irritable mood will less often be diagnosed as bipolar according to DSM-5 because patients with an irritable mood do not usually have increased energy/activity.

### 2.3. The validity of the DSM-5 diagnosis of bipolar disorder

Few data are available on the validity of the DSM-5 diagnosis of bipolar disorder, but we find it important to highlight these knowledge gaps. Validity of the DSM-5 diagnosis of bipolar disorder is described and discussed according to the Robin and Guze criteria of diagnostic validity (Robins and Guze, 1970), moderated to including also treatment effects as a sixth criterion, also concurrent with the later endophenotype concept (Gottesman and Gould, 2003) and extended criteria suggestions (Kendler and Neale, 2010). The rationale for the Robin and Guze criteria was to develop criteria distinguishing between various psychiatric disorders and aiming for a valid psychiatric classification system (Robins and Guze, 1970). Characteristics of bipolar disorder diagnosed according to DSM-5 versus DSM-IV within the sixth areas according to the extended Robin and Guze criteria (Robins and Guze, 1970) are listed below.

#### 2.3.1. Clinical presentation according to DSM-5 versus DSM-IV

Patients with bipolar disorder defined according to DSM-5 criteria compared to patients with bipolar disorder defined according to DSM-IV criteria are characterized by more severe manic episodes according to scores on the Young Mania Rating Scale (Fredskild et al., 2019, 2020), more comorbidity with obsessive-compulsive disorder (Machado-Vieira et al., 2017) and a higher annual income (Machado-Vieira et al., 2017). No differences have been found in sex (Fredskild et al., 2019, 2020; Machado-Vieira et al., 2017), age (Fredskild et al., 2019, 2020; Machado-Vieira et al., 2017), family history (Fredskild et al., 2020; Machado-Vieira et al., 2017), bipolar disorder subtype I or II (Fredskild et al., 2020; Machado-Vieira et al., 2017), number of previous hospitalizations (Fredskild et al., 2020), comorbid panic disorder, posttraumatic stress disorder, social phobia, substance use (Machado-Vieira et al., 2017), suicide attempts (Machado-Vieira et al., 2017) or use of medication (Machado-Vieira et al., 2017).

#### 2.3.2. Associations of the phenotype with para-clinical data

Para-clinical data may include blood-based data, brain imaging and Electronic Ecological Momentary Assessment (EMA), such as smartphones that are particularly useful for continuous monitoring of daily activity levels in adults (Faurholt-Jepsen et al., 2020; Stanislaus et al., 2020) and young patients with bipolar disorder (Melbye et al., 2020).

Due to its potentially higher specificity, the DSM-5 diagnosis of bipolar disorder (see point 3 below) may be associated with a higher chance of identifying para-clinical biomarkers but currently we are not aware of any published data to support this.

#### 2.3.3. Delimitation from other disorders

No data are available comparing the delimitation of bipolar disorder from schizophrenia, schizoaffective disorder, depressive disorder, personality disorders or other disorders when using the DSM-5 versus the DSM-IV or ICD-10 criteria. Nevertheless, in a sample of patients with first-episode psychosis, activation and manic dimensions according to scores on the Young Mania Rating Scale (Young et al., 1978) discriminated between patients with bipolar disorder and other psychoses (Arrasate et al., 2014). Activation predicted a bipolar diagnosis at 5 years (odds ratio = 1.383; 95% confidence interval, 1.205-1.587;  $P = 0.001$ ) as the only dimension, and showed higher levels of sensitivity (86.2%), specificity (71.7%), positive (57.8%) and negative predictive value (90.5%) than the manic dimension (Arrasate et al., 2014). It should nevertheless be noted that the manic dimension was broadly defined besides including elevated mood also included increased sexual interest and reduced sleep (Arrasate et al., 2014). As previously noted, the additional activity criterion A in DSM-5 probably increases specificity at the expense of sensitivity, but is unclear whether the DSM-5 optimize the balance of sensitivity and specificity from a clinical perspective (Calabrese et al., 2017).

#### 2.3.4. Pathogenesis - associations to family history/genetics and environmental stressors

Due to the possibly higher specificity there might likely be a higher chance with DSM-5 criteria of identifying familial loading for bipolar disorder, but the current data does not support this, finding no differences in first or second-generation family history of bipolar disorder in the DSM-5 defined group compared with the DSM-IV defined group of patients (Fredskild et al., 2020; Machado-Vieira et al., 2017).

#### 2.3.5. Prognosis - long-term follow-up

In the study including patients with newly diagnosed ICD-10 bipolar disorder (Fredskild, 2020) fewer patients, i.e. 40%, fulfilled DSM-5 criteria for bipolar disorder than in the two studies including patients with more progressed or chronic disorders, in which 52% (Machado-Vieira et al., 2017) and 66% (Fredskild et al., 2019) fulfilled DSM-5 criteria for bipolar disorder. In the two studies with lifetime diagnoses as much as 94% of patients in each study fulfilled a lifetime diagnosis of DSM-5 bipolar disorder (Angst et al., 2020; Gordon-Smith et al., 2017). These findings are intuitively reliable as the broad population of newly diagnosed patients are more heterogeneous by nature with fewer patients fulfilling the narrower DSM-5 criteria for bipolar disorder than among patients with more progressed and chronic disorders. In addition, among patients with an ICD-10 diagnosis of bipolar disorder the probability of fulfilling criteria for a DSM-5 diagnosis of bipolar disorder was shown to increase with the number of clinical visits (Fredskild et al., 2019, 2020) implying that the threshold for a DSM-5 diagnosis of bipolar disorder is reached later in the course



of the illness. A corollary of these findings is that DSM-5 might not capture less severe bipolar disorder, especially during the early course of illness. This may cause increased diagnostic delay (Baldessarini et al., 2007; Dagani et al., 2017), because patients may not fulfill criteria for bipolar disorder until later stages of the illness, resulting in delayed early intervention (Kessing, 2019; Kessing et al., 2013; Kessing et al., 2014). Several studies conducted in many countries worldwide have reported delays in DSM-IV and ICD-10 diagnosis for bipolar disorder as well as frequent misdiagnoses with other disorders. One of them conducted in 30 European countries for example indicated that, on average, a bipolar disorder patient was expected to wait for 5.7 years for a correct diagnosis from the first onset of symptoms (Morselli and Elgie, 2003). A substantial proportion of patients, constituting more than 40%, initially present with prodromal syndromes such as transient psychosis, reaction to stress/adjustment disorder or mental and behavioural disorder due to psychoactive substance use before they get an ICD-10 diagnosis of bipolar disorder later on (Kessing, 2005). Especially younger but also female patients are at increased risk of delay of the diagnosis of bipolar disorder (Kessing, 2005). If less severe bipolar disorders may be overlooked with the DSM-5 criteria one may expect even longer delays in correct diagnosis for bipolar disorder. This is a critical issue since early intervention is a key tool to prevent further complications, cognitive, and functional decline (Carvalho et al., 2020; Kessing and Andersen, 2017; Vieta, 2015; Vieta et al., 2018). Further, we have no good definition for at risk/prodromal bipolar disorder emphasizing the challenges with the DSM-5 classification system, delaying early recognition and intervention. Alternatively, the proportion of patients diagnosed with the DSM-5 categories of “other specified bipolar and related disorders” and “unspecified bipolar disorder” may increase, with the latter adding to the unspecified or “gray” diagnostic zone.

### 2.3.6. Treatment effects

Ultimately, the clinical utility of any diagnostic system is to inform the choice of right treatment. The effects of lithium and other mood stabilizing agent may be different in bipolar disorder as defined by DSM 5 vs. DSM-IV as their effects on behavioral disturbances (activation/energy levels) differ. Using the DSM-5 criteria, there might be larger treatment effects with lithium, which may show greater efficacy in bipolar disorder type I, but we have no data to support this other than the fact that lithium is more often prescribed in bipolar I disorder than in bipolar II (Grande et al., 2013; Vieta et al., 2011; Vinberg et al., 2017). In fact, core features of lithium responsive bipolar disorder do not include energy/activation among the most reliable predictors (Alda, 2015). Further, an out-of-sample lithium response prediction was not significantly informed by disorder subtype I in a recent machine learning study in a large sample of direct interview-based clinical data from lithium-treated DSM-IV bipolar disorder patients (Nunes et al., 2020).

On the other hand, as at least the short term-prevalence of mania is decreased when using DSM-5 criteria, there is a considerable number of patients which will not be given lithium or other effective anti-manic substances. Whether this relates to better or worse outcome must be shown in future. It can be argued that, as lithium has proven prophylactic

effects, it is unlikely that the care of patients suffering from mental disorders will benefit. However, there is a lack of precision in prescribing (identification of lithium responders is still predominantly based on trial and error), so refining clinical phenotypes may prove to have clinical utility (Scott et al., 2018). In addition, there might be less effects of lamotrigine and other drugs mainly prescribed for bipolar disorder type II.

## 3. Discussion

### 3.1. Implications and knowledge gaps in relation to DSM-5 defined bipolar disorder and recommendations of areas for future research

The present review highlights that implications of the DSM-5 diagnostic system are poorly known with few studies investigating consequences for the prevalence of the diagnosis of bipolar disorder and for the validity of the diagnosis according to the Robin and Guze criteria.

### 3.2. Implications

It is likely but poorly investigated so far whether the use of DSM-5 and ICD-11 will result in diagnostic delay and delayed early intervention. This would be a concern, since early detection and intervention is regarded as crucial to improve long term outcome in bipolar disorder (Carvalho et al., 2020; Kessing, 2019; Kessing and Andersen, 2017; Kessing et al., 2013; Kessing et al., 2014; Vieta, 2015; Vieta et al., 2018). The need for a common international language has fostered the convergence between DSM-5 and ICD-11, irrespective of their internal and external validity (Stein et al., 2020). Hence, conservative attitudes and fear of accusations of broadening too much the borders of the diagnosis of bipolar disorder have resulted in misinterpretations of the evidence base (the BRIDGE study does not imply that increased activity should be used as a requirement for the diagnosis (Angst, 2013)) and neglect of innovative proposals, which should be addressed in further editions of the DSM (Vieta, 2016). In fact these data more suggest increased activity as an OR than an AND addition to criterion A for the diagnosis of hypomanic/manic episodes (Angst, 2013).

### 3.3. Knowledge gaps

Can we identify the patients with bipolar disorder who meet the DSM-IV or ICD-10 diagnostic criteria but who may no longer be diagnosed with bipolar disorder using the DSM-5 criteria or whose diagnosis may be delayed until A criterion symptoms become established? Current data do not tell us which patients will be diagnosed at a later stage, but these may comprise patients with bipolar disorder, type II, “other specified bipolar and related disorders” according to DSM-5 as well as patients experiencing recurrent depressive episodes, who do not fulfill DSM-5 criteria but DSM-IV or ICD-10 for hypomania or mania. This may result in either sub-optimal guideline-driven treatments, e.g. as antidepressant

have shown small effects on depressive episodes in patients with bipolar disorder, or non-guideline-based treatments as clinicians could consider patients as having bipolar disorder, but not yet fulfilling full diagnostic criteria. The latter may result in a poorer diagnostic reliability as well as a less reliable epidemiological data. On the other hand, at least in some cases (ADHD, personality syndromes/disorders, affective dysregulation, tighter diagnostic criteria as those introduced with DSM-5 might spare patients from lifelong treatment with lithium or antipsychotics that would not help them (Severus and Bauer, 2013).

### 3.4. Areas for future research

The DSM-5 criteria for hypomania/mania requiring increased energy or activity as an additional criterion A alongside mood disturbances (American Psychiatric Association, 2013) were introduced in 2013 without compelling evidence or thorough consideration of possible implications. Subsequently the four mentioned published studies and one ongoing study (Angst et al., 2020; Fredskild et al., 2019, 2020; Gordon-Smith et al., 2017; Machado-Vieira et al., 2017) have investigated the prevalence of bipolar disorder according to DSM-5 versus DSM-IV or ICD-10 criteria, but further studies are greatly needed. Thus, further studies are needed within the sixth mentioned validation areas: 1) Clinical presentation according to DSM-5 versus DSM-IV/ICD-10, 2) Associations of the phenotype with paraclinical data such as brain imaging and blood-based data, 3) Delimitation from other disorders, specifically schizophrenia, schizoaffective disorder, depressive disorder, personality disorders, 4) Pathogenesis - associations to family history / genetics and environmental stressors, 5) Prognosis, specifically in relation to implications for diagnostic delay and early intervention as well as long-term diagnostic stability (Kessing, 2005; Kessing et al., 2015; Laursen et al., 2020), 6) Medical treatment effects of lithium and other mood stabilizers. At some point, the official classification systems will need to incorporate information from sources other than symptoms, and this may come not only from genetic, neuroimaging, and biomarker data, but also from the increasing use of digital markers, in the frame of so-called precision psychiatry (Manchia et al., 2020; Salagre et al., 2018). This however requires the identification of specific neurobiological mechanisms that define mental disorders by their pathophysiology rather than their symptoms; the jury is still out whether this will adhere to current diagnostic boundaries.

## 4. Conclusion

The review highlights that few studies have investigated consequences for the prevalence of the diagnosis of bipolar disorder and for the validity of the diagnosis. Findings from these studies suggest a substantial decrease in the point prevalence of a diagnosis of bipolar with DSM-5 compared with DSM-IV, ranging from 30-50%, but a smaller decrease in the prevalence during lifetime, corresponding to a 6% reduction. It is concluded that it is likely that the use of DSM-5 and ICD-11 will result in diagnostic delay and delayed

early intervention in bipolar disorder. Specific analyses of the reliability (Freedman et al., 2013) and validity of the DSM and ICD criteria, and an evidence-based, data driven approach to every proposed change in the criteria are urgently needed.

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### Contributors

LVK drafted the first version of the manuscript together with EV. All other authors contributed substantially during iterative subsequent revisions and accepted the final version of the manuscript.

### Conflict of interest

LVK has received consultancy fees from Lundbeck and Teva in the past three years.

AB has received research grants from Lundbeck, Otsuka Pharmaceuticals and Janssen for investigator initiated clinical trials and received speaking fees from Bristol-Myers Squibb, Astra Zeneca, Janssen, Lundbeck and Otsuka Pharmaceuticals,

BE has received consultancy fees from Sanofi Aventis in the past three years.

GMG is a NIHR Emeritus Senior Investigator and Medical Director at P1vital products, holds shares in P1vital and P1Vital products and has served as consultant, advisor or CME speaker in the last 3 years for Beckley Psytech, Clerkenwell Health, Compass pathways, Evapharma, Janssen, Lundbeck, Medscape, Novartis, P1Vital, Sage, Servier. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

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