How Does Adding the DSM-5 Criterion Increased Energy/Activity for Mania Change the Bipolar Landscape?

Anna Grunze[1], Christoph Born[2], Mette U. Fredskild[3] and Heinz Grunze[2]*

[1] Psychiatrisches Zentrum Nordbaden, Wiesloch, Germany, [2] Psychiatrie Schwäbisch Hall & PMU, Nuremberg, Germany, [3] Department of Psychiatry and Behavioral Sciences, School of Medicine, Stanford University, Palo Alto, CA, United States

According to DSM-IV, the criterion (A) for diagnosing hypomanic/manic episodes is mood change (i.e., elevated, expansive or irritable mood). Criterion (A) was redefined in DSM-5 in 2013, adding increased energy/activity in addition to mood change. This paper examines a potential change of prevalence data for bipolar I or II when adding increased energy/activity to the criterion (A) for the diagnosis of hypomania/mania. Own research suggests that the prevalence of manic/hypomanic episodes drops by at least one third when using DSM-5 criteria. Whether this has positive or negative impact on clinical practice and research still needs further evaluation.

Keywords: bipolar disorder, diagnosis, DSM-5, hypomania, mania, activity, energy

HISTORY OF DSM-5

The initial impetus for developing a classification of mental disorders in the United States was the need to collect statistical information. The first official attempt was the 1840 census, which used a single category: "idiocy/insanity." Over the years, classifications became more refined. The intention of all categorial classifications is to base psychiatric diagnoses on defined operational criteria, giving different weight to observable behavioral changes, and resulting in high inter-rater reliability. Whereas, the Diagnostic and Statistical Manual (DSM), first edition (DSM-I), published in 1952, enumerated 106 psychiatric diagnoses, the fourth edition DSM-IV, released in 1994, counts already 297. However, when examining DSM-IV, it was found that it was only able to formally diagnose <50% of treatment-seeking patients with a variety of major psychiatric disorders (1). There was an obvious large gap between what represents a mental disorder of significance in clinical practice and what DSM-IV defines as such, and this appears especially true for bipolar disorder. Ongoing discussion since the introduction of DSM-IV identified several potential pitfalls in diagnosing bipolar disorder. These shortcomings include duration criteria that were based upon some kind of consensus but not on evidence, prioritization of other comorbid disorders, e.g., substance abuse, that in many instances exclude a primary diagnosis of bipolar disorder, and arbitrary cut-offs of number of symptoms in order to fulfill diagnostic criteria of bipolar disorder. Clinical reality is that patients do not always fulfill the full house of diagnostic criteria, and there is a lack of operationalized subthreshold diagnoses (2). As a consequence, many bipolar patients end up in the residual, catch-all diagnosis "Not otherwise specified (NOS)" with a lack of evidence-based treatment guidance.

Except for the arbitrary duration criteria where especially the 4-day criterion for a hypomanic episode receives legitimate criticism, DSM-5 made an attempt to approach clinical reality, but at

the same time introduced a new hurdle that will massively impact on bipolar diagnosis, namely expanding the gate criterion (A). In his early Twentieth century description of mental disorders, Kraepelin identified three shared core features of mania and depression: disturbances of mood, cognition, and volition (3). However, no single feature was ascribed primacy. Starting with DSM-III, there was not only a partition into axis I and -II disorders, but also an assignment of primacy of some symptoms over others, and elated or irritably mood became the primary gate criterion in the DSM for diagnosing (hypo)mania, whereas volition, expressed as activity/energy, and changes in cognition were relegated to optional features. The assumed motivation behind it is that reliability and reproducibility of the diagnostic categories has been assigned priority in the DSM, even at the expense of validity, i.e., the criteria really measure what the true nature of bipolar disorder constitutes (4). However, so far nobody could set out a unique and universally valid delineation of bipolar disorder, a variety of concepts and theoretical constructs exist and none of it would satisfy full criteria for validity of a psychiatric diagnosis as formulated by Robins and Guze (5)—content validity, concurrent validity, predictive validity, and discriminant validity. To make things even more complicated, it is still up for discussion whether all affective manifestations are just dimensions of the same disorder, or discrete categories—not only Major Depressive Disorder and BD (6), but also BD-I and BD-II (7). The journey toward a descriptive, discriminant but valid diagnosis of BD based on clinical observation is still ongoing, e.g., the "Assessment, Revision and Evaluation of DSM and other Operational Criteria" (AREDOC) project (8, 9), and future revisions of DSM and ICD criteria can be expected.

DIFFERENCES OF DSM-5 COMPARED TO DSM IV-STRENGTHS AND WEAKNESSES

Whereas, there is practically no change in defining a major depressive episode from DSM-IV to DSM-5, the definitions of both manic and hypomanic episodes have been radically revised, which will impact on both bipolar I and II diagnosis. Major changes are:

- Adding a second (A) criterion besides elated or irritable mood, namely persistently increased goal-directed activity or energy. This will be the focus of the next paragraphs.
- A reduction in the number of exclusion criteria. This concerns especially substance or treatment induced and persisting mood changes, e.g., mood episodes induced by illicit drugs, but also antidepressant, or by treatments such as ECT. Persistence of syndromal criteria beyond the physiological effects of a substance or treatment modality is now considered a sufficient evidence for an underlying bipolar disorder.
- A vigorous effort to operationalize bipolar subthreshold syndromes, hitherto unified under the NOS heading. DSM-5 includes defined subthreshold syndromes, which hopefully will also stimulate research and allow a more dimensional view (10).
- Another change from DSM-IV to DSM-5 criteria constitutes the new specifier "with mixed features," which can be applied

to episodes of mania or hypomania concurrent with depressive features, as well as to episodes of depression when symptoms of (hypo)mania are present. This clearly lowers the former DSM-IV threshold for identifying mixed states (11).

However, there are still several unresolved issues intrinsic to attempts of categorial classification based on symptomatology. We mentioned already arbitrary time criteria. Another one is with symptom-overlapping co-morbidities and with differential diagnosis. For example, approximately 20% of adult patients with ADHD also have bipolar disorder while 10–20% of patients with bipolar disorder have adult ADHD (12). Categorial symptom-based diagnosis will not be able to resolve whether this is syndromal overlap or true co-morbidity.

Whereas, DSM-5 constitutes a progress compared to DSM-IV in several aspects, it also introduced a new diagnostic nuisance, the reshaping of the gate criterion (A).

THE RE-DEFINED GATE CRITERION (A)

With DSM-IV it was sufficient for a bipolar diagnosis to have either abnormally elated or irritable mood. Now either of these criteria needs a mandatory linkage with co-occurring activity/energy increase that had been promoted from a secondary "B" criterion to an "A" gate criterion. DSM-5 criterion (A) for diagnosing a manic or hypomanic episode now reads as follows:

- A distinct period of abnormally and persistently elevated, expansive, or irritable mood *and abnormally* and persistently increased goal-directed activity or energy, lasting at least 1 week *(4 consecutive days for hypomania)* and present most of the day, nearly every day (or any duration if hospitalization is necessary) (13).

CHANGES IN EPIDEMIOLOGY OF BP I AND II

There is no doubt that psychomotor agitation and increased energy are frequent in mania (present in 85–95% of mania cases (14) diagnosed according the Diagnostic and Statistical Manual, Third revised edition [DSM-IIIR (15)], and might be key to identify bipolarity, especially in bipolar II patients (16, 17). Increased activity or energy appears also to be a useful gate question to identify subthreshold hypomania and bipolarity, for example in patients with MDE. Angst and colleagues reported that an additional 6% of patients otherwise not recognized by DSM-IV standard criteria as Bipolar II could be identified in a large cohort of MDE patients when asking for increased energy/activity (18). However, the critical issue is the dogmatic specification that both criteria, mood change *and* increased activity/energy need to be present simultaneously.

Manic stupor is a well described, but rather rare condition (19, 20) and needs to be differentiated from a malignant neuroleptic syndrome (21). However, in up to 10–15% of DSM-III-R manic patients, catatonic symptoms such as inactivity punctuated by sudden acts of impulsivity or mutism alternating with explosive

laughter, has been described as the eye-catching symptom (22–24). With the postulate of increased activity as an enduring symptom, these patients will fall through the cracks. But DSM-5 might not only miss out these less frequent manifestations of (hypo)mania, there is also substantial evidence that many more patients with a DSM-IV episode of (hypo)mania will not be identified with DSM-5. Already Kraepelin (25), and more recently Malhi et al. (26) in their ACE model (Activation, Cognition, Emotion) pointed out the changing primacy and desynchronization of fluctuations between these three domains, e.g., when emotions are high, cognition, and activation might be still within or below the normal range.

Using data from the Systematic Treatment Enhancement Program for Bipolar Disorder study, Machado-Vieira and colleagues analyzed point prevalence data collected at initial visit to assess the diagnostic validity of this new DSM-5 criterion (27). Of the 310 patients who met DSM-IV criteria for a manic or hypomanic episode, only 52% also met the stricter DSM-5 criteria including increased activity/energy. Comparing DSM-IV only and DSM-5 manic or hypomanic patients, the DSM-5 diagnosed (hypo)manic patients had significantly less DSM-IV-diagnosed major depressive disorder in the past whereas other variables showed no differences. At one year-follow-up, no differences in clinical rating scales [Global Assessment of Functioning (GAF), Clinical Global Impressions (CGI)] were observed between those who met DSM-5 criteria at baseline and those who did not. Their findings confirm that including increased activity or energy as part of DSM-5 criterion (A) decreases the prevalence of manic and hypomanic episodes but appear not to affect longitudinal clinical outcomes.

The finding of the STEP-BD study that we face 50% reduction of (hypo)mania diagnoses with DSM-5 is almost identical with a more recent study using regular electronic patient self-ratings. One hundred-seventeen Patients with Bipolar disorder evaluated mood, irritability and activity level daily for six to nine months via a smartphone-based system. During follow-up, participants reported elevated mood 8.0% of the time, irritability 28.4% of the time, and increased activity 20.6% of the time. Co-occurring elevated/irritable mood and activity were predominant 12% of the time for four consecutive days (the duration criterion for a hypomanic episode), compared to 24% of the time with elevated/irritable mood without concurrent increase of activity (28).

Our own analysis (29) is based on a *post-hoc* analysis of prospectively collected data from the Bipolar Collaborative Network (BCN) between 1995 and 2002 that includes 907 DSM-IV-TR–diagnosed bipolar outpatients with 14,306 visits. The full methodology of the BCN Network (formerly Stanley Foundation Bipolar Network, SFBN) has been described elsewhere (30, 31). As part of the routine assessment, the Young Mania Rating Scale (YMRS) (32) was administered at monthly intervals and used to check DSM-IV and DSM-5 criterion (A) fulfillment during a (hypo)manic visit. The clinician's rating on the distinct items 1, 2, and 5 on the YMRS allows for an evaluation of the separate symptoms: mood, energy or activity, and irritability, respectively. A score on item 1 (mood) ≥ 2 is considered reflective of objectively "elevated mood," item 2 (energy/activity) ≥ 2 is

considered objectively "increased energy or activity," and item 5 (irritability) ≥ 4 is considered objectively "increased irritability." By this, study definition of fulfilling DSM-IV criterion (A) for a hypomanic/manic visit was defined as item $1 \geq 2$ and/or item $5 \geq 4$. Study definition of DSM-5 criterion (A) for a hypomanic/manic visit, however, was defined as (item $1 \geq 2$ and/or item $5 \geq 4$) *and* item $2 \geq 2$. Applying DSM-5 criterion (A) resulted in a reduction of the number of patients experiencing a hypomanic/manic visit by 34%, compared to DSM-IV. When a visit fulfilled DSM-5 criterion (A), elevated levels of all other mania symptoms were also more likely in comparison to visits fulfilling DSM-IV criterion (A) only. As also shown in the STEP-BD study (27) and the smart phone- based study by Faurholt-Jepsen et al. (28) association between individual symptoms was strongest with mood elevation and energy or activity.

A question still unanswered is the diagnostic fate of those patients failing now the gate criterion "A" of increased energy/activity. Strictly speaking, they would not qualify for any genuine bipolar diagnosis except the catch-all "Unspecified Bipolar and related disorder) (DSM-5 296.80)- a nuisance every taxonomist would like to eliminate instead of inflating it.

CONSEQUENCES TO ICD 11

Historically, DSM-I was succeeding by the International Classification of Diseases (ICD), sixth edition (ICD-6) published in 1949, but in the meantime revisions of DSM are ahead of ICD and, by this, setting the trend. With the aim to harmonize DSM and ICD, the upcoming ICD-11 (33) also asks for the additional requirement of an increase in activity, besides mood elation or irritability, for the diagnosis of hypo/mania. Thus, it is fair to assume that the impact of elevating the gate criterion will be not different in countries using ICD 11 for coding Bipolar disorder.

DISCUSSION

The important question is whether this change of the gate criterion (A) will distort identification of Bipolar patients not at the time of interview (point prevalence) but in the long run (life time prevalence. The smart phone-based study by Faurholt-Jepsen and colleagues used daily ratings, and after one year half of the patients with mood elation still had no rating of concomitant activation/energy increase. On the other hand, the UK Bipolar Disorder Research Network (BDRN) study (34) found that 94 and 93% of their cases with a lifetime DSM-IV diagnosis of bipolar -I and - II disorder, respectively, experienced overactivity in the context of at least one manic or hypomanic episode and therefore would meet lifetime DSM-5 criteria for a bipolar disorder diagnosis. As a spin-off, these findings also underline the validity of increased activity/energy *per se* for diagnosing bipolar II disorder.

For the reliability of the bipolar diagnosis, and by this inter-rater and re-test concordance, change of the A criterion might have opposing consequences. On one hand, narrowing the number of "positives" by adding an additional inclusion criterion might result in a more homogenous sample easier to identify by

different raters. On the other hand, different raters might judge differently what constitutes "goal- directed activity," and levels of activity are likely to fluctuate reducing test- retest accordance.

Long-term consequences for the course of illness from meeting the increased activity/energy criterion during (hypo)manic episodes appear negligible. Comparing adolescent with bipolar disorder who had increased activity during their worst life-time episode with those without found no significant group differences on clinical/psychosocial functioning outcomes after 12.5 years (35).

Literature describes both over- and underdiagnosis of bipolar disorder (36–38) largely depending on mental health infrastructure, habits, and whether diagnosis is made according to patient reports or formalized interviews and criteria. But what is the real need to add up symptoms for the gate criterion A to correctly identify bipolar patients? The BRIDGE Study examining 5,635 patients seeking treatment for major depressive episodes (diagnosed according to DSM IV-TR) demonstrated clearly that increased activity is a primary symptom of bipolar disorder, but also that any of the three primary criteria (changes in mood, increased energy or activity, and irritability) has diagnostic validity on its own, according to the criteria established by Robins and Guze (5) and Angst et al. (18). In addition, an increase in energy might be a more sensitive warning sign of an upcoming new manic episode than mood or sleep ratings (39). These findings are in line with a recent review of latent factor models studies in manic patients by Martino and colleagues (40). It confirmed the multidimensional nature of mania. Hyperactivity, increased speech, and thought disorder appeared as core features of the clinical construct whereas the mood flavor could be heterogeneous. Recent developments as machine learning might help to improve accuracy of diagnosis, not only to distinguish between BD and Schizophrenia as major mental disorders (41), but also to differentiate abnormally elated mood from happiness in a person with a history of depression (42). If the scientific field decides to stick to increased goal-directed activity/energy as a mandatory criterion for BD, development of a similar ML algorithm wouldn't go amiss and increase diagnostic validity.

Taken together, adding activity/energy as mandatory (A) criterion seems to have a large impact on point prevalence— and by this probably initial diagnosis of bipolar disorder. The important role of increased activity energy is clear from previous research that explored the factor structure of the criteria for mania, and found that increased energy has the highest factor loading on mania severity in adults with BD (35). Increased energy is a core symptom of mania, and should be more highly considered than changes in mood when diagnosing mania in adults (43). Factor analytic studies also provide fairly consistent evidence that mood and activation represent distinct dimensions of bipolar disorder (44). Furthermore, increased activity is amendable to objective measurement, e.g., by actigraph (45), smartphone-based activity measurements (46), or in a human Behavioral Pattern Monitor (hBPM) study (47). The problem with the DSM-5 criterion (A) definition is the "and" instead of an "or" unnecessarily elevating the threshold for a (hypo)mania diagnosis in clinical practice.

With diverging findings, it remains to some degree unclear whether this new criterion (A) definition will not only change point prevalence but will also change lifetime diagnosis of Bipolar disorder, and further research is needed. With the DSM-5 conditioned reduction of point prevalence of mania and hypomania it also remains unclear whether this will change results of previous treatment research, and by this, guidelines and treatment habits in clinical practice. Theoretically, it might, e.g., lead to a preferential use of antidepressant monotherapy instead of mood stabilizers as the depressive episodes still stand as they were during the reign of DSM-IV, whereas (hypo)mania remains undiagnosed. Whether this will lead to inferior outcomes has to be awaited and constitutes still a matter of controversy, especially in bipolar II patients (48, 49). For research, narrowing and restricting the criteria for bipolar disorder might be advantageous as it might result in more homogenous well-defined study populations (50). However, with new criteria we also might need to revise our standard rating instruments to fit their purpose (51). Once there is a consensus what the very nature of BD constitutes, computational psychiatry and advanced machine learning might help to increase accuracy of BD diagnosis.

AUTHOR CONTRIBUTIONS

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