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Disclosure:

No potential conflicts of interest relevant to this article were reported.

Abstract

Current psychiatric disorders classifications are based exclusively on categorical models, which were designed to increase the reliability of the diagnosis. However, this system has some limitations and various psychiatric disorders may be classified using a dimensional approach, which is more appropriate when no clear boundaries exist between entities or when examining various features on a continuum. Thus, the forthcoming DSM-V appears to undertake a hybrid approach, by including categorical models associated with dimensions. We aimed to review examples of dimensions or symptom clusters, associated with a categorical approach, which could be useful in refining bipolar disorder classification. We selected predominant polarity, psychotic symptoms, inhibition/activation behavioral level and emotional reactivity to define mood episodes, impulsivity/suicidality/substance misuse and cognitive impairment. The selection was based on the fact that these dimensions or symptom clusters are currently discussed to be implemented in the DSM-V and/or may orientate towards the choice of specific treatments and represent more homogeneous and thus more appropriate sub-groups for research purpose. In the future, there will be a need to identify biomarkers that can definitively validate the use of these criteria.

Introduction

Current classifications of psychiatric disorders are based on categorical models and were previously created to increase the reliability of diagnoses and to facilitate communication between clinicians and researchers (1, 2). These classifications can be used across various cultures and allow a reliable comparison of clinical definitions used in studies coming from all around the world.

However, these systems of classification fail on several fronts. These can be summarized as follows.

(i) Clinicians are often frustrated by the reductionism and the rigidity of these classifications.

(ii) Some patients cannot be classified under a particular category and are then classified vaguely under a "not-otherwise-specified" category in the DSM-IV (1).

(iii) This system generates excessive diagnostic co-occurrence, in particular when considering comorbidities with anxiety and substance misuse, leading to the merging of different diagnoses.

(iv) This categorical model has already proven its limitations, i.e. the creation of intermediate categories due to non-resolvable boundary debates. The most illustrative examples are schizoaffective disorders, but also the so-called controversial mixed states.

(v) This categorical model is not based on etiology and there is no biomarker to demonstrate the validity of its categories.

(vi) There is no strict correspondence between categories and guidelines for pharmacological treatment, with the exception for rapid cycling (3). Relations between clinical entities and differential responses to treatments require a better understanding.

Conversely, there are many advantages using a dimensional approach. First, it is probably more suitable to place patients along a gradient of symptom intensity, instead of artificially categorizing them for some entities based on arbitrary cut-offs. For example, misclassifications are likely to occur if comparing patients with and without rapid cycling. In the non rapid cycling subgroup, bipolar patients with one episode occurring every five years, for example, will have the same weight as patients with three major episodes per year. By contrast, in the rapid cycling subgroup, patients with four major episodes per year will have the same weight as patients with ultra-rapid cycling or ultradian cycling. Similarly, Bauer et al. stated 'a dimensional approach to episode frequency, as a continuum between the extremes of no cycling and continuous cycling, may be more appropriate and it provides a framework to include ultra-rapid and ultradian cycling (…) the evidence does not exist today to refine the DSM-IV definition in a less arbitrary manner' (4). Instead of a rigid definition, each patient can be placed along a continuous gradient of the density of episodes per year, representing an illustrative example of a possible dimensional symptomatology approach. This approach is particular relevant when defining entities with no clear boundaries. It can also provide relevant information, such as the severity of impairment, chronicity or outcome.

In spite of these advantages, the forthcoming DSM-V appears to undertake a hybrid approach for future nomenclatures, including categorical classification associated with dimensions, thus navigating between the two approaches. Indeed, the ease of DSM-IV use clinically is a strong argument for the continuation of categorical definitions. Moreover, basic science has yet to reach the level where it provides explanations for etiological factors in order to reshape the nosography entirely. Adding dimensions and/or clusters of symptoms might make this tool

more flexible, and might lead to diagnoses that are closer to the pathophysiology of the disorders, hence making it more indicative of the treatments required.

We reviewed several dimensions or symptom clusters, associated with a categorical approach that could be useful in refining bipolar disorders classifications. These dimensions were chosen since they have been discussed to be implemented in the DSM-V and/or may be used as predictive indicators for response to specific treatments and/or help identifying more homogeneous sub-groups in order to study potential mechanisms involved in the pathophysiology. For each dimension, we will highlight how it can be a potential indicator of response to specific treatment and how it can be useful for research.

Predominant polarity

Recent studies have suggested that predominant polarity in bipolar disorder type I might be associated with various patterns of clinical expression, course and comorbidities (5, 6••). Most bipolar type I individuals exhibit a depressive predominant polarity. A depressive predominant polarity correlates with more suicide attempts and more episodes, whereas a manic predominant polarity correlates with more hospitalization (5, 7, 8). The predominant polarity correlates with the polarity at onset of the disease (9••). Given these arguments, predominant polarity has been suggested for inclusion in future classifications, as a course specifier for bipolar disorders (9••).

This could be of a major importance in terms of preventive strategies, clinical management and drug prescription (5). As predominant polarity is associated with onset polarity, the drug strategy may be anticipated and defined very early during the course of the disorder and the

polarity at onset may help to select the most effective treatments. Indeed, drug strategies might be required to be adapted to the most frequently observed polarity. Three drugs have a significant effect in preventing manic relapses (lithium, olanzapine and aripiprazole) and three, in preventing depressive symptoms (valproate, lamotrigine and imipramine) (10). Their choice may thus be guided by a close examination of the predominant polarity. The serum levels of mood regulators might also require some adjustment according to the polarity patterns. Lithium levels at the lower range of the therapeutic range may be sufficient for the optimal prevention of depressive episodes, whereas higher lithium levels within this range may be required for optimal protection against manic/mixed episodes (11, 12). As some comorbidities may be associated with the polarity (onset and/or predominant), prevention strategies could be anticipated, particularly in terms of suicidal behaviour or substance misuse. This suggests that future classifications of bipolar disorders should include predominant polarity as relevant specifier, as suggested by some researchers (6••, 9••).

Lifetime psychotic symptoms

Psychotic symptoms are excluded from the current definitions of bipolar disorders and their presence is only considered as a criterion for severity during current/most recent episodes. No specification exists for defining subgroups of lifetime psychotic and non-psychotic bipolar patients. Psychotic symptoms exist in 50% of bipolar patients (13); thus this condition is not rare. However, clinical presentation is heterogeneous with some bipolar patients presenting only one episode with psychotic symptoms (mainly the first episode), whereas others experience psychotic features in most episodes. Occurrence of psychotic symptoms according to the polarity of episodes may be crucial, as psychotic features are much less predictive of future psychosis when they occur within a manic syndrome than when they occur within a

depressive syndrome (14). Thus, the patient may be more or less prone to delusions, which can be assessed using dimensional tools and is thought to be shared between some bipolar patients and schizophrenic patients (15).

This delusion proneness is of a major clinical importance, as psychotic symptoms are thought to be strongly linked to a diagnosis of schizophrenia for many clinicians. As a consequence, bipolar disorders with psychotic symptoms (in particular during manic episodes and/or with mood-incongruent characteristics), are often routinely diagnosed clinically as schizoaffective disorders or as schizophrenia (16).

From a therapeutic point of view, applications with these dimensions remain putative. Indeed, there is no clear evidence that psychotic bipolar disorders respond better to certain maintenance therapies. Atypical antipsychotics may intuitively be more appropriate. From a research point of view, psychotic symptoms could shed some light on some common genetic and/or environmental factors between bipolar disorders and schizophrenia (17, 18).

Inhibition/activation behavioral level and emotional reactivity as dimensions to characterize mood episodes with mixed features

In addition to the classic manic and depressive states, Kraepelin described, for manic depressive illness, six mixed states; these range from agitated depressive states, to manic syndromes with depressive affects (19). These different states are no longer part of current classifications and only three classifications for bipolar mood episodes remain: depressive, manic and mixed, plus a hypomanic state, which is defined with the same characteristics as manic states, except the level of severity and functioning impairment.

Recent studies highlight a wide diversity of mood states in which both manic and depressive symptoms may co-exist within the same episode. Mixed depressive states have been

described, first by Koukopoulos (20) but also by Benazzi (21) (i.e. “depressive mixed states” defined by the presence of three manic symptoms during bipolar depressive episodes). Mixed depressive states are frequently observed, as the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) has shown that two-thirds of bipolar depressed patients had concomitant manic symptoms (22). Conversely, “Mixed hypomania” has also been described (i.e. episodes simultaneously presenting hypomanic and depressive features) (23).

However, the optimal number of symptoms belonging to each polarity when defining a “mixed state” remains unclear and there is much confusion over a clear definition of what should be called a mixed state. A dimensional approach, based on quantitative attributes rather than the assignment to categories, appears to be more appropriate for describing this phenomenon, which is distributed continuously without clear boundaries (24).

For this purpose, we built and validated the MATHYS (Multidimensional Assessment of Thymic States) scale to define mood states based on a dimensional approach assessing symptoms on their quantitative aspects (acceleration/retardation; increase/decrease) (25•). This scale can be used to assess all types of bipolar mood episodes and provide a total score quantifying an overall level of behavioral inhibition/activation and a score of emotional reactivity (hypo versus hyper, characterizing the intensity of emotions), thus replacing the classic euphoric/depressive mood dichotomy. Using this scale among bipolar patients presenting various mood states, we found a continuum ranging from inhibition to activation (respectively from major depressive episodes without manic symptoms to manic states, through depression with manic symptoms and mixed states), with a gradual increase in the intensity of the activation (26). Regarding emotional reactivity, this approach allows a clear separation of two sub-forms of depression: the first is characterized by overall behavioral inhibition and emotional hyporeactivity, and the second is defined by mild activation associated with emotional hyperreactivity.

This may have some implications on treatment choice. Guidelines for the pharmacological treatment of depressive states currently recommend several types of treatment, including mood stabilizers, atypical antipsychotics and antidepressants (27, 28). The choice of whether to use an antidepressant or an atypical antipsychotic in bipolar depression would be facilitated by distinguishing inhibited/emotional hyporeactive depression from activated/emotional hyperreactive depression. Using this characterization, this last type of depression appears to belong to a broad spectrum of mixed states and patients with this form of depression may respond better to mood stabilizers or antipsychotics (4). Concerning research, such dimensional approach could reduce the heterogeneity of patients included in studies on depression.

Impulsivity, suicidality and substance misuse

Impulsivity represents a criterion for some DSM-IV psychiatric diagnoses, including manic episodes, attention deficit with hyperactivity disorder, impulse dyscontrol disorders, and antisocial or borderline personality disorders. Impulsivity has been the focus of a major interest in bipolar disorders, as it was supposed to increase behavioural problems associated with mood lability (29) and to influence the clinical expression of the disorder (30•), with more relapses or poor prognosis, higher rates of mortality and generate greater complexity in the management of the disorder (13).

Available findings suggest that impulsivity is a trait component of bipolar disorders, might represent a core feature of the disorder (31-33) since it has been shown elevated scores among euthymic bipolar patients compared to controls. However, impulsivity appears to be diversely related to depressive or manic episodes, with increased motor impulsivity thought to be specific to manic episodes and non-planning impulsivity, to major depressive episodes.

Impulsivity may influence the clinical expression and the pattern of comorbities in bipolar disorders (30•), particularly in terms of suicidal behaviour and substance misuse. Several studies have investigated the relationship between trait-impulsivity and suicide attempt among bipolar disorder patients (30•). Most studies are in favor of an association between trait-impulsivity and suicidal attempts, but this association is yet to achieve consensus (34). Two studies have demonstrated that trait impulsivity increases cumulatively in cases of bipolar disorder and substance misuse (35, 36). Bipolar and substance-use disorders are thought to share common mechanisms, including impulsivity, poor modulation of motivation and responses to rewarding stimuli, and susceptibility to behavioral sensitization. This may be one way of explaining why these conditions are often comorbid.

Impulsivity, suicidality and substance misuse are important dimensions/clusters of symptoms, as they have a great impact on the outcome of bipolar disorders, require active prevention and require aggressive management. The therapeutic implications require further clarification. However, data from meta-analyses consistently indicated marked reductions in suicidal behavior and mortality during long-term treatment with lithium salts in bipolar disorder patients (37). Thus, high levels of impulsivity might orientate the treatment choice, possibly with lithium salts as first line choice (38).

Cognitive impairment

Several studies have shown that bipolar patients exhibit cognitive disturbances even during euthymic periods. The most remarkable impairments in adult euthymic bipolar patients cut across the domains of attention/processing speed, verbal learning/memory, and executive functions, including cognitive flexibility, inhibitory control, working memory and verbal

fluency (39•). The impairment is less severe than in schizophrenia and it is not clear if it concerns all patients or only a group of them.

A subgroup of patients with pronounced cognitive impairment should be delineated. Indeed, the outcome and global level of functioning of patients appear to be linked to the severity of these cognitive disturbances (40). Moreover, some authors have suggested the existence of a subgroup that is at a particular risk of progressing towards dementia (bipolar type VI) (41).

The usefulness of this neurocognitive symptoms cluster on therapeutic choice remains further clarification. It has been suggested that short-term lithium therapy has negative effects on cognition (42). However, meta-analyses have shown that lithium treatment appears to only have a few minor negative effects on cognition (43); they also show that continued treatment with lithium is associated with a reduced rate of dementia in patients with bipolar disorders, in contrast to continued treatment with anticonvulsants, antidepressants, or antipsychotics (44). The role of cognitive remediation in treating bipolar disorders with cognitive impairment remains to be defined, although with preliminary promising results (45). As proposed elsewhere, 'convergent data indicate a compelling need for formal assessment of cognition in patients with bipolar disorder, and for researchers and clinicians alike to consider the necessity for treatment specific to cognition in this population'. The place of specific pharmacotherapy to enhance cognitive functions among bipolar patients remains further investigation, because of major importance to improve global level of functioning (46).

Future direction

The concept of bipolar spectrum disorders has progressively expanded to reflect the heterogeneity of the clinical presentation, course and comorbid patterns. However, an increasing number of bipolar disorder subtypes (type I to VI with some intermediates such as

II½ and so on) are described using a categorical approach. This attempt to better define the disorder in patients who cannot be strictly classified as types I or II and are therefore likely to be classified as 'not otherwise specified' has led to a significant increase in sub-categories and greater confusion, while its usefulness in treatment management and prevention remains questionable (47).

In this article, we reviewed how some dimensions the clinical description could be used to define more homogeneous sub-groups in bipolar disorders and we discussed how these dimensions could help clinicians and managing this heterogeneous and complex disorder. All of these dimensions or sub-groups are thought (currently or in the future) to be useful in terms of treatment management but also in terms of research, because they may be more suitable to identify the underlying mechanisms.

Where is the DSM-V going (48)? Various work groups have been responsible for addressing some revisions based on new criteria and the addition of relevant dimensions or specifiers. Some reflections seem to have already led to concrete proposals. Considering the issue of mixed states, the proposal is to remove the category of mixed states and to replace it with a mixed features specifier that applies to manic, hypomanic and depressive episodes. It should characterize episodes in which subthreshold symptoms from the opposing pole are present during a complete mood episode. (i.e. depressive symptoms during hypo/manic episodes and vice versa). This specifier might be also used to characterize a single major depressive disorder episode or recurrent depressives episodes (49••). If patients suffering from depressive episodes with mixed features are shown to respond better to mood stabilizers, this could crucially lead to significant changes in terms of treatment (3).

Others proposals for specifiers or subgroups require further analysis. Although suggested as a specifier (6••, 9••), predominant polarity does not appear likely to be included in the future DSM-V, despite its potential impact in terms of treatment regimens. A DSM-V psychotic disorders work group is testing a dimensional approach for key aspects that will be used across all diagnostic categories in the psychoses section of the DSM-V; these will probably overlap with dimensions in the mood disorders section (50). There is also a proposal for developing new criteria for schizoaffective disorder, to improve reliability and face validity (49••). A suicide risk dimension is planned for use in various disorders (49••). The DSM-V committee is also proposing a clinical anxiety scale that can be implemented for the systematic assessment of all mood disorder categories. Anxious features can represent a component for mood disorders, due to their high prevalence during mood episodes but cannot be considered as a strict comorbidity, mostly because of the absence of the criterion 'duration' (49••).

Moving to a DSM-V which is a mixture of categories and dimensions will certainly help to better understand the complexity of bipolar disorders without significantly increasing exclusive categories, but with the addition of few specifiers (for example predominant polarity) and/or trans-nosographical dimensions (suicide risk, anxiety and psychosis dimension). Although very promising, this new way of classifying bipolar disorders will undoubtedly raise some methodological considerations. First, assessment tools have to be designed to capture the dimensions, using short screening methods or validated instruments, which can be used reliability across various cultures. Second, new categories or proposed dimensions are required to demonstrate relevance in their ability to indicate different patterns of response to treatment (pharmacological and/or non pharmacological). This requires systematic and formal investigation. These new ways of classifying bipolar disorders should

help to improve the management of patients, leading to the development of new algorithms for better use of existing therapeutic strategies, which take into account the heterogeneity of the disease. Otherwise, such redefinition will remain purely descriptive, meaningless and without practical application for clinicians and patients. Third, there is also a clear need to identify biomarkers that validate these refined criteria in bipolar disorders. We can expect neuropsychological tests, genotyping, and neuroimagery to provide these validators overt the next few decades. Finally, to be considered markers for the disorder or outcome, longitudinal assessment of the stability of categories and dimensions should be investigated, as stable characteristics are probably more useful when defining long-term prevention and treatment strategies.

Conclusions

Current classic nosographical classifications have stimulated a running debate on dichotomy/continuum or overlap/comorbidity between several apparently distinct clinical entities, in which bipolar/unipolar disorders (51, 52•) and bipolar disorder/schizophrenia (50) are the main subjects of controversy. Moving to hybrid system classifications that conserve strict categorical disorders, but which are less rigid through the use of specifiers and/or dimensions, may provide a new look to modern psychiatry. This in turn would provide a greater degree of freedom to clinicians, would better capture complex phenomenology and would provide applications for prevention and treatment management that are more practical. Not only useful to clinicians and patients, this system could also be applied to research, as most dimensions (that will be shared or overlap between clinical entities) are supposed to be underpinned by specific genetic, environmental or neurodevelopmental risk factors. These risk factors are more likely to be identified if the clinical entities are not studied separately but

together with a focus on their shared characteristics. In research, these dimensions and/or clusters of symptoms may also be considered as intermediate traits that are closer to the underlying physiopathological process, thus favoring their identification.

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(25•)
This clinical study validates the MATHYS as a useful quantitative tool to distinguish bipolar patients presenting various mood states.
(9••)
This review presents arguments to remove, reconceptualize, modify and add bipolar episode and course specifiers in DSM-V, in particular psychosis and predominant polarity.
(30•)
This review suggests that impulsivity is not only state-related, but also a trait component of bipolar disorder, which could represent a core feature of the illness.
(39•)
This review provides an overview of selected aspects of neurocognition in bipolar disorder with a focus on the relative contributions of medication, as well as medical and psychiatric comorbid conditions, to cognitive dysfunction and provides recommendations for future research in this field.
(52•)
This article reviews 86 studies of the literature evaluating outcomes resulting from the expansion of the bipolar disorder diagnostic categories and fails to identify any randomized controlled trials or prospective cohort studies evaluating modified diagnostic or therapeutic practices.
(49••)
The DSM-V development website of the American Psychiatric Association proposes preliminary draft revisions of the current diagnostic criteria for psychiatric disorders.
(6••)
The International Society for Bipolar Disorders Task Force reports consensus on the definition of predominant polarity and other nomenclature (response, remission, recovery, relapse, recurrence, subsyndromal states, switch, and functional outcome) in order to stimulate research on the validity of proposed concepts.