

New Concept, Definition and Clinic of Mixed Unit in Bipolar Disorder

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Abstract

Objective: To explore a clinical and practical method for diagnosing and evaluating mixed states of bipolar disorder.

Method: Starting from a theoretical perspective, to analyze the forms of expression of mixed states, propose a concept that is different from mixed episode and mixed features to make up for the lack of understanding of mixed states, and this concept is the mixed unit.

Result: The mixed unit is a concept different from mixed episodes and mixed features. It focuses on the mutual modification and influence of depressive and manic symptoms, not only losing the original color of depressive and manic symptoms, but also producing some new symptoms. This, together with mixed episodes and mixed features, constitutes a comprehensive understanding of the mixed state.

Conclusion: The proposal of the mixed unit has completed the understanding of the mixed state of bipolar disorder. The mixed state is a complex phenomenon. The proposal of the mixed unit concept may be beneficial for a comprehensive understanding of the mixed state. The three together form the complete image of the mixed state.

Keywords: Mixed state, Mixed episode, Mixed feature, Mixed unit, Bipolar disorder

Background

Mixed affective states, defined as the coexistence of depressive and manic symptoms, are complex presentations of manic-depressive illness. In ICD10 and DSM-4, the mixed state of bipolar disorder is defined as a mixed episode, what is clear is that both manic and depressive episodes exist, are equally severe, and each meets the criteria for depression and manic illness [1]. Clearly, these criteria are too stringent [2].

Such episodes occur in less than 5% of cases [3], leaving many episodes undiagnosed and delaying the right treatment that represent a challenge for clinicians at the levels of diagnosis, classification, and pharmacological treatment [1]. The evidence shows that patients with bipolar disorder who have manic/hypomanic or depressive episodes with mixed features tend to have a more severe form of bipolar disorder along with a worse course of illness and higher rates of comorbid conditions than those with non-mixed presentations.

Perhaps recognizing the diagnostic limitations of mixed episodes, DSM-5 changed the diagnostic model, Defining mixed states as “with mixed feature”. In the updated Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5), the definition of “mixed episode” has been removed, and subthreshold non-overlapping symptoms of the opposite pole are captured using a “with mixed features” specifier applied to manic, hypomanic, and major depressive episodes. However, the list of symptoms proposed in the DSM-5 specifier has been widely criticized, because it includes typical manic symptoms (such as elevated mood and grandiosity) that are rare among patients with mixed depression, while excluding symptoms (such as irritability, psychomotor agitation, and distractibility) that are frequently reported in these patients [1,4]. The mixed features at least prove lower ratio in the diagnosis and recognition of bipolar mixed state [4]. Thus, according to the DSM-5 standard, about a quarter of the mixed state can be recognized, which is increased compared to 5% recognition rate by DSM-IV and ICD-10 [5]. Approximately 40% of patients with bipolar disorder experience mixed episodes had been diagnosed and recognized [6]. However, because this diagnostic model separates two symptoms of opposite symptoms, it also leaves a considerable number of mixed state undiagnosed and delays treatment [1,3].

Depressive and manic symptoms are opposite pairs of symptoms. When they are concentrated together, they will affect and modify mutually. This influence and modification will produce some new symptoms, and also make the original depression and mania lose their original color, thus forming a special group of symptoms [7,8]. This symptom group is not the superposition of depression and mania, but a new group of symptoms. We call it mixed unit [7].

The mixed state of bipolar disorder has at least the following three manifestations. One of them is the mixed episode described in ICD-10 and DSM-IV, which requires both manic and depressive episodes to meet the criteria and last for at least one week. Therefore, such criteria are very strict. The second is that DSM-5 proposed in 2013 to replace the mixed episode subtypes in DSM-IV-TR with mixed features. However, it is incomprehensible to put manic and depressive symptoms of opposite polarity together [3], which poses challenges in diagnosis to clinical psychiatrists. However when manic symptoms and depressive symptoms are intertwined, the “collision” of manic and depressive episodes can produce “new” symptoms, such as irritability, agitation, impulsive self-injury, psychotic symptoms, hostility, and distractibility [7,8]. Obviously, these symptoms are highly disproportionate to the “mixed features” described in DSM-5, but they are indeed a common mixed state in clinical practice, which is different from the previous mixed episodes and mixed features and is therefore called a mixed unit [7].

Although mixed episodes are strictly defined in the ICD-10 and DSM-IV, they do exist, even if they are rare or even rare.

Similarly, although the DSM-5 wrongly superimposes two opposing conditions, manic and depressive, making these mixed features largely inoperable in clinical diagnosis. It is therefore necessary to correctly understand and recognize the mutual modification and decoration of the two opposite symptoms of mania and depression combined. This causes new symptoms, such as irritability, hyperactivity, distractibility, impulsivity, agitation, suicide, self-injury, and psychotic symptoms which generate a new symptom cluster. These symptoms are not belong to manic symptoms or depressive symptoms. It can be seen that the introduction of the concept of mixed units is scientific, academically valuable, timely, and necessary.

Mixed episodes, mixed features, and mixed units reflect the understanding of the mixed state of bipolar disorder in different eras. These three different types also jointly constitute the whole of the mixed state of bipolar disorder. Among them, the mixed unit is the latest concept proposed and the newest concept.

Clinical Symptomatology

The DSM-5 idea of mixed features may have originated from an earlier concept of mixed depression proposed by Benazzi [9,10]. An early definition of mixed depression is when the background of depression is accompanied by three or more mania symptoms. But the DSM-5 definition of manic symptoms in mixed feature is very typical, and apparently its sensitivity for diagnosing bipolar disorder is 5.1%, but its specificity is 100%, suggesting DSM-5-defined mixed features were too restrictive to discriminate bipolar disorder from major depressive disorder (MDD) in patients with depression compared with Benazzi’s definition [9]. The psychopathology and research on mixed depressive states in the DSM-5 proposal has weak scientific basis and does not identify a large number of mixed depressive states. This may be harmful because of the different treatment required by these conditions [10].

The present findings suggest that distractibility and psychomotor agitation may represent the core of mixed states, as they are more common in patients with mixed depression and bipolar spectrum disorder than patients diagnosed with unipolar depression and bipolar I disorder [11]. But multiple studies have shown that depression with hypomanic symptoms are closer to bipolar patients than depressed individuals without comorbid hypomanic or manic symptoms.

Racing thinking, also known as crowding thinking, largely belongs to manic symptoms. However, bipolar depression also has such symptoms, patients often say that “I can’t stop”, or “my brain is filled with things”, which, together with irritability and distractibility, constitute the three major symptoms of mixed depression. Therefore, racing thinking is also an important component of mixed state [1,11].

The notion of “mixture” of the dysphoric phases of the bipolarity includes the most insidious symptoms of the bipolar spectrum of mood disorders: the overlapping between depression-restlessness-irritability-grief-tension-anxiety can cause worsening of the mood disorders and in the most acute phases may cause increased risk of major behavioral disruption including murder and suicide. The “mixture” is a dynamic notion describing the presence of overlapping symptoms of mixed states, in an increasing intensity level [12].

In general, mixed subjects were significantly more likely to have following features: (i) have other mixed episodes, (ii) have higher irritable and agitated ratings, (iii) have more substance abuse, (iv) switch into mixed episodes, (v) have more suicide attempts and higher suicidal ratings, (vi) change diagnosis from depression to bipolar disorder, (vii) have higher hypomania scores when depressed or depression scores when [hypo]manic, (viii) be unmarried or separated with fewer children and siblings, (ix) be diagnosed more with bipolar disorder than MDD, (x) be unemployed, (xi) have bipolar disorder, suicide and divorce among first-degree relatives, (xii) be female, (xiii) be younger at illness-onset [13].

Diagnostic Criteria

The mixed unit of bipolar disorder is not only different from the mixed episode in ICD-10 and DSM-IV, but also different from “with mixed feature” in DSM-5, which is a clinical manifestation of bipolar disorder with a new cluster of symptoms. Its onset and manifestation usually consist of the following states [7,8,13,14].

1. It is a history of bipolar disorder in the past, mixed unit need with four items of the following nine states.
2. It was a depressive episode in the past and received antidepressant treatment, mixed unit need following four items.
3. It was a depressive episode and did not take antidepressant treatment, mixed unit need following five items.
4. It is the first episode, mixed unit must be six items on most occasions every day for one week, with MDQ ≥ 7 or /and HCL-32 > 10 [15].

Clinical signs are:

1. Irritability, or agitation, or both coexist.
2. Psychotic symptoms.
3. Obvious self-blame, low self-esteem or repeated suicide or NSSI (no suicide self injury).
4. Verbal disorganization or clutter, talkative or unable to stop thinking, often self-reporting “the brain can’t stop” or “the head is full”.

5. Extremely unstable emotions, both in the self-description of “too much fluctuation” and in the experience of “wanting to hit people or wanting to go crazy.”
6. Especially sensitive to the outside world, very hostile, can have repeated verbal or physical conflicts, easily provoked.
7. Adventurous behavior, or exaggerated ornamentation.
8. Vigorous energy, obvious coordination or lack of coordination of psychomotor excitement.
9. Significant changes in biological rhythms, day-night reversal, or rapid mood changes throughout the day.

The diagnostic criteria of mixed unit in bipolar disorder were also called “tongde criteria” due to institution of authors.

Management

The assessment of the mixed unit of bipolar disorder can use the mixed feature assessment scale. The clinical practical depression episode with mixed features scale and the bipolar mixed features scale can both be used [16]. From a clinical perspective, G.T.MSRS is more suitable, as the symptoms listed in this scale are more in line with clinical performance [17]. However, CUDOS-M does not meet the assessment of the mixed unit, as the symptoms listed are very typical manic symptoms [7]. The creators of the DSM-5 were probably concerned with compensating for the inadequacies of the DSM-IV, to take into account the clinical importance of mixed states. The proposed criteria partly meet these objectives. But the reflection was not, in our opinion, pushed to the end, particularly, by avoiding an in-depth semiological analysis. Finally, the diagnostic criteria are not very clinically relevant, and in the perspective of progress in epidemiological and therapeutic knowledge of mixed depression, the change in the DSM-5 could be a step for nothing. Making the diagnosis remains unlikely from a rigorous scientific perspective, the criteria being not very suitable, and the consequence could be a halt to the development of this type of research [18].

The pharmacotherapy of the mixed unit of bipolar disorder is basically equivalent to the treatment of mixed episodes or mixed features. The prohibition of antidepressant drugs is one of the basic principles. Generally, mood stabilizers for treatment of bipolar disorder with mixed unit should choose antiepileptic drugs, which are more suitable than lithium, but lithium carbonate has a greater advantage for bipolar disorder in children and adolescents [19,20].

Atypical antipsychotics are also important drugs for treating mixed units of bipolar disorder. Almost all atypical antipsychotics can be used. In general, the combination with mood stabilizers is more beneficial.

Declaration

Ethics approval and consent to participate

Not applicable.

Consent to publication

All authors agree to publish the manuscript.

Availability of data and material

Not applicable.

Competing interests

There were no financial or non-financial competing interests.

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Author’s contribution

Our authors have made different contributions to this article and study. Dr. Chen HH participated in the collection of references and wrote the draft. Dr. Zhu JF, Dr Shen D, and Dr Gao ZH participated in references review work and abstracted the main results. Prof. SFL and Prof. JWD participated in design and final review of article.

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