Shanghai Archives of Psychiatry, 2014, Vol. 26, No. 5

•Forum•

Should major depressive disorder with mixed features be classified as a bipolar disorder?

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Summary: The new diagnostic category in the Depressive Disorders chapter of DSM-5 entitled 'Major Depressive Disorder With Mixed Features' is applied to individuals who meet criteria for Major Depressive Disorder and have concurrent subsyndromal hypomanic or manic symptoms. But the operational definition of this new specifier is much closer to that of hypomania and mania than to the definition of atypical depression or the older 'mixed depression.' Moreover, multiple studies have shown that the characteristics of individuals with this condition and the clinical trajectory of their illness is much closer to that of bipolar patients than to that of depressed individuals without comorbid hypomanic or manic symptoms. Thus we believe that this condition would be more appropriately placed in the Bipolar Disorders chapter of DSM-5. We also believe that this blurring of the depressive disorder- bipolar disorder boundary is one cause for the low inter-rater reliability in the diagnosis of Major Depressive Disorder.

Keywords: major depressive disorder, depression with mixed features, mixed depression, bipolar disorder, DSM-5

[*Shanghai Arch Psychiatry*. 2014; **26**(5): 294-296. doi: http://dx.doi.org/10.11919/j.issn.1002-0829.214146]

One of the major surprises of the DSM-5 field trials was the very poor inter-rater reliability of clinicians when diagnosing major depressive disorder (MDD). Independent assessments of patients interviewed on separate occasions using standard clinical interview methods in routine clinical settings at eleven academic centers in the United States and Canada found that clinician agreement about the MDD diagnosis was in the questionable range (Kappa=0.20-0.39). The pooled intraclass Kappa was 0.28 (95% CI 0.20-0.35) at the adult field trial sites, and 0.28 (95% CI 0.15-0.41) at the Child/Pediatric field trial sites, respectively.[1]

Why are clinicians so inconsistent in their recognition of MDD, one of the most frequently treated conditions in clinical psychiatry? One possible explanation is that the bewildering array of proposed diagnostic subtypes – which seem to change at least once a decade – confounds the diagnostic process. In most cases, clinical psychiatrists diagnose the subtype of depression as part of a comprehensive evaluation of a depressed patient and are expected to use information about the presumed subtype to decide on the treatment plan that is most likely to effectively treat the symptoms and relieve patient distress. But which of the proposed classifications of subtypes are most clinically useful? Depressive disorder has been variously subtyped in a wide variety of ways depending on its clinical features and presumed etiology: endogenous or reactive depression, organic or psychogenic depression, retarded or agitated depression, anxious depression, depression with psychotic symptoms, mixed depression, atypical depression, and so forth.

The recent DSM-5[2] addition of the 'Major Depressive Disorder With Mixed Features' moniker to this alphabet soup of depressive subtypes (called a 'specifier' in DSM-5 newspeak) may have further muddied the waters. By including individuals with subsyndromal manic symptoms who may be better

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A full-text Chinese translation of this article will be available at www.shanghaiarchivesofpsychiatry.org on November 25, 2014.

classified with the bipolar disorders[3,4] under the MDD umbrella, this specifier expands the scope of MDD and, thus, may increase the difficulty of improving the inter-rater reliability of clinicians diagnosing MDD. The criteria for this specifier listed in DSM-5[2] are as follows: (pp. 184,185)

A. At least three of the following manic/hypomanic symptoms are present nearly every day during the majority of days of a major depressive episode:

1. *Elevated, expansive mood.*
2. *Inflated self-esteem or grandiosity.*
3. *More talkative than usual or pressure to keep talking.*
4. *Flight of ideas or subjective experience that thoughts are racing.*
5. *Increase in energy or goal-directed activity (either socially, at work or school, or sexually).*
6. *Increased or excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, foolish business investments).*
7. *Decreased need for sleep (feeling rested despite sleeping less than usual; to be contrasted with insomnia).*

B. Mixed symptoms are observable by others and represent a change from the person's usual behavior.

C. For individuals whose symptoms meet full criteria for either mania or hypomania, the diagnosis should be bipolar I or bipolar II.

D. The mixed symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication or other treatment).

This 'with mixed features' specifier can apply to depressive episodes experienced in Major Depressive Disorder and to depressive episodes that occur as part of any type of bipolar disorder. In the Bipolar and Related Disorders chapter of DSM-5[2] item 'C' (above) is changed to read "C. For individuals whose symptoms meet full episode criteria for both mania and depression simultaneously, their diagnosis should be manic episode with mixed features." (reference 2, p.150)

This characterization of MDD with mixed features is quite different from previous descriptions of 'mixed depression', a subtype that clearly fits within the overall group of depressive disorders. It includes typical manic symptoms that are rare among patients with mixed depression (such as elevated mood and grandiosity) and excludes other symptoms that occur frequently in mixed depression (such as irritability, psychomotor agitation, and distractibility).[3] Given this fundamental change in the characterization of the condition, should this subtype remain within the group of depressive disorders or be re-classified as one of the bipolar disorders?

Over the past 20 years, many studies have shown that depressed patients frequently have manic symptoms intermixed with depressive symptoms.[5,6] Mixed syndromes are more common in bipolar depression than in unipolar depression, but a substantial subgroup of patients who meet MDD criteria have concurrent manic or hypomanic symptoms.[7] The mixture of symptoms may be most evident when patients present for treatment, or they may appear during ongoing treatment. In some patients, treatment with antidepressant medication precipitates the emergence of mixed states.[8] In patients with MDD, the presence of co-occurring manic symptoms has been associated with an increased risk of suicidal behavior,[9] more depressive episodes,[10] poorer response to treatment,[10] more atypical features of depression,[6] younger age of onset,[6] and increased familial risk of bipolar disorder.[6]

Given the different trajectories of MDD patients with and without mixed features, some authors have suggested that antidepressants should be avoided or only used with caution in depressed patients with co-occurring manic or hypomanic symptoms, and that mood stabilizers should be used before antidepressants are started.[11] Long-term prospective studies are needed to assess the validity of such an approach, but if treating MDD with mixed features with mood stabilizers results in better clinical outcomes than treating them with antidepressants, this would be a strong rationale for considering this condition a bipolar disorder, not a depressive disorder.

A definitive answer about this issue may be many years in the coming, so in the interim clinicians need to carefully distinguish MDD patients with and without co-occurring manic symptoms and consider the early use of mood stabilizers in their treatment of MDD patients with mixed features.

Conflict of Interest

The authors report no conflict of interest related to this manuscript.

Funding

There was no funding support provided for the preparation of this report.

Shanghai Archives of Psychiatry, 2014, Vol. 26, No. 5

伴混合特征的重性抑郁障碍应当归类于双相障碍吗?

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概述：DSM-5 抑郁障碍一章中有一新的诊断类别为“伴混合特征的重性抑郁障碍”，指的是符合重性抑郁障碍的诊断标准并伴有亚综合征的轻躁狂或躁狂症状的患者。但是这一新类别的操作定义相比较于非典型抑郁症或过去“混合性抑郁症”的定义更加接近于轻躁狂和躁狂症。而且，多项研究表明，这类患者的特征和他们疾病的临床转归更接近于双相障碍患者，而不同于不伴有轻躁狂或躁狂症状的抑郁症患者。因此，我们认为，将这种情况归类于 DSM-5 的双相障碍更为恰当。我们还认为，这种抑郁障碍 – 双相障碍之间的界线模糊不清是产生重性抑郁障碍诊断信度低的原因之一。

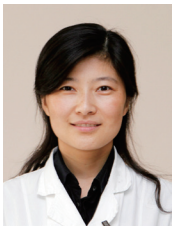
关键词：重性抑郁症，伴有混合特征的抑郁症，混合抑郁症，双相情感障碍，DSM-5

本文全文中文版从 2014 年 11 月 25 日起在 www.shanghaiarchivesofpsychaitry.org 可供免费阅览下载

References

1. Regier DA, Narrow WE, Clarke DE, Kraemer HC, Kuramoto SJ, Kuhl EA, et al. DSM-5 field trials in the United States and Canada, Part II: test-retest reliability of selected categorical diagnoses. *Am J Psychiatry*. 2013; **170**(1): 59-70. doi: http://dx.doi.org/10.1176/appi.ajp.2012.12070999
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5). Arlington, VA: American Psychiatric Association; 2013
3. Koukopoulos A, Sani G. DSM-5 criteria for depression with mixed features: a farewell to mixed depression. *Acta Psychiatr Scand*. 2014; **129**(1): 4-16. doi: http://dx.doi.org/10.1111/acps.12140
4. Uher R, Payne JL, Pavlova B, Perlis RH. Major depressive disorder in DSM-5: implications for clinical practice and research of changes from DSM-IV. *Depress Anxiety*. 2014; **31**(6): 459-471. doi: http://dx.doi.org/10.1002/da.22217
5. Angst J, Azorin JM, Bowden CL, Perugi G, Vieta E, Gamma A, et al. Prevalence and characteristics of undiagnosed bipolar disorders in patients with a major depressive episode: the BRIDGE study. *Arch Gen Psychiatry*. 2011; **68**(8): 791-798. doi: http://dx.doi.org/10.1001/archgenpsychiatry.2011.87
6. Benazzi F. Intra-episode hypomanic symptoms during major depression and their correlates. *Psychiatry Clin Neurosci*. 2004; **58**(3): 289-294. doi: http://dx.doi.org/10.1111/j.1440-1819.2004.01234.x
7. Benazzi F, Akiskal HS. Psychometric delineation of the most discriminant symptoms of depressive mixed states. *Psychiatry Res*. 2006; **141**(1): 81-88. http://dx.doi.org/10.1016/j.psychres.2005.07.024
8. Goldberg JF, Perlis RH, Ghaemi SN, Calabrese JR, Bowden CL, Wisniewski S, et al. Adjunctive antidepressant use and symptomatic recovery among bipolar depressed patients with concomitant manic symptoms: findings from the STEP-BD. *Am J Psychiatry*. 2007; **164**(9): 1348-1355. doi: http://dx.doi.org/10.1176/appi.ajp.2007.05122032
9. Olgiati P, Serretti A, Colombo C. Retrospective analysis of psychomotor agitation, hypomanic symptoms, and suicidal ideation in unipolar depression. *Depress Anxiety*. 2006; **23**(7): 389-397. doi: http://dx.doi.org/10.1002/da.20191
10. Smith DJ, Forty L, Russell E, Caesar S, Walters J, Cooper C, et al. Sub-threshold manic symptoms in recurrent major depressive disorder are a marker for poor outcome. *Acta Psychiatr Scand*. 2009; **119**(4): 325-329. doi: http://dx.doi.org/10.1111/j.1600-0447.2008.01324.x
11. Benazzi F. Reviewing the diagnostic validity and utility of mixed depression (depressive mixed states). *Eur Psychiatry*. 2008; **23**(1): 40-48. doi: http://dx.doi.org/10.1016/j.eurpsy.2007.07.003

(received: 2014-09-29; accepted: 2014-10-09)



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