See article by Perugi et al

"Mixed" Depression: Drawbacks of *DSM-5* (and Other) Polythetic Diagnostic Criteria

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At the end of the 19th century, Weygandt,[1] Kraepelin,[2] and Hecker[3] described an "agitated" or "excited" depression, ie, a depressive syndrome with psychomotor agitation, talkativeness, flight of ideas, and irritability, and classified it as a "mixed state."

Since the late 1980s, a condition usually called "mixed depression," consisting of a major depressive episode with at least 2 or 3 concurrent symptoms interpreted as contropolar ("manic"), has been extensively studied. The most frequently reported contropolar symptoms have been irritability, psychomotor agitation, racing or crowded thoughts, increased or pressured speech, and distractibility. Increased goal-directed activity and decreased need for sleep have been found to be uncommon, while elevated or expansive mood, inflated self-esteem or grandiosity, and excessive involvement in pleasurable activities have been reported to be very rare or absent.[4,5]

This condition has been found to occur in a proportion of patients with unipolar major depression ranging from 7% to 60%, and to be associated with an earlier onset than "pure" major depression; a more common family history of bipolar disorder; a higher prevalence of suicidal behavior, psychiatric comorbidity, traumatic brain injury, and alcohol abuse; a more frequent unipolar to bipolar switch; and a poorer response to antidepressants.[6,7]

The *DSM-5* has acknowledged the occurrence of this condition by introducing a specifier "with mixed features" to the diagnosis of major depressive disorder. However, the list of contropolar symptoms proposed in this specifier has been widely criticized,[8,9] because it includes typical manic symptoms (such as elevated mood and grandiosity) that have been found to be rare among patients with mixed depression, while excluding symptoms (such as irritability, psychomotor agitation, and distractibility) that are frequently reported in these patients. The rationale for excluding the latter symptoms has been that they are nonspecific, also appearing in the definition of depression. However, it has been counterargued that "criteria may be common for an illness but nonspecific" and "it makes no scientific sense to exclude them entirely, without any scientific evidence that the remaining criteria are sufficiently sensitive to identify that condition."[10(p11)] It would be—it has been noticed[8]—like proposing a new definition for migraine headaches that excludes pain in the head because it is a nonspecific symptom. Remarkably, *DSM-5* mixed features have been found to be associated with a better (rather than worse) antidepressant treatment outcome in patients with major depressive disorder, with expansive mood and cheerfulness being strongly associated with that better outcome.[11] The omission of irritability, psychomotor agitation, and distractibility among contropolar symptoms in the specifier has been considered as a possible explanation of that finding.[11]

A further problem with the *DSM-5* specifier is that it leads to classify as "unipolar" a patient who displays nearly every day, during the majority of days of a major depressive episode, elevated mood plus grandiosity plus increased involvement in activities with a high potential for painful consequences. Is our faith in *DSM* operational criteria so strong to induce us to believe that a patient with 3 typical manic symptoms is unipolar while a patient with 4 typical manic symptoms is bipolar? Of course, a patient with 3 manic symptoms may develop a fourth symptom (or have a fourth symptom moving from a subthreshold to a threshold level) during the same or a following episode. Will this count as a unipolar to bipolar switch? Will a high rate of transition from major depressive disorder with mixed features to bipolar disorder be regarded as a finding that validates the new *DSM-5* specifier?

On the other hand, the research diagnostic criteria for mixed depression proposed by Perugi et al[12] in their article have their own problems. *Mixed depression* is defined by the presence of a major depressive episode plus 3 of the following 14 hypomanic symptoms for at least a week: irritable mood, emotional/mood lability, distractibility, psychomotor agitation, impulsivity, aggression (verbal or physical), racing thoughts, more talkative/pressure to keep talking, hyperactivity, increased energy, risky behavior, grandiosity, elation, and hypersexuality. This means that a major depressive episode will be classified as "mixed" if the patient displays emotional lability plus impulsivity plus aggression. These symptoms, however, are very common in several mental disorders, including those that the authors found to be very frequently comorbid with major depression in their patient sample, such as borderline personality disorder and substance use disorders. The risk of false positives is, therefore, high.

The authors state that a diagnosis of mixed depression according to their research diagnostic criteria "was associated with a much larger number of variables" in

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multivariate logistic regression analysis than the *DSM-5* diagnosis of major depression with mixed features.[12] However, from a careful reading of their article, it emerges that the former diagnosis was associated with 11 variables, while the latter was associated with 8 variables—not a great difference in predictive validity. It is also true, however, that a crucial variable such as lifetime suicide attempts was associated with the former definition, but not with the latter.

Overall, the above controversy seems to reflect the limitations of our current categorical systems and polythetic diagnostic criteria. There appears to be a continuum between pure mania and pure depression as well as between unipolar and bipolar disorder, and it may be difficult to devise a characterization of mixed or intermediate conditions that shows a definite superiority over the others in terms of predictive validity. On the other hand, the diagnosis of "agitated" or "excited" depression as delineated by Weygandt, Kraepelin, and Hecker may require a gestaltic, prototypical approach, because it may be the overall clinical picture that is characteristic, while the individual elements are nonspecific. Definitions based on an artificial balance between manic and depressive symptoms may reduce our sensitivity in recognizing a clinical syndrome that has been described consistently for many decades and seems to have significant prognostic and therapeutic implications.

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