See article by Perugi et al

Mixed Depression: A Farewell to Differential Diagnosis?

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In this issue of the *Journal*, Perugi and colleagues[1] delve into the murky and controversial diagnostic boundaries between unipolar and bipolar mood disorders. As the authors intimate, the decision by *DSM-5*'s crafters to loosen the operational definition of mixed episodes adds to ongoing debate over the beleaguered document's various symptom tweaks and diagnostic reshufflings. *DSM-5* rightly acknowledged that many depressed bipolar patients experience subthreshold mania symptoms while depressed and that simultaneous symptoms of both poles can and often do coexist in bipolar II as well as bipolar I mood states. *DSM-5* also took notice of empirical findings that high energy states robustly differentiate bipolar from unipolar disorder,[2] underscoring the principle that bipolar illness is as much a disorder of energy and psychomotor functioning as mood. But the shortcomings of *DSM-5*'s revisions involving "mixedness" are important and risk dwarfing these nosologic advances.

DSM-5's decision to apply the "mixed features" specifier to both unipolar and bipolar depressive episodes when subsyndromal mania symptoms also exist harkens to Kraepelin's view that polarity was not an all-or-none phenomenon and was less important than other characteristics (such as excitation-agitation, or high recurrence) in his original conception of manic-depressive illness. In practice, though, efforts to articulate valid operational criteria for "mixedness" create their own problems—particularly when asking diagnosticians to cherry-pick only some "possible" mania symptoms, side-stepping those that could also reflect depression. Researchers who conduct criteria-based diagnostic interviews may thus agonize all the more over ambiguous cases, while time-pressured everyday clinicians will probably ignore such nuanced distinctions altogether and potentially make "mixed features" (never mind polarity) a wastebasket descriptor for any and all forms of irritable moody people.

Throughout its editions and revisions, the *DSM* has included as its final criterion for virtually every described entity the proviso that observed symptoms should not be attributed to a particular disorder if they can be better accounted for by another condition. This caveat becomes especially difficult when evaluating diagnostically nonspecific symptoms such as irritability or mood instability (or other such broad mental phenomena as "inattentiveness" or "apathy"). When considering depressive mixed states, Perugi et al[1] (and other authors[3]) confront us with the challenge of how best to classify an important nosologic entity without "double counting" symptoms, or conflating 2 or more disease states that share common elements. The BRIDGE data[1] invite us to consider whether depressed patients with such diagnostically nonspecific symptoms as irritability, mood instability, distractibility, agitation, and anxiety belong to the bipolar spectrum, or whether they may be better accounted for by other nonbipolar comorbidities. In doing so, they draw our attention to the *DSM-5* conundrum of whether to include or exclude transdiagnostic symptoms when characterizing a distinct clinical entity. (By analogy, should a newly recognized inflammatory disease exclude fever as part of its core symptom constellation in order to avoid conflation with a comorbid infectious process? Or, while dyspnea and chest pain do not help to differentiate angina from pneumonia, can those symptoms really be ignored when considering either diagnosis?)

If phenomenology studies in psychiatry have taught us anything over the past century, it is that no psychiatric symptom is pathognomonic of any one disorder. Bizarre thought content no longer figures so prominently as it once did in considering a diagnosis of schizophrenia. Nor does catatonia, paranoia, or even Schneiderian first-rank symptoms. In the case of mood disorders, while "mixedness" is no doubt a real phenomenon, its "truest" definition remains messy. Prominent irritability, for example, was found in almost half of unipolar depressed patients in the National Institute of Mental Health (NIMH) Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, and was more closely related to anxiety and depression severity than to occult "bipolar spectrum" features.[4] Similarly, in the NIMH Collaborative Depression Study, irritability and anger were evident in over half of unipolar depressed patients, and were in turn linked to an array of complex illness characteristics, including more anxiety and substance misuse, greater depression severity and chronicity, and personality disorders.[5] While some authors feel that irritable depression is practically synonymous with "bipolarity,"[6] it may simply be an indicator of overall severity and complex psychopathology.

"Affective instability" also poses a quandary for differential diagnosis. No edition of the *DSM* has ever identified affective instability as a criterion for mania or hypomania, although popular perception sometimes leads both patients and practitioners to assume that moment-to-moment "mood swings" are a defining element of bipolar disorder. Our own group found that community practitioners often diagnose bipolar disorder based mainly on the presence of mood lability—yet, when compared alongside individual *DSM-IV* symptom criteria for mania or hypomania, "affective

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instability" had the lowest positive predictive value, and lowest sensitivity, of any symptom predictor for a *DSM-IV* diagnosis of bipolar I or II disorder.[7]

As Perugi and colleagues[1] note, affective instability is more common in people with than without bipolar disorder; importantly, however, it differs qualitatively from forms of affective instability seen in nonbipolar conditions. For example, in borderline personality disorder, affective vicissitudes typically are reactions "triggered" by interpersonal skirmishes and usually involve "swings" from euthymia to anger, or depression to anxiety, whereas mood states in bipolar patients are less overtly mediated by interpersonal sensitivities and tend more to vary from euthymia to depression, euthymia to elation, or depression to elation.[8–10] In fact, emotional dysregulation has been described in the literature as a broad, complex, heterogeneous phenomenon with no fewer than 2 dozen operational definitions,[11] spanning numerous psychiatric conditions including posttraumatic stress disorder and substance misuse,[12,13] attention-deficit/hyperactivity disorder (ADHD),[14] borderline and other personality disorders,[15] anxiety disorders,[16] and eating disorders.[17]

Herein lies perhaps the most fundamental challenge facing clinicians, theorists, and future authors of *DSM-5*.1 and beyond—namely, how best to conceptualize and treat symptoms that overlap diverse psychiatric conditions. The BRIDGE dataset—a laudable and ambitious endeavor of unprecedented international scale—illustrates the shortcomings, given that dilemma of a symptom-shuffling approach to differential diagnosis. Perugi and colleagues[1] observe that many adults across the world who seek treatment for depression have complex presentations that often may include substance use disorders, ADHD, and borderline personality disorder. Their proposed "core" symptoms of depressive mixed states—affective instability, irritability, anxiety, and agitation—cut across all of these conditions. While Perugi et al criticize *DSM-5* for "arbitrarily" discounting such nonpathognomonic features as these in its reconfiguration of mixed states, it seems scientifically disingenuous to extract symptoms found across common psychiatric comorbidities of major depression and declare them as de facto reflections of bipolarity.

It is hard to formulate a cogent treatment plan before making a careful diagnosis, and the findings on mixed depression by Perugi et al[1] raise more questions than answers about therapeutic approaches to depressed patients with mixed features. Antidepressants are generally considered ill-advised when patients with unequivocal bipolar disorder manifest even low-grade symptoms of mania,[18] but little if anything is known about whether antidepressants help or hurt anxious, mood-unstable, or agitated nonbipolar depressed patients. Inasmuch as mood destabilization from antidepressants is a relatively rare phenomenon in general[19] and seldom seen in nonbipolar I patients,[20] should we extrapolate that risk to depressed patients who have never been clearly manic or hypomanic? Affective instability, as a target of pharmacotherapy in borderline personality disorder, responds similarly to antidepressants or mood stabilizers, but overall efficacy appears modest[21]; would either agent work better to ameliorate affective instability in depressive mixed state patients? And in bipolar disorder itself, quite surprisingly, affective instability has never even been the primary outcome of any published randomized pharmacotherapy trial, making the term *mood stabilizer* itself something of a misnomer with respect to a drug's expected pharmacodynamic properties.

Perhaps future studies must examine, rather than presume, the best treatment approaches for complex forms of depression, whether labeled as mixed state, or multicomorbid, or otherwise. When major depression co-occurs with borderline personality disorder (a scenario found about 3 times more often among "mixed depression" BRIDGE patients[1]), recent longitudinal studies show delayed remission of mood symptoms, and faster relapse, irrespective of the presence of bipolar disorder—prompting calls for "prioritized" treatment of borderline personality features to facilitate recovery from depression.[22] Should dialectical behavior therapy therefore become a first-line treatment for depressive mixed states? Or, if affective instability occurs in the setting of major depression plus ADHD, should it be the intended target of treatment with psychostimulants? Or should psychostimulants instead be avoided altogether for fear of unmasking a possible bipolar diathesis? And in unipolar mixed depression patients, should lithium be discouraged based on findings from trials in bipolar disorder showing that depressive symptoms during mania portend an unfavorable response?[23]

Perhaps NIMH's decision to discard *DSM-5* altogether in favor of its alternatively proposed Research Domain Criteria (RDoC)—where no symptom receives consideration unless it maps to a known gene or brain circuit—partly reflects dismay and resignation at the federal level over the gerrymandering of psychiatric symptoms. Meanwhile, clinicians and patients continue to struggle with how best to understand and treat complex forms of depression with the hope for an eventual clearer direction, by whatever name we call the problem.

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