

## Letter to the Editor

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# Emil Kraepelin's taxonomic unitary view of manic-depressive insanity in the 21st century: the never-ending diagnostic conundrum of bipolar depression

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**To the Editor:**

We read with great interest the article titled *Using classification and regression tree modeling to investigate appetite hormones and proinflammatory cytokines as biomarkers to differentiate bipolar I depression from major depressive disorder* exploring potential biomarkers to help differentiate bipolar depression from major depressive disorder (MDD).<sup>1</sup> In this work, elevated levels of ghrelin and TNF- $\alpha$  presented as a composite predictor of bipolar disorder versus MDD (unipolar depression). The differential diagnosis of depressive syndrome presentations is a problematic area and source of controversy. Due to the challenges we have faced in our clinical practice over the years, we have previously briefly explored aspects related to this topic. We have addressed the impact of pharmacological interventions with the so-called “antidepressants” (serotonergic and noradrenergic drugs) on mood instability and concerning the wider range of bipolar spectrum disorders.<sup>2</sup> We believe no opportunity should be missed as we are adamant that it is increasingly important to raise awareness about certain clinical features suggesting the nonunipolar nature of individual mood episodes that present as depressive syndromes. These include aspects related to clinical presentation, natural history, family history of mood disorders, and treatment resistance.<sup>2–4</sup>

Emil Kraepelin's innovative nosology arose in a prepsychopharmacology era and was very influential despite criticisms.<sup>3</sup> Based on extensive clinical observations he suggested the division of functional psychoses in *dementia praecox* and *manic-depressive insanity (MDI)*. Nowadays, there is often an oversimplification of what is meant by *MDI* or *manic-depressive illness* as an old-fashioned term that refers to the same disorder that today is known as *bipolar disorder*. This is inaccurate. Kraepelin's unitary view of MDI, built upon works from other authors, included the concepts of *periodic insanity*, *circular insanity*, *simple mania*, *melancholy*, and *fundamental mood dispositions*.<sup>3</sup> Kraepelin based his taxonomy on common hereditary features shared between different presentations, their natural history with individual patients frequently transitioning between mania, depression, and episodes with mixed features throughout their lifetime.<sup>3</sup> Also, he stressed the possibility of acute mood episodes manifesting in patients with fundamental affective states (translated from the German *persönlichen veranlagungen* as temperaments) of opposed polarity.<sup>3</sup> Despite Kraepelin's major influence in modern psychiatric nosology his taxonomy was met with criticism and did not get wide acceptance from many of his peers at the time. As such, throughout the year's mood polarity came to the forefront in terms of defining the categories of individual mood disorders with a clear-cut dichotomic separation between unipolar depression and bipolar disorder. In our current classification and official diagnostic manuals, mood disorders are still classified categorically as unipolar depression (depressive episodes, MDD), bipolar disorder (manic and hypomanic episodes, bipolar types 1 and 2), and persistent mood disorders (dysthymia). Cyclothymia is often conceptualized as belonging to the bipolar disorders group. DSM includes mixed features specifiers that can apply to depressive, manic, or hypomanic episodes if symptoms of opposed polarity are also present. However, these modern “mixed” mood episodes are far narrower than Kraepelin's mixed states (*excited depression*, *depression with flight of ideas*, *depressive mania*, *mania with poverty of thought*, *manic stupor*, and *inhibited mania*). One source of criticism from several modern authors (such as Hagop Akiskal, Athanasios Koukopoulos, Giulio Perugi, Nassir Ghaemi, and their colleagues) is the undermining of certain mixed symptoms from mainstream criteria because of their lack of specificity (particularly psychomotor agitation or psychomotor retardation as a criterion for a major depressive episode).<sup>2–4</sup> In essence, the overall trajectory of these

concepts has been toward an increasingly narrower concept of bipolar disorder and wider concept of depressive disorder.<sup>3</sup>

Despite these different views in terms of conceptual framework, there has always been consensus and recognition of the clinical heterogeneity of bipolar disorder. Lifetime prevalence of bipolar I disorder according to DSM-5 criteria is estimated at approximately 2%.<sup>4</sup> Interestingly though, it is estimated that there is a rate of about 60% of misdiagnosis of bipolar depressive episodes as unipolar depression.<sup>4</sup> This is in part due to what some would argue as inadequacy of current diagnostic manuals but also, as we particularly would like to highlight here, a failure to actively explore, recognize and consider signs suggesting bipolarity in routine clinical examinations.<sup>2,4</sup> Any patient with depressive symptoms should be carefully probed for (a) *presentation and psychiatric mental status examination* with features of atypical depression (mood reactivity, exaggerated interpersonal sensitivity, increased appetite, and hypersomnia) or mixed features of agitated depression (racing or crowded thoughts, irritability, subjective sense of inner tension, restlessness, psychomotor agitation, and talkativeness); (b) *past psychiatric history* with treatment resistance or worsening with monoaminergic antidepressants, several comorbidities (personality disorders, anxiety, and impulse control disorders), early onset, postpartum depressive episodes, seasonal depression, and suicidal attempts; (c) *family history* of bipolar disorder, suicide, cyclothymia, cyclothymic or hyperthymic affective temperaments, and psychotic disorders including diagnosis of schizoaffective disorder.<sup>2,4</sup>

This is extremely relevant because misdiagnosis of bipolar depression has major clinical implications regarding 2 main factors that we derive from establishing a diagnosis: prognosis and treatment approach.<sup>2,4</sup>

Despite various studies addressing those factors that might predict the higher probability of a given depressive episode being part of an underlying bipolar diathesis there is still a lack of clear biological or neuroimaging markers to aid in differential diagnosis. However, there is ongoing research on this topic as exemplified by several studies exploring etiological, genetic, and biomarkers in these disorders.<sup>1,5</sup> In another recent study including patients with diagnosis of bipolar disorder, schizophrenia, and schizoaffective disorder, it showed a shared liability associated with mania;

moreover, bipolar disorder clinical heterogeneity appeared to be influenced by risk alleles.<sup>5</sup> Translational and clinical research in psychiatry faces many challenges because it is built upon shifting categorical diagnoses with mostly consensus-based pragmatic diagnostic criteria hence for the most part lacking a clear underlying neurobiological basis. In this exciting age with flourishing research in neuroscience, steps are already being taken to address these limitations (eg, with the development of the Research Domain Criteria—RDoC). Until significant new insights emerge, we need to monitor ourselves in our everyday practice, so we remain aware of the practical value of detecting bipolar depression. This awareness is particularly important in primary care but also in mental health care settings including every multidisciplinary team involved in the care of patients with these prevalent symptoms

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