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EDITORIAL

Mixed features and mixed states in psychiatry: from calculus to geometry

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Mixed features in psychiatry have historical, conceptual, nosological, and therapeutic implications. The historical perspective begins with Hippocrates and Aretaeus of Cappadocia and, after a hiatus, was followed by the writings of Heinroth, Falret, Kahlbaum, Weygandt, and Kraepelin. The conceptual motif consistent across Weygandt's and (his mentor) Kraepelin's model was combinatorial. Ostensibly, Weygandt and Kraepelin proposed a "calculus" approach to codifying nondementia praecox disorders, wherein the diagnosis was established by combining ratings along the 3 dimensions of mood, thought, and volition/activity (MTV). Uniform increases across all 3 domains defined mania; conversely, a decrease in each domain defined depression. Mixed states were the consequence of various combinations along MTV dimensions. Effectively, Weygandt and Kraepelin categorized the dimensions of psychopathology.

Throughout much of the 20th century, the Kraepelinian notion was dominant in psychiatry and promulgated the notion of dimensionality. In 1980, the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (DSM-III), balkanized manic depression into major depressive disorder (MDD) and bipolar disorder. An externality of the DSM-III and the subsequent DSM iterations was the orphaning of many psychiatric phenotypes (eg, agitated depression). Until the arrival of the DSM-5, the categorical approach to diagnosing mood disorders had largely supplanted the dimensional approach in use prior to 1980.

Between the 2 decades of 1996 and 2016, more psychotropic agents were FDA-approved for bipolar disorder than in the previous 5 decades combined. The availability of mechanistically dissimilar agents for bipolar disorder, robust pharmaceutical sales and marketing, the absence of a biologically informed disease classification system, and insufficient access to high quality comprehensive assessment and care of persons with mood disorders resulted in a significant increase in the detection, diagnosis, and misdiagnosis of bipolar disorders. Moreover, outcomes for individuals with bipolar disorder and for the majority of persons with MDD have remained woeful and unacceptable, despite the availability of a surfeit of treatments.

A modifiable deficiency in the management of adults with mood disorders is the delay in establishing an accurate diagnosis. Contributing to this deficiency was the lack of ecological validity in the diagnostic construct of mixed states in the DSM-IV-TR. Moreover, it is recognized that in some circumstances, the prescription of select psychotropic agents (eg, antidepressants) may inadvertently engender and/or amplify psychopathology in at-risk individuals. Amplifying concerns further were reports of suicidality associated with antidepressants (ie, activation syndrome). The foregoing provided the impetus for the American Psychiatric Association to discontinue the construct of mixed states, as it was operationalized in DSM-IV, and supplant it with the new "mixed features" specifier in the DSM-5. In essence, the mixed features specifier is neo-Kraepelinian and has removed the gap, introduced in 1980, between unipolar and bipolar disorders.

Highly replicated symptom structure studies provide empirical support for the mixed features specifier. Debates continue as to the validity of restricting the specifier to 3 or more symptoms and the type of symptoms that are requisite (eg, non-overlapping symptoms). At first glance, what is tacit to the DSM-5 approach is a unidimensional formulation. A transdisciplinary approach along with a different diagnostic matrix could, however, take a more

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"geometric" or "orthogonal" approach to mixed features. For example, individuals with mixed features may be at higher risk for cardiovascular comorbidity when compared to those without mixed features, underscoring the somatic phenotypes of mixed features. Also, morbidity studies indicate that persons with mixed features are more likely to have psychosocial and workplace impairment, hospitalizations, and endorse suicidality, suggesting more profound cognitive dysfunction in affected persons when compared to individuals without mixed features.

In addition to higher rates of select comorbid medical conditions, individuals with mixed features are differentially affected by psychiatric comorbidity (eg, substance and alcohol use disorders, ADHD) with differential illness course characteristics. The multiple psychiatric and medical co-occurring conditions and the different illness trajectories indicate that a unidimensional conceptualization is insufficient, and perhaps a multidimensional (ie, orthogonal) approach may be more comprehensive and coherent.

The biobehavioral matrix Research Domain Criteria (RDoC) proposes a convergence of transdiagnostic psychopathology across general cognitive processes, cognitive emotional function, social cognition, and arousal/circadian rhythms. Employing the RDoC framework, mixed features are the quintessential multidomain psychopathology, likely subserved by multiple interacting (in some cases, orthogonal) circuit/subcircuit alterations. It seems that for the future, genuinely novel treatment discovery and development for mixed features may benefit from a more dimensional/domain approach to disambiguating the complex psychopathology of this phenotype.

The implications are not simply academic; they are significant, urgent, and clinically relevant. For example, adults with MDD may also receive the specifier mixed features. Despite the absence of a robust body of evidence informing treatment decisions for MDD with mixed features, there is sufficient published evidence and clinical experience indicating that these persons are more likely to have an insufficient outcome with conventional antidepressants. For the first time, a treatment guideline has been made available (ie, Florida Medicaid Guidelines) that provides first-line treatment recommendations in major depressive disorders with mixed features.[1] It is axiomatic that appropriately designed studies that seek to determine the most effective and safe approach to managing such individuals are needed.

This special issue of *CNS Spectrums* broadly aims to provide deeper understanding of mixed features and how to best relieve suffering for affected persons. Towards this aim, we take a historical, phenomenological, measurement-based, diagnostic, and therapeutic approach. We have invited contributions from international experts who have made independent substantive and high-impact contributions to this space. It is tempting to speculate that the availability of big data, machine learning, advances in bioinformation analytics, and a novel conceptual framework (eg, RDoC) will "unmix" mixed features.

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