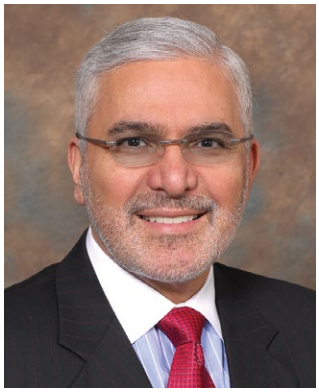

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Beyond DSM-5: Clinical and biologic features shared by major psychiatric syndromes

Imagine the rich landscape of psychopathology as an Amazon jungle. The DSM diagnostic schema describes the individual trees but overlooks the fascinating patterns within the forest.

It does not adequately inform psychiatric practitioners about the many clinical and biologic features shared across the various diagnostic categories. It does not do justice to the galloping advances in the neurobiology of psychiatric brain disorders and the wealth of potential biomarkers that will eventually endow psychiatry with an objective and ultimately more valid, not just reliable, diagnostic model that is compatible with a future of precision medicine.

The Research Domain Criteria (RDoC) Project[1] is a valiant attempt to transcend the DSM's "Chinese menu" approach to diagnosis. It was championed by the former director of the National Institute of Mental Health (NIMH), who used his authority to encourage investigators applying for federal grants to employ the RDoC principles in their research programs. Who does not recall the awkward moment, a few weeks before the official baptism of DSM-5 as psychiatry's latest diagnostic Bible in May 2013? The NIMH director's unflattering portrayal of the incipient DSM-5 was a well-publicized shot across the bow. The kerfuffle was later resolved, but its effects linger among clinical researchers who relentlessly hope for neuroscience advances to translate into a more objective diagnostic approach to psychiatric diagnoses. The neurobiologic foundations of psychopathology are bound to guide us to a more valid set of diagnostic categories, yet the pace remains painfully slow.

However, the copious advances in brain research are providing other dividends beyond a better diagnostic forest. Many intriguing insights are emerging about the connectedness among major psychiatric "trees," including schizophrenia, bipolar disorders, and major depressive disorder. The following are examples of neurobiologic, clinical, and treatment commonalities across those psychotic and mood disorders.

Many intriguing insights are emerging about the connectedness among major psychiatric 'trees'

Shared neurobiology

Progressive brain tissue loss/ neurodegeneration. Numerous studies have established that abnormal neuroplasticity is a common theme during psychotic, manic, and depressive episodes. These findings have demonstrated that the more recurrent the episodes, the more prominent the atrophy

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in either overall brain volume or specific brain regions, especially in the hippocampus, prefrontal cortex, and cerebellum as measured on MRI.

White matter pathology. Multiple studies have reported loss of myelin integrity in psychotic and mood disorders. Abnormalities are detected by using diffusion tensor imaging and measuring anisotropy and diffusivity of water flow in white matter traits. White matter pathology can be associated with intra- and inter-hemispheric disconnectivity and impairment of brain functional integration that may contribute to positive, negative, and cognitive symptoms.

Neuroinflammation. Acute psychotic and mood episodes have been shown to be associated with significant elevation in inflammatory cytokines in CSF and serum, including interleukins (such as interleukin-6), tumor necrosis factor-alpha, interferon gamma, and C-reactive protein. Those inflammatory biomarkers subside when the acute episodes are treated. It is believed that activation of the microglia leads to release of proinflammatory cytokines.

Mitochondrial dysfunction. Many studies document various dysfunctions of the mitochondria in schizophrenia, bipolar disorders, and major depressive disorder. The consequences include oxidative stress due to a decrease in the antioxidant glutathione, produced in the mitochondria, which is vital for neutralizing the reactive oxygen and nitrogen species referred to as free radicals. There is a substantial increase of free radicals during acute psychotic and mood episodes, which contributes to neurodegeneration.

Glutamate pathway abnormalities. A large body of literature has focused on the glutamate *N*-methyl-D-aspartate receptor (NMDAR) dysfunction as a key pathophysiology in schizophrenia and mood disorders. Interestingly, the NMDAR appears to be hypoactive in schizophrenia as evidenced by the schizophrenia-like effects of potent NMDAR antagonism by phencyclidine and hyperactive in unipolar and bipolar depression as evidenced by the remarkably rapid improvement of treatment-resistant depression with the NMDAR antagonists ketamine or nitrous oxide. Glutamate pathways may ultimately shed light on the neurochemical pathology underpinning psychotic and mood disorders. The NMDAR is also likely linked to both neuroplasticity and cognitive impairments in the major psychiatric disorders because both are related to calcium passing through the NMDAR ion channel.

Gene/environment interaction. Neurogenetic advances have demonstrated some shared genes among schizophrenia, bipolar disorders, and major depressive disorder (such as the CACNA1C gene).[2] Also, environmental factors, such as severe childhood maltreatment, lead to high rates of psychosis and mood disorders in adulthood. Risk genes in schizophrenia and mood disorders are likely to be overexpressed with adverse environmental factors and epigenetics.

Shortened telomeres. Patients with psychotic and mood disorders have been reported to have shorter telomeres—proteins that cap the end of chromosomes and shorten with repeated cycles of mitosis and aging—at a younger age, predicting early senescence and mortality. Telomere shortening is associated with multiple factors, including chronic stress, smoking, poor diet, obesity, infections, inflammation, and free radicals, all shared by major psychiatric disorders.

Genetic heterogeneity. Schizophrenia, bipolar disorders, and major depressive disorder are associated with complex genetics (eg, risk genes, mutations, and copy number variants) and various perinatal complications (eg, infections, gestational diabetes, vitamin D deficiency, hypoxia at delivery), which makes them highly heterogeneous syndromes, comprised of hundreds of biotypes. There are many established endophenotypes that a future diagnostic system should adopt.

Elevated cortisol levels. Increased serum cortisol levels are found in depression and schizophrenia related to HPA axis dysregulation as well as life stress. Hypercortisolemia can contribute to neurodegeneration as well as to multiple systemic medical disorders often encountered in mood and psychotic disorders.

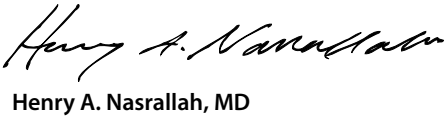
Shared clinical features

Psychotic and mood disorders share several key clinical features, including:

- cognitive deficits
- substance use disorders (especially *Cannabis* and alcohol) as a common comorbidity
- increased suicide risk
- high prevalence of smoking
- premature mortality, by 10 to 20 years
- anxiety as a common comorbidity
- elevated cardiometabolic risk factors, even before pharmacotherapy
- recurrent relapses lead to treatment resistance
- various degrees of fixed false beliefs (delusions)
- perceptional aberrations (various types of hallucinations)
- response to dopamine-serotonin antagonists (atypical antipsychotics) as monotherapy or adjunctive therapy.

While it is fair to say that a diagnostic manual like DSM-5 should focus on the diagnosis of individual psychiatric diseases and syndromes, it is also reasonable to say that focusing primarily on clinical features does not do justice to the biologic complexities of psychiatric disorders and the importance of including biomarkers to increase the validity of psychopathological categories. The shared neurobiologic and clinical features across major psychiatric syndromes, such as schizophrenia, bipolar disorders, and depression, indicate how multifaceted psychiatric diagnosis can be. The same approach is applicable to other psychiatric syndromes, such as anxiety, personality disorders, attention-deficit/hyperactivity disorder, or dementia. Our field should move firmly and steadily toward a diagnostic schema that incorporates ongoing breakthroughs in psychiatric neuroscience as soon as they are replicated.

If psychopathology is a forest, then DSM-5 is a simplistic depiction of each tree's structure as roots, a trunk, branches, and leaves. Psychiatry needs to move to a far more sophisticated perspective of each tree as an amazingly complex, dynamic, and evolving organism, designed genetically but continuously influenced by its environment. Psychiatry also should keep an eye on the entire forest and detect distinctive patterns as well as idiosyncratic or shared features among the trees. Major insights will ensue about the etiology, course, and management of each diagnostic tree or the mosaic of related trees.



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