Re-inventing the DSM as a transdiagnostic model: Psychiatric disorders are extensively interconnected

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It’s time for a necessary paradigm shift in re-conceptualizing the nosology, epidemiology, etiology, and treatment of major psychiatric disorders, including schizophrenia, bipolar disorder, major depressive disorder (MDD), autism spectrum disorder, attention-deficit/hyperactivity disorder (ADHD), anxiety, obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), and substance use disorders.

For a long time, and prior to the neuroscience revolution that enabled probing the human brain and exploring the neurobiology of psychiatric disorders, the field of psychiatry was descriptive and simplistic. It categorized psychiatric disorders essentially as silos, defined by a set of signs and symptoms. If one or more psychiatric conditions co-occurred with a “primary diagnosis,” they were labeled as “comorbidities,” with no implications of a shared etiology or biology. Amazingly, despite the rapid accrual of evidence of shared developmental or genetic etiopathogenesis, shared dysplasia of the same brain regions on neuroimaging, and improvement with the same class of medications, the DSM-5 and its outdated schema remain the diagnostic “bible of psychiatry,” and comorbidities are not being recognized as genetically overlapping disorders.

This archaic model is ripe for change and a major update. Highlights of emerging advances that justify the re-conceptualizing of the nosology of major DSM diagnostic entities, and reinterpreting the comorbidities as evidence of the substantial clinical and biological overlap and interconnectivity of psychiatric brain disorders, include:

Neurodevelopmental pathology. Disruption of brain development during fetal life has been well-established across the schizophrenia spectrum syndrome and practically all the so-called comorbidities.1,2,3

Genetic pleiotropy. Approximately 50% of the 22,000 protein-coding genes in the human chromosomes are expressed in the brain during development. Schizophrenia and most psychiatric disorders are heavily genetic. Genetic pleiotropy has been identified across several
psychiatric syndromes.\textsuperscript{4,5} For example, the calcium channel A1 gene is shared by schizophrenia, autism, bipolar disorder, MDD, and ADHD.\textsuperscript{6} This indicates that the DSM separation of those disorders is artificial and based on specific symptoms without integrating what is regarded as comorbid conditions into a unified model. Copy number variants have also been found in schizophrenia, ADHD, and autism spectrum disorders.\textsuperscript{5,7}

**Neuroimaging concordance.** Three brain regions—the dorsal anterior cingulate, left insula, and right insula—have been reported to be abnormal in patients with schizophrenia, bipolar disorder, MDD, OCD, and anxiety. Those shared structural abnormalities are associated with various degrees of hypoplasia or atrophy.\textsuperscript{8}

**Endophenotypes and intermediate phenotypes** have been redefined to accommodate transdiagnostic vulnerabilities and etiological complexity.\textsuperscript{9,11}

**Shared symptoms** have long been observed across various psychiatric disorders, including delusions, hallucinations, depression, anxiety, impulsivity, and autistic and cognitive symptoms.\textsuperscript{12,15}

**Response to pharmacotherapy.** It is well recognized that the same class of psychotropic medications exert therapeutic efficacy across a variety of DSM disorders.\textsuperscript{16} The selective serotonin reuptake inhibitors and second-generation antipsychotics exert efficacy in many psychiatric disorders beyond their original indications, which were FDA-approved based on a specific DSM diagnosis.

**Neural circuits.** “Connectomics” are now regarded as the neurobiologic underpinnings of schizophrenia and other psychiatric disorders, and that may be a key reason for the transdiagnostic overlap.\textsuperscript{17,19}

**Similar neurobiological pathologies** have been found to exist in several major psychiatric disorders, including neuroprogression, white matter pathology neuroinflammation, oxidative stress, mitochondrial dysfunction, glutamate pathway disruptions, and shortened telomeres.\textsuperscript{13}

**Familial clustering.** Various psychiatric disorders have been found to have significantly increased odds ratios (OR) among the first-degree relatives of patients with schizophrenia, including bipolar I (4.27), bulimia (3.81), generalized anxiety disorder (3.49), separation anxiety (3.10), drug abuse (2.83), conduct disorder (2.53), dysphasia (2.51), PTSD (2.30), alcohol abuse (2.27), MDD (2.18), and social phobia (2.0).\textsuperscript{20}

**Medical comorbidities.** Schizophrenia, mood disorders, and anxiety disorders are all associated with a significant increase in various medical illnesses.\textsuperscript{21} In genome-wide association studies (GWAS) of schizophrenia, the histocompatibility complex genetic locus on chromosome 6 was significantly abnormal compared with healthy controls. This points to immune dysregulation that may predispose to many physical diseases of the body and the brain.

**The “p” factor.** Multiple reports have suggested the presence of a single shared psychopathological predisposition to various dimensions of psychiatric disorders, called the “p” factor.\textsuperscript{22–25} Kendler\textsuperscript{26} elaborated on the conceptual evolution within psychiatric nosology from one disorder prior to the introduction of the DSM to numerous disorders in the DSM schema, and now back again to a single psychopathological foundation, with the accelerating evidence for a unified model that stands in contrast to the widely held current DSM model.

**Transformative changes are on the way**

To summarize, it is quite evident that transformative changes may be forthcoming in the diagnostic framework of psychiatric disorders, and there is a burgeoning literature to propel them. That cumulative research evidence will trigger a seismic change to the DSM structure as it currently exists, and the shift will catalyze a disruptive transformation in re-conceptualizing the transdiagnostic underpinnings of psychiatric disorders. Once adopted, the new model may lead to diagnostic and therapeutic innovations. Several emerging models should also be considered in shaping the change, including:

- **HiTOPS (Hierarchical Taxonomy to Psychopathology)**\textsuperscript{27}
- **RDoC (Research Domain Criteria)**\textsuperscript{28}
- **Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP)**\textsuperscript{29,30}
- **Neuroscience-Based Nomenclature (NBN).**\textsuperscript{31}

A brave new approach to developing novel treatment modalities and interventions will emerge, exploiting the shared genetic, neurobiologic, and clinical interconnectedness of multiple psychiatric brain disorders.\textsuperscript{22,33} The transdiagnostic model is the future not only for elucidating psychiatric nosology and symptoms, but also for shared etiology, genetics, neurobiology, and treatments, as well as for various medical conditions that frequently accompany psychiatric disorders. ■
REFERENCES

22. Kendler KS. From many to one to many - the search for causes of psychiatric illness. JAMA Psychiatry. 2019;76:1085-1091.