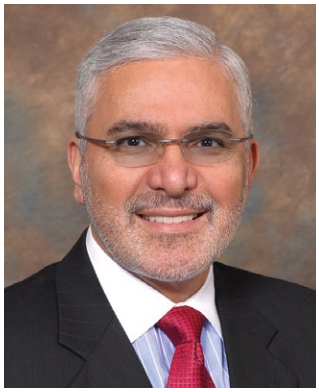

Henry A. Nasrallah, MD
Editor-in-Chief

Pleiotropy of psychiatric disorders will reinvent DSM

The future of psychiatric diagnosis is destined to be reshaped by the rapidly unfolding and disruptive genetic and neuroscience discoveries.

Momentous discoveries about the shared neurogenetics of psychiatric disorders eventually will render DSM-5 obsolete

Although it has been slow in coming, the pace clearly is accelerating and new findings are bubbling up at a breathtaking rate. The insights that genetic underpinnings of neuropsychiatric disorders will bring to psychiatry unquestionably will be a disruptive body of scientific knowledge that will drastically change the current descriptive psychiatric diagnostic schema as well as the therapeutic and preventative approaches to psychiatric illness. Pleiotropy—when one gene can influence multiple clinical phenotypic traits—will transform our view of psychiatric disorders into interrelated components of a syndrome. This is not unlike the metabolic syndrome, where ≥1 features (obesity, insulin resistance, hyperglycemia, dyslipidemia, and hypertension) cluster in the same individual or family, and may be caused by a genetic risk factor.

A study of 33,332 psychiatric patients and 27,888 healthy controls published in February 2013 found a genetic link among 5 major psychiatric disorders: attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorders (ASD), bipolar disorder (BD), major depressive disorder (MDD), and schizophrenia.[1] The specific genetic link across those 5 disorders, identified by a commonly used genetic method called a genome-wide association study (GWAS), was a set of 4 risk loci on chromosomes 3 and 10, as well as a single nucleotide polymorphism (SNP) of 2 genes called calcium channel α-1C (CACNA1C) and CACNB2, both of which are involved in neuronal calcium channel signaling. This finding implicates calcium balance in all 5 disorders. Many clinicians may recall that calcium channel blockers have been proposed as a treatment for BD for the past 2 decades.[2] CACNA1C has been associated with ASD and identified as a gene in common in BD and schizophrenia in prior studies, and even may influence cognition[3] and schizotypal personality.[4]

Although these findings may come as a surprise, they shouldn't. We have observational clinical data in psychiatry that show clustering of ≥2 disorders in the same patient or family. BD often is accompanied by ADHD in childhood and with obsessive-compulsive disorder (OCD), panic disorders, social anxiety, borderline personality disorder, and alcohol abuse in adults. MDD frequently clusters with alcohol abuse, anxiety disorders, cognitive dysfunction, and personality disorders. Studies have established that rates of MDD, substance use, OCD, cognitive deficits, and personality disorders are higher in the families of patients with schizophrenia. Anorexia nervosa patients often manifest body dysmorphic disorder, OCD, depression, or per-

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sonality disorders. Finally, psychiatric practitioners know all too well that the same medication may exert efficacy in several DSM disorders. Pleiotropy may play a role in all of these clusters and it is only a matter of time before genetic evidence emerges, helping psychiatry connect the observational clinical dots with indisputable genetic evidence. We can hardly wait!

Psychiatrists should start conceptualizing DSM-5 disorders not as free-standing medical conditions but as syndromes—collections of inter-related clinical phenotypes resulting from pleiotropic genes. Given the extensive structural and neurochemical interconnectedness of brain cells, regions, and circuits, it is surprising that we have not approached psychiatric disorders in this fashion long ago, instead of falling in the trap of manufacturing artificially isolated mental disorders and then inventing the concept of "common comorbidity" to explain what we are seeing instead of seeking a genetic linkage between them. It took a century before Syndrome X, later called metabolic syndrome, was recognized as a cluster of several metabolic disorders, and psychiatry may be evolving in the same direction. Further, pleiotropy eventually can help us understand the co-occurrence of disorders of the body with disorders of the brain, explaining why glucose intolerance, dyslipidemia, and hypertension tend to be 2- to 3-fold higher in schizophrenia patients and BD patients even before they are exposed to medications, which can add an iatrogenic exaggeration of those metabolic symptoms. Cognitive impairment observed across major psychiatric disorders may be a product of pleiotropy. In short, many DSM-IV-TR axes I, II, and III disorders that have been eliminated in DSM-5 may one day be shown to have pleiotropic roots and lead to a completely new conceptualization of psychiatric and medical syndromes and novel approaches to treating them.

The plot thickens, and that's welcome news for the future of psychiatry. We are on the verge of a stunning new era where disease models, diagnostic paradigms, treatment strategies, and prevention approaches will be driven by glorious insights into our patients' DNA. Biotherapies will be based on unambiguous, genetically (or epigenetically) driven pathophysiologies, which will be confirmed in the lab by various biomarkers, including recognized SNPs and mutations and abnormal proteins produced by specific abnormalities in genetic transcription (for a discussion of potential genetic biomarkers of schizophrenia, see "Genetics of schizophrenia: What do we know? Current Psychiatry, March 2013, p. 24-33; http://bit.ly/SchGEN313). Our patients will be the beneficiaries of far more rational diagnostic and therapeutic approaches and their outcomes will be far more optimal than what they currently are.

This is why I tell our medical school students there has never been a better time to choose psychiatry as a career.

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