Searching Across Diagnostic Boundaries

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Until very recently, schizophrenia (SZ) and bipolar disorder (BP) have been conceived as 2 separate conditions. This distinction is taught in medical and graduate studies, is maintained in diagnostic classifications, and relied on by regulatory bodies, drug companies, researchers, clinical care and research funding agencies, and advocacy groups. Not being able to know if BP, SZ, and schizoaffective disorders belong to a continuum or are separate disorders is an example of one of the most debated topics in psychiatry. Indeed, because the advent of descriptive psychiatry over 2 centuries ago, attempts to validate psychiatric diagnosis, including SZ and BP, have been an ongoing source of controversy and disillusionment. Psychiatrists know that between these diagnostic entities, there are not only symptom, diagnostic, and treatment overlap but also shared genetic and environmental risk factors. This confusing situation may be explained by 3 types of conceptual issues regarding classification systems:

1. Diagnostic classification claim that they are “a-theoretical,” offering a pragmatic system without making any assumption on mechanisms and possible validators.
2. Most classification fail to acknowledge differences in clinical presentations associated with stages of illness, thus failing to acknowledge the fact that BP and SZ are chronic, multisystemic disorders evolving through different stages.
3. Diagnoses rely mainly on assessment of symptoms and course, but not on biomarkers or pathophysiological measurements.

In addition, after 100 more years of research, most of the scientific results that document BP and SZ distinctions from nonill control subjects do not support consistent biosignatures that distinguish BP from SZ. Rather, these studies suggest a shared etiology to both SZ and BP with brain structural abnormalities, such as whole brain, total gray and white matter volume reduction, increase of lateral ventricular volume, shared genetic risk factors that confer susceptibility across a BD-SZ continuum as shown by family, high-risk subjects, twin studies, molecular studies, and biological factors such as low-grade inflammation. Developmental risk factors such as prenatal maternal nutritional deficiency, second-trimester infections, winter-spring season of birth, obstetrical complications, and urbanicity are all shared environmental risk factors reported both in BP and SZ.

As clinical syndromes, SZ and BP have been clinically useful with some interesting differences such as the role of lithium therapy or the pattern of development of cognitive impairment. But these categories also limit the acquisition of new knowledge. To draw attention to important differences and similarities between SZ and BP, the Schizophrenia Bulletin is encouraging submission of high-quality research addressing the BP/SZ boundary and will launch a new Special Feature on concepts exploring the BD/SZ boundary.

Four areas of research aiming at the identification of subgroups, stages, quantitative profiling, and precision tools are important in our quest to see beyond the traditional boundaries.

Toward Subgroup Identification

We need to identify biomarker-defined subtypes providing a new stratified psychiatry. However, so far, examples of identification of disease process, defining a scientifically valid diagnosis with biological markers, mechanisms, and treatment effects, have rarely been obtained in psychiatry. Two insightful examples of efficient identification of subgroups can nevertheless be described: Narcolepsy, a lifelong sleep disorder, sometimes viewed as a psychiatric disorder because of hallucinations and cataplexia, is now known to be a valid clinical entity caused by the autoimmune-mediated loss of hypocretin producing neurons in the hypothalamus, found to be triggered by H1N1 infections, which interact with human leukocyte antigen gene variants. Along the same vein, elevated anti-N-methyl-D-aspartate antibodies have been found in the serum of
patients having pure psychiatric symptoms, acute manic episode, and schizophrenic patients, with potentially effective immunomodulatory treatments used to alleviate psychiatric symptoms in this biomarker subgroup of patients. The first illustrates moving from a syndrome to a specific disease entity and the second illustrates understanding pathophysiology across diagnostic boundaries.

Toward Staging Identification
We need tools to take into account the now well-recognized fact that major mood and psychotic disorders are “not static, sharply defined illnesses with separate etiologies and courses, but rather syndromes that overlap and develop in stages.” Clinical staging, determined by the dimensions of severity of symptoms, distress, disturbances in relationships, and functioning, aims to bring us closer to other branches of medicine and to provide an accurate guide for the choice of therapeutic intervention. Understanding how the genetic, environment, biochemical, and neurobiological biosignatures provides tool to define stages would be a major advance, not only in the quest for personalized medicine but also for validity in psychiatric diagnosis.

Toward Precision/Personalized Psychiatry
We need a more precise and objective clinical system for everyday clinical practice. In other field of medicine, in order to overcome unexplained medical heterogeneity, precision diagnostic tools have been introduced such as measure of blood pressure or of glycemia, allowing to precisely monitor individualized information enabling precise monitoring of treatment needs and responses. Similar systems need to be developed in psychiatry to improve quality of assessments for domains such as sleep, emotions, stress, and lifestyle, enabling better collaboration with patients who will be asked to actively collaborate to collect and to interpret the data. Examples of Momentary Assessment Approach provide new approaches to identification of environmental risk factors, symptom patterns, and innovative treatment tools. Another example can be found in computerized adaptive tests that allow self-assessment of multidimensional data using a small set of items for each examinee out of a much larger bank of test items, thus reducing the time needed to assess symptoms and increasing precision of measurement.

Toward Quantitative Psychopathological Profiling
Recently, it has been suggested that the best diagnostic strategies should be based on assigning individuals to diagnostic categories in combination to measurement of quantitative dimensions such as positive, negative, depressive, and manic symptoms. Mental disorders possibly represent the end point of different sets of symptoms and dimensions that interact which would explain their co-occurrence and comorbidity in a given patient. Thus, new models need to be described based on intra- and intersymptom feedback loops representing the dynamics of symptoms impacting on each other. Momentary Assessment Technology phenotypes capturing dimensional variation in mental states in response to other mental states and environmental events will provide a fertile model for investigation of psychopathology.

Studying the diagnostic overlap and explaining comorbid pathologies will address the complex nature of psychotic disorders and provide a better conceptual framework for translational research. To further advance research, it may be necessary to create shared data sets as well as draw on successful models outside of psychiatry (eg, computational engineering) to explore complex networks, deciphering common pathways of BD and SZ; to apply new technologies such as mobile phone–based assessment that allows data uploading in real time, helping to facilitate earlier intervention; and ultimately to question, in a dynamic and integrative way, our classical vision of nosography.

To succeed, we will need, eg, to use new tools brought by mathematicians in order to explore complex networks, to decipher progress of technology such as the use of mobile phone for data collection, to be able to analyze big data, and finally to question in a dynamic way our classical vision of nosography.

References


