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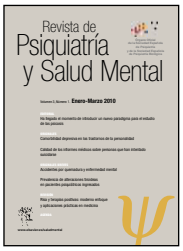

EDITORIAL

It is Time for a New Paradigm for the Study of Psychoses

Ha llegado el momento de introducir un nuevo paradigma para el estudio de las psicosis

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Is the Kraepelinian dichotomy dead? It is timely to consider this issue in that DSM-V and ICD-11 are currently being developed. The question gains momentum as evidence of overlap between schizophrenia and bipolar disorder accumulates. The most compelling evidence for the porous boundary comes from genetic, endophenotypic, and imaging studies.[1] Linkage and association studies tend to reveal overlap while family pedigree studies tend to support separateness.[1] Endophenotypes such as pre-pulse inhibition and P300 are associated with both disorders, but others such as mismatched negativity and initiation of smooth pursuit are differentially associated with schizophrenia. The conundrum is nicely illustrated by Litchenstein et al[2] who estimate that about 60% of the variance in each disease is based on genetic effects. But these effects are about evenly distributed among shared and non-shared genetic effects. It is not known which is decisive [if either] for validation of diagnostic class. In any event, Kraepelin would not be very impressed with the nature of the debate.

Modern diagnostic criteria for schizophrenia and bipolar disorders relate to concepts quite different from the phenomenology of dementia praecox and manic-depressive disease.[3] Kraepelin stressed the combination of avolition and dissociative thought pathology together with a chronic course for dementia praecox and manic and depressive pathology in an episodic pattern with a substantially more favorable course for manic-depressive illness. The diagnostic systems most used in research studies for the past four decades have stressed reality distortion pathology for schizophrenia. Criteria A for schizophrenia in DSM-IV-TR can be met by hallucinations and delusions, or even delusions alone if bizarre. Even Bleuler considered these symptoms secondary and not decisive for a diagnosis of schizophrenia.[4] The negative symptom construct was not even an A criterion in DSM-III. Course requirements for both disorders have been set aside, and an episodic pattern with recovery periods is not required for bipolar. The result is two large syndromes with extensive overlap rather than two putative disease entities modestly separated by phenomenological features. Cuesta and Peralta[5] describe the main changes in ICD-10 and DSM-III and IV and how these changes increase similarity and decrease points of rarity between the major syndromes. The extensive data generate in the past four decades are not generated by studies with fidelity to Kraepelin's formulation.

If one accepts the proposition that schizophrenia and bipolar disorders represent syndromes, the first challenge is to reduce heterogeneity. Traditional schizophrenia subtypes and bipolar I and II have not been decisive in this regard. Another approach, relating more closely with Kraepelin's emphasis on avolition, has put negative symptom pathology at the forefront of heterogeneity reduction for schizophrenia.[6-9] Studies at the MPRC resulted in the hypothesis that deficit schizophrenia is a separate disease within the schizophrenia syndrome with support from clinical features, etiologic risk factors and neuropathology.[10] Nonetheless, attempts to define specific disease entities within the syndromes have not resulted in substantial advances in clinical methods or understanding of diagnostic classes.

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One alternative is to simply combine the syndromes with the argument that there is a psychosis continuum.[11,12] There are two immediate problems with this approach. The first is the assumption that psychosis is the organizing factor and fundamental to etiopathophysiology. To the contrary, it is clear that psychosis, especially reality distortion, occurs in disease states known to differ in etiology [e.g., temporal lobe epilepsy, Alzheimer's Disease, amphetamine and PCP induced psychoses]. Reality distortion may be similar to pain when it comes to diagnostic validation: both are clinically important and must be addressed, but are not specific to a unique disease process. The second problem is that combining syndromes simply increases the heterogeneity that already weakens hypothesis-testing research.[13]

A second alternative approach moves in an entirely different direction. Dormant for many years, a domains of pathology approach may more robustly address the heterogeneity of syndromes and clarify the between syndrome overlap of pathologies and etiologies.[5,13-16] John Strauss pointed the way with an emphasis on dimensions long ago,[17] and we explicitly recommended that etiology and treatment discovery move from the syndrome to specific domains of pathology (6 1974). This approach to psychopathology is further elaborated by Peralta and Cuesta.[18,19] Domains of pathology was endorsed by the NIMH MATRICS project (http://www.matrics.ucla.edu/matrics-psychometrics.shtml) that isolated cognition impairment as an unmet treatment need that required novel drug discovery. This therapeutic need has not been addressed by refinement of antipsychotic drugs. The FDA in the United States has indicated that cognition as an indication within schizophrenia can be approved if efficacy is established.[20] To date all drugs have been approved for schizophrenia as a class rather than specific indications. A similar advance has been made with the negative symptom construct, and clinical trial designs essential for isolating efficacy for these two domain have been published as consensus statements.[20,21]

It now appears that the field may be ready to take a major step in this direction as DSM-V and ICD-11 are being prepared. As chair of the Psychosis Work Group and Task Force member for DSM-V, I am familiar with proceeding to date. However, the views expressed here are personal and are not official positions of the Work Group or Task Force.

The central purpose of diagnostic manuals is to provide clinicians with a systematic approach to diagnoses for the multiple purposes essential to clinical practice, therapeutics, record keeping and communication. Heterogeneous syndromes, especially schizophrenia, provide little guidance to clinical practice and are inadequate for educational purposes. Clinicians do not treat schizophrenia. Rather, they evaluate persons with this diagnosis to determine therapeutic targets in each individual. Is the person psychotic? Depressed? Manic? Anxious? Low energy? Avolitional? Restricted affect? Suicidal? Sleep disturbed? Aggressive? Cognitively impaired? Psychomotor problems? Not to mention the myriad of functional and relationship issues routinely encountered. In short, the clinician gains a general orientation with the syndrome diagnosis and immediately moves assessment to psychopathology and functional dimensions. While this information is considered in the diagnostic process, it becomes central when considering management and therapeutics. This is why it is so important that drug discovery for psychotic illnesses shift from the paradigm that repeatedly produces dopamine antagonists for psychosis, to a paradigm that produces novel compounds for discrete domains of pathology.[22,23]

DSM-V is very likely to establish a dimensional system parallel in importance to diagnostic categories. This will give emphasis to the evaluation of psychopathology in the therapeutic spectrum as well as in the classification spectrum. As important as a shift to this new paradigm is for clinical practice, it may be even more heuristic for scientific investigations. The porous boundaries between schizophrenia and bipolar disorders may be understood at the domain level. A working hypothesis is that most bipolar patients experience pathological depression and that the majority of schizophrenia patients also experience pathological depression. Vulnerability genes for depression may be associated with both syndromes producing genetic overlap. Avolition may occur in a substantial minority of persons with schizophrenia, but in very few people with bipolar disorder. Genetic vulnerability for avolitional pathology may be restricted to schizophrenia [and schizoid and schizotypal personality disorders] and support the two-syndrome model. But in this instance, avolitional schizophrenia may also be distinguished from schizophrenia without avolitional pathology.

In addition to reducing heterogeneity at the syndrome level and providing more meaning clinical targets for treatment and research, the dimensions will provide a more robust approach to relating neural systems to pathology, of determining the relevance on endophenotypes, and providing clinical concepts to guide development of animal models. In fact, one can envision this paradigm shift benefiting almost all aspects research. In particular, it should enable non-replicating studies to be hypothesis falsifying rather than type II errors caused by sampling a different component of a heterogeneous syndrome.

The questions will move from how are schizophrenia and bipolar similar and how are they different to a new set of questions. These will include questions of similarities and differences between psychotic and non-psychotic bipolar patients; between avolitional and non-avolitional schizophrenia subjects; and similar questions comparing depressed schizophrenia subjects with depressed bipolar subjects. It is envisioned that research conducted within the domains of pathology paradigm will be informative regarding the porous boundaries between syndrome classes, will guide within syndrome heterogeneity reduction, and will become the defining pathologies for investigations ranging from animal models and gene associations to neural networks and biomarker discovery. Most importantly, DSM-V guided clinical assessment will dealt more directly with the aspects of illness that require clinical action.

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