Conceptualizing Schizophrenia Through Attenuated Symptoms in the Population

In this issue of the *Journal* (1), Dominguez and colleagues report that attenuated symptoms associated with the schizophrenia spectrum occur frequently in a representative population. Critical new information is provided on domains of pathology involved, risk factors and timing for each domain, and psychopathology that increases clinical relevance. This study touches on themes of substantial interest in conceptualizing schizophrenia (and other psychotic syndromes) and is informative on controversial issues in the development of DSM-5.

Briefly stated, Dominguez et al. report that attenuated negative symptoms, disorganization, and positive psychotic symptoms are observed in a representative population cohort of adolescent and young adult citizens. Negative symptoms and disorganization join to form one factor, and they co-occur with positive psychotic symptoms that involve distortion of reality more frequently than expected by chance. The former are associated with developmental risk factors and the latter with later exposure to environmental risks. Negative/disorganized symptoms tend to predict the subsequent appearance of positive psychotic symptoms, and together these domains increase the probability of being a clinical case.

The data in this study touch on issues of interest to me over the past 40 years, and relate to changes that are being considered for DSM-5. First is the issue of separate domains of pathology within the schizophrenia syndrome as proposed by Strauss et al. (2). Many succeeding studies support disorganization of thought and behavior as separable from both negative symptoms and positive psychotic symptoms (i.e., hallucinations and delusions) (3). Kraepelin considered avolition and dissociative pathology the two clinical maladies that, when co-occurring, present as dementia praecox. Avolition is a component of current concepts of negative symptoms and anchors one of the factors, while restricted affect anchors the second negative symptom factor (4). Disorganization pathology today is broader than Bleuler's dissociative pathology, but it includes the "split" within thought and between thought, affect, and behavior. Finding that co-occurrence in a representative population exceeds chance gives special emphasis to the original Kraepelinian construct. It is important to note that in combination the prognosis is worse, and the probability of the individual having a case of schizophrenia is increased. It is possible that the separation of these two pathologies in established cases of schizophrenia is partly related to treatment, since antipsychotic drugs have efficacy for disorganization but not for negative symptoms. Also, disorganization can lead to secondary negative symptoms that further confound the relationship (5).

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It has been established that negative symptoms often precede the onset of psychosis in schizophrenia. Confirming this pattern in a population-based cohort is important, but the more interesting finding is a differential relationship with risk and prognostic variables. Earlier age of onset, being male, being single, and a lower level of education

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were associated with negative/disorganization pathology. The authors suggest that this aspect of pathology is developmental in nature and postulate that it represents a genetic liability. This seems likely since some genes associated with schizophrenia are expressed only during brain development, but a number of environmental risk factors also occur early. Prenatal stressors including infection and complications at delivery are among a number of risk factors reviewed recently by Brown and Derkits (6). Neurodevelopmental etiological pathways surely include genes, epigenetic alterations, and environmental insults directly impacting on brain development.

The later onset of positive psychotic symptoms and their association with environmental risk factors that develop later suggests a different causal pathway. Urbanicity, cannabis exposure, low level of education, and trauma are the associated environmental variables. The low level of education probably reflects impairment in cognition and motivation, but the other variables are credible as contributing to the causal pathways. These data raise the interesting possibility that neurodevelopmental pathology is manifest in negative and disorganized symptoms but also creates a vulnerability for positive psychosis in the context of later environmental insults. This adds specificity to the familiar "two-hit" hypothesis. It also raises the question of a distinct pathway to psychosis in the absence of developmental pathology, a pattern observed often in schizophrenia as presently defined. There are also a number of classes of psychotic disorders in DSM-III and DSM-IV that are not associated with the avolitional and disorganizational pathology or with the early morbid (or poor premorbid) variables associated with some forms of schizophrenia. Because DSM-III did not include negative symptoms as an A criterion and DSM-IV provides, but does not require, a negative symptom criterion, cases of schizophrenia can be diagnosed only on the basis of psychotic reality distortion symptoms, especially the Schneiderian first-rank symptoms. In studies at the Maryland Psychiatric Research Center, we have found that schizophrenia patients with avolitional pathology are a minority and that the presence of that pathology helps define a separate putative disease entity within the schizophrenia syndrome that we have termed the deficit syndrome (7).

The Dominguez et al. report is especially timely as it relates to two areas of potential innovation in the psychoses chapter of DSM-5. I chair the Psychosis Work Group and Dr. van Os, an author of the report with Dominguez, is a member. Finding that positive psychotic symptoms are a separate pathology domain from negative/disorganized symptoms in young people with attenuated symptoms reinforces the view of schizophrenia and other psychotic disorders as syndromes rather than disease entities, and that individuals in the same class have substantial differences in psychopathology. This calls for deconstruction of the syndrome into component parts, something we advocated prior to DSM-III (2) and more recently clarified by Peralta and Cuesta (8) and in a DSM-5 lead-in conference (9–12). We plan to field test the user-friendliness and reliability of a set of dimensions representing clinical phenomena such as hallucinations, delusions, disorganization, restricted affect, avolition, cognition impairment, anxiety, depression, and mania. These dimensions are supported by empirical study and may become primary targets for research and treatment development.

The second issue is very controversial. There is substantial evidence that attenuated psychotic symptoms can be used to identify persons at increased risk for developing a full psychotic syndrome (13). The data from Dominguez et al. support this proposition and suggest that combining negative/disorganized symptoms with attenuated psychotic symptoms increases the identification of clinical relevance. But the data also remind us that attenuated positive psychotic symptoms are not uncommon in the non-ill population, thus raising concerns that clinical caseness will come to include non-ill individuals. Nonetheless, early detection and intervention is a meritorious goal throughout medicine and there is ample evidence that early treatment of schizophrenia is most effective. The potential for this new diagnostic class is illustrated in a recent report that omega-3 fatty acid was substantially more efficacious than placebo

in a random assignment, masked, controlled study in which 12 weeks of treatment appeared to provide protection from psychosis for the next 40 weeks (14). This raises the interesting possibility that disease progression may be prevented at a critical time-point intervention, potentially altering the life course of illness. Replication is essential, and at present the standard of care for persons with attenuated psychotic symptoms is clinical monitoring and psychosocial interventions aimed at stress reduction, maintaining social and occupational niche, avoiding drugs of abuse, and more specific intervention only if attenuated symptoms exacerbate into a psychotic disorder.

Although there is little doubt as to the validity of attenuated psychotic symptoms marking vulnerability for psychotic illness, legitimate concerns include the extension of psychiatric diagnosis into non-ill populations, the potential for excessive and risky medication use, the stigma that may be associated with the diagnosis, and whether it requires special expertise to apply the criteria reliably. A response to these concerns is as follows: 1) criteria proposed for DSM-5 strictly require that the person not meet criteria for another DSM disorder and that the person is help seeking with the presence of distress, disability, and dysfunction; 2) antipsychotic drugs are already used in excess in this age group and it is possible that organizing awareness and education around this classification will decrease rather than increase the use of these drugs before psychosis is manifest; 3) stigma may also be associated with the development of abnormal behaviors, deterioration of friendships and role performance, and seeking of clinical care with some other diagnosis; and 4) field trials will be used to determine reliability, including specificity and sensitivity, in ordinary clinical settings.

While the Dominguez et al. report is focused on attenuated symptoms in a representative population of young people, these data are informative on several broad issues that challenge the field. Their report supports the use of dimensions of pathology in addition to diagnostic classes for psychotic disorders, an outcome likely for DSM-5. It also adds important data to the vexing issue of whether to establish a diagnostic class for help-seeking persons who manifest attenuated psychotic symptoms.

References

1. Dominguez MDG, Saka MC, Lieb R, Wittchen H-U, van Os J: Early expression of negative/disorganized symptoms predicting psychotic experiences and subsequent clinical psychosis: a 10-year study. Am J Psychiatry 2010; 167:1075–1082
2. Strauss JS, Carpenter WT Jr, Bartko JJ: The diagnosis and understanding of schizophrenia, part III: speculations on the processes that underlie schizophrenic symptoms and signs. Schizophrenia Bulletin 1974; 11:61–69
3. Buchanan RW, Carpenter WT: Domains of psychopathology: an approach to the reduction of heterogeneity in schizophrenia. J Nerv Ment Disord 1994; 182:193–204
4. Blanchard JJ, Cohen AS: The structure of negative symptoms within schizophrenia: implications for assessment. Schizophrenia Bull 2006; 32: 238–245
5. Kirkpatrick B, Fenton WS, Carpenter Jr WT, Marder SR: The NIMH-MATRICS consensus statement on negative symptoms. Schizophrenia Bull 2006; 32: 214–219
6. Brown AS, Derkits EJ: Prenatal infection and schizophrenia: a review of epidemiologic and translational studies. Am J Psychiatry 2010; 167:261–280
7. Kirkpatrick B, Buchanan RW, Ross DE, Carpenter WT: A separate disease within the syndrome of schizophrenia. Arch Gen Psychiatry 2001; 58:165–171
8. Peralta V, Cuesta MJ: The nosology of psychotic disorders: a comparison among competing classification systems. Schizophrenia Bull 2003; 29:413–425
9. van Os J, Tamminga C: Deconstructing psychosis. Schizophrenia Bull 2007; 33:861–862
10. Allardyce J, Gaebel W, Zielasek J, van Os J: The validity of schizophrenia and alternative approaches to the classification of psychosis. Schizophrenia Bull 2007; 33:863–867
11. Dutta R, Greene T, Addington J, McKenzie K, Phillips M, Murray RM: Biological, life course, and cross-cultural studies all point toward the value of dimensional and developmental ratings in the classification of psychosis. Schizophrenia Bull 2007; 33:868–876
12. Owen MJ, Craddock N, Jablensky A: The genetic deconstruction of psychosis. Schizophrenia Bull 2007; 33:905–911
13. Woods SW, Addington J, Cadenhead KS, Cannon TD, Cornblatt BA, Heinssen R, Perkins DO, Seidman LJ, Tsuang MT, Walker EF, McGlashan TH: Validity of the prodromal risk syndrome for first psychosis: findings from the North American Prodrome Longitudinal Study. Schizophrenia Bull 2009; 35:894–908

14. Amminger GP, Schafer MR, Papageorgiou K, Klier CM, Cotton SM, Harrigan SM, Mackinnon A, McGorry PD, Berger GE: Long-chain-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. Arch Gen Psychiatry 2010; 67:146–154

WILLIAM T. CARPENTER, JR., M.D.

Address correspondence and reprint requests to Dr. Carpenter, Maryland Psychiatric Research Center, University of Maryland School of Medicine, P.O. Box 21247, Baltimore, MD 21228; wcarpent@mprc.umaryland.edu (email) *Editorial accepted for publication June 2010 (doi: 10.1176/appi.ajp.2010.10060854).*

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