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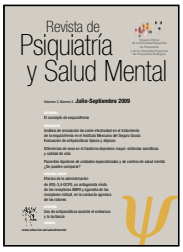

EDITORIAL

The Concept of Schizophrenia

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All clinicians who work with people with schizophrenia are teachers, as we teach patients and their families about the disease and its management. What, then, should we say? What kind of disease is schizophrenia?

In the Diagnostic and Statistical Manual of the American Psychiatric Association, schizophrenia is classified as a psychotic disorder; and the most common model that clinicians present is that it is a psychotic disorder that is primarily due to abnormal dopamine function. This model has dominated thinking about the disorder for decades. Although dopamine is central to the mechanism of action of current antipsychotics, other neurotransmitter systems are also an important part of the pathophysiology of psychosis.[1,2] If therapeutic agents with another mechanism of action had come first, the dopamine theory would not dominate thinking the way that it does now. In short, the simple equation schizophrenia = dopamine abnormality = psychosis is something of a historical aberration, due to the fact that the dopamine antagonists were the first treatment with strong evidence for efficacy, and for many years have been—leaving aside any contribution of serotonin to their efficacy—the only class of drug with such evidence. Contrast this situation with the therapeutics of, for instance, hypertension, for which diuretics, beta blockers, angiotensin-converting enzyme inhibitors, and other drugs have all been available.

The concept that schizophrenia is exclusively or primarily a psychotic disorder is also somewhat misleading. Psychosis is integral to schizophrenia, but so are other neuropsychiatric syndromes, including depression, substance abuse, and anxiety disorders.[3] Cognitive impairment—difficulties in memory, attention, executive function, etc.—is widespread, with many cognitive domains affected,[4] it may precede the onset of psychosis, and it is a strong predictor of function.[5] Cognitive impairments are also found in relatives of schizophrenia probands, some abnormalities have been used as endophenotypes to explore the genetics of schizophrenia, and these impairments have become therapeutic targets for pharmaceutical companies. Antipsychotic-naïve patients also have an increased prevalence of dyskinetic movements, as do their relatives.[6] Increased neurological signs that cannot be attributed to antipsychotic treatment are found in patients with schizophrenia, as well as in their families.[6] These neuropsychiatric syndromes are not comorbid with schizophrenia; for many patients, they are part of schizophrenia. Psychosis can be terribly impairing, but it may not be a coincidence that diagnostic criteria focus primarily on psychosis in an era in which that is one of the most treatable aspects of the disorder.

Another weakness of the common concept of schizophrenia is that it is thought to be exclusively a brain disease. However, there has been evidence for many years that as a group, people with schizophrenia have a number of subtle anatomical variants that can only be explained as abnormal organ formation during gestation.[7] These are not confined to the head and neck, but include abnormalities in the toes, the venous plexus of the fingernails, fingerprints, and others. Patients with schizophrenia also have a distinctive developmental pathway, with low birth weight and a thin body build from childhood into early adulthood.[8]

The pathology found in schizophrenia may also extend to metabolic problems. Although there are also some negative studies, there is increasing evidence for an increased risk of diabetes in newly diagnosed,

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antipsychotic-naïve patients with schizophrenia and related disorders; diet, socioeconomic status, and health habits do not appear to account for this risk.[9,10] Other problems that are associated with both diabetes and an increased mortality rate have also been found in schizophrenia, including increased inflammation, a shortened telomere, and an increased pulse pressure.[10-13]

A more accurate concept of schizophrenia can be summarized as follows:

— Schizophrenia is not a psychotic disorder; it is a developmental disorder with abnormalities in many brain functions, including psychosis.
—Schizophrenia is not a brain disease; it is a developmental disorder that affects other parts of the body as well as the brain.

This broader model has important clinical advantages. If they have this concept of schizophrenia, clinicians are more likely to attend to the metabolic problems and neuropsychiatric syndromes other than psychosis that are so common in people with schizophrenia. If patients and family members have this same concept, they are more likely to bring these other problems to the attention of clinicians.

The model also raises questions that deserve investigation. Outside of populations with psychosis, inflammation and diabetes are associated with cognitive impairment. One preliminary study suggests diabetes is associated within greater cognitive impairment within schizophrenia as well.[14] There are studies that show that exercise, which decreases inflammation and improves glucose tolerance, improves cognition in the elderly. Might exercise improve cognition in schizophrenia? Will the preliminary evidence[15,16] that anti-inflammatory drugs improve the symptoms of schizophrenia in patients during an acute relapse be confirmed? Adults appear to have circulating stem cells that aid in normal repair processes, such as healing a fracture, recovery from myocardial infarction, or recovery from a stroke. In a study that showed a decrease in the chemokine that regulates the trafficking of these cells in antipsychotic-naïve patients with nonaffective psychosis, lower concentrations of this chemokine were associated with more severe positive symptoms.[17] Could the circulating stem cell system provide an avenue for therapeutic intervention for any of the problems found in schizophrenia?If the familial relationship between diabetes and schizophrenia is confirmed,[18-20] such a finding would have uses as well. It might point to specific mechanisms of diabetes, or be useful for finding genes of risk in both disorders.

Clinicians need to remember that schizophrenia is more than psychosis, and that people with schizophrenia have a heavy burden of medical problems and an increased mortality.[21] We should teach the most accurate concept of schizophrenia to our students, our patients, and our patients' families. The dopamine theory is a useful model for the therapeutics of current antipsychotics, but it is not a useful model of the disorder of schizophrenia.

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