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Schizophrenia: A Systemic Disorder

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Abstract

The concept of schizophrenia that is most widely taught is that it is a disorder in which psychotic symptoms are the main problem, and a dysregulation of dopamine signaling is the main feature of pathophysiology. However, this concept limits clinical assessment, the treatments offered to patients, research, and the development of therapeutics. A more appropriate conceptual model is that: 1) schizophrenia is not a psychotic disorder, but a disorder of essentially every brain function in which psychosis is present; 2) it is not a brain disease, but a disorder with impairments throughout the body; 3) for many patients, neuropsychiatric problems other than psychosis contribute more to impairment in function and quality of life than does psychosis; and, 4) some conditions that are considered to be comorbid are integral parts of the illness. In conclusion, students, patients, and family members should be taught this model, along with its implications for assessment, research, and therapeutics.

Keywords

Schizophrenia; Psychosis; Neurodevelopment; Dopamine; Endophenotype

> "When you make a description, you bring into being a class of explanations which is later held to be relevant."
>
> —Trenton Wann

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Introduction

Because of its severity, chronicity, early age of onset, and prevalence, schizophrenia is the source of enormous human and economic costs. The World Health Organization has labeled it one of the top ten causes of disability in developed countries worldwide (1). For schizophrenia—as for other disorders—the conceptual model that clinicians utilize directly dictates assessment, and assessment limits the interventions that will be offered to the patient. As therapeutic tools become available, clinicians are more likely to make appropriate choices about the use of these tools if they have an accurate understanding of the disorder they are treating. The conceptual model of a disorder can also limit research. Current evidence suggests the usual conceptual model of schizophrenia needs to be revised. We present here a model emphasizing that schizophrenia is a complex disorder with several manifestations outside the brain and, commonly, neuropsychiatric conditions in addition to psychosis.

The evidence for this concept is extensive, and is based on evidence from several lines of research. However, we do not propose that this is a comprehensive concept of the disorder, and within the scope of this single article it is not possible to discuss such important concepts as a dimensional *versus* categorical nosology, genes and other risk factors, or the presence or absence of a degenerative process. However, this is a more appropriate concept to present trainees, and is useful for both clinical care and research. Moreover, this concept may aid in unraveling some of these other long-standing questions in the future.

The Usual Model

The most common concept of schizophrenia focuses on positive psychotic symptoms—hallucinations, delusions, and disorganized speech and behavior. In more recent years, negative symptoms and cognitive impairment have also been considered, but both positive and negative symptoms are considered to be the result of dopaminergic dysregulation. The psychosis-centered model was not the initial conceptual formulation of schizophrenia, as described by Kraepelin and Bleuler, but the presence, temporal aspects, and nature of psychotic symptoms are the basis of the American Psychiatric Association's *Diagnostic and Statistical Manuals' (DSM)* diagnostic criteria, as well as other diagnostic criteria used worldwide, in part because of its superior inter-rater reliability. Moreover, antipsychotic drugs have been the only proven treatments for any aspect of the disorder.

Empirical evidence supports the use of the *DSM* criteria for distinguishing schizophrenia from other disorders, but diagnostic criteria are not the same as the concept one has of a disease. For instance, diabetes is defined on the basis of serum glucose concentrations, but students are routinely given a concept of the disorder that includes the pathophysiological role of inflammation, as well as long-term complications such as neuropathy, retinopathy, and nephropathy. In the same way, schizophrenia might be considered a clinical entity with psychiatric and non-psychiatric features, rather than exclusively a positive and negative symptoms disorder.

Problems with the Usual Concept

The concept that schizophrenia is nearly equivalent to psychosis is flawed in several ways. First, psychotic symptoms are not specific to schizophrenia. Such symptoms are relatively common in affective disorder, and can also be found in some cases of Huntington's disease, Alzheimer's disease, delirium, and other neuropsychiatric conditions. Second, people with schizophrenia usually have other serious problems that are part of the illness, including neuropsychiatric syndromes other than psychosis, as well as anatomical and physiological abnormalities in the rest of the body. Although we are not able to provide an exhaustive bibliography in the scope of this article, it will be apparent that most of these abnormalities have been replicated.

Neuropsychiatric Syndromes Other Than Psychosis

Most people with schizophrenia have significant impairment in their function despite treatment with antipsychotic medications. This is the case even among patients whose positive psychotic symptoms—hallucinations, delusions, and disorganization—are well controlled with medications. Other neuropsychiatric problems make a substantial contribution to this impairment. These syndromes other than psychosis are not only common in schizophrenia, but are important determinants of the patient's degree of suffering, disability, and even survival. Estimates of the lifetime prevalence of major depression in schizophrenia are typically about 30–35%, and this problem undoubtedly makes a significant contribution to the high suicide rate in schizophrenia (2–4). Depression and schizophrenia may share some early-life risk factors (5–8), suggesting that these may share some aspects of etiopathophysiology. A population-based survey estimated 34% of subjects with schizophrenia have a lifetime diagnosis of alcohol abuse or dependence, while 47% had a lifetime diagnosis of any substance abuse or dependence (9), and estimates are even higher in clinical samples. Comorbid drug abuse is associated with a variety of poor outcome measures, such as an increased risk of relapse, poor treatment compliance, poor adherence to antipsychotic treatment, and greater use of crisis-oriented services (10, 11).

For many patients, cognitive symptoms are the answer to a common question posed by family members to health professionals: "My son/daughter doesn't hear the voices any more; why isn't he/she back to normal?" Several studies have shown that in outpatient settings, cognitive impairments are better predictors of a patient's level of function than is the severity of psychotic symptoms (12–14). The cognitive impairments found in schizophrenia are widespread (15), and not one of these cognitive domains has a degree of severity that is remarkably greater than that of other domains (16). Cognitive impairment also may be present prior to the onset of psychosis (17).

Anxiety disorders are also common in schizophrenia (18, 19–29). Anxiety per se is a strong predictor of subjective quality of life (30), and the presence of an anxiety disorder is associated with poorer role function in people with schizophrenia (31–33). Anxiety is associated with poor quality of life even after accounting for demographics, akathisia, cognitive impairment, depressive symptoms, and overall psychopathology, and the size of the impact on quality of life may be greater than that accounted for by depressive symptoms

(34). In a longitudinal, population-based study, the odds ratio for subsequently developing schizophrenia was >3.5 for subjects with obsessive-compulsive disorder (35).

Other brain dysfunction is also common in schizophrenia. Neurological impairments found in the disorder include problems with eye movements (36), motor coordination (37), sensory processing (38), and an increased prevalence of neurological signs (39). Patients with schizophrenia also exhibit abnormal movements prior to antipsychotic treatment (40–42). Several of these “comorbid” symptoms have been reported to have an increased prevalence in the first-degree relatives of schizophrenia probands: cognitive impairments (43), neurological signs (44, 45), anxiety disorders (46, 47), abnormal eye tracking (36), and dyskinetic movements (41). This shared familial risk undercuts the usual model of schizophrenia as mainly or exclusively a psychotic disorder, as it suggests that these other abnormalities are integral parts of the familial schizophrenia spectrum.

General Medical Conditions and Anatomical Abnormalities

Physiological and metabolic abnormalities are common in schizophrenia prior to antipsychotic treatment. There is extensive evidence for an increased pro-inflammatory state, and a meta-analysis suggests that there are both state inflammatory markers as well as trait markers (48, 49). People with schizophrenia have also been found to have a wide pulse pressure (50), a shortened telomere (51), and abnormal signaling of adult stem cells (52), which are involved in normal repair processes; these are found in newly diagnosed, antipsychotic-naive patients who are compared to well-matched control subjects. There are also mild immunological abnormalities, including an increase in autoantibodies (53–55), antibodies to intestinal antigens (56) or poor lymphocyte proliferation (57). Subtle endocrine abnormalities that do not appear to be due to antipsychotic treatment are also found (58–63), as are stigmata of early developmental problems, including low birth weight, abnormal dermatoglyphics, and other minor physical anomalies literally from head to toe (64–70). In addition to the variables in the widely used Waldrop scale, the minor anatomical anomalies are also found in the venous plexuses at the base of the fingernails (71, 72) and in the terminals of the peripheral motor nerves (73–75). The autonomic nervous system also functions abnormally in schizophrenia (76).

Some evidence suggests diabetes may have an increased prevalence in schizophrenia, independently of antipsychotic administration (50, 77, 78). Studies predating the advent of antipsychotics also suggested that impaired glucose tolerance has an increased prevalence within schizophrenia (79–83). These findings are consistent with the evidence that schizophrenia and diabetes may share risk factors, including shared familial risk (84–88, recently replicated, 89), prenatal famine (8, 90), and birth and gestational problems (91–95). In animals, prenatal stress (such as a swim test and restraint) increases risk of diabetes, and causes pharmacological and behavioral abnormalities—homologous to those in schizophrenia— in the offspring (96).

Recent studies underline the potential clinical importance of these general medical conditions. Friedman et al. (97) have shown that the severity of hypertension is related to the severity of cognitive impairment and, in randomized trials, treatment with aspirin (98) or a COX2 inhibitor (99), antibiotics with an anti-inflammatory effect (100, 101) or

pregnenolone (102) as an adjunct to antipsychotics, hastens recovery from an exacerbation of symptoms. The results of using omega-3 fatty acids are still inconclusive (103).

Dopamine and the Concept of Schizophrenia

Another aspect of the usual model of schizophrenia is that it is equivalent to an abnormality of dopaminergic dysregulation. It is difficult to dispute the dopaminergic theory of the therapeutic effects of antipsychotics, notwithstanding the contribution that serotonergic actions may make in the case of some drugs (104); however, a theory of therapeutics is not necessarily a strong theory of disease pathophysiology. Indeed, new approaches suggest that dopamine might by correlated only with the reality distortion domain, but not to the other psychopathologic domains (105). Dopaminergic abnormalities not due to antipsychotic treatment do exist in schizophrenia, but several observations show that a dopaminergic theory cannot account for all of the problems found in schizophrenia:

1. the response of psychotic symptoms to dopaminergic agents is highly variable; many patients have a poor response, with persistent hallucinations, delusions, or disorganization persisting whatever dopaminergic agent they take;
2. double-blind infusion studies and post mortem studies have implicated other neurotransmitters, especially serotonin and glutamate, in the pathophysiology of psychosis (106–108); and,
3. the response of other aspects of the neuropsychiatric problems associated with schizophrenia, such as cognitive impairment (109), is poor at best.

The Concept of a Neurodevelopmental Disorder

A conceptual model for schizophrenia that has gained increasing influence is that of a neurodevelopmental disorder, defined as a disorder in which “a fixed ‘lesion’ from early in life interacts with normal brain maturational events that occur much later” (110). However, the concept of schizophrenia as a *neuro*developmental disorder focuses on the brain as the site of abnormal development. A neurodevelopmental model that focuses exclusively on the brain is not adequate for considering the problems found in the rest of the body that are found in people with schizophrenia. Instead, schizophrenia is a developmental disorder, with problems in the periphery (111) as well as the central nervous system, as is the case with, for instance, Down’s syndrome or 22q11.2 deletion syndrome.

This model is also useful in integrating the neuropsychiatric syndromes other than psychosis: the problems are widespread, because the lesion affects many brain (and other body) regions. That is, the presence of so many problems in the disorder is not surprising given the nonspecific nature of the environmental risk factors (96) associated with schizophrenia, several of which are adverse gestational events (112).

A More Inclusive Concept

In view of the evidence outlined above, a contemporary conceptual model of schizophrenia would include the following elements:

- schizophrenia is not a psychotic disorder; it is a developmental disorder in which many brain functions are impaired and psychosis is present.
- schizophrenia is not a brain disorder; it is a disorder with abnormalities found throughout the body.
- to some extent, it is misleading to consider certain neuropsychiatric syndromes "comorbid" with schizophrenia: comorbidity is the rule, not the exception, and some of the "comorbid" syndromes appear to share etiopathophysiological factors. The same may be true of some "non-psychiatric" abnormalities (impaired glucose tolerance, inflammation, immunity, etc.) as well.
- in many patients, there are phases of illness in which psychosis is not the neuropsychiatric syndrome with the greatest impact on function.

This model has important clinical implications:

- evaluation of psychotic symptoms does not constitute thorough evaluation of schizophrenia, which should include psychiatric and non-psychiatric symptoms and signs.
- treatment of psychotic symptoms alone is not comprehensive treatment of schizophrenia.

This is also a better model for clinicians to teach their patients, family members, and trainees (113). The clinical advantage of teaching a more inclusive concept of schizophrenia is that patients are more likely to get a thorough evaluation—and comprehensive treatment—if students use this model. Most "comorbid" disorders, such as anxiety disorders, depression, and substance abuse, are associated with poorer function in schizophrenia (21, 31, 32, 114, 115), and treatment of these disorders leads to improved function (116–120); a comprehensive evaluation is, therefore, appropriate.

Another advantage of this more inclusive concept over the concept of schizophrenia as a psychotic disorder is that much of what has been recently discovered becomes more comprehensible and easier to integrate into practice. For instance, this model also helps students to distinguish between a dopamine theory of the therapeutic action of antipsychotics in current clinical use and a simplistic dopamine theory of the pathophysiology of schizophrenia, as it is easy to understand that many neurotransmitter systems would be disrupted by early developmental problems (121–124). Additionally, the overwhelming number of reports about different physiological abnormalities linked with schizophrenia *per se* would be easily integrated.

There are also implications for research. For instance, the evidence for pro-inflammatory states and for the clinical efficacy of anti-inflammatory medications (98–101) is more readily comprehensible with the more inclusive concept, and becomes more plausible as a subject of future research. Other research areas which appear both more plausible and more important than with the older concept include:

1. given the evidence that schizophrenia and diabetes have shared familial risk, do they have shared genetic risk as well?

2. would normalizing adult stem cell signaling have a metabolic or neuropsychiatric therapeutic effect?
3. can animal models of prenatal stress be used to understand the metabolic problems found in schizophrenia?

Conclusions

If we consider such well-replicated perinatal risk factors for schizophrenia as prenatal stress (125), obstetrical complications, or gestational diabetes in the mother, one would not expect a discrete effect on dopaminergic systems, or even an effect restricted to the brain. In fact, what is found are widespread brain dysfunction and a number of abnormalities in the periphery. A more inclusive model as presented above does not imply that psychotic symptoms are unimportant. Hallucinations, delusions, and disorganization can torment patients and ravage their lives. Furthermore, much of the research on other symptom domains in schizophrenia and the development of strong psychological interventions have been possible because effective antipsychotic drugs are in use. However, because schizophrenia is associated with many causes of both suffering and impairment, we should instill in students the habit of considering targets for treatment in addition to psychotic symptoms, and discuss these problems with patients and family members. Clinicians should also teach students, patients, and family members that some of the problems associated with schizophrenia lie outside the brain. If we continue to focus primarily on psychotic symptoms, students, patients, family members and policy makers will overlook or fail to discuss the other serious problems their patients have and, as a consequence, our patients will endure avoidable suffering.

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