REVIEW

CNS Neuroscience & Therapeutics

# Revisiting the Diagnosis of Schizophrenia: Where have we been and Where are We Going?

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**Keywords**
Diagnosis; Dimensions; Psychoses; Schizophrenia.

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doi: 10.1111/j.1755-5949.2010.00229.x

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## SUMMARY

Appropriate and reliable classification of mental illness is crucial for advancing the field of psychiatry as agreement on diagnosis has broad implications for treatment of mental disorders and research into the etiopathophysiology of mental disorders. Since schizophrenia was first recognized by Kraepelin (as dementia praecox), there has been much discussion about what does and does not diagnostically constitute the disorder. The importance placed upon different symptoms and course types associated with schizophrenia has been as heterogeneous as the disorder itself. This article focuses upon the classification of schizophrenia over the last 100 years, the current diagnosis of schizophrenia, changes for schizophrenia planned in the upcoming DSM 5, future directions for improving the diagnosis of schizophrenia, and the implications of a new diagnostic paradigm for the illness.

Attempts to classify mental illness have been around for centuries. Early examples are the Ayur-Veda, an ancient Indian diagnostic system based on demonic possession [1], and the humors of Hippocrates. Yet despite this long-standing preoccupation with the categorization of mental illness, the concept of schizophrenia is both relatively recent and largely misunderstood. In this review, we examine the initial concept of schizophrenia [i.e., dementia praecox], how this concept has been altered in current diagnostic schemes, alternate ways of conceptualizing the illness, and future directions in diagnosis. This last topic is particularly relevant as the field prepares for revisions of the DSM and ICD.

## Initial Descriptions of Schizophrenia

Although the first use of the term "dementia praecox" can be credited to the French psychiatrist Benedict Morel, it was Emil Kraepelin who defined the disorder. He examined patients with paranoia, hebephrenia, and catatonia, which were considered distinct disease entities at the time, and discovered that there was a common presentation among the patients with the worst prognosis. This common presentation included "dissociative" and "avolitional" pathologies. Dissociative pathology was described as a disruption of an inner cohesion of intellect, emotion, and volition. Avolitional pathology was "emotional dullness, failure of mental activities, and loss of mastery over volition" [2]. It was the co-occurrence of these pathologies in an individual that defined dementia praecox, and the poor prognosis and chronic course that appeared to validate the concept.

It is important to emphasize that it was the co-occurrence of dissociation and avolition that described individual "caseness." Hallucinations or delusions alone were not diagnostic. In fact, even chronic hallucinations and delusions, in the absence of a "disintegration of personality," was *not* dementia praecox. Rather, Kraepelin referred to this condition as "paraphrenia" [2]. Later, he acknowledged that poor prognosis was not inevitable in dementia praecox; nor was diagnosis in adolescence required [2].

Eugen Bleuler, believing that the name "dementia praecox" was misleading, coined the term "schizophrenia" for the illness. In contrast to Kraepelin, who believed a single "morbid process" would eventually be found for the disorder [2], Bleuler believed that schizophrenia was actually a group of several diseases with a similar presentation [3]. He defined schizophrenia by "simple," fundamental pathologies. These were: abnormalities in making associations, abnormal affective expression and regulation,

and the capacity to hold contradictory thoughts simultaneously (ambivalence) [3]. Frequently observed "compound" pathologies arose from these fundamental disturbances and included the primacy of an inner world of experience ("autism") and impaired/altered attention [3]. However, symptoms such as delusions and hallucinations, catatonia, and stereotypies were "accessory" and need not be present in individuals with schizophrenia at all.

Despite the suggestion of a "group of disorders," it was Bleuler's view that dissociative pathology was fundamental to each case which supported the view of schizophrenia as a syndrome unified by dissociation within thought and between thought and emotion and behavior– the split in schizophrenia.

## The Emphasis on Reality Distortion in Current Diagnosis

Many European psychiatrists saw Bleuler's concept of schizophrenia as too overly inclusive because of its lack of emphasis on prognosis. They believed that a schizophrenia diagnosis needed to include an inevitably poor prognosis. To explain the varied prognosis that even Kraepelin had observed, the Norwegian Gabriel Langfeldt developed the concept of "true" or "nuclear" schizophrenia, which had a poor outcome, and "pseudo-schizophrenia" or "schizophreniform disorder" which did not. Although he accepted Kraepelin's formulation of personality deterioration and the lack of diagnostic specificity of general psychotic symptoms, he found that special forms of reality distortion experiences [e.g., massive dissociation or derealization, chronic and bizarre forms of hallucinations] were indicative of true schizophrenia [4] and that "insidious development" of the psychopathology distinguished true from pseudo-schizophrenia [p. 124, ref. 5].

Gradually, the field became focused on reality distortion symptoms and moved further and further from Kraepelin's initial avolition/dissociation concept. The culmination of this move was the diagnostic system of Kurt Schneider, a student of the phenomenologist Karl Jaspers. Schneider attempted to be atheoretical in identifying psychopathology that was unique in distinguishing between nuclear schizophrenia and other forms of psychotic disorders. The eleven symptoms of first rank for the purpose of identifying cases of schizophrenia included third party auditory hallucinations commenting on the patient; the certainty that one's feelings, thoughts and actions originated externally; and other experiences that were "un-understandable" as conceptualized by Jaspers [6–8].

In the United States, the first two editions of the Diagnostic and Statistical Manual [of] Mental Disorders (DSM) contained vague clinical descriptions of schizophrenia that did not require avolitional symptoms, but did not strictly require reality distortion or poor prognosis either [9,10]. Bleuler's inclusion of Simple Schizophrenia as a subtype and the Kraepelinian/Bleulerian emphasis on deterioration of the personality appeared to broaden the concept to include persons who did not manifest severe disorganization of thought or specific forms of reality distortion. During an era when specific and efficacious therapies were not available and interest in understanding the individual life story in a psychodynamic framework was prominent, it appeared that the schizophrenia construct as used in the United States was substantially different from that used in much of the rest of the world. A landmark study contrasting the research and clinical diagnoses of schizophrenia in the United States and the United Kingdom found that U.S. clinical diagnoses identified a much broader cohort of patients than research diagnoses based more specifically on special forms of reality distortion [11]. In the U.K. comparison cohort, research and clinical diagnoses were much more concordant.

In Europe, there had been an untested assumption that the concept of nuclear schizophrenia, based on Schneiderian First Rank Symptoms, identified the exact same poor-prognosis disorder described by Kraepelin. Although family study data suggested that a broader concept of the illness had greater validity in capturing the genetic component of schizophrenia, the nuclear schizophrenia concept reduced heterogeneity- and the narrower construct was associated with greater reliability.

Eventually, the United States accepted the need for international, uniform illness definitions. This acceptance was hastened as differential pharmacotherapy became available and diagnosis made a substantial impact on clinical approach. And in part because attempts to establish efficacious psychotherapy based on a psychodynamic understanding of schizophrenia had not been successful. Thus, the disparity between U.S. and international standards for diagnosing schizophrenia was emphatically addressed in the 1970s. DSM-III was produced and embraced the European concept of nuclear schizophrenia. Negative symptoms including avolition were not diagnostic criteria, disorganization of thought was not required, and reality distortion symptoms became prominent. Schizophrenia could now be diagnosed with a single First Rank Symptom as the only symptom criterion.

When looking at the 5 rank A criteria of the current DSM [ref. 12; see Table 1.] at least 2 are generally necessary for a diagnosis of schizophrenia with the exception of certain auditory hallucinations (a voice providing a running commentary on the patient or voices conversing with each other) and bizarre delusions. Bizarre delusional content is considered a sufficient diagnostic feature of schizophrenia in the DSM IV TR as long as course and social dysfunction criteria are also met. The presence of bizarre delusions is thus a weighted criterion. Bizarreness is difficult to quantify. The current definition in DSM IV TR is "clearly implausible and not understandable and not derived from ordinary life experiences" [12]. The diagnosis of delusions has been found reliable with structured interviews and standardized assessments, but the reliability of assigning bizarreness to delusions was not acceptable when using these methods [13]. Although only a small fraction of individuals receive their diagnosis because of the presence of bizarre delusions [14], there is a question of why bizarre delusions should be weighted so heavily when considering the diagnosis of schizophrenia.

Schizophrenia is also currently diagnosed as a disorder with subtypes, but it has not been established as a unitary pathophysiological entity and has the formal status of a syndrome. Subtypes attempt to address the heterogeneity of the illness, but subtypes are based upon the combination of several clinical features none of which is unique to the subtype (e.g., disorganization can be observed within the catatonic subtype). Defining symptoms of subtypes are also not unique to schizophrenia (e.g., catatonia may

**Table 1** DSM-IV-TR criteria for schizophrenia

| Diagnosis of Schizophrenia |
|---|
| A. Two or more of the following symptoms present for one month: |
| 1. Delusions. |
| 2. Hallucinations. |
| 3. Disorganized speech. |
| 4. Grossly disorganized behavior or catatonic behavior. |
| 5. Negative symptoms (i.e., affective flattening, alogia, avolition). |
| B. Decline in social and/or occupational functioning since the onset of the illness. |
| C. Continuous signs of illness for at least six months with at least one month of active symptoms. |
| Criteria for Subtypes of Schizophrenia |
| A. Paranoid type schizophrenia |
| 1. Characterized by a preoccupation with one or more delusions or frequent auditory hallucinations. |
| 2. Paranoid type schizophrenia is characterized by the absence of prominent disorganization of speech, disorganized or catatonic behavior, and flat or inappropriate affect. |
| B. Disorganized type schizophrenia |
| 1. Prominent disorganized speech, disorganized behavior, and flat or inappropriate affect. |
| C. Catatonic type schizophrenia is characterized by at least two of the following: |
| 1. Motoric Immobility. |
| 2. Excessive motor activity. |
| 3. Extreme negativism or mutism. |
| 4. Peculiar voluntary movements such as bizarre posturing. |
| 5. Echolalia or echopraxia. |
| D. Undifferentiated type schizophrenia |
| 1. Meets criteria for schizophrenia, but it cannot be characterized as paranoid, disorganized, or catatonic type. |
| E. Residual type schizophrenia |
| 1. Characterized by the absence of prominent delusions, disorganized speech and grossly disorganized or catatonic behavior and continued negative symptoms or two or more attenuated positive symptoms. |

be more common in mood disorders and in certain medical conditions [15,16]). The classical subtypes of schizophrenia have not provided a strong basis for advancing knowledge in the area of pathophysiology. This is due to the variable clinical presentation of the psychotic and mood components of the illness and subtype instability across episodes as the illness progresses. The current subtypes of schizophrenia should not be viewed as diagnostic entities, but as overlapping constructs that convey some clinical information about the most recent presentation.

Although the DSM-III system has produced greater diagnostic reliability and a definition that increases similarity of the construct internationally, the reality distortion symptoms that have become prominent are not pathognomonic for schizophrenia [17–19]. Furthermore, none of the reality distortion symptoms predict course or outcome [20–23] which are mainly related to negative symptoms of restricted affect and avolition [23–26]. In fact, the frequent misrepresentation of the course of schizophrenia as chronic and progressive is simply incorrect. The course of schizophrenia is an important aspect of the syndrome given the current diagnosis of schizophrenia is time dependent and dysfunction must be present for at least 6 months in order to diagnosis an individual with schizophrenia. However, the course of schizophrenia within individuals is extremely variable. Some individuals with schizophrenia do quite well, while other individuals have much more difficulty and are not able to live outside of an institutionalized setting. Schizophrenia is a heterogeneous illness with a heterogeneous outcome. Subgroups of individuals with schizophrenia have shown periods of remission [27,28] and recovery [29,30] during their illness [26,31,32]. Attempts have been made to classify the course of schizophrenia and a minimal set of course descriptors has been suggested: rate of syndrome onset, post-onset patterns of psychotic and residual symptoms, post-onset patterns of social, work, and self-care activities, and ultimate outcome [33].

## Conceptualizing Schizophrenia as a Syndrome

The failure to establish schizophrenia as a single disorder or disease entity has profound implications. Studies of etiology and pathophysiology are seriously undermined when only some of the subjects may have a given pathology. The challenge of determining the cause of schizophrenia necessarily turns to the challenge of determining various causes for either subgroups of patients or for subcomponents of the schizophrenia construct. That is, ascertaining disease entities within the syndrome and/or deconstructing the syndrome into relevant pathophysiological components. Deconstructing the diagnosis of schizophrenia into further refined entities will ultimately lead to better treatment and more improved prognostic information for individuals. As the schizophrenia syndrome is further divided, it may be related individually to patients and bring focus to their specific treatment needs. This focus may be

achieved by establishing subgroups based on unique presentations and examining other symptoms that cut across subgroups.

### The Subgroup Approach

Although most attempts at establishing subgroups of schizophrenia have yielded little beyond a current clinical description (see subtype discussion above), there have been some more productive subgroupings. In particular, Andreason's Positive, Negative, and Mixed subgroups [34,35] and Crow's Type I and Type II subgroups [36,37], while ultimately not producing reliable divisions within the syndrome, have been useful steps towards thinking about etiopathology. One current subgrouping of schizophrenia does seem to produce reliable divisions within the syndrome: deficit versus nondeficit schizophrenia.

Deficit schizophrenia includes people with schizophrenia who have stable pronounced avolitional, or negative, symptoms which are not due to secondary sources such as co-occurring depression or dopamine antagonism [38,39]. When compared to nondeficit schizophrenia cohorts, they have less suicide risk, different drug use patterns, and less depression while having similar intensity of psychosis [40–45]. Other differences include risk factors [46–52], neurohistology [53,54], and neuroimaging [55–64].

Deficit schizophrenia also seems to track in families. People with deficit schizophrenia are more likely to have relatives with schizophrenia [65–67] and a three-fold risk that those relatives will have *deficit* schizophrenia [68]. In fact, the concordance rate between deficit/nondeficit categorization in siblings with schizophrenia has been found to be upwards of 74% [69]. Relatives of nondeficit schizophrenia subjects have a wide range of psychiatric disorders and are unlikely to have the deficit form of schizophrenia [68].

### The Deconstruction Alternative

Schizophrenia is associated with a wide array of signs and symptoms. These include reality distortion, disorganization, psychomotor abnormalities, restricted affect, avolition, impaired cognition, loss of insight, depression, anxiety, obsessive-compulsive, social affiliation, and mania. Individual patients will manifest some, but usually not all, of these domains of pathology. Patients will vary substantially as to which of these pathologies constitute their particular form of the syndrome.

The categorical assignment of cases to diagnostic classes continues to be essential, but considering symptom dimensions can add and enrich the information of class [70]. Dimensions based on the various psychopathologies observed within the syndrome can provide a more homogenous target for research and clinical care. The pathological dimensions need not be unique to the syndrome class, and may help define the nature of overlap currently observed across diagnostic boundaries (e.g., in some genetic studies comparing schizophrenia and bipolar).

This approach was presented by Strauss et al. [23] when six domains were proposed to capture the pathology of schizophrenia: disorders of content of thought and perception, disorders of affect, disorders of personal relationships, disordered speech and thought, disordered motor behaviors, and lack of insight. Important work from Cuesta and Peralta has further clarified dimensions that are relevant to understanding schizophrenia: psychosis, disorganization, negative symptoms, catatonia, mania, depression, excitement, and lack of insight [71].

Strauss et al. and Peralta and Cuesta both proposed models of three components that accounted for schizophrenia psychopathology better than a single or a two-component model (e.g., the positive and negative symptom model. However, the best fit was a four-component model that merged the two three-component models and included: reality distortion, negative symptoms, disorganization, and social dysfunction [72].

Deconstructing the syndrome places the construct closer to the needs of clinicians and patients. Doctors do not treat or manage schizophrenia, but rather have the task of treating patients based on assessment of the particular pathologies manifested by each individual. The categorical class of schizophrenia provides a general orientation to the condition, but the assessment of the domains of pathology clarifies the needs and therapeutic targets for that individual. This shift in paradigm has already influenced the approach to therapeutic discovery and the FDA has recognized research designs necessary for testing efficacy hypotheses for cognition and negative symptom indications in schizophrenia [73,74].

## Future Directions in Diagnosis

It is axiomatic that current nosology provides syndrome categories that bear an unknown relationship with specific disease entities that may be identified in the future. Some distinctions between nearby syndromes are profoundly important. For example, the pharmacotherapy of bipolar disorder can be substantially different from the pharmacotherapy of schizophrenia. Lithium and anticonvulsive drugs have a prominent role in bipolar, but not in schizophrenia. On the other hand, the effectiveness of antipsychotic drugs for hallucinations and delusions across many disorders also reveals overlap between syndromes in symptoms and therapeutic responsiveness. The field can anticipate the day when nosology can produce classification based on fundamental knowledge regarding etiology, pathophysiology and neural networks, and associated biomarkers. The landscape may change dramatically at that time. However, in the immediate future advances will be more modest. Here we mention several advances that will make nontrivial contributions to understanding and treating persons with psychotic disorders, especially schizophrenia.

First, the early course presentation of schizophrenia and other psychotic disorders has received extensive recent attention. The effectiveness of treatment in the first psychotic episode and knowledge of prodromal symptomatic development has led to the identification of individuals at high risk for psychosis, especially schizophrenia. Identification can be based on the emergence of attenuated psychotic symptoms. When these symptoms are associated with impaired function, distress, and help seeking, a classification is required to enable clinicians to recognize, diagnose and provide clinical care. One of the most interesting and important developments at present is the suggested validity of case identification [75,76]. These cases have a disorder and need for care at presentation, and are at increased risk for conversion to a full psychosis in the near future.

Second, is the utility of dimensions across clinical and research endeavors. Clinically, the future will see the combination of dimensional and categorical ascertainment. Focused attention on domains of pathology in each person will advance individualized therapeutics, provide new targets for therapeutic discovery, and begin to clarify the porous boundaries between syndromes associated with psychosis. The emphasis on domains of pathology will advance the study of illness genetics by moving the dependent variable away from heterogeneous syndrome and towards a more circumscribed pathology. Dimensions based on domains of pathology will begin to replace syndrome class as a basis for therapeutic discovery and testing of efficacy hypotheses. Finally, domains of pathology will be studied in the context of neural networks most relevant to the specific pathology. NIMH has initiated the Research Domain Criteria (RDoC) program explicitly inviting investigators to address research questions at the level of neural network supporting the disordered functions that are observed across several diagnostic categories. Understanding the neuroanatomy and physiology of working memory, for example, can be approached at the behavioral/neural network level rather than syndrome level. This approach explicitly anticipates that a dysfunction that is similar across several syndromes will be similar regarding pathogentic mechanisms.

Much of the above is already approaching implementation as DSM-V is developed. Plans for lessening the influence of reality distortion, increasing attention to negative symptoms, providing dimensions, and developing a class for attenuated positive psychotic symptoms was presented for public comment during the winter/spring of 2010, and current status can be followed at dsm5.org [77].

## Conflict of interest

The authors have no conflict of interest.

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