

Chapter 2

The Evolving Nosology of Schizophrenia: Relevance for Treatment

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Introduction

The formulation of our current nosology for psychiatric disorders began in the late nineteenth century and culminated in publication of a section related to mental disorders (Section V) in the sixth revision of the International Classification of Disease (ICD-6) in 1949 and in the first edition of the American Diagnostic and Statistical Manual of Mental Disorders (DSM-I) in 1952 [1, 2]. In subsequent revisions of these texts (ICD-7–ICD-10 and DSM-II–DSM-5), substantial changes in diagnostic criteria were made but the basic structure was preserved. Differences between the two systems narrowed and there is now marked concordance between DSM-5 and ICD-10 [3, 4]. DSM-5 became operational in 2013, but ICD-10 is currently being revised and ICD-11 will likely be released in 2016. Schizophrenia is one of the major diagnostic categories in all versions of both manuals.

Although schizophrenia has been studied as a specific disease entity for the past century, its precise nature (core definition, boundaries, causes, and pathogenesis) remains undefined [5, 6]. Since its designation as dementia praecox by Kraepelin (1856–1926) and schizophrenia by Eugen Bleuler (1857–1939), its definitions have varied and its boundaries expanded and receded over the past century (Fig. 2.1) [7, 8]. Thus, it is instructive to examine the varying definitions of schizophrenia over the past 150 years and trace its evolution to the present DSM-5 and soon-to-be released ICD-11 [9, 10].

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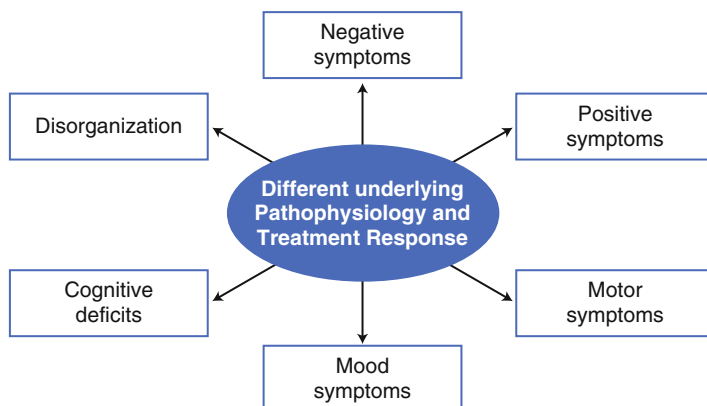


Fig. 2.1 Dimensions of schizophrenia (Adapted with permission from Tandon et al. [29])

The Concept of Schizophrenia from the Nineteenth Century to DSM-IV and ICD-10

The current concept of schizophrenia derives from Emil Kraepelin's formulation of dementia praecox in the late nineteenth century and his elaboration of this idea in the early part of the twentieth century [7, 11]. Until that time, there were two broad prevailing constructs of major psychiatric illness or psychosis. Griesinger postulated that there was only one basic form of psychosis with diverse manifestations attributable to endogenous and environmental factors (*einheitspsychose*), while others suggested that there were several distinct psychotic disorders (e.g., catatonia, hebephrenia, folie circulaire, dementia paranoides, melancholia) [12–15].

Kraepelin discerned two distinct patterns for the course of illness among the various psychotic disorders and used them to define and classify mental conditions. His approach was influenced by the contemporaneous classification of general paresis of insanity (neurosyphilis or tertiary syphilis). The distinctive course and outcome among patients with this illness in psychiatric hospitals led to its delineation, etiological identification, development of the diagnostic Wasserman test, and later to definitive treatment. Kraepelin concluded that course and outcome of illness are the best disease characteristics to use in defining and demarcating psychiatric disease entities. Based on his study of several hundred cases of hospitalized patients, he delineated two distinct disorders: *dementia praecox*, which included catatonia, hebephrenia, and paranoid states; and *manic-depressive insanity*, which comprised folie circulaire and melancholia [16]. Kraepelin identified schizophrenia on the basis of its onset (in adolescence or early adulthood), course (deteriorating), and outcome (dementia or “mental dullness”) [7, 11]. He distinguished dementia praecox from manic-depressive insanity on the basis of the chronicity and poor outcome of the former contrasted with the episodic nature and better outcome of the latter.

During the same time period, Eugen Bleuler renamed this condition “schizophrenia” because he considered the splitting of different psychic functions to be its defining characteristic [8]. He postulated that schizophrenia was defined by a set of basic or fundamental symptoms which were unique and always present in those with this group of diseases, whereas its course and outcome were variable [8, 11]. He called delusions and hallucinations accessory symptoms and considered them to be variable and nonspecific. He described fundamental symptoms (now identified as negative symptoms) which included autism, ambivalence, flat affect, and loosening of associations. He further believed that many mild cases existed and considerably broadened the scope of the disease construct. He included latent and simple forms as part of this entity which he called the group of schizophrenias.

Influenced by the thinking of Karl Jaspers, Kurt Schneider (1887–1967) believed that impairment of empathic communication was the fundamental defect in schizophrenia [17]. He considered “un-understandability” of the personal experience as pathognomonic. Based on this premise, he defined 11 first-rank symptoms which he considered diagnostic of schizophrenia [11, 17]. Given central importance in the Present State Examination, these symptoms were incorporated into both ICD-9 and DSM-III definitions of schizophrenia [18].

Definitions of schizophrenia over the past half-century from DSM-I–DSM-IV and ICD-6–ICD-10 all incorporated Kraepelinian chronicity, Bleulerian negative symptoms, and Schneiderian positive (first-rank) symptoms as part of their definition. The relative emphasis paid to these three roots, however, has varied. In the 1960s and 1970s, there was significant discordance between the DSM (I and II) and ICD (7 and 8) systems with regard to this issue. Whereas DSM-I and DSM-II highlighted the Bleulerian perspective (emphasis on negative symptoms and very broad definition of the schizophrenias, including latent, pseudoneurotic, pseudo-psychopathic, and residual subtypes), ICD-7 and ICD-8 stressed Kraepelinian chronicity [1, 19]. This overly broad definition of schizophrenia in the DSM system led to poor reliability in diagnosing schizophrenia and a marked discrepancy between its diagnosis in the USA and the rest of the world which utilized the ICD system [20]. In reaction to these anomalies, the operationalized criteria of DSM-III provided the narrowest definition of schizophrenia with an emphasis on Kraepelinian chronicity and Schneiderian positive (first-rank) symptoms [21]. In fact, the imperative of improved reliability and the belief that positive symptoms could be more reliably diagnosed resulted in positive symptoms becoming the defining characteristic of schizophrenia in DSM-III and ICD-9. Further, certain positive symptoms such as Schneiderian first-rank symptoms were accorded special importance and the presence of any single bizarre delusion or special auditory hallucinations (voices arguing or commenting) was considered sufficient for a diagnosis of schizophrenia in DSM-III and DSM-IV and ICD-9 and ICD-10 [22, 23]. Although there were modest changes in the definition of schizophrenia from DSM-III to DSM-IV, the importance of positive symptoms with the special significance placed on bizarre delusions and special hallucinations in the diagnostic criteria remained.

The Present: DSM-5 and Towards ICD-11

The reliability of diagnosing schizophrenia improved substantially after the introduction of DSM-III in 1980, but several limitations in its definition and description became apparent over the past three decades [24]. Although the significant heterogeneity of schizophrenia was always recognized, with multiple etiological factors and pathophysiological processes, it has been treated as a singular entity [6, 25, 26]. Now, however, it is almost certain that our construct of schizophrenia encompasses not one but several diseases [27]. In the past, we tried to explain the heterogeneity of the illness by defining distinct subtypes—paranoid, disorganized, catatonic, simple, and undifferentiated. These classic subtypes, however, provided a very poor description of the enormous heterogeneity of this condition. Subtypes' stability is low, reliability of diagnosing them weak, their validity questionable, and only the paranoid and undifferentiated subtypes were utilized with some frequency [28, 29]. Because these subtypes have virtually no clinical or research utility, they are being eliminated from the classification system in DSM-5 and ICD-11 [10, 30, 31]. Instead, the heterogeneity of schizophrenia is now formally described in terms of psychopathological dimensions (discussed below) which will be measured in all patients throughout the course of the illness [32]. Since the severity of different symptom domains varies in each patient over the illness course and in response to treatment, such dimensional assessments will be an invaluable tool, allowing clinicians to provide individualized, measurement-based care [33].

Another significant limitation in definitions of schizophrenia until DSM-IV and ICD-10 was the inability to characterize the distinct stages of the illness [34]. The classification system did not allow clinicians to adequately describe the course of their patient's illness (e.g., first episode, chronic) or denote the patient's current clinical status (e.g., active symptoms, in partial or full remission). The provision of modified course specifiers in both DSM-5 and ICD-11 helps to redress this anomaly [10]. Additionally, there was no provision in DSM-IV or ICD-10 to describe the early or late prodromal phases of the illness when there is the possibility of arresting active pathology and preventing disease progression [35, 36]. The addition of Attenuated Psychosis Syndrome as a condition for further study in Section 3 of DSM-5 will partly address this deficiency.

Revisions in DSM-5 and currently proposed changes in ICD-11 will correct the major failure in properly characterizing the clinical heterogeneity of schizophrenia and denoting stages in the evolution of the disease. Additionally, revisions in DSM-5 and ICD-11 correct other discrepancies in the DSM-IV and ICD-10 description of schizophrenia. The four major changes made in DSM-5 (and likely to be made in ICD-11) are separately summarized below.

Changes in Characteristic Symptoms of Schizophrenia in DSM-5 and ICD-11

The changes in the diagnostic criteria of schizophrenia in DSM-5 were modest and continuity with DSM-IV is broadly maintained. No changes were made in the

Table 2.1 Characteristic symptoms of schizophrenia (Criterion A) in DSM-IV and DSM-5

DSM-IV-TR criterion A	DSM-5 criterion A
<i>Schizophrenia</i>	
Criterion A. <i>Characteristic symptoms:</i> ≥2 of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated)	Criterion A. <i>Characteristic symptoms:</i> ≥2 of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). <i>At least one of these should include 1–3</i>
1. Delusions	1. Delusions
2. Hallucinations	2. Hallucinations
3. Disorganized speech	3. Disorganized speech
4. Grossly disorganized or catatonic behavior	4. Grossly disorganized or catatonic behavior
5. Negative symptoms, i.e., affective flattening, alogia, or avolition	5. Negative symptoms, i.e., restricted emotional expression or avolition
<i>Note:</i> Only one criterion. A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person’s behavior or thoughts, or ≥2 voices conversing with each other	<i>Note:</i> Deleted

Source: Reprinted with permission from Tandon R, et al. [51]

minimum duration (6 months), functional impairment (necessary), and exclusion (psychotic mood disorder, schizoaffective disorder, substance-induced psychotic disorder, psychosis secondary to a general medical condition) criteria. Two key changes, however, were made in the definition of characteristic symptoms required in the active phase of the illness (Table 2.1):

- Elimination of special treatment of *bizarre delusions and other Schneiderian first-rank symptoms*. In DSM-IV, only one characteristic symptom was required if it was a bizarre delusion or special hallucination (voices arguing or commenting). Since Schneiderian first-rank symptoms are not pathognomonic for schizophrenia, do not have diagnostic specificity or prognostic significance, and the reliability of distinguishing bizarre from non-bizarre delusions is poor, they will be treated like any other “positive symptom” with regard to their diagnostic implication in DSM-5 and ICD-11 [37–40]. Thus, two characteristic symptoms will be necessary to make a diagnosis of schizophrenia even if one of them is a bizarre delusion or “special hallucination.” This change affects a very small number of patients, who will now more appropriately receive a diagnosis of delusional disorder [41].
- Requirement in both DSM-5 and ICD-11 that at least one of the two required symptoms to meet characteristic criterion A be delusions, hallucinations, or disorganized thinking. These are core “positive symptoms” diagnosed with high reliability and might reasonably be considered necessary for a diagnosis of schizophrenia. Less than 1 % of patients with DSM-IV schizophrenia will be affected by this change and in such patients a necessary exploration of other causes of catatonia will be required [41–43].

Elimination of Classic Subtypes of Schizophrenia in DSM-5 and ICD-11

As noted previously, the schizophrenia subtypes had limited diagnostic stability, low reliability, poor validity, and little clinical or research utility. Further, except for the paranoid and undifferentiated subtypes, the others were rarely utilized in most mental healthcare systems. Consequently, these subtypes are eliminated in DSM-5 and ICD-11. This change should simplify clinical description of schizophrenia.

Addition of Psychopathological Dimensions of Schizophrenia

Schizophrenia is characterized by several psychopathological domains which have distinctive courses, patterns of treatment response, and prognostic implications (Box 2.1 and Fig. 2.1). The relative severity of these symptom dimensions varies across patients, as well as within patients at different stages of their illness. Measuring their relative severity through the course of illness and in the context of treatment can provide useful information to the clinician about the nature of the illness in a particular patient and the specific impact of treatment on different aspects of the illness (e.g., analogous to measuring pulse, temperature, blood pressure, respiratory rate). As a simple rating scale (akin to a thermometer or a sphygmomanometer), it should encourage clinicians to explicitly assess and track changes in the severity of these dimensions and to use this information to guide treatment. Six symptom domains with a total of eight items are described in DSM-5 and each item is scored on an anchored 0–4 scale (see Box 2.1) [32]. In addition to their clinical utility, dimensional measurement should prove useful from a research perspective and thereby permit studies on etiology and pathogenesis which cut across current diagnostic categories [44, 45]. Such approaches are consistent with recent findings in genetics and neuroscience and the recent Research Domain Criteria (RDoC) project initiated by the National Institutes of Mental Health [46, 47].

Box 2.1 Dimensions of Psychotic Disorders: Assessment of Severity

All dimensions will be assessed on a 0–4 scale cross-sectionally, with severity assessment based on symptoms in the past 7 days.

1. Delusions
2. Hallucinations
3. Disorganization
4. Negative symptoms
5. Impaired cognition
6. Depression
7. Mania
8. Psychomotor symptoms including catatonia

Attenuated Psychosis Syndrome

It is believed that the still unsatisfactory outcome of schizophrenia in a significant proportion of individuals with the disorder is due to the identification of the illness and initiation of treatment late in its course after a substantial amount of damage has occurred. The introduction of Attenuated Psychosis Syndrome (Box 2.2) in Section 3 of DSM-5 will support the efforts of clinicians to recognize and monitor psychotic symptoms early in the course of their evolution, and, if necessary, intervene during these crucial stages [35, 36, 48]. Early recognition and intervention are important in other branches of medicine and these changes in DSM-5 should stimulate the development of a similar practice in psychiatry. Although recognition of Attenuated Psychosis Syndrome is important, the ability to reliably diagnose the condition in routine practice is not demonstrated and its nosologic relationship to other psychiatric diagnostic entities is not precisely defined [36, 49]. Consequently, it is not in the main body (Section 2) of the DSM-5 but in Section 3 as a condition needing further study [35]. It should be emphasized that its diagnosis is *not* an indication for routine antipsychotic treatment but should instead prompt a careful search for comorbidities (e.g., anxiety, depression, substance use disorder) and their appropriate treatment along with close monitoring for a possible transition to psychosis.

Box 2.2 Criteria for Attenuated Psychosis Syndrome in DSM-5 [3]

All six of the following:

1. *Characteristic symptoms*: at least one of the following in attenuated form with intact reality testing, but of sufficient severity and/or frequency that it is not discounted or ignored.
 - (a) Delusions
 - (b) Hallucinations
 - (c) Disorganized speech
2. *Frequency/currency*: symptoms meeting criterion A must be present in the past month and occur at an average frequency of at least once per week in past month.
3. *Progression*: symptoms meeting criterion A must have begun in or significantly worsened in the past year.
4. *Distress/disability/treatment seeking*: symptoms meeting criterion A are sufficiently distressing and disabling to the patient and/or parent/guardian to lead them to seek help.
5. *Exclude other DSM-5 disorder*: symptoms meeting criterion A are not better explained by any DSM-5 diagnosis, including substance-related disorder.
6. *Exclude prior psychotic disorder*: clinical criteria for any DSM-5 psychotic disorder have never been met.

Treatment Implications of Current Conceptualization of Schizophrenia: 2014 and Beyond

For the past century, schizophrenia was conceptualized as a singular disorder with a distinctive pathology, albeit with multiple etiological factors and diverse manifestations. This formulation dictated a single specific treatment directed at the common pathology (i.e., antipsychotic medications). These agents, however, are ineffective against some core features of the illness, such as negative symptoms and cognitive deficits [50]. Although researchers assiduously searched for an alternative core pathology in schizophrenia, no single mechanism has been found and no single treatment is effective against all aspects of the illness. With DSM-5, schizophrenia is explicitly conceptualized as a multidimensional illness with each dimension potentially explained by a distinct pathophysiology and the target of a unique treatment [51].

In DSM-5, six distinct dimensions of schizophrenia are defined (Fig. 2.1). Whereas positive symptoms and mood symptoms have two items (delusions and hallucinations for positive symptoms, and depression and mania for mood symptoms), the other four dimensions have one item (Box 2.1). Each item is scored on an anchored 0–4 scale (Section 3 of DSM-5) [3]. Different schizophrenia patients exhibit varying admixtures of symptom severity across the six dimensions. Additionally, these dimensions respond differently to various treatments and different patients show dissimilar patterns of treatment response. Unique measurement of how each of these distinct dimensions responds to specific treatments in individual patients enables monitoring of response and appropriate treatment adjustments. The availability of a simple scale which provides measures of symptom severity across these distinct dimensions enables measurement-based, individualized treatment.

Antipsychotic medications are particularly effective for treating positive symptoms and disorganization in schizophrenia. Specific treatments are in development to address negative symptoms and cognitive deficits in schizophrenia. Hopefully, some of these will be effective and safe, becoming available for clinical practice in the near future. Antidepressants and mood stabilizers are moderately effective for the mood symptoms in schizophrenia. Antipsychotic medications, benzodiazepines, and electroconvulsive therapy all demonstrate efficacy for motor symptoms (including catatonia) in schizophrenia. As better treatments for various symptom dimensions are developed, more effective, “evidence-based” pharmacotherapy will be possible.

It is clear that schizophrenia is not one but several disorders. The delineation of unique psychopathological dimensions facilitates the identification of distinct etio-pathophysiological pathways to schizophrenia; development of specific biological tests for the “different schizophrenias”; elaboration of specific treatments for the “different schizophrenias”; construction of an etio-pathophysiological nosology of the schizophrenias; and most importantly, better outcomes for our patients [47, 52–54]. As DSM-5 provides a better bridge to this anticipated future, it also provides tools for more effective treatment of schizophrenia today [24, 45, 55].

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