Phenomenology of First-Episode Psychosis in Schizophrenia, Bipolar Disorder, and Unipolar Depression: A Comparative Analysis

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Abstract

Objective: This study sought to identify similarities and differences in symptom characteristics at initial presentation of first psychotic episodes in schizophrenia, bipolar disorder and unipolar depression. **Methods:** The Structured Interview for DSM-IV (SCID) and Positive and Negative Syndrome Scale (PANSS) were administered to consecutive admission study-eligible patients (n=101) presenting for treatment during their first acute phase of psychotic illness. Forty-nine percent of patients met diagnostic criteria for schizophrenia, 29% for psychotic bipolar disorder and 22% for unipolar depression with psychosis. The PANSS was analyzed using five-factor scoring that included Positive, Negative, Cognitive, Excitement, and Depression factors, and composite cluster scores that assessed Anergia, Thought Disturbance, and Paranoia. **Results:** Schizophrenia and bipolar disorder patients demonstrated significantly more Positive symptoms, Thought Disturbance and Paranoia than unipolar depressed patients. Schizophrenia and unipolar depressed patients demonstrated significantly more Negative symptoms and Anergia than bipolar patients. Patients with schizophrenia reported more severe Cognitive Disorganization than patients with either bipolar disorder or unipolar depression ($p<.05$). **Conclusions:** Findings from this study demonstrate an informative pattern of similarities and differences in the phenomenology of psychotic disorders at first illness presentation. Commonalities in symptom profiles reflect considerable symptom overlap among psychotic disorders and, thus, the importance of multidimensional differential diagnosis for these conditions. The differences across disorders in Positive and Negative symptom severity, Thought Disorder, Paranoia, and Anergia, and especially the higher level of Cognitive Disorganization seen in schizophrenia patients, point to clinically informative differences across these disorders that are relevant to clinical diagnostic practice and models of psychopathology.

Key Words: First Episode, Psychosis, Phenomenology

Introduction

The *DSM-IV* and the *ICD-10* systematize psychotic illnesses as distinct, complex, multifactorial categorical conditions defined by a broad range of symptom characteristics used to guide differential diagnosis (1-3). Diagnostic differentiation is achieved using psychological, cognitive and behavioral symptomatology, as well as information about illness course. Efforts to refine these diagnostic criteria are reflected in ongoing revisions of diagnostic manuals used worldwide. No unique or disorder-specific symptoms have been identified for psychotic disorders, and so multidimensional criteria sets are used to make differential diagnoses in clinical practice (4). Recent studies of clinical characteristics of psychotic disorders have highlighted their common and overlapping clinical features (5, 6). For example, it is not uncommon for patients with schizophrenia to have symptoms of depression and for Schneiderian first-rank symptoms to be present in patients with psychotic affective disorders (7-9).

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Clinical Implications

Given the clinical importance of the differential diagnosis of psychotic disorders as early as possible to guide differential treatment, this study was undertaken to contrast the clinical presentation of consecutive study-eligible patients with a first episode of affective and nonaffective psychosis presenting for clinical evaluation and treatment. Importantly, the study sample had limited exposure to antipsychotic medications that can influence assessment of both primary Positive and Negative symptoms. This study is unique in comparing first-episode patients with schizophrenia to both bipolar disorder and unipolar affective disorders with psychotic symptoms in the absence of antipsychotic medication.

Our data show that during the first episode of psychosis the clinical presentation of a patient with psychosis supports a modest diagnostic specificity of clinical features, as we found an overlap of Positive symptoms in schizophrenia and bipolar disorder, and Negative symptoms in schizophrenia and unipolar depression. This may account for why there was the least diagnostic differentiation of schizophrenia in the discriminant analysis. However, the Cognitive Disorganization factor was greater in schizophrenia, and Depression severity was greater in unipolar depression. These findings suggest that these two dimensions should receive careful attention for clinical differential diagnosis in early phases of psychotic disorders. Perhaps later in the course of illness, when combined with family history, course of illness, and subsequent treatment response, greater diagnostic differentiation might be achieved. The evolution of symptoms needs to be compared in these disorders, independently and in relation to stability of diagnosis. Thus, learning about the differential phenomenological manifestations of psychotic disorders and their relevance to treatment remains an ongoing challenge for clinical studies of affective and nonaffective psychotic disorders.

The examination of phenomenological similarities and differences in psychotic disorders at illness onset is important for at least two reasons. First, such studies conducted close to illness onset can potentially identify differentiating clinical features of these disorders independent from effects of illness course and chronic medication treatments and, thus, offer evidence about relatively unique and common manifestations of these disorders. Secondly, from a practical point of view, studies of the phenomenology of these disorders early in course of illness can guide differential diagnosis and treatment planning for first-episode patients when course of illness information is not yet available (10, 11).

Schizophrenia and psychotic affective disorders have been classified both categorically and dimensionally. Emil Kraepelin played an important role in differentiating disorders now named bipolar disorder and schizophrenia, using both symptom and course of illness information (12). He considered manic depression as an episodic illness with periods of considerable recovery of function, and *dementia praecox* as a degenerative persistent condition leading to poor outcome and negative symptoms as primary characteristics. Of note, in later writings, Kraepelin came to view this diagnostic dichotomy as insufficient to explain the dimensional heterogeneity in the clinical presentation of these conditions (13). It has even been argued that many of Kraepelin's patients he considered to have dementia praecox may not meet current diagnostic criteria for schizophrenia (14).

Eugen Bleuler developed the concept of schizophrenia (15, 16). Bleuler's concept expanded the fundamental psychological characteristics of schizophrenia to include disorganization (i.e., the "loss of association" in thought processes), recognition of affective features, and the existence of a continuum within schizophrenia (schizophrenia simplex to complex). His views generally had a greater use of defining symptoms relative to course of illness for clinical diagnosis. Recently, models have been proposed that treat bipolar disorder and schizophrenia as ends of a continuum rather than discrete diagnostic entities (17-19), reflecting the ongoing uncertainties concerning the boundaries of these conditions. This blurring of the boundaries of schizophrenia and affective psychoses is reflected in the consideration of variants such as schizoaffective disorder, and has led to proposals that these psychotic disorders may result from similar or overlapping pathophysiological mechanisms (20, 21).

The primary aim of this study was to examine differences in clinical symptom presentation in a sample of consecutive patients presenting with their first psychotic episode to determine the extent of overlap and differentiation in psychopathological signs and symptoms of schizophrenia, bipolar disorder and psychotic depression in a sample of young adult patients who were not receiving active treatment with antipsychotic medications.

Methods

Patient Recruitment

Patients presenting with a first episode of psychotic symptoms at a large urban university medical center, referred from community agencies, private referrals, and state-operated facilities between 2001 and 2008, were recruited for this study. Sixty-four percent of the sample was recruited from the inpatient unit and 36% percent from the outpatient clinic. Many patients entering the study had no prior history of antipsychotic medication (n=57), and the rest had

Table 1 Characteristics of First-Episode Psychosis Patients with Schizophrenia, Bipolar Disorder, and Unipolar Depression

Demographic Measures	Schizophrenia (n=49)		Bipolar Disorder w/Psychosis (n=29)		Unipolar Depression w/Psychosis (n=23)		P Value
Gender (m/f)	36/13		15/14		11/12		**.05**
Race							**n.s.**
Caucasian	10		7		6		
Black	27		17		9		
Hispanic	8		2		6		
Other	4		3		2		
DUP (median # months)	7		3		5		**.02**
Antipsychotic naive	22 (50%)		19 (66%)		18 (78%)		**.04**
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**P Value**
Age of first psychiatric evaluation	21.9	7.4	20.5	6.8	22.2	7.7	**n.s.**
Current age	23.1	6.6	23.9	6.5	26.7	10.2	**n.s.**
IQ	90.8	18.2	94.0	20.8	91.5	16.6	**n.s.**
SES	30.57	14.60	34.03	14.54	32.08	12.83	**n.s.**
Education (yrs)	11.94	2.66	13.41	3.20	12.35	2.20	**n.s.**

n.s.=not significant; DUP=duration of untreated psychosis;
SD=standard deviation; SES=socioeconomic status

less than 16 weeks of total lifetime antipsychotic treatment (n=44). For the latter group, all were not taking antipsychotic medication for at least 3 days prior to evaluation. Of the 44 patients who had previous exposure to antipsychotic medications, 33 had received antipsychotic medications within 30 days prior to baseline procedures. Of these 33 patients, the median number of days from the last dose of antipsychotic medications to the initiation of baseline clinical evaluation for patients with schizophrenia spectrum (n=19) was 4.0 (range 3–17); bipolar disorder with psychosis (n=10) was 3.5 (range 3–8); and, unipolar depressed with psychosis (n=4) was 8.0 (range 3–23). There was no significant diagnostic difference in the median number of antipsychotic-free days before evaluation. They were between the ages of 12 and 55, and had no history of seizure disorder or other neurological conditions, head injury followed by loss of consciousness for greater than 10 minutes, current major medical illness, or recent substance dependence. Demographic characteristics for the sample and duration of untreated psychosis (DUP) were obtained at the initial evaluation. DUP was defined as number of months between first expression of psychosis and study recruitment. Socioeconomic status was presented as a mean score (22) and IQ was estimated using the 2-subtest version of the Wechsler Abbreviated Scale of Intelligence (WASI) (23). The research protocol was approved by the University's Institutional Review Board, and all subjects provided written informed consent.

Consensus diagnoses were determined by members from the clinical and research team using the Structured Clinical Interview for DSM-IV (1) and all available collateral information from families and/or previous caregivers, medical records, and information provided from the clinical and research teams. This information generally included not only initial symptom information but information obtained from direct and ancillary source observations over the course of 6–8 weeks of acute treatment. Of 101 study-eligible patients, 49 patients were diagnosed with a schizophrenia spectrum disorder, including schizophreniform disorder (n=4), schizophrenia (n=41), schizoaffective depressed (n=3), schizoaffective bipolar (n=1); 29 patients with bipolar disorder with psychosis, including bipolar manic (n=13), bipolar depressed (n=9), bipolar mixed (n=7); and, 23 patients with unipolar depressed with psychosis.

Table 2 PANSS Five-Factor and Cluster Scores for Schizophrenia, Bipolar Disorder and Unipolar Depression

	Schizophrenia (n=49)		Bipolar Disorder w/Psychosis (n=29)		Unipolar Depression w/Psychosis (n=23)		
PANSS Five-Factor Scores	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**P Value**
Positive	14.79	3.5	15.03	3.4	10.78	3.2	.001
Negative	18.71	7.7	12.20	5.7	16.78	6.5	.001
Depression	13.67	3.3	13.58	3.7	16.04	2.8	.011
Cognitive	13.28	4.0	10.82	3.8	10.78	0.80	.008
Excitement	8.36	3.5	10.13	3.7	7.00	0.50	.004
PANSS Cluster Scores	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**P Value**
Anergia	9.55	3.7	6.24	2.6	9.65	3.5	.001
Thought Disturbance	12.67	2.9	11.55	3.7	8.86	2.8	.001
Paranoia	8.03	2.7	7.71	2.5	6.04	2.0	.009

Measures

The primary clinical measure for this study was the Positive and Negative Syndrome Scale (PANSS) (24). PANSS items are scored along a continuum of severity between 1 (asymptomatic) to 7 (extreme symptom severity). Analysis was conducted via data reduction strategies guided by prior empirical studies of symptom domains assessed by the PANSS. First, scores were calculated for five factors assessing Positive symptoms (delusions, grandiosity, suspiciousness/persecution, unusual thought content); Negative symptoms (blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, lack of spontaneity and flow of conversation, and active social avoidance); Cognitive Disorganization (conceptual disorganization, difficulty in abstract thinking, mannerisms and posturing, disorientation, and poor attention); Excitement (excitement, hostility, tension, and poor impulse control); and, Depression (somatic concern, anxiety, guilt feelings, depression, and preoccupation). Items were pooled in this way based on previous factor analytic findings (25, 26). Secondly, PANSS items that have been shown to identify related symptom domains in cluster analyses that assess Anergia (blunted affect, emotional withdrawal, motor retardation, and disorientation); Thought Disturbance (conceptual disorganization, hallucinatory behavior, grandiosity, and unusual thought content); and, Paranoia (suspiciousness/persecution, hostility, and uncooperativeness) were also obtained. PANSS items were pooled into these dimensions based on previous cluster analysis research (27-29).

Statistical Analyses

Demographic data were analyzed by using Chi Square and analysis of variance (ANOVA). DUP data showed a skewed distribution, and thus were analyzed using a nonparametric statistic (Kruskal-Wallis test). Clinical symptom data were compared across diagnostic groups using analyses of variance (ANOVAs). When ANOVAs yielded significant results, Newman-Keuls post hoc tests were used to identify significant pair-wise group differences. Additionally, the five-factor score data were analyzed using a discriminant function analysis to determine profiles of symptoms that best distinguished the patient groups, and the degree to which such multidimensional profiling could classify patients into diagnostic groups as determined by the consensus diagnosis.

Results

Group comparisons of demographic characteristics (see Table 1) revealed a significant gender difference between diagnostic groups, with the schizophrenia group including more male patients compared with the bipolar disorder and unipolar depression groups (χ^2=5.94, df=2, p<.05). There was a significant difference in DUP across patient groups, showing patients with schizophrenia having a longer DUP prior to presenting for care than bipolar disorder or unipolar depression patients (χ^2=8.29, df=2, p<.05). There was also significant difference across diagnostic groups in patients who were antipsychotic naive at baseline assessment, showing patient with schizophrenia were less likely to present antipsychotic naive (χ^2=6.48, df=2, p<.05). There were no significant differences between diagnostic groups in age, race, age of onset of first psychotic symptom, IQ, education level, or parental socioeconomic status.

Table 2 shows PANSS Five-Factor and Cluster scores comparing schizophrenia, bipolar disorder with psychosis, and unipolar depression with psychosis. Patient groups showed different levels of Positive symptoms (F(2,100)= 12.95, p<.001), Thought Disturbance (F(2,100)=11.75, p<.001) and Paranoia (F(2,100)=4.91, p<.009). Post hoc analyses revealed that patients with schizophrenia and bipolar disorder had higher levels of Positive symptoms, Thought Disturbance, and Paranoia than patients with unipolar depression. Patient groups also differed in Negative symptom severity (F(2,100)=8.46, p<.001) and Anergia cluster scores (F(2,98)=10.06, p<.001). Post hoc analyses showed that patients with schizophrenia and unipolar depression had higher levels of Negative symptoms and Anergia than patients with bipolar disorder. Patient groups also differed in ratings of Depression symptoms (F(2,100)=4.72, p<.011). Post hoc analysis indicated that patients with unipolar depression had higher Depression ratings than patients with schizophrenia and bipolar disorder. Groups differed in ratings of Excite-

ment (F(2,100)=5.88, p<.004). Patients with bipolar disorder and schizophrenia had higher ratings on the Excitement domain than patients with unipolar depression.

Patient groups also differed in ratings of Cognitive Disorganization (F(2,100)=5.13, p<.008). Post hoc analysis showed that patients with schizophrenia had higher levels of Cognitive Disorganization than patients with bipolar disorder or unipolar depression (p<.05). Of note, this was the only PANSS factor score in which significantly greater impairment was observed in schizophrenia relative to both other psychotic disorders. As shown in Table 2, the severity of PANSS factor scores and item clusters highlights the symptom overlap across diagnostic groups at the acute phase of a first episode of psychosis.

Table 3 Diagnostic Prediction of Clinical Diagnosis using Five-Factor Scores from the PANSS in a Discriminant Function Analysis

SCID Consensus Diagnosis	Predicted Group Membership		
	Schizophrenia	Bipolar Disorder w/Psychosis	Unipolar Depression w/Psychosis
Schizophrenia n=49	49%	37%	14%
Bipolar w/Psychosis n=29	14%	69%	17%
Unipolar Depressed w/Psychosis n=23	13%	4%	82%

A discriminant function analysis of the five-factor scores was performed to determine the extent to which the simultaneous use of the factor score data could differentiate the different psychotic disorders in terms of their symptom profiles. The accuracy of diagnostic classifications using PANSS data was considered relative to consensus diagnoses as the gold standard (see Table 3). Overall, only 62% of patients were correctly classified. Of note, the lowest accurate classification among the individual patient groups was that of the schizophrenia sample (only 49%), highlighting the considerable overlap in symptom presentation between schizophrenia and affective psychoses. Importantly, this observation shows that the symptom overlap across disorders was apparent not only when specific symptom domains were considered independently as in the preceding analyses, but even when the profile of illness domains was examined.

Discussion

Given the clinical importance of the differential diagnosis of psychotic disorders as early as possible to guide differential treatment, this study was undertaken to contrast the clinical presentation of consecutive study-eligible patients with a first episode of affective and nonaffective psychosis presenting for clinical evaluation and treatment. Importantly, the study sample had limited exposure to antipsychotic medications that can influence assessment of both primary Positive and Negative symptoms. This study is unique in comparing first-episode patients with schizophrenia to both bipolar disorder and unipolar affective disorders with psychotic symptoms in the absence of antipsychotic medication.

Our findings are consistent with previous reports in showing considerable symptomatic overlap between schizophrenia and psychotic bipolar disorder in Positive symptoms (30-32), and between schizophrenia and psychotic depression in Negative symptoms (33, 34). These findings support a dimensional view or a continuum of positive symptoms that overlap defined diagnostic boundaries of psychotic disorders, and highlight the strengths and limitations of psychotic and other symptoms in the differential diagnosis of psychotic disorders early in their course.

We observed significant overlap in Negative symptoms and Anergia between patients with schizophrenia and patients with unipolar depression. However, that similarity did not extend to depressive symptoms that were higher in patients with psychotic depression. To date, there has been limited research in the area of first-episode unipolar depressive disorder (35, 36).

Similar to our findings, previous studies have shown substantial depressive symptoms in the presence of psychosis in patients who did not meet criteria for a unipolar depressive disorder (37, 38). We also observed higher levels of Negative symptoms in schizophrenia than bipolar disorder and unipolar depression, as others have reported (39-41). These data point to the importance of Negative symptoms which are more prominent in schizophrenia and Depression which are more prominent in unipolar depression in the differential diagnosis of first-episode patients, as these features tend to be distinct and less prominent in patients presenting with bipolar illness.

Cognitive Disorganization was more prominent in schizophrenia than in bipolar disorder and unipolar depression. Thus, the presence of difficulty in abstract thinking, concentration, conceptual disorganization, and other signs of cognitive impairment had a greater degree of diagnostic specificity for schizophrenia than ratings of positive and negative symptoms. It is important to note that this sample was matched on IQ, which suggests that the cognitive differences across disorders are related to diagnostic differences in Cognitive Disorganization rather than a differential decline in overall intellectual ability. Epidemiological data

comparing first-episode psychosis patients with schizophrenia, bipolar disorder, and unipolar depression found greater neuropsychological impairment in schizophrenia at baseline and 24 months later (42). Thus, the Cognitive Disorganization factor of the PANSS has some measure of diagnostic specificity for schizophrenia patients at initial onset relative to other symptom domains evaluated by the PANSS.

Our finding that cognitive symptoms are worse in schizophrenia during the first episode of psychosis is consistent with other studies (43-47). It is important to note that the literature is mixed regarding the degree of specificity of neuropsychological dysfunction for schizophrenia (48). The relation of this finding to other neuropsychological measures requires future examination. Nonetheless, our data suggest that abnormalities in this domain may have greater relative diagnostic specificity for schizophrenia than other symptom domains. Thus, cognitive disturbances might be considered for differential diagnostic assessment or a "point of rarity" in the diagnostic criteria of schizophrenia (49-53).

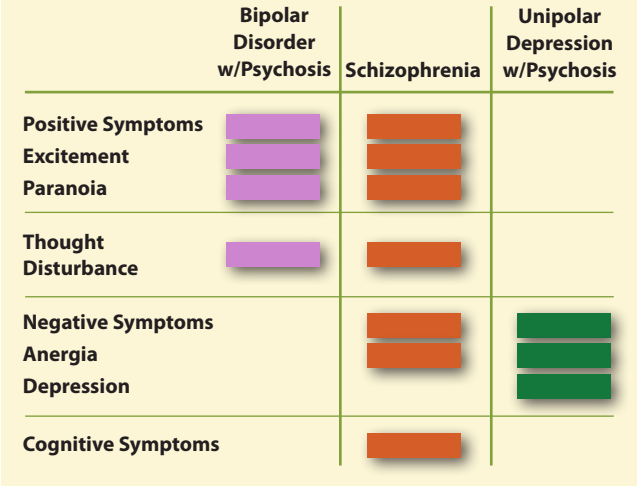
Clinicians evaluating patients upon their first presentation of psychosis are presented with two types of symptoms. First, there are primary symptoms inherent to the illness that arguably best define its core clinical boundary. At the same time, there is a second set of symptoms which is a manifestation of illness-environment interaction or consequences of other symptoms, such as isolative behavior or anxiety due to paranoid delusions. Conceptually, the primary symptoms should be more diagnostically specific, while secondary symptoms might be expected to be more common across psychotic disorders. Given our current level of knowledge, it is not yet possible to differentiate these symptom groups or their evolutionary change over the course of illness (54, 55). Without laboratory tests linked to a systematic understanding of illness pathophysiology, or the ability to differentiate primary and secondary symptoms, it is difficult to know whether the high degree of overlap of symptoms across psychotic disorders results from a high prevalence of secondary symptoms, or a more fundamental problem in the model of categorically differentiated diagnostic categories for psychotic disorders that has been guided by Kraepelin's thinking for over a century. However, biological and phenomenological studies remain mixed in their findings of competing ideas that psychotic disorders are best understood as a dimensional framework or as categorically distinct disease entities (56). Recent genetic (57, 58), neuroimaging (59, 60), and neuropsychological (6, 61) studies have shown overlap in findings across psychotic disorders, so further work is needed to resolve this important question over coming years.

During the first episode of psychosis, the diagnostic differential is complex and the lack of historical data can sometimes lead to misdiagnosis (62). Some investigators have recommended a dimensional paradigm to understand the complex phenomenological manifestation of psychosis (63-66). Diagnostic reliability has primarily been improved from *DSM-III* onward by focusing on externally observable symptoms in connection with illness expression and behavior. This dimensional analysis of clinical features early in the course of psychotic disorders failed to identify clear diagnostic boundaries based on "points of rarity" in psychological and behavioral aspects of illness expression. This is consistent with prior studies, but the large majority of these studies have looked at diagnostic differences in psychotic disorders in partially stabilized and medicated samples. Studies of first-episode patients hopefully get closer to primary symptoms, so the lack of diagnostic differences in symptomatology in the present study raises further questions about a fine categorical distinction between affective and nonaffective psychotic disorders. The literature examining the diagnostic boundaries of symptom overlap in unmedicated first-episode psychosis is limited. Thus, this sample is unique in its ability to inform the field of diagnostic differences in a sample of first-episode psychosis patients evaluated at index without antipsychotic medications.

As future work better clarifies the common and distinguishing clinical and neurobiological features of psychotic disorders, ideally in ways that are linked to differential pathophysiology, the boundaries of these illnesses may be better defined. Importantly, work is needed to clarify the conceptual model for psychotic disorders in terms of whether they should be considered in dimensional or categorically differentiated terms—or some combination of these two approaches. The investigation of the phenomenological aspects of psychosis, either dimensional or categorical, may lead to greater understanding of the biological underpinnings of psychosis by way of identifying homogeneous subgroups of patients with similar and specific brain abnormalities. The dimensional alternative to categorical diagnosis opens the possibility of spectrum or dimensional illnesses, in which specific traits exist within a continuum from normal to pathologic. This approach would allow clinicians and researchers to focus on psychosis rather than the differential diagnosis of psychotic disorders, furthering the development of clinical interventions and research strategies.

Our data show, as is highlighted in Figure 1, that during the first episode of psychosis the clinical presentation of a patient with psychosis supports a modest diagnostic specificity of clinical features, as we found an overlap of Positive symptoms in schizophrenia and bipolar disorder, and Negative symptoms in schizophrenia and unipolar depression. This may account for why there was the least diagnostic differentiation of schizophrenia in the discriminant analysis. However, the Cognitive Disorganization factor was greater in schizophrenia, and Depression severity was

Figure 1 **PANSS Domains with Significantly Increased Symptom Severity Relative to Other Psychotic Disorders**



greater in unipolar depression. These findings suggest that these two dimensions should receive careful attention for clinical differential diagnosis in early phases of psychotic disorders. Perhaps later in the course of illness, when combined with family history, course of illness, and subsequent treatment response, greater diagnostic differentiation might be achieved. The evolution of symptoms needs to be compared in these disorders, independently and in relation to stability of diagnosis. Thus, learning about the differential phenomenological manifestations of psychotic disorders and their relevance to treatment remains an ongoing challenge for clinical studies of affective and nonaffective psychotic disorders.

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