The schizophrenias, the neuroses and the covered wagon; a critical review

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Objective: In order to compare their validity, this review applies scientific standards for sustaining the neuroses, the schizophrenias and bipolar disorders as separate "bona-fide" psychiatric diseases. The standards for disease validation demand specific and unique symptoms.

Method: We review a wide variety of clinical and basic science comparisons between schizophrenia and psychotic bipolar in a select English-language literature.

Results: Like covered wagons, the neuroses once served us well but became obsolete and were discarded or reorganized based on what was known about commonalities of symptoms, causation and pharmacological responsivity. Bipolar patients meet unique and specific diagnostic criteria and demonstrate consistent results across a variety of scientific disciplines. Neither the neuroses nor the schizophrenias have such unique or disease specific diagnostic criteria. Psychotic mood disorders account for the DSM diagnostic criteria for schizophrenia. A recent, selected but diverse basic science literature demonstrates surprising similarities between schizophrenia and psychotic bipolar which should not exist if these disorders are distinct.

Conclusions: Like the neuroses, there is stigma, confusion and misunderstanding about the condition called schizophrenia, resulting in substantial negative impact on bipolar patients misdiagnosed as having schizophrenia. The psychoses, including the schizophrenias, likely are explained by a single disease, psychotic bipolar disorder, that has demonstrated a wide spectrum of severity of symptoms and chronicity of course, not traditionally recognized.

Keywords: schizophrenia, mania, depression, bipolar mood disorder, neurosis, psychosis, Kraepelinian dichotomy

A history of the neuroses and the schizophrenias

In contrast to some medical specialties where diagnostic criteria are based on objective and often quantifiable pathophysiology, the diagnostic criteria of psychiatric disorders depend largely on subjective interviews, observations and opinions. Between the mid 19th and mid 20th centuries, the absence of objective findings stimulated individual mental health professionals to create their own idiosyncratic, redundant and often confusing names and diagnostic criteria for various psychiatric syndromes and subtypes. During this time mental illness was divided into two groups, the neuroses and the psychoses, the latter being further subdivided into the schizophrenias and manic-depressive insanity with schizophrenia the dominant disease of the two. The neuroses, with few exceptions, were less disabling than the schizophrenias. Patients called neurotic were likely to function adequately in most aspects of job, family life, and society with only a circumscribed area of dysfunction that could lead to temporary incapacitation. In contrast, patients diagnosed with schizophrenia were more globally dysfunctional and for longer periods of time, often spending months to years in psychiatric hospitals. While the neuroses were treated with psychoanalysis or other "talk therapies," the schizophrenias received more invasive physical treatments or

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management including cold showers, various wraps and straight jackets, insulin and electro-shock therapies, and neurotoxic, antipsychotic drugs. Some of these may have constituted punishments. According to Freud, the neuroses were caused by fixations in personality development in childhood that led to personality and behavioral dysfunctions in adulthood. Early descriptions of the schizophrenias blamed organic brain defects. Freud's groupings of adult symptoms formed the foundations for the classification of the neuroses, (Table 2b) while the opinions of Kraepelin, Bleuler, Schneider, and others, discussed below, established the current diagnostic criteria and subtypes of the schizophrenias and the concept that manic-depressive insanity (bipolar disorder) was a separate, minor disorder (Tables 1 and 2) (Bleuler 1911/1950; Kraepelin 1913; Schneider 1959).

The DSM and the extinction of the diagnosis of "neurosis"

The Diagnostic and Statistical Manual for Mental Disorders (DSM), the most widely accepted and authoritative publication of definitions and classifications of mental disorders, first addressed the problems of definition and nomenclature for mental disorders. Reflecting the multiple, idiosyncratic subtypes of the neuroses and the schizophrenias, the DSM, Second Edition (DSM-II) (APA 1968) listed 10 neurotic disorder subtypes and 12 schizophrenic subtypes (Tables 1a and 2). For some diagnoses but not others, beginning with the DSM-III (APA 1980) there was an attempt to replace subjective observations and opinions with available scientific data as the basis for subtypes and diagnostic criteria. This led to substantial changes in the DSM-III (APA 1980) regarding the neuroses but not the schizophrenias. Recognizing that the diagnosis of neurosis was confusing, misunderstood, socially stigmatizing and lacked a scientific basis, the DSM-III (APA 1980) eliminated the term "neurosis" from the official nomenclature and either dropped or reorganized and renamed its subtypes. Some were renamed and integrated into other diagnostic categories such as the anxiety disorders. In contrast, there have been minimal changes in the diagnostic criteria for the schizophrenias and their subtypes since the 1800's. Of the nine core subtypes of schizophrenia for adults listed in the DSM-II (1968), six remain in the DSM-IV-TR (2000) (Tables 1 and 2). Only "simple" and "acute schizophrenic episode" have been dropped. "Latent" has been compressed into "residual" and schizoaffective disorder is still given in the section on schizophrenia although it is no longer considered a specific subtype.

Table 1 From the Diagnostic and Statistical Manual of Mental Disorders, Second Edition (DSM-II; published in 1968)

a. The schizophrenias (psychoses not attributed to physical conditions)

DSM Code #	Subtype
295	Schizophrenia
.0	Schizophrenia, simple type
.1	Schizophrenia, hebephrenic type
.2	Schizophrenia, catatonic type
.23	Schizophrenia, catatonic type, excited
.24	Schizophrenia, catatonic type, withdrawn
.3	Schizophrenia, paranoid type
.4	Acute schizophrenic episode
.5	Schizophrenia, latent type
.6	Schizophrenia, residual type
.7	Schizophrenia, schizo-affective type
.73	Schizophrenia, schizo-affective type, excited
.74	Schizophrenia, schizo-affective type, depressed
.8	Schizophrenia, childhood type
.9	Schizophrenia, chronic undifferentiated type
.99	Schizophrenia, other [and unspecified] types

b. The neuroses:

DSM Code #	Subtype
300	Neuroses
.0	Anxiety neurosis
.1	Hysterical neurosis
.13	Hysterical neurosis, conversion type
.14	Hysterical neurosis, dissociative type
.2	Phobic neurosis
.3	Obsessive compulsive neurosis
.4	Depressive neurosis
.5	Neurasthenic neurosis (Neurasthenia)
.6	Depersonalization neurosis
.7	Hypochondriacal neurosis
.8	Other neurosis
.9	Unspecified neurosis

The history of the concept of the schizophrenias

Descriptions of aberrant, psychotic behaviors have been recorded for over 4000 years, with textbooks of Psychiatry attributing the ancient cases to schizophrenia. However, these ancient writings were certainly descriptive of psychotic behavior but not specific to any particular disease. The "modern" history of schizophrenia, first called dementia praecox or dementia of the young, dates to the mid-1800s (Doran et al 1986). Morel, in 1860, first used this term to describe young patients who had suffered "developmental arrest and personality disorganization" with dysfunction somewhat similar to old-age dementia. In the early 1870s Hecker added a subtype

Table 2 DSM-IV-TR section on schizophrenia (modified for brevity)

a. Diagnostic criteria

A. Characteristic symptoms (Sx): patients must have 2 Sx during a 1 month (active) phase[1]:
   (1) delusions
   (2) hallucinations
   (3) disorganized speech (frequent derailment, incoherence)
   (4) grossly disorganized or catatonic behavior
   (5) negative symptoms (affective flattening, alogia, or avolition)
   [NOTE: Only 1 symptom is required if delusions are bizarre or hallucinations are a voice commenting on one's behavior/thoughts; or 2 or more voices are conversing with each other] [1,2]

B. Social/occupational dysfunction: work, interpersonal relations or self-care have markedly deteriorated [1]

C. Duration: continuous signs for 6 months with a 1 month active phase (may include prodromal or residual symptoms) [1]

D. Exclude schizoaffective and mood disorder with psychotic features [3]

E. Exclude substance and general medical condition [1]

F. Exclude preexisting pervasive developmental disorder [1]

b. Subtypes of schizophrenia[1]

1) Paranoid type, (initiated by Kraepelin, 1880): Preoccupation with one or more delusions or frequent auditory hallucinations; no prominent disorganization of speech, no disorganized or catatonic behavior or flat or inappropriate affect [1].
2) Disorganized type, (initiated by Hecker, 1871): All of the following are prominent: disorganized speech and behavior, flat or inappropriate affect without catatonia.
3) Catatonic type, (initiated by Kahlbaum, 1874): (1) motoric immobility including waxy flexibility or stupor; (2) excessive but purposeless motor activity; (3) extreme negativism or mutism; (4) peculiarities of voluntary movement to include inappropriate or bizarre posturing, stereotyped movements, prominent mannerisms or grimacing; (5) echolalia or echopraxia [1].
4) Undifferentiated type: Symptoms from criterion A for schizophrenia (characteristic symptoms) present but without the criteria given above for the paranoid, disorganized or catatonic types [1].
5) Residual type, (similar to E. Bleuler's latent subtype, 1911): absence of prominent delusions, hallucinations, disorganized speech or behavior or catatonia; presence of continuing evidence of the disturbance, ie, negative symptoms or 2 or more symptoms from criterion A of schizophrenia in an attenuated form, ie, odd beliefs or unusual perceptual experiences[1].

[1] the symptoms/criteria in each of these sections of the diagnostic criteria that "define" schizophrenia, ie, A, B, C, E, and F and the symptoms of the subtypes are disease non-specific and occur frequently in mood disorders, severe with psychotic features
[2] these qualifications that allow a diagnosis of schizophrenia with only one of the characteristic symptoms in section A is from K. Schneider's first rank symptoms (see Table 4)
[3] criterion D is under emphasized and often overlooked when psychotic symptoms from criterion A are elicited, especially in the US (in contrast to UK)

of dementia praecox, hebephrenia (now called disorganized schizophrenia) and 3 years later Kahlbaum named catatonia as a second subtype (Bleuler 1911/1950). Kraepelin, in the 1880s, described the paranoid subtype and divided severe mental illness into dementia praecox and manic-depressive insanity (now called bipolar mood disorder) that, he wrote, had a mild, remitting course (Kraepelin 1913). E. Bleuler first used "schizophrenia" instead of dementia praecox in 1911 to describe an incapacitating and often unremitting disease of early-adulthood onset that he recognized as differing from dementia because memory and orientation remained intact (Bleuler 1911/1950). He incorporated the three subtypes noted above and established broad diagnostic criteria called "fundamental symptoms," as well as the accessory symptoms of hallucinations and delusions (Tables 2, 3) (Bleuler 1911/1950; APA 2000). The fundamental symptoms, known as Bleuler's "four As" were considered diagnostic well into the 1970s but only "flat affect" remains in use today as one of the three "negative symptoms" of schizophrenia (APA 2000). Bleuler taught that schizophrenia was the most common mental illness after mental retardation and alcoholism and emphasized that hallucinations and/or delusions without identifiable organic origin, although not mandatory for the diagnosis, were disease specific for schizophrenia. In 1959, Schneider reinforced Bleuler's broad perspective on schizophrenia and minimization of bipolar in concluding that any one of his own "first-rank symptoms of schizophrenia" was pathognomonic of schizophrenia (Table 4) (Schneider 1959). Schneider agreed that the presence of hallucinations and/or delusions mandated a diagnosis of schizophrenia, regardless of even marked alterations in mood. According to Bleuler and Schneider there could be no psychotic mood disorder. Later editions of the DSM narrowed the definition of schizophrenia by requiring (and equating) the presence of psychotic symptoms such as hallucinations, delusions, disorganization and catatonia for a set period of time. Bleuler's extremely general "fundamental symptoms" were mostly eliminated as diagnostic but

Table 3 E. Bleuler's pathognomonic symptoms and other signs of schizophrenia

a. 4 As of schizophrenia/fundamental symptoms[1]

1) Ambivalence[2] (can be normal or due to distractibility)[3]
2) Affect, inappropriate[2] (usually due to anxiety and embarrassment)
3) Associations, loose[2] (likely represents distractibility, racing thoughts, and flight of ideas associated with mania)[4]
4) Autistic thinking (only means delusional, unable to distinguish fantasy from reality)[4]

b. Accessory symptoms:[1,4]

1) Hallucinations
2) Delusions

c. Other signs often thought indicative of schizophrenia[1,4]

1) Loner, poor premorbid personality [2]
2) Onset of psychotic illness in late adolescence or early adulthood[4]
3) A disorder of thought; formal thought disorder[4]
4) Derailment, tangentiality, loose associations, disorganization, blocking, incoherence, word salad, clanging, echolalia, echopraxia, speaking in tongues[4]
5) Catatonia[1,4]
6) Coprophagia, coprophilia[4]
7) Downward drift in society and employment [2,4]
8) Multiple, brief jobs [2,4]
9) Street person [2,4]
10) Ideas of control or reference, paranoia [2,4]
11) Mood incongruent hallucinations and/or delusions[4]

[1] none of these symptoms alone or in any combination, are disease specific; they occur frequently in severe mood disorders with psychotic features
[2] these signs and symptoms can overlap with normal behavior or be caused by multiple circumstances or causes other than a psychotic process
[3] statements in parentheses added by author
[4] common in severe mood disorders.

Schneider's "first-rank symptoms" remain especially diagnostic (compare Tables 2, 3, and 4).

Doubt about the schizophrenias: the non-specificity of the diagnostic criteria and chronicity of course

The first departure from Kraepelin's initial description of two separate diseases, dementia praecox and manic depressive insanity, came from Kraepelin himself in 1920 when he recanted somewhat, stating, "It is becoming increasingly clear that we cannot distinguish satisfactorily between these two illnesses and this brings home the suspicion that our formulation of the problem may be incorrect" (Crow 1990; Taylor 1993). Another movement away from Bleuler's concept equating psychosis with schizophrenia and toward a single disease to explain psychoses came in 1933 with Kasanin's new diagnosis, "schizoaffective psychosis", describing psychotic patients with symptoms of mania or depression and moving the diagnoses of some psychotic patients away from schizophrenia and toward mood disorders (Kasanin 1933). The wide acceptance of the predominance of schizophrenia over bipolar in psychotic patients may have discouraged Kasanin from diagnosing his patients "psychotic manic-depressives" and his schizoaffective concept was not widely embraced for several decades (Lake and Hurwitz 2006a).

Skepticism about the disease specificity of psychotic symptoms and the prevalence of schizophrenia over psychotic mood disorders appeared in the psychiatric literature by the 1970s. In 1978, Pope and Lipinski reviewed 166 papers dealing with the predictive value of "schizophrenic" symptoms and course, outcome, lithium response and family history in patients diagnosed with schizophrenia (Pope and Lipinski 1978). They and others concluded that there are no pathognomonic symptoms, courses, or outcomes that are specific to or valid in diagnosing schizophrenia (Kendell and Gourlay 1970; Fowler et al 1972; Ollerenshaw 1973; Abrams et al 1974; Pope and Lipinski 1978; Pope 1983; Dieperink and Sands 1996; Lake and Hurwitz 2006b). Conclusions by Pope and Lipinski, still relevant today, include: 1) "It seems likely that the findings summarized in this review (that many schizophrenics are actually misdiagnosed, mood-disordered patients) have not been adequately acknowledged by many modern American diagnosticians." 2) "The non-specificity of 'schizophrenic' symptoms brings into question all research that uses them as the primary method of diagnosis" (Pope and Lipinski 1978). Further evidence for the subjectivity of the diagnostic criteria

Table 4 K. Schneider's pathognomonic symptoms of schizophrenia

a. First rank symptoms[1]

1) Hearing one's thoughts spoken aloud
2) Hearing voices arguing about oneself [2]
3) Hearing voices commenting on one's actions [2]
4) Having bodily sensations imposed from outside
5) Having one's thoughts/feelings inserted or withdrawn by external sources
6) Having one's thoughts broadcast
7) Having delusional perceptions

b. Second rank symptoms[1]

1) Other disorders of perception [3]
2) Sudden delusional ideas
3) Perplexity [3]
4) Depressive and euphoric mood changes [4]
5) Feelings of emotional impoverishment [3]
6) "... and several others as well" [3]

[1] none of these symptoms alone or any combination, are disease specific and they occur frequently in severe mood disorders with psychotic features
[2] either of these two symptoms are recognized as pathognomonic alone in the DSM-IV-TR since the presence of either by itself satisfies criteria under "NOTE" in section A, characteristic symptoms of schizophrenia (see Table 2)
[3] probably not indicative of any mental illness
[4] diagnostic of a mood disorder.

comes from the discrepancy in the prevalence of diagnoses used for psychotic patients between the UK and the US with the diagnosis of psychotic bipolar disorder rather than schizophrenia more common in the UK than the US (Kendell and Gourlay 1970; Cooper et al 1972; Ollerenshaw 1973).

The mood disorders section of the DSM-IV-TR (APA 2000) recognizes that the psychotic features (hallucinations, delusions, disorganization and catatonia), and the chronic, persistent course, traditionally diagnostic for schizophrenia, occur in mood disorders that are severe with psychotic features (Table 5). According to the clinical literature, mood-congruent or mood-incongruent hallucinations and/or delusions occur in 50%–80% of acutely manic patients (Carlson and Goodwin 1973; Guze et al 1975; Tohen et al 1992). Disorganization of speech, thought, and behavior —criteria supposedly specific for schizophrenia—occur in most, if not all, hospitalized manic or mixed bipolar patients and are indicative of mania. Catatonia is accounted for by severe bipolar over 71% of the time (Kruger and Braunig 2000). In the DSM-IV-TR (APA 2000) catatonia is a core diagnostic symptom and a major subtype of schizophrenia (Table 2) but in the DSM section on mood disorders, the wording for catatonia as a "specifier" is the same (compare Tables 2, b,3 and 5,c). The "negative characteristic symptoms" from Criterion A for schizophrenia are most likely due to severe depression. Paranoia, another subtype and a diagnostic criterion of schizophrenia, typically "hides" the guilt or grandiosity of a psychotic mood disorder (Lake CR Unpublished 2007). According to the DSM-IV-TR (APA 2000) section on mood disorders, patients with psychotic mood disorders can evince all five of the diagnostic symptoms for schizophrenia, sustain chronic, non-remitting courses, and yet not have schizophrenia. Criteria B, C, E, and F for schizophrenia are entirely compatible with mood disorders. Criterion D attempts to rule out psychotic mood disorders but can be overlooked or dismissed when psychotic features are focused upon in keeping with the traditional "hierarchical principle that schizophrenia takes priority" and that "even a trace of schizophrenia is schizophrenia" (Table 2) (Pope 1983; Maier et al 1992).

More recent data reinforce the contention that hallucinations and delusions are predominantly explained by psychotic mood disorders. Of 236 consecutive admissions with functional psychoses, 78% were diagnosed with psychotic mood disorders (Pini et al 2001). The percentage explained by psychotic mood increases to about 90% when the 12% diagnosed schizoaffective are moved to the psychotic mood category (Lake and Hurwitz 2006a). With such an overlap of diagnostic symptoms, the existence of two disorders rather than only one is questioned (Craddock and Owen 2005; Lake and Hurwitz 2006b). If only one disease, similarities and overlap in results from various basic science studies comparing patients diagnosed with schizophrenia and psychotic bipolar patients would be expected and would further indicate only one disorder to explain the psychoses.

Recent basic science data linking schizophrenia and psychotic bipolar disorder as one disease

Because schizophrenia was considered the most severe of psychiatric illnesses, research efforts to elucidate the cause of schizophrenia focused on comparisons of these patients with normal volunteers. Schizophrenia gained acceptance as hundreds, if not thousands, of studies found differences between schizophrenia and normals. However, in subsequent studies of psychotic bipolar or studies comparing schizophrenia to psychotic bipolar, similarities and overlap have been reported. Specific examples of this phenomenon are the D-amino acid oxidase activator (DAOA/(G72)/G30) on chromosome 13q22-34 that was initially linked to

Table 5 DSM-IV-TR diagnostic criteria and specifiers for mood disorders (d/o) and mania (modified for brevity)

a. Diagnostic criteria for a manic episode (defines bipolar mood D/O)

A. Distinct period ≥ 1 week (or inpatient hospitalization necessary) of abnormal and persistently elevated, expansive or irritable mood

B. In the period, 3 symptoms (4 if mood is only irritable) persist to a significant degree:

1) distractibility
2) insomnia with increased energy
3) grandiosity/increased self-esteem
4) flight of ideas
5) increased activities: including phoning, spending, travel, investing, gambling, sex; excessive involvement in pleasurable activities with high potential for negative outcome
6) speech: pressed to incoherent [(1)]
7) thoughts: racing, loose, tangential[(1)]

C. Symptoms cause marked impairment in functioning[(1)] (job, social, family) or hospitalization[(1)] warranted because of severity of symptoms

D. Symptoms not due to substance or general medical condition

b. Specifiers for mood D/O diagnoses

A. Presenting state:

- for BP: manic, depressed, mixed
- for UP: single episode or recurrent

B. Severity: mild, moderate, severe without, severe with psychotic features [(1)], partial, full remission

C. Course/Onset: chronic (symptoms > 2 years) [(1)], seasonal affective D/O, rapid cycling [(1)] (≥ 4 episodes/year), postpartum onset (within 4 weeks), with or without full interepisode recovery [(1)]

D. Features: catatonic [(1)], melancholic, atypical[(1)]

c. Catatonic features specifier

(1) motoric immobility including waxy flexibility or stupor; (2) excessive but purposeless motor activity; (3) extreme negativism or mutism; (4) peculiarities of voluntary movement to include inappropriate or bizarre posturing, stereotyped movements, prominent mannerisms or grimacing; (5) echolalia or echopraxia [(1)].

[(1)]underlines added to denote symptoms that can cause the misdiagnosis of schizophrenia or are listed in the DSM-IV-TR section on schizophrenia as diagnostically specific for and/or as a subtype of schizophrenia.

schizophrenia (Chumakov et al 2002) but subsequently found by at least 5 independent studies to be linked to bipolar (Badner and Gershon 2002; Hattori et al 2003; Schumacher et al 2004; Craddock et al 2005; Green et al 2005a,b) and the DISC-1 locus at 1q42 that was perhaps prematurely named "disrupted in schizophrenia" since it was first associated with patients diagnosed schizophrenic (Millar et al 2000; Devon et al 2002). Similarly to the DAOA/G30 site, more recent data from several labs suggest linkage of DISC-1 to bipolar and "schizoaffective" pedigrees (Millar et al 2000; Blackwood et al 2001; Hodgkinson et al 2004; Macgregor et al 2004; Hamshere et al 2005).

A recent, selected, rapidly expanding and provocative literature from diverse basic science laboratories in the US and UK demonstrates surprising similarities between schizophrenia and psychotic mood disorders, similarities that should not occur if these are two distinct disorders. A 2005 editorial noted that ". . . of the (eleven) chromosome loci found for the transmission of schizophrenia and bipolar disorder, eight have been found to overlap . . " (Fawcett 2005). Selected results also showing similarities derive from genetic (Berrettini 2000, 2001, 2003; Cardno et al 2002; Schurhoff et al 2003; Korn 2004; Schumacher et al 2004; Craddock and Owen 2005; Craddock et al 2005; Fawcett 2005; Green et al 2005a; Hamshere et al 2005; Schulze et al 2005), imaging (Roy et al 1998; Bilder et al 1999; Dasari et al 1999), auditory evoked potential (Olincy and Martin 2005), brain metabolic (al-Mousawi et al 1996; Cohen et al 1998), neurochemical (Knable et al 2001; Koh et al 2003; Tkachev et al 2003; Rosack 2003), and epidemiological (Berrettini 2000; Korn 2004) studies.

More details from the literature noted above are enlightening. The two disorders overlap extensively in epidemiological aspects including age of onset, lifetime risk, course of illness, worldwide distribution, risk for suicide, gender influence, and genetic susceptibility (Berrettini 2000). Korn

(2004) finds similarities in "family studies, genetic analyses, common symptom complexes and psychopharmacological responses" and implies that the "evolving interface between the two disorders is closing". One author suggests that schizophrenia and bipolar disorders are "chemical cousins" (Rosack 2003). Cardno et al (2002) applied a "biometrical model fitting" to clinical data from twins to investigate whether schizophrenia and manic-depressive disorder share genetic risk factors. Results of their studies of 77 monozygotic and 89 same-sex dizygotic twin pairs indicate "significant genetic correlations" between these two disorders. The authors conclude that "there is a degree of overlap in the genes contributing" to schizophrenia and bipolar disorder. At least two groups, Schulze et al (2005) and Schurhoff et al (2003) find that delusional proneness is an inherited predisposition common to schizophrenia and bipolar. The DAOA/GT30 locus on 13q34 appears to confer persecutory delusions similarly in schizophrenia and bipolar implying genotypic overlap (Schultz et al 2005). Based on their molecular genetic research, Craddock and Owen (2005) published an editorial titled "The beginning of the end for the Kraepelinian dichotomy" and conclude that, "Now molecular genetic studies are beginning to challenge and will soon, we predict, overturn the traditional dichotomous view" (that schizophrenia and bipolar are separate).

Tkachev et al (2003) studied the oligodendrocyte-specific and myelination-associated gene expression in schizophrenia and bipolar disorder finding similar downregulation of key genes, including transcription factors that regulate these genes, in schizophrenic and bipolar brains, as compared to controls. They conclude that there are "similar expression changes" in schizophrenic and bipolar brains which, they state, "lends support to the notion that these disorders share common causative and pathophysiological pathways". Koh et al (2003) identified a recently recognized group of dopamine receptor-interacting proteins as possible novel sites of dysfunction in schizophrenic and bipolar patients. This group, studying tissue from the Stanley Foundation Neuropathology Consortium, find that the dorsolateral prefrontal cortex in both schizophrenic and bipolar brains has significantly elevated levels of the D2 dopamine receptor-desensitization regulatory protein, neuronal calcium sensor-1. Their study "supports the hypothesis that schizophrenia and bipolar disorder may be associated with abnormalities in dopamine receptor-interacting proteins".

We acknowledge that there are ample data indicating that the two diseases are separate (Alsthuler et al 2000; Lapierre 1994) but question whether the diagnostic confounders related to non-specificity of diagnostic symptoms invalidate some of these conclusions. The patients in the "schizophrenia" study groups might really suffer from severe psychotic bipolar (Pope and Lipinski 1978). Differences in comparative studies might be explained by inherent variabilities across the spectrum of severity between "ordinary" and severely psychotic bipolar patients. The conclusions of some reviews are ambivalent regarding similarities and differences between the two (Ketter et al 2004).

Several authors including Taylor (1993) and Crow (1990) imply that the three psychotic diseases, schizophrenia, schizoaffective and bipolar disorders, form a spectrum of severity (Dieperink and Sands 1996; Kendell and Gourlay 1970; Moller 2003; Ollerenshaw 1973). We extend this hypothesis to propose that only one disease, psychotic bipolar disorder, has such a wide spectrum of severity of symptoms and chronicity of course without remission, that it alone can explain all three of the current psychotic diagnoses. A basic tenet of medicine states that if one disease can explain a spectrum of symptoms that generate two or more diagnoses, there is likely only one disease, in this case, a mood disorder.

If psychotic patients do not have schizophrenia or symptoms of a mood disturbance, what do they have?

Severely psychotic mood patients can suffer psychotic symptoms that obscure mood symptoms for months (Post 1992; Korn 2004). Such patients typically do not complain of their mood symptoms in their initial diagnostic interviews but often focus instead on paranoid symptoms if they are able to communicate at all (Lake 2006). The absence of obvious mood symptoms in patients presenting in psychotic states warrants aggressive pursuit of symptoms of a mood disturbance from such patients and any significant others available. In those psychotic patients still without obvious current or past mood symptoms, we suggest a temporary diagnosis of "psychotic disorder not otherwise specified" while mood symptoms or subtle organic causes are pursued. This diagnosis is already in place in the DSM-IV-TR, code number 298.9 (APA 2000). A less stigmatizing diagnosis than schizophrenia, it more accurately reflects our knowledge or lack thereof. As noted by Swartz and reviewed by Martin, there are multiple subtle organic causes of psychosis such as epilepsy, tardive psychosis, congenital abnormalities,

obstetric brain trauma, stroke and narcolepsy (Martin 1983; Doran et al 1986; Swartz 1995, 2002, 2004; Douglass 2003). Further, past use of phencyclidine or other neurotoxic, "designer", or illegal drugs can cause a chronic psychosis and may not be identified in drug screens.

The scientific data supporting schizophrenia and bipolar disorder as "bona-fide" diseases

A sound scientific basis for establishing a disease demands diagnostic criteria or pathophysiology that are unique and specific for that disease. The belief that hallucinations, delusions, and a chronic course are disease specific for schizophrenia has been widely held and all research data are based on this presumption, leading to the accumulation of "a massive body of clinical and biological evidence" and lending confidence as to the validity of schizophrenia as a "bona-fide" disease (Pope and Lipinski 1978; Nasrallah 2006). Despite recognition that these "diagnostic" symptoms for schizophrenia are disease non-specific, its acceptance as a disease is so firmly entrenched that it persists. In contrast to schizophrenia, for classic bipolar disorder, the changes in behavior and cognition are so extreme between mania and depression in the same patients that the diagnostic symptoms are strikingly unique and widely different from euthymia or any other medical condition. No other disease causes such a pattern of symptom occurrence. Descriptions of such cycling have been numerous and consistent for over 2000 years (Goodwin and Jamison 1990). Such "classic" patients are identifiable with a high degree of confidence. These characteristic symptoms and cycling courses have been identified and constitute disease-specific diagnostic criteria that are given in the DMS-IV-TR (Table 5) (APA 2000). Patients with cycles of the characteristic symptoms have been rigorously diagnosed and sequestered on research units and have demonstrated consistent genetic (Barrett et al 2003; Green et al 2005a, b), epidemiologic (Berrettini 2000, 2001, 2003) and pharmacologic (Carlson and Goodwin 1973; Korn 2004) results, validating bipolar mood disorder as a specific disease (Table 6) (Goodwin and Jamison 1990). For the mood disorders, hallucinations and delusions only indicate the level of severity and are not utilized as diagnostic criteria, as they are for schizophrenia. Further documentation of the veracity of bipolar stems from several candidate bipolar susceptibility loci that have been recently isolated (Barrett et al 2003; Green et al 2005a, b). Patients studied on research units for schizophrenia were selected primarily because they evidenced hallucinations and/or delusions (Table 6). As implied by Pope and Lipinski, many, if not most, of these patients suffered from psychotic bipolar disorder and putting research conclusions about schizophrenia in doubt (Pope and Lipinski 1978; Lake and Hurwitz 2006a,b).

Why the schizophrenias have not followed the neuroses

The concept of schizophrenia as "insanity" was narrowly focused, with high morbidity and chronicity usually requiring hospitalization. The costs for patients diagnosed with schizophrenia on government disability status have garnered considerable attention from government, taxpayers, and society in general. The neuroses, which may have been more common but were usually managed in outpatient clinics at lower costs received less attention and rarely had disability status. As a result, hundreds of millions of federal dollars have funded research on the schizophrenias while relatively few dollars have supported research into the neuroses. Like numbers of pharmaceutical dollars have supported the development and clinical trials of new antipsychotic or "anti-schizophrenic" drugs, encouraging the diagnosis of schizophrenia and solidifying it as a disease. These factors have stimulated research that generated lectures, seminars and publications about schizophrenia, including at least 3 journals dedicated to schizophrenia alone. Such a large database magnified the importance of schizophrenia as a "bona-fide" disease. The power base of researchers, academics, editors and administrators invested in the schizophrenias has been greater and more influential than that of those studying the neuroses. Schizophrenia has received media attention both in the news and in film and has been evoked as the explanation for numerous high-profile murders. The term "schizophrenic" is misused as an adjective in the media and by the public to signify "flip-flops" in behaviors, statements or policies. For reasons such as these, schizophrenia has maintained its place as the most widely-known mental disorder in the world.

Summary

The schizophrenias, like the neuroses, 1) were described in the 19th century, 2) have diagnostic symptoms based on observation and opinion, 3) have no disease-specific signs or symptoms, 4) convey considerable social stigma, and 5) are confusing and misunderstood by many including the public and the media. A distinctive pathophysiology for schizophrenia remains elusive despite enormous, costly research

Table 6 Scientific bases for bipolar (BP) disorder (D/O) and for schizophrenia

a. Bipolar mood D/O

1) The striking extremes in mood and behavior from mania to depression that occur in cycles in the same individuals make such patients easy to identify with confidence. These symptoms of BP mood D/O have been described in patients for over 2000 years, date from 100 BC and have been numerous and consistent. These symptoms form the diagnostic criteria in the DSM-IV-TR and do not include hallucinations and delusions that only indicate level of severity for the BP D/O.

2) That these diagnostic criteria define a specific disease, ie, BP mood D/O, has been verified over the past 30 years by several lines of data; patients with the diagnostic criteria of BP mood D/O from the DSM have been gathered on research units, studied, and have yielded consistent data; they:

- Respond to Lithium (large, double blind, placebo controlled, crossover studies)
- Have a 10% concordance in primary family members including dizygotic twins
- Have about a 70% concordance in monozygotic twins
- When 1 parent has a BP-I D/O, any child has a 25% chance of developing a mood D/O; when both parents have BP-I, any child has a 50%–70% chance
- Adoption studies show that biological children of affected parents remain at the same risk even if adopted in infancy by non-affected families
- Gene studies of several large families with a high prevalence of BP D/O have identified specific loci in affected individuals (loci different across the different families)
- When treated with MAO-Is, TCAs, or SSRIs, 10%–15% of BP depressed patients can "switch" into mania (these antidepressants effect neurotransmitters involved in modulation of mood)
- BP D/Os have a tight age of onset distribution (mean, about 20 years)
- Have a generally predictable and common course (pattern of cycles that shorten with relapses and occur more frequently)

b. Schizophrenia:

Our current concept of Schizophrenia is based on the 19th and early 20th century observations, descriptions and beliefs of E. Bleuler and later K. Schneider, who stated that hallucinations and delusions were unique to Schizophrenia after organicity is ruled out. By their criteria a patient cannot have a primary diagnosis of mood D/O and have hallucinations or delusions. The DSM-IV-TR (2000) essentially endorses their descriptive, non-disease specific diagnostic criteria in the section on Schizophrenia while under the mood D/O section, the DSM acknowledges the potential for hallucinations, delusions, disorganization, catatonia, chronic presence of symptoms and the absence of a full interepisode recovery in a mood D/O patient.

Abbreviations: BP, bipolar; D/O, disorder; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th ed, text revision; MAO-I, monoamine oxidase inhibitor; TCA, tricyclic antidepressant; SSRI, serotonin specific reuptake inhibitor.

efforts. While bipolar disorder is scientifically grounded as a "bona-fide" disease, schizophrenia is not. So what is schizophrenia?

The select clinical and recent, diverse basic science literature summarized above is striking in its consistency of results which indicate that schizophrenia and psychotic bipolar disorder are more alike than different over a wide array of variables. Many, if not most, of the patients diagnosed with schizophrenia in research studies may have suffered from psychotic mood disorders (Pope and Lipinski 1978). Taken together, these data invite speculation that schizophrenia and bipolar disorder are in fact one, and that schizophrenia, previously identified by psychotic symptoms, is really the extreme end of the severity continuum of bipolar mood disorder and not a different disease. Three psychotic disorders would have traditionally been invoked to account for the severity continuum of only one disease—a mood disorder that is now recognized to evince the furthest extremes of insanity. Such a mood disorder can be sufficiently severe, with an overwhelming predominance of psychotic features, to obscure obvious mood symptoms.

The potential for negative outcomes is substantial for mood-disordered patients who are misdiagnosed with schizophrenia, in that instead of first-line mood stabilizing drugs they are given antipsychotic drugs in greater doses and for longer periods of time. Bipolar patients cycle faster and get worse without first-line mood-stabilizing drugs and they get antipsychotic drugs with more malignant side-effect profiles (Dieperink and Sands 1996; Carlson and Goodwin 1973). Social stigma associated with schizophrenia is considerably more detrimental than that of most other mental health disorders.

Among psychotic patients, adoption of the assumption that "even a trace of mood disturbance is a mood disorder" seems appropriate. In the small percentage of psychotic patients who have no current or historic mood disturbances, a diagnosis of "psychotic disorder not otherwise specified" is more useful and safer than schizophrenia. The literature of this review, though selected, is substantial and persuasive. The authors recognize that its thesis is controversial and may be received with skepticism or dismissed; nevertheless, it may be time to consider retiring the historic diagnosis of schizophrenia as were the neuroses and covered wagons.

This review has shortcomings. We may have inadvertently missed some comparative studies that documented differences. There is as yet no definitive pathophysiology to conclude that these are one or two diseases. The overlap in susceptibility loci provides for the most compelling argument for a single disease but a positive conclusion awaits further molecular genetic studies.

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