Will The Kraepelinian Dichotomy Survive DSM-V?

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Abstract

Kraepelin proposed dementia praecox and manic-depressive illness as the two major psychotic disorders. This paradigm is still prevalent, but observations of overlapping boundaries between bipolar disorder and schizophrenia challenge this dichotomy. However, the concept of schizophrenia has been radically altered from the original Kraepelinian proposal. We defend the two psychoses position, but suggest two flaws in the heuristic application: 1) overlapping features such as psychotic symptoms are not decisive in differential diagnosis; and 2) each disorder is a syndrome, not a disease entity. An alternative paradigm based on domains of pathology is more powerful for studies of etiology, pathophysiology, and therapeutic discovery.

Introduction

Over 100 years ago Kraepelin conceptualized dementia praecox and manic-depressive psychosis as two distinct diseases. This dichotomy continues today in the nosological classes of schizophrenia and the bipolar disorders. However, many similarities between these two classes have been noted and the validity and heuristic value of this dichotomy is in question, especially when recent genetic findings are considered (Lake, 2007; Craddock & Owen, 2005; Moller, 2003). With the Diagnostic and Statistical Manual of Mental Disorders (DSM) set to undergo some significant changes in its fifth edition, the time is right to explore whether Kraepelin's dichotomy remains a useful concept. [*] We defend the position of separate disorders and point out two major problems in joining the diagnoses. We explain why overlapping features, including psychosis, are not decisive in the debate. We also posit that each disorder is a clinical syndrome rather than a specific disease entity. As such, a "domains of pathology" approach is a more heuristic paradigm for etiologic, pathophysiologic, and therapeutic discovery, and may clarify points of similarity and decisive differences between the two syndromes.

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Problem #1: Psychosis

The problem with using psychosis, especially reality distortion symptoms such as delusions and hallucinations to define a disease entity, is simple. Psychosis is a common manifestation of many diseases that are distinguished at the level of etiology. Causes of psychotic experience range from sensory isolation to temporal lobe epilepsy and a number of psychotic conditions have known causes (e.g., PCP psychosis or Huntington's Disease). Psychosis is on a continuum in human experience and is not uncommon in population surveys (Rossler et al., 2007; van Os et al., 2000; Kendler et al., 1996). Psychosis also occurs in circumstances not considered pathological (e.g. religious ecstasy). Defining psychosis as an illness has required secondary criteria relating to disability and/or distress. But for schizophrenia and bipolar illnesses, disability and discomfort are more robustly associated with cognitive impairments, negative symptoms (in schizophrenia), and mood pathology (in bipolar).

Indeed, the brain generates hallucinations and delusions in so many conditions that it is difficult to understand how these symptoms have maintained primacy in the diagnosis of any specific disease. Psychotic experience is to the diagnosis of mental illness as fever is to the diagnosis of infection–important, but non-decisive in differential diagnosis.

Some studies contrasting schizophrenia and bipolar disorder document important differences. For example, McIntosh et al (2008) probe language dysfunction and observe decreased brain activation in both disorders, but an anatomic distinction with anterior insula in bipolar and dorsal prefrontal cortex in schizophrenia. Nonetheless, the boundary between the two major psychoses is porous. Hallucinations, delusions and disordered thought are observed in both. Similar forms of symptoms may be phenomenologically distinguished (e.g, pressured thought in mania and dissociative thought in schizophrenia; mood congruent delusions in bipolar and more bizarre delusions in schizophrenia [Solovay et al., 1987; Shenton et al., 1987]), and causal mechanisms may be different even if the neural substrate is similar. With important similarities and differences, the paramount issue is whether the two diagnostic classes comprise one heterogeneous disorder with an artificial boundary or two disorders with overlapping features.

The challenge to the Kraepelinian dichotomy may not have become relevant had the *core* pathologic features, which originally distinguished dementia praecox and manic-depressive psychosis, survived in DSM-III and IV. Kraepelin described the two "general maladies" of dementia praecox: dissociative pathology, i.e. disorganization of thought and/or behavior, and "a weakening of the well-springs of volition", i.e. the negative symptom complex (Kraepelin, 1971/1919). Bleuler also considered these pathologies fundamental (Bleuler, 1950/1911) and considered reality distortion symptoms as secondary. The fundamental features of dissociation and avolition were critical in distinguishing schizophrenia from manic-depressive psychosis. Debate as to whether the Kraepelinian dichotomy is valid presumes that the current concept and criteria for schizophrenia relate closely with the original construct. This is not the case. For these pioneers it was the closely linked dissociative and avolitional pathology that described schizophrenia, and their co-occurance in individuals that defined caseness. Manic-depressive illness was defined by mood excesses

and episodic pattern. Long-term course was also discriminating. Contrast this with the DSM-III and IV. The presence of hallucinations and delusions, or just delusions if bizarre, satisfy Criteria A for schizophrenia even in the absence of dissociative and avolitional pathologies. Avolition was not even included as a criterion in DSM-III.

In an effort to improve diagnostic reliability, Schneider proposed that certain reality distortion symptoms (referred to as First Rank Symptoms) were highly discriminating of schizophrenia (1959). In Europe, coupled with Langfeldt's distinction between true and pseudoschizophrenia (1969), these concepts gelled in the concept of "nuclear" schizophrenia. During this time in the United States, scientists from Washington University were organizing diagnoses with explicit criteria and validation based on onset, manifest pathology, course, treatment, and associated biologic features. This approach, modified and put forward as the Research Diagnostic Criteria (RDC) by Spitzer and colleagues (1979), joined the European nuclear schizophrenia tradition as the foundation for the DSM-III approach to psychoses. However, in the transition from Kraepelin/Bleuler to DSM-III, the concept of schizophrenia has been remarkably altered.

That the original conceptualization of schizophrenia differs from current diagnostic criteria does not automatically indicate that the current system is flawed. However, studies conducted during the late 1960s and early 1970s tested several versions of the nuclear schizophrenia concept and suggested just such a conclusion. First Rank Symptoms were observed in psychotic classes other than schizophrenia (Carpenter & Strauss, 1974; Strauss et al., 1974; Carpenter et al., 1973a); none of the definitions of nuclear schizophrenia based on supposedly pathognomonic reality distortion symptoms predicted course and outcome (Hawk et al., 1975; Strauss & Carpenter 1974a; Strauss & Carpenter 1974b; Carpenter et al. 1973b); and functional outcomes were mainly related to other aspects of the syndrome (Hawk et al., 1975; Strauss & Carpenter 1974a; Strauss & Carpenter 1974b; Carpenter et al. 1973b). The most robust symptomatic distinction between schizophrenia and non-schizophrenia psychotic diagnostic classes were restricted affect, poor rapport, and poor insight (Carpenter et al., 1973b). For DSM-III, presumptions of validity of the nuclear schizophrenia concept trumped this empirical data falsifying the key hypotheses relating to the Schneiderian and Langfeldt systems. This shift in concept has profound implications and moves bipolar illness and schizophrenia closer together by emphasizing common features while de-emphasizing the pathological attributes that originally distinguished the conditions.

Kraepelin also distinguished manic depression from dementia praecox based on course, the former being cyclical and the latter chronic. Does this difference carry any nosological information in an era of chronic mania (Malhi et al., 2001) and remission/recovery in schizophrenia (Fischer & Carpenter, 2008)? Two current issues complicate testing of Kraepelin's original observation: The first is the concept alteration in our modern diagnostic scheme. Recent longitudinal studies in schizophrenia use diagnostic criteria that emphasize psychosis and do not require avolitional pathology. Restricted affect was the most robust predictor of poor 5-year outcome in the Washington Center of the International Pilot Study of Schizophrenia (Carpenter et al., 1978), and prominent negative symptoms are associated with a more chronic course (Strauss et al., 2008; Moller et al., 2002). The second issue is therapeutic intervention. From the mid-20th Century onward, treatment has been robustly

influenced by movement away from chronic institutionalization and by pharmacotherapy. Nonetheless, longitudinal data from pre- and post- antipsychotic drug eras reveal heterogeneity of course for schizophrenia (Marengo, 1994). Since most studies follow cohorts of already chronic cases, a bias towards chronic morbidity is present and good outcome cases may be excluded. A typical course for schizophrenia is difficult to define, let alone use as a validating criteria for classification. The course pattern early in bipolar disorder is primarily mood pathology and episodic, but long-term follow-up also report eventual chronic course sometimes including apparent negative symptoms. Course heterogeneity in each condition precludes identification of a "typical" course that can validate diagnostic classification.

Problem #2: Syndromes versus disease entities

The debate over whether schizophrenia and bipolar disorder are one disease or two is based on the assumption that each diagnosis is homogeneous enough to consider the combination. But there has been no documentation of a unifying etiopathophysiology *within* either schizophrenia or bipolar disorder. If this were the case, the debate would be settled by determining whether the specific pathological causal pathway is the same for both diagnostic classes. However, each diagnosis is likely a clinical syndrome comprising several specific disease entities. The hypothesis that deficit schizophrenia represents a separate disease within the syndrome of schizophrenia illustrates this concept (Kirkpatrick et al., 2001; Carpenter et al., 1988). Realization that schizophrenia and bipolar disorders have syndrome status shifts the question to whether there is a disease entity within one of the syndromes that is a better fit in the other syndrome. And, if so, how cases will be identified.

Consider asking whether dementia and delirium are one disease or two. Sharing some prominent cognitive impairment would not justify the question. The heterogeneity within each syndrome would undermine any investigation designed to answer the one disease or two question. Dementia with Alzheimer's disease removed is a different syndrome. Then remove multi-infarct dementia and the syndrome is more narrowly defined, but still a heterogeneous condition comprising pernicious anemia dementia, dementia associated with traumatic brain injury, Parkinson's disease, and other discrete conditions. Most investigations of schizophrenia and bipolar disorders are conducted as though a disease entity has been defined. Unlike dementia and delirium, the tools to reduce heterogeneity of these two mental illness syndromes are not yet clearly established. Nonetheless, study designs that treat a syndrome as though it were a specific disease entity provide a weak methodology for decisive hypothesis testing (Carpenter et al., 1993).

Studies within schizophrenia that contrast subjects with and without primary negative symptoms (deficit versus non-deficit schizophrenia) reveal differences in some clinical features (e.g. vulnerability to depression and substance abuse) while being similar in psychotic symptoms (Kirkpatrick et al., 1996; Fenton & McGlashan, 1994; Kirkpatrick et al., 1994; Kirkpatrick & Buchanan, 1990). Importantly, risk factors (e.g. an excess of summer births in the deficit syndrome as opposed to late winter-early spring births in schizophrenia in general [Messias et al., 2004; Kirkpatrick et al., 2002a; Kirkpatrick et al., 2002b; Tek et al., 2001; Messias & Kirkpatrick, 2001; Kirkpatrick et al., 2000; Kirkpatrick

et al., 1998]) and neuropathology [Kirkpatrick et al., 2003; Kirkpatrick et al., 1999]) seem to distinguish the two forms of schizophrenia. Results of comparing bipolar subjects to schizophrenia subjects would be quite different on key variables if the schizophrenia cohort is exclusively deficit or exclusively non-deficit.

In principle the question of one disease or two is meaningless if each construct subsumes two or more entities that are importantly distinct from each other. This seems to be the case in schizophrenia (Tandon and Maj, 2008) and is likely the case in bipolar disorder as well (Potash et al., 2003; Potash et al., 2001; Akiskal & Pinto, 1999).

A Heuristic Model as Alternative to Syndrome or Disease Entity

There are many features commonly observed in cases within both schizophrenia and mood disorders such as anxiety, depression, reality distortion, insomnia, and cognitive impairment. Family pedigree studies generally support the dichotomy, but linkage and association studies suggest overlap or shared genetic vulnerability (Berrettini, 2000). Endophenotypes have been identified in both syndromes, often overlapping, sometimes not (Ivleva et al., 2008; Hill et al., 2008; Thaker, 2008). Consider this thought experiment:

a. risk alleles for genes x, y and z have been identified for hallucinatory experience in the general population

b. these risk alleles distinguish bipolar from non-ill controls

c. these risk alleles distinguish schizophrenia from non-ill controls

d. the association is stronger in schizophrenia compared to bipolar

This pattern of finding seems plausible, but would not suggest that the two illness syndromes are the same disease. Rather, it would suggest that hallucinatory behavior is associated with risk genes across cohorts that differ in the proportion of hallucinating subjects. Testable hypotheses include: a. risk alleles for genes x, y, and z will distinguish bipolar subjects with hallucinations from bipolar subjects without a history of hallucinations; and, b. overlap between schizophrenia and bipolar associations to these risk alleles will increase if all subjects in each class are required to have a history of hallucinations. How, then, should the field proceed in order to advance knowledge on the relationships among the diseases contained in the two syndromes?

One approach is illustrated by Owen, Craddock and Jablensky (2007) in their genetic deconstruction of psychosis. They propose that overlapping genes such as DISC1 and NRG1 contribute to psychotic and mood pathology and that other genes (e.g., DAOA and BDNF) lead to the mood disorders prototype. Genes such as Dysbindin would move the picture towards typical schizophrenia. This concept places the psychotic disorders on a continuum with differential etiopathophysiological factors defining the two extremes. If mood and psychotic features are central, this is compatible with one disease with different co-morbid pathologies at the two extremes. If the pathologies at the two extremes are considered central to diagnostic class, this model would imply that mood disorder and schizophrenia are separate diseases with shared psychotic and mood pathology. A more explicit approach to this second alternative is the "domains of pathology" paradigm (Strauss et al, 1974;

Carpenter and Buchanan, 1989). Breaking down each diagnostic class into domains of pathology gives more specificity to developing treatments and elucidating etiopathophysiology. The unit of study moves from diagnostic classes with porous boundaries to specific psychopathologies which are important to class but not unique. Rather than porous boundaries confounded study designs, the pathological domains become the focus even though observed in more than one class [and not necessarily in all subjects within a class].

Genetic studies can be refined using a domain-based approach. Inconsistency in replication is expected when heterogeneous syndromes are studied. This inconsistency has been the case in schizophrenia. A focus on certain pathological domains to make samples more homogeneous may lead to more consistent findings and, therefore, better understanding of the genetic etiology of diseases. This appears to be the case in preliminary studies where a different pattern of morbid risk was observed between deficit schizophrenia probands and non-deficit schizophrenia probands (Kirkpatrick et al., 2001). Indeed, an analysis of genetic data using latent class analysis to identify subgroups of *psychosis* revealed genes associated with the deficit subgroup that were not observed when data was analyzed by *diagnostic class* (Fanous et al., 2008). Endophenotypes (Gottesman and Gould, 2003) may be even more decisive in this regard (Braff et al., 2007; Calkins et al., 2007; Gur et al., 2007; Turetsky et al., 2007; Aukes et al., 2008; Javitt et al., 2007; Thaker, 2007; Freedman et al., 1999) and were critical in identifying an alpha 7 nicotinic receptor gene on chromosome 15 as a candidate for involvement in schizophrenia pathology (Freedman et al., 1997). A recent article by Thaker (2008) describes the current status and challenges involved in application of endophenotypes across bipolar and schizophrenia.

Genes that confer risk for both bipolar disorder and schizophrenia may best be understood at the level of a specific psychopathological dimension. The general hypothesis is that shared risk factors and pathophysiology will be associated with domains of pathology that overlap between classes. Non-shared risk factors and pathophysiology will be associated with non-overlapping pathology. The importance of addressing these issues is made clear by Lichtenstein et al (2009) in a study of over 76,000 schizophrenia and bipolar probands and their families. In the best estimate to date, about 60% of the variance in each group is attributed to genetic factors, about equally divided between shared and unique genetic effects. Do the unique factors simply add to liability for diagnostic class, or are they more specifically related to domains such as avolition in schizophrenia and episodic affect disruption in bipolar? It remains to be determined which pathologies are critical for diagnostic class or, for that matter, how classification will be revised based on new data related to this paradigm shift.

Another crucial issue comes from the observation that both people with schizophrenia and people with bipolar disorder demonstrate cognitive impairments. In general, people with schizophrenia have worse cognitive impairment than people with bipolar disorder (Keefe & Fenton, 2007; Krabbendam et al., 2005). Cognitive impairments in schizophrenia are observed during pre-psychotic development and are remarkably constant in individuals over the course of their illness whereas cognitive impairments in mood disorders have shown variability depending on phase of illness (Keefe & Fenton, 2007; Hill et al., 2008).

However, evidence is accumulating that, among mood disorders, the presence of psychosis indicates worse cognitive impairment and people with psychotic bipolar disorder demonstrate cognitive impairment similar to that observed in schizophrenia (Seidman et al., 2002; Glahn et al., 2006; Glahn et al., 2007). Impaired cognition associated with bipolar disorder has also recently been observed during non-medicated and euthymic states and in first-degree relatives suggesting at least a subtle trait impairment (Malhi et al., 2007; Pavuluri et al., 2006; Bora et al., 2008). Is impaired cognition in the two disorders based on the shared genetic effects with greater load for schizophrenia, or does similarity of impairment represent a common final pathway based on unique genetic or environmental effects?

Similarly, vulnerability genes for depressed mood may be shared among depressed cases in both syndromes. Kempf, Hussain and Potash, (2007) conclude that dimensions are the critical unit of analysis when comparing mood disordered schizophrenia subjects to major mood disorder subjects experiencing psychosis. Another interesting example is reported by McDonald et al., (2007) who reduced syndrome heterogeneity by relating genetic risk for schizophrenia or for bipolar disorder with brain structural endophenotypes. Anatomical variations in white matter overlapped between the two disorders while each disorder was associated with a distinctive pattern of variation in gray matter.

The examples above help clarify differences in scientific methodology used to address observations of porous boundaries between current diagnostic classes. We propose that it is data at the level of pathologic domains rather than syndrome class that will provide the information critical to re-conceptualizing nosology and advancing knowledge on biomarkers and therapeutic targets. This approach presupposes that unique effects are associated with pathological processes that occur in several diagnostic classes, but in substantially different proportions [e.g, depression is ubiquitous in mood disorders, less frequent in schizophrenia]. An alternative supposition is that unique factors combine with shared factors to create distinctive diagnostic classes and that porous boundaries are caused by the shared factors rather than pathological domains in different proportions.

Conclusions

The question as to whether schizophrenia and bipolar disorder are one disease or two is relevant only if, in fact, these are two diseases at most. If either or both are a syndrome comprising several disease entities, the question is two or more, not two or less. If these classes are syndromes, then their combination creates a broader and more heterogeneous syndrome. This will decrease robustness of study designs, lead to Type II error, and be an unnecessary impediment to hypothesis testing.

To ask the question in the dichotomous, Kraepelinian context ignores the remarkable alteration in diagnosis associated with modern criteria. Furthermore, psychosis is a "final common pathway" produced by the brain in response to many different insults. Similarity across diagnostic classes based on psychotic symptoms may not be more definitive than similarity in anxiety across different classes.

We propose that the current separation of schizophrenia and bipolar disorder into two syndromes captures some important distinctions. However, much more information is needed to determine the critical areas of similarity and difference. For this purpose, the domains of pathology paradigm provides a heuristic unit of analysis. A number of critical dimensions can be proposed for each syndrome.

The failure to make use of "strong inference" in psychiatry has contributed to the slow pace of advancement in the field (Carpenter et al., 1993). Platt proposed that scientific fields with the most rapid progress design studies where the data can force theory modification and move the field to the next branch point (1964). A century of research on psychoses has been rich in hypothesis generation and slender on theory falsification. Data have not yet been produced to decisively falsify the Kraepelinian dichotomy or even to identify specific disease entities within the major syndromes. Heterogeneity reduction in syndromes is essential.

It seems very likely that DSM-V will take the approach of maintaining current classes of disorders with refined criteria while bringing a new emphasis to the domains of pathology paradigm (Regier, 2007; van Os & Tamminga, 2007; Allardyce et al., 2007; Dutta et al., 2007; Keller et al., 2007; Owen et al., 2007; Gur et al., 2007). Research in this context will then clarify similarities and differences at the domain or dimension level. Only then will the field be sufficiently informed to radically re-conceptualize classification of what we identify today as the psychotic and mood disorders.

Acknowledgments

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