Rethinking psychosis: the disadvantages of a dichotomous classification now outweigh the advantages

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Emil Kraepelin would clearly recognize his 19th century dichotomy within current operational classifications of psychosis. However, he might be surprised at its survival, given the extent to which it has been undermined by the weight of currently available empirical evidence. The failure of this evidence to influence diagnostic practice reflects not only the comfortable simplicity of the dichotomous approach, but also the fact that this approach has for many years continued to receive support from some areas of research, particularly genetic epidemiology. This, however, is changing and findings from genetic epidemiology are being reappraised. More importantly, the potential of molecular genetics to indicate biological systems involved in psychopathology has been recognized, and with it the potential to develop diagnostic classifications that have greater biological validity. Crucially, this will facilitate diagnostic schemes with much greater clinical utility, allowing clinicians to select treatments based on underlying pathogenesis. Recent molecular genetic findings have demonstrated very clearly the inadequacies of the dichotomous view, and highlighted the importance of better classifying cases with both psychotic and affective symptoms. In this article we discuss these issues and suggest ways forward, both immediately and for DSM-V and ICD-11. If psychiatry is to translate the opportunities offered by new research methodologies, we must move to a classificatory approach that is worthy of the 21st century.

Key words: Nosology, classification, diagnosis, schizophrenia, bipolar disorder, psychosis, schizoaffective disorder, genetics

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Theoretical constructs in science, including diagnoses in medicine, have a finite lifespan and should be discarded when the weight of research data against them becomes critical and when more satisfactory alternatives become apparent. In this paper we summarize the evidence that such a tipping-point has been passed with regard to the traditional dichotomous approach to diagnosis of the functional psychoses. We argue that reliance on 19th century approaches to classification will impede translation of powerful 21st century research tools into benefit for psychiatric patients, and that we need new, more appropriate approaches to diagnosis and classification.

Emil Kraepelin is rightly regarded as one of the most important figures in the history of psychiatry. His writings remain rewarding to this day and his clinical descriptions are amongst the very best we have (1). He continued to develop and refine his ideas about psychiatric diagnoses, and his thinking had in many ways moved on from the dichotomous classification by the end of his life (2). However, it is not the goal of this article to consider Kraepelin's views in relation to modern nosological practice. A discussion of this sort, although of historical interest, is not of direct relevance to contemporary clinical psychiatry. Rather we wish to highlight the failure of the dichotomous classification, which originated with Kraepelin, to account for key research data and to consider alternative approaches.

A LONG HISTORY OF DISSENT FROM THE DICHOTOMOUS VIEW

Although the dichotomous view has dominated clinical psychiatry for over 100 years, there has been a long history of dissent (2,3). Many nosologists have developed their own models and approaches. Important recent examples include Crow's continuum model (4), the spectrum models of bipolarity of Angst and Akiskal (3,5), Marneros' focus on schizoaffective (6) and brief psychotic illnesses (7), and the polychotomous Leonhardian diagnostic system (8). Furthermore, a minority of practicing clinical psychiatrists have continued to recognize one or more distinct illness categories in addition to the two Kraepelinian prototypes (e.g., cycloid psychoses, psychogenic psychoses, bouffée délirante).

WHY HAS THE DICHOTOMY SURVIVED SO LONG?

In the absence of "laboratory" tests based on a solid understanding of pathogenesis, the criteria used in psychiatry for validating nosological categories have usually been restricted to clinical features, outcome and family history (9). These tools were used by Kraepelin in formulating his ideas and by more recent nosologists in shaping the modern operational classifications. One of the key scientific observations supporting the Kraepelinian dichotomy was that the prototypical disorders tend to "breed true". Thus, a consistent finding has been a substantially increased risk of schizophrenia but not bipolar disorder in the relatives of probands with prototypical schizophrenia and vice versa in corresponding studies of bipolar disorder. It is also true that groups of individuals classified as having typical schizophrenia can be dis-

criminated from sets of individuals classified as having typical bipolar disorder on the basis of a variety of clinical features and outcome.

As well as having some empirical support, the Kraepelinian view holds attractions for clinicians: it is conceptually simple and allows psychiatrists to demonstrate diagnostic expertise by exercising judgment over an often complex clinical picture and to reach a clear diagnosis. However, most experienced psychiatrists, whilst willing to make use of these advantages, are fully aware of the limitations and operate under conditions of dissonance in which management decisions are made based on a personal model of illness that has evolved from their own clinical experience. Although cogent arguments for abandoning an essentially dichotomous approach in favour of alternative formulations (categorical, dimensional or continuous) have been advanced, these have failed to gain widespread support, in part because of lack of robust scientific data, but possibly also because of the practical complexity of applying alternative classifications in clinical practice and research settings.

WHY SHOULD WE CHANGE OUR DIAGNOSTIC APPROACHES NOW?

Given that psychiatry has continued for many years to use a diagnostic approach that most nosological researchers have known provides an unsatisfactory model of mental illness, why should we make changes now? We consider two broad domains of rationale: a) the compelling research data that challenge the validity of the dichotomy, and b) problems with the general properties of the current approach to classification.

Research data are inconsistent with the dichotomy

There is now an overwhelming body of research data that challenge the validity of the dichotomous classification. Any psychiatrist with experience of functional psychotic illness knows that many patients do not have disorders that conform to either prototypical dichotomous category. Many individuals receive one diagnosis at one time or from one team and the alternative diagnosis at a different time or from another team. This clinical reality is supported by formal studies of symptom profiles that have typically failed to find a clear discontinuity between the clinical features of the two categories (what nosologists refer to as a "point of rarity") (10). Further, findings emerging from many fields of psychiatric research, such as neuroimaging, neuropathology and neuropsychology, do not fit well with the traditional dichotomous model (11). Of crucial relevance to our arguments are findings from recent genetic studies.

Evidence has been gradually accumulating over 10-20 years from genetic epidemiology that is inconsistent with the dichotomous view. Recent molecular genetic findings are most persuasive. Key pieces of evidence include the following:

- *Family studies*. Recent family studies point to the existence of a non-trivial degree of familial co-aggregation between schizophrenia and bipolar illness and between schizoaffective disorders and both bipolar disorder and schizophrenia (reviewed in 12-15).
- *Twin study*. A recent twin study – the only one that used an analysis unconstrained by the diagnostic hierarchy inherent in current systems of classification – demonstrated an overlap in the genetic susceptibility to mania and schizophrenia (16) and provided evidence that there are genes that confer susceptibility across the Kraepelinian divide.
- *Linkage studies of schizophrenia and bipolar disorder*. Systematic, whole-genome linkage studies of schizophrenia and bipolar disorder have implicated some chromosomal regions in common. This is consistent with shared susceptibility genes (reviewed in 12,17).
- *Linkage studies of schizoaffective disorder*. The only linkage study to date that has selected families through a proband meeting criteria for schizoaffective disorder strongly supports the existence of loci that provide specific susceptibility to psychosis with both schizophrenic and bipolar features (18).
- *Association studies*. Most recently, and most convincingly, genes have been identified whose variation appears to confer risk to both schizophrenia and bipolar disorder (reviewed in 17).

We, and others, have reviewed these recent genetic findings in detail elsewhere (17,19-21) and have considered their implications for psychiatric nosology (22). Here we will provide some examples of findings that demonstrate very clearly the shortcomings of the dichotomous classification.

Neuregulin 1 (NRG1)

The NRG1 gene was first implicated in studies of schizophrenia in the Icelandic population (23). A set of DNA variants, which we will collectively refer to as the "risk haplotype", showed association with susceptibility to illness. Meta-analyses confirm the strong evidence from several studies that genetic variation in NRG1 confers risk to schizophrenia (24,25). NRG1 has not yet been extensively studied in bipolar disorder. However, we found significant evidence for association of the risk haplotype with susceptibility to bipolar disorder with a similar effect size to that seen in our schizophrenia sample (26,27). Unlike other studies of NRG1, we undertook further analysis to search for evidence of phenotypic specificity of the effects of the NRG1 risk haplotype. In the bipolar cases, the effect of the NRG1 risk haplotype was most marked in cases with predominantly mood-incongruent psychotic features. In schizophrenia cases, the effect was greatest in the subset which had experienced mania. Our findings suggest that NRG1 plays a role in influencing susceptibility to a subset of functional psychosis that has both manic and mood-incongruent psychotic features; there is little effect in cases without such "dual" features. We would, therefore, expect that in any

sample the ability to detect the effect of the risk haplotype will be dependent on the proportion of cases with these dual features. Uncritical application of the dichotomy as if it captures homogeneous disease entities leads to the erroneous and unhelpful conclusion that there is a small, non-specific effect in both categories and that the only way to increase chances of replication is to increase sample size. In reality, by far the best way to increase the chances of replication will be to select a *smaller* sample from the total available – namely, the subset that has dual features.

G72/G30(D-amino acid oxidase activator, DAOA) locus

This locus was first implicated in studies of schizophrenia (28) and association was later reported also in bipolar disorder (29). Meta-analysis supports significant association in both diagnostic categories (30). We have reported the largest study to date, which included 2831 individuals: 709 who met criteria for DSM-IV schizophrenia, 706 with DSM-IV bipolar I disorder, and 1416 ethnically matched controls (31). We found significant association with bipolar disorder but failed to find association with schizophrenia. Analyses across the traditional diagnostic categories revealed significant evidence for association in the subset of cases (N=818) in which episodes of major mood disorder had occurred. A similar pattern of association was observed both in bipolar cases and in schizophrenia cases who had experienced major mood episodes. In contrast, there was no evidence for association in the subset of cases (N=1153) in which psychotic features occurred. This finding suggests that, despite being originally reported as a schizophrenia susceptibility locus, variation at the G72/G30 (DAOA) locus does not primarily increase susceptibility for prototypical schizophrenia nor psychosis. Instead, it appears that this variation influences susceptibility to episodes of mood disorder across the traditional bipolar and schizophrenia categories.

Importantly, the findings at the G72/G30(DAOA) locus also imply that whether or not significant associations are seen in schizophrenia samples will depend upon the proportion of cases that have suffered from episodes of mood disorder. As with NRG1, using the dichotomous view leads researchers to assume that increasing sample size is the way to replicate the small, apparently non-specific effects, whereas the most effective way forward will be to select a subset of the schizophrenia sample that has the specific clinical features that are influenced by the G72/G30 (DAOA) locus.

We could give other examples but will here mention briefly just one other locus, the 1q42 region of chromosome 1. This is strongly implicated in susceptibility to functional psychosis by observations in an extended Scottish pedigree, in which both schizophrenia and major affective illness co-segregated with a translocation that disrupts this part of chromosome 1 (32). In the only linkage study of schizoaffective disorder undertaken to date, we found genome-wide significant evidence for linkage at this same locus in 35 affected sibling pairs identified through a proband with DSM-IV schizoaffective disorder, bipolar type (18). That this reflects a phenotype-specific effect rather than some general effect in both schizophrenia and bipolar disorder is demonstrated by the absence of evidence for linkage at this locus in our much larger samples of sib-pairs selected through probands with schizophrenia (N=353) (33) or bipolar disorder (N=400) (34) from which these 35 sibling pairs were selected.

The molecular genetic findings at NRG1 and the 1q42 locus demonstrate a phenotypic specificity for mixed "mood" and "schizophrenia" features and, thus, provide evidence of biological validity for one or more subsets of cases of "schizoaffective" illness that may represent useful disease entities. These findings also suggest that it is important to take a longitudinal approach to diagnosis and to consider the nature and occurrence of psychotic and affective symptoms across the patient's illness history.

"Schizoaffective" illness: the importance of recognizing cases with mixed features

The term "schizoaffective" disorder is applied to cases with a mix of clinical features associated with prototypical schizophrenia and prototypical bipolar disorder. Such cases are common, but definitions have varied substantially (35-38). Within the context of neo-Kraepelinian operational classifications such as the DSM-IV (39) and ICD-10 (40), "schizoaffective disorder" tends to be used only when cases cannot be fitted to definitions of schizophrenia or bipolar disorder. Thus, in clinical practice and the vast majority of research, the diagnosis is treated like a "not otherwise specified" category that represents supposedly atypical cases. As a result, although some excellent work has been undertaken, cases with a rich mix of psychotic and bipolar features have not received the same attention as schizophrenia and bipolar disorder in research into treatment and pathogenesis. Indeed, the approach has often been to treat schizoaffective cases as a "nuisance" and to either exclude them from analysis or combine them with one or other of the dichotomous categories. For example, in molecular genetic research on schizophrenia, it is common for researchers to undertake a "narrow" analysis with only DSM-IV schizophrenia and a "broad" analysis that includes also schizoaffective disorder.

This approach to schizoaffective spectrum cases is highly problematic if such cases actually reflect the expression of one or more relatively specific underlying disease processes. As noted in an earlier section, some clinicians and researchers have certainly believed that at least some schizoaffective cases represent distinct clinical entities and have continued to apply minority diagnostic concepts, such as "bouffée délirante" (France; e.g., 41), psychogenic psychoses (Scandinavia; e.g., 42) and cycloid psychoses (43) – the latter being part of the rich but complex classification of endogenous psychoses of Leonhard (8). Further, the existence of one or more relatively discrete nosological entities

with mixed features is supported by latent class analyses (44-47). Genetic epidemiology supports a strong genetic component to schizoaffective illness (48-53). Indeed, the effect size may be higher in this phenotype than in prototypical schizophrenia or bipolar disorder (52). As we have already discussed, there is now molecular genetic evidence for the existence of at least two loci that specifically influence susceptibility to this phenotype.

One of the criticisms of "schizoaffective disorder" by clinical and research psychiatrists is the lack of reliability and temporal stability that has been reported using current definitions (54). However, this is an almost inevitable consequence of the overly restrictive nature of current definitions of "schizoaffective disorder", together with the tendency of clinicians to make diagnoses "cross-sectionally" rather than longitudinally. We know that the precise clinical presentation of any individual with psychosis varies over time and, given the very restrictive definition of the schizoaffective category compared with the much broader definitions of schizophrenia and mood disorder, it is inevitable that the latter categories will seem much more reliable and stable than the schizoaffective category. If cases with "schizophrenic" and affective symptoms do indeed represent a group with shared underlying pathogenesis and strong genetic loading, then the neo-Kraepelinian dichotomous approach, with its narrow definition of schizoaffective disorder, will simply serve to impede aetiological research.

General properties of the classification system

Current operational diagnostic systems: the theory and the practice

The neo-Kraepelinian operational classification systems that were developed in the latter part of the 20th century in response to concerns over poor diagnostic reliability were an important advance for clinical and academic psychiatry. The theorists who developed these systems to provide descriptive categories acknowledged their uncertain validity (55). However, despite the clear caveats within the diagnostic guidelines (39,40), there has been a strong tendency for the categories to be reified and credited with properties of homogeneity and validity that were never intended. This tendency is arguably most marked amongst individuals who do not have direct experience of mental illness, such as non-clinical researchers, medical managers, politicians, etc. However, it is also surprisingly common amongst clinical psychiatrists, particularly those whose training post-dated the requirement to use operational diagnostic classification for clinical work and research. This must serve as a lesson for future classifications: we need to ensure, perhaps by the structure of the classification, that all users are completely aware of the limitations as well as benefits.

Practical and organizational problems that result from continued use of the dichotomy

The thinking and actions of those involved with mental illness is shaped and constrained by "official" classifications. If psychotic illness is not really separable into two major categories with distinct pathologies and treatment responses, there can be negative consequences to continuing to act as if it were. We provide some examples:

- *Clinical services.* Many clinical services, particularly but not exclusively in the US, are divided according to the dichotomy. For example, clinics serving schizophrenia and bipolar disorder are often staffed by different clinicians and even located on different floors of a hospital.
- *Scientific meetings.* Sessions at scientific meetings and often whole meetings are divided according to the dichotomy.
- *Drug licenses*. Typically, legal approval of a drug is restricted to a specific diagnostic category with a license granted only for one of the dichotomous categories.
- *Therapeutic research*. Clinical trials are conducted according to diagnostic category. Many studies of individuals meeting criteria for schizophrenia find effects in some but not all individuals; likewise for mood disorder. It is entirely possible that specific, predictable effects may fail to be recognized if analyses are not undertaken that take account of clinical variation within a diagnostic category and across diagnostic categories.
- *Research into causation*. The vast majority of psychiatric research studies report findings according to operational diagnostic categories and do not consider more detailed clinical descriptors.
- *Understanding by non-professionals*. When the terms "schizophrenia" and "mood disorder" are used by individuals without clinical training and experience (such as politicians, lawyers and health service managers), there is a strong tendency for them to be used as robust categories without any of the caveats required. Further, much of the neuroscience research in psychiatry is carried out by non-clinical scientists, and many of these have a faith in the diagnostic categories that is completely unjustified by the evidence.

Practical problems with applying current operational diagnostic classifications to real patients

Clinicians and researchers experience several major problems in using the current systems for making *lifetime* diagnoses (Table 1) (56). We need to minimize such difficulties in our future classifications.

THE WAY FORWARD FOR CLASSIFICATION: WHAT VALIDATORS TO USE?

The most useful validators for diagnosis of a given group of disorders will vary over time according to a) what techniques are available, and b) the over-riding aim of diagnosis. In Krae-

Table 1 Major limitations of current operational categorical approach to diagnosis

- The focus is on episode rather than lifetime experience of psychopathology
- Hierarchies lead to loss of information
- Boundaries between diagnostic categories are often arbitrary
- Boundaries between categories often require substantial subjective judgement
- Available diagnostic categories are relatively unhelpful in distinguishing severity
- Sub-clinical cases are usually not accommodated usefully
- "Not Otherwise Specified (NOS)" categories are highly heterogeneous

pelin's time, with no effective treatments available, the practical aim of diagnosis was mainly to predict prognosis. It was, thus, entirely logical that Kraepelin developed his dichotomy on this basis, and it performs relatively well against this validator. Given that the main goal of modern psychiatrists is (or should be) to provide effective treatment, it is our view that the ultimate validator for our diagnostic systems must be *treatment response* (57). Over the half century that effective psychotropic drugs have been available, it has become clear that they do not respect diagnostic boundaries. Perhaps the most elegant demonstration of this comes from the landmark Northwick Park study (58), which found that, in patients with functional psychosis, psychotic symptoms responded to a neuroleptic and mood symptoms to a mood stabilizer (lithium); there was no diagnostic specificity.

We now have at our disposal powerful molecular genetic tools that should allow us to identify the biological systems that are involved in disease pathogenesis. These techniques allow us to study biological systems in large numbers of individuals whilst they are alive. For the first time in psychiatry, this provides the opportunity to validate our diagnostic concepts and procedures against biologically relevant criteria that in many cases will relate to the effectiveness of treatments. In time the impressive developments in neuroimaging are likely to provide us with the power to study the functioning of specific, relevant brain systems *in vivo* in individuals during differing phases of illness and in response to varying environmental situations. These approaches will, we imagine, be complemented by developments in many other fields. This will facilitate the bringing together of diverse domains of research evidence that can be synthesized into models of brain function and dysfunction and their relationship with psychopathology. We must now grasp this opportunity and develop approaches to classification that are explicitly designed to take advantage of the new research tools.

THE WAY FORWARD FOR CLASSIFICATION: WHAT NEEDS TO HAPPEN IMMEDIATELY?

There are some relatively simple changes to our thinking and general approach that could be taken immediately and would be of great benefit for research, clinical practice and improving lay understanding of mental illness (Table 2).

The key practical issue is, of course, how we can start to better recognize and describe the cases that share relevant clinico-pathological features and facilitate their grouping close together in "classification space". One approach is to use quantitative, ordered descriptions of key domains of psychopathology and to apply these longitudinally. Such clinical dimensions can be used alongside categories (existing or novel) as a way of providing a richer representation of individual psychopathology and allow individuals with similar lifetime experiences of psychopathology to be recognized and grouped. We have used this approach for our own research on psychosis by developing the Bipolar Affective Disorder Dimension Scale (BADDS) (56). This provides a description of an individual's lifetime experience of psychopathology using four ordered integer scales (0-100), or "dimensions": mania; depression; psychosis; incongruence of psychosis. It is important to stress that this is a descriptive-classificatory tool that may help in moving from the current classification towards classifications that are anchored in an understanding of pathogenesis. It is not driven by any particular model of illness and does not presuppose that psychopathology is distributed continuously.

Table 2 Steps that need to be taken immediately

1. Change our thinking to accept that:
   a) we must move towards a classification offering greater clinical utility
   b) this will be an iterative process and the first steps must facilitate this
   c) clinical utility requires biological validity
2. Change our practice to ensure that:
   a) clinical psychiatrists are supported in treating across diagnostic categories
   b) researchers routinely use and report more sophisticated clinical phenotypes
   c) the diagnostic utility of schizoaffective spectrum illness is better recognized
3. Change our organization such that:
   a) clinical service provision is not constrained by invalid diagnostic boundaries
   b) research is encouraged across the functional psychosis spectrum

Recognizing schizoaffective illness

As we have seen, current data demonstrate that, amongst illnesses with mixed features of the dichotomous prototypes, there are likely to be one or more subsets of cases that may constitute relatively distinct disease entities. To facilitate the research necessary to explore this, it is essential that such cases are recognized, classified together and acknowledged as worthy of at least as much attention as is given to cases of "schizophrenia" and "mood disorder". In our own research, based on our genetic findings to date, we adopt one simple approach that uses DSM-IV lifetime diagnosis supplemented by some additional information about lifetime psychopathology (which comes from our BADDS scores). We also use the concept of "schizoaffective spectrum phenotype" (SASP) to denote an illness meeting one of the following criteria: a) DSM-IV schizoaffective disorder, bipolar type, or b) DSM-IV schizophrenia with at least one episode of DSM-IV mania during lifetime or c) DSM-IV bipolar I disorder with psychotic features in at least half of all episodes of major mood disorder. We make no claims that our definition is somehow

"correct". Rather, we have taken a simple pragmatic approach informed by our data (18,59,60).

We believe that this approach, or similar, would provide immediate benefits at minimal cost and would facilitate a transition from our current state to the first iterations of the new classifications that we need.

THE WAY FORWARD FOR CLASSIFICATION: WORKING TOWARDS CLASSIFICATIONS THAT WILL BE OF GREATER BENEFIT FOR PSYCHIATRIC PATIENTS

Those charged with the responsibility of developing DSM-V and ICD-11 are well aware of the shortcomings of the current approach (61), and the process of considering options has already been under way for several years. Data from the ongoing large scale molecular genetic studies (particularly, but not exclusively, whole genome association studies), together with data from other areas of neuroscience, offer the opportunity of starting to put psychiatric classification on a robust framework that has biological validity. Although it is too soon to know the details of such classifications, it is already possible to identify several important properties that are highly desirable and should be used to inform the development of new biologically valid, clinically useful classification systems (Table 3).

Table 3 Desirable properties of a classification system

1. Uses measures that are likely to map onto biological systems
2. Uses multiple descriptors of an individual's psychopathology:
   - Symptomatology, severity, course, impairment, etc.
   - Categorical and dimensional measures
3. Explicitly recognizes that the scheme will develop in response to new data:
   - Forward and backward compatibility with other classification systems
4. Can accommodate sub-clinical psychopathology
5. Facilitates grouping together of individuals likely to share similar pathology
6. Is flexible for different needs:
   - Allows different versions for different uses (clinical, research, service, etc.)
7. Is longitudinal rather than cross-sectional
8. Is developmentally sensitive:
   - Provides continuity across the lifespan

Phenotype boundaries

Here we have focussed our discussion on the need to move from the traditional dichotomous approach to diagnosis of mood-psychotic disorders and towards approaches that have demonstrable biological validity and greater clinical utility. We do not have space here to consider the various other phenotypic boundaries relevant to mood-psychotic disorders. However, in general, similar considerations apply. For example, we anticipate the need to consider improved approaches to representing the interfaces between bipolar spectrum illness and attention-deficit/hyperactivity disorder. We think it extremely likely that there will be an important overlap in the biological systems involved in the pathogenesis of the psychopathology experienced by individuals who meet criteria for these diagnoses (specifically those systems involved in attention and motor activity) (62). Likewise, we anticipate the need to refine our thinking about the distinction between "illness" and "personality". For example, it is highly likely that there will be remarkable overlaps in the systems and dysfunctions contributing to the substantial mood instabilities seen in individuals meeting criteria for borderline personality disorder and some individuals meeting criteria for rapid cycling bipolar disorder (63).

CONCLUSIONS

Kraepelin himself fully recognized the difficulties in applying the dichotomy he had suggested. He was a clinical scientist capable of major feats of synthesis and demonstrated an ability and willingness to modify his thinking in response to new data. We suspect that, had he lived, he would have abandoned the dichotomous view completely at some point during the 20th century. Further, we think he would have been surprised and disappointed at the failure to move forward in any significant way.

We now have a large body of research data that are inconsistent with the dichotomy and powerful tools at our disposal that allow us to start developing a biologically valid framework for classification that is likely to offer much improved clinical utility. We do not claim that the current genetic findings are sufficient to decide on precise alternatives to the current classifications. Neither do we claim that every current finding will turn out to be robustly replicated. Rather, our argument is that they are sufficient to show that there is an urgent need to change our approach *now*.

Changing to definite distinct systems of psychiatric classification every few years is confusing and wasteful. What we need is an approach that is not misleading about the current level of understanding, is clinically useful, and helps, rather than hinders, researchers to unravel the biological basis of disorders. Typically, "physical" disease classifications include mixtures of defined pathological entities and more or less well-defined clinical syndromes according to the state of understanding of each disease entity. Thus, it is to be expected that this will be the case in psychiatry as our knowledge develops. Therefore, we might find some relatively discrete syndromes that have discrete biology but others that are better conceptualized on a continuum. We should be prepared for this.

Given the lowly status accorded to "schizoaffective" cases in our current official classifications, it would be an embarrassment if genetic and other biological risk factors turned out to have the greatest impact on schizoaffective spectrum illness. That this might be so is hinted at by studies of familiality and the striking linkage findings at 1q42. Should this turn out to be the case, it will be a sobering academic exercise to estimate how many patients will have suffered from the delay to progress in psychiatry caused by continuing to apply a classification that, instead of carving nature at the joints, has ensured that we have been "sawing through bone" (64).

We summarize the key points of our article in Table 4. Finally, we note that, as a general rule, human beings do not like change and tend to treat proposals for change with suspicion and resist-

Table 4 Key messages

- Valid diagnostic classification is crucial for clinical research and practice
- Data, rather than opinion or tradition, must inform classification
- Research data from many fields are inconsistent with a dichotomous classification
- Powerful new research tools provide biological validators for classification
- Current classifications are inhibiting progress in research and clinical practice
- Simple steps can, and should, be taken immediately as "first aid" measures
- Development of biologically valid classification will be an iterative process
- Key desirable properties can already be identified for new classification systems

ance. However, as responsible clinicians, we owe it to our patients to take action urgently.

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