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G. Andrews
University of New South Wales

D. P. Goldberg
King's College London - Institute of Psychiatry

R. F. Krueger
Washington University School of Medicine in St. Louis

W. T. Carpenter Jr
University of Maryland - Baltimore

S. E. Hyman
Harvard University

See next page for additional authors

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Recommended Citation

Andrews, G.; Goldberg, D. P.; Krueger, R. F.; Carpenter, W. T. Jr; Hyman, S. E.; Sachdev, P.; and Pine, D. S., ,"Exploring the feasibility of a meta-structure for DSM-V and ICD-11: Could it improve utility and validity." Psychological Medicine. 39,12. 1993-2000. (2009).
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Authors
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Psychological Medicine (2009), **39**, 1993–2000. © Cambridge University Press 2009
doi:10.1017/S0033291709990250

REVIEW ARTICLE

Exploring the feasibility of a meta-structure for DSM-V and ICD-11: could it improve utility and validity?

Paper 1 of 7 of the thematic section: 'A proposal for a meta-structure for DSM-V and ICD-11'

G. Andrews[1]*, D. P. Goldberg[2], R. F. Krueger[3], W. T. Carpenter Jr.[4], S. E. Hyman[5], P. Sachdev[1] and D. S. Pine[6]

[1] *School of Psychiatry, University of New South Wales, Sydney, Australia*
[2] *Institute of Psychiatry, King's College, London, UK*
[3] *Departments of Psychology and Psychiatry, Washington University in St Louis, USA*
[4] *University of Maryland School of Medicine, the Maryland Psychiatric Research Center, and the VISN 5 Mental Illness Research, Education and Clinical Center, Baltimore, MD, USA*
[5] *Harvard University, Cambridge, MA, USA*
[6] *National Institute of Mental Health, Bethesda, MD, USA*

Background. The organization of mental disorders into 16 DSM-IV and 10 ICD-10 chapters is complex and based on clinical presentation. We explored the feasibility of a more parsimonious meta-structure based on both risk factors and clinical factors.

Method. Most DSM-IV disorders were allocated to one of five clusters as a starting premise. Teams of experts then reviewed the literature to determine within-cluster similarities on 11 predetermined validating criteria. Disorders were included and excluded as determined by the available data. These data are intended to inform the grouping of disorders in the DSM-V and ICD-11 processes.

Results. The final clusters were neurocognitive (identified principally by neural substrate abnormalities), neurodevelopmental (identified principally by early and continuing cognitive deficits), psychosis (identified principally by clinical features and biomarkers for information processing deficits), emotional (identified principally by the temperamental antecedent of negative emotionality), and externalizing (identified principally by the temperamental antecedent of disinhibition).

Conclusions. Large groups of disorders were found to share risk factors and also clinical picture. There could be advantages for clinical practice, public administration and research from the adoption of such an organizing principle.

Received 22 May 2008; Revised 5 May 2009; Accepted 12 May 2009; First published online 1 October 2009

Key words: Classification, DSM-V, ICD-11, mental disorders, meta structure.

Introduction

The American Psychiatric Association (APA) and the World Health Organization (WHO) have begun revising DSM-IV and ICD-10. DSM-III was a very significant advance and was the first widely used nomenclature that listed the diagnostic criteria for mental disorders. DSM-IV has some 16 major categories and 160 diagnoses defined by four digit numbers and 10 major categories and as many diagnoses are included in ICD-10. Both classifications are complex.

DSM-III/IV and ICD-10 were deliberately atheoretical with chapters and disorder definitions that focused on symptom pictures. Considering that there have been considerable advances in psychiatry since the publication of DSM-IV, an APA Diagnostic Spectra Study Group was charged to examine the possible boundaries of DSM-V. Could large clusters of diagnoses be identified by shared external validating factors rather than by symptom pictures alone? Are there now sufficient data from neuroscience, genetics, epidemiology and therapeutics to identify groups of disorders? DSM-III/IV and ICD-10 described diagnostic categories that limited co-morbidity by use of exclusion criteria. Could co-morbidity within clusters inform rather than impair our understanding of the natural structure of mental disorders? DSM-III/IV and ICD-10 were designed to facilitate clinical care as the first priority but the classifications and their thresholds are too complex for many clinicians to use

* Address for correspondence: Professor G. Andrews, 299 Forbes Street, Darlinghurst, NSW, Australia 2010.
(Email: gavina@unsw.edu.au)

(Andrews *et al*. 2008). Could grouping disorders into clinically meaningful clusters facilitate both patient care and research?

Establishing criteria to define a disorder is not new. Robins & Guze (1970) listed five criteria for establishing the validity of a psychiatric diagnosis: (1) clinical description, (2) laboratory studies, (3) delimited from other disorders, (4) follow-up studies, and (5) family studies. Subsequently Kendler (1980), Kendell (1989) and Andreasen (1995) have all supported the Robins & Guze position. Kendell & Jablensky (2003) additionally argued that 'delimited from other disorders' by a zone of rarity was an important prerequisite for being a valid category.

Establishing groups that share criteria is also not new. Goldberg *et al*. (1987) and Andrews *et al*. (1990, 2002) have argued that high rates of co-morbidity between the anxiety and depressive disorders indicated the action of some common aetiological agent. Krueger *et al*. (1998) showed that the patterns of co-morbidity in the internalizing and externalizing disorders indicated the existence of higher-order dimensions of psychopathology. Several studies have found similar groupings of mental disorders in which there were additional correlated distress and fear factors (which were best considered lower-order facets of a broader internalizing factor) that were separated by a zone of relative rarity from the externalizing disorders including drug and alcohol dependence (Krueger, 1999; Vollebergh *et al*. 2001; Cox *et al*. 2002; Kendler *et al*. 2003; Slade & Watson, 2006). Thus the delimitation advocated by Robins & Guze and by Kendell & Jablensky might be best observed at the cluster rather than the disorder level, and be associated with risk or validating factors operative within that group of disorders.

In the series of papers in this issue, groups of experts examine the evidence that the majority of DSM-IV disorders could be grouped into clusters or groups of disorders that share external validating factors.

Method

This series of papers used a two-stage method. First we identified possible clusters and then examined the internal coherence of these clusters using external validating criteria. Such a grouping was not intended to be prescriptive, but a thoughtful evidence-based grouping being placed in the public domain to generate discussion.

Identifying possible a priori clusters of disorders

The authors used the relationships (reviewed above) between the depressive and anxiety disorders to identify the hallmarks of the Emotional cluster, and the substance-related and antisocial disorders to identify the characteristics of the Externalizing cluster. Additional disorders were added to the Emotional cluster because they are known to share several features with these disorders, for example somatic disorders were included here because such symptoms often co-occur with anxious and depressive symptoms and may be better understood as a facet of a Emotional spectrum (e.g. Krueger *et al*. 2003). Once these two clusters had been proposed, other mental disorders in DSM-IV were surveyed. We concluded that many of the disorders in the 'Delirium, Dementia, and Amnestic and Other Cognitive Disorders', in the 'Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence' and in the 'Schizophrenia and Other Psychotic Disorders' chapters were likely to share features within, but not between, clusters. This warranted the consideration of these groups as separate clusters. Herein, these clusters are referred to as the Neurocognitive, Neurodevelopmental and Psychosis clusters respectively. The disorders considered in these three latter clusters largely reflect the extant chapter groupings except, for example, decisions to examine the evidence on placing conduct disorder with the externalizing disorders or bipolar disorder with the psychoses (First, 2009). We have not considered a sixth group, disorders of bodily function, which includes a wide range of disorders such as eating, sexual and sleep disorders, because there are at present insufficient data to allow consideration of cluster membership.

This proposal concerns the primary mental disorders. Mental Disorders Due to a General Medical Condition are characterized by the presence of mental symptoms that are judged to be the direct physiological consequence of a general medical condition. They are not considered in this model. We examined placing some personality disorders in the disorder groups that included similar Axis I disorders; for example, Schizotypal Personality Disorder with the Psychoses, and Antisocial Personality Disorder with the Externalizing Disorders. It was not possible on the basis of the data to allocate all personality disorders to one of the five clusters, nor, for the same reason, was it possible to allocate all mental disorders to a cluster.

Criteria used to examine the similarities between disorders within these a priori *clusters*

The Diagnostic Spectra Study Group of the DSM-V Task Force considered the possibility of there being larger groupings within the classification. They extended the Robins & Guze (1970) validators for a disorder to serve as criteria for a cluster of several related

disorders (Hyman *et al*., personal communication, 3 December 2007). The Study Group's list of 11 'validators' to be considered when grouping related disorders into a cluster were:

(1) shared genetic risk factors;
(2) familiality;
(3) shared specific environmental risk factors;
(4) shared neural substrates;
(5) shared biomarkers;
(6) shared temperamental antecedents;
(7) shared abnormalities of cognitive or emotional processing;
(8) symptom similarity;
(9) high rates of co-morbidity;
(10) course of illness;
(11) treatment response.

The Task Force Study Group did not provide guidance as to which similarities and differences on particular criteria are crucial to the definition of the disease entity or a larger group of disorders. Nonetheless, the validating items may fall into two groups: those more likely to be causal risk factors (items 1–6) and those more likely to be aspects of the clinical picture (items 7–11). These validating criteria were used as a systematic way of examining the relationships between disorders in terms of the risk and clinical factors.

Grouping disorders together in terms of shared characteristics has been a recurring theme across the research planning conferences organized by the APA during 2004–2008. Michael First prepared summaries of all these conferences (First, 2009). In the initial conference on Personality Disorders in 2004, First reported that 'the goal of this conference … [is] to stimulate research … with respect to behavioural genetics, neurobiological mechanisms, childhood antecedents … diagnostic thresholds and treatment implications.' In the Stress-Induced and Fear-Circuitry Disorders conference in 2005, the co-chairs designed the programme to explore the commonalities in these disorders in relation to other anxiety and mood disorders in terms of clinical manifestations, course, genetic basis, neurotransmitters, information processing, environmental stressors, functional neuroanatomy, and neurochemical and neuroendocrine markers. In the Psychosis conference in 2006, one of the recommendations was 'replacing the current categories with a general psychosis syndrome that would cover a broad range of disorders ranging from schizophrenia, schizoaffective, delusional, and brief psychotic disorders, to bipolar disorder and psychotic depression'. In the Obsessive Compulsive Spectrum Disorders conference in 2006, the co-chairs argued that the disorders could be grouped together because of potential commonalities in brain circuitry, familial/genetic factors, neurotransmitter/peptide systems, phenotypes and treatment responses and phenomenology, co-morbidity and course of illness. In the Somatic Presentations conference in 2006, one of the first speakers noted the strong relationship with anxiety and depressive disorders and that their symptoms loaded onto one common factor of 'internalizing disorders'. In the conference on the Externalizing Disorders of Childhood, the strong relationship between the addictive disorders, conduct disorder and antisocial personality disorder was raised. In the conference on Co-morbidity of Depression and Generalized Anxiety Disorder in 2007, it was questioned whether it was now time to move towards an aetiologically based classification although, it was cautioned, we would need to establish a deeper set of principles that might be applied more generally to other areas of DSM-IV. Although using the DSM-V Task Force's criteria is only one way of identifying whether there are within-cluster similarities that would support the disorder clusters identified by the authors, the idea that disorders could be grouped together in terms similar to these is part of the zeitgeist.

The authors using these predetermined criteria and then led teams to examine the literature about one cluster, including and excluding disorders from that group as determined by the literature. Sachdev *et al*. (2009) determined the features shared by disorders in the Neurocognitive cluster; Andrews *et al*. (2009) determined the shared features in the Neurodevelopmental cluster; Carpenter *et al*. (2009) determined the shared features in the Psychosis cluster; Goldberg *et al*. (2009*a*) determined the shared features in the Emotional (internalizing) cluster; and Krueger & South (2009) determined the shared features in disorders in the Externalizing (disinhibitory) cluster.

In their reviews, the authors do not alter or advocate altering the definition of any DSM-IV or ICD-10 disorder. They simply specify probable relationships between disorders as currently defined, in terms of shared antecedent risk factors, likely course and possible treatments. The evidence in favour of these clusters is dependent on commonalities in the risk factors and clinical manifestations. The reviews at times comment on their differences with other clusters, but this is done at the cluster level. The differences, at the disorder level, have been presented in problematic cases. For example, in heterogeneous disorders, such as attention deficit hyperactivity disorder, there is some support for inclusion in the Neurodevelopmental and in the Externalizing clusters. This is discussed in the former review. There has been growing debate within the literature regarding the relationship between bipolar disorder, unipolar depression and schizophrenia. Goldberg *et al*. (2009*b*)

evaluate the differences and provide an example of how the Task Force criteria could be used to determine the placement of individual disorders once the hallmarks of the larger clusters have been identified. There are other disorders in which cluster membership may be controversial and would benefit from a similar analysis.

Results

The clusters, the nominated disorders, and the patterns of validators in the subsequent papers are as follows.

Neurocognitive cluster

The nominated disorders were delirium, dementias, amnestic and other cognitive disorders. There was a paucity of data concerning delirium and the other cognitive disorders. This cluster distinguishes itself by demonstrable neural substrate abnormalities that have both genetic and environmental underpinnings. The aetiology of the disorders is varied, but the neurobiological underpinnings are better understood than for mental disorders in any other cluster. Shared biomarkers, co-morbidity and course offer less persuasive evidence for a valid cluster of neurocognitive disorders. The occurrence of these disorders subsequent to normal brain development sets this cluster apart from neurodevelopmental disorders. There are cognitive processing abnormalities but there are no shared temperamental antecedents. Cognitive symptoms and deficits are the defining features. Progression in severity is common but there is no shared response to treatment.

Neurodevelopmental cluster

Mental retardation, learning, motor skills and communication disorders, and pervasive developmental disorders were retained in this cluster. There was support for considering attention deficit hyperactivity disorder and separation anxiety disorder with the Externalizing and the Emotional Disorders respectively. There was little evidence to either include or exclude the feeding, eating, tic, elimination and the other childhood disorders in the Neurodevelopmental cluster. They have been assigned to the 'disorders not yet assigned' group for further investigation. These Neurodevelopmental disorders date from birth, even if not recognized until the lack of appropriate development is observed. There is evidence of a broad genetic liability to neurodevelopmental symptoms but the environmental causes are non-specific. There are some data on changes in the neural substrate and evidence on the shared deficits in cognitive and emotional processing. There are no temperamental antecedents. There are high rates of co-morbidity within the cluster and little evidence of remission in symptom severity. There is no shared response to treatment.

Psychosis cluster

The nominated disorders were schizophrenia and related psychoses as defined in DSM-IV-TR, bipolar disorders, and schizotypal personality disorder. There were few data for comparison among the psychoses grouped in DSM-IV-TR, and thus the review examines the boundaries of the psychoses represented by schizophrenia with bipolar disorders and schizotypal personality disorder. There is strong evidence for the influence of genetic factors and some sharing of these between the disorders in the cluster. There is some minor evidence for causal environmental risk factors. There is evidence of shared neural substrate abnormalities, biomarkers, shared cognitive processing abnormalities and clinical manifestations. There is co-morbidity within the cluster and some shared response to treatments. However, in each of these areas, significant differences are also documented.

Emotional cluster

The nominated disorders were: unipolar depression; dysthymia; generalized anxiety; panic; phobias; obsessive–compulsive disorder, body dysmorphic disorder, hypochondriasis; post-traumatic stress disorder; adjustment disorders; somatoform disorders (including neurasthaenia); and avoidant personality disorder. There was a paucity of data concerning body dysmorphic disorder, adjustment, and avoidant personality disorders. They are not discussed further. Many of the disorders that were examined share genetic risk factors that are also shared with the temperament of negative emotionality. Many also share causal environmental risk factors related to loss and threat. There are some common neural substrates, and cognitive and emotional processing abnormalities. All emotional disorders share elevated scores on the temperament of negative emotionality. Most emotional disorders follow an episodic path with high risk of relapse, and co-morbidity within the cluster is very significant. Most disorders respond to similar treatments.

Externalizing cluster

The disorders originally nominated were the substance-related disorders; antisocial and borderline personality disorders; impulse control disorders; and

conduct disorder. The literature indicates that the core members of the cluster are the conduct, antisocial personality and substance-related disorders. Other potential members of the cluster are defined in ways that combine features of different clusters (e.g. borderline personality disorder has both emotional and disinhibitory features) and are not discussed at length. Many of the disorders that were studied share genetic risk factors that are also shared with the temperament of disinhibition. Environmental risk factors can facilitate and inhibit the development of the disorders. There is emerging evidence for shared neural substrates, biomarkers, and cognitive processing features linking disorders within the cluster, but the key feature is the shared temperamental antecedent of disinhibition. Co-morbidity within the cluster is very common. These disorders ameliorate with age but there is little shared response to treatment.

Disorders not yet assigned

There were insufficient data on the Study Group criteria for the tic and elimination disorders, feeding, eating and other disorders of infancy or early childhood; paranoid, schizoid, histrionic and narcissistic personality disorders; body dysmorphic, adjustment, factitious and dissociative disorders; the avoidant and obsessive–compulsive personality disorders; and the primary sleep; sexual and gender identity disorders; and the eating disorders to warrant their membership to one of the five identified clusters. It is not intended that this residual group of disorders form a heterogeneous 'cluster'. Instead, their assignment here indicates the strength of association on the Study Group criteria with the five identified clusters.

The findings of the following six papers support a more parsimonious organization of the forthcoming classifications that could incorporate both the shared risk and the clinical characteristics for the majority of the DSM-IV and ICD-10 disorders. Few of the shared features are either necessary or sufficient to define any cluster, but they are shared risk factors or features of the disorders in the cluster, and are more likely to be present than not. The aim, to identify clusters of disorders on the basis of features not confined to clinical picture, seems feasible, but whether it is useful remains to be seen.

Discussion

The present set of papers is an exercise to organize disorders in DSM-V and ICD-11 that takes account of what the DSM-V Task Force has deemed to be the characteristics that could contribute to clusters of disorders. It is a step away from a classification based on symptom picture alone.

This exercise is limited in the following ways. It is not based on systematic reviews; to perform such a review for each disorder would have been a Herculean task even if the appropriate data (disorder *versus* controls *versus* all other disorders within cluster *versus* all disorders in other clusters) were available for all disorders. They are not. It did not rely on statistical procedures to identify broad disorder groupings although the latent structures in the emotional and externalizing clusters did go some way along this path. Unfortunately, there were insufficient data on the other clusters to repeat this approach. We have insufficient knowledge of aetiology and pathophysiology to make definitive assignments of many disorders to clusters. None of the clusters have data on all validators, and many of the comparative data fail to distinguish state from trait, and state similarities may not capture crucial trait differences. Furthermore, data are often based on comparisons with healthy controls, and inferences of differences between disorders may be unwarranted and confounded by cohort and other effects. We will need direct comparisons between disorders to distinguish the shared characteristics that warrant membership in the same cluster and direct comparisons between disorders in different clusters to confirm the expected differences.

There are commonalities between the disorders that fall within a given cluster, and the shared pattern of features is characteristic only of that cluster. Therefore, we imply that there are differences between clusters. This set of reviews emphasizes the similarities between disorders within a cluster. Important differences receive less emphasis. We do not, and cannot, explore all the differences between clusters and between disorders because of lack of data. Nonetheless, it will be important to test disorders on the border between clusters. For instances, this was done for bipolar disorder, which is tested as a member of the emotional cluster as well as the psychosis cluster (Goldberg *et al*. 2009*b*). It is provided as an example of how, in cases where disorders share similarities with multiple clusters, the criteria could be used to determine cluster membership. It is possible that different evaluations of the literature may result in differing opinions as to 'where disorder X should appear in DSM-V/ICD-11'. Carpenter *et al*. (2009) conclude that bipolar disorder shares some similarities with schizophrenia, but also find significant differences. Goldberg *et al*. (2009*b*) suggest that a separate but related cluster could reflect the similarities and differences between bipolar disorder and schizophrenia, and argue that there is little support for placement in the emotional cluster.

If the DSM-V Task Force decides that information on similarities within clusters and differences between clusters could be of interest, the DSM-V Work Groups could, as part of their literature reviews, apply their greater knowledge of specific disorders to decide which disorders fit and which do not fit within the nominated clusters. The present exercise was top-down whereas the work of the Work Groups is bottom-up. If the two approaches agree then this proposal will be supported.

This set of reviews reports that five large groups of disorders can be thought of in terms of risk factors, clinical picture and course. Whether these clusters could be useful to the field is yet to be tested. However, we must have proof of concept before determining utility. Nevertheless, there could be advantages in recognizing these clusters. In broad terms, neuroscience, genetics, epidemiology and therapeutics are the variables that validate cluster membership and the following six papers discuss the details. These are also the variables that can inform a clinician's understanding of the patient and determine treatment and prognosis. The clinical advantage of a cluster approach is that, although the specific requirement of a detailed diagnosis remains, the patient can now be viewed within a much broader context. When a disorder belongs to a cluster, clinicians should treat the symptoms and ensure that the risk factors characteristic of that cluster are modified to reduce their potential impact. Cluster membership may be more permanent than the illness episode. Recovered patients often retain their risk factors for a cluster and relapse is likely to be within the cluster but not necessarily to the specific disorder, which of course explains the high levels of lifetime co-morbidity seen among mental disorders.

Identification of clusters may enhance clinical utility in primary care and also in general specialist psychiatric care. For internists and general practitioners, the clustering will simplify an otherwise confusing system, and encourage clinicians, for instance, to assess anxious and depressive symptoms whenever they are faced with a patient with psychosomatic symptoms. Clusters are likely to be more useful in teaching and training of clinicians, simply because they emphasize the core features of disorders rather than emphasizing a detailed list of diagnostic criteria.

Clusters may also be useful for data reporting and public health planning and could provide more useful estimates of the quantity and nature of service needs. For example, the second Australian burden of disease study condensed the anxiety and depression diagnoses into one cluster of 'anxiety and depression' on the basis that co-morbidity was high and that service needs were similar. This cluster accounted for 58% of the burden of mental disorders (Begg *et al*. 2007). Gathering together disorders that are at present spread over different chapters of the DSM and ICD into a cluster will make it simpler for public health experts to consider services for such patients in a more rational way. The neurodevelopmental disorders require special training and long-term supervision. The psychoses and neurocognitive disorders form the 'severe mental disorders' that are a major burden on specialist mental health services. The externalizing and emotional disorders form a major burden on both general practice and general hospital services and are often referred to as 'common mental disorders'. These major groupings call for different responses from a public health perspective and this is reflected in the current proposal.

Research in neuroscience, genetics, epidemiology and therapeutics will be required to explicate the risk factors common to a cluster. Clusters will encourage comparative research on biological concomitants and on the epidemiology of specific disorders in the cluster. The existence of clusters will encourage researchers to seek differences between them, in addition to comparing each disorder with healthy controls. For instance, relatively few neuroimaging studies compare schizophrenia with bipolar disorders; and few neuroimaging studies compare generalized anxiety disorder and depression. Such comparative studies are essential. Intervention research may now focus on more heterogeneous, real-life groups of patients, rather than being focused on criteria-driven cases. Although there are several disorders in each cluster, this does not mean that there are not differences between them, merely that they have important points in common.

These reviews give rise to further questions. Could a person be located in terms of a liability score within a broad multi-dimensional vulnerability to a set of mental disorders? Are there distinct subclusters within each cluster? For example, are there distinct depressive, obsessional, fear, and trauma-induced subclusters in the emotional disorders cluster; and are there mental retardation, communication/learning/motor, and pervasive developmental disorder subclusters in the neurodevelopmental disorders cluster? We are familiar, for instance, with the suggestions of an obsessive–compulsive spectrum including obsessive–compulsive, body dysmorphic and tic disorders, and hypochondriasis (First, 2009). We considered this but, given the need for the most parsimonious meta-structure (as opposed to subdivisions), and that most of this spectrum shares features with the emotional disorders, these disorders, except for the tic disorders, were considered in the Emotional cluster. In what way are disorders within each subcluster similar or different

to each other? Can some disorders be combined as having similar aetiology, course, outcome and treatment response? For example, are the three variants of panic and agoraphobia in fact one disorder; are social phobia and avoidant personality also one disorder; and does the substance matter in substance abuse? It is only when we look at the relationships across multiple disorders that these questions can be answered.

Conclusions

A classification based on the features in the DSM-V Task Force Study Group list above suggests the possibility of a classification based on aetiological risk factors. A more parsimonious meta-organization of the classifications could emphasize risk factors, increase clinical utility, and potentiate research into the cause and prevention of mental disorders. The six papers that follow are an attempt to achieve this. The final aim is to espouse a classification reflective of neuroscience, genetics, epidemiology, clinical features and therapeutics. We now have time, as the DSM-V and ICD-11 literature reviews are prepared, criteria revised and field trials conducted, to fine-tune the clusters and the disorders included in them on the basis of an informed search for evidence that would confirm or disconfirm, augment or revise the suggested meta-structure.

Declaration of Interest

Drs Andrews, Goldberg, Krueger, Sachdev and Pine report no conflicts of interest relating to this paper. Dr Carpenter reports European Regional Patent No. 1487998 (6 June 2007) on 'Methods for Diagnosing and Treating Schizophrenia' with no potential personal financial reward (proceeds pledged to the Maryland Psychiatric Research Center). In the past 12 months Dr Carpenter has been a consultant to Teva and Eli Lilly. Dr Hyman reports that in the past 12 months he has consulted for Novartis and GlaxoSmithKline.

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