

## Editorial

The classification of depression:  
are we still confused?

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**Summary**

Recent developments in the classification of major depressive disorder are reviewed in light of the predictions made by Kendell in the 1970s. Particularly, the institution of operational diagnoses along with the contentious issues of subdividing major depressive disorder and its characterisation on a dimensional as opposed to a categorical scale.

**Declaration of interest**

The authors are employed by the Medical Research Council at the Social, Genetic, and Developmental Psychiatry Research Centre, part of the Institute of Psychiatry, King's College London, UK.

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**A history of confusion**

In 1976, Robert Kendell published a seminal article in the *Journal* outlining the many problems (the 'contemporary confusion') relating to the classification of depression.<sup>1</sup> Some of these, he argued, also had implications for the classification of mental illness as a whole. Farmer & McGuffin<sup>2</sup> revisited and updated the issues in 1989 against the background of the *Diagnostic and Statistical Manual 4th Edition* (DSM-IV) and the then impending publication of the *International Classification of Diseases 10th Edition* (ICD-10). Now, 30 years after Kendell's original paper and as we enter the run up to DSM-V and ICD-11, another update is timely.

In the mid-1970s the problems outlined by Kendell included how to validate diagnosis in the absence of any known pathological mechanism, how to subdivide depressive disorders and how to resolve uncertainty over the use of categories or dimensions. In particular, Kendell noted that the introduction of research operational criteria to define psychiatric disorders could have an impact on improving the reliability and the international standardisation of diagnosis – an issue of major importance at the time. He hoped that improving diagnostic reliability between researchers would be the first step in ensuring the validity of diagnosis, recognising that this could not be fully achieved until the aetiopathology of depression is elucidated. What Kendell did not foresee in 1976 was the profound effect operational definitions would have on national and international nosologies. The DSM was produced in completely operationalised format in 1980, while the World Health Organization's ICD was produced in operationalised form for research purposes in 1993.

The operationalised approach to defining diagnostic categories has become so firmly entrenched in modern psychiatry that few who use the two classification systems routinely in research or

clinical practice stop to reflect on them, let alone question their scientific veracity. Operational definitions provide a 'top down', rigid and explicit set of rules for making a diagnosis. This allows good interrater reliability, whereby researchers or clinicians can achieve good agreement about the presence or absence of a disorder, and it is also relatively straightforward to generate standardised diagnostic interviews with computerised scoring algorithms to apply the criteria. Alongside these strengths, however, there are crucial weaknesses that should be kept in mind.<sup>3</sup>

One disadvantage of operational definitions is that individuals who do not precisely fulfil criteria are often placed in a 'not otherwise specified' category. In some instances, the definitions are so narrow that ragbag, 'atypical' categories (e.g. DSM-III psychosis not otherwise specified) can contain more individuals than 'typical' categories (e.g. DSM-III schizophrenia).<sup>3</sup> Conversely, some definitions of disorder, for example DSM-III major depression, are broad and tend to be 'unstable', showing disappointing retest reliability.<sup>4</sup> Operational definitions are also somewhat limited in the number and type of item included in their combinatorial rules. They necessarily focus on more positive, concrete phenomena, inevitably leaving some pathological experiences or observations unaccounted for.

One specific example of the problems the operational criteria approach can cause is when people with bipolar disorder are 'misclassified' as unipolar, and thus receive inappropriate treatments that can be ineffectual and in some cases harmful.<sup>5</sup> This can happen when patients report clear-cut depressive episodes but only experience hypomanic periods which do not meet the threshold for bipolar disorder. Clearly, this is a situation that clinician and researcher alike strive to avoid; however, the rigidity of the operational criteria in the DSM and ICD hamper such efforts.

Another concern regarding operational criteria is the 'obstinate challenge' of bringing diagnoses and aetiology together.<sup>6</sup> The authors of DSM-III and its subsequent versions aimed to be 'atheoretical', deliberately attempting to avoid including putative causal mechanisms in their classification schemes. McHugh suggests that this makes our current systems akin to bird and botanical field guides in that they enhance the accuracy of identification without explaining distinctions. In contrast, in general medicine, classification is organised around systems (respiratory, renal, etc.) and aetiologies (vascular, neoplastic, infectious, etc.).

**Subdivisions and overlaps**

Kendell proposed that a bipolar/unipolar subdivision of affective disorder had a persuasive research base<sup>1</sup> and further supporting

evidence, including data from genetic studies, had firmly established the taxonomy in the later review by McGuffin & Farmer.<sup>2</sup> The authors proposed a two-threshold model whereby unipolar and bipolar disorder are quantitatively rather than qualitatively different, with both disorders lying on the same continuum of liability but bipolar disorder being the more extreme or severe form. Recent genetic advances have shown this model to be overly simplistic. In particular, a twin analysis convincingly refuted the two-threshold approach, whereby the data were better explained by a model of a distinct, but partly overlapping, set of genes.<sup>7</sup> The genetic correlation between mania and depression was 0.65 but approximately 71% of the genetic variance of liability for mania was not shared with depression. A separate set of twin analyses, that involved relaxing the inbuilt hierarchy of diagnosis in DSM-IV, strongly suggested that there are also partly distinct and partly overlapping genes contributing to bipolar disorder and schizophrenia.<sup>8</sup> Although considered controversial at the time, this was soon followed by supporting molecular genetic evidence from linkage and association studies.<sup>9</sup> Yet other twin studies suggest that there is also considerable overlap between risk factors for anxiety and depression.<sup>10</sup>

The genetic overlap between depression and anxiety is hardly surprising given the high rates of comorbidity that exist between the two disorders, as findings from the National Comorbidity Survey testify.<sup>11</sup> This poses important questions for the treatment of comorbidity<sup>12</sup> and also future diagnostic systems. Moffitt and colleagues recently attempted to address this issue from a prospective, longitudinal approach.<sup>13</sup> They reported that 72% of individuals with generalised anxiety disorder (GAD) were diagnosed with comorbid depression and 48% of individuals with depression also had GAD. Evidently there is a strong association between the disorders in this large sample, and it would be informative to ascertain how near the diagnostic thresholds those not classified as comorbid are. The authors claim that there is sufficient evidence to use the umbrella term of 'distress disorders' to cover both syndromes of depression and anxiety. They go on to say that the current hierarchical superiority of depression over anxiety may also be questionable as the two disorders show symmetrical developmental trajectories, so there is no evidence to prioritise one over the other. These conclusions should be of interest to those researchers charged with revising the classification systems of depression and anxiety. However, the key point from a clinical perspective is that the rates of comorbidity in depression are often underestimated, and that the treatment and management of depression is likely to vary dependent on whether the comorbidity is with anxiety or with other common psychiatric disorders.

Another pertinent issue concerning how depression is subdivided arises from the recent revival of interest in the concept of melancholia. The rationale behind this resurgence is that major depressive disorder is too heterogeneous a concept, while a melancholic subtype offers a reliable, valid and more homogenous group with specific treatment recommendations, specifically tricyclic antidepressants and electroconvulsive therapy. The editor of *Acta Psychiatrica Scandinavica* even felt sufficiently compelled by the concept of melancholia to devote an entire recent issue to the topic.<sup>14</sup> The intentions of the authors to help homogenise depression for both clinical and research purposes are admirable. However, some of the fundamental assumptions, such as the underlying neurobiology of melancholia being well-defined and distinct from other mood disorders, is somewhat dubious, as is the evidence presented in the issue, particularly regarding the epidemiological findings. It appears as though melancholia is merely another term for severe major depressive disorder, and there seems little point in reintroducing the term as a confusing synonym for an already well-established concept.

## Categories v. dimensions

The operational approach to defining depression is categorical in that it defines cases or non-cases of disorder. However, when originally proposed by Hempel, he accepted that the individual items of psychopathology that make up each definition were dimensional, where experience ranged in severity from mild, self-limiting and present in the general population to severe, persistent and pathological.<sup>15</sup> Hempel suggested that for each criterion the rater had to ask 'does the respondent exhibit this amount of (symptom) X?' In terms of criteria for depression, this translates as 'has the individual experienced at least 2 weeks of unremitting low mood?' This imposes a severity threshold on a continuous variable: in this case, mood. Thus, recognition that symptoms of mental health are continuously distributed across individuals within the general population as well as in those with disorders has been implicit since operational definitions were first proposed. However, depression is a ubiquitous syndrome that is associated with various mental disorders (schizophrenia, substance misuse, eating disorders, anxiety) along with physical disorders such as Parkinson's disease, myocardial infarction, stroke and obesity. Not all of these different manifestations of depression respond well to antidepressant medication, suggesting that they may be aetiologically distinct. Depression also ranges in severity and symptom profile from the severe psychotic type of disorder found in bipolar illness to mild neurotic depressive symptoms associated with some personality disorders. Recent taxonomic studies exploring whether there is a discontinuity between clinical depression and subthreshold depressive symptoms have been inconclusive.<sup>16</sup>

In fact, the ICD-10 classification of depression incorporates a quasi-dimensional approach, inasmuch as there are mild, moderate and severe forms which some authorities suggest have implications for treatment. For example, the UK National Institute for Health and Clinical Excellence (NICE) guidelines indicate that the preferred first line of treatment for mild depression should be psychological therapy and that drug treatment should be reserved for those with moderate or severe forms of illness.

Arguing for dimensions v. categories becomes somewhat spurious since both approaches are necessary.<sup>17</sup> Certainly, there is a clinical requirement to define cases of a particular disorder, since this determines management and prognosis as well as facilitating service planning. However, defining psychopathology dimensionally probably has greater utility for basic science research especially neuropsychology and genetics. The dimensional structures of the psychopathology of unipolar depression,<sup>18</sup> as well as their bipolar counterparts (L. Forty, personal communication, 2007), have already been established using multivariate statistical approaches. Thus, there is an accepted dimensional structure for depression that can provide the continuous measures required in certain spheres of research. This indicates that DSM-V and ICD-11 probably need to incorporate both categories and dimensions; not one or the other.<sup>19</sup>

## Conclusions

So what has changed over the past 30 years? Is there still confusion over the classification of depression? The answer to the first question is that the main taxonomies have not been altered drastically. An operationalised approach to diagnosis is still predominant in the main nosologies, although this may be challenged in the next revision of the DSM.<sup>6</sup> The subdivision of unipolar and bipolar depression is well established by the research evidence and the melancholic definition of depression is also receiving a

resurgence in research interest. However, new aetiological clues about shared and specific risk factors for depression, mania and schizophrenia are emerging from genetic and neuroimaging research and this may increasingly challenge traditional classifications. It is possible that we could see wholesale shifts in classificatory groups, as has happened in other branches of medicine (e.g. peptic ulcer being reclassified from inflammatory to infectious diseases).

Similarly, after much debate comparing dimensional *v.* categorical approaches to diagnosis, it is now evident that both have their specific applications and both are necessary to psychiatry. It seems highly likely at the time of writing that DSM–V will be cast in both dimensional and categorical formats.

Are we still confused? Since it remains the case that we still have little understanding of the precise aetiology of depression, the answer to this question is surely 'yes'. Our current nosologies remain as 'working hypotheses' and have no greater validity than the definitions of depression that existed when Kendell wrote in 1976. Consequently, the 'true' classification of depression remains as elusive as it was 30 years ago, though this is by no means reason to give up hope for the future.

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## References

- Kendell RE. The classification of depressions: a review of contemporary confusion. *Br J Psychiatry* 1976; **129**: 15–28.
- Farmer A, McGuffin P. The classification of the depressions. Contemporary confusion revisited. *Br J Psychiatry* 1989; **155**: 437–43.
- Farmer AE, Wessely S, Castle D, McGuffin P. Methodological issues in using a polydiagnostic approach to define psychotic illness. *Br J Psychiatry* 1992; **161**: 824–30.
- Rice JP, Rochberg N, Endicott J, Lavori PW, Miller C. Stability of psychiatric diagnoses. An application to the affective disorders. *Arch Gen Psychiatry* 1992; **49**: 824–30.
- Hirschfeld RMA, Cass AR, Holt DCL, Carlson CA. Screening for bipolar disorder in patients treated for depression in a family medicine clinic. *J Am Board Fam Pract* 2005; **18**: 233–9.
- McHugh PR. Striving for coherence: psychiatry's efforts over classification. *JAMA* 2005; **293**: 2526–8.
- McGuffin P, Rijsdijk F, Andrew M, Sham P, Katz R, Cardno A. The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. *Arch Gen Psychiatry* 2003; **60**: 497–502.
- Cardno AG, Rijsdijk FV, Sham PC, Murray RM, McGuffin P. A twin study of genetic relationships between psychotic symptoms. *Am J Psychiatry* 2002; **159**: 539–45.
- Craddock N, Forty L. Genetics of affective (mood) disorders. *Eur J Hum Genet* 2006; **14**: 660–8.
- Middeldorp CM, Cath DC, Van Dyck R, Boomsma DI. The co-morbidity of anxiety and depression in the perspective of genetic epidemiology. A review of twin and family studies. *Psychol Med* 2005; **35**: 611–24.
- Kessler RC, Nelson CB, McGonagle KA, Liu J, Swartz M, Blazer DG. Comorbidity of DSM–III–R major depressive disorder in the general population: results from the US National Comorbidity Survey. *Br J Psychiatry* 1996; **168** (suppl 30): 17–30.
- Andreescu C, Lenze EJ, Dew MA, Begley AE, Mulsant BH, Dombrowski AY, Pollock BG, Stack J, Miller MD, Reynolds CF. Effect of comorbid anxiety on treatment response and relapse risk in late-life depression: controlled study. *Br J Psychiatry* 2007; **190**: 344–9.
- Moffitt TE, Harrington H, Caspi A, Kim-Cohen J, Goldberg D, Gregory AM, Poulton R. Depression and generalized anxiety disorder: cumulative and sequential comorbidity in a birth cohort followed prospectively to age 32 years. *Arch Gen Psychiatry* 2007; **64**: 651–60.
- Fink M, Bolwig TG, Parker G, Shorter E. Melancholia: restoration in psychiatric classification recommended. *Acta Psychiatr Scand* 2007; **115**: 89–92.
- Hempel CG. Introduction to problems of taxonomy. In *Field Studies in the Mental Disorders* (ed J Zubin): 3–22. Grune and Stratton, 1961.
- Solomon A, Ruscio J, Seeley JR, Lewinsohn PM. A taxometric investigation of unipolar depression in a large community sample. *Psychol Med* 2006; **36**: 973–85.
- Helzer JE, Kraemer HC, Krueger RF. The feasibility and need for dimensional psychiatric diagnoses. *Psychol Med* 2006; **36**: 1671–80.
- Korszun A, Moskvina V, Brewster S, Craddock N, Ferrero F, Gill M, Jones IR, Jones LA, Maier W, Mors O, Owen MJ, Preisig M, Reich T, Rietschel M, Farmer A, McGuffin P. Familiality of symptom dimensions in depression. *Arch Gen Psychiatry* 2004; **61**: 468–74.
- Brown TA, Barlow DH. Dimensional versus categorical classification of mental disorders in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders and beyond: comment on the special section. *J Abnorm Psychol* 2005; **114**: 551–6.