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CONFERENCE REPORT

Towards DSM-V: the relationship between generalized anxiety disorder and major depressive episode

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Introduction

A conference was organized by the American Psychiatric Association's Division of Research in June 2007, in order to discuss the relationship between generalized anxiety disorder (GAD) and major depressive disorder (MDD). The task was to produce new findings from research in order to influence any changes that may be made to DSM-V in the relationship between the two common disorders. Kendler (in press) opened the conference by reminding the participants of the changing definitions of GAD since DSM-III, and asked whether one should give more emphasis to causal relationships that explored the aetiology of each, or descriptive relationships based upon clinical characteristics. In the event, both approaches were used. He also asked whether we should continue with clinical categories, or whether continuous measures such as dimensions were preferable.

There was general agreement that, as defined at present, they were not the same disorder, and could not usefully be merged into a single illness. There was also general agreement that the two disorders shared a number of features, but there are some differences in the aetiological factors associated with each one.

Factors shared by both disorders

Shared causal features

In his comprehensive review of the field Hettema (in press) argued that family, twin, and high-risk transmission studies all indicate that GAD and MDD share some, if not most, of their genetic risk factors (Kendler *et al*. 1992; Roy *et al*. 1995). He also showed that the genetic risk for each disorder was mainly shared – a genetic correlation of about +0.96 being shared about equally between variance related to neuroticism and variance unrelated to it (Hettema *et al*. 2006). Neuroticism was common to both, and families of each show a higher incidence of anxiety disorders. Moffitt *et al*. (2007) reported that negative emotionality – which is closely related to neuroticism, is also shared.

Parents of either disorder were more likely to show low care and high over-protection, and both were associated with parental neglect, and both sexual and physical abuse during childhood (Kendler *et al*. 2000). Periods of parental separation were also shared, and both disorders were more likely to show personality disorders – although there were inconsistent differences between them in the kinds of personality disorder. Similar findings were reported from the repeat US National Comorbidity Survey: the childhood risk factors were almost identical, with all three forms of abuse and parental divorce being more common in the early lives of each (Kessler *et al*. in press).

Moffitt *et al*. (2007) showed that in the Dunedin cohort some of these findings were confirmed, and in addition both were more likely to have a higher rate of anxiety disorders in other family members, and mothers with high rates of internalizing disorders, and were more likely to have been maltreated relative to normal controls. Co-morbid cases had lower self-esteem, and higher neuroticism in adolescence than either disorder on its own. Richards presented data from the MRC National Survey of Health and Development (Wadsworth *et al*. 2005), showing that co-morbid cases were more likely to have experienced chronic illness before age 5 years, and parental divorce or separation by age 15 years (Richards, in press). With such similarities in aetiological factors shown by

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Hettema and Moffitt, much of the observed co-morbidity in adult life is inevitable.

Shared descriptive features

Hettema (in press) argued that there is a female preponderance in each disorder, with higher rates of each in middle age, among the separated and divorced, in those with low income and amongst the unemployed. Odds ratios for co-morbidity between the two were 6.9, 8.2 and 6.4 respectively in the Dunedin study, the US National Comorbidity Survey and the US NCS – Replication Survey. Kessler *et al*. (in press) presented data from the US National Comorbidity Survey and showed that the cumulative age-of-onset curves for the two disorders are identical. Parental divorce is more common in both than in controls.

Furukawa presented meta-analyses showing that benzodiazepines, antidepressants and azopirones were effective in reducing counts of both depressive and anxious symptoms in cases of GAD and major depressive episode (MDE). One possible explanation is that cases of either have some symptoms of both, while another was that any psychotropic can be shown to be superior to placebo. However, they could also be explained if the two diagnostic entities were in fact the same (Furukawa *et al*. in press).

In Moffitt's (2007) Dunedin study, subjects with either diagnosis were more likely to have experienced conduct problems between the ages of 5 and 11 years, and to have elevated counts of internalizing symptoms by age 18 years. Her study also showed that the longer symptoms of either last, the more likely co-morbidity becomes – after 3 years all cases starting as anxiety, and almost all cases of depression have become co-morbid.

Factors specific to generalized anxiety and major depression

Specific causal factors

Depression has an additional familial aggregation component (Hettema, in press; Kessler *et al*. in press; Weissman *et al*. in press).

In the Dunedin prospective cohort study it was shown that while co-morbid cases have the highest rates of childhood maltreatment, mother's internalizing symptoms, and neuroticism reported by an informant during childhood relative to non-cases, GAD has the next highest, as well as higher inhibited temperament and informant-rated neuroticism and more maltreatment during childhood than MDE.

Moffitt *et al*. (2007) speculated that GAD is a more severe disorder than depression.

Among working-class women in North London pure depression was more likely to be preceded by loss events, anxiety by danger, and cases of both anxiety and depression by a combination of both sorts of events (Finlay-Jones & Brown, 1981). This co-morbidity was directly proportional to the number of risk factors. Hettema (in press) and Brown (in press) showed that these findings have been partially replicated by others.

Social support has been found to overall reduce the risk of MDD in most studies (Paykel, 1994; Brown, in press), but one population study in Oslo suggested that social support has little association with GAD (Cramer *et al*. 2005). In contrast to earlier claims, MDE preceded GAD almost as often as GAD preceded MDE (Moffitt *et al*. 2006).

Specific descriptive features

The most striking differences between anxiety and depression are undoubtedly in their underlying biology (Martin & Nemeroff, in press), which is underpinned by much research in depression, but rather less in anxiety disorders.

Neuroimaging studies

Depression activates the dorsal insular cortex and the anterior cingulate cortex, while anxiety activates the ventral insular cortex and deactivates the posterior cingulate cortex. The amygdala is overactive at rest in depression, but not overactive at rest in anxiety, but becomes overactive during anxiety provocation. The ventrolateral subregional cortex is associated with both GAD and MDD, and successful treatment with antidepressant drugs influences frontal cortical activity in MDD in both disorders.

Neuroendocrine studies

Major depression is characterized by hypothalamic–pituitary–adrenal (HPA) axis overactivity, and hypothalamic–pituitary–thyroid (HPT) axis alterations are common, but the hypothalamic–pituitary–gonadal (HPG) axis is underactive. There are fewer neuroendocrine studies in GAD, but while there is some evidence of HPG underactivity, activity of both the HPA and HPT axis is usually normal. Neuropeptide Y is decreased in depression and may be a neural correlate of resiliency to mood and anxiety disorders, while cholecystokinin provokes panic and anxiety but not depression.

Neurotransmitters

The well-documented effectiveness of selective serotonin reuptake inhibitors (SSRIs) in the treatment of

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both depression and anxiety disorders probably results from the diverse role of 5-HT in the CNS and the manifold effects of SSRIs rather than a common underlying pathophysiology of serotonergic circuits. MDE has normal autonomic activation, while GAD has autonomic arousal.

It was also pointed out that each have characteristic, and distinct, somatic symptoms.

Psychometric aspects of anxious and depressive symptoms

Negative affect (or neuroticism) is the common characteristic of all internalizing disorders, including the closely related fear disorders.

However, MDE has low positive affect, while GAD has normal positive affect (Krueger, 1999). Depressive states are associated with memory biases for negative information about the self, while anxiety is associated with automatic attentional biases for threatening material (Goldberg, in press).

While the purpose of the conference was to discuss GAD and MDE, several speakers pointed out that like was not being compared with like. To do this, we would need to compare GAD with depressions that have lasted 6 months, or MDE with anxiety states lasting as little as 2 weeks. Kessler came close to the latter by considering different decision rules for the duration of GAD, and shortening the requirement from 6 months to 1 month (Kessler *et al*. 2005). This has the effect of approximately doubling the lifetime prevalence (from 6.1 at 6 months, to 12.7 at 1 month). One-month episodes of GAD were comparable to 6-month episodes in terms of onset, persistence, impairment during episodes, co-morbidity, parental GAD, and sociodemographic correlates.

When the relationship between depressive symptoms and anxious symptoms is considered, the two are inextricably linked. Two of the research interviews used in studies presented by UK speakers used the same time-frames for diagnoses – the past month – these were the revised Clinical Interview Schedule (CIS) and the Present State Examination. When this is done, the two sets of symptoms are even more highly correlated than the two diagnoses of GAD and MDE. Jacob (in press) quoted work in six developing countries using the CIS, and showed that a single factor provides almost as good a fit as a two-factor (anxiety and depression) solution. These high correlations between the symptom dimensions – as opposed to the diagnoses GAD and MDE – occur because many patients with 'anxiety only' also have sub-syndromal levels of depression, and vice versa.

It is clear that that long-term vulnerability factors – both genetic and environmental – are common to both disorders, but since GAD is defined to last much longer than MDE, it may well need more long-term vulnerability factors. This is consistent with the findings from the longitudinal studies quoted. If we consider MDE, one can argue that sometimes severe loss events will be followed by brief episodes of depression. Kessler *et al*.'s (in press) finding of a greater tendency of those with MDE to be 'open to experience' would fit with the observation that only a minority of those who have experienced a severe loss event go on to develop MDE. The attentional biases associated with each disorder fit well with the partial association with life events associated with threat and loss.

Categories or dimensions?

Dimensions allow consideration of the severity of a disorder – and this often has treatment implications. The provision of three degrees of severity of depression by both ICD-10 and DSM-IV has been useful, in that optimal treatments for each are not the same (NICE, 2004). These are pseudo-dimensional categories, and argue for severity measures – and thus dimensional measures, to be available when differences of clinical management are indicated.

Conclusion

Those that considered that the two disorders were 'distally related' were influenced by the biological differences described above, by the extra aggregation of depression in families of those with MDE, and by the (rather small) differences in the causal factors involved. It followed that the two disorders should remain in separate categories.

Persuasive as the biological data undoubtedly is, it is hardly conclusive. It is arrived at by considering extreme ends of a continuous distribution, and fails to take into account the commonest sort of distressed patient seen in general medical practice. While all were agreed that depression and anxiety are not the same disorder, others thought that the two disorders were 'closely related'. Hettema (in press) reminded us that panic disorder shares co-morbidity with MDE, and Angst that in the Zurich study GAD is more closely related to bipolar disorder than it is to MDE (Angst & Gamma, in press). In Krueger's (1999) analysis of data from the National Comorbidity study, although the tetrachoric correlations were highest between MDE and GAD, those between the other internalizing disorders are almost as high. However, close or distant they are, the causes of each are almost the same, and the symptom dimensions are themselves are closely related.

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Declaration of Interest

None.

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