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COMMENTARY TO SPECIAL ARTICLE

The chicken and egg of anxiety and depression

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The paper of Kessler and co-workers on epidemiologic relationships between anxiety and depression is a major contribution, in that it presents data on a very large number of subjects studied across multiple countries and ethnicities. The findings confirm the earlier, pioneering work of Kessler's group (Magee *et al*. 1996) as well as others including our own (Regier *et al*. 1998; Ohayon & Schatzberg, 2010) on two major points. Major depression is characterised by high rates of co-occurring anxiety disorders and anxiety disorders more commonly presage the onset of the depression than *vice versa*. Both our and Kessler's group reported a number of years ago that social anxiety or phobia in adolescence occurred some 10 years before the onset of the depression in adulthood (Magee *et al*. 1996; Regier *et al*. 1998). The relationship between these disorders has been the subject of some study and there are considerable speculations but the definitive answers have remained somewhat elusive. Recent work using functional imaging may provide us some clues to shared characteristics as well as potential differences.

In the paper, Kessler and co-workers noted that both disorders may reflect variants of an internalising disorder but this still does not address the sequence of the onsets. Why would anxiety presage depression? One possibility is that some anxiety disorders such as social phobia impair the subject's ability to succeed at school or work and that failure results ion demoralisation and ultimately depression. That would fit a model that depression is essentially learned similar to the helplessness that results from exposure of lower animals to specific stressors. The model would also suggest that anxiety is in some ways primary or virtually instinctual – an observation consistent with the primate work of Kalin's group looking at fears of snakes and stranger intrusion (Oler *et al*. 2010). As indicated in the Kessler's paper, a number of years ago our group reported that cognitive behaviour therapy administered to socially phobic adolescents reduced the risk of recurrence of depression during the following 1 year (Hayward *et al*. 2000) in keeping with the depression being learned and preventable.

Another model might be that depression reflects biological processes involving depletion of monoamines over time. Here, one could posit that catecholamines released during highly stressful periods eventually deplete stores and result in a low catecholamine state and depression. There is little to support uniquely low catecholamine levels in unipolar depression. However, there do appear to be unipolar depressives with very high catecholamine metabolite levels (Schatzberg *et al*. 1982) whose norepinephrine system might be viewed as functionally inefficient requiring greater turnover to evoke transmission. In depression, high catecholamine and metabolite levels appear to be positively correlated with cortisol (Rosenbaum *et al*. 1983), whereas norepinephrine and cortisol levels are negatively correlated in healthy states (i.e., higher norepinephrine or metabolite levels are associated with lower cortisol levels). Whether this difference has to do with comorbid anxiety or the stages of the disorders is unclear, but it could explain a progression from anxiety to major depression where specific abnormalities in these two systems may not be consistently concordant between the disorders. This area would require further study.

Another approach has been to explore possible differences in functional imaging in depression and anxiety. Etkin's group has done elegant work here in exploring subjects' ability to implicitly regulate emotional conflict using functional magnetic resonance imaging (f-MRI). In many ways, implicit emotion regulation more closely approaches the innate ways

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we handle emotions because the challenge is free from explicit or conscious responses. Generalised anxiety disorder patients (with or without major depression) and major depressives all demonstrated deficits involving activation and connectivity of the amygdala and anterior cingulate (Etkin & Schatzberg, 2011). These data would fit a common 'internalising' biology as hypothesised by Kessler. However, only the generalised anxiety patients (comorbid with depression or not) failed to implicitly regulate emotional conflict. The major depression-only patients were able to overcome the deficit by also activating anterior lateral prefrontal cortical regions bilaterally. This activation correlated with successful implicit regulation. These data point to key compensatory abilities in depression that may explain why not all subjects with major depression experience comorbid anxiety. Thus, the relative ability to deal with negative emotions may underlie differences among the disorders.

An important issue in the relationship of anxiety and depression has to do with whether anxiety is occurring as a full anxiety disorder (i.e., categorical) or rather as a set of symptoms that fall short of a specific anxiety disorder diagnosis (dimensional model). Using f-MRI connectivity data, Oathes *et al*. (2015) from Etkin's group recently reported that neither a dimensional nor categorical model explained the findings on f-MRI. Rather, the relationships appear to involve both categorical and dimensional relationships. This state of affairs is in some ways indicated in the recently promulgated Diagnostic and Statistical Manual of Mental Disorders, 5th Editon (DSM5) where both categorical and dimensional approaches are recommended.

Much of the recent interest in the relationship of these disorders stems from large-scale clinical trials in major depression. In the Sequenced Treatment Alternatives to Relieve Depression study (STAR*D), anxiety as a dimension largely predicted poorer responses to monotherapy with the antidepressant citalopram in Phase I as well as various combinations and switches in later phases (Fava *et al*. 2008). In the more recent International Study to Predict Optimised Treatment in Depression (i-SPOT-D), anxiety as a dimension predicted poorer responses to escitalopram, sertraline or venlafaxine (Saveanu *et al*. 2015). Fully comorbid anxiety disorder/major depression was not a predictor of poorer rate of response than that seen in non-comorbid major depression (Arnow *et al*. in press). Thus, anxiety symptoms *per se* are the key predictors of poorer response to monotherapy in major depression and require alternative strategies.

A number of strategies have been reported and these involve using agents with 5HT-2 antagonist properties or sedating benzodiazepines. For example, clonazepam added to the Selective Serotonin Reuptake Inhibitor (SSRI) fluoxetine appears to produce greater response than the SSRI alone (Papakostas *et al*. 2010). Benefit has also been reported with the atypical antipsychotic quetiapine (Montgomery *et al*. 2014) and the antidepressant mirtazapine (Schatzberg *et al*. 2002) both of which have potent 5-HT2 antagonist effects and thus are calming and potentially sedating. These studies indicate the anxiolytic effects of the commonly used SSRI or serotonin noreprinephrine reuptake inhibitor (SNRI) antidepressants fail to provide sufficient relief of the anxiety symptoms to provide overall relief from the depression. Working backwards, these results would suggest that anxiety as a dimension in the context of depression needs to be addressed specifically but that the presence of anxiety may represent a different biological process than fully comorbid anxiety and depression.

Experience with treating anxious depressives may tell us something about the staging from anxiety to depression. Clinically, psychopharmacologists all the time treat and write about refractory depression – i.e., patients who fail to respond to one or more adequate trials of antidepressants. Less commonly do we write about refractory anxiety. One explanation is that refractory anxiety develops into major depression as we discussed above. Thus, we commonly do not see anxious patients who become refractory. They tend to respond when treated adequately and if not, they may develop major depression. This situation has been less well studied than the converse but could provide clues regarding the nature of the relationships.

The area of anxiety and depression has been largely enhanced by the work of Kessler and co-workers over the past two decades and the paper in this issue is entirely in keeping with their important contributions to the field.

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