The case for cothymia: mixed anxiety and depression as a single diagnosis

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Every psychiatrist and general practitioner diagnoses mixed anxiety and depression readily. The combination of typical depressive symptoms, such as low mood, lassitude and pessimism about the future, and anxious ones, such as tension, insomnia and irritability, is so common that about one in seven of the population is suffering from them at any one time in the UK (Meltzer *et al*, 1994). Yet the diagnosis is not allowed in either DSM–IV (American Psychiatric Association, 1994) or ICD–10 (World Health Organization, 1992) classifications except as what is curiously called a 'sub-syndromal' disorder, one that is allowed only if "neither the anxiety nor depressive symptoms reach the threshold for diagnosis of another psychiatric disorder" (World Health Organization, 1992). For such a common and important diagnosis this restriction might seem to be a little odd and may explain the acronym that is given to the condition: MADD – mixed anxiety and depressive disorder. Although the mixed diagnosis is not permitted except in this diluted form, general practitioners are invited to use it because ostensibly these disorders are very common in primary care and are seen most frequently in this setting. Oddly enough, mixed anxiety and depression is also formally permitted in the unduly neglected diagnostic grouping of adjustment disorders (Casey, 2001), where mixed anxiety and depression (code 43.22) is allowed as a category of diagnosis and also in combination with other symptoms. Why is the syndromal diagnosis of mixed anxiety and depression – a diagnosis that can be called cothymia, a term suggested some years ago (Tyrer, 1989) because it represents two moods of equal significance occurring together – not used in routine diagnostic practice? It is worth reviewing the evidence, both in favour of the status quo and the reasons for change.

REASONS FOR MAINTAINING THE SEPARATION OF ANXIETY AND DEPRESSION EXCEPT IN SUB-SYNDROMAL FORM

Anxiety and depression are different moods

There is no doubt that despite the frequency with which anxiety and depression coexist they are different mood states and common sense tells us that they should be classified in different parts of the psychiatric classification. Indeed, a great deal of work has established that their symptoms are generally separate. The evidence of this distinction has led to anxiety and depression being placed in different sections of both ICD–10 and DSM–IV, with depression in all its aspects being classified under mood disorders and anxiety being placed among neurotic and stress-related disorders. Once this decision was reached, however, it is difficult to justify joining two diagnoses across a major boundary of classification. No other example exists and even mixed anxiety and depression in its sub-syndromal form (in ICD–10) is uncomfortably classified together with the mood disorders. Allowing a syndromal equivalent into the classification would undermine the validity of the main classification system.

Comorbidity is an accepted part of classification in mental disorder

After DSM–III (American Psychiatric Association, 1980) had attempted to impose a hierarchical system for depressive and anxiety disorders but demonstrably failed to do this satisfactorily, many diagnoses were allowed together and the comorbidity industry was born. If major depressive disorder can coexist with social phobia, simple phobia, obsessive–compulsive disorder and post-traumatic stress disorder as comorbid conditions, why should not anxiety and depression do likewise? The fact that there is a high degree of association between them does not invalidate their descriptions as comorbid disorders. Similar degrees of association are found in, for example, social anxiety disorder and avoidant personality disorder (Herbert *et al*, 1992), but this does not mean that they should be diagnosed together.

Combined diagnoses would greatly increase the classification system and make it unworkable

This is an understandable argument. There are already nearly 500 diagnostic groups in ICD–10 (excluding the second digit after the point in the F codes) and many more in DSM–IV. Allowing common comorbid conditions to exist as separate diagnoses would more than double this number and, if multiple comorbidity also became similarly classified, the system would become so large and cumbersome that it would cease to be of any value and collapse under its own weight. Like the Victorian passion for classifying phobias by their situational components, there would be regular new additions to the classification as nosologists demonstrated more and more recondite associations.

REASONS FOR INCLUDING COTHYMIA (OR A SIMILAR TERM) AS A SYNDROMAL DIAGNOSIS OF MIXED ANXIETY AND DEPRESSION

Evidence from genetics

Although none of the common mental disorders is inherited by a single genetic mechanism, work on individual genes can help to determine the vulnerability to disorder and establish a set of risk factors, each of which is subject to a degree of genetic influence on the developmental psychopathology. Twin studies provide no evidence that the genes responsible for generalised anxiety disorder and major depressive disorder are different, and at least one study suggests that they are actually the same (Kendler *et al*, 1992). Other studies in which anxiety and depression are studied together show support for the notion of at least a partly inherited general neurotic syndrome (Tyrer, 1985; Andrews *et al*, 1990) in which personality features in the anxious/fearful group (cluster C in DSM) are important accompaniments.

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Evidence from neurobiology

There are several different experimental models of anxiety and depression and for years attempts have been made to find those that can be used independently to evaluate anti-anxiety and antidepressant drugs. All these models have failed demonstrably, possibly because there has been a failure to understand the interrelationship between cholinergic, dopaminergic and adrenergic systems in the brain and, in particular, for the role of ascending serotonergic pathways in opposing the effects of other symptoms (Robbins, 1997). Newer models that better fit the data posit a greater role for serotonin than other monoamines and show that an interactive model involving both depression and anxiety is the 'best fit' for the data. Thus, for example, the difference between the antidepressant and anxiolytic effects of compounds such as selective serotonin reuptake inhibitors (SSRIs) may depend only on whether they are acting on presynaptic (anxiolytic) or post-synaptic (antidepressant) 5-HT_{1A} receptors (de Vry, 1995). The persistent efforts to find different mechanisms for anxiety and depressive symptoms therefore are likely to fail and the evidence that pharmacological treatments for depression are just as appropriate for anxiety and depression is consistent with the neuropharmacological evidence.

Epidemiological studies

Mixed anxiety and depression is the most common mental disorder by far in epidemiological studies in which it has been possible to be measured (Meltzer *et al*, 1994). Unfortunately, because it is not in the DSM classification, international comparisons are not possible and this hinders interpretation. Evidence from the data of the mixed category and of anxiety and depression separately suggests that they possess the same factor structure and therefore it is not surprising that mixed conditions are more common than pure ones (Jacob *et al*, 1998). There are also social class differences that support the recording of anxiety and depressive conditions together (Lenzi *et al*, 1993).

Evidence from treatment studies

There has long been an interest in diagnosis acting as a selection process for treatment. This notion of treatment being dissected by diagnosis is seductive because one important way of demonstrating that conditions that appear to be similar are really different is if only a proportion responds to a specific treatment (e.g. the dissection of iron-deficiency anaemia from pernicious anaemia through the effect of iron supplements). The different diagnoses within the anxiety group have largely failed to be effective dissectors of treatment. However, both psychological therapies and drug treatments, such as benzodiazepines, tricyclic antidepressants, SSRIs and newer compounds (selective noradrenaline and serotonin reuptake inhibitors, e.g. venlafaxine), show some differences between anxiety and depressive disorders and it is important to know whether the linked anxiety–depressive disorders respond differently as well. The possible differences in the efficacy of these agents have been handicapped by the Procrustean diagnostic straightjackets forcing a primary diagnosis of anxiety or depression. Allowing the joint diagnosis would be likely to improve the scope of treatment studies and improve recommended guidelines.

Research studies in this area should test the effect of treatments in single anxiety and depressive disorders as well as in cothymia. This would prevent the counteracting tendency of what could be described as 'pharmacopsychiatric creep', in which the pharmaceutical industry greets every new single diagnosis with enthusiasm in the hope that a specific therapeutic agent can be tailored to fill 'a hole in the market'. Clinicians seldom get an opportunity to determine whether any agent found to be effective in a specific disorder (e.g. generalised anxiety disorder) is equally effective in others that are similar, because treatment studies are generally carried out only within the confines of specific diagnosis, not between them.

The use of psychological approaches, such as cognitive–behavioural therapy and other psychotherapies, also needs to be assessed in joint disorders, and may require modification in such conditions. Prospective studies of the treatment of cothymia would add much more than *post hoc* evaluations of comorbid anxiety and depression studies and also would help in determining whether there is real merit in combining these moods in a single diagnosis.

Evidence from outcome studies

The outcome of cothymia, or mixed anxiety–depression in which both anxiety and depression are present at a syndromal level, is significantly worse than the outcome of either diagnosis alone (Emmanuel *et al*, 1998). The difference between the outcome of the combined diagnosis and the individual diagnoses is much greater than the differences between anxiety and depressive conditions compared separately, which are generally small and not significant overall (Emmanuel *et al*, 1998; Seivewright *et al*, 1998), although more information is needed from less selected populations. The outcome studies to date support the value of the cothymia diagnosis to a greater extent than individual anxiety and depressive diagnoses.

CONCLUSIONS

On balance, the evidence in favour of a diagnosis of syndromal combined anxiety and depressive disorder as useful in clinical practice is good. Selection of treatment and prediction of prognosis are two possible practical advantages of such a diagnosis, but more needs to be done to determine its clinical importance in prospective intervention studies. Other labels for this condition are possible, but the suggested title of cothymia (Tyrer, 1989) implies that anxiety and depression are equal partners in its presentation. Greater awareness of these important mood states in combination would automatically follow the granting of at least provisional diagnostic status, and act as a spur to improving a part of psychiatric classification that remains in some disarray.

DECLARATION OF INTEREST

None.

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