Introduction

Depression and Anxiety: Implications for Nosology, Course, and Treatment

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International epidemiologic and clinical studies have shown that comorbid depression and anxiety is of major importance, resulting in more severe symptoms, impairment, subjective distress, and longitudinal course than either anxiety or depression alone. Threshold and subthreshold levels of anxiety ("A," "a") and depression ("D," "d") can be defined on the basis of duration, frequency, impairment, and number of symptoms. These letters can then be used to designate the various combinations of depression and anxiety, e.g., AD, aD. Current evidence demonstrates the importance of evaluating both threshold and subthreshold levels of depression and anxiety.

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The interaction between symptoms of depression and anxiety is a well-established clinical fact. As early as 1934, Sir Aubrey Lewis[1] proposed a continuum between symptoms of depression and anxiety, stressing that anxiety was a general, and probably integral, aspect of depression itself. Sir Martin Roth,[2] the leader of the Newcastle school in the United Kingdom, subsequently considered the relationship between syndromes of depression and anxiety as central for the classification of affective and/or mood disorders, and it has been suggested that most depressive patients are anxious and most patients with anxiety are depressed.[3,4] Nevertheless, a series of investigations in hospitalized patients conducted by the Newcastle group came to the conclusion that depression and anxiety disorders should be clearly separated.[5–8] This opinion has been supported by a number of similar studies in the United States,[9–12] as well as by outpatient studies.[4,13–16]

Today, the boundary between depression and anxiety disorders is internationally accepted and is an essential feature of DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition)[17] and ICD-10 (International Classification of Diseases–Tenth Revision),[18] the division having been validated by family studies as well as those investigating the course and outcome of these disorders.[19,20] Nevertheless, the question of a continuum has never been completely abandoned and a group of "in-between" patients manifesting symptoms of both anxiety and depression has been repeatedly observed and described. Moreover, cluster analysis suggests the existence of an anxiety-depressive syndrome[13,21–23] and, more recently, the dimensional approach has been reutilized by Goldberg and Huxley[24] in their model for neurosis with the application of latent traits analysis for anxiety and depression.

Epidemiologic studies devoted to the association of anxiety and depression are rare. However, in a review of the available evidence on the overlap between anxiety and depression, Angst and Dobler-Mikola[25] could not disprove the hypothesis of a continuum between depression and anxiety by discriminate analysis. General practice studies have repeatedly stressed the importance of an association between anxiety and depression.[26] The most recent findings on this topic come from a World Health Organization (WHO) study[27] conducted in 26,000 consecutive primary care patients, 5438 of whom were interviewed using the Composite International Diagnostic Interview (CIDI),[28] General Health Questionnaire (GHQ),[29] and other questionnaires. This study again confirmed the existence of inter-associations between anxiety and depression and reported a prevalence rate of around 1% to 2% for subthreshold mixed anxiety-depression in 14 countries worldwide; the mean point prevalence rate was 1.3%. A recent review of general practice studies by Stein et al.[30] corroborates these findings from the WHO and shows that some type of combined anxiety and depression occurs in approximately 13% of general practice patients.

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Table 1. A Matrix of Comorbidity Between Depression and Anxiety*

Anxiety (A)	Threshold Depression (D)	Subthreshold Depression (d)	No Diagnosis
A	AD	Ad	A
a	aD	ad	a
No Diagnosis	D	d	No diagnosis

*Abbreviations: A = threshold anxiety, e.g., panic disorder, generalized anxiety disorder; D = threshold depression, e.g., major depressive episodes, dysthymia; a = subthreshold anxiety; d = subthreshold depression.

Further research in this field is essential and should be based on well-defined subgroups taking into account both the diagnostic threshold and the subthreshold level; diagnostic thresholds can be investigated in terms of duration, frequency, number of symptoms, and level of impairment. Terminology based on upper- and lowercase letters was first introduced to characterize mania and hypomania as "M" and "m," respectively, and a similar strategy was applied to depression ("D" or "d").[31] This system was extended to cover anxiety disorders by Angst and Dobler-Mikola[25] and, more recently, by Stahl.[32] As shown in Table 1, subthreshold and threshold anxiety are denoted as "a" and "A," respectively, and subthreshold and threshold depression as "d" and "D," respectively; a combination of threshold levels of depression and anxiety is therefore denoted in uppercase letters as "DA."

The results of recent epidemiologic and clinical studies also suggest a significant degree of overlap between anxiety and depression at the subthreshold level (ad). Such subthreshold syndromes may be either a prodrome of major syndromes or a sequela of threshold episodes from which the patients are in varying levels of remission/recovery or for which treatment is not totally effective. For this reason, a longitudinal approach must be applied to diagnosis. Interestingly, a number of studies have shown that depression and/or anxiety at the subthreshold level is particularly common among the elderly and among patients who have concomitant medical illnesses.[33]

More methodological questions involve consideration of whether subthreshold disorders should be defined by DSM-IV or ICD-10 criteria and how such subthreshold syndromes should be validated. Furthermore, the question remains as to whether the diagnosis is more valid if made cross-sectionally, as suggested by the diagnostic manuals, or whether longitudinal factors should also be taken into account. A comparison with bipolar manic depressive disorders clearly shows the importance of this question.

Irrespective of whether these syndromes or symptoms occur at the threshold or subthreshold levels, patients who have comorbid anxiety and depression exhibit more severe symptoms, impairment, subjective distress, and longitudinal course than those who have pure symptoms of either anxiety or depression alone. For example, in our community study mixed anxiety-depression appears to be clinically more significant than either subthreshold anxiety or depression alone.[34]

The following papers will present new evidence on the phenomenology, epidemiology, and course of the anxiety and depression spectrum. The findings will demonstrate the importance of evaluating both threshold and subthreshold levels of anxiety and depression in clinical and community settings. They will also show that patients who have mixed or comorbid anxiety and depression manifest marked distress, impairment, and persistence of symptoms that are of sufficient magnitude to warrant treatment. In this context, the recent development of serotonin selective reuptake inhibitors is extremely important as this class of drugs clearly has a broad therapeutic action, not only against depression, but also against anxiety states.

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