Mixed Anxiety and Depression: From Theory to Practice

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The 10th International Classification of Disease (ICD-10) introduced the concept of mixed anxiety-depression to define patients presenting both anxiety and depressive symptoms of limited number and/or intensity, not sufficiently severe to fulfill criteria for a specific diagnosis of depressive or anxiety disorder. Epidemiologic surveys have shown that these patients may display significant levels of functional impairment, have unexplained somatic symptoms and a high use of nonpsychiatric medical care, have long-lasting symptoms, and are at risk for more severe psychiatric disorders. A DSM-IV field trial concluded that patients with affective symptoms not meeting thresholds for DSM-III-R disorders were at least as common as patients with anxiety or mood disorders, and that their symptoms were associated with significant distress or impairment. Although some of these patients present residual symptoms from previous psychiatric episodes and may request treatment specific to these conditions, it is not known if those without a psychiatric history could benefit from pharmacologic or psychological treatments usually used in mild outpatient cases.

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Over the last decade, epidemiologic surveys have shown that comorbidity between anxiety and depressive diagnoses is common among psychiatric patients[1] and the clinical and theoretical issues related to this overlapping symptomatology have recently been extensively reviewed.[2–4] However, Hiller et al.[5] demonstrated that the overlap rate for anxiety and depression in psychiatric outpatients was almost twice as high when symptoms were considered rather than DSM-III-R diagnoses (52% vs. 29%), and that intermediary rates were obtained when syndromes were taken into consideration. In a recent review, Katon and Roy-Byrne[2] also stated that, in contrast to major depressive and anxiety disorders which have distinct cross-sectional symptomatology and which show similarities only when they are examined longitudinally, experience in primary care settings suggests that more minor forms of anxiety and depression may show greater overlap in symptom profiles and be more difficult to distinguish cross-sectionally. In the current review, the diagnostic label of mixed anxiety-depression will be reserved for these minor forms of mixed symptomatology that do not fulfill the criteria for any of the specific psychiatric disorders defined in the DSM classification. Clinical and epidemiologic data relating to these subsyndromal conditions will be reviewed, and our clinical experience obtained during recruitment of patients with mixed anxiety-depression into a clinical trial will be discussed. Despite the absence of specific studies related to the treatment of mixed anxiety-depression, suggestions concerning the practical management of patients suffering from these symptoms will also be considered in an attempt to define which of the available treatments may be most suitable for these subsyndromal cases.

FROM ICD-10 TO DSM-IV

The 10th International Classification of Disease (ICD-10) introduced the concept of mixed anxiety-depression in order to provide a clinical definition for patients who present with both anxiety and depressive symptoms of only limited number and/or intensity, i.e., not sufficiently severe to fulfill criteria for a specific diagnosis of depressive or anxiety disorder. Although clear-cut diagnostic criteria do not yet exist for mixed anxiety-depression in this classification, the ICD-10 manual for clinical descriptions and diagnostic guidelines[6] defines the syndrome as a mixture of anxiety and depressive symptoms of equal importance, associated with at least some autonomic symptoms (e.g., tremor, palpitations, stomach churning), and mainly seen in primary care settings or in the general population. Several studies have since demonstrated that such cases

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are common and may suffer from at least limited degrees of impairment. For example, in a study involving 1242 patients seen in a primary care clinic, Von Korff et al.[7] found that over 50% had anxiety or depressive disorders confirmed by either the primary care provider, the General Health Questionnaire, or the Diagnostic Interview Schedule. However, only 8% attained the threshold necessary to fulfill the criteria for one or more of five DSM-III diagnoses (major depression, panic disorder, dysthymia, generalized anxiety disorder, or obsessive-compulsive disorder), thus demonstrating the requirement for a specific diagnostic category in primary care patients presenting with subthreshold levels of symptomatology. In another study involving 1160 patients from a rural primary care practice, Barrett et al.[8] also showed that, when assessed with a structured interview, many patients with psychiatric symptoms did not easily fit into the official psychiatric nosology despite clear symptom-related impairment in occupational or social functioning. Some of these patients had mixed anxiety-depression, while others had masked/suspected depression characterized by evidence of depression on interview coupled with denial of depressed mood or a symptom profile inconsistent with any diagnostic category.

Katon and Roy-Byrne[2] have also observed that general population subjects with mixed anxious-depressive symptoms not severe enough to meet psychiatric diagnosis may nevertheless have significant impairments in their social and vocational activities. In addition, they tend to have many medically unexplained somatic symptoms and therefore use more nonpsychiatric medical care facilities. These same subjects may also be at risk for more severe anxious and depressive disorders and thus cycle in and out of "caseness" depending on their current life circumstances.[2] Indeed, several studies now clearly suggest that many patients with mixed anxiety-depression are not simply subjects overreacting to various stressful life-events who could therefore fulfill diagnostic criteria for adjustment disorders, but represent patients with chronic symptoms[9,10] who have higher rates of lifetime psychiatric disorders and prior psychiatric treatment[11,12] and a higher risk of developing major mood and/or anxiety disorders over time.[7,9,13–16]

DSM-IV FIELD TRIAL

In order to identify criteria that could be used to categorize mixed anxiety-depression, and to investigate the reliability and validity of these criteria, the American Psychiatric Association organized a field trial involving five primary care and two mental health clinics in the United States.[17] Six hundred sixty-six patients who attained a given cutoff score on the subjective distress scale of the General Health Questionnaire were recruited into the study. Evaluation involved a semistructured diagnostic questionnaire using DSM-III-R criteria: the Anxiety Disorders Interview Schedule Revised (ADIS-R). Patients with psychiatric symptoms secondary to medical problems, current medication, or substance abuse were excluded. The results revealed that patients with symptoms not meeting criteria for DSM-III-R Axis I disorders were at least as common as those with specific psychiatric disorders, and that their symptoms were associated with significant distress or impairment.[18] Moreover, 14% of these patients with subsyndromal symptomatology had previously fulfilled diagnostic criteria for major depressive disorder, and 84% reported that their problems had begun more than 6 months prior to the assessment. As previously discussed, some of these patients therefore appeared to have long-lasting symptoms possibly associated with residual symptomatology secondary to previous psychiatric problems, and not simply related to a diagnosis of adjustment disorder. In a subsequent analysis involving only the patients recruited in primary care settings, Roy-Byrne et al.[19] confirmed that 95% of these subsyndromal patients had a lifetime history of psychiatric disorders and 40% a history of psychiatric treatment; both these incidences are similar to those found in patients meeting criteria for major mood or anxiety disorders.

A principal component analysis of items on the scales (Hamilton Rating Scales for Depression and Anxiety) used to rate patients in this field trial was conducted in order to determine whether a consistent syndrome existed in patients with mixed anxiety and depressive symptoms who did not fulfill criteria for Axis I disorders. This analysis led to the identification of four main symptomatic criteria (anxiety, physiologic arousal, depression, and negative affect); patients were characterized by a higher mean score on the negative affect scale than on the anxiety, depression, and physiologic arousal scales. Moreover, subsyndromal patients had less anxiety than patients with generalized anxiety disorders, less depression than patients with major depression, and less physiologic arousal than panic disorder patients. It is noteworthy that the 10 symptoms composing the negative affect dimension (difficulty concentrating or mind going blank; sleep disturbance; fatigue or low energy; irritability; worry; easily moved to tears; hypervigilance; anticipating the worst; hopelessness; low self-esteem or worthlessness) are very similar to those of the general distress dimension. This dimension is common to both anxious and depressed syndromes and is thought to be a manifestation of chronic personality traits related to negative affectivity and/or neuroticism.[20]

The negative affect symptom list was then used to define operational criteria for the mixed anxiety-depression category in DSM-IV; a cutoff score of four or more symptoms was considered necessary to reliably distinguish these patients from patients without mental disorders. By using these criteria, and excluding all patients with a history of Axis I disorder, 54% of the subsyndromal patients received a final diagnosis of mixed anxiety-depression. However, the symptomatic profile of these patients did not

differ from that of subsyndromal patients with a previous history of psychiatric disorders.[18]

Insufficient information was available on mixed anxiety-depression to warrant its inclusion as an official diagnosis under Axis I disorders in DSM-IV; it is therefore currently included among the group of disorders requiring further study. In addition to displaying persistent or recurrent dysphoric mood for at least 1 month, patients must have experienced (at the same time) at least 4 of the 10 negative affect symptoms previously mentioned and must suffer from significant distress or impairment in social, occupational, or other important areas of functioning. A diagnosis of mixed anxiety-depression is excluded in any of the following conditions:

1. symptoms due to direct physiologic effects of a substance or general medical condition;
2. life-history of major depressive, dysthymic, panic, or generalized anxiety disorders;
3. presence of an anxiety or mood disorder, even if in partial remission.[21]

THE EPIDEMIOLOGY OF MIXED ANXIETY-DEPRESSION

Epidemiologic studies carried out in the community have shown that subsyndromal mixed anxiety-depression occurs in 0.8% to 2.5% in the general population.[22] In the Munich follow-up study, the prevalence of mixed anxiety-depression (0.8%) was less than that of subsyndromal depression (2.4%) or anxiety (21.9%).[22] In a U.S. study using the same DSM-III-R criteria, the 1-year prevalence of mixed subsyndromal anxiety and depressive symptoms was found to be 2.5%, while that of subsyndromal symptomatic depression was 7.7%.[23] These results are similar to findings from previous studies using diagnostic criteria other than DSM-III in which the prevalence rates of subsyndromal mixed anxiety-depression were also reported to be between 2% and 2.5%. Prospective longitudinal data also gathered in these studies suggested that mixed anxiety-depression patients had an increased risk of developing full syndromal anxiety or depressive disorders compared with the general population.[9,13] Several studies have demonstrated higher rates of mixed anxiety-depression symptomatology (5%–15%), but similar risk factors, in the general practice setting.[7,8,19] These findings have been confirmed in other studies[14,16] and by the results of a recent survey in which general practice patients experiencing limited depressive symptoms were also more likely to develop depressive syndromes within a year, the risk of depression increasing with the number of depressive symptoms reported.[15] In a study of medical and psychiatric outpatients, Sherbourne et al.[24] also reported that the percentage of patients with subthreshold depression who had a family history of depression (41%) was nearly as high as that of patients with depressive disorder; the two groups had similar levels of medical and psychiatric morbidity, suggesting that subthreshold depression may be a variant of affective disorder and thus the expression of prodromal or residual symptoms of this condition. It is unclear, however, if similar conclusions could be drawn from studies of patients with subsyndromal anxiety.

The DSM-IV field trial indicated that the incidence of subsyndromal symptomatology was even higher in psychiatric outpatient clinics (12%) than in primary care (6.5%), although a number of patients reported a previous history of psychiatric disorder.[18] In our experience, such cases may represent 10% to 15% of patients presented at an anxiety clinic and raise difficult diagnostic and therapeutic issues owing to the chronicity of their condition.[1]

HOW COMMON IS MIXED ANXIETY-DEPRESSION IN THE PSYCHIATRIC SETTING?

Our university psychiatric outpatient clinic was recently required to recruit patients with DSM-IV mixed anxiety-depression diagnosis for inclusion in a clinical trial. The majority of the many patients we identified met the full set of diagnostic criteria with the exception of E1 (i.e., never met criteria for major depressive, dysthymic, panic, or generalized anxiety disorders); we therefore advertized in a number of newspapers in order to find patients fulfilling the entire set of inclusion criteria for mixed anxiety-depression. However, after telephone screening, only 16 patients were selected for clinical interview and assessment with a semistructured diagnostic questionnaire (ADIS-4), which was adapted to include DSM-IV criteria for mixed anxiety-depression. Among these patients, only 4 fulfilled the criteria for mixed anxiety-depression; 1 was excluded because he did not meet any specific diagnosis, 2 did not complete the entire evaluation, and 9 were excluded because they met other diagnostic criteria (3 dysthymic disorder, 3 major depressive disorder, 1 panic disorder with agoraphobia, and 1 generalized anxiety disorder). The 4 patients fulfilling DSM-IV criteria for mixed anxiety-depression all reported chronic symptoms lasting for at least a year; these symptoms did not impair their professional life but considerably diminished their quality of life. They all had a family history of psychiatric disorders belonging to the "neurotic" spectrum (anxiety, depression, alcoholism) and described themselves as having been more anxious and shy than the average person for most of their lives. None of them, however, fulfilled criteria for any specific personality disorder. The following case reports describe two of these patients diagnosed with mixed anxiety-depression.

Case Reports

Case 1. Mr. A is a 24-year-old single man who works as a carpenter. He is the youngest of seven children; one of his brothers committed suicide 10 years ago and his father

attempted suicide following this event. He has a lifelong history of gastrointestinal symptoms secondary to stress, but has never sought any medical help to relieve them. For the past year, he has been complaining of various physical symptoms (stomach pain, difficulty swallowing, palpitations, chest tightening, and muscular tension) and occasional feelings of vague insecurity; because of this, he sometimes feels tired and discouraged and has difficulty concentrating or falling asleep, although not to the point that it affects his abilities at work. The patient has never worried about daily life events or activities and has never experienced catastrophic or long-lasting depressive symptoms. He does not describe any life event that could explain his symptoms over the last year and had not talked to any health-professional about his problems before reading the newspaper advertisement recruiting patients for the clinical trial. During the interview, the patient appeared quite shy and had difficulties expressing his emotions, but did not display any symptoms of specific anxiety or depressive disorders.

Case 2. Mr. B is a 32-year-old married man who works as a computer assistant at the University. He is the youngest of five children and describes his mother as very anxious; in addition, one of his aunts has been treated for depression. He describes himself as having always been shy and uncomfortable in crowds and social gatherings, but never to the point of panicking or avoiding these situations. He is also a perfectionist and hard-worker, but does not fulfill the criteria for obsessive-compulsive personality. Eight years ago he consulted his general practitioner because of subacute chest pain and oppression that troubled him for several weeks. For the last 2 years, during which he has been employed at the university, he has complained of frequently being easily stressed, irritable, anxious, and tired, and of having occasional difficulties falling asleep. These problems have been accompanied by a lack of motivation and difficulty concentrating for periods of several days, although he has never felt depressed and/or suicidal. These periods are sometimes, but not always, related to increased pressure at work and are usually relieved when he takes lorazepam 1 mg at bedtime for a few days. The patient has never stopped work because of his problems, but says that his quality of life has been impaired most days for several months because of his symptoms.

Although our limited experience of patients with mixed anxiety-depression does not allow us to draw any definite conclusion regarding the significance of this condition in psychiatric outpatient settings, our observations suggest that the majority of these patients have fulfilled DSM criteria for anxiety and/or depressive disorders at some time in the past. However, among the few patients without a history of psychiatric disorders, mixed anxiety-depression symptoms often followed a chronic course and developed against a background of personality features belonging to the "neurotic spectrum," but not fulfilling criteria for any specific personality disorder. Combined with a family history of psychiatric disorders, such a clinical picture would suggest that these patients may be at risk of developing more severe psychiatric problems and may therefore require follow-up evaluations in order to prevent the development of specific anxiety or depressive disorders. Furthermore, the chronic nature of their symptoms may make differential diagnosis from other conditions where anxiety and/or depressive symptoms also display a chronic evolution (e.g., generalized anxiety disorder, dysthymic disorder, or personality disorders) especially difficult. Only future longitudinal studies will confirm whether, with time, these patients will develop new symptoms and so fulfill DSM criteria or whether they will continue to suffer from stable limited symptoms equivalent to subsyndromal personality disorders.

TREATING PATIENTS WITH MIXED ANXIETY-DEPRESSION

While the recommended treatment for mixed anxiety-depression patients with a previous psychiatric history is similar to that for chronic or residual cases of anxiety or depressive disorders, the optimal treatment for patients with mixed anxiety-depression but without such a psychiatric history remains to be clarified. To date, only a limited number of studies have investigated the treatment of subsyndromal mixed anxiety-depression and, to our knowledge, no published study has employed the DSM-IV diagnostic criteria for mixed anxiety-depression to assess the efficacy of various therapeutic approaches in this condition. However, evidence from general practice studies of patients with milder forms of anxiety and depressive disorders may be useful in determining which of the various therapeutic approaches (anxiolytics, psychotherapy, antidepressants) is most suitable for the treatment of mixed anxiety-depression.

Anxiolytic Drugs

If further studies confirm the chronic nature of mixed anxiety-depression symptoms in the majority of patients, long-term management with benzodiazepines should probably be avoided because of the potential for rebound and/or withdrawal effects. In addition, clinical trials in general practice have shown that the therapeutic effects of the benzodiazepines may be difficult to distinguish from those of placebo in patients with mild-to-moderate generalized anxiety.[25] For example, in a multicenter, international trial organized by the World Health Organization[26] to compare benzodiazepine treatment with counseling in 617 general practice patients, those patients who initially reported physical or minor emotional complaints responded better to counseling than to diazepam, even if treatment

was limited to only 3 hours of counseling. There were no significant interactions between drug treatment and counseling. Similar results were obtained in a study carried out in two group practices in the United Kingdom[27] in which 90 patients with new episodes of minor affective disorder were treated either with anxiolytic medications or brief nonspecialized counseling (listening, explanation, advice, and reassurance). Both groups showed a similar level of improvement after a follow-up of 7 months. Moreover, there was no evidence that withholding medication increased consumption of other substances, nor that counseling made increased demands on the general practitioner's time.

The recent development of cognitive-behavioral techniques (CBT) has lent further support to the suggestion that nonpharmacologic management of patients with anxiety and/or depressive symptoms can result in improvements similar or superior to those obtained with benzodiazepines. In particular, techniques such as anxiety management, cognitive exposure, and cognitive restructuring (recognizing, challenging, and formulating alternatives to anxious thoughts), as well as applied relaxation and electromylogram biofeedback, have all been used successfully in various combinations in patients with generalized anxiety disorders. The benefits of these techniques compared with analytic psychotherapy,[28] nondirective therapy,[29] and supportive therapy[30] have been clearly demonstrated in well-controlled clinical studies. In a recent review of psychological treatments, Durham and Allan[31] concluded that, on average, such treatments resulted in a 50% reduction in the severity of somatic symptoms and a 25% reduction in measures of trait-anxiety, with approximately 50% of patients attaining normal functioning at the end of the therapy. Moreover, in most studies, the effects of CBT do not appear to be dependent on initial levels of depression (if mild-to-moderate), and they persist even after treatment has been terminated (6–12 month follow-up). However, several questions concerning the efficacy of CBT remain unanswered[31]:

1. The effective components of these cognitive-behavioral therapies and their diagnostic specificity in the treatment of anxiety disorders remain unknown;
2. It is unclear which of the multiple features associated with anxiety are specifically affected by these treatments (hypervigilance, tension, physical symptoms, cognitive bias toward threatening stimuli or interpretations, elevated evidence requirement, intolerance to uncertainty, poor problem solving, confidence, and perception of lack of personal control etc.);
3. Their respective benefits compared with pharmacologic treatments have not so far been studied on a large scale.

A limited number of studies comparing CBT with benzodiazepines have been carried out in primary care patients presenting with mild-to-moderate levels of symptomatology. In one study comparing the effects of a cognitive-behavioral information course with a control situation in minor depressives, the CBT course was successful in reducing both depressive symptomatology and somatization, although only in patients with mild-to-moderate levels of depression.[32] Two other studies have compared the effects of CBT with benzodiazepine therapy in general practice patients presenting with generalized anxiety symptoms. However, the drugs were only given for a limited period of time and thus allowed only short-term comparisons between the two types of treatment. Although one study using fixed doses of diazepam (5 mg t.i.d.) did not demonstrate any superiority of drug treatment over placebo in patients receiving CBT,[33] the other showed that the most immediate and greatest improvements occurred in the group receiving drug treatment.[34] However, these improvements diminished as the trial progressed, and a progressive withdrawal of the drug after 4 to 6 weeks resulted in superiority of CBT after 6 to 8 weeks. Clearly, comparisons using nonbenzodiazepine drugs that can be used on a long-term basis in generalized anxiety disorders (e.g., buspirone or antidepressants) are required in order to assess the efficacy of drug treatments in comparison to CBT. The only data currently available for long-term follow-up evaluations (6–12 months) pertain exclusively to nonpharmacologic approaches.[31] Furthermore, future studies should assess whether the outcome of CBT is dependent on initial levels of anxiety in order that conclusions may be drawn about its potential application in patients with mixed anxiety-depression. Azapirones (e.g., buspirone) should also be studied for the treatment of mixed anxiety-depression as their efficacy in both anxiety and depressive disorders has now been widely demonstrated in outpatient populations.[35,36] Although buspirone has been used successfully in patients with generalized anxiety and coexisting depressive symptoms,[37] it is not currently clear whether its efficacy over placebo would be maintained in patients with milder conditions or subsyndromal symptoms. However, as buspirone appears to be superior to benzodiazepines in the treatment of the psychic component of anxiety symptoms (the reverse is true for the somatic component of these symptoms), and as psychic symptoms of general distress appear to characterize mixed anxiety-depression better than somatic symptomatology, buspirone could be a drug of choice in the treatment of patients with mixed anxiety-depression. Moreover, in contrast to the benzodiazepines, buspirone is not associated with rebound and/or withdrawal effects.

Antidepressant Drugs

Clinical trials comparing tricyclic antidepressants and placebo in general practice patients fulfilling Research Diagnostic Criteria for major and minor depression have clearly shown that active treatment is beneficial in patients

with major depression but not in those with minor depression; the only patients who showed a statistically significant improvement compared with placebo were those having Hamilton Rating Scale for Depression scores above 12 at the start of the study.[38] However, several studies have also shown antidepressants to be superior to benzodiazepines in patients with mixed anxiety and depression and in patients who have generalized anxiety disorders without depressive features, thus suggesting a possible role in patients with mixed anxiety-depression.

In a study conducted by Johnstone et al.[39] in 240 neurotic outpatients with both anxiety and nonendogenous depressive features, amitriptyline (150 mg/day) was superior to both diazepam and placebo after 4 weeks of treatment. When the same patients were retrospectively separated in terms of those with primary anxiety or primary depression, diazepam was still not superior to amitriptyline even among those suffering from primary anxiety. The same results were reported by Kahn et al.[40] in an 8-week, double-blind study of 242 outpatients with primary anxiety (as diagnosed by two independent psychiatrists); panic and phobic cases were excluded. Imipramine (135 mg/day) was found to be superior to both chlordiazepoxide and placebo; the reduction in anxiety seen with imipramine was independent of its effects on depression or panic attacks. Similarly, imipramine was also the most effective treatment among the 387 outpatients who were diagnosed as primarily depressed, independent of their levels of anxiety.[41] In a 6-week double-blind study of 60 patients who had DSM-III generalized anxiety disorder of over 6 months duration, Hoehn-Saric et al.[42] reported a superiority of imipramine (91 mg/day) over alprazolam (2.2 mg/day) in the treatment of psychic symptoms, while the reverse was true when somatic symptoms were considered. More specifically, the results suggested that patients who are chronic worriers, who tend to fear interpersonal relationships, and who have strong tendencies toward rumination do better when taking tricyclic antidepressants than when taking benzodiazepines.

The therapeutic effects of antidepressants on anxiety symptoms were recently confirmed by Rickels et al.,[43] who compared the efficacy of imipramine, trazodone, diazepam, and placebo in 230 patients with DSM-III generalized anxiety disorder in whom major depression and panic had been excluded. Although patients treated with diazepam (26 mg/day) showed the most improvement during the first 2 weeks, trazodone (255 mg/day) achieved comparable, and imipramine (143 mg/day) better, anxiolytic efficacy from the third week onward when compared with diazepam. As suggested in previous studies, psychic symptoms of tension, apprehension, and worry were more responsive to antidepressants than to the benzodiazepine. The therapeutic efficacy of imipramine was not related to pretreatment levels of depression, although in patients treated with diazepam, the presence of depressive symptoms was associated with a poor therapeutic response. Whether or not these results are relevant to the treatment of mixed anxiety-depression it remains, however, a matter of speculation for the following reasons:

1. Although encouraging, the findings obtained with tricyclic antidepressants cannot be generalized to the management of patients with mixed anxiety-depression symptoms;
2. Studies are required to assess the efficacy of the newer antidepressants (e.g., serotonin selective reuptake inhibitors and reversible monoamine oxidase inhibitors) in nondepressed generalized anxiety patients or in the milder or subsyndromal forms of this condition;
3. The efficacy of antidepressants compared with nonpharmacologic approaches remains to be evaluated.

THEORETICAL IMPLICATIONS

The fact that at least some antidepressants appear to relieve anxiety symptoms suggests that both anxiety and depressive disorders may share some common etiopathological mechanisms.[1] Evidence from populations with generalized anxiety disorders, abnormal dexamethasone suppression tests, and blunted growth hormone response to clonidine suggest some degree of overlap in neurobiological measures.[43] Furthermore, several family and twin studies also indicate that generalized anxiety disorder and depression may share a common genetic susceptibility. For example, in a cohort of 30,344 twins in Sweden, Allgulander et al.[44] demonstrated that the 280 who became neurotic within the subsequent 10 years differed substantially in their reported health profile from the control population. However, when subclassified into anxiety, depressive, and other neuroses, they were indistinguishable from each other regarding self-perceived health and personality traits. Similarly, in a sample of 3798 pairs of unselected twins, Kendler et al.[45,46] showed that while traditional factor analysis of self-reported symptoms indicates that depression and anxiety tend to form separate symptom clusters, multivariate genetic analysis indicates that genes act largely in a nonspecific way to influence the overall level of psychiatric symptomatology. The same study also suggested that certain features in the environment are largely responsible for the separation between anxiety and depression symptom clusters. Although different from those reported by Torgersen,[47] these results are confirmed by a large Australian study, cited by Tyrer,[48] that also supports the hypothesis of a common diathesis to "neurotic" anxiety and depression that can be manifested in any disorder listed in the DSM-III-R classification. According to Tyrer, the same conclusions can be drawn by examining data from family studies showing that, although only a small proportion of relatives has the same specific disorders as the index cases, these individuals

tend to have a higher rate of all "neurotic" diseases in general.[48]

It is also interesting to note the similarity between the negative affect factor found in subsyndromal patients, as well as in those patients with anxiety and depressive disorders, in the DSM-IV field trial, and in the general distress component described by psychological studies of the general population. In an extensive review of psychometric and other evidence pertinent to mixed anxiety-depression, Clark and Watson[20] proposed a tripartite model for these symptoms. They suggested the presence of a common neurotic factor, characterized by feelings of inferiority and rejection, demoralization, self-consciousness, and general affective distress, which is normally shared by anxious and depressive patients. However, these syndromes are distinguished by specific features, namely physiologic hyperarousal and panic attacks for anxiety, and anhedonia and absence of positive affect for depression. Numerous studies have demonstrated that the general distress factor, also present in many patients without specific components, is a stable personality trait that also shows a significant heritability.[20] Although the implications of this tripartite model of anxiety and depression remain a matter of speculation, it is noteworthy that the existence of a pathogenic factor shared by a substantial number of patients with anxiety and/or depressive diagnoses, as well as by patients with subsyndromal levels of both types of symptoms, could explain the common therapeutic value of various types of intervention.

Finally, Tyrer has hypothesized, both from clinical experience and research studies, that a large subgroup of patients with anxiety and depression, including those with subsyndromal mixed anxiety-depression, could fulfill criteria for a diagnosis of "general neurotic syndrome."[48] Such a diagnosis is confirmed by showing that primary anxiety and depressive symptoms:

1. Show changes of primacy at different times during the patient's life;
2. Are manifest in the absence of major life events;
3. Occur against a background of personality disturbance in which dependent and/or inhibited qualities are prominent;
4. Are likely to be associated with a positive family history of a similar condition.

In this syndrome, anxiety and depression are manifested in the form of panic attacks and/or persistent anxiety and tension sufficient to cause distress and impaired social and occupational performance, even if insufficient to fulfill criteria for a given diagnosis.[47] Furthermore, some of these patients may develop full anxiety or depressive disorders on a longitudinal basis and even change diagnosis over time, despite showing identical responses to various types of treatment. In a subsequent study involving 210 outpatients with mixed DSM-III diagnoses of generalized anxiety, dysthymic disorder, and panic disorder, Tyrer et al.[49] found no marked difference between the effects of diazepam, dothiepin, cognitive behavior therapy, and self-help instructions when diagnostic groups were considered separately (patients who met diagnostic criteria for moderate or severe depression or agoraphobia were excluded from the study). The same study also showed that diazepam was less effective than the other treatments, and thus could not be recommended for this group of disorders. In relation to these results, Tyrer et al.[49] suggested that tricyclic antidepressants may have a general "patholytic" effect in neurosis and therefore improve the symptoms of anxiety, depression, and panic independently of their respective intensity and syndromal profile. Confirmation that antidepressants are effective in patients who have mixed anxiety-depression, with or without a history of anxiety or depressive disorders, is critical for corroboration of this interesting hypothesis.

PRACTICAL MANAGEMENT OF PATIENTS WITH MIXED ANXIETY-DEPRESSION

Although many issues concerning the understanding of mixed anxiety-depression and its treatment remain to be clarified, the evidence reviewed to date leads us to propose the following guidelines for the clinical management of these patients:

1. Investigate previous psychiatric history and, if positive, consider treatment of chronic or residual symptoms. Such cases should be diagnosed as having anxiety or depressive disorders not otherwise specified according to DSM criteria.
2. If psychiatric history is negative, consider diagnostic alternatives; e.g., adjustment disorders if symptoms are recent or other chronic conditions (generalized anxiety, dysthymia, personality disorders) if they have a duration of more than 6 months without a continuing stressor. If these conditions are not present, the patient may fulfill DSM-IV criteria for mixed anxiety-depression.
3. If mixed anxiety-depression criteria are met, the first goal should be to develop a therapeutic relationship in order that the patient can be followed-up at regular intervals. A substantial number of patients with mixed anxiety-depression may have chronic symptoms and thus be at risk of developing anxiety and depressive disorders in the long term.
4. Assess previous therapies and their results; nonpharmacologic approaches such as counseling or cognitive-behavioral techniques should be employed initially.
5. If unsuccessful or functional impairment persists, treat with psychotropic agents. Imipramine or buspirone are the only drugs so far to have demonstrated efficacy in both generalized anxiety and depressive disorders.

Drug names: alprazolam (Xanax), amitriptyline (Elavil and others), buspirone (BuSpar), chlordiazepoxide (Librium and others), clonidine (Catapres) diazepam (Valium and others), imipramine (Tofranil and others), lorazepam (Ativan and others), trazodone (Desyrel and others).

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