

REVIEW ARTICLE

Comorbid anxiety and depression: illumination of a controversy

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Abstract

Depression and anxiety frequently coexist in the same individual, either concurrently or at different times, and numerous studies show that the presence of an anxiety disorder is the single strongest risk factor for development of depression. When the two coexist simultaneously, either as diagnosed disorders or subsyndromal states, they may be viewed as mixed anxiety–depression or as comorbid syndromes, i.e. separate disorders occurring concurrently. Controversy continues over the nature of the relationship between depression and anxiety, some believing they are distinct, separate entities while others – now the majority – view them as overlapping syndromes that present at different points on a phenomenological and/or chronological continuum, and share a common neurobiology, the degree of overlap depending on whether each is described at the level of symptoms, syndrome or diagnosis. Community data likely underestimate true prevalence, since affected individuals frequently present in primary care with somatic, rather than psychological, complaints. Irrespective of the nature of the relationship, patients with both disorders experience significant vocational and interpersonal impairment, and more frequent recurrence, with greater likelihood of suicide, than individuals with single disorders. Various classes of antidepressant drugs offer symptom relief for these patients, the most selective of the SRIs holding the greatest promise for sustained clinical improvement. Yet, the crucial parameter of successful pharmacotherapy seems to be the length of treatment, ensuring enhancement of the compromised neuroprotective and neuroplastic mechanisms. Further clarification of the relationship is a prerequisite for offering effective treatment to the many patients who experience lifetime depression and anxiety.

Key Words: *Depression, anxiety, comorbidity, diagnosis, etiology, treatment, antidepressants, neuroplasticity*

The relationship between anxiety and depression

A close relationship between anxiety and depression has been acknowledged since ancient times (“patients with fear . . . of long standing are subject to melancholia” Hippocrates, *Epidemics III*). As early as 1934, Sir Aubrey Lewis proposed a continuum between symptoms of anxiety and depression, stressing that anxiety was probably an integral aspect of depression [1], while Slater and Roth stated that the distinction between anxiety and depression “is nevertheless a valid one, although the disorders overlap in their clinical features” [2].

One school of contemporary thought defines mixed anxiety–depression states as having a stable core of subsyndromal symptoms that do not reach the threshold for the diagnosis of generalized anxiety disorder (GAD) or depression, but which, under stress, will decompensate to an overt anxiety disorder or depression [3,4]. This concept shares

similarities with Peter Tyrer’s theory of a broad affective diathesis, which he named a “general neurotic syndrome” [5]. According to that hypothesis, at least some patients present with co-existent primary anxiety and depressive symptoms that: (1) are more or less prominent at different times of 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 traits are prominent; and (4) are likely to be associated with a positive family history of a similar condition. Such patients may change diagnoses frequently over time, while showing identical responses to various types of treatment. In the latest development of his theory, Tyrer states that the mixed anxiety–depression syndrome, which he terms “cothymia”, is the most common (and, in fact, the core) affective disorder [6,7]. This view stands sharply in contrast to the findings of the DSM-IV field study, according to which mixed

anxiety–depression can be differentiated phenomenologically from other mood and anxiety conditions [8].

Other investigators view mixed anxiety–depression as being defined by recurrent depression, with a tendency to experience residual anxiety symptoms between full-blown episodes [9]. Such symptoms may be indicators of a risk for relapse [10] and, in this manner, such individuals may cycle in and out of medical care, depending on life circumstances [11].

At a theoretical level, the common co-occurrence of anxiety and depression may be explained in several ways (Table I) [12–24], although none of the proposed models capture in entirety their complex relationship. Causal relationships may exist in some cases, while in others a common [25,26] or multifactorial [17] aetiology likely has a part to play.

Two major conceptual pathways can be applied to address the question of whether anxiety and depression represent distinct clinical syndromes or different aspects of a continuum [27]:

Hierarchical diagnoses. this classical approach assumes that certain disorders include others within their diagnostic category, and allows only the primary diagnosis to be made, leaving the concept of severity unspecified.

Comorbidity diagnoses. this approach allows the application of algorithms based on all existing symptoms, irrespective of how many and what type of diagnostic criteria are fulfilled. Additional complexity arises if comorbidity with “subthreshold conditions” is allowed.

“Splitter” and “lumper” theories

There are several theories that frame depression and anxiety as phenomenologically distinct disorders, and these are supported by empirical [28], experimental [29] and psychometric data [30]. One well-known “splitter” hypothesis holds that anxiety symptoms cluster around mental and physical activation, whereas depressive symptoms centre around

exhaustion [31,32]. Another theory suggests that both anxiety and depressive disorders have, as a central theme, high negative affect; however, while depression is characterized by anhedonia (and generally low positive affect), physiological hyperarousal is the central focus in anxiety disorders [33].

“Lumper” theories support the position that anxiety, depression, and the comorbid condition lie on a continuum and represent sequential stages of the same disorder [34,35]. The unitary concept of anxiety and depression can be supported by the symptomatic overlap of the two syndromes, lack of stability of clinical diagnosis, the tendency for patients suffering from long-standing anxiety states to develop depressive symptoms, the failure to find separate dimensions of anxiety and depression in both self-rated and observer-rated scales, and by the lack of a specific response to drug treatment [19,36,37].

One of the unitary hypotheses ascribes a pivotal role to neuroticism – a stable personality trait defined by emotional instability and vulnerability to stress and anxiety [38,39]. Higher scores of neuroticism significantly increase the risk for anxiety disorders and depression. According to research conducted by the proponents of this hypothesis, the comorbidity (phenotypic correlation) between major depressive disorder (MDD) and GAD was 0.41 and neuroticism accounted for 39% of the observed correlation in both sexes [39].

The role of genetics

Genetic studies could give strong support to either the “splitter” or the “lumper” concept. Most authors agree that family history is the factor most strongly correlated with comorbid anxiety–depression states [35,40,41], but findings remain equivocal. The results from one group of studies argue against the common diathesis hypothesis. Thus, the families of probands with depression and anxiety syndromes had the same rates of primary depression as did the families of probands with uncomplicated primary depression, and probands’ anxiety

Table I. Potential explanations for the common occurrence of comorbid anxiety and depression [12–21].

Reason for co-occurrence	Potential explanation
Comorbidity	The common co-occurrence is due to the randomly distributed incidence of two common, but distinct, conditions
Interaction	The presence of one distinct disorder increases the likelihood of the other, because the specific diathesis for the first makes the subject vulnerable to the other
Continuum	Anxiety and depression are different aspects of a single, gradually evolving, illness and emerge from a common neurobiological predisposition, in which the preponderance of anxiety and depressive symptoms varies over time; the diagnosis depends on the stage when the patient is evaluated
Unique syndrome	The co-occurring symptoms of the two conditions are aspects of a single, more complex disorder
Non-etiological processes	Anxiety and depression are similar adaptive responses to common childhood experiences, similar personality profiles, precipitating life events, and/or psychological stressors. Alternatively, the only commonalities are shared and overlapping definitions, common rating instruments and similar responses to drug therapy

syndromes did not necessarily conform to anxiety disorders in the family [26]. Several groups found that the relatives of patients with mixed anxiety–depressive conditions were more likely to have a history of unipolar depression or/and alcoholism, but not of anxiety disorders, and therefore seemed to resemble depressive, rather than anxiety, disorders [42,43]. Patients with comorbid depression and GAD had twice as many relatives with depression, compared with patients suffering from either depression or GAD alone [44].

A second series of genetic studies found support for a common, genetically driven, neurobiological vulnerability to anxiety and depression. Several family studies reported increased risk of anxiety disorders among the relatives of probands with major depression, and *vice versa* [45–49]. Increased rates of anxiety and depression were found in the parents of subjects who had anxiety only, depression only, or anxiety and depression [50]. The children of depressed patients on the one hand, and the children of patients with anxiety disorders on the other, were at high risk for both depression and anxiety [14,49].

Currently, there is only limited evidence of common genetic risk factors for depressive and anxiety disorders, but one notable exception might be GAD [51]. In a study of 1033 female twin pairs and 97 individual female twins, major depression and GAD were found to share the same genetic factors, which accounted for 30–40% of the variation in risk for these disorders [47,52]. No evidence could be found for genes that specifically affect symptoms of depression without also strongly influencing symptoms of anxiety. By contrast, the environment seemed to have specific effects: a substantial proportion of non-familial environmental experiences were depressogenic, without being anxiogenic and *vice versa* [52]. In other words, these data suggested that in women, depression and GAD resulted from the interplay of identical genetic factors but different environments, and that individual-specific environmental risk factors were solely responsible for the differentiation between major depression and GAD [52,53].

The same group of investigators studied 608 male twin pairs [47]. In this sample, the shared liability for major depression and GAD was estimated to be 61%, and nearly three-quarters of individuals with a history of GAD had also experienced a major depressive episode. Among monozygotic pairs, the correlation of major depression in one twin and GAD in the co-twin was 34%, suggesting that the co-twin of a monozygotic twin with a history of major depression had an equal chance of developing GAD or major depressive disorder. In contrast, among dizygotic twins, major depression in one twin had no correlation with GAD in the co-twin, indicating that in males, the overlapping liability was partially due to genetic factors, with no role for environmental risk.

Thus, for both sexes, major depression and GAD do not appear to be genetically distinct disorders, but to rather have a common genetic predisposition – perhaps a vulnerability to dysphoric mood, which is shaped by individual experiences into symptoms of anxiety, depression, or both [47].

Neurobiology of anxiety and depression: a brief overview

Normal arousal is due to increased excitability and firing of neurons in the noradrenergic and serotonergic systems. Anxiety and depression are associated with disturbances in central serotonin, dopamine, noradrenaline, and γ -aminobutyric acid (GABA) neurotransmitter circuits, which act as a broad functional network with complex interconnections and regulatory mechanisms [54,55]. Sustained central arousal, as seen in anxiety states, may deplete forebrain neurotransmitters over time, precipitating the emotional and somatic symptoms of depression. According to this hypothesis, inappropriate serotonin neurotransmission may be the primary common neurochemical disturbance [56–61].

Activity within the serotonergic dorsal raphe nucleus creates anticipatory anxiety and drives avoidance behaviour [62]; its projections innervate dopaminergic structures, such as the corpus striatum and frontal cortex. Mesolimbic dopaminergic neurons in the ventral tegmental area are involved in functions such as motivation and reward [63]. It has been demonstrated that high-anxiety individuals have more sensitive presynaptic D2 autoreceptors and central α_2 -receptors, compared with low-anxiety subjects, and that stimulation of dopaminergic neurons may have anxiogenic effects in such individuals [64,65].

Overlapping findings in the neurobiology of both anxiety and depression include blunted growth hormone response after a clonidine challenge [66] and there are also recent data that suggest a role for estradiol in the modulation of both conditions [67]. Anxiety and depression share one major central abnormality – corticotrophin releasing hormone (CRH) hypersecretion and disruption of neurosteroid functions [68]. It is plausible that all neuroendocrine disturbances are secondary to hypothalamic pituitary axis (HPA) dysfunction, which could be the most important biological commonality between anxiety and depressive disorders, having profound effects on neurodevelopment and neuroplasticity, hormonal secretion, response to stress, and behaviour [68,69]. In the post-mortem hippocampal tissue of depressed individuals, there is a reduction of neuronal size and increased neuronal packing density [70]. The structural and functional deficits in the hippocampus, together with the HPA hyperarousal observed in depression, may be a

vulnerability factor for greater emotional reactivity, and a suitable target for treatment.

Nonetheless, there are sufficient neurochemical differences between anxiety and depression to justify their separation into two distinct conditions. Thus, for example, increased production of CRF is reported in both disorders, but patients with depression often display abnormal HPA axis parameters at baseline, while GAD patients do not. Sleep architecture also distinguishes the two disorders: depressed patients show decreased REM latency and increased REM percentage of total sleep, while GAD patients do not. When GAD patients are under stress, their responses are slower and they require longer recovery time than do subjects with depression.

After analysis of all the available data, leading researchers remain divided in their opinion of whether anxiety and depression share a common neurobiology [71], or not [72].

Defining comorbidity

The term comorbidity has been coined to designate the presence of “any distinct additional clinical entity that has existed or may occur during the clinical course of a patient who has the index disease under study” [73]. A useful definition for clinical practice is “*the presence of more than one specific disorder in a person in a defined period of time*” [74]. As highlighted by the National Comorbidity Survey (NCS), the vast majority of lifetime psychiatric disorders (79%) are comorbid disorders [75]; 59.2% of the depressed subjects in the NCS Replication survey, which expanded on findings from the baseline NCS, had at least one comorbid anxiety disorder, and researchers using GAD as a model have failed to discriminate cross-sectionally between anxiety and depressive states [15,76–80]. A meta-analysis of the literature concluded that a mean 67% of patients with depression had a current or previous comorbid anxiety disorder, and in a mean 40% of patients with an anxiety disorder, depression was also present [27]. A multitude of studies show that the presence of an anxiety disorder is the single most significant risk factor for the development of depression, increasing that probability from twice to 14 times above the baseline rate [41,81,82]. Furthermore, frequent shifts between anxiety and depressive syndromes are to be expected [83–86].

Classification and diagnostic challenges

The two major classification systems for mental health disorders both include distinct categories for depression of varying severity and features, and for the spectrum of anxiety disorders. However, they differ significantly in their treatment of the distinct disorder of “Mixed Anxiety–depression”. *The Inter-*

national Classification of Diseases, 10th edition (ICD-10) reserves a specific category for this syndrome (F41.2), defining it as a mix of equally prominent anxiety and depressive symptoms, each of a severity insufficient to warrant a diagnosis, and associated with some autonomic symptoms such as tremor, palpitations, and stomach churning. ICD-10 further comments that the disorder is generally seen in primary care settings and the general population [3]. In contrast, the *Diagnostic and Statistical Manual of Mental Disorders – 4th edition (DSM-IV)* includes the syndrome in an appendix for states deserving further research. According to DSM-IV, a person with mixed anxiety–depressive disorder would present with a persistent or recurrent dysphoric mood lasting at least 4 weeks that should be accompanied by at least four of the following symptoms:

- concentration or memory difficulties,
- sleep disturbance,
- fatigue or low energy,
- irritability,
- worry,
- being easily moved to tears,
- hypervigilance,
- anticipating the worst,
- hopelessness or pessimism about the future,
- low self-esteem or feelings of worthlessness.

Depending on whether anxiety and depression are classified at the level of symptoms, syndrome or diagnosis, their degree of relatedness varies markedly (Figure 1). A number of symptoms (low energy, difficulties with concentration and memory, irritability, disturbed sleep pattern, disturbances in appetite) can be detected in both anxiety and

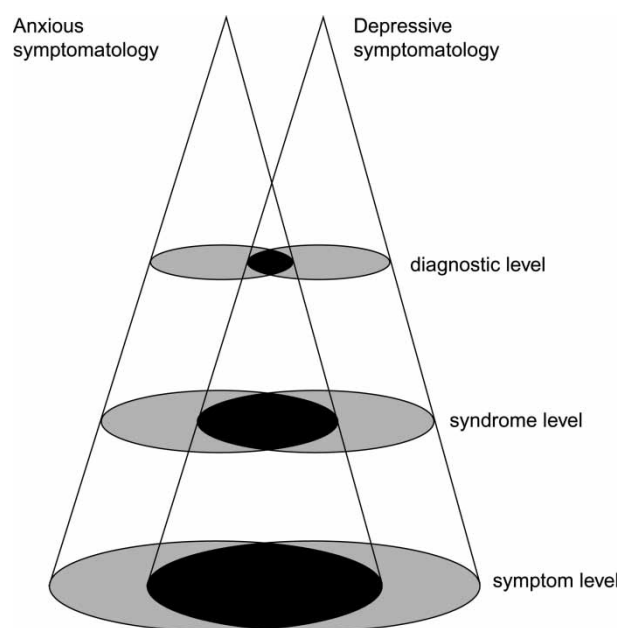


Figure 1. A model of the ways in which anxiety and depression, and their inter-relationship, may be conceptualized. Reprinted from [83] (Copyright (1989), with permission from Elsevier BV).

depressive states. Negative affectivity, e.g., sadness, low mood, loneliness, hostility and anxiety, feelings of inferiority and rejection, oversensitivity to criticism, self-consciousness, and social distress, is common to anxiety and depression and has no discriminative validity. At the same time, positive affectivity, e.g., energy, enthusiasm, self-determination and joy, can validly discriminate anxiety from depression [33,87].

The study of Hiller et al. on a sample of 150 patients with anxiety and depressive disorders highlights how different methods of classification produce very different comorbidity prevalence statistics [83]. If only one symptom in each syndrome was considered sufficient for a definition of overlap, a 52% overlap was obtained. By contrast, when formal diagnosis was used to distinguish the two conditions, overlap (i.e., comorbidity) was seen in only 28.7% of the sample (Table II).

Today, the boundary between anxiety and depressive disorders is widely accepted, and seems to have been validated by family, outpatient and inpatient studies [88–94]. Nevertheless, due to extensive overlap between the symptoms of each disorder; the fact that virtually all psychiatric illnesses are associated with an increased risk of developing major depression [26]; and that anxiety symptoms are extremely common in most mental disorders, many clinicians and researchers support the use of dimensional models, rather than categorical classification, both in research and clinical practice [5–7,86,90,95–97].

Neither simple clinical description, nor sophisticated statistical approaches, allows an unequivocal conclusion, and the nature of the relationship remains controversial. Efforts to modify symptom profiles in both classification systems continue, in order that a better definition and more robust validation of the mixed anxiety–depression syndrome can be achieved [27,98].

Epidemiology of anxiety and depression

Depression and anxiety disorders are under-diagnosed and inadequately treated

One widespread and profound problem in mental health is that at least one-third of primary care patients with mental disorders escape early detection

Table II. Comorbidity of anxiety and depression at different levels of clinical description. Reprinted with permission from [83] (Copyright (1989), Elsevier).

Level of description	Probability of overlap when depressed	Probability of overlap when anxious
Diagnosis	0.35	0.61
Syndrome	0.32–0.58	0.75–0.83
Symptom	0.58	0.83

[99,100]. Diagnostic difficulty is increased by the fact that affected individuals frequently present with somatic complaints; the symptoms of anxiety and depression are typically intermingled with real-life problems; and the patient may have limited insight into underlying psychological issues [81].

The association between comorbid anxiety–depression and functional somatic symptoms is particularly strong [101]. Such patients perceive their health as poorer, and experience more pain and poorer physical functioning than patients suffering from other chronic medical conditions [102,103], which may explain in part why physicians fail to diagnose clinically significant anxiety or depression in nearly 52% of such patients [61]. Sufferers are often dismissed as being the “worried well” and even when a diagnosis is made, treatment may not be prescribed [60,61,104–107]. Too few such patients are appropriately treated and most remain at risk for more severe anxiety and depressive disorders [11,17]; it seems readily apparent that they live in a state of ongoing dysfunction, increasing the potential for morbidity and suicidal acts. Furthermore, from a health economics perspective, these patients continue to be frequent users of health services, with implications for the cost-effectiveness of medical care [108,109].

Burden of disease

Surveys consistently demonstrate that subjects with combinations of anxiety and depression form the largest group of patients in both community and primary care, while relatively few of them are referred to mental health professionals [110,111].

Community studies demonstrate that subsyndromal mixed anxiety–depression occurs in 0.8–2.5% of the general population [4,78], but the prevalence of comorbid anxiety and depression in the community could be as high as 10–20% [11,112–114]. The one-year prevalence of mixed anxiety–depression in a sample of 2956 individuals in the general population was found to be 2.9%, with 11.3% of subjects affected by comorbid anxiety and depressive disorders [115]. In another large study, comorbid anxiety–depression was found in 6% of 60,869 individuals from a general population sample, more commonly in women [116]. The NCS demonstrated that 39.5% of subjects with a lifetime diagnosis of GAD also had major depression [100]. Of persons suffering from a mood disorder in community samples, 43% had at least one comorbid lifetime anxiety disorder diagnosis, while 25% of patients with an anxiety disorder had at least one lifetime mood disorder diagnosis [106]. Other studies have reported lifetime comorbidity rates of 31–62%.

In an important study of long-term comorbidity, Angst et al. found significant comorbidity between anxiety and depression during follow-up of a

Table III. Long-term comorbidity rates (%) between different levels of anxiety and depression in the general population. Reprinted with permission from [50] (copyright (1990), the American Psychiatric Association).

	Depressive disorder	Subthreshold depression	No depression	Total
Anxiety disorder	10.0	5.4	2.2	17.6
Subthreshold anxiety	11.5	8.1	5.4	25.0
No anxiety	10.2	11.8	35.4	57.4
Total	31.7	25.3	43.0	100

community sample of 591 subjects from age 20 to age 35 (Table III) [50].

In reviewing the available literature, one can conclude that results pertaining to the prevalence of lifetime comorbidity depend largely on the diagnostic subtypes studied, the severity of symptoms and the methodology applied in different community studies and surveys (Table IV) [17].

All the above data suggest that anxiety, depression, and the combination are highly prevalent in the general population and present a major challenge for community healthcare systems. Such individuals have substantial impairments in their social and vocational roles, tend to present with a variety of medically unexplained somatic symptoms, and may make extensive use of non-psychiatric medical care. They also represent a population-at-risk for the more severe major affective and anxiety disorders when exposed to significant life stressors [11,117].

Special populations

Comorbid anxiety and depression are well-recognized at both ends of the age spectrum, and among pregnant women. Research findings from several groups suggest that approximately 30% of children and adolescent outpatients with anxiety disorders have diagnosable depression, while up to 41% of those suffering from major depression had a lifetime anxiety disorder that preceded the depression [118–121]. In a separate population sample of 3056 individuals aged 55–85 years, 47.5% of the subjects with MDD had a concurrent anxiety disorder, while 26.1% of those with anxiety disorders also met criteria for MDD [40]. 5.1% of 333 nursing home patients, aged approximately 79 years, were found to

have comorbid anxiety–depression [122], and 85% of 361 patients with a late-life major depressive episode suffered from at least one comorbid mental disorder which, in 74%, was GAD [123].

A meta-analysis of five studies carried out between 1968 and 1985 found that dimensional anxiety during pregnancy was a strong predictor of postpartum depression [124]. More recent data suggest that women presenting with one anxiety disorder during pregnancy are four times more likely to also present with MDD, and carry an independent risk of developing postpartum depression [125].

It is worth noting that the general practitioner's attention is often diverted to other medical problems in these subpopulations, leaving the pressing need for treatment of existing psychopathology largely unmet.

Patients in psychiatric specialist settings

Concurrent anxiety and depression is the most common presentation of comorbid psychiatric symptoms in primary care [126], but the DSM-IV field trial indicated that the incidence of subsyndromal anxiety/depressive conditions was even higher in psychiatric outpatient clinics (12%) than in primary care (6.5%) [127]. According to a review presented in 1999, 21–91% of patients with panic disorder, agoraphobia, or GAD also met criteria for major depression [82]. Also, from the alternative perspective, a study of 200 patients diagnosed with major depression found that 72% exhibited moderate worry, 62% displayed moderate psychic anxiety, 42% had moderate somatic anxiety, 29% had a history of panic attacks, and 19% experienced moderately severe phobic symptoms [90]. Comorbid

Table IV. Prevalence of mixed anxiety–depression in the general population. Reprinted with permission from [17] (Copyright (1999), Elsevier BV & the European College of Neuropsychopharmacology).

Study	Centre	N	Duration (years)	Prevalence (%)
Angst et al. 1984	Zurich	395	4	4.2
		457	7	9.4
Murphy et al. 1986	Stirling County	618	17	2.2–2.5
Brown et al. 1987	Islington	345	1	2
Blazer et al. 1988	ECA (NC)	2993	1	9.9
Eaton and Ritter 1988	ECA (Baltimore)	2768	1	13
Lepine et al. 1993	France	1746	1	males: 5.3 females: 14.1
Wittchen and Von Zerssen 1998	Munich	1366	7–14	1

anxiety disorders appear to be even more frequent in patients with bipolar than in those with unipolar depressive illness [128].

Implications of diagnosing psychiatric comorbidity

The co-existence of more than one psychiatric diagnosis has major practical implications for patient care and healthcare delivery, and the way in which patients are diagnosed bears heavily upon both treatment and prognosis. The consequences of comorbid anxiety and depression can be viewed from various perspectives [129]:

- forms of presentation in primary care,
- detection, diagnosis and health service utilization,
- impairments and disabilities,
- course and prognosis.

Presentation, detection, diagnosis and health service utilization

Depressive disorders are more likely to co-occur with anxiety symptoms or syndromes than with any other form of mental disorder [126]. Nearly two-thirds of depressed patients have concomitant symptoms of anxiety, e.g., agitation, obsessive-compulsive symptoms, non-specific gastrointestinal complaints, hypochondriasis, and feelings of depersonalization [130].

A review of general practice demonstrated that some type of anxiety/depression combination occurs in one third of general practice patients [131] (Figure 2). Mixed anxiety–depression has been estimated to be the third most common ambulatory diagnosis in primary care practice [132], and in one

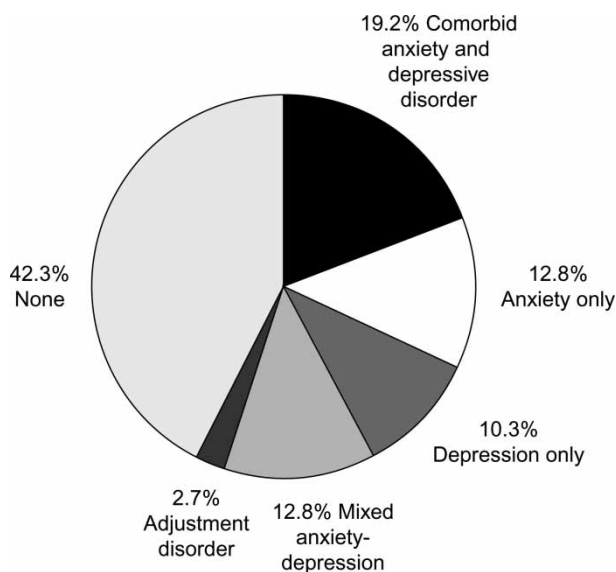


Figure 2. Distribution of depressive and anxiety states in primary care attendees. Reprinted with permission from [131] (Copyright (1995), Elsevier).

primary care prevalence study, the majority of patients had mixed anxiety–depressive syndrome (42.3%) or depression with comorbid anxiety (19.2%) [133]. Other studies in several primary care centres estimated the point prevalence of mixed anxiety–depression to be between 4.1% and 8% [8,134].

The WHO Study on Psychological Problems in General Health Care [126], which included 5438 patients in 14 countries, found an odds ratio of 9.3 for current depression occurring with one or more anxiety disorders, and 3.9 for current depression with subthreshold anxiety [126] (Figure 3).

The same study determined current prevalence rates of 1.3% for mixed anxiety–depressive disorder and 1.4% for subsyndromal depression (defined as at least two depressive symptoms present for at least 2 weeks). A total of 41% of the individuals in the former group were moderately or severely disabled by their symptoms [126]. In the 12-month follow-up of that study, 54.5% of comorbid cases continued to fulfil criteria for one or the other disorder, compared with only 32.9% of patients who had pure anxiety and 36.5% with pure depression.

At present, there is a general consensus that most cases of mixed anxiety–depression represent comorbidity, while a small proportion may represent a distinct mixed anxiety–depression disorder [135]. Indeed, data from cluster analyses suggested the existence of a separate anxiety–depressive syndrome [88,136]. Yet, it is quite possible that subthreshold and mixed anxiety–depressive states may in fact be either mild forms of a more severe anxiety or mood disorder, or their prodromal/residual phases [8,83]. Some experts consider that the acceptance of a distinct mixed anxiety–depression disorder trivializes symptoms of anxiety and depression in primary care, discourages diagnostic precision, and prevents the recognition of target patient groups who have symptoms of sufficient intensity to justify treatment [137].

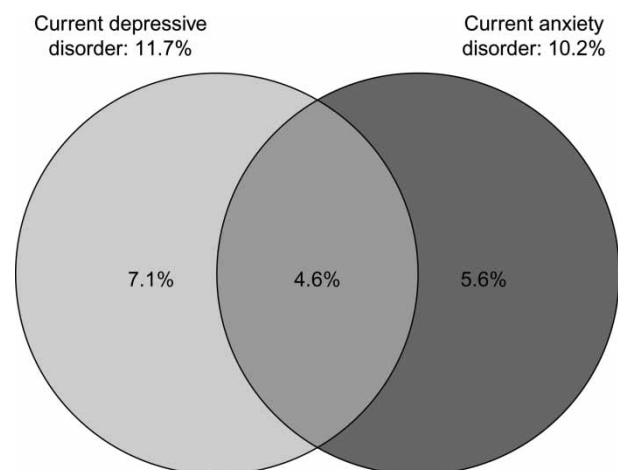


Figure 3. Comorbidity of current depression and anxiety. Reprinted with permission from [126] (Copyright of the Royal College of Psychiatrists).

As explained above, factors that influence diagnostic classification also have an impact on health service utilization. In a large community study, 39% of individuals with comorbid anxiety–depression had sought help for mental problems at some time, compared with 25% of the individuals with a pure anxiety disorder, 13% of subjects with depression and 6.7% of persons with no current anxiety or depressive disorder [116]. In the NCS, the major burden of psychiatric illness was concentrated in the 14% of individuals who had a history of three or more comorbid conditions, reflecting the degree to which individuals with comorbid mental health diagnoses require psychological care and intervention, and therefore make use of a country’s health-care system, with the inherent implication of additional healthcare costs. Providing further support that comorbidity is associated with greater health service utilization, the Munich follow-up study demonstrated that the proportion of patients utilizing mental health services was significantly higher in patients with comorbid anxiety and depression (51%) than in patients with a pure anxiety disorder (14%) or depression (35%) [4].

Furthermore, the profound burden of comorbid psychological distress may hasten the patient’s search for treatment. For example, it has been suggested that comorbid anxiety may be the impetus for seeking treatment in depression [138].

The diagnostic challenge of subthreshold symptoms

Over 95% of patients with depressive disorders have at least one symptom of anxiety, and 20–65% of patients with anxiety also experience low mood [37,132,139]. Data from community surveys, primary care, and psychiatric populations suggest strongly that there is a subgroup of persons with mixed anxious–depressive symptoms who have insufficient symptoms of either disorder alone to meet diagnostic thresholds (Figure 4) [3,37]. Patients

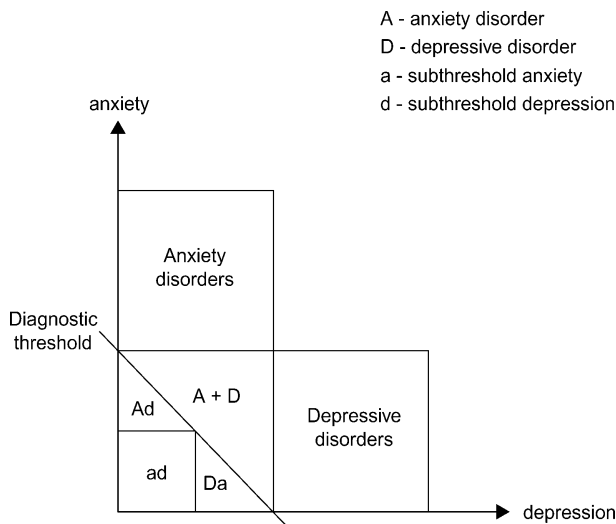


Figure 4. Anxiety–depression comorbidity spectrum [3,37].

presenting with subthreshold affective symptoms appear to be at least as common as patients with several of the classifiable anxiety and depressive disorders. Subthreshold depression or/and anxiety are particularly common among the elderly and among the patients with concomitant medical disorders [1,110,138,140].

Experience in primary care settings suggests that the less severe forms of anxiety and depression may show greater symptom overlap and be more difficult to distinguish cross-sectionally [11]. The modal presentation among those patients is a non-specific pattern of anxiety and depressive symptoms. Compared with individuals with major depression, a relative absence of pervasive anhedonia and low interest/motivation is apparent, while compared with patients with GAD, there is a relative absence of pervasive, excessive worry and tension. A further distinguishing factor is that patients with subthreshold anxiety–depression rarely report experiencing symptoms “nearly every day” or “more days than not” [8].

Impairments and disabilities

While anxiety disorders appear to have a worse long-term prognosis than depression, patients with mixed anxiety–depression fare even less well, with a remission rate of less than 25% after several years of follow-up [35,141–144]. Studies demonstrate that comorbidity is associated with a poorer prognosis for each index disorder in terms of chronicity, recurrence, and duration of suffering, work impairment, need for treatment and risk of attempted suicide. All the available data [11,15,19,34,35,42,76,129,138,145–166] point to the fact that when compared with patients with a single disorder, those with comorbid anxiety and depression tend to exhibit:

- earlier age of onset,
- greater symptom severity,
- a more chronic course with multiple episodes,
- greater impairment in everyday functioning,
- poorer overall quality of life,
- greater physical and mental disability,
- medically unexplained somatic symptoms,
- substantially increased (30–60%) utilization of healthcare services,
- greater likelihood of suicide,
- increased composite rates of mortality,
- higher rates of negative placebo response,
- exaggerated sensitivity to most common medication side-effects,
- delayed and reduced treatment response to pharmacotherapy and psychosocial interventions in comparison with matched non-anxious uni- and bipolar depressive patients.

Compared with patients with “pure” GAD, the proportion of patients with comorbid diagnoses in

the NCS who reported symptoms that interfered with their lives, had sought professional help, and who were using medication for symptom control was approximately 80, 40 and 90% higher, respectively [167]. Mixed anxiety–depression is associated with greater impairment of overall functioning than either disorder alone, especially as regards loss of productivity and intimate relationships [82]. Thus, a total of 60% of patients with comorbid anxiety and depression had marked impairment in social functioning, compared with 48% of patients with pure depression and 19% of those with anxiety [17]. A comparison of clinical and epidemiological data [168] found that subjects with lifetime anxiety and depression comorbidity had lower psychosocial functioning scores, as measured by the Global Assessment Scale (GAS), lower remission rates, and achieved a favourable long-term course and outcome considerably less frequently than those with pure depressive disorders. Both the mean duration and number of depressive episodes were significantly increased in the comorbid patients. In another sample of 327 depressed patients, those with high anxiety scores took a median of 26 weeks to recovery, compared with 13 weeks for those with low anxiety levels [42]. This effect extends to subjects at the older end of the age spectrum. The Groningen Longitudinal Aging Study [169,170], which evaluated 5,279 people in late middle age and older, demonstrated that comorbid depression significantly impaired physical and social functioning, activities of daily living, and life satisfaction.

It is not necessary for the comorbid condition to meet full diagnostic criteria in order to produce significant vocational impairments, increased need for disability and welfare benefits, and increased use of healthcare resources (consultation time and treatment) [4,11,17,19,159,171–176] (Table V).

Course and prognosis

Longitudinal course has been considered to be among the most important characteristics in classifying and distinguishing mental disorders since Kraepelin.

A community survey of 3021 individuals demonstrated that anxiety disorders occur primarily in

childhood and early adolescence, long before the development of depressive disorders [41]. The 2003 National Comorbidity Survey Replication study found that 85% of cases of MDD were preceded by anxiety disorders [177]. Medium-term follow up of patients with anxiety disorders demonstrates that after four to five years the majority of individuals have developed depression, whereas it is highly unlikely for individuals with depression or with mixed anxiety–depression to have developed GAD or panic disorder at this stage of follow-up. This suggests that the temporal pattern of onset is fairly predictable [35,41,178], and many researchers believe that one-way transitions on the stress–anxiety–depression axis can alone explain the relationship between the two disorders [179]. There are compelling data to suggest that the most common lifetime pattern of comorbidity is GAD followed by MDD; simultaneous onset and offset is the exception [153].

Kendell studied the stability of clinical diagnosis over a period of 5 years in 2000 patients and found that there was a change in diagnosis from anxiety to depressive disorder for 24% of the sample, while in only 2% did the transition occur in the opposite direction [11,84]. Reviewing the large Zurich population sample followed for 15 years, Merikangas et al. found that comorbid anxiety–depression was much more stable than both the non-comorbid conditions [180]. Subjects with pure anxiety had moderate probability of developing depression in the course of their lives, whereas only isolated cases of pure depression developed pure anxiety. However, both non-comorbid conditions had a substantial propensity to evolve to the comorbid state, with 21% of subjects with depression and 24% of those with anxiety undergoing that transition [180].

The mixed anxiety–depression disorder may follow a more malignant course than that of either depression or anxiety alone. The mixed disorder often begins insidiously in the early 20s, developing into a chronic condition with a low remission rate, greater risk of relapse, more pronounced therapeutic resistance, significant impairments in the patient's everyday life, and an altogether worse outcome [19,145,181–185]. Patients with bipolar depression and a comorbid anxiety disorder had a significantly greater number of prior affective episodes and

Table V. Impairment in overall and social functioning in anxiety and depressive disorders. Adapted with permission from [4] (Copyright Physicians Postgraduate Press Inc.).

Indices	Diagnostic categories (%)			Subthreshold disorders (%)			Controls (%)
	A (%) <i>n</i> = 42	D (%) <i>n</i> = 45	A+D (%) <i>n</i> = 5	a (%) <i>n</i> = 101	d (%) <i>n</i> = 12	a+d (%) <i>n</i> = 11	
Marked impairment in social function	19	47	60	9	42	54	12
Contacts with mental healthcare system	14	35	51	4	17	36	1
Number of physician visits in the past year	17	15	19	11	10	14	9
Remission rates in past 6 months	26	67	28	41	79	6	–

hospitalizations, greater severity of depressive and manic symptoms, spent a significantly greater percentage of time symptomatic post-treatment, and had poorer response to treatment of their depression than “pure” bipolar patients [128].

Mortality

Both anxiety and depression are being increasingly recognized as risk factors for cardiovascular events; additionally, these disorders accelerate the rate of death once a cardiovascular event has occurred. When associated with depression, severe anxiety is a major risk factor for suicide [107,150,186,187]; suicidal ideation is more than twice as common in depressed patients with a comorbid anxiety disorder [188] than without. A collaborative study of depression that followed 955 depressed patients for more than 10 years demonstrated that a high level of anxiety was an accurate predictor of suicide within one year of assessment [189]. A recent history of panic attacks in patients with major depression also appeared to be an important predictor of suicide. In another study, 15.3% of the mixed anxiety–depression group and 10.9% of the comorbid group had attempted suicide *versus* only 8.4% of the group with pure major depressive disorder [115].

Treatment of comorbid depression and anxiety

General principles

Effective treatment of the patient with comorbid/mixed anxiety–depression depends on early recognition, diagnostic accuracy, and awareness of subthreshold states, bearing in mind that subsyndromal does not equate with subclinical. There is ample empirical evidence that subsyndromal symptoms can precipitate relapse and recurrence, worsening the long-term prognosis; the fact that these patients do not meet diagnostic criteria does not mean that they do not have a disorder that can, and should, be treated.

When explaining to a patient in primary care that their symptoms suggest a psychiatric disorder, it is helpful to frame their experience as a common and highly treatable medical illness characterized by certain symptoms and signs, and associated with a biochemical disturbance in the CNS. Appropriate medical workup is indicated based on the physician’s weighting of the probable differential diagnoses; in all cases, the potential risk of harm from diagnostic procedures, particularly those that are invasive, and the need to initiate psychological or pharmacological therapy while the diagnostic workup proceeds, should be balanced against the need for such testing [109].

After the disorder has been thoroughly evaluated and identified, the physician can choose among various pharmacological or psychotherapeutic inter-

ventions of relatively equal efficacy. The selection of a particular drug for a specific patient should be guided by at least the following considerations [61]:

- typical short- and long-term side-effects of each medication,
- patient’s previous positive or negative response to medication,
- history of first-degree relatives response to a particular drug,
- present comorbid medical illnesses that could affect the drug’s safety and toxicity,
- concomitant use of other medications that can alter the drug’s metabolism or increase its side-effects,
- cost of the medication,
- physician’s own experience with the medication.

Patients with anxiety and depression can be difficult to treat pharmacologically because they are often hypervigilant (and may be hypersensitive) to minor side-effects. Consequently, patient preference should serve as an important additional criterion in selecting a particular treatment.

Throughout the course of therapy, the clinician should keep in mind the immediate and long-term goals, and assess symptomatic response by asking about intensity, frequency, impact upon functioning and quality of life (QoL), giving consideration to the potential to modify the environment with regard to situational stressors and dynamics [190,191].

Typical limitations of acute phase and follow-up care

Data from several surveys point to the fact that the quality of acute-phase pharmacotherapy often fails to reflect the severity of illness or clinical need. Conventional treatment is generally based on the “best-fit” diagnosis and targeted to the most prominent symptoms, while secondary symptoms are expected to resolve spontaneously as the primary disorder improves [192]. This is not always the case in comorbid anxiety–depressive conditions. Many anxious–depressed patients are started on anxiolytic drugs for their clinical symptoms of “anxiety”, and when their symptoms do not improve or deteriorate, it is very likely that the dose of anxiolytic will be increased [193]. This approach to treatment explains why benzodiazepines are favoured by so many, since the daily dose can be altered quickly, they can be given on an “as needed” basis, and such treatment may acutely aid antidepressant efficacy by dampening early activation symptoms and thus enhancing compliance. Unfortunately, medium- to long-term benzodiazepine monotherapy can prove not only useless but deleterious [194]. Some studies suggest that treatment of even subsyndromal anxiety/depression with benzodiazepine monotherapy shows no superiority over a modest amount of

supportive counselling [195], and might have long-lasting harmful consequences for the patients, even causing depressive symptoms [196].

Due to the overwhelming body of empirical data showing robust efficacy in this clinical population, pharmacotherapy is now typically initiated with an antidepressant that treats both the anxiety and the depressive disorders. A low dose is necessary when starting, in order to minimize exacerbation of anxiety, but gradual upward titration to optimal doses is crucial. In contrast to the limitations of benzodiazepine monotherapy, using benzodiazepines in combination with antidepressants can provide the following benefits: rapid anxiolysis during antidepressant lag, decrease of the early activation associated with initiation of an antidepressant, treatment of residual anxiety after successful treatment of depression, and even prevention of full-blown depression [197,198]. Unfortunately, however, these benefits are not reliable, and this combination of agents tends to be associated with significant negative effects, including drug–drug interactions, attention/memory and motor impairment, and withdrawal reactions, among others. Furthermore, even in combination with antidepressants, benzodiazepines rarely help patients achieve complete remission and restored function.

A very common clinical situation is the persistence of anxiety symptoms after depression resolves following treatment with antidepressants [10,199–201] and there is considerable agreement across studies that residual symptoms contribute to relapse vulnerability. The clinician's first responsibility then should be to evaluate existing residual symptoms and try to determine if they are an integral part of the primary disorder, an adverse effect of treatment, or an independent comorbidity [202]. It is often the case that after treatment to remission, residual symptoms in patients with MDD or GAD are similar to those observed before treatment, suggesting that residual symptoms are a natural part of the course of these disorders, similar to prodromal symptoms [203].

It has become evident that follow-up is often erratic, and that treatment frequently falls short of recommended standards for duration and intensity. The need to monitor the course of treatment, and of improvement, carefully and regularly cannot be overemphasized. Resolution of disturbing individual symptoms and signs can cause the patient – and the uninformed physician – to assume that the entire syndrome has improved, and to discontinue therapy [109]. Treatment should be continued for at least several months after full recovery and should include frequent evaluation for changes in symptoms that may demand a change in treatment. The psychiatrist should differentiate responders from remitters, combine not drugs but pharmacological mechanisms, and try augmentation strategies, including psychotherapy.

Specific approaches to treatment

Unfortunately, since patients with comorbidity are often excluded from clinical trials of antidepressant and anti-anxiety drugs, there is a paucity of evidence on treatment responses in this population. Still, antidepressants remain the treatment of choice for anxiety and/or depression for the time being. The question remains, therefore, if an antidepressant has demonstrated efficacy in each separate disorder, is that sufficient to ensure efficacy in comorbid occurrence of these disorders? Clinical wisdom tells us that it is not always true, and the reasons for the frequent therapeutic failures under “standard conditions” remain unclear. Irrespective of which antidepressant is selected, reliable symptomatic relief takes more time and requires higher doses for comorbid psychopathology [204].

Tricyclic antidepressants appear to be effective in treating both depression and anxiety [205–207], but it is well recognized that SSRIs have a superior safety and tolerability profile. The findings of numerous clinical trials of tricyclics and SSRIs have been widely disseminated and do not need further comprehensive review. All SSRIs, given at optimal dose and for the recommended duration, work for both types of symptoms [208]. Fluoxetine, fluvoxamine, paroxetine, and citalopram have a long history of efficacy in the treatment of depressed patients with significant anxiety symptoms or psychomotor agitation [209]. A meta-analysis of the worldwide paroxetine clinical trials' database including 4169 patients, confirmed its efficacy in patients with depression and anxiety [210]. In an analysis of 22 double-blind, randomized controlled trials in major depression, including 3800 patients, Montgomery et al. [211] demonstrated that fluoxetine relieves the symptoms of anxiety and of depression, showing comparable efficacy with TCAs, independent of a patient's baseline anxiety status, and concluded that the choice of antidepressant should not be influenced by the presence or absence of anxiety. A triple head-to-head comparison of fluoxetine, sertraline, and paroxetine did not demonstrate any consistent differences in efficacy, onset of action or tolerability in depressed patients with high levels of anxiety [208]. Of clinical interest, a very comprehensive clinical development programme has demonstrated that escitalopram shows faster onset of action and superior efficacy in reducing anxiety symptoms in depression than citalopram (Table VI) [212].

In a large group of patients escitalopram showed robust efficacy in improving both depressive and anxiety symptoms in major depression irrespective of the baseline severity of anxiety and of the presence, absence, or nature of a comorbid anxiety disorder [213]. Very recent data confirm escitalopram's significantly superior efficacy over paroxetine in a large sample of severely depressed patients with a high

Table VI. Improvement of depression and anxiety symptoms: pooled analysis of three 8-week clinical trials in depressed outpatients [212].

	Placebo	Escitalopram	Citalopram
<i>Depression measures</i>			
HAM-D	-8.6	-10.8 ($P < 0.001$ vs. placebo)	-10.6 ($P = 0.008$ vs. placebo)
MADRS	-11.2	-13.8 ($P < 0.001$ vs. placebo)	-13.1 ($P = 0.002$ vs. placebo)
<i>Anxiety measures</i>			
HAM-D anxiety subscale	-1.9	-2.2 ($P = 0.011$ vs. placebo)	-2.3 ($P = 0.048$ vs. placebo)
HAM-A	-4.6	-6.1 ($P = 0.002$ vs. placebo)	-6.5 ($P = 0.002$ vs. placebo)
MADRS inner tension	-0.93	-1.34 ($P < 0.001$ vs. placebo)	-1.32 ($P < 0.001$ vs. placebo)

HAM-A, Hamilton Anxiety Scale; HAM-D, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale.

level of comorbid anxiety throughout the 24-week study period [214].

Another set of recent data seem to support the existing notion that antidepressants have impact mainly on psychic, and not on somatic anxiety [215]. Thus, the reduction in HAM-A scores during treatment of patients with mixed anxiety–depression with fluvoxamine was highly correlated with the reduction in HAM-D scores, while the reduction in HAM-D scores correlated with the reduction of psychic, but not of somatic anxiety [216]. In this context, it is encouraging to learn that escitalopram significantly improves somatic symptoms of depression in the majority of treated patients [217].

Slow onset of efficacy is typical for the SSRIs. Treatment with an SSRI diminishes the exaggerated reactivity of the amygdala, the pivotal brain structure subserving stress, fear and anxiety [218], thus alleviating the intensity of emotional turmoil and allowing for a greater choice in cognitive responses. The necessity of higher doses in comorbid patients could suggest that higher initial levels of 5-HT transport inhibition may be needed to treat anxiety [216]. As for the longer time needed to achieve a meaningful clinical response, it is possible that different extracellular concentrations of 5-HT affect unique populations of 5-HT receptors, as receptor sensitivities change across time [216,219].

Many different classes of antidepressant drugs have shown efficacy in treating anxiety symptoms in depression: nefazodone, a 5-HT₂ antagonist [220,221], mirtazapine, a presynaptic antagonist at α_2 , 5-HT₂ and 5-HT₃ receptors [222], venlafaxine, a serotonin and noradrenaline reuptake inhibitor [223], bupropion, a noradrenaline and dopamine reuptake inhibitor [224], and moclobemide, a reversible inhibitor of monoamine oxidase A [225]. Yet the need for symptom-specific treatment is supported by preclinical data showing that in humans there is central noradrenergic dysfunction that is found specifically in anxiety, not depression [68,226].

Antidepressants as modulators of neuronal plasticity

Antidepressant therapy may directly or indirectly up-regulate glucocorticoid receptor (GR) activity, nor-

malizing HPA axis function, particularly its down-regulation with the termination of stress [227]. Tricyclic antidepressants seem to have prominent effects on GR2 expression, while serotonergic antidepressants may have a more potent effect on GR1 expression [228]. The change in the setpoint of monoamine transmission induced by the intake of SSRIs/SNRIs appears much faster than the plastic changes in the hippocampus, amygdala and cortex: cessation of hippocampal atrophy and of stress-induced dendritic shrinkage, and increase in hippocampal neurogenesis, which might prove to be essential for the therapeutic effects in depression and anxiety [229]. Chronic treatment with TCA, SSRI, SNRI and other antidepressants enhances neurogenesis in the hippocampus through the sustained activation of the intracellular cAMP signal transduction pathway and increased synthesis and expression of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) that ultimately influence synaptic plasticity [230]. BDNF can actively re-induce the formation of new synaptic elements, which is probably the final common goal of both anti-anxiety and antidepressant treatments [231].

Supplementary pharmacological and psychological interventions are often necessary to achieve a satisfactory clinical response. Bearing in mind that the key neurotransmitters in the fear/anxiety response are fast-acting GABA and glutamate, and that their activity is strongly affected and modulated by serotonin and noradrenaline, one could search for still other modulatory influences. Thus, pregabalin binds to the α_2 - δ subunit of voltage-gated calcium channels, reducing the presynaptic release of noradrenaline, glutamate and substance P, enhancing the presynaptic influx of GABA, and attenuating the postsynaptic influx of Ca^{2+} . It has an early anxiolytic effect and might add to the neuroprotective/neurotrophic effects of antidepressants. Another putative therapeutic category of anxiolytics/antidepressants may be substance P antagonists, acting directly upon the brain structures involved in the neurocircuitry of human emotions, especially fear and dysphoria.

Cognitive behavioral therapy (CBT) is a well-established treatment for MDD, panic disorder,

GAD, and social anxiety disorder. Although specific techniques are developed for each disorder, all of them include psychoeducation, cognitive restructuring, exposure, and relaxation [232]. CBT can target both depressive and anxiety symptoms by motivational interventions, focusing on cognitive distortions, etc. [233–235], and may have an especially beneficial impact on outcome in patients exhibiting subsyndromal residual symptoms [236,237]. Changes in cognitive schemata, improvements in self-regulation, and social skills training are also helpful in depressive, as well as anxiety disorders [37]. When examined as a whole, the data from well-controlled clinical studies show that psychological treatments in patients with anxiety and/or depressive symptoms can result 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 therapy [238].

Conclusions

Individuals suffering from comorbid depression and anxiety have an earlier age at onset, greater illness severity at onset of treatment, greater illness chronicity and recurrence, and poorer response to treatment than those with depression or with an anxiety disorder alone and present a major challenge to the health services worldwide. There is a pressing need to study the clinical presentation, course, neurobiology and potentially different treatment responses of individuals with anxiety, depression and the associated comorbid conditions. Modern treatment with potent antidepressants, with or without CBT, can help most patients with anxiety/depression manage their symptoms and gain satisfactory functioning and quality of life, but questions remain as to the difference between treatments with respect to long-term tolerability, the risk/benefit ratio of ongoing treatment, optimal maintenance doses, optimal duration of treatment after recovery, and even whether long-term maintenance treatment alters the natural course of the comorbid disorder [192]. Through further research, and greater understanding of the neurobiology of depression and anxiety, data can be used to develop classification systems that encompass all modes of presentation of these common mental disorders, screen techniques can be improved, and appropriate treatment instituted sooner so that the unmet needs of the large population of sufferers may be better served.

Key points

- Depression and anxiety are common, and frequently coexist in the same individual, either as diagnosed disorders or subsyndromal states

- Coexistent, simultaneous depression and anxiety may be viewed as mixed anxiety–depression or as comorbid syndromes, i.e. separate disorders occurring concurrently.
- Controversy remains over the extent to which the two disorders intersect aetiologically and phenomenologically.
- Irrespective of their relationship, coexisting depression and anxiety cause significant vocational and interpersonal impairment to the individual, and place a heavy burden on society in terms of workplace and healthcare costs.
- Several different classes of antidepressant drugs offer symptom relief for individuals with coexisting anxiety/depression, although the highly selective SRIs hold the greatest promise for sustained clinical improvement.
- The ultimate goal of any antidepressant and/or anxiolytic therapy is to enhance compromised neuroprotective, neurotrophic, and neurogenic mechanisms.

Statement of interest

The authors have no conflict of interest with any commercial or other associations in connection with the submitted article.

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