Comorbid anxiety and depression in adults: Epidemiology, clinical manifestations, and diagnosis

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Literature review current through: **Oct 2023.**
This topic last updated: **Jul 22, 2022.**

INTRODUCTION

Anxiety disorders and depressive disorders are highly prevalent conditions that frequently co-occur. Individuals affected by both anxiety and depressive disorders concurrently have generally shown greater levels of functional impairment, reduced quality of life, and poorer treatment outcomes compared with individuals with only one disorder.

Studies of the clinical presentation, course, assessment, and diagnosis of these conditions have largely focused on the co-occurrence of depression and generalized anxiety disorder. The diagnosis of these conditions is complicated by the presence of mixed anxiety and mood states as well as substantial overlap in physical and emotional symptoms of the disorders. Anxious distress was included as a subtype of major depression in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [1].

This topic describes the epidemiology, pathogenesis, clinical manifestations, course, and diagnosis of comorbid anxiety and depression. The epidemiology, pathogenesis, clinical manifestations, course, diagnosis, and treatment of individual depressive and anxiety disorders are described separately.

- (See "Unipolar depression in adults: Epidemiology".)
- (See "Unipolar depression in adults: Assessment and diagnosis".)
- (See "Unipolar depression in adults: Course of illness".)

- (See "Generalized anxiety disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis".)
- (See "Social anxiety disorder in adults: Epidemiology, clinical features, assessment, and diagnosis".)
- (See "Obsessive-compulsive disorder in adults: Epidemiology, clinical features, and diagnosis".)
- (See "Panic disorder in adults: Epidemiology, clinical manifestations, and diagnosis".)
- (See "Agoraphobia in adults: Epidemiology, pathogenesis, clinical manifestations, course, and diagnosis".)

EPIDEMIOLOGY

Population-based samples — There is a high rate of comorbid anxiety and depressive disorders in population-based samples. The lifetime prevalence of anxiety disorders and major depression among adults in the United States has been reported to be 28.8 percent and 16.6 percent, respectively [2].

Three international studies found that depression is significantly associated with every anxiety disorder [2-4], with the highest associations in patients with generalized anxiety disorder (GAD) and the lowest in those with agoraphobia and specific phobias.

Lifetime prevalence of comorbid anxiety and depression in the general population is very high [5-11]. As examples:

- In a study of 1783 individuals, 75 percent of those with depression met criteria for an anxiety disorder in their lifetime; 79 percent of those with an anxiety disorder met criteria for lifetime major depression (table 1) [5].

- A study of 74,045 adults across 24 countries found an average lifetime prevalence of DSM-IV/Composite International Diagnostic Interview major depressive disorder (MDD) of 11.2 percent; 45.7 percent of those individuals also had one or more lifetime anxiety disorders [7].

- A study of 20,013 United States adults with unipolar MDD found lifetime prevalence rates of SAD to be 0.77 percent and an anxiety disorder other than SAD to be 3.71 percent [11].

A study found that the 12-month prevalence of comorbid mood and anxiety disorders (3.5 percent) in the Netherlands was higher than the prevalence of a pure mood disorder (ie, a mood disorder without a co-occurring anxiety disorder, eating disorder, or schizophrenia; 3.1

percent) but lower than pure anxiety disorder (7.7 percent) [12]. Of patients with mood disorders, 60.5 percent were diagnosed as having another mental disorder. Anxiety disorders were the most common category of disorders, with a prevalence of 54.3 percent among patients with a co-occurring disorder.

Clinical samples — High rates of comorbidity between anxiety disorders and depression have been observed in samples of patients receiving mental health care.

- Studies of patients with anxiety disorders have yielded a point prevalence of comorbid depression ranging from 2 to 69 percent, with lifetime rates as high as 81 percent [13-18].

Examples include:

- In a sample of 1127 outpatients with anxiety disorders, current and lifetime prevalence rates of mood disorders were 57 and 81 percent, respectively [16]. In those with a primary anxiety disorder, 30 percent met criteria for a comorbid mood disorder (major depression and/or dysthymia). The prevalence of comorbid major depression ranged from 3 percent in specific phobia to 69 percent in posttraumatic stress disorder.

- In a sample of 223 outpatients from a general hospital in Korea with MDD, 33 percent were found to have a comorbid panic disorder [17].

Small studies of samples of patients with depressive disorders have yielded variations in the point prevalence of comorbid anxiety of 44.7 to 92.1 percent [19-21].

- In an analysis of 255 depressed outpatients, 44.7 percent met diagnostic criteria for an anxiety disorder [21].

- In a sample of 72 inpatients with major depression, 54.1 percent met diagnostic criteria for at least one anxiety disorder [20].

- In a sample of 120 depressed patients who were participating in a genetics study, the odds of having a comorbid anxiety disorder with “familial” MDD were 6.6 (95% CI 3.8-11.4, p <0.001) [22].

Risk factors — Analyses of data of 3021 individuals from the Early Developmental Stages of Psychopathology study have been used to assess risk factors, temporal patterns, and longitudinal outcomes of anxiety, depression, and co-occurring anxiety and depressive disorders [23].

- A study examined the relationship between risk factors for anxiety disorders compared with depressive disorders and with co-occurring anxiety and depressive disorders [23]. Factors common to both disorder classes were: female gender, perinatal factors, and parental psychiatric history. Risk factors for the co-occurrence were a direct combination of the risk factors for either disorder alone. There were no risk factors detected specific to comorbid anxiety and depression that were not risk factors for the individual disorders as well.

- The risk of depression in individuals with anxiety disorders was significantly associated with female gender, number of anxiety disorder diagnoses, severity of anxiety disorder at baseline, and the presence of panic attacks [24].

- In older adults, risk factors for comorbid anxiety in late-life depression have been found to include lower age, female sex, less education, higher depression severity, early traumatization, neuroticism, extraversion, conscientiousness, and socioeconomic stressors [25,26].

- A study of 1024 Chinese outpatients found that individuals with co-occurring MDD and GAD, compared with those with MDD without co-occurring GAD, were more likely to be female, have a marital status of "other" (single, divorced, widowed, separated), be depressed, have poor physical and psychological quality of life, have less objective support, and have poor sleep quality [18].

An epidemiological study of a nationally representative sample of 7076 adults in the Netherlands found the following factors to be associated with co-occurring anxiety and mood disorders compared with either disorder in its pure form [12]:

- Female gender
- Younger age (25 to 34 years)
- Lower education level
- Living alone
- Unemployment
- Parental psychiatric history
- Childhood trauma

PATHOGENESIS

While our understanding of the etiology of co-occurring anxiety and depression is limited, research has identified similarities between the two disorders in their neurobiology, genetic

structure, and presence of neuroticism and harm avoidance.

Neurobiology — Research findings suggest that mood and anxiety symptoms result from a disruption in the balance of impulses from the brain's limbic system. A 2015 study reported that individuals with comorbid depression and anxiety have increased resting-state functional connectivity of the limbic network when compared with depression or anxiety alone [27].

Brain imaging studies have most consistently implicated the amygdala, anterior cingulate cortex, and insula in the pathophysiology of anxiety [28]. As examples, neuroimaging studies in posttraumatic stress disorder (PTSD), social phobia, and specific phobia found significant hyperactivity in the amygdala and insula across all three disorders [29]. Neuroimaging studies in depression have not been as consistent. Evidence suggests abnormal activity levels in the anterior cingulate, dorsolateral, medial and inferior prefrontal cortex, insula, superior temporal gyrus, basal ganglia, and cerebellum.

The most consistent abnormality across both disorder classes has been found to be hyperactivity within the amygdala. This hyperactivity appears to manifest differently in anxiety and depression. In depressed patients, baseline amygdalar activity is higher than healthy controls; however, in patients with anxiety disorders, amygdalar activation is higher only during provocation tasks [30]. Event-related potential evidence has shown that when compared with patients with anxiety disorder or depression alone, comorbid patients have abnormal frontal-greater-than-parietal P3b topography in the right hemisphere and the highest P3a amplitude at frontal and central sites. In addition, comorbid patients presented decreased activity in the cingulate gyrus, right perirhinal cortex, and right posterior parietal cortex, and increased activity in the left prefrontal cortex and left insular cortex [31].

Individuals with comorbid depression and anxiety have also been found to have lower levels of omega-3 polyunsaturated fatty acids. These levels appear to decrease as anxiety severity increases [32].

Neuropsychological factors — Personality traits and neuropsychological factors may play a role in the risk for co-occurring depression and anxiety disorders. In two large-scale studies, neuroticism was found to be the strongest and most significant predictor of comorbidity between different disorders, particularly anxiety and depression [33,34]. One of the studies examined whether comorbid anxiety and depression differed from either disorder cluster alone on neuropsychological and genetic dimensions, finding that those with the co-occurring disorders had:

- Greater impairments in working memory and attention compared with those with an anxiety disorder alone.

- Higher levels of harm avoidance and neuroticism compared with patients with depression alone, anxiety alone, or substance and alcohol disorders alone.

- A study of 74,045 adults across 24 countries found that the severity of role impairment (home management, ability to work, social life, and close relationships) and suicidal ideation were higher in those with co-occurring major depressive disorder (MDD) and anxiety compared with those with MDD alone [7].

- A study of 223 Korean outpatients found that individuals suffering from co-occurring MDD and panic disorder had increased impulsivity and more severe suicidal ideation compared with those with MDD alone [17].

- A greater likelihood of having two distinct genetic markers for harm avoidance (catechol-O-methyltransferase Met158 and brain derived neurotrophic factor Met66) compared with either disorder alone [35].

Genetics — Two studies suggest that the comorbidity between anxiety (generalized anxiety disorder [GAD] in particular) and depressive disorder could be explained in part by similarities in genetic structure.

- A study of more than 5600 same-sex twin pairs attempted to decipher the heritability of common psychiatric disorders [36]. Multivariate twin modeling analysis was used to examine clustering of DSM-III-R symptoms. Vulnerability to these phenotypes could be grouped into two clusters for anxiety and depression. The first cluster described risk for depression and generalized anxiety disorder while the second cluster described a broad risk for phobic disorders. Risk for panic disorder was shared by both clusters.

- Another analysis of same-sex twin pairs from the Virginia Twin Study showed a similar two-factor structure, with GAD, panic, agoraphobia and, to some extent, social anxiety disorder in one cluster and specific phobias in another [37].

Twin studies have suggested that the anxiety disorders and major depression were distinct entities and not simply phases of the same disease [38]. A possible explanation for the comorbidity between anxiety and depression is a common genetic etiology and the presence of neuroticism, with environmental factors playing a small role [38].

FK506 binding protein 51 (FKBP5) is a co-chaperone binding protein which modulates the function of glucocorticoid receptors. In a study examining allelic variants of FKBP5, the T allele was more frequent among patients with comorbid depression and anxiety [39].

In a study examining females with the fragile X premutation gene (ie, FMRI gene), 43 percent reported comorbid history of depression and anxiety. Comorbid women had the highest number of CGG repeats in the gene [40].

Conceptual issues — Anxiety and depression overlap in some cognitive components and clinical symptoms (table 2). In the tripartite model of emotion, a prevailing conceptual theory for emotional disorders, anxiety and depression can be deconstructed into three principal components: negative affect, physiologic hyperarousal, and low positive affect [41].

- Negative affect encompasses a wide range of negative emotional responses from fear and distress to disgust and anger. Negative affect is seen in both anxiety and depression.
- Low positive affect describes a state lacking positive emotional responses, such as happiness or pleasure. Positive emotional responses are absent in depression, but not in anxiety disorders.
- Physiologic hyperarousal is characteristic of anxiety disorders but not depression. Signs and symptoms include excessive agitation, edginess, and feeling “keyed up” or tense.

Overlap between anxiety and depression can be partially explained by the shared concept of negative affect. This conceptualization was supported in a study of outpatients with moderate levels of psychopathology and DSM-III diagnoses of major depression (262 patients), dysthymia (82), panic disorder (156), or generalized anxiety disorder (79) [42]. Factor analysis found 12 symptom components.

Depression was best explained by the presence of:

- Negative self-view
- Anhedonia
- Dysphoria

Anxiety was best explained by the presence of:

- Panic attacks
- Threatening thoughts
- Subjective worry and tension

Negative affect (eg, anhedonia, worry, and tension) was shared by both depression and anxiety. Physiologic hyperarousal (panic attacks) was unique to anxiety. Low positive affect (dysphoria) was unique to depression. Among all the factors, negative self-view had the largest influence, accounting for 17.1 percent of the variance seen in anxiety and depression.

The study showed areas of symptom overlap between anxiety and depression. Using the factor structure to predict each diagnosis, strong reliability was found for major depression and panic disorder. However, two-thirds of those diagnosed with GAD were misclassified as having panic disorder or major depression, indicating substantial overlap in symptoms.

A similar pattern of symptom overlap in major depression and anxiety disorders has been seen in other outpatient samples. An analysis of mean scores on anxiety and depression rating scales in 126 outpatients referred to an anxiety specialty clinic found substantial overlap between the two disorder classes [43]. Patients with major depression scored significantly higher on the anxiety scale than those with social phobia. Patients with major depression and patients with obsessive-compulsive disorder had the highest scores on the depression rating scale, with no differences observed among patients with one of the other anxiety disorders.

CLINICAL MANIFESTATIONS

Study of the clinical presentation of anxiety co-occurring with depression has largely focused on symptoms of generalized anxiety disorder. Co-occurring generalized anxiety disorder (GAD) and depression can present on a continuum, from principally anxiety symptoms to mixed anxiety and depression, to principally depressive symptoms.

Some of the symptoms of GAD and depression are characteristic of both disorders, while others are specific to GAD or depression (table 2) [44]:

- Symptoms specific to depression:
  - Loss of interest
  - Weight change
  - Poor appetite
  - Bradykinesia
  - Guilt or worthlessness
  - Thoughts of death
- Symptoms common to GAD and depression:
  - Dysphoric mood
  - Irritability
  - Agitation or restlessness
  - Concentration difficulties
  - Insomnia

- Fatigue

- Symptoms specific to GAD:

  - Excessive worry
  - Autonomic hyperactivity
  - Exaggerated startle response
  - Muscle tension

COURSE

Comorbid anxiety (symptoms of generalized anxiety disorders or GAD) and depressive disorders have been found to differ from the individual disorder categories in age of onset [2,21,45], life course [46], and treatment outcome. Presence of both disorders together significantly decreases the odds of recovery, increases the time to therapeutic onset for pharmacotherapy [2,23], and is associated with a more chronic course [47,48], higher symptom severity, and more functional impairment [11,49]. However, the course of the co-occurring conditions can be complex.

Onset and life course — Age of onset patterns for anxiety and mood disorders appear distinct. In a 2005 nationally representative epidemiological study in the United States, the median age of onset was 11 years for anxiety disorders and 30 years for mood disorders [2].

Data from the Early Developmental Stages of Psychopathology (EDSP) study found that [23]:

- Onset of anxiety was most likely to occur early in life, with few new cases after age 20
- Prevalence of major depression increased significantly after age 20

Age of onset for comorbid anxiety and depressive disorders varied depending on which disorder class was used as the indexing disorder. For an anxiety disorder with comorbid depression, age of onset for the comorbid conditions closely followed that of an anxiety disorder alone. The age of onset for a depressive disorder and comorbid anxiety disorder closely followed that of a depressive disorder alone.

Age of onset appears to vary by anxiety disorder. Subsequent EDSP analysis with additional follow-up data found that age of onset for GAD, panic disorder, and agoraphobia was generally in adolescence and early adulthood (similar to depression), while social anxiety disorder and specific phobias began in early childhood [45]. In a study of 255 depressed outpatients, 44.7 percent met diagnostic criteria for an anxiety disorder. The onset of both social anxiety disorder and GAD was more likely to precede the development of major depression, with the opposite

being true for obsessive-compulsive disorder (OCD), panic disorder, agoraphobia, and simple phobias [21].

Co-occurrence of anxiety and depression is associated with a more chronic course compared with either disorder alone [47]. Analysis of data from a nationally representative epidemiologic study in the United States found that, compared with individuals without GAD, patients with a primary lifetime diagnosis of GAD had an increased likelihood of both subsequent onset and persistence of a major depressive episode (MDE). A primary lifetime diagnosis of an MDE predicted the onset but not persistence of GAD. The study found that a temporal association between an MDE and GAD was highest among respondents aged 15 to 24 years. More than one-third of individuals with co-occurring MDE and GAD experienced the onset of both disorders within the same year. Despite the more chronic presentation, few differences in functional impairment have been observed between comorbid anxiety and depression and either disorder alone [21].

Depression is generally episodic in nature with modest rates of recovery, but rates of relapse are high. Anxiety disorders conversely tend to be chronic and unremitting, with low levels of recovery and moderate levels of relapse [46].

A younger age of onset for the first mental disorder was found in those with major depressive disorder (MDD) comorbid with SAD compared with a comorbidity with any other anxiety disorder or to MDD alone [11]. MDD-SAD patients also demonstrated an earlier age of onset for the first depressive episode and an earlier onset of MDD compared with those who had MDD alone.

In a similar study comparing individuals with lifetime MDD and anxiety disorder comorbidity, 68 percent reported an earlier age of onset of an anxiety disorder while 13.5 percent reported an earlier age of onset of MDD. The authors suggest that temporally primary comorbid anxiety may be a large factor in predicting MDD persistence and onset [7].

Co-occurring anxiety disorders and depression may have a worse course than the anxiety disorder alone:

- In a 12-year prospective study of patients with GAD or panic disorder with or without agoraphobia, those with comorbid major depression were half as likely to recover, compared with either disorder alone [46].
- Data from the National Epidemiologic Survey of Alcohol and Related Conditions study indicated that those with GAD and major depression were significantly more impaired in

perceived mental health quality and social functioning, compared with those with GAD alone [50].

- A 15-year prospective analysis found that prevalence of anxiety and depression together did not change over the course of the study, while prevalence of anxiety alone and depression alone increased over time [51]. This finding suggests that comorbid anxiety and depression is a more stable condition than either disorder alone. Once comorbidity develops, it is unlikely that an individual will experience a recurrence of either disorder alone, particularly anxiety.

- In a community sample of 915 women age 42 to 52 years, women with a lifetime history of a co-occurring anxiety disorder and major depression were more likely to report a history that included recurrent major depression, multiple lifetime anxiety disorders, higher rates of treatment seeking, and current elevations in current anxiety and depressive symptoms, compared with women without a history of an anxiety disorder or major depression occurring concurrently or separately [8].

Treatment response — The presence of both depression and anxiety appears to have a poorer response to treatment than either disorder individually:

- In the Sequenced Treatment Alternative to Relieve Depression trial, outpatients with anxious depression (ie, a diagnosis of major depression and an anxiety/somatization subscale score greater than seven on the Hamilton Rating Scale for Depression) had significantly lower response and remission rates and poorer outcomes, compared with patients with non-anxious depression [52,53]. Depressed patients with anxiety took longer to improve than depressed patients without anxiety [54].

- In multiple clinical trials of patients diagnosed with anxiety disorders (GAD, panic disorder, social anxiety disorder, and OCD), the presence of co-occurring depression has been associated with poorer response of the anxiety disorder to pharmacotherapy and psychotherapy, compared with those with the anxiety disorders alone [55-59]. These trials suffered from several methodologic limitations, including that participants with comorbid depression had more severe symptoms of anxiety at baseline in some of the trials. Findings on functional outcomes and change in depressive symptoms were mixed.

ASSESSMENT AND DIAGNOSIS

A diagnostic assessment for potential co-occurring anxiety disorders and depressive disorders should include careful patient history, a complete physical examination, and appropriate

laboratory studies. The medical history should address medical illnesses, medication side effects, and substance use or withdrawal that can produce anxiety or anxiety-like symptoms (table 3 and table 4) or depressive symptoms. (See "Unipolar depression: Pathogenesis", section on 'Secondary depression'.)

The psychosocial history should screen for stressful life events, family psychiatric history, current social history, substance use history (including caffeine, nicotine, and alcohol), and past sexual, physical, and emotional abuse, or emotional neglect.

Diagnoses of co-occurring depressive and anxiety disorders are based on DSM-5 criteria for the individual disorders [1]. Two syndromes – mixed anxiety and depression, and anxious depression – include symptoms of anxiety, depression, or both that are beneath the threshold required by DSM-5 criteria for individual anxiety or depressive disorders. These emerging constructs may prove to be clinically useful, but require further research.

After diagnoses of both depression and an anxiety disorder have been made, the primary diagnosis should be established. The disorder incurring the greatest distress and impairment to the individual is typically considered the primary diagnosis.

Co-occurring depression and anxiety disorders — DSM-5 diagnostic criteria for depression and anxiety disorders are described below.

- Major depressive disorder (MDD) (table 5)
- Dysthymia (table 6)
- Generalized anxiety disorder (GAD) (table 7)
- Obsessive-compulsive disorder (OCD) (table 8)
- Panic disorder (table 9)
- Social anxiety disorder (table 10)
- Specific phobia (table 11)
- Agoraphobia (table 12)

PTSD and OCD, classified as anxiety disorders in DSM-IV, were moved to newly formed categories of their own in the revision to DSM-5 [1]. Co-occurring PTSD and depression is discussed separately. (See "Posttraumatic stress disorder in adults: Epidemiology, pathophysiology, clinical features, assessment, and diagnosis".)

Major depressive disorder with anxious distress — Anxious distress was included as a specifier of major depression in DSM-5 [1]. Anxious distress is characterized by the presence of two or more of the following symptoms during most days of the depressive episode (see

"Unipolar depression in adults: Assessment and diagnosis", section on 'Depressive episode subtypes (specifiers)'):

- Feeling keyed-up or tense
- Feeling unusually restless
- Difficulty concentrating because of worry
- Fear that something awful will happen
- Feeling that the individual might lose control of themselves

DSM-5 criteria characterize the current severity of anxious distress as follows:

- Mild: Two symptoms
- Moderate: Three symptoms
- Moderate-severe: Four to five symptoms
- Severe: Four to five symptoms with motor agitation

Analyses of data from the Sequenced Treatment Alternative to Relieve Depression clinical effectiveness trial [52,60] have supported the diagnosis of major depressive disorder with anxious distress. In an analysis of data on 1450 outpatients meeting DSM-IV-TR criteria for major depression, 46 percent had a Hamilton Rating Scale for Depression anxiety/somatization subscale score ≥7. Compared with depressed patients without high levels of anxiety, these patients were more likely to be [60]:

- Older
- Less educated
- Severely depressed
- Suicidal

Their rates of treatment response and remission were significantly lower, with a greater time to the onset of a clinical response [54]. High levels of anxiety have generally been associated with increased suicide risk, longer duration of illness and greater likelihood of treatment non-response. These results support the addition of the anxious distress specifier to diagnostic criteria for major depression.

DSM-5 does not require patients with comorbid anxiety disorders to be excluded when diagnosing a patient with major depressive disorder with anxious distress. There is some concern among experts that use of the anxious distress specifier may lead clinicians to forget about diagnosing comorbid anxiety disorders under the assumption that the “anxious distress” sufficiently characterizes the clinical presentation of the patient. Clinicians should instead be

prompted by the use of the specifier to then take the next step of assessing the patient for a comorbid anxiety disorder, for which specific treatments may be indicated.

Mixed anxiety and depression — Mixed anxiety and depression (MAD) has been defined in the International Classification of Diseases, 10th Revision (ICD-10) as a condition where the symptoms of both anxiety and depression are present for at least one month, with neither being clearly predominant nor sufficient to meet diagnostic criteria for either an anxiety or a depressive disorder [61]. ICD-10 does not provide additional criteria for diagnosing the disorder. Proposed criteria appeared in the appendix of DSM-IV-TR as a disorder in need of further study. MAD was not included in DSM-5, owing to the fact that systematic review of research failed to support its existence.

Differential diagnosis — The differential diagnoses of individual anxiety disorders and depressive disorders are described separately.

- (See "Unipolar depression in adults: Epidemiology".)
- (See "Unipolar depression in adults: Assessment and diagnosis".)
- (See "Unipolar depression in adults: Course of illness".)
- (See "Generalized anxiety disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis".)
- (See "Social anxiety disorder in adults: Epidemiology, clinical features, assessment, and diagnosis".)
- (See "Obsessive-compulsive disorder in adults: Epidemiology, clinical features, and diagnosis".)
- (See "Panic disorder in adults: Epidemiology, clinical manifestations, and diagnosis".)
- (See "Agoraphobia in adults: Epidemiology, pathogenesis, clinical manifestations, course, and diagnosis".)

A table distinguishes among symptoms shared by depression and GAD, symptoms specific to depression, and symptoms specific to GAD (table 2).

Diagnostic reliability — Given the overlap in DSM diagnostic criteria for depression and anxiety disorders, the accuracy of diagnosis of these disorders has been questioned, and study findings have been mixed:

- A study of clinical diagnosis in 362 outpatients found good to excellent inter-rater reliability for the disorders [62]. Structured interviews were conducted by clinical psychologists and advanced graduate students.

- A cross-sectional study found evidence of poor diagnostic accuracy in clinical samples of 666 patients with "pure" GAD, 772 "pure" with a major depressive episode, and 278 with co-occurring GAD and major depression [63]. Primary care clinicians made accurate diagnoses in only 34 percent of patients with GAD and 64 percent of patients with a major depressive episode.

Rating scales — Scales that have demonstrated good reliability and validity in the assessment of anxiety and depression, either presenting individually or co-occurring, include the following:

- **Depression and anxiety** – The Depression and Anxiety Stress Scale (DASS) is potentially the most useful instrument for the assessment of patients with co-occurring depression and GAD symptoms, or when discrimination among mixed anxiety and depressive symptoms is unclear [64]. DASS has been shown to be reliable, accurate in its assessment of global anxiety, and able to separate anxiety and depressive symptoms.

- **Depression** – The Montgomery Asberg Depression Rating Scale has been shown to be superior to other clinician-administered instruments, best capturing symptoms of depression [65]. It has demonstrated excellent discrimination between depressed and non-depressed individuals [66], and between self-assessed depression and personality disorders [67]. It has also demonstrated good reliability and validity in older adult populations [68].

- **Generalized anxiety** – The Hamilton Rating Scale for Anxiety (HAMA) is the gold standard measure for the assessment of GAD symptom severity. This scale is reliable and valid, particularly when used with a structured interview guide [69]. The HAMA has demonstrated good ability to discriminate between anxiety and depression [70].

- **OCD** – The Yale Brown Obsessive Compulsive Scale (YBOCS) has shown good discrimination between OCD and depression as well as other anxiety disorders in initial validation study, and good sensitivity to change [71,72]. The self-report adaptation of the 10-item YBOCS scale and symptom checklist has shown similar reliability patterns [73].

- **Panic disorder** – The most commonly used observer-rated scale for panic disorder is the seven-item Panic Disorder Severity Scale (PDSS), which has demonstrated good inter-rater reliability and internal consistency with favorable validity and sensitivity to change when compared to diagnostic interview [74,75].

- **PTSD** – The Clinician Administered PTSD Scale (CAPS) has emerged as the most widely used instrument in clinical trials and has proven to be both an effective assessment tool

and severity measure, despite substantial correlation with other measures of depression and anxiety [76].

Despite their wide use, the State Trait Anxiety Inventory and the Hamilton Rating Scale for Depression have been criticized for an inability to distinguish between anxious and depressive symptoms [77-80].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Anxiety and anxiety disorders in adults".)

SUMMARY AND RECOMMENDATIONS

- **Comorbid mood and anxiety disorders** – Population-based studies conducted in several countries have shown high rates of co-occurrence between anxiety disorders and mood disorders. Mood disorders have shown the highest correlations with generalized anxiety disorder (GAD) and the lowest with agoraphobia and specific phobias (table 1). (See 'Epidemiology' above.)

- **Risk factors** – Research has found that patients with co-occurring anxiety and mood disorders are more likely to be female, younger (25 to 34 years), have a lower education level, live alone, be unemployed, have a parental psychiatric history, and to have experienced childhood trauma than those with purely an anxiety or mood disorder. (See 'Risk factors' above.)

- **Pathogenesis** – While our understanding of the etiology of co-occurring anxiety and depression is limited, research has identified similarities between the two disorders in their neurobiology, genetic structure, and presence of neuroticism and harm avoidance. (See 'Pathogenesis' above.)

- **Clinical manifestations** – Co-occurring GAD and depression can present on a continuum, from principally anxiety symptoms to mixed anxiety and depression, to principally depressive symptoms. Symptoms commonly present in either disorder include irritability, agitation/restlessness, difficulties concentrating, insomnia, and fatigue (table 2). (See 'Clinical manifestations' above.)

- **Course** – Co-occurring anxiety and depressive disorders have been found to differ from the individual disorder categories in age of onset, life course, and treatment outcome. Presence of both disorders together significantly decreases the odds of recovery, increases the time to therapeutic onset for pharmacotherapy, and is associated with a more chronic course. (See 'Course' above.)

- **Assessment and diagnosis** – Our diagnostic assessment for potentially co-occurring anxiety and depressive disorders includes a careful history and complete physical examination. We screen for stressful life events, family psychiatric history, social history, history of substance use and history of past sexual, physical, or emotional abuse.

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