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Defining Anxious Depression: A Review of the Literature

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Abstract

The diagnosis of anxious depression is presently inconsistent. The many different definitions of anxious depression have complicated its diagnosis, leading to clinical confusion and inconsistencies in the literature. This paper reviewed the extant literature in order to identify the varying definitions of anxious depression, which were then compared using Feighner's diagnostic criteria. Notably, these suggest a different clinical picture of patients with anxious depression. For instance, relying on ICD-10 or DSM diagnoses yields a clinical picture of a comparatively mild or transient disorder; in contrast, using dimensional criteria such as DSM criteria combined with additional rating scales—most commonly the anxiety somatization factor score from the Hamilton Depression Rating Scale (HAM-D)—yields a more serious clinical picture. The evidence reviewed here suggests that defining anxious depression in a dimensional manner may be the most useful and clinically relevant way of differentiating it from other types of mood and anxiety disorders, and of highlighting the most clinically significant differences between patients with anxious depression versus depression or anxiety alone.

Keywords

Mixed anxiety depressive disorder; DSM-V; anxious depression; diagnosis; anxiety; depression

Introduction

The concept of anxious depression as a separate diagnostic entity or subtype is presently both unclear and controversial. Although depression and anxiety are traditionally conceptualized as two independent disorders, they are highly co-morbid, with rates ranging from 40%–50%.^{1–3} Despite this, no consistent criteria have been established to define anxious depression as a distinct disease state. In fact, clinicians and researchers conceptualize the idea of mixed anxiety and depressive states several different ways. Our lack of knowledge in this area underscores how important nosological exploration of this disease is, given that relevant treatment recommendations are often based on diagnostic criteria. In addition, the terms 'anxious depression', 'mixed anxiety depressive disorder', and 'mixed anxiety depression', are often used interchangeably, further complicating this diagnosis from both clinical and research standpoints.

This review investigated the notion of anxious depression as a separate diagnostic entity, and the manner in which uncertainty surrounding its diagnosis has created clinical confusion. A review of the literature was conducted to explore the various ways that anxious

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depression is currently defined. Feighner's diagnostic criteria⁴ (Table 1) have previously been set forth as a framework for establishing diagnostic validity in psychiatric disease, and are useful in comparing data between various research groups. In this review, Feighner's diagnostic criteria were used to organize the disparate findings, and to review and compare the extant evidence supporting the definition of anxious depression as an independent diagnosis.

Methods

A PubMed search was conducted for articles written in English, pertaining to adult human research, and published through October 2012 using the following search terms: *mixed anxiety depressive disorder*; *cothymia*; *anxious depression*; *agitated depression*; and *comorbid anxiety depression*. A total of 372 articles were initially found. Further review narrowed the data to 29 studies related to anxious depression as a diagnostic entity. Because different terms and criteria are used to describe anxious depression, this paper uses several different terms consistent with the respective sets of criteria that define them.

In a landmark 1972 paper, Feighner and colleagues proposed a set of standardized diagnostic criteria to define a variety of psychiatric diseases as a way to improve diagnostic consistency.⁴ These widely-used and influential criteria emphasize several key points in psychiatric research: the systematic use of operationalized diagnostic criteria; an emphasis on illness course and outcome; and an emphasis on the need, whenever possible, to base diagnostic criteria on empirical evidence. Feighner's original criteria were broken down using the following headings: Clinical Description, Laboratory Studies, Delimitation from Other Disorders, Follow-up Studies, and Family Studies (Table 1). Here, we used Feighner's framework to compare the different definitions of anxious depression, using the same subheadings.

Culling the extant literature yielded four main ways of breaking down the data: ICD-10 criteria, DSM criteria (both DSM-IV and DSM-5), Dimensional Criteria, and Syndromal Criteria. Table 2 gives a brief overview of these various diagnostic criteria, which are reviewed in greater detail below.

ICD Criteria

Clinical Description—The ICD-10 was the first to introduce the diagnosis of “mixed anxiety-depression” in 1992 in response to mounting evidence that co-morbid anxiety and depression were prevalent in patients who did not meet full criteria for either disorder.⁵ ICD-10 requires the presence of mild symptoms of both anxiety and depression that are not severe enough to qualify for either full diagnosis (Table 3). The ICD-10 further acknowledges the imprecision of the definition for research purposes.

Laboratory Studies—None.

Delimitation from Other Disorders—Symptoms for mixed anxiety depression could not meet criteria for another diagnosis.

Follow-up Studies—One study found that primary care patients with ICD-10-diagnosed mixed anxiety depression were twice as likely to be psychologically distressed three months from baseline compared to those with no diagnosis, though this lessened to non-significant levels at one year; no predictors of persistent or recurrent distress were found.⁶ They were more likely to be female, to endorse somatic symptoms, and to have a history of psychiatric difficulties. Subjects were no more likely to have a documented psychiatric problem by their

general practitioner and were no more likely to frequently attend a primary care clinic than subjects with other ICD-10 psychiatric diagnoses.⁶

Data from the Munich Follow-Up Study found a rate of mixed anxiety depression of only 0.8% in the general adult population.⁷ Another primary care study showed a low rate of diagnostic stability.⁸ In that study, only 1.2% of patients diagnosed with mixed anxiety depression at baseline had the disease 12 months later; patients had either remitted or progressed to other diagnoses. In contrast, of 78 patients with no psychiatric history interviewed in a primary care setting, 12.8% met ICD-10 criteria for mixed anxiety depression.⁹ Their level of disability was comparable to that of patients with full syndromal depression and anxiety. Notably, in addition to using ICD-10 criteria, the authors also used the following modified DSM criteria: 1) failure to meet any DSM-III-R diagnosis for a depressive or anxiety disorder; 2) at least 10 days of either a) feeling depressed or down most days or, b) noticeable loss of interest in activities nearly every day; 3) consistent presence of at least two remaining DSM-III-R criteria for major depressive disorder (MDD); and 4) consistent presence of at least three of 18 DSM-III-R symptoms of generalized anxiety. This modification did not require the presence of autonomic symptoms (unlike the ICD criteria) and did not exclude patients with a history of anxiety or depressive disorders (unlike the DSM criteria).

As part of the National Psychiatric Morbidity survey conducted in Great Britain, the Clinical Interview Schedule – Revised (CIS-R) generated ICD-10 diagnoses for the general population.¹⁰ Those not meeting full criteria for anxiety or depression, but with scores 12 on the CIS-R overall psychological morbidity scale, were given the diagnosis of mixed anxiety depression. This group comprised 8.8% of all participants, and was the most prevalent among mental health disorders.¹⁰

Family Studies—None.

DSM-IV Criteria

Clinical Description—Field trials provided insufficient evidence to include anxious depression as an official Axis I diagnosis in the DSM-IV. Instead, mixed anxiety depressive disorder was included as an area for further research in the DSM-IV's *Appendix* (see Table 3 for the full criteria).^{11–12} Interestingly, the final criteria did not require the presence of *both* anxiety and depressive symptoms.

Laboratory Studies—None

Delimitation From Other Disorders—Symptoms could not be due to the direct physiological effects of a substance, general medical condition, another anxiety or mood disorder, and could not be better accounted for by any other mental disorder. Past diagnoses of MDD, dysthymic disorder, panic disorder (PD), or generalized anxiety disorder (GAD) were not permitted.

Follow-up Studies—Perhaps reflecting an increased need for diagnostic clarity, many studies used modified criteria instead of strictly using criteria proposed by DSM-IV. For instance, one group allowed for a history of MDD, dysthymic disorder, PD, or GAD in their primary care sample; 10 of the 539 participants (2%) had mixed anxiety depressive disorder at baseline.¹³ However, when strict DSM-IV criteria were applied, this dropped to four participants, or 0.2%. No significant differences in physical or emotional well-being were found between those with mixed anxiety depressive disorder and those with other anxiety disorders.¹³ None of the participants with mixed anxiety depressive disorder endorsed a

history of suicide attempts, and they had higher global assessment of functioning (GAF) scores. In addition, mixed anxiety depressive disorder did not appear to be a stable diagnosis. The probability of remission at six- and 12-month follow-up were 70% and 80%, respectively; these remission rates were significantly higher than those for GAD, MDD, and PD with agoraphobia for the same time frame.¹³ None of the patients who remitted were taking psychiatric medication, and only one was in psychotherapy. One of the remaining cases of mixed anxiety depressive disorder converted to MDD. As a result, the authors called into question the utility of mixed anxiety depressive disorder as a separate diagnostic category, as it appeared to often be transient and not require intervention.

Another group modified DSM-IV criteria by asking questions about generalized anxiety, depression, interference from symptoms, and recency of symptoms.¹⁴ They found that of 37 patients eligible for a diagnosis of mixed anxiety depressive disorder, none actually met their modified DSM-IV criteria. Another study changed the DSM-IV criteria slightly by decreasing length of criteria from four weeks to two weeks, and omitted criteria 3 and 5c (see Table 3); they found no difference between those with mixed anxiety depressive disorder and those with subthreshold anxiety or subthreshold depression with regard to care utilization, functioning, and course of illness over two years.¹⁵ The authors concluded that mixed anxiety depressive disorder was not a relevant diagnosis in terms of consequence or prevalence.

Family Studies—Patients with mixed anxiety depressive disorder did not differ with regard to familial depression or anxiety compared to those with no psychiatric diagnosis. When compared to either co-morbid patients or to those with at least one depressive or anxiety disorder, mixed patients showed *less* familial depression and anxiety.¹⁶

DSM-V Criteria

The DSM-V committee decided to omit the diagnosis of mixed anxiety depressive disorder for several reasons. Most notably, a recent estimate of test-retest reliability of mixed anxiety depressive disorder found that the diagnosis could not be reliably separated from MDD or GAD.¹⁷ In this field trial, MDD and GAD had low reliability, in part because of their high co-morbidity with other disorders and their heterogeneous populations. To address this, the DSM-V added an anxious distress specifier to MDD as a way to incorporate common anxious symptoms. Batelaan and colleagues¹⁸ had separately proposed several arguments against having mixed anxiety depressive disorder in the DSM-V, including: 1) the new criteria might inflate prevalence rates compared to DSM-IV, as the duration of symptoms would be lowered to two weeks instead of one month; this loosening of the criteria might increase the false-positive rate, leading to unnecessary treatment; 2) few differences were found to exist between mixed anxiety depressive disorder and subthreshold anxiety or depression,¹⁵ thus the need for a separate category was questionable;¹⁸ and 3) concern had been expressed regarding the validity of the diagnosis, given that it has low diagnostic stability over time. Indeed, several studies have shown that most patients did not continue to meet criteria at follow up^{15, 18}, either because of remittance or change in diagnosis.⁸

Dimensional Criteria

Clinical Description—When defined in a dimensional matter, anxious depression most often consists of MDD (based on DSM criteria) plus concurrent high levels of anxiety (defined as a baseline anxiety/somatization factor score of ≥ 7 from the 17-item or 21-item Hamilton Depression Rating Scale; HAM-D).^{19–22} This score encompasses hypochondriasis, insight, general and gastrointestinal somatic symptoms, and psychic and somatic anxiety.²³

Alternative dimensional criteria have also been proposed. Seo and colleagues defined anxious depression as a DSM-IV diagnosis of either MDD, dysthymic disorder, or depressive disorder not otherwise specified (NOS), plus a score on the Hamilton Anxiety Rating Scale (HAM-A) of ≥ 20 .²⁴ Another group recommended a score of ≥ 18 on the HAM-D and ≥ 9 on the HAM-A,²⁵ regardless of DSM or ICD diagnoses. Similarly, Clayton and colleagues²⁶ based their dimensional diagnosis of anxious depression on a score of ≥ 16 on six items from the Schedule for Affective Disorders for Schizophrenia (SADS): 1) worry, brooding, painful pre-occupation, and inability to get rid of unpleasant thought, 2) panic attacks, 3) somatic anxiety, 4) psychic anxiety, 5) phobia, 6) obsessions or compulsions. In addition, several groups used Research Domain Criteria (RDC) for depression combined with scores from various scales to define anxious depression.^{26–28}

Laboratory Studies—None

Delimitation From Other Disorders—Patients could not meet dimensional criteria for anxious depression if they met exclusion criteria from the DSM or ICD for MDD. Patients would also be excluded for not meeting anxiety cut-off scores, which varied based on the study.

Follow-up Studies—Fava and colleagues found that 44 to 53.1% of MDD participants in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study had anxious depression,^{19–21} defined as having MDD plus a baseline HAM-D anxiety/somatization factor score of ≥ 7 . In this sample, anxious depression was more common among women, African Americans, and Hispanics, and those who were married, divorced, or widowed compared to those who never married. It had a higher prevalence in primary care settings than specialty psychiatric care settings. Subjects with anxious depression were also more likely to be unemployed, less educated, publically insured, older, and with lower income. No difference in age of onset or number of episodes was found.^{19–21} Another study using the criteria found that inpatients with anxious depression were older, had less education, and were more often (prematurely) retired.²²

Interestingly, in the STAR*D study, subjects with anxious depression had a unique clinical profile that was independent of severity of depression, and included longer duration of current episode, higher endorsement of melancholic depression symptoms, and more medical co-morbidities. They were also more likely to meet criteria for an anxiety disorder,^{20, 22} to endorse suicidal ideation, to have attempted suicide, and to have lower remission and response rates.²⁰ In addition, subjects with anxious depression showed poorer treatment outcomes and reported a greater frequency, intensity, and burden of side effects.^{20, 22} These subjects also had lower remission rates, kept fewer appointments, and spent less time in treatment.^{20, 29} Furthermore, and using the same dimensional criteria as Fava and colleagues, Papakostas and colleagues found that anxious depression negatively influenced the relative degree of symptom reduction.³⁰

Using RDC for depression as well as SADS scores, Clayton and colleagues²⁶ observed that depressed subjects with high anxiety took twice as long to recover from index depressive episodes as depressed subjects with low anxiety. Using the RDC, Joffe and colleagues²⁸ found that depressed patients with high anxiety had worse scores on both the Beck Depression Inventory (BDI) and the 17-item HAM-D, and more functional impairment. However, they were only slightly less likely to respond to antidepressants than depressed patients with low anxiety levels. Fawcett and colleagues²⁷ found that depression associated with severe psychic anxiety and panic attacks was associated with suicide within one year, further underscoring the links between anxiety, depression, and suicidal behavior.

Seo and colleagues used DSM-IV criteria for MDD and depression not otherwise specified plus a HAM-A score of ≥ 20 to define anxious depression.²⁴ They found that those with anxious depression had a longer duration of illness, endorsed more suicidal ideation, and had more past suicide attempts than those with non-anxious depression, findings that echoed the STAR*D data. They also found that subjects with anxious depression reported more depressive episodes and younger age of onset.

Family Studies—Fava and colleagues found that anxious depression was associated with a greater likelihood of a family history of drug abuse,²⁰ but not depression or other mood disorders.²¹ Similarly, Seo and colleagues²⁴ found no significant family history of depression or other psychiatric disorders in subjects with anxious depression. However, another study found that individuals with anxious depression had more family history of depression—but not anxiety or alcoholism—in first-degree relatives.²⁶

Syndromal Criteria

Clinical Description—A syndromal approach has been proposed to include patients with co-morbid anxiety and depressive disorders based on either ICD or DSM criteria. Similarly, the term “cothymia” has been proposed to describe those with dysthymic disorder and either PD, GAD, or all three disorders as defined by DSM criteria.³¹

Laboratory Studies—None

Delimitation From Other Disorders—Subjects must have met criteria for at least one anxiety disorder and one depressive disorder; one disorder plus symptoms of the other would not be enough to qualify for the diagnosis.

Follow-up Studies—Data from the Munich Follow-Up Study showed that co-morbidity of anxiety and depressive disorders based on DSM-III criteria was 44.7% in an epidemiologic sample and 67.8% in a clinical setting.⁷ Another study of co-morbid patients based on DSM-IV criteria showed that their index episodes were more severe and protracted, occurred at an earlier age, and more often required treatment than those with depression or anxiety disorders alone.³² In that sample, 55.3% went on to develop a chronic course and their median episode duration was over 24 months, worse than either diagnosis alone. Another study using ICD-10 criteria found that 26.1% of those with co-morbid anxiety and depression continued to have both diagnoses at one year follow-up.⁸ Co-morbid subjects were more likely to report poor health, worse functioning, and unemployment than those with ICD-10-diagnosed mixed anxiety depression.¹⁰ Strikingly, several groups reported that anxiety co-morbid with depression increases risk of suicide,³³ including both lifetime suicide attempts¹⁰ and completed suicides.³⁴

Another study found that cothymic patients had worse social functioning and worse scores on the Neurotic Disorder Outcome Scale at 12-year follow-up than patients with only one diagnosis.³¹ Jeste and colleagues³⁵ examined 352 depressed inpatients and outpatients aged 59 and older. They found that 42% had anxious depression, as determined by the Duke Depression Evaluation Schedule, which assessed DSM diagnoses of MDD and lifetime GAD symptoms using the NIMH Diagnostic Interview Schedule. In addition, co-morbid subjects were younger, endorsed more suicidal ideation, and had worse subjective social support.

Interestingly, Diefenbach and colleagues³⁶ defined anxious depression as a combination of dimensional and syndromal criteria. In their urban sample of subjects aged 60 and older, anxious depression was defined as MDD plus symptoms of GAD or anxiety symptoms not

otherwise meeting diagnostic criteria. In those with MDD, anxious symptoms were more common in Puerto Ricans (60.6%) than African Americans (48.4%), and those with anxious depression reported more depressive symptoms and suicidality.

Family Studies—Jeste and colleagues found no significant family history in subjects with anxious depression.³⁵ One twin study examined the association between life events and anxious depression, as measured by the Young Adult Self Report.³⁷ Although DSM criteria were not used, scores from this scale had previously been found to correlate with DSM-IV MDD and anxiety diagnoses by this research group. No gene-environment correlations were found for life events and the development of anxious depression.

Conclusions

Current definitions of anxious depression are inconsistent. As the evidence reviewed above has underscored, this diagnostic confusion has also led to considerable clinical confusion vis-à-vis the clinical profile of a patient with anxious depression. This is an issue of considerable nosological importance.

Using DSM and ICD-10 diagnostic criteria yields a clinical picture of a disorder that is often milder and more transient than a diagnosis of either depressive or anxiety disorders alone, bringing into question the usefulness of these diagnoses clinically and for research. Under those criteria, a diagnosis of anxious depression may represent transient variants of normal mood, or prodromal states for anxiety and mood disorders. Indeed, the DSM-V no longer includes mixed anxiety depressive disorder as an area warranting further research.

In contrast—and perhaps in response to the difficulty in capturing a “true” syndrome using ICD-10 or DSM criteria alone—defining anxious depression in a dimensional manner yields a considerably more serious clinical picture, and may be the most useful way of differentiating anxious depression from other types of mood and anxiety disorders. The evidence from dimensional studies suggests that anxiety accompanies depression at higher rates than expected, worsens depression outcome, and increases risk of suicide, all of which have important implications for clinical care. Notably, dimensional diagnoses of anxious depression—which typically combine DSM-diagnosed MDD with anxiety/somatization scores on the HAM-D—have, thus far, provided the most clinically relevant data on differences between subjects with anxious depression and their non-anxious counterparts. One key explanation for these differences in severity is that dimensional criteria, by definition, rely on more serious diagnoses. Because patients must meet full criteria for MDD in order to meet dimensional criteria for anxious depression, their illness will be more severe than those who only manifest subsyndromal symptoms in order to meet diagnostic criteria (eg, those with ICD-10 and DSM diagnoses).

This review has also highlighted the dearth of information regarding laboratory and family studies, and thus the need for future research projects in these areas. In addition, few studies have examined the stability of anxious depression over time, particularly using dimensional criteria. Over the last few decades, and despite significant research, no real reductions in prevalence, morbidity, or mortality have been seen for patients with depression.³⁸ Diagnostic clarification may help, and thus future efforts should be aimed at projects that use consistent definitions of anxious depression. With the release of the DSM-V, the anxious distress specifier for MDD will allow for investigations into anxious depression using this new category. In addition, using dimensional criteria to conduct further research may elucidate the usefulness of this diagnosis for both clinicians and researchers alike, and determine whether a mixed anxious depression state warrants a separate diagnosis in future DSM and ICD editions.

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References

1. Fava M, Rankin MA, Wright EC, et al. Anxiety disorders in major depression. *Compr Psychiatry*. Mar-Apr;2000 41(2):97–102. [PubMed: 10741886]
2. Sanderson WC, Beck AT, Beck J. Syndrome comorbidity in patients with major depression or dysthymia: prevalence and temporal relationships. *Am J Psychiatry*. Aug; 1990 147(8):1025–1028. [PubMed: 2375436]
3. Zimmerman M, Chelminski I, McDermt W. Major depressive disorder and axis I diagnostic comorbidity. *J Clin Psychiatry*. Mar; 2002 63(3):187–193. [PubMed: 11926716]
4. Feighner JP, Robins E, Guze SB, Woodruff RA Jr, Winokur G, Munoz R. Diagnostic criteria for use in psychiatric research. *Arch Gen Psychiatry*. Jan; 1972 26(1):57–63. [PubMed: 5009428]
5. World Health Organization. International statistical classification of diseases and related health problems. 10. Geneva: World Health Organization; 1992. revision. ed
6. Walters K, Buszewicz M, Weich S, King M. Mixed anxiety and depressive disorder outcomes: prospective cohort study in primary care. *Br J Psychiatry*. Jun; 2011 198(6):472–478. [PubMed: 21628709]
7. Wittchen HU, Essau CA. Comorbidity and mixed anxiety-depressive disorders: is there epidemiologic evidence? *J Clin Psychiatry*. Jan; 1993 54(Suppl):9–15. [PubMed: 8425875]
8. Barkow K, Heun R, Wittchen HU, Bedirhan Ustun T, Gansicke M, Maier W. Mixed anxiety-depression in a 1 year follow-up study: shift to other diagnoses or remission? *J Affect Disord*. Apr; 2004 79(1–3):235–239. [PubMed: 15023500]
9. Stein MB, Kirk P, Prabhu V, Grott M, Terepa M. Mixed anxiety-depression in a primary-care clinic. *J Affect Disord*. May 17; 1995 34(2):79–84. [PubMed: 7665808]
10. Das-Munshi J, Goldberg D, Bebbington PE, et al. Public health significance of mixed anxiety and depression: beyond current classification. *Br J Psychiatry*. Mar; 2008 192(3):171–177. [PubMed: 18310574]
11. American Psychiatric Association., American Psychiatric Association. Task Force on DSM-IV. Diagnostic and statistical manual of mental disorders : DSM-IV. 4. Washington, DC: American Psychiatric Association; 1994.
12. Zinbarg RE, Barlow DH, Liebowitz M, et al. The DSM-IV field trial for mixed anxiety-depression. *Am J Psychiatry*. Aug; 1994 151(8):1153–1162. [PubMed: 8037250]
13. Weisberg RB, Maki KM, Culpepper L, Keller MB. Is anyone really M.A.D.?: the occurrence and course of mixed anxiety-depressive disorder in a sample of primary care patients. *J Nerv Ment Dis*. Apr; 2005 193(4):223–230. [PubMed: 15805817]
14. Means-Christensen AJ, Sherbourne CD, Roy-Byrne PP, et al. In search of mixed anxiety-depressive disorder: a primary care study. *Depress Anxiety*. 2006; 23(4):183–189. [PubMed: 16511832]
15. Spijker J, Batelaan N, de Graaf R, Cuijpers P. Who is MADD? Mixed anxiety depressive disorder in the general population. *J Affect Disord*. Feb; 2010 121(1–2):180–183. [PubMed: 19577307]
16. Balestrieri M, Isola M, Quartaroli M, Roncolato M, Bellantuono C. Assessing mixed anxiety-depressive disorder. A national primary care survey. *Psychiatry Res*. Apr 30; 2010 176(2–3):197–201. [PubMed: 20129676]

17. Regier DA, Narrow WE, Clarke DE, et al. DSM-5 Field Trials in the United States and Canada, Part II: Test-Retest Reliability of Selected Categorical Diagnoses. *Am J Psychiatry*. Oct 30;2012
18. Batelaan NM, Spijker J, de Graaf R, Cuijpers P. Mixed anxiety depression should not be included in DSM-5. *J Nerv Ment Dis*. Jun; 2012 200(6):495–498. [PubMed: 22652614]
19. Fava M, Alpert JE, Carmin CN, et al. Clinical correlates and symptom patterns of anxious depression among patients with major depressive disorder in STAR*D. *Psychol Med*. Oct; 2004 34(7):1299–1308. [PubMed: 15697056]
20. Fava M, Rush AJ, Alpert JE, et al. Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR*D report. *Am J Psychiatry*. Mar; 2008 165(3):342–351. [PubMed: 18172020]
21. Fava M, Rush AJ, Alpert JE, et al. What clinical and symptom features and comorbid disorders characterize outpatients with anxious major depressive disorder: a replication and extension. *Can J Psychiatry*. Nov; 2006 51(13):823–835. [PubMed: 17195602]
22. Wiethoff K, Bauer M, Baghai TC, et al. Prevalence and treatment outcome in anxious versus nonanxious depression: results from the German Algorithm Project. *J Clin Psychiatry*. Aug; 2010 71(8):1047–1054. [PubMed: 20673545]
23. Cleary PGW. Factor analysis of Hamilton depression scale. *Drugs Exp Clin Res*. 1977; (1):115–120.
24. Seo HJ, Jung YE, Kim TS, et al. Distinctive clinical characteristics and suicidal tendencies of patients with anxious depression. *J Nerv Ment Dis*. Jan; 2011 199(1):42–48. [PubMed: 21206246]
25. Silverstone PH, von Studnitz E. Defining anxious depression: going beyond comorbidity. *Can J Psychiatry*. Nov; 2003 48(10):675–680. [PubMed: 14674050]
26. Clayton PJ, Grove WM, Coryell W, Keller M, Hirschfeld R, Fawcett J. Follow-up and family study of anxious depression. *Am J Psychiatry*. Nov; 1991 148(11):1512–1517. [PubMed: 1928465]
27. Fawcett J, Scheftner WA, Fogg L, et al. Time-related predictors of suicide in major affective disorder. *Am J Psychiatry*. Sep; 1990 147(9):1189–1194. [PubMed: 2104515]
28. Joffe RT, Bagby RM, Levitt A. Anxious and nonanxious depression. *Am J Psychiatry*. Aug; 1993 150(8):1257–1258. [PubMed: 8328574]
29. Farabaugh A, Alpert J, Wisniewski SR, et al. Cognitive therapy for anxious depression in STAR(D): What have we learned? *J Affect Disord*. Dec 15; 2012 142(1–3):213–218. [PubMed: 22877961]
30. Papakostas GI, Fan H, Tedeschini E. Severe and anxious depression: combining definitions of clinical sub-types to identify patients differentially responsive to selective serotonin reuptake inhibitors. *Eur Neuropsychopharmacol*. May; 2012 22(5):347–355. [PubMed: 22099607]
31. Tyrer P, Seivewright H, Simmonds S, Johnson T. Prospective studies of cothymia (mixed anxiety-depression): how do they inform clinical practice? *Eur Arch Psychiatry Clin Neurosci*. 2001; 251(Suppl 2):II53–56. [PubMed: 11824837]
32. Penninx BW, Nolen WA, Lamers F, et al. Two-year course of depressive and anxiety disorders: results from the Netherlands Study of Depression and Anxiety (NESDA). *J Affect Disord*. Sep; 2011 133(1–2):76–85. [PubMed: 21496929]
33. Nock MK, Hwang I, Sampson N, et al. Cross-national analysis of the associations among mental disorders and suicidal behavior: findings from the WHO World Mental Health Surveys. *PLoS Med*. Aug.2009 6(8):e1000123. [PubMed: 19668361]
34. Pfeiffer PN, Ganoczy D, Ilgen M, Zivin K, Valenstein M. Comorbid anxiety as a suicide risk factor among depressed veterans. *Depress Anxiety*. 2009; 26(8):752–757. [PubMed: 19544314]
35. Jeste ND, Hays JC, Steffens DC. Clinical correlates of anxious depression among elderly patients with depression. *J Affect Disord*. Jan; 2006 90(1):37–41. [PubMed: 16325261]
36. Diefenbach GJ, Disch WB, Robison JT, Baez E, Coman E. Anxious depression among Puerto Rican and African-American older adults. *Aging Ment Health*. Jan; 2009 13(1):118–126. [PubMed: 19197697]
37. Middeldorp CM, Cath DC, Beem AL, Willemsen G, Boomsma DI. Life events, anxious depression and personality: a prospective and genetic study. *Psychol Med*. Nov; 2008 38(11):1557–1565. [PubMed: 18294422]

38. Insel TR. Next-generation treatments for mental disorders. *Sci Transl Med.* Oct 10.2012 4(155): 155ps119.

Table 1

Feighner and Colleagues' Five Diagnostic Criteria for Use in Psychiatric Research

1	Clinical Description: Describes the clinical picture of the disorder (i.e., one striking feature or a combination of features thought to be associated with one another). Examples: race, sex, age at onset, precipitating factors, and other items that may define the clinical picture precisely.
2	Laboratory Studies: Chemical, physiological, radiological, and anatomical (biopsy or autopsy) findings, as well as certain psychological tests.
3	Delimitation from Other Disorders: Specify exclusion criteria so that patients with other illnesses are not included in the study group.
4	Follow-up Studies: Determine whether or not the original patients are now suffering from some other defined disorder that could account for the original clinical picture. Evolution of the original illness to another disorder suggests that the original patients were not of a homogenous group.
5	Family Studies: Most psychiatric illnesses run in families. Increased prevalence of the same disorder among close relatives.

Table 2
Diagnostic Criteria for Use in Psychiatric Research Applied to Anxious Depression

Reference	Term Used	Clinical Description	Laboratory Studies	Delimitation From Other Disorders	Follow-up Studies	Family Studies
ICD-10	Mixed Anxiety-Depression	Presence of mild/moderate anxiety and depression, and at least a temporary occurrence of vegetative symptoms	None	Symptoms not fulfilling the criteria of an anxiety or depressive disorder	Very heterogeneous group; little evidence for stability of diagnosis; no stable or consistent findings in distress or disability.	None
DSM-IV	Mixed Anxiety Depressive Disorder	See Table 3	None	Exclusions based on criteria outlined by DSM-IV: Symptoms cannot be explained by mental disorder and cannot have ever met criteria for MDD, PD, GAD, or dysthymic disorder	Low prevalence; low stability over time; no significant differences in physical or emotional well-being; no increases in suicide; no findings in sociodemographic variables of care use, functioning, and course of illness.	Have been found to have no or lower proportions of familial depression and anxiety
DSM-V	Mixed Anxiety Depressive Disorder	See Table 3	None	Cannot have any other mental disorders recognized by DSM-V	Few studies done, but it cannot be reliably separated from MDD or GAD	None
Various research groups ^{19-21, 24-28, 30}	Anxious Depression (Dimensional)	DSM Axis I diagnosis of MDD, or RDC depression, plus high levels of anxiety symptoms defined by scores on certain scales (eg, HAM-D, SADS)	None	Varies based on dimensional score used; depression exclusions are same as for DSM and ICD exclusion criteria	High prevalence; longer duration of current episode; higher endorsement of melancholic depression symptoms; greater illness severity and medical co-morbidities; were more likely to meet criteria for an anxiety disorder; more likely to endorse suicidal ideation and have more suicide attempts; had lower remission and response rates; poorer treatment outcomes with a greater frequency, intensity, and burden of side effects	Higher family history of depression in first-degree relatives; more likely to endorse family history of drug abuse.
Various research groups ³¹⁻³⁵	Anxious Depression (Syndromal)	ICD-10 or DSM Axis I diagnosis of MDD, plus ICD-10 or DSM Axis I	None	Same as DSM and ICD exclusion criteria	High prevalence; index episodes were more severe and protracted, occurred at an	No significant findings

		Reference	Term Used	Clinical Description	Laboratory Studies	Delimitation From Other Disorders	Follow-up Studies	Family Studies
				diagnosis of an anxiety disorder			earlier age of onset, and more often required treatment; more likely to report poor health, worse functioning, lifetime suicidal ideation and attempts, and unemployment; worse social functioning and support	

Abbreviations: GAD, generalized anxiety disorder; HAM-D, Hamilton Depression rating scale; MDD, major depressive disorder; PD, panic disorder; RDC, Research Domain Criteria; SADS, Schedule for Affective Disorders and Schizophrenia.

Table 3

Comparison of ICD-10 and DSM-IV Criteria for Anxious Depression

ICD-10	DSM-IV
Symptoms of anxiety and depression are both present, but neither is clearly predominant, and neither type of symptom is present to the extent that justifies a diagnosis if considered separately. When both anxiety and depressive symptoms are present and severe enough to justify individual diagnoses, both diagnoses should be recorded and this category should not be used.	<ol style="list-style-type: none"> 1 Persistent or recurrent dysphoric mood lasting at least 1 month 2 The dysphoric mood is accompanied by at least 1 month of 4 of the following symptoms: <ol style="list-style-type: none"> a. Difficulty concentrating or mind going blank b. Sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep) c. Fatigue or low energy d. Irritability e. Worry f. Being easily moved to tears g. Hypervigilance h. Anticipating the worst i. Hopelessness (pervasive pessimism about the future) j. Low self esteem or feelings of worthlessness 3 The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. 4 The symptoms are not due to the direct physiological effects of a substance or general medical condition 5 All of the following: <ol style="list-style-type: none"> a. Criteria of never having met Major Depressive Disorder, Dysthymic Disorder, Panic Disorder, or Generalized Anxiety Disorder b. Criteria are not currently met for any other Anxiety or Mood Disorder (including an Anxiety or Mood Disorder, In Partial Remission) c. The symptoms are not better accounted for by any other mental disorder

* ICD-10 criteria based on 2010 Version