



What is anxious depression? Overlap and agreement between different definitions

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ARTICLE INFO

Keywords:
Depression
Anxiety
Anxious depression
DSM-5 anxious distress specifier

ABSTRACT

Anxiety is common in depressed patients. However, a problem with the research on the significance of anxiety in depressed patients is that anxiety has been characterized in different ways. Little research has examined the concordance and overlap between the various definitions of anxious depression. With research on the DSM-5 anxious distress specifier just beginning, it will be important to understand how defining anxious depression according to DSM-5 agrees with previously studied definitions. In the present report from the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project we examined the association between the DSM-5 anxious distress specifier and 6 other approaches towards defining anxious depression. Three hundred thirty-one patients with a principal diagnosis of major depressive disorder were evaluated with semi-structured diagnostic interviews. The mean number of anxious depression definitions met was 4.7 (SD = 2.1). Only 4.2% (n = 14) of the 331 patients did not meet any anxious depression definition, and 28.1% (n = 93) met all 7 definitions. The level of agreement between the definitions was significant, albeit modest (median kappa = .28). The modest association between the different definitions of anxious depression suggests that the results based on one approach towards subtyping may not generalize to the DSM-5 anxious distress specifier. It therefore cannot be assumed that the DSM-5 anxious distress specifier is valid just because other definitions of anxious depression have been shown to be valid.

1. Introduction

The importance of anxiety in patients with depression has been recognized and discussed for nearly a century. While much of the early discussion on the identification of depressive subtypes focused on describing the characteristics of endogenous or melancholic depression, and distinguishing endogenous from reactive or neurotic forms of depression, the authors of these descriptive studies noted the frequent presence of anxiety in depressed patients (Harrowes, 1933; Lewis, 1934; Muncie, 1934).

In the 1960s and 1970s, empirical approaches towards parsing the heterogeneity of depression took hold, and factor analytic (Shafer, 2006) and cluster analytic (Blashfield and Morey, 1979; Paykel, 1971) studies regularly identified an anxiety factor, or anxious cluster. Studies examined the clinical correlates of anxiety (Paykel, 1972a) as well as the treatment significance of the empirically derived typologies (Overall et al., 1965; Paykel, 1972b). Pharmacological treatment options were limited 50 years ago, and the primary question was whether the presence of anxiety predicted differential response to monoamine oxidase inhibitors and tricyclic antidepressants (Nelson, 2008; Rowan

et al., 1982). Today, of course, there are several more classes of medication that have been demonstrated to be effective in treating depression.

During the past 30 years, building on the descriptive literature and the early statistical approaches towards classification, specified criteria for diagnosis and subtyping has prevailed. However, it was not until the latest, fifth, iteration of the American Psychiatric Association's Diagnostic and Statistical Manual (DSM) that the significance of anxiety in depressed patients has been codified. Neither the Washington University criteria (Feighner et al., 1972), the Research Diagnostic Criteria (Spitzer et al., 1978), or preceding versions of the DSM, specifically accounted for clinically significant anxiety in depressed patients.

Anxiety is common in depressed patients. At least half of depressed patients are diagnosed with a co-occurring anxiety disorder (Fava et al., 2000a; Simon et al., 2003; Zimmerman et al., 2000), and an even larger proportion have elevated scores on dimensional measures of anxiety (Chan et al., 2012). Compared to depressed patients without anxiety, depressed patients with high levels of anxiety are characterized by higher levels of suicidal ideation and history of suicide attempts (Fava

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et al., 2006; Goes et al., 2010; Sareen et al., 2005; Seo et al., 2011), poorer functioning (Fichter et al., 2010; Lin et al., 2014), poorer health-related quality of life (Lin et al., 2014; Rhebergen et al., 2011), and greater chronicity (Brown et al., 2000; Coryell et al., 1988; Fichter et al., 2010; Gaynes et al., 1999; Grunhaus, 1988; Melartin et al., 2004; Rhebergen et al., 2011; Shankman and Klein, 2002; Sherbourne and Wells, 1997; VanValkenburg et al., 1984). Treatment studies of major depressive disorder (MDD) have found that the presence of high levels of anxiety are associated with poorer response to treatment (Fava et al., 2008; Howland et al., 2009; Papakostas and Larsen, 2011), poorer response to placebo (Trivedi et al., 2018), and differential response to medication (Davidson et al., 2002; Papakostas et al., 2008), though other studies have not found that anxiety predicts treatment response (Nelson, 2010) or differential treatment response (Russell et al., 2001; Simon et al., 1998).

However, a problem with the research on the significance of anxiety in depressed patients is that anxiety has been characterized in different ways. Studies of the treatment and longitudinal course of depression have examined single anxiety disorders (Goodnick et al., 1999; Liebowitz et al., 2017), any anxiety disorder (Dold et al., 2017; Lenze et al., 2003; Pini et al., 2003; van Bronswijk et al., 2018), different anxiety disorders (Dold et al., 2017), scores on anxiety scales (Altamura et al., 2017; Baldwin et al., 2016; Thase et al., 2012; Trivedi et al., 2018; van Bronswijk et al., 2018), and, most commonly, scores on an anxiety factor of a depression scale (Alpert et al., 2004; Chan et al., 2012; Fava et al., 2000b, 2008; Ionescu et al., 2016; Nelson, 2010; Papakostas and Larsen, 2011; Thase et al., 2012; Tollefson et al., 1994; Wiethoff et al., 2010).

DSM-5, for the first time, officially acknowledged the importance of anxiety in depressed patients by providing criteria for an anxious distress specifier of major depression. It is likely that the inclusion of this specifier in the official diagnostic nomenclature will encourage research on the clinical significance of anxiety in the treatment of depression. Hopefully, one benefit of defining an anxious distress specifier is that it will bring some order to this literature as anxious depression has been defined in several different ways (Ionescu et al., 2013).

Little research has examined the concordance and overlap between the various definitions of anxious depression. Two recent studies using diagnostic interviews for the DSM-5 anxious distress specifier have examined the association between anxious distress subtyping and an alternative method of classifying anxious depression. Rosellini and colleagues (Rosellini et al., 2018) found that patients with major depressive disorder (MDD) who met the anxious distress specifier were significantly more likely to be diagnosed with generalized anxiety disorder compared to patients who did not meet the DSM-5 specifier, though the level of agreement was low ($k = 0.30$). The relationship between the anxious distress specifier and panic disorder or other anxiety disorders was nonsignificant. Our clinical research group examined the association between the anxious distress specifier and the Hamilton depression scale (HAMD) anxiety/somatization factor (Zimmerman et al., 2018). The HAMD anxiety/somatization factor has been the most common method of classifying patients into anxious and nonanxious subgroups in controlled studies of antidepressant treatment (Ionescu et al., 2013). We found that DSM-5 anxious distress subtyping was marginally associated with the HAMD anxiety/somatization factor subtyping approach ($k = 0.21$), and dimensional scores were only moderately correlated ($r = 0.50$).

With research on the DSM-5 specifier just beginning, it will be important to understand how defining anxious depression according to DSM-5 agrees with previously studied definitions. In the present report from the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project we examined the association between the DSM-5 anxious distress specifier and 6 other approaches towards defining anxious depression. We did not have an a priori hypothesis regarding the level of agreement between the different approaches towards defining anxious depression.

2. Method

Three hundred thirty-one patients with a principal diagnosis of current DSM-IV/DSM-5 MDD presenting for an intake evaluation at the Rhode Island Hospital Department of Psychiatry partial hospital program were interviewed by a trained diagnostic rater. The Rhode Island Hospital institutional review committee approved the research protocol, and all patients provided informed, written consent.

The patients were interviewed by a highly trained rater who administered the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1997) supplemented with questions from the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott and Spitzer, 1978) and the DSM-5 Anxious Distress Specifier Interview (DADSI) (Zimmerman et al., 2017). Additional questions were included to rate the items on the 17-item HAMD (Hamilton, 1960) and Hamilton Anxiety Rating Scale (HAMA) (Hamilton, 1959). The same rater administered the clinician-rated scales to the patients.

The anxious distress specifier entered DSM-5 in the absence of prior research on its empirical validity or clinical utility. Rather, the criteria were based on clinical consensus. The DADSI assesses the 5 symptoms of the anxious distress specifier (feeling keyed up or tense, feeling restless, difficulty concentrating because of worry, fear that something awful might happen, and feeling that one might lose control). The DSM-5 specifier requires the presence of at least two of the anxiety symptoms for the majority of the depressive episode. The probes of the DADSI inquire about symptom presence and severity for the past week and also determine if the symptom is present for the majority of the depressive episode. The joint-interview inter-rater reliability of the DADSI was examined in 25 patients (Zimmerman et al., 2017). The reliability of the total scale dimensional score was high (ICC = 0.93), as was the reliability of anxious distress subtyping ($kappa = 1.00$). The test-retest inter-rater reliability of the DADSI was examined in a separate sample of 25 patients. The test-retest reliability of the total scale dimensional score was excellent (ICC = 0.80), and the reliability of anxious distress subtyping was good ($kappa = 0.60$).

Anxious depression was defined in 7 ways: 1) DSM-5 anxious distress specifier; 2) DSM-IV anxiety disorder diagnosis (panic disorder, agoraphobia, specific phobia, social phobia, generalized anxiety disorder, obsessive-compulsive disorder, posttraumatic stress disorder); 3) DSM-5 anxiety disorder diagnosis (panic disorder, agoraphobia, specific phobia, social phobia, generalized anxiety disorder); 4) HAMD anxiety-somatization factor score ≥ 7 (Fava et al., 2008), 5) HAMD 3-item anxiety subscale ≥ 6 (Fawcett and Barkin, 1998), 6) HAMA ≥ 20 (Baldwin et al., 2016; Davis et al., 2016; Thase et al., 2012), and 7) SADS psychic anxiety item ≥ 3 . This last approach towards identifying anxious depression probably comes closest to how clinicians identify anxiety in depressed patients. Clinicians underrecognize anxiety disorders in depressed patients (Zimmerman and Chelminski, 2003) and do not routinely use measures such as the HAMD and HAMA in clinical practice (Gilbody et al., 2002; Zimmerman and McGlinchey, 2008). Yet, anxiety, based on clinicians' unstructured assessments rather than standardized scales, often influences clinicians' selection of pharmacotherapy (Zimmerman et al., 2004).

3. Data analyses

We computed the overall percentage agreement and kappa (k) coefficient to examine the absolute and chance corrected level of agreement between the different definitions of anxious depression. We also computed the Pearson correlation between the dimensional scores. For the DSM-IV and DSM-5 anxiety disorder definitions we totaled the number of current disorders that were diagnosed. For the DSM-5 anxious distress specifier we used the DADSI dimensional score.

4. Results

The sample included 84 (25.4%) men, 235 (71.0%) women, and 12 (3.6%) transgender/gender queer patients who ranged in age from 18 to 80 years (mean = 37.0, SD = 14.8). Approximately one-fifth of the subjects were married (21.8%, $n = 72$) and nearly half were never married (46.5%, $n = 154$). The remainder were divorced (13.3%, $n = 44$), separated (3.6%, $n = 12$), widowed (2.7%, $n = 9$), or living with someone as if in a marital relationship (12.1%, $n = 40$). Approximately one-third of the patients graduated from a 4-year college (32.0%, $n = 106$). The racial composition of the sample was 72.8% ($n = 241$) white, 5.1% ($n = 17$) black, 10.0% ($n = 33$) Hispanic, 3.6% ($n = 12$) Asian, and 8.5% ($n = 28$) other.

The majority of the patients were diagnosed with an anxiety disorder based on DSM-IV (73.1%, $n = 242$), and the average number of DSM-IV anxiety disorder diagnoses across all patients was 1.6 (SD = 1.4; range: 0–6). The most common DSM-IV anxiety disorder diagnosis was generalized anxiety disorder (56.8%, $n = 188$). DSM-5 removed post-traumatic stress disorder and obsessive-compulsive disorder from the anxiety disorder category; therefore, it is not surprising that the frequency of DSM-5 anxiety disorder diagnoses (71.0%, $n = 235$) and average number of DSM-5 diagnoses (1.4, SD = 1.2; range: 0–5) was a little lower than it was for DSM-IV. The mean score on the HAMD was 21.4 (SD = 5.4; range: 8–35), and the mean HAMA score was 24.0 (SD = 8.4; range: 5–48).

The mean number of anxious depression definitions met was 4.7 (SD = 2.1; range: 0–7). Only 4.2% ($n = 14$) of the 331 patients did not meet any anxious depression definition, less than the 28.1% ($n = 93$) who met all 7 definitions. The data in Table 1 shows that broadest definition was the SADS psychic anxiety item, and the narrowest was HAMD 3-item anxiety subscale. For each definition, almost all of the patients met at least one other definition (Table 1).

The level of agreement between the definitions was significant, albeit modest (median kappa = .28) (Table 2). The DSM-5 anxious distress specifier was most highly associated with the SADS psychic anxiety item, and least associated with the HAMD 3-item anxiety subscale. Concordance was greatest between DSM-IV anxiety disorder diagnosis and DSM-5 anxiety disorder diagnosis, and least between the SADS psychic anxiety item and DSM-IV anxiety disorder diagnosis.

Correlations between the dimensional scores were higher than the agreement coefficients of dichotomous subtyping (median $r = 0.51$) (Table 3). The DSM-5 anxious distress dimension was most highly correlated with the HAMA total score and the HAMD 3-item anxiety subscale and least highly correlated with the number of DSM-5 anxiety disorder diagnoses.

5. Discussion

The DSM-5 anxious distress specifier is the first approach in an official diagnostic system to codify anxiety in depressed patients. As such, one can anticipate studies examining the treatment significance of the anxious distress specifier. As the literature emerges it will be important to understand to what degree this newly created method to denote clinically significant anxiety in depressed patients agrees with prior approaches.

The results of the present study indicate that the DSM-5 anxious distress specifier was only modestly associated with other approaches towards identifying anxious depression. In fact, the level agreement between most pairs of definitions was generally low. The pairs of definitions that were most highly associated with each other, HAMD anxiety/somatization factor—HAMD 3-item anxiety/agitation symptoms; DSM-IV anxiety disorder—DSM-5 anxiety disorder—overlapped in content. Consistent with the modest association between the different definitions, the correlations between dimensional scores were also generally modest.

The modest association between the different definitions of anxious depression suggests that the results based on one approach towards subtyping may not generalize to the DSM-5 anxious distress specifier. It therefore cannot be assumed that the DSM-5 anxious distress specifier is valid just because other definitions of anxious depression are valid.

The frequency of DSM-5 anxious depression was high. Other studies have also found that the majority of depressed patients met criteria for the anxious distress specifier, though the rate was higher in the present study. However, other studies “diagnosed” the anxious distress specifier with scales designed for other purposes and thus did not fully assess all of the anxious distress criteria (McIntyre et al., 2016a; Shim et al., 2016). The lack of full coverage of the anxious distress criteria could account for the lower frequency. The two studies using a semi-structured interview to assess the DSM-5 anxious distress criteria reported a rate similar to the present study (Hasin et al., 2018; Rosellini et al., 2018). In a large general population epidemiological study, the rate of anxious distress in the individuals who experienced a lifetime major depressive episode was 74.6% (Hasin et al., 2018), and in a sample of psychiatric outpatients with MDD the rate was also above 70% (Rosellini et al., 2018).

Some studies have already appeared in support of the validity of the DSM-5 anxious distress specifier; however, they did not use measures that were designed to assess the criteria of the specifier but instead these studies approximated the DSM-5 criteria from scales that were part of an already existing data base (Gaspersz et al., 2017a, b; McIntyre et al., 2016a; McIntyre et al., 2016b; Shim et al., 2016). The concordance of these approximations to the DSM-5 criteria is uncertain because in most of these studies not all the criteria were assessed

Table 1

Percentage of depressed patients classified as anxious depression according to different definitions.

	Frequency		Meets criteria for Another Definition ^a		Number of Additional Anxious Depression Definitions Met ^b	
	%	n	%	n	Mean	SD
DSM-5 Anxious Distress Specifier	78.2	259	97.7	253	4.3	1.7
Hamilton Depression Rating Scale (HAMD) Anxiety Somatization Factor ≥ 7 ^c	57.1	188	100.0	188	5.1	1.2
SADS Psychic Anxiety Item ≥ 3	79.2	262	98.5	258	4.3	1.7
HAMD 3-item Anxiety Subscale ≥ 6 ^c	41.3	136	100.0	136	5.4	1.0
Hamilton Anxiety Rating Scale ≥ 20	69.2	229	98.7	226	4.6	1.5
DSM-IV Anxiety Disorder Diagnosis	73.1	242	100.0	242	4.5	1.6
DSM-5 Anxiety Disorder Diagnosis	71.0	235	100.0	235	4.6	1.5

^a Indicates the number of patients meeting the criteria for the index definition of anxious depression who meet the criteria for at least one other definition. The denominator for this calculation therefore varies for each definition of anxious depression.

^b Indicates the average number of additional definitions of anxious depression met for patients meeting the index definition (range 0–6).

^c HAMD $n = 329$.

Table 2
Concordance among different approaches towards classifying anxious depression.

	DADS		HAMD A/S Factor		SADS Psychic Anxiety Item		HAMD 3-item Anxiety Subscale		HAMA		DSM-IV Anxiety Disorder Diagnosis	
	kappa	% agreement	kappa	% agreement	kappa	% agreement	kappa	% agreement	kappa	% agreement	kappa	% agreement
DSM-5 Anxious Distress Specifier (DADS)	-	-	-	-	-	-	-	-	-	-	-	-
Hamilton Depression Rating Scale (HAMD) Anxiety/Somatization	.23	64.7	-	-	-	-	-	-	-	-	-	-
(A/S) Factor $\geq 7^a$												
SADS Psychic Anxiety Item ≥ 3	.29	76.1	.34	69.9	-	-	-	-	-	-	-	-
HAMD 3-item Anxiety Subscale $\geq 6^a$.16	53.8	.59	78.7	.29	60.8	-	-	-	-	-	-
Hamilton Anxiety Rating Scale (HAMA) ≥ 20	.28	71.6	.52	77.5	.35	74.9	.39	67.2	-	-	-	-
DSM-IV Anxiety Disorder Diagnosis	.21	70.7	.30	67.2	.14	68.6	.17	55.0	.19	66.5	-	-
DSM-5 Anxiety Disorder Diagnosis	.19	69.2	.30	66.9	.16	68.3	.18	55.9	.19	66.2	.95	97.9

^a HAMD n = 329.

(McIntyre et al., 2016a, 2016b; Shim et al., 2016), and in other studies the authors noted that some of the proxy items may not have been accurate representations of the DSM-5 criterion (Gaspersz et al., 2017a, b). Moreover, in each of these studies the proxy assessment of the DSM-5 criteria was cross-sectional, based on symptom presence during the past week. The DSM-5 definition, on the other hand, requires the criteria to be present for the majority of the depressive episode. Thus, the relationship between these approximations and the DSM-5 criteria is uncertain.

We are aware of only two studies that examined the validity of the DSM-5 anxious distress specifier as written. Both used semi-structured interviews to assess the criteria. Rossellini and colleagues (Rossellini et al., 2018) found that anxious distress was associated with more severe functional impairment, autonomic arousal, stress, symptoms of panic disorder and generalized anxiety, and depression. In an earlier report from our group, we found that patients with anxious distress had a higher frequency of anxiety disorders, particularly panic disorder and generalized anxiety disorder, as well as higher scores on measures of anxiety, depression, and anger (Zimmerman et al., in press). The patients meeting the anxious distress subtype reported higher rates of drug use disorders, poorer functioning during the week before the evaluation, and poorer coping ability compared to the patients who did not meet the anxious distress specifier. Moreover, anxious distress was associated with poorer functioning and coping after controlling for the presence of an anxiety disorder. However, the breadth of data supporting the validity of the DSM-5 specifier remains limited compared to some of the other definitions. Future research should examine other indicators of validity such as longitudinal course, family history, and biological variables.

In determining the best approach to identifying anxious depression one should consider clinical utility. The anxious distress specifier is easier to assess than the presence or absence of each of the DSM-5 anxiety disorders. Future studies of the anxious distress specifier should examine whether the more time-consuming evaluation of the DSM-5 anxiety disorders offers incremental validity after controlling for anxious distress subtyping.

Before concluding, the limitations of the present study should be recognized. The present study was conducted in a single clinical practice in which the majority of the patients were white, female, and had health insurance. Replication in samples with different demographic characteristics is warranted. It will also be important to replicate these findings in an outpatient sample. The ratings on the clinician scales were not independent of each other. That is, the same rater completed the DADSI, the HAMA, the HAMD, and the SADS items. It would be preferable to have independent interviewers complete the clinician rating scales though this is not practical in an integrated clinical research setting in which the interview is conducted primarily for clinical purposes and the use of the information for research purposes is a secondary goal. It is likely that the level of agreement between the different scales would be lower if independent interviewers were used.

Using symptom severity scales to identify anxious depression requires the use of a cutoff score for classification, and the cutoff that is used will impact on the prevalence rate of anxious depression. For example, on the HAMA we used a cutoff of 20 to identify anxious depression, a cutoff that has been used in several studies of the treatment of anxious depression (Baldwin et al., 2016; Davis et al., 2016; Thase et al., 2012). However, other studies have used other cutoffs on the HAMA to denote anxious depression (Akkaya et al., 2006; Altamura et al., 2017; Baldwin et al., 2016; Jiang et al., 2017; Lin et al., 2018). We are unaware of any studies examining the most valid cutoff on the HAMA to indicate high anxiety in depressed patients. While our choice of cutoff has precedent, it was to some degree arbitrary. Most importantly, we chose this cutoff before analyzing the data, and we did not examine other cutoffs.

In conclusion, while the importance of anxiety in depressed patients has been recognized for years, the different approaches towards

Table 3
Correlation between dimensional assessments of different approaches towards assessing anxious depression.

	DADS	HAMD A/S Factor	SADS Psychic Anxiety Item	HAMD 3-item Anxiety Subscale	HAMA	DSM-IV Anxiety Disorder Diagnosis
DSM-5 Anxious Distress Specifier (DADS)	–	–	–	–	–	–
Hamilton Depression Rating Scale (HAMD) Anxiety/ Somatization (A/S) Factor ^a	.52	–	–	–	–	–
SADS Psychic Anxiety Item	.51	.58	–	–	–	–
HAMD 3-item Anxiety Subscale ^a	.56	.83	.65	–	–	–
Hamilton Anxiety Rating Scale (HAMA)	.56	.75	.52	.73	–	–
DSM-IV Anxiety Disorder Diagnosis	.36	.32	.25	.31	.29	–
DSM-5 Anxiety Disorder Diagnosis	.33	.30	.23	.30	.36	.95

^a HAMD n = 329.

identifying anxious depression are only modestly associated. The validity of the DSM-5 anxious distress specifier will need to be further established, and its validity cannot be assumed from prior research on the significance of anxiety in depressed patients.

Conflicts of interest

Dr. Zimmerman has been on an advisory board for Alkermes, and has prepared educational material for Otsuka.

Funding/support

None.

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