Longitudinal Predictive Validity of the *DSM-5* Anxious Distress Specifier for Clinical Outcomes in a Large Cohort of Patients With Major Depressive Disorder

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ABSTRACT

Objective: While the new *DSM-5* anxious distress specifier is of great clinical importance, no evidence exists for its longitudinal predictive validity for clinical outcomes in patients with major depressive disorder (MDD). We examined the longitudinal validity of this specifier and validated it against *DSM-IV*–based comorbid anxiety disorder diagnoses.

Methods: Data are from 1,080 patients with current MDD at baseline (September 2004 to February 2007), of which 911 participated in the 2-year follow-up (September 2006 to April 2009). Patients are from the Netherlands Study of Depression and Anxiety, which is an ongoing longitudinal cohort study, and were sampled from the community, primary care, and outpatient specialized care settings. The specifier was constructed in the existing sample by 5 matching self-report items. Predictive outcomes were 2-year chronicity, time to remission of MDD, and functional disability. Discriminant performance and convergent validity of the specifier were also assessed.

Results: The specifier was present in 54.2% of the sample. The specifier significantly outperformed anxiety disorders in predicting chronicity (OR = 1.96, $P < .001$, vs OR = 1.11, $P = .49$), time to remission of MDD (HR = 0.75, $P = .002$, vs HR = 0.94, $P = .55$), and functional disability (B = 10.03, $P < .001$, vs B = 2.53, $P = .07$). The specifier significantly discriminated in clinical characteristics, had convergent validity for anxiety characteristics, and poorly overlapped with *DSM-IV*–based anxiety disorder diagnoses (Cohen $\kappa = .09$).

Conclusions: The short anxious distress specifier outperforms *DSM-IV*–based anxiety disorder diagnoses as a longitudinal predictor for clinical outcomes in patients with MDD.

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High levels of anxiety in major depressive disorder (MDD) have been associated with worse clinical outcomes than in MDD alone.[1] These patients with anxious depression are found to have greater depression severity and chronicity,[2–5] greater functional impairment,[3] more suicidal ideation,[6,7] and worse treatment outcomes[2,3,8] than their counterparts. While these important clinical implications underscore the need for further investigation, inconsistent diagnostic criteria have resulted in significant variability in the samples studied. This hampers our ability to draw conclusions about the population and the efficacy of treatment interventions.

DSM-5 includes an anxious distress specifier to acknowledge the clinical significance of anxiety features in MDD[9] and to aid clinicians in identifying patients with significant anxiety, which is well known to affect clinical course and outcomes.[10,11] It is of significant interest to establish how well this specifier predicts clinical outcomes when compared with a formal comorbid anxiety disorder diagnosis. This has important implications: assessment of anxiety by means of a short specifier is easier than formally diagnosing a *DSM*-based anxiety disorder. Further, its use might aid in identifying patients with significant anxiety not meeting full criteria for anxiety disorder but who may require a different treatment than patients without anxiety.

The *DSM-5* anxious distress specifier was derived from the 5-item scale of anxiety from the study by Goldberg and others.[12] To date, hardly any studies have been conducted on the validity of the anxious distress specifier,[13] although the importance of testing the specifier as a predictor and prognostic indicator have been emphasized by several researchers.[14,15] One exception is the study by Zimmerman et al,[13] in which a self-report measure was developed to test the specifier. After examination of its discriminant and convergent validity, the self-report measure was found to be reliable and valid.[13] However, the Zimmerman et al[13] study provides no longitudinal data. Therefore, although potentially of great clinical value, the longitudinal validity of the *DSM-5* anxious distress specifier in patients with MDD is largely unknown.

We aimed to test the discriminant performance and convergent and longitudinal predictive validity of the *DSM-5* anxious distress specifier in a large, existing cohort of persons with MDD. The specifier was constructed by identifying items on various self-report measures that corresponded directly with the 5 criteria of the specifier. First, the discriminant performance of the specifier was examined by comparing important clinical characteristics in patients with current MDD with and without the specifier. Next, the convergent validity of the specifier was examined by comparing different anxiety characteristics in patients with current MDD with and without the specifier. Finally, the predictive validity of the specifier was longitudinally examined for

Clinical Points

- *DSM-5* includes an anxious distress specifier to acknowledge the clinical significance of anxiety features in major depressive disorder, but the validity and prognostic value of this specifier have not been studied extensively.
- To identify significant comorbid anxiety features predictive of poor clinical course and outcomes in depressed patients, clinicians can use the *DSM-5* anxious distress specifier rather than formally diagnosing patients with an anxiety disorder.

subsequent 2-year chronicity of MDD, time to remission of MDD, and functional disability and was then compared with that of *DSM-IV*–based anxiety disorder diagnoses.

METHODS

Study Sample

The Netherlands Study of Depression and Anxiety (NESDA)[16] is a longitudinal cohort study. A total of 2,981 persons (18–65 years) were included in the baseline assessment (September 2004 to February 2007), consisting of healthy controls, persons with a prior history, and patients with a current depressive and/or anxiety disorder. Participants were recruited from the community (19.0%), primary care (54.0%), and outpatient mental health care services (27.0%). Exclusion criteria were a primary clinical psychiatric disorder diagnosis other than depressive or anxiety disorders and not being fluent in Dutch. Broad assessments took place for all participants: an extensive interview, self-report questionnaires, and a medical assessment performed by trained research staff. All participants provided written informed consent after the procedure had been fully explained, and the project was approved by the ethics committees of all participating universities. Two years later, a follow-up assessment (September 2006 to April 2009) was conducted among 2,596 persons (87.1%). More details can be found elsewhere.[16]

We included participants with a current (in past 6 months) MDD diagnosis (n = 1,115) at baseline, assessed by the Composite International Diagnostic Interview (CIDI), version 2.1, according to *DSM-IV* criteria.[17,18] Thirty-five participants had incomplete data on the self-report questionnaires used to construct the *DSM-5* anxious distress specifier, leaving 1,080 patients with MDD eligible for analysis. Of these, 911 (84.4%) also participated in the 2-year follow-up and were included in the predictive validity analyses.

Anxious Distress Specifier

The *DSM-5* criterion for the anxious distress specifier is the presence of at least 2 of the following criteria during the depressive episode: (1) feeling keyed up or tense, (2) feeling unusually restless, (3) difficulty concentrating because of worry, (4) fear that something awful might happen, and (5) feeling that the individual might lose control of himself or herself.[9] The specifier was constructed by selecting 5 items that matched these 5 criteria from the Inventory of Depressive Symptomatology (IDS)[19] and the Beck Anxiety Inventory (BAI).[20] Both questionnaires assess the presence of specific symptoms in the past week on a 0–3 (not at all severely) scale. The selected IDS items were item 7 "feeling anxious or tense" (criterion 1), item 15 "concentration/decision making" (criterion 3), and item 24 "feeling restless" (criterion 2). The selected BAI items were item 5 "fear of worst happening" (criterion 4) and item 14 "fear of losing control" (criterion 5) (see Supplementary eTable 1 at PSYCHIATRIST.COM). Symptoms that were scored with at least 2 (ie, moderate or severe options) on the 0–3 scale were considered present. When at least 2 symptoms were present, the specifier was considered present (dichotomous indicator). We also constructed a continuous indicator by counting the number of anxious components present (range, 0–5 symptoms).

Discriminant Performance

We assessed sociodemographic characteristics, which included age, gender, and years of education. Discriminant performance was assessed by comparing subsequent baseline depression characteristics, functional disability, and suicidal ideation between patients with MDD with and without the specifier. Recurrence, number of depressive episodes, and age at onset of depression were assessed in the clinical interview. Severity of depression was measured by the Quick IDS (QIDS),[21] a shortened, 16-item version of the IDS (range, 0–27). The overlapping selected IDS items were excluded from the QIDS, leaving 14 items that cover only depression domains. Duration of depressive illness was based on the Life-Chart Interview (LCI),[22] of which its methodology has high reliability and validity,[23] and was used to determine the percentage of time with depressive symptoms during 4 years prior to baseline. Antidepressant medication use within the past month was assessed by patient report of prescribed medications and was coded using the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system.[24] Antidepressants consisted of selective serotonin reuptake inhibitors (ATC code N06AB), tricyclic antidepressants (ATC code N06AA), and other antidepressants (ATC code N06AF/N06AX). Functional disability was assessed by the WHO Disability Assessment Schedule II (WHODAS II),[25] which assessed functioning and disability in the past 30 days. Suicidal ideation was measured as "suicidal thoughts in the past week" by the Scale for Suicide Ideation.[26]

Convergent Validity

Convergent validity was assessed by comparing baseline anxiety characteristics between patients with MDD with and without the specifier. Presence of current (past 6 months) and lifetime anxiety disorders and number and age at onset of anxiety disorders were determined by the *DSM-IV*–based CIDI,[17] which assessed social phobia, panic with or without agoraphobia, agoraphobia, and generalized anxiety disorder. Duration of anxiety symptoms 4 years prior to baseline was obtained by the LCI[22] and assesses the proportion of time in which anxiety symptoms were present. Benzodiazepine

use in the past month (>50% of the time) was assessed and coded by the ATC classification. Different anxiety scales and subscales were evaluated: IDS anxiety/arousal subscale[27] (the overlapping selected IDS items were excluded), BAI[20] (the overlapping selected BAI items were excluded), Fear Questionnaire,[28] Mood and Anxiety Symptoms Questionnaire-anxious arousal subscale,[29] Anxiety Sensitivity Index,[30] and the Penn State Worry Questionnaire-anxiety subscale.[31] These scales all have shown high reliability and validity.

Predictive Validity

The predictive outcomes of the specifier over 2 years were chronicity of MDD, time to first remission of MDD, and functional disability. To examine equal predictive validity between the specifier's dichotomous and continuous indicator, both indicator types were evaluated. To examine whether the specifier outperforms *DSM-IV*–based anxiety disorders as a predictor, the dichotomous specifier indicator (absence/presence of specifier) was compared with the dichotomous anxiety disorder indicator (absence/presence of anxiety disorder), while the continuous specifier indicator (number of specifier items) was compared with the continuous anxiety disorder indicator (number of anxiety disorders) to optimize its comparison. Chronicity of MDD was assessed by the CIDI and defined as the presence of a current (past 6 months) diagnosis of MDD at the 2-year follow-up. Time to first remission of MDD was assessed by the LCI assessed at the 2-year follow-up[22] and defined by the time point since baseline when 3 consecutive months without any depressive symptoms were present.[16] For this specific analysis, a number of persons were excluded because they were asymptomatic at baseline (n = 19), lacked the central outcome indicator LCI[22] (n = 204), or lacked coverage of the whole follow-up period (n = 8). Functional disability was obtained by the WHODAS II assessed at the 2-year follow-up.[25]

Statistical Analysis

Statistical analysis was conducted with SPSS, version 21 (IBM Corp; Armonk, New York). All statistical tests were 2-tailed, with the significance threshold set at .05. In the MDD sample, frequencies were determined for each of the selected specifier items and for the count variable. Subsequently, item-total correlations and a Cronbach α of the specifier were computed.

In the discriminant performance and convergent validity analyses, χ^2 tests were used for dichotomous variables, *t* tests for continuous variables, and nonparametric tests (Mann-Whitney *U*) for nonnormally distributed variables. Cohen κ was calculated to assess agreement on concurrence of the specifier and comorbid *DSM-IV*–based anxiety disorders.

To assess predictive validity, we used logistic regression for MDD chronicity, Cox proportional hazards regression for time to MDD remission, and linear regression analyses for functional disability. Three models were analyzed for predictive validity of all outcomes. Model 1 analyzed the specifier alone. Model 2 analyzed *DSM-IV*–based anxiety disorders alone. Model 3 examined the specifier together with the anxiety disorders in 1 model. All models were conducted for both the dichotomous and continuous indicators, and all were adjusted for age, gender, and educational years at baseline. Since treatment was not found to be a significant course determinant for depression and anxiety when depression severity was considered,[10] this was not included for adjustment. To assess whether the specifier has equal predictive validity within different depression severity classes, we stratified for baseline depression severity by creating a nonsevere and a severe group based on the median IDS score (median = 32) and repeated analyses in each stratum.

Table 1. Descriptives of the *DSM-5* Anxious Distress Specifier in Persons With Current MDD (N = 1,080)

Variable	Persons With Current MDD, n (%)
Items of *DSM-5* anxious distress specifier	
Feeling keyed up or tensed	476 (44.1)
Feeling unusually restless	458 (42.4)
Difficulty concentrating because of worry	385 (35.6)
Fear that something awful may happen	368 (34.1)
Feeling that the individual might lose control of himself or herself	343 (31.8)
No. of *DSM-5* anxious distress specifier items	
0	248 (23.0)
1	247 (22.9)
2	201 (18.6)
3	208 (19.3)
4	123 (11.4)
5	53 (4.9)
Presence of *DSM-5* anxious distress specifier[a]	585 (54.2)

[a]The *DSM-5* anxious distress specifier is present when 2 or more items are met.
Abbreviation: MDD = major depressive disorder.

RESULTS

Anxious Distress Specifier

The *DSM-5* anxious distress specifier was common, occurring in half of the patients with MDD (Table 1). The frequencies for the 5 individual specifier items varied from 32% to 44%, and the specifier's internal consistency was moderate (Cronbach α = .71). The inter-item correlations of the proxy items for the specifier were all significant ($P < .001$) (Supplementary eTable 2).

Discriminant Performance

Among patients with MDD with and without the specifier, sociodemographics were comparable, except for fewer years of education in those with the specifier (Table 2). The specifier discriminated for several clinically important characteristics of depression. In patients with MDD with the specifier compared to those without, depression severity (QIDS score: mean = 12.9, SD = 3.8, vs mean = 8.3, SD = 3.8) and duration (percentage of time with depressive symptoms: mean = 45.3%, SD = 31.3%, vs mean = 29.3%, SD = 26.5%), functional disability (WHODAS II score: mean = 40.3, SD = 14.6, vs mean = 24.3, SD = 13.0) and suicidal ideation

Table 2. Discriminant Performance of the *DSM-5* Anxious Distress Specifier at Baseline in Persons With MDD With and Without the Specifier

Variable	Persons With MDD: With Anxious Distress Specifier (n = 585)	Persons With MDD: Without Anxious Distress Specifier (n = 495)	P[a]
Age, mean (SD), y	41.4 (12.0)	40.4 (12.1)	.21
Female sex, n (%)	389 (66.5)	336 (67.9)	.63
Education, mean (SD), y	11.3 (3.3)	12.1 (3.1)	< .001
Recurrent depression type, n (%)	283 (48.4)	288 (58.2)	.001
No. of depressive episodes, mean (SD)	5.4 (11.4)	5.2 (9.2)	.66
Depression age at onset, median (IQR), y	24.0 (17.0–35.0)	25.0 (18.0–37.0)	.12
QIDS score (severity of depression), mean (SD)	12.9 (3.8)	8.3 (3.8)	< .001
Duration of illness (percentage of time with depressive symptoms), mean (SD), %	45.3 (31.3)	29.3 (26.5)	< .001
Antidepressant use, n (%)			
SSRI	185 (31.8)	128 (26.0)	.04
TCA	22 (3.8)	21 (4.2)	.69
Other antidepressant	69 (11.8)	50 (10.2)	.40
WHODAS II score (functional disability), mean (SD)	40.3 (14.6)	24.3 (13.0)	< .001
Suicidal ideation, n (%)	201 (34.5)	65 (13.1)	< .001

[a]For *P* value, *t* tests were used for continuous variables, χ^2 tests were used for dichotomous variables, and Mann-Whitney *U* tests were used for nonnormally distributed variables.
Abbreviations: IQR = interquartile range, MDD = major depressive disorder, QIDS = Quick Inventory of Depressive Symptomatology, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant, WHODAS II = World Health Organization Disability Assessment Schedule II.

(n = 201 [34.5%] vs n = 65 [13.1%]) were significantly worse (*P* < .001 for all). In contrast, 283 patients (48%) with MDD with the specifier reported recurrence of depression compared to 288 (58%) without the specifier (*P* = .001).

Convergent Validity

Comorbidity of current *DSM-IV*–based anxiety disorders was significantly higher among patients with MDD with the specifier versus those without (*P* ≤ .01), with the exception of agoraphobia (*P* = .11) (Table 3). All other anxiety characteristics were also significantly more common in patients with MDD with the specifier compared to those without (*P* < .001 for all anxiety characteristics; age at onset *P* = .01). Nonetheless, overlap with formally diagnosed anxiety disorders was poor (Cohen κ = .09). Some patients with MDD with the specifier did not have a comorbid anxiety diagnosis (n = 132, 22.6%), and the majority of patients with MDD with a comorbid anxiety disorder did not meet criteria for the specifier (n = 254, 51.3%; *P* < .001). The overlap with *DSM-IV*–based anxiety disorders was not very different across different types of anxiety diagnoses, indicating that the specifier does not seem to pick up a specific disorder selectively.

Predictive Validity

The specifier has clear predictive validity in that half of those with the specifier had a diagnosis of MDD at the 2-year follow-up assessment, while only one-third of those without the specifier had an MDD diagnosis. The median time to MDD remission was 50% longer, and functional disability scores at 2-year follow-up were higher in patients with MDD with the specifier compared to those without (time to remission: 6 vs 4 months; functional disability: mean = 27.7, SD = 17.3, vs mean = 16.5, SD = 13.7; *P* < .001 for all). The dichotomous specifier significantly predicted chronicity, time to MDD remission, and functional disability. Moreover, its performance seemed to outperform that of the dichotomous comorbid *DSM-IV*–based anxiety disorder indicator, as the predictive value of the presence of a comorbid anxiety disorder (model 2) was less than that of the presence of the specifier. In model 3, which included

Table 3. Convergent Validity of the *DSM-5* Anxious Distress Specifier at Baseline in Persons With Current MDD With and Without the Specifier

Variable	Persons With MDD: With Anxious Distress Specifier (n = 585)	Persons With MDD: Without Anxious Distress Specifier (n = 495)	P[a]
Current anxiety disorders, n (%)			
Social phobia	270 (46.2)	108 (21.8)	< .001
Panic with agoraphobia	176 (30.1)	67 (13.5)	< .001
Panic without agoraphobia	91 (15.6)	50 (10.1)	.01
Agoraphobia	56 (9.6)	34 (6.9)	.11
Generalized anxiety disorder	221 (37.8)	103 (20.8)	< .001
Current anxiety disorder diagnoses, n (%)			
0	132 (22.6)	241 (48.7)	
1	179 (30.6)	165 (33.3)	< .001
2	187 (32.0)	70 (14.1)	
3	87 (14.9)	19 (3.8)	
Any lifetime anxiety disorder, n (%)	488 (83.4)	329 (66.5)	< .001
Anxiety age at onset, median (IQR), y	18.0 (11.0–27.0)	20.0 (13.0–30.0)	.01
Duration of illness (percentage of time with anxiety symptoms), mean (SD), %	50.9 (33.6)	34.1 (30.1)	< .001
Benzodiazepine use, n (%)	77 (13.2)	33 (6.7)	< .001
Anxiety scale score, mean (SD)			
Inventory of Depressive Symptomatology-anxiety subscale[b]	10.2 (3.4)	6.0 (2.9)	< .001
Beck Anxiety Inventory[b]	21.2 (9.5)	9.5 (6.0)	< .001
Fear Questionnaire	41.0 (21.9)	24.8 (17.3)	< .001
Mood and Anxiety Symptoms Questionnaire-anxious arousal subscale	22.0 (7.0)	15.4 (4.8)	< .001
Anxiety Sensitivity Index	20.7 (10.8)	13.3 (7.9)	< .001
Penn State Worry Questionnaire-anxiety subscale	41.9 (8.8)	34.3 (9.7)	< .001

[a]For *P* value, *t* tests were used for continuous variables, χ^2 tests were used for dichotomous variables, and Mann-Whitney *U* tests were used for nonnormally distributed variables.
[b]The items from the Inventory of Depressive Symptomatology and Beck Anxiety Inventory scales, which are used as a proxy for the specifier, are not included.
Abbreviations: IQR = interquartile range, MDD = major depressive disorder.

Table 4. Predictive Validity on Longitudinal Course of the *DSM-5* Anxious Distress Specifier, and Compared With That of the Presence of *DSM-IV*–Based Comorbid Anxiety Disorders

Model	Indicator		Chronicity of MDD OR (95% CI)	*P*[a]	Time to First Remission of MDD HR (95% CI)	*P*[b]	Functional Disability B (SE)	*P*[c]
	Dichotomous indicator							
1	Presence of anxious distress specifier	No	Reference		Reference		Reference	
		Yes	2.01 (1.53–2.65)	<.001	0.73 (0.62–0.87)	.001	10.78 (1.29)	<.001
2	Any current anxiety disorder[d]	No	Reference		Reference		Reference	
		Yes	1.34 (1.01–1.78)	.05	0.87 (0.72–1.04)	.12	5.61 (1.37)	<.001
3	Presence of anxious distress specifier	No	Reference		Reference		Reference	
		Yes	1.96 (1.47–2.61)	<.001	0.75 (0.62–0.90)	.002	10.03 (1.35)	<.001
	Any current anxiety disorder[d]	No	Reference		Reference		Reference	
		Yes	1.11 (0.83–1.50)	.49	0.94 (0.78–1.14)	.55	2.53 (1.37)	.07
	Continuous indicator							
1	No. of anxious distress specifier items		1.28 (1.17–1.41)	<.001	0.89 (0.84–0.94)	<.001	4.00 (0.44)	<.001
2	No. of current anxiety disorder diagnoses[d]		1.29 (1.12–1.48)	<.001	0.90 (0.82–0.98)	.02	3.79 (0.69)	<.001
3	No. of anxious distress specifier items		1.24 (1.12–1.37)	<.001	0.90 (0.84–0.96)	.002	3.57 (0.47)	<.001
	No. of current anxiety disorder diagnoses[d]		1.14 (0.98–1.33)	.08	0.96 (0.87–1.05)	.36	1.66 (0.72)	.02

[a]For chronicity of MDD, logistic regression analyses were used and were adjusted for age (standardized), sex, and years of education (standardized).
[b]For time to first remission of MDD, Cox proportional hazards regression analyses were used and were adjusted for age (standardized), sex, and years of education (standardized).
[c]For functional disability, linear regression analyses were used and were adjusted for age (standardized), sex, and years of education (standardized).
[d]Including social phobia, panic disorder with agoraphobia, panic disorder without agoraphobia, agoraphobia, and generalized anxiety disorder within the past 6 months.
Abbreviations: MDD = major depressive disorder, SE = standard error.

both indicators, significant effects for the specifier indicator but not for anxiety disorder indicator were found for all predictive outcomes (Table 4). When repeating the analyses with the continuous specifier indicator, and comparing it to the continuous anxiety disorder indicator, these results were confirmed: the continuous specifier indicator predicted all 3 course outcomes better than the number of anxiety disorders present.

Stratification for depression severity, in which nonsevere (n = 537) and severe (n = 542) groups were created based on the median IDS score (median = 32), showed no striking differences between the stratified effect sizes for the dichotomous specifier indicator. In the nonsevere group (chronicity: OR = 1.66, 95% CI = 1.07–2.58, $P = .03$; time to remission: hazard ratio [HR] = 0.81, 95% CI = 0.61–1.08, $P = .15$; disability: B = 6.91, standard error [SE] = 1.72, $P < .001$) and in the severe group (chronicity: OR = 1.37, 95% CI = 0.83–2.24, $P = .22$; time to remission: HR = 0.93, 95% CI = 0.68–1.28, $P = .66$; disability: B = 8.04, SE = 2.95, $P = .007$), overall risk estimates were largely similar, although they were less significant than that of the overall sample, which could be largely due to the reduced sample size within these stratified analyses. Stratified analyses for the continuous anxious distress indicator also showed equal predictive validity in both the nonsevere and severe subgroups (data not shown). These stratified analyses overall suggest that the anxious distress specifier has equal predictive validity across different severities of illness.

DISCUSSION

This study examined the discriminant performance, convergent validity, and longitudinal predictive validity of the *DSM-5* anxious distress specifier, which was constructed by matching the *DSM-5* criteria for the specifier with matching items drawn from the IDS and the BAI. The specifier was present in 54.2% of the patients with MDD. The specifier significantly discriminated in depression severity and duration, functional disability, and suicidal ideation. The specifier had significant convergent validity for all anxiety characteristics, although the presence of the specifier poorly overlapped with the presence of comorbid *DSM-IV*–based anxiety disorders. The specifier significantly predicted 2-year chronicity of MDD, time to remission of MDD, and functional disability at 2-year follow-up. Moreover, the specifier outperformed *DSM-IV*–based anxiety disorders as a longitudinal predictor and appears robust across a range of severity of illness.

Interestingly, one-fifth (n = 132, 22.6%) of patients with MDD with the specifier had no anxiety disorder, while half (n = 254, 51.3%) of the MDD patients without the specifier did have an anxiety disorder. The latter finding suggests that the specifier is capturing a somewhat distinct, but yet clinically valid, construct. Because 4 of the 5 specifier items are typical for generalized anxiety disorder and 1 for panic,[14] it might be expected that the specifier would differentiate better for these 2 anxiety disorders. However, the results showed that the specifier did not differentiate better for any 1 specific anxiety disorder and was thus a more generic marker for anxiety.

In line with previous research in populations with anxious depression, the patients with MDD with anxious distress defined in this sample by the *DSM-5* anxious distress specifier had worse clinical outcomes (eg, MDD severity and chronicity, functional impairment, presence of comorbid anxiety disorders, and suicidal ideation) than their counterparts with nonanxious depression.[4–7,13,32] In contrast, they showed less recurrence of their depression than those

without the specifier. This may be due to greater chronicity: failure to achieve remission may underlie the lower recurrence rates for patients with MDD with the specifier compared to those without. In this sample, chronicity was indeed negatively associated (albeit not significantly) with recurrence. Overall, the specifier's discriminant performance and convergent validity appear satisfactory and in line with the Zimmerman et al study.[13] In addition to Cronbach α, we also computed item-total correlations, and these were slightly lower than those reported by Zimmerman et al,[13] which may be the result of the difference in used proxy items regarding concentration. Nevertheless, this suggests that our proxy of the specifier reflects the same concept as that in Zimmerman et al.[13] However, in Zimmerman and colleagues' study,[13] more than two-thirds of the patients met the anxious distress specifier compared to half of the patients in our study. Since the sample in Zimmerman and colleagues' sample is comparable to ours, this difference in prevalence of the specifier might be explained by the content difference. These results support the validity of the *DSM-5* anxious distress specifier in identifying comorbid anxiety features that are related to poor clinical outcomes and provide insight into its validity beyond the identification of comorbid anxiety disorders. Overall, the findings not only contribute to the validation of the *DSM-5* specifier but also support the hypothesis that the concept of anxious distress is clinically meaningful and significant.

Among the study's strengths are the large sample size (N = 1,080) and the fact that this is the first study to evaluate the longitudinal predictive validity of the *DSM-5* anxious distress specifier in terms of clinical outcomes over 2 years in patients with MDD. Limitations of the study include that self-reported proxy items from acquired anxiety scales instead of clinician-based assessments were used to construct the specifier. Next, our proxy item regarding concentration is somewhat different than the *DSM-5* criterion in that concentration difficulties due to depression may be different than those due to anxiety and anxiety disorders. However, our aim was to study the concept of anxious distress rather than developing and validating an instrument to assess it (as Zimmerman et al[13] did). Although the content of our specifier differed slightly from that of Zimmerman et al,[13] comparable reliability and validity results were obtained, suggesting that a reflection of the specifier by means of a conceptual assessment holds similar consequences. Also, the cutoff scores that were determined for the proxy items were somewhat arbitrary. However, we accounted for this by also examining a continuous indicator of the specifier next to a categorical indicator, and similar results were obtained. Finally, our set of anxiety disorders did not include other anxiety disorders such as posttraumatic stress disorder or obsessive-compulsive disorder. However, as patients with such clinically overt disorders were not included in NESDA, and therefore these conditions are not as common as the ones we have measured for this study, it is not likely that this would have had a major influence on the conclusion about the specifier.

This study has several important clinical implications. First, it provides preliminary validation of the *DSM-5* anxious distress specifier. Second, it suggests that this simple specifier rather than anxiety disorders may be useful to clinicians in identifying clinically relevant comorbid anxiety features that are predictive of a worse clinical outcome in patients with depression. Of course, it could still be legitimate to measure comorbid anxiety disorder features in more detail, as this could provide other clinical information relevant for, eg, a specific treatment regimen. The specifier may have particular value in primary care, where time and expertise limitations often prevent thorough psychiatric assessment. However, even within psychiatric practices, our results indicate that the specifier may capture patients with MDD with significant anxiety symptoms predictive of poorer outcomes, who are not captured within the *DSM*-based anxiety disorder diagnoses. Clearly, further research on the *DSM-5* anxious distress specifier is necessary; for instance, more information is needed to determine its usefulness in differential treatment response in clinical trials and whether the anxious distress specifier is characterized by a differential biological profile. The population defined by the specifier should also be compared to other, dimensional definitions of anxious depression, such as that employed in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study.[4,5,8]

In summary, the *DSM-5* anxious distress specifier has significant discriminant performance and convergent validity and does not fully overlap with the presence of *DSM-IV*–based anxiety disorders, suggesting that it is capturing a somewhat different, yet valid, clinical construct. The patients with MDD with the *DSM-5* anxious distress specifier had a worse clinical outcome than their counterparts without the specifier. Furthermore, the *DSM-5* anxious distress specifier significantly predicted all longitudinal outcomes and outperformed the presence of *DSM-IV*–based anxiety disorders as a predictor.

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however, Janssen did not have direct access to the data and was not involved in the conduct of the data collection, management, and analyses.

Additional information: The NESDA database is owned by the NESDA consortium. For information on accessing the database, contact Brenda W. J. H. Penninx (b.penninx@vumc.nl).

Supplementary material: Available at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Longitudinal Predictive Validity of the *DSM-5* Anxious Distress Specifier for Clinical Outcomes in a Large Cohort of Patients With Major Depressive Disorder

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List of Supplementary Material for the article

1. eTable 1 DSM-5 anxious distress criteria and the nearest equivalent self-reported items
2. eTable 2 Item-total correlations of the anxious distress specifier items (based on proxy items)

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary eTable 1. DSM-5 anxious distress criteria and the nearest equivalent self-reported items.

DSM-5 anxious distress criteria	Nearest equivalent self-reported items	Response options of the self-reported items
Feeling keyed up or tense	IDS[a] item 7 – Feeling anxious or tense	**0** I do not feel anxious or tense. **1** I feel anxious (tense) less than half the time. **2** I feel anxious (tense) more than half the time. **3** I feel extremely anxious (tense) nearly all of the time.
Feeling unusually restless	IDS[a] item 24 – Feeling restless	**0** I do not feel restless. **1** I'm often fidgety, wring my hands, or need to shift how I am sitting. **2** I have impulses to move about and am quite restless. **3** At times, I am unable to stay seated and need to pace around.
Difficulty concentrating because of worry	IDS[a] item 15 – Concentration/decision making	**0** There is no change in my usual capacity to concentrate or make decisions. **1** I occasionally feel indecisive or find that my attention wanders. **2** Most of the time, I struggle to focus my attention or to make decisions. **3** I cannot concentrate well enough to read or cannot make even minor decisions.
Fear that something awful might happen	BAI[b] item 5 – Fear of worst happening	**0** Not at all **1** Mildly, but it did not bother me much **2** Moderately, it was not pleasant at times **3** Severely, I could barely stand it
Feeling that the individual might lose control of himself or herself	BAI[b] item 14 – Fear of losing control	**0** Not at all **1** Mildly, but it did not bother me much **2** Moderately, it was not pleasant at times **3** Severely, I could barely stand it

Abbreviations: IDS = Inventory of Depressive Symptomatology, BAI = Beck Anxiety Inventory.
[a] For the IDS, participants were asked to circle the response for each item that describes them best in the past seven days.
[b] For the BAI, participants were asked to rate how much they had been bothered by each symptom over the past week.
Note. Symptoms for which a participant scored at least 2 (i.e. the moderate or severe response options) were considered present.

Supplementary eTable 2. Item-total correlations of the anxious distress specifier items (based on proxy items).

	Persons with MDD *N*= 1080
	Item-total correlations[a]
	r
Items anxious distress specifier	
Feeling keyed up or tensed	0.60
Feeling unusually restless	0.30
Difficulty concentrating because of worry	0.39
Fear that something awful may happen	0.53
Feeling that the individual might lose control of himself or herself	0.53

[a]All correlations are significant at $P < .001$.