Prevalence and Treatment Outcome in Anxious Versus Nonanxious Depression: Results From the German Algorithm Project

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Objective: The objective of this study was to explore the prevalence of anxious depression in an inpatient population, to describe its clinical and sociodemographic correlates, and to compare treatment outcomes between patients with anxious and nonanxious depression. Furthermore, the efficacy of algorithm-guided treatment versus treatment as usual in patients with anxious versus nonanxious depression was evaluated.

Method: Data were collected on 429 inpatients with the diagnosis of a depressive episode (according to *ICD-10*) and a score of ≥ 15 on the 21-item Hamilton Depression Rating Scale (HDRS-21). The German Algorithm Project, phase 3 (GAP3), was conducted between 2000 and 2005 in 10 psychiatric departments throughout Germany. A baseline HDRS-21 anxiety/somatization factor score of ≥ 7 was considered indicative of anxious depression. Remission was defined as an HDRS-21 score ≤ 9. To evaluate the efficacy of algorithm-guided treatment, patients were randomly assigned into 3 groups: 2 different treatment algorithms or treatment as usual.

Results: The prevalence of anxious depression was 49%. Patients with anxious depression were more likely than those with nonanxious depression to be older (mean ± SD = 45.3 ± 12.8 vs 42.9 ± 12.0 years, odds ratio [OR] = 1.02 [95% CI, 1.00–1.03], $P = .046$), retired (70% vs 30%, OR = 3.09 [95% CI, 1.70–5.62], $P = .000$), without school qualification (74% vs 26%, OR = 3.11 [95% CI, 1.09–8.83], $P = .035$), more severely depressed (mean ± SD HDRS-21 score = 20.1 ± 5.0 vs 18.5 ± 4.4, OR = 1.08 [95% CI, 1.03–1.12], $P = .001$), and more likely to have a longer duration of the current episode (mean ± SD = 20.9 ± 26.2 vs 13.7 ± 14.3 weeks, OR = 1.02 [95% CI, 1.01–1.03], $P = .011$). Patients with anxious depression were more likely to display a variety of melancholic features. In patients with anxious depression compared to those with nonanxious depression, remission was less likely to be achieved (48.6% vs 61.5%, OR = 0.63 [95% CI, 0.42–0.92], $P = .018$) and took longer to occur (mean ± SD = 44 ± 3.4 vs 30 ± 2.8 days, HR = 0.65 [95% CI, 0.50–0.85], $P = .001$). There was no significant interaction with the treatment mode with regard to remission (Wald = 0.20, $P = .890$).

Conclusions: Anxious depression is common in patients diagnosed with depression. The poorer treatment outcome in patients with anxious depression demonstrates the need to address the issue of specific treatment strategies for this subgroup. However, anxious depression has no moderating effect on the efficacy of algorithm-guided treatment.

Trial Registration: http://www.germanctr.de/ Identifier: DRKS00000161

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Mood and anxiety disorders represent the largest group of mental disorders in Europe and the United States.[1–3] They are not only highly prevalent but frequently coexist. Studies on patients with mood disorders show comorbidity rates of 40%–50%.[4–7] There are 2 different approaches to address the relationship between major depressive disorder (MDD) and anxiety: *anxious depression*, defined as MDD with high levels of anxiety symptoms, follows a dimensional approach, whereas, when defined by comorbidity of major depression with comorbid anxiety disorder, a syndromal approach is used.[8] The dimensional approach seems more applicable to clinical practice since many patients with MDD have prominent anxiety symptoms that are not clearly identifiable as a distinct entity or do not fully meet criteria for a *DSM-IV* or *ICD-10* diagnosis.[6] Although neither classification system (*DSM-IV*, *ICD-10*) specifically addresses anxious depression as a subtype of MDD, there is evidence that this may be a valid diagnostic subtype.[9] The presence of anxious depression is related to greater illness severity and functional impairment,[8–10] greater chronicity,[10,11] delayed response to treatment,[12,13] and an increased risk of suicidality.[8,9,14] Recently, Fava et al[8,9] described sociodemographic features associated with anxious depression: namely, patients were more likely to be older, unemployed, less educated, female, and in a relationship. Patients with anxious depression were more likely to show melancholic features of depression. Moreover, a difference in response to antidepressant treatment was found in some[15,16] but not in all[14,17] short-term studies. Recently, Fava et al[13] have shown in a sample of 2,876 outpatients (Sequenced Treatment Alternatives to Relieve Depression [STAR*D] study) that remission was significantly less likely and took longer to occur in patients with anxious depression. Side effect frequency, intensity, and burden were also greater in the anxious subgroup. Papakostas et al[18] reported that the presence/severity of psychic and somatic anxiety symptoms of MDD at baseline predicted an increased likelihood of nonresponse to fluoxetine in MDD.

While all of the previously mentioned studies were carried out in outpatients, this is the first study to our knowledge to investigate the concept of anxious depression in a sample of

inpatients. The study was part of the multiphase German Algorithm Project, phase 3 (GAP3),[19,20] the third and final phase of the project. The GAP3 evaluated algorithm-guided treatment of inpatients with MDD compared to treatment as usual.[21] The GAP3 was part of a naturalistic study within the German Research Network on Depression, which aimed at assessing all inpatients with the primary diagnoses of a depressive episode according to *ICD-10*[22] from admission to discharge. The objective of the presented post hoc analysis of the GAP3 database was to determine the prevalence of anxious depression in the GAP3 sample, to define its clinical correlates, to compare treatment response to that of nonanxious patients, and to test the efficacy of algorithm-guided treatment in patients with anxious versus nonanxious depression.

METHOD

Study Overview

Study subjects were drawn from GAP3, a randomized controlled multicenter trial to compare 2 different treatment algorithms (standardized stepwise drug treatment regimen and computerized decision and expert system) with treatment as usual. Within standardized stepwise drug treatment regimen, 3 different "second-step strategies" (lithium augmentation, high dose monotherapy, change of antidepressant) were compared in patients nonresponsive to a 4-week antidepressant monotherapy during inpatient treatment. For standardized stepwise drug treatment regimen–treated patients, physicians could choose from 4 different antidepressants (sertraline, a selective serotonin reuptake inhibitor [SSRI]; venlafaxine, a serotonin-norepinephrine reuptake inhibitor; reboxetine, a norepinephrine reuptake inhibitor; amitriptyline, a tricyclic antidepressant). The computerized decision and expert system linked individual patient response data to a probability matrix. Depending on the patient's probability of responding or not responding to current treatment, the computerized decision and expert system proposes either continuing or changing the present strategy, without providing explicit recommendations. Lorazepam and nonbenzodiazepine hypnotics (zopiclone and zolpidem) were permitted for all patients to manage agitation, anxiety, or sleeping problems.

The GAP3 was performed between 2000 and 2005 in 6 academic and 4 nonacademic hospitals throughout Germany.

Participants

Adult inpatients (aged 18–70 years) with the primary diagnosis of a depressive episode (mild, moderate, or severe with or without psychotic symptoms) according to *ICD-10,*[22] single or recurrent, were eligible for the study. An additional inclusion criterion was a score of 15 or higher on the 21-item Hamilton Depression Rating Scale (HDRS-21).[23] Exclusion criteria were depression caused by another medical condition, pregnancy/breastfeeding, preexisting long-term medication treatment that could not be discontinued, and medical conditions that presented a limitation for any of the possible treatments in the study. All patients admitted to either of the participating centers were systematically assessed for eligibility and randomly assigned into 1 of the 5 study groups. The study was fully approved by the local ethics committees for each participating site. Study participants gave their written informed consent to initial treatment as well as to subsequent treatment steps in case of nonresponse.

Clinical Measurements

Diagnostic evaluation was confirmed with the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID-I),[24] a fully structured diagnostic interview for the assessment of mental disorders. Comorbid personality disorders were assessed with the Structured Clinical Interview for *DSM-IV* Axis II Personality Disorders (SCID-II).[25] Baseline and follow-up evaluations included the Beck Depression Inventory (BDI),[26] the HDRS-21,[23] and the Utvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale[27] for the assessment of medication-induced side effects. For further analysis, only those symptoms were taken into account in which causal relationship with the medication was rated as likely. At baseline, clinical and sociodemographic characteristics were assessed using a systematic basic assessment scale of clinical and sociodemographic variables in psychiatry (Basic Documentation).[28]

Treatment outcome and tolerability were assessed every 2 weeks (± 3 days) by research staff who, while not blinded for the treatment group, were not involved in the patient treatment. Details of algorithm-guided decision making are published elsewhere.[21] The primary outcome criteria were the remission and response rates and time to remission. The primary outcome variable was the score on the HDRS-21. Remission was defined as an HDRS-21 score ≤ 9. Participants remained inpatient until remission and were rated until discharge, unless they dropped out of the study and refused further ratings. Follow-up assessments were performed at 1 and 2 years after discharge.

Definition of Anxious Depression

Anxious depression, defined as MDD with high levels of anxiety symptoms, was determined based on the Hamilton anxiety/somatization factor score.[7–9] The anxiety/somatization factor, derived from a factor analysis of the HDRS-17 scale conducted by Cleary and Guy,[29] includes 6 items: anxiety (psychic), anxiety (somatic), somatic symptoms (gastrointestinal), somatic symptoms (general), hypochondriasis, and insight. In accordance with previous studies,[8,9,13] a Hamilton anxiety/somatization factor score ≥ 7 based on the HDRS-21 assessment at baseline was used to define anxious depression.

Statistical Analysis

Statistical Package for Social Science (SPSS) Version 18.0 (SPSS Inc, Chicago, Illinois) was used for statistical operations. Descriptive statistics included frequencies and percentages for categorical variables, mean and standard deviations or

median and range for continuous variables. To allow for adjustments for baseline severity of depression, bivariate logistic regression models were used to assess the association between the independent variables of interest and the presence of anxious depression. Baseline depression severity was measured by the HDRS-21 score, not including the items used to identify anxious depression. Survival analysis was conducted to be able to use all patient data including right-censored cases due to dropout. It was assumed that treatment response did not differ between patients remaining in the study until remission and dropout. Median survival times were calculated using Kaplan-Meier statistics. Differences in probability (hazard) of remission between groups were analyzed using log-rank test and Cox regression modeling. Anxious depression, treatment mode (standardized stepwise drug treatment regimen, computerized decision and expert system, treatment as usual), depression severity (HDRS-21 baseline without anxiety-specific items), age, education, employment, and duration of current episode were included as independent variables as they were significantly different in the comparison of anxious versus nonanxious depression. The direct entry method was chosen for the multivariate analysis.

No adjustments were made for multiple testing. Therefore, all significant associations must be viewed with caution. Sample sizes may differ between specific steps of analysis depending on available data.

RESULTS

Sample Description

Of 593 patients who entered the naturalistic study between 2000 and 2005, 475 (80.1%) took part in GAP3. Of these 475 patients, 46 had to be excluded post hoc after randomization (9 patients because of incomplete data, 11 patients because of baseline HDRS-21 scores < 15, 26 because of a diagnosis other than major depressive episode), so that 429 were included in the final analysis. Table 1 summarizes the clinical and sociodemographic characteristics of the sample.

The majority of the patients were female (63%), suffered from recurrent depression (53%), and were rated as having moderate to severe depression, with a mean ± SD HDRS-21 baseline score of 25.9 ± 6.0. The prevalence of anxious depression in this population was 49%. There was no significant difference in distribution among the 3 treatment modes (anxious depression: standardized stepwise drug treatment regimen (48.3%), computerized decision and expert system (50.6%), treatment as usual (61.9%); $\chi^2 = 4.48$, $P = .093$). The distribution of the HDRS-21 anxiety/somatization factor scores appears to be continuous, with a range of 0 to 14 and a median score of 7 (Figure 1).

Sociodemographic and Clinical Features at Baseline

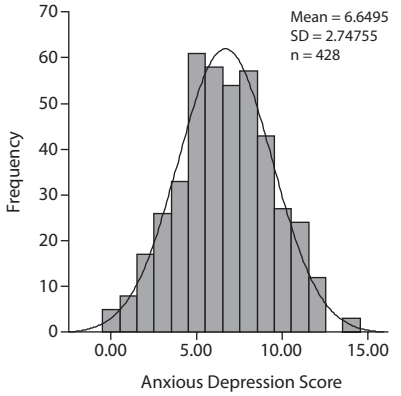
Tables 2 and 3 provide the results of the nonadjusted and adjusted (for baseline severity of depression) relationships between the presence or absence of anxious depression and both sociodemographic and clinical variables.

Table 1. Baseline Characteristics of the Sample

Characteristic	n	Mean (SD)	Median (range)
Age, y	429	44.2 (12.5)	44 (18–69)
No. of children	356	1.2 (1.1)	1.0 (1–6)
Depression severity at baseline (HDRS-21 score)	429	25.9 (6.0)	26.0 (15–49)
Depression severity at baseline (BDI)	355	29.2 (10.4)	29 (3–58)
Duration of current episode, wk	246	19.4 (37.5)	10.0 (2–499)
Duration since illness onset, y	262	7.7 (10.1)	3.0 (0–46)
Total no. of depressive episodes, including current episode	251	2.4 (2.2)	2.0 (1–20)
		n	%
Women	428	271	63.3
Married/partnership	397	160	40.3
Employed (fulltime or parttime)	385	157	40.8
High school diploma	389	115	29.6
Any school qualification	389	370	95.1
Vocational qualification	388	306	78.9
Depressive episode, single	420	197	46.9
Psychotic symptoms	420	28	6.7
Comorbidity			
Psychiatric	420	100	23.8
Personality disorder	429	39	9.1

Abbreviations: BDI = Beck Depression Inventory, HDRS-21 = 21-item Hamilton Depression Rating Scale.

Figure 1. Distribution of the Hamilton Anxiety/Somatization Factor Scores in Patients of GAP3 (n = 429)



Abbreviation: GAP3 = German Algorithm Project, phase 3.

Anxious depression was significantly more likely among older subjects (45.3 ± 12.8 vs 42.9 ± 12.0 years, OR = 1.02 [95% CI, 1.00–1.03], $P = .046$), among (prematurely) retired patients (70% vs 30%, OR = 3.09 [95% CI, 1.70–5.62], $P = .000$), and among those without school qualifications (74% vs 26%, OR = 3.11 [95% CI, 1.09–8.83], $P = .035$). Patients with more severe depression, as measured by the BDI (32.1 ± 10.3 vs 26.2 ± 9.7, OR = 1.05 [95% CI, 1.03–1.08], $P = .000$) and the HDRS-21 (not including the anxiety specific items, 20.1 ± 5.0 vs 18.5 ± 4.4, OR = 1.08 [95% CI, 1.03–1.12], $P = .001$), and those with a longer duration of the current episode (20.9 ± 26.2 vs 13.7 ± 14.3 weeks, OR = 1.02 [95% CI, 1.01–1.03], $P = .011$) were more likely to have anxious depression (see Tables 2 and 3). The differences remained significant after adjusting for baseline severity of depression.

There was no significant difference between patients with anxious and nonanxious depression in gender, marital

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Table 2. Baseline Characteristics and Their Association With Anxious Depression (bivariate logistic regression models)

Characteristic	n, Total	Nonanxious Depression n	Nonanxious Depression %	Anxious Depression n	Anxious Depression %	Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)[a]	P	Replication of Fava et al[9] (2006)?
Sex										
Male	157	80	51	77	49	0.87 (0.59–1.29)	.480	0.84 (0.56–1.25)	.383	No
Female	270	128	47	142	53				.334	No
Marital status										
Unmarried	237	118	50	119	50	0.83 (0.55–1.23)	.349	0.82 (0.54–1.23)		
Married	160	72	45	88	55					
School										
No qualification	19	5	26	14	74	2.77 (0.98–7.85)	.055	3.11 (1.09–8.83)	.035	Yes (Fava et al[9] assessed in years of education)
Any qualification	370	184	50	186	50					
Vocational qualification										
Yes	306	148	48	158	52	1.03 (0.63–1.68)	.897	1.01 (0.61–1.66)	.979	Not assessed
No	82	39	48	43	52					
Employment status										No (Fava et al[9] found more unemployed than employed)
Employed	157	89	57	68	43					
Homemaker	47	26	55	21	46	1.06 (0.55–2.04)	.868	1.14 (0.58–2.23)	.701	
Unemployed	98	45	46	53	54	1.54 (0.93–2.56)	.095	1.50 (0.90–2.51)	.122	
Retired prematurely	73	22	30	51	70	3.03 (1.68–5.48)	.000	3.09 (1.70–5.62)	.000	
Suicidal (HDRS item baseline)[b]	268	128	47.8	140	52.2	1.09 (0.74–1.62)	.654	0.76 (0.49–1.19)	.233	No
Comorbid personality disorder	39	19	48.7	20	51.3	1.01 (0.52–1.94)	.987	1.14 (0.58–2.25)	.698	Not assessed

[a]Adjusted for the HDRS-21 score, not including the items used to identify anxious depression.
[b]Suicidal = HDRS single item score ≥ 2.
Abbreviations: HDRS-21 = 21-item Hamilton Depression Rating Scale, OR = odds ratio.

Table 3. Baseline Characteristics and Their Association With Anxious Depression (bivariate logistic regression models)

	n, Total	Nonanxious Depression n	Nonanxious Depression mean	Nonanxious Depression SD	Anxious Depression n	Anxious Depression mean	Anxious Depression SD	Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)[a]	P	Replication of Fava et al[9] (2006)?
Age, y	428	208	42.9	12.0	220	45.3	12.8	1.02 (1.00–1.03)	.041	1.02 (1.00–1.03)	.046	Yes
Age at onset, y	262	123	37.7	12.1	139	38.0	12.4	1.00 (0.98–1.02)	.811	1.00 (0.98–1.02)	.699	No
No. of episodes	251	120	2.1	2.0	131	2.6	2.3	1.13 (0.98–1.25)	.086	1.11 (0.97–1.28)	.127	Yes
Duration of episode, wk	245	117	13.7	14.3	128	20.9	26.2	1.02 (1.00–1.04)	.014	1.02 (1.01–1.03)	.011	Yes
Duration since illness onset, y	262	123	6.5	9.1	139	8.7	10.9	1.02 (0.99–1.05)	.091	1.02 (0.99–1.05)	.130	Yes
No. of psychiatric comorbidities	420	204	0.3	0.6	216	0.3	0.6	0.94 (0.69–1.29)	.708	0.94 (0.69–1.29)	.715	No
HDRS-21[b]	428	208	18.5	4.4	220	20.1	5.0	1.08 (1.03–1.12)	.001			Yes
BDI	355	178	26.2	9.7	177	32.1	10.3	1.06 (1.94–1.09)	.000	1.05 (1.03–1.08)	.000	Not assessed
No. of children	256	166	1.2	1.2	190	1.2	1.1	0.98 (0.82–1.18)	.859	1.00 (.83–1.21)	.987	Not assessed

[a]Adjusted for the HDRS-21 score, not including the items used to identify anxious depression.
[b]Without anxiety specific items.
Abbreviations: BDI = Beck Depression Inventory, HDRS-21 = 21-item Hamilton Depression Rating Scale, OR = odds ratio.

status, number of children, age at illness onset, number of depressive episodes, number of psychiatric comorbidities, suicidality, or presence of a comorbid personality disorder (see Tables 2 and 3).

Patients with anxious depression were more likely, after we adjusted for baseline depression severity, to agree with the BDI items concerning sadness, negative body image, retardation, fatigability, loss of appetite, and somatic preoccupation (Table 4).

Response to Treatment

Patients with anxious depression had significantly lower response (59.5% vs 69.7%, OR = 0.63 [95% CI, 0.42–0.94], $P = .023$) and remission rates (48.6% vs 61.5%, OR = 0.63 [95% CI, 0.42–0.92], $P = .018$) during the study period. These results remained significant even after controlling for baseline severity of depression (Table 5).

The presence or absence of anxious depression was not the only significant predictor of remission and response. The total score of the HDRS anxiety/somatization factor also showed a significant association to remission (OR = 0.91 [95% CI, 0.85–0.98], $P = .016$) and response at the study endpoint (OR = 0.92 [95% CI, 0.85–0.99], $P = .032$), again even after controlling for baseline severity of depression.

Kaplan-Meier survival analysis showed a significant difference in median ± SD time to remission between the 2 groups (30 ± 2.8 days for nonanxious depression vs 44 ± 3.4 days for anxious depression; log-rank test, $\chi^2 = 16.99$, $P = .000$). The subsequent Cox regression analysis revealed a significantly lower probability of achieving remission for anxious depression as compared to nonanxious depression (HR = 0.65 [95% CI, 0.50–0.85], Wald = 10.15, $P = .001$), even when adding baseline severity of depression (HR = 0.96 [95% CI, 0.93–0.99], Wald = 6.16, $P = .013$) or treatment mode (Wald = 8.97, $P = .011$) to the model (Figure 2). Compared to treatment as usual, patients from standardized stepwise drug treatment regimen had a higher probability of achieving remission (HR = 1.48 [95% CI, 1.05–2.07], Wald = 4.88, $P = .027$), but

Table 4. Symptoms in Anxious and Nonanxious Depression Based on the Beck Depression Inventory (bivariate logistic regression models)

	Nonanxious Depression				Anxious Depression							
	Present		Absent		Present		Absent		Unadjusted OR		Adjusted OR	
Item	n	%	n	%	n	%	n	%	(95% CI)	*P*	(95% CI)[a]	*P*
Sadness	156	88.1	21	11.9	173	95.6	8	4.4	2.91 (1.25–6.76)	.013	2.70 (1.15–6.37)	.023
Pessimism	129	73.3	47	26.7	151	83.4	30	16.6	1.83 (1.10–3.07)	.021	1.51 (0.89–2.58)	.127
Social withdrawal	110	62.5	66	37.5	130	72.6	49	27.4	1.59 (1.02–2.49)	.042	1.47 (0.93–2.32)	.100
Negative body image	102	59.0	71	41.0	139	78.5	38	21.5	2.55 (1.59–4.07)	.000	2.26 (1.40–3.65)	.001
Retardation	161	91.0	16	9.0	175	97.8	4	2.2	4.35 (1.42–13.28)	.010	4.70 (1.52–14.52)	.007
Fatigability	146	82.5	31	17.5	167	92.8	13	7.2	2.73 (1.37–5.41)	.004	2.75 (1.37–5.53)	.005
Loss of appetite	116	65.9	60	34.1	150	83.3	30	16.7	2.59 (1.57–4.27)	.000	2.19 (1.31–3.66)	.003
Somatic preoccupation	88	49.7	89	50.3	125	69.4	55	30.6	2.30 (1.49–3.54)	.000	2.33 (1.50–3.63)	.000

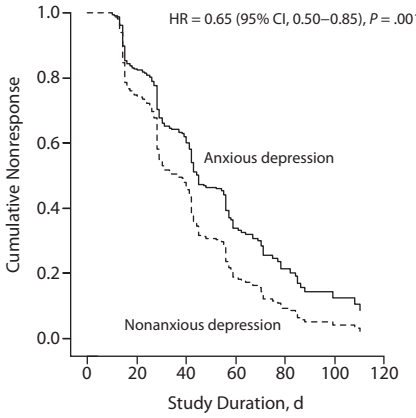
[a]Adjusted for the 21-item Hamilton Depression Rating Scale score, not including the items used to identify anxious depression; only significant results are presented.
Abbreviation: OR = odds ratio.

Table 5. Remission (HDRS-21 ≤ 9) and Response Rates (reduction of HDRS-21 score ≥ 50%) in Patients of GAP3, by Presence of Anxious Depression (bivariate logistic regression models)

	Anxious Depression									
	No		Yes		Total		Unadjusted		Adjusted	
Outcome	n	%	n	%	n	%	OR (95% CI)	*P*	OR (95% CI)[a]	*P*
Remission										
No	80	38.5	113	51.4	193	45.1	0.59 (0.40–0.86)	.008	0.63 (0.42–0.92)	.018
Yes	128	61.5	107	48.6	235	54.9				
Response										
No	63	30.3	89	40.5	152	35.5	0.64 (0.43–0.95)	.028	0.63 (0.42–0.94)	.023
Yes	145	69.7	131	59.5	276	64.5				

[a]Adjusted for baseline severity of depression (HDRS rating scale without anxiety factor).
Abbreviations: GAP3 = German Algorithm Project, phase 3; HDRS-21 = 21-item Hamilton Depression Rating Scale; OR = odds ratio.

Figure 2. Time to Remission in 429 Patients of GAP3 by Anxious Versus Nonanxious Depression (Cox regression analysis)—Adjusted for Baseline Depression Severity



Abbreviation: GAP3 = German Algorithm Project, phase 3.

there was no difference between computerized decision and expert system and treatment as usual (HR = 0.95 [95% CI, 0.61–1.48], Wald = 0.05, *P* = .822). Even when factoring in age (HR = 1.02 [95% CI, 0.99–1.03], *P* = .084), education (HR = 0.59 [95% CI, 0.23–1.48], *P* = .259), employment (Wald = 7.00, *P* = .072), and duration of illness (HR = 0.99 [95% CI, 0.97–1.01], *P* = .224), we found that anxious depression remained a significant predictor (HR = 0.66 [95% CI, 0.46–0.93], *P* = .017). A further Cox regression analysis revealed no significant statistical interaction between treatment mode (standardized stepwise drug treatment regimen vs computerized decision and expert system vs treatment as usual) and presence of anxious symptoms (anxious vs nonanxious depression) (Wald = 0.20, *P* = .890).

Anxious patients in standardized stepwise drug treatment regimen (n = 154) displayed a significantly lower probability of achieving remission after an initial antidepressant monotherapy compared to patients with nonanxious depression, even when controlling for severity of depression (OR = 0.63 [95% CI, 0.42–0.92], *P* = .018). Anxious and nonanxious patients did not differ in their use of tranquilizers (anxious, 61.5%, vs nonanxious, 56.6%; $\chi^2 = 0.87$, *P* = .350). They also did not show differences in tranquilizer dosages used per day (*F* = 1.22, *P* = .270).

Compared to patients with nonanxious depression, mean ± SD length of treatment until discharge was longer for patients with anxious depression (59.16 ± 40.51 days vs 50.25 ± 35.54 days, *t* = −2.416, *P* = .016). At discharge, patients with anxious depression had a lower probability of being remitted than patients with nonanxious depression (73% vs 82%, $\chi^2 = 3.85$, *P* = .050), independent of study completion or dropout.

Treatment Tolerability

A significant difference between anxious and nonanxious patients was found neither in overall dropout frequency (43.2% vs 34.6%, $\chi^2 = 3.30$, *P* = .069) nor in side effect–related dropout frequency (7% vs 5.8%, $\chi^2 = 3.71$, *P* = .716).

There was also no significant difference between anxious and nonanxious patients in reporting versus never reporting side effects (51.1% vs 60.6% reporting side effects, $\chi^2 = 3.36$, *P* = .067). Of those patients with side effects (n = 205), 5.9% reported side effects up to 25% of the time; 31.7%, up to 50% of the time; 18%, up to 75% of the time; and 44.4%, up to 100% of the time—with no significant difference between anxious and nonanxious patients ($\chi^2 = 3.77$, *P* = .287).

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DISCUSSION

We showed in this multisite study of inpatients diagnosed with MDD that anxious depression is common in a German inpatient sample, with a prevalence of 49%. This finding is consistent with the frequencies of anxious depression found in other studies (44%–46% in the STAR*D outpatient sample[8,9]) and with the lifetime comorbidity rate for depression and anxiety disorders of 40%–50%[6,30] or for bipolar disorder and anxiety of 50%.[31]

As in previous studies, the incidence of anxious depression was related to distinct sociodemographic and clinical correlates, even after adjustment for severity of depression. Our study showed that patients with anxious depression were older, less educated, and more often (prematurely) retired, before and after controlling for depression severity at baseline. Although patients in the STAR*D study were more likely to be unemployed than retired, the results taken together confirm the view of anxiously depressed patients as more often carrying unfavorable social determinants and negative predictors of disease course.[13] Patients with anxious depression were also more likely to report greater illness severity, as measured with the HDRS-21 and the BDI self-rating instrument, which also is in line with the results of the STAR*D study,[8,9] although different instruments were used to measure illness severity (30-item Inventory of Depressive Symptomatology–Clinician-Rated and the 16-item Quick Inventory of Depressive Symptomatology–Self-Report). Consistent with the greater illness severity at baseline is the significantly longer duration of the current episode among patients with anxious depression in our sample, both factors being possible indicators of an association between anxious depression and chronicity of depression as earlier described by Fava et al[8,9] and VanValkenburg et al.[11] However, in contrast to their results, we did not find a significant difference in suicidality between anxious and nonanxious patients.

As in the STAR*D sample, our study observed differences in the self-assessment of patients with anxious depression, ie, a higher frequency of items related to sadness, retardation, fatigability, and loss of appetite, although different rating scales were used. This lends further support to the assumption by Fava et al[13] that anxious depression may share some core features with the endogenous, melancholic subtype of depression.

In addition to the clinical and sociodemographic differences, the present study shows that patients with anxious depression had poorer treatment outcomes than patients with nonanxious depression, independent of the predictor used (total score of HDRS anxiety/somatization factor or presence/absence of anxious depression). In our sample, about 49% of anxious patients achieved remission in contrast to 61% of nonanxious patients. In addition, anxious patients also took longer to remit than nonanxious patients, even after controlling for depression severity. The 10% difference in remission rates between anxious and nonanxious patients and the longer time to remission for anxious patients highlights the similarity of Fava and colleagues'[13] findings and the results of the present study.

Dunlop et al[32] and Furukawa et al[33] discuss that benzodiazepines appear to improve treatment outcomes for depression characterized by anxious features. Poorer treatment outcome of anxious depressed patients in our sample cannot be attributed to restrictions in the use of benzodiazepines as they were equal for patients with and without anxious features.

In contrast to the results of Fava et al,[13] our study did not find any difference between anxious and nonanxious patients with regard to the reporting of side effects, side effect frequency, or side effects related dropouts. This difference in results could partly be due to the different treatment modalities of the 2 studies. The STAR*D sample is an outpatient sample, whereas the GAP sample is an inpatient sample. Patients with anxious depression may be particularly prone to overreporting side effects, particularly under the conditions of outpatient treatment. In inpatients, closer monitoring and reassurance by the treating staff may reduce the sensitivity to side effects. In addition, side effects in our study were clinician-rated, which further minimizes the risk of side effect overreporting in anxious patients. The inpatient setting may also explain the lack of difference in the use of tranquilizer between anxious and nonanxious patients in our sample. Continuous reassurance by the staff as well as close monitoring of medication and daily controlled prescription of tranquilizers may equalize their use in the 2 subgroups. However, prescription rates for tranquilizers were rather high in both groups (61.5% and 56.6%), which further minimizes the chance of showing a difference.

A noteworthy finding was that anxious depression had no moderating effect on the efficacy of algorithm-guided treatment found in the total population. The superiority of an algorithm-guided treatment according to standardized stepwise drug treatment regimen equally applies to the anxious and nonanxious subtype of MDD. Among remitted patients, those with nonanxious depression were more likely to respond to an initial antidepressant monotherapy than patients with anxious depression.

In summary, the current study shows that patients with anxious depression are a "harder-to-treat" subgroup and that further research is needed to address the issue of specific first-line treatments for these patients to avoid and overcome treatment resistance and chronic courses of illness. On the basis of a literature review, Silverstone et al[34] conclude that drugs inhibiting the reuptake of both norepinephrine and serotonin may have greater clinical utility than single-acting drugs such as the SSRIs. Further, in a pooled analysis of 10 studies, Papakostas et al[35] found a modest advantage for the SSRIs compared to bupropion in the treatment of anxious depression, a finding that stresses the effectiveness of a serotonergic mechanism in these patients. So far, there are no clear recommendations for the treatment of anxious depression. Whether antidepressants that have shown their effectiveness in panic disorder or generalized anxiety disorder[36] are also more effective in patients with anxious depression requires further study.

Our results highlight the need for a stronger emphasis on the identification of symptoms of anxious depression in patients with MDD. The question as to whether anxious depression should be regarded as a distinct subtype of MDD, as proposed by Fava et al,[13] cannot be conclusively answered with our data. Robins and Guze[37] and Kendler[38] describe differentiating features, evidence of familiality, and specific treatment responsivity as indicators of a distinct psychiatric diagnostic entity. In our study, anxious depression appears to be associated with specific features and different response patterns. As we did not obtain any data on anxious depression in relatives, we cannot comment on familiality. Recently, the functional −399C/T polymorphism of the neuropeptide Y gene (rs16147) has been shown to be associated with antidepressant response in the clinical phenotype of anxious depression,[39] which supports a genetic difference between anxious and nonanxious depression. The authors propose that the current state of genetic and imaging genetics research on the clinical phenotype of anxious depression might inspire a redefinition and restructuring of the present nosologic concepts in *DSM-V*. Clearly, further studies are needed to provide information on the specific treatment responsivity and on familiality to support the utility of anxious depression as a distinct subtype of MDD. The question remains if anxious depression should be regarded as a distinct subtype or rather as a clinical phenotype of major depression that, as with severe depression, merits a higher intensity of care.

More importantly from our point of view is the need for stronger diagnostic and therapeutic attention toward patients with anxious depression. The dimensional approach and the use of a threshold value instead of a continuous dimension could be of particular clinical utility. We used the definition of anxious depression based on the HDRS anxiety/somatization factor score ≥ 7, as had been done in previous studies[8,9,13,14] to make results comparable. Undoubtedly, this cutoff point should be examined for sensitivity and specificity in future studies.

Generalizability of our results is limited to an inpatient population that is generally more severely depressed than an outpatient sample, although we have controlled for depression severity. Further, a limitation in comparability to the STAR*D sample is the lower chronic disease burden of the GAP3 sample. Our data have been collected within the German health care system, which is characterized by a higher rate of inpatient admissions that occur rather early in the course of the disease. Another limitation of our results is the inclusion of patients with psychotic symptoms, which, although limited in number (n = 28), might have confounded the analysis. Despite the different treatment modalities, Fava et al[8,9,13] and our study come up with very similar results with regard to sociodemographic and clinical characteristics as well as response patterns of patients with anxious depression.

In conclusion, our results show that special attention should be paid to the assessment and diagnosis of anxious depression in clinical practice. There is growing evidence that anxious depression might be a valid clinical predictor for treatment response.

Drug names: bupropion (Aplenzin, Wellbutrin, and others), fluoxetine (Prozac and others), lithium (Lithobid and others), lorazepam (Ativan and others), sertraline (Zoloft and others), venlafaxine (Effexor and others), zolpidem (Zolpimist, Ambien, and others), zopiclone (Lunesta).

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