"Caseness" for Depression and Anxiety in a Depressed Outpatient Population: Symptomatic Outcome as a Function of Baseline Diagnostic Categories

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Objective: To examine the diagnostic status of patients enrolled in the Factors Influencing Depression Endpoints Research (FINDER) study and symptomatic outcomes and baseline characteristics associated with remission 6 months after commencing antidepressant therapy.

Method: Status of clinically diagnosed depressed patients was based on self-rated Hospital Anxiety and Depression Scale (HADS) scores. Five diagnostic categories were defined: noncaseness, mixed anxiety-depression (subthreshold depressive and anxious symptomatology), caseness for depression, caseness for anxiety, and caseness for comorbid anxiety-depression. Assessments included the Somatic Symptom Inventory and health-related quality of life (HRQoL) using the Medical Outcomes Study 36-item Short-Form Health Survey. Remission rates (based on HADS noncaseness for both depression and anxiety) and their associations with baseline characteristics were investigated. Patients were enrolled between May 2004 and September 2005.

Results: Of the 3,353 patients enrolled, 66.4% met the HADS criteria for probable depressive disorder and 74.1% met the HADS criteria for probable anxiety disorder. Somatic symptom severity (painful and nonpainful) was highest and HRQoL was lowest in the comorbid anxiety-depression group. After 6 months, remission rates were 50.2% for caseness for depression, 40.4% for caseness for anxiety, and 40.6% for caseness for comorbid anxiety-depression. A lower number of previous depressive episodes, shorter current episode duration, lower painful and nonpainful somatic symptom scores, being married, a higher educational level, and working for pay were most consistently associated with higher remission rates.

Conclusions: Physicians do not always differentiate between anxiety and depressive symptoms when making a clinical diagnosis of depression. At baseline, most enrolled patients had significant emotional depressive and anxious symptoms, as well as significant nonpainful and painful somatic symptomatology, and these factors were associated with outcome.

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A strong relationship is expected between diagnosis and prescription pattern in psychiatry, but this is challenged by the available literature. The European Study on the Epidemiology of Mental Disorders (ESEMeD) investigated the relationship between the diagnosis of depressive or anxiety disorders and psychotropic medication use.[1] The study found that less than one-third of subjects with a 12-month prevalence of major depressive disorder (MDD) were taking antidepressants, and the most important predictors of the use of antidepressants were seeking help for emotional problems and age rather than the presence of a formal *DSM-IV* diagnosis. This finding suggests that prescription of psychotropic medication may not always be in accordance with the licensed indications.

Clinicians do not always comply with diagnostic and treatment guidelines.[2] One reason for this may be the limited ecological validity of the findings in antidepressant randomized controlled trials (RCTs), which aim to have a homogeneous patient sample by having multiple inclusion and exclusion criteria. However, these stringent criteria increase the likelihood that patients taking part in RCTs of antidepressants are not representative of the heterogeneous patient samples found in daily clinical practice.[3] Two studies found that only about 14% of routine practice patients with MDD could be enrolled in RCTs, and that the main reason for exclusion was because of comorbid conditions.[4–6]

Another reason for noncompliance of clinicians with guidelines is the number of patients presenting with subthreshold conditions (eg, minor depressive disorder, recurrent brief depressive disorder, subsyndromal symptomatic depression, adjustment disorder with depressed mood).[7,8] These conditions are highly prevalent and have a substantial impact on functioning.[9] Given the limited data from RCTs for these subthreshold depressive disorders, evidence-based treatment recommendations

cannot be given at this point.[7] "Close monitoring and problem-solving therapy may be useful, and a treatment trial with one of the well-tolerated antidepressants is worth trying in more chronic and unremitting cases."[7(p82)] The latter reason can logically result in off-label prescription of antidepressants.[7]

There are few studies of depressive disorder treatments in a naturalistic setting. The Factors Influencing Depression Endpoints Research (FINDER) study is a large (N = 3,468) European, prospective, observational study of health-related quality of life (HRQoL) outcomes in adult patients with a clinically diagnosed depressive episode at baseline (untreated) and at 3 and 6 months after commencing antidepressant medication.[10–12] The only included psychometric tool allowing assessment of a formal diagnosis of a depressive or anxiety disorder in the FINDER study was the patient-rated Hospital Anxiety and Depression Scale (HADS), a well-known screening instrument.[13] This questionnaire was originally used in the FINDER study as a patient-rated symptom severity scale.

This article examines the FINDER population from the perspective of their baseline HADS status (based on probable caseness, doubtful caseness, and noncaseness for depression and anxiety) and investigates the sociodemographic, clinical, and quality of life correlates of these patient subgroups. This article also investigates the symptomatic outcomes and the association of baseline characteristics with HADS diagnostic outcomes after 6 months of commencing antidepressant therapy.

METHOD

The FINDER study was a 6-month, prospective, observational study conducted in 12 European countries and designed to investigate the HRQoL of outpatients with depression initiating antidepressant treatment. Adult patients (N = 3,468) were eligible for enrollment when presenting within the normal course of care, were diagnosed by their physician (psychiatrist or general practitioner [GP], n = 1,818 and n = 1,650, respectively) as suffering from depression, and were about to commence antidepressant treatment for a first episode or new episode of recurrent depression. In order to keep the study as naturalis-

tic as possible, no structured diagnostic criteria were requested for the diagnosis of depression. Assessments were performed at baseline and at 3 (± 1 month) and 6 months (± 1 month) during the follow-up period. Patients were enrolled between May 2004 and September 2005.

The detailed study design and methods have been reported elsewhere[10] and are only briefly described here. The study was approved in all countries according to local requirements for ethics and/or regulatory approvals for observational studies, and all patients gave written informed consent.

Psychometric Instruments

Symptom scales assessed at baseline and at 3 and 6 months' follow-up. The symptom scales used in the present study assessed both emotional and somatic symptoms. Emotional symptoms were assessed with the HADS,[13] a well-documented screening instrument for anxiety and depression, in order to have a more detailed evaluation during treatment. For both the anxiety (HADS-A) and the depression (HADS-D) subscales, a score of 0–7 can be regarded as within a normal range (noncase), while a score ≥ 11 indicates a probable case; scores between 8 and 10 are suggested to be doubtful cases.

In an attempt to align all potential combinations of subscale ratings (for anxiety: noncase [A–], doubtful case [A?], and probable case [A+]; for depression: noncase [D–], doubtful case [D?], and probable case [D+]) with the more broadly used *DSM-IV* diagnostic categories, the following 5 subgroups were defined:

(1) noncaseness: D–A–, D–A?, or D?A–
(2) mixed anxiety-depression: D?A? (subthreshold depressive and anxious symptomatology)
(3) caseness for depression: D+A– or D+A?
(4) caseness for anxiety: D–A+ or D?A+
(5) caseness for comorbid anxiety-depression: D+A+

All patients with complete HADS ratings (at baseline as well as at 3- and 6-months' follow-up) were classified within these diagnostic categories.

The change in HADS symptoms of these patients were investigated as follows. *Remission*, traditionally defined as reaching a status of no significant symptomatology,

was defined as D–A– at 3 and 6 months, independent of caseness status at baseline. *Nonremission* or *still caseness* was defined in different ways depending on the baseline status.

(1) For those with caseness for depression (D+A–, D+A?) at baseline, still caseness was defined as D+A+ (worsening to comorbid anxiety-depression) or D+A– or D+A?.

(2) For those with caseness for anxiety (D–A+, D?A+) at baseline, still caseness was defined as D+A+ (worsening to comorbid anxiety-depression) or D–A+ or D?A+.

(3) For those with caseness for comorbid anxiety-depression (D+A+) at baseline, 3 subgroups of still caseness were defined: caseness for depression (D+A–, D+A?), caseness for anxiety (D–A+, D?A+), and comorbid anxiety-depression (D+A+).

Somatic symptoms were assessed with the 28-item Somatic Symptom Inventory (SSI-28).[14,15] The SSI is a patient self-report scale that assesses the degree to which various physical complaints have been bothersome to the patient. Each complaint is rated on a defined scale from 1 (not at all) to 5 (great deal). The pain subscale (SSI-pain) is derived by calculating the mean score over 7 pain-related items, and the somatic subscale (SSI-somatic) uses the remaining 21 items. Overall pain severity was also rated using a visual analog scale (VAS) from the extremes of experiencing "no pain" (0 mm) to experiencing pain "as severe as I can imagine" (100 mm). A threshold score of 30 mm has been identified to distinguish no or mild pain from moderate/severe pain.[16,17]

HRQoL scale assessed at baseline and at 3 and 6 months' follow-up. HRQoL was assessed using the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36).[18] The SF-36 consists of 36 questions that generate scores across 8 health domains (4 mental and 4 physical subscales) and 2 summary scores, the Physical Component Score (PCS) and the Mental Component Score (MCS). Each subscale is scored by summing the individual terms and transforming the scores into a 0 to 100 scale, with higher scores indicating better quality of life. Any score below 50 indicates worse than average quality of life.[19] As several of the 8 health domains of the SF-36 are known to show considerable content overlap with symptom scales, this article reports on the 2 component summary scores and on the 3 domains that specifically assess functioning (role-physical, role-emotional, and social functioning).

Sociodemographic and psychiatric history variables at baseline. The following sociodemographic variables were collected: age, gender, education (further or none/mandatory), marital status (married/domestic partner or other), occupational status (working for pay, unemployed, or other), number of dependents, body mass index (BMI), and current smoker.

The following clinical variables were collected: duration of current depressive episode, number of previous episodes of depression, age at first depressive episode, patients with at least 1 additional psychiatric illness in previous 2 years, and presence of any chronic medical condition.

Statistical Methods

All eligible patients with nonmissing HADS data at the first observation were included in the present analyses. Counts and percentages of patients falling into the defined diagnostic categories at baseline were calculated, and suitable summary statistics are presented for the characteristics of these patients. In the text, differences between the diagnostic categories at baseline are noted descriptively only since no direct statistical comparisons were made due to the multiple confounding factors that affect the characteristics observed. For patients with follow-up data on the HADS, percentages of still case and remitted patients, as defined above, were calculated.

For each of the 3 baseline categories of caseness for depression, caseness for anxiety, and caseness for comorbid anxiety-depression (ie, subgroups 3, 4, and 5), logistic regression analyses were performed to model each of the log odds of still caseness and of remission, as defined above, using backward elimination methods. Country was retained in all models even if not statistically significant. Results are reported using Wald χ^2 statistics, and P values and odds ratios and their 95% CIs are presented for all statistically significant (P ≤ .05) independent variables in the model.

In the figures, independent variables are placed in order of the strength of the association with the dependent variable, with the most strongly associated variable at the top of the figure. The independent variables included in the models were as follows: age, gender, education (none/mandatory or further), occupational status (working for pay, unemployed, or other), marital status (married/domestic partner or other), BMI, number of dependents, smoking, country, number of previous episodes of depression, age at first MDD episode, any psychiatric illnesses in the 24 months before baseline, duration (at baseline) of the current MDD episode, baseline HADS anxiety and depression scores, VAS overall pain and SSI-somatic scores, and any chronic medical conditions.

RESULTS

Results at Baseline

Of the 3,468 eligible patients at baseline, 3,353 had nonmissing HADS ratings and were included in the current analyses.

Table 1A. Baseline Distribution of All Patients by HADS Caseness Subgroups (N = 3,353)[a]

	Noncase Depression D–	Doubtful Case Depression D?	Probable Case Depression D+	
Noncase Anxiety A–	4.5	2.2	2.7	Caseness for Anxiety (independent of depression)
Doubtful Case Anxiety A?	4.3	4.3	7.8	
Probable Case Anxiety A+	6.2	12.0	55.9	74.1
Careness for Depression (independent of anxiety)		66.4		

[a]Data are presented as %.
Abbreviation: HADS = Hospital Anxiety and Depression Scale.

Table 1B. Baseline Distribution of All Patients by HADS Diagnostic Categories (N = 3,353)[a]

	Noncaseness D–A– D–A? D?A–	Mixed Anxiety Depression D?A?	Caseness for Depression D+A– D+A?	Caseness for Anxiety A+D– A+D?	Caseness for Comorbid Anxiety-Depression D+A+
All Patients	11.0	4.3	10.6	18.2	55.9

[a]Data are presented as %.
Abbreviation: HADS = Hospital Anxiety and Depression Scale.

Baseline HADS subgroups and diagnostic categories. Tables 1A and 1B show the distribution of the 3,353 patients for each HADS caseness subgroup and HADS diagnostic category, respectively (status for depression: no, doubtful, or probable case and status for anxiety: no, doubtful, or probable case). Caseness for depression was identified in 66.4% of patients (irrespective of anxiety) and for anxiety in 74.1% of patients (irrespective of depression). When the HADS caseness subgroups were determined by investigator specialty (GP/psychiatrist), we observed some differences in the proportions of patients in the subgroups: probable case for depression was found in 59.8% and 72.5% of patients enrolled by GPs and psychiatrists, respectively; probable case for anxiety was found in 75.6% and 72.7% of patients enrolled by GPs and psychiatrists, respectively; and comorbid anxiety-depression was found in 52.6% and 58.9% of patients enrolled by GPs and psychiatrists, respectively. The sociodemographic and psychiatric history data for each diagnostic category are shown in Table 2.

Baseline painful and nonpainful somatic symptom severity according to diagnostic category (Table 3). The comorbid anxiety-depression diagnostic category had the highest mean scores on the SSI-somatic, SSI-pain, and VAS overall pain severity subscales and the greatest impairment on the SF-36 bodily pain domain.

On the basis of the VAS overall pain severity subscale, moderate/severe pain was found in 40%, 43%, 51%, 54%, and 62% for noncaseness, mixed anxiety-depression, caseness for depression, caseness for anxiety, and caseness for comorbid anxiety-depression, respectively.

Baseline HRQoL (SF-36) according to diagnostic category (Table 4). The mean PCS was only mildly impaired compared to population norms (from about 0.1 SD in the noncaseness subjects to 0.5 SD in the comorbid anxiety-depression subjects). On the contrary, the mean MCS was markedly impaired (from about 1.5 SDs in the noncaseness subjects to more than 3.0 SDs in the comorbid anxiety-depression subjects).

Physical functioning in the SF-36 (role-physical) was impaired from about 1.0 SD in the noncaseness subjects to more than 1.5 SDs in the comorbid anxiety-depression subjects. The functional impairment due to emotional problems (role-emotional) ranged from about 1.5 SDs in the noncaseness subjects to more than 2.5 SDs in the comorbid anxiety-depression subjects. The impairment in social functioning due to emotional or physical symptoms (social functioning) ranged from about 1.0 SD in the noncaseness subjects to about 2.5 SDs in the comorbid anxiety-depression subjects.

Results at Follow-Up

Still caseness and remission rates at 3 and 6 months' follow-up (Tables 5A, 5B, and 5C). Remission rates were consistently higher at 6 months' follow-up than at 3 months' follow-up. Rates were also higher in the caseness for depression group (50%) than in the caseness for anxiety group (40%) or caseness for comorbid anxiety-depression group (41%). The caseness for anxiety and caseness for comorbid anxiety-depression groups had comparable remission rates. The percentage of patients with a moderate improvement (no longer fulfilling criteria for caseness but not fulfilling criteria for remission) was similar in the caseness for depression group, caseness for anxiety group, and caseness for comorbid anxiety-depression group (24%, 26%, and 21%, respectively). In noncaseness for depression subjects, the HADS-D and HADS-A scores changed (from baseline to 6 months) from 5.2 to 4.6 and from 9.6 to 6.7, respectively, and the SF-36 mental health score changed from 33.5 to 43.6. In noncaseness for anxiety subjects, the HADS-D and the HADS-A scores changed (from baseline to 6 months) from 8.0 to 5.4 and from 5.4 to 5.0, respectively, and the SF-36 mental health score changed from 32.7 to 43.5.

Somatic symptom severity and HRQoL at 6 months for patients in remission. All patients in remission (from the 5 HADS diagnostic categories at baseline) were

Table 2. Sociodemographic and Psychiatric History Data for HADS Diagnostic Categories at Baseline

Variable	Noncaseness (n=369)	Mixed Anxiety-Depression (n=145)	Depression Caseness (n=354)	Anxiety Caseness (n=610)	Comorbid Anxiety-Depression (n=1,875)
Age, mean (SD), y	50.3 (15.4)	48.3 (15.4)	50.0 (16.0)	44.9 (14.8)	45.8 (14.0)
Gender, female, %	63.7	60.7	69.7	69.5	69.4
Mandatory or no education, %	50.5	56.3	53.1	55.5	51.0
Married/domestic partner, %	59.3	66.9	54.5	63.4	57.2
Paid employment, %	50.1	54.5	41.3	56.4	50.2
Unemployed, %	8.7	9.7	12.5	13.5	14.6
No. of dependants, mean (SD)	1.1 (1.2)	1.1 (1.2)	1.1 (1.2)	1.0 (1.2)	1.2 (1.3)
Body mass index, mean (SD)	25.5 (4.6)	25.7 (4.6)	26.0 (4.8)	25.3 (5.7)	25.4 (5.3)
Current smoker, %	26.4	24.8	28.2	29.0	36.4
Duration of current depressive episode, mean (SD), wk	12.3 (14.8)	15.1 (17.1)	14.1 (16.4)	14.6 (17.9)	13.5 (16.7)
No. of episodes of depression in previous 2 y, mean (SD)[a]	1.9 (1.5)	1.8 (1.1)	1.9 (1.3)	1.7 (1.1)	1.9 (1.5)
Age at onset of first depressive episode, mean (SD), y	41.1 (16.1)	40.8 (15.5)	40.4 (16.5)	37.0 (14.8)	37.7 (13.8)
Patients with any psychiatric illness in previous 2 y, %	47.4	44.8	44.9	56.7	59.4
Patients with any chronic medical condition, %	49.9	42.7	48.0	40.1	40.5

[a]Only for patients with 1 or more previous episodes.
Abbreviation: HADS=Hospital Anxiety and Depression Scale.

Table 3. Somatic Symptom Severity by HADS Diagnostic Categories at Baseline[a,b]

Category	Noncaseness	Mixed Anxiety-Depression	Depression Caseness	Anxiety Caseness	Comorbid Anxiety-Depression
SSI pain score	2.0 (0.8)	2.0 (0.7)	2.1 (0.8)	2.3 (0.8)	2.5 (0.9)
SSI somatic score	1.7 (0.5)	1.8 (0.4)	2.1 (0.6)	2.1 (0.6)	2.5 (0.7)
VAS overall pain score	29.3 (26.8)	31.8 (26.5)	37.5 (28.6)	36.3 (27.5)	43.6 (28.9)
SF-36 bodily pain score	46.4 (11.7)	45.1 (11.6)	42.9 (12.0)	43.9 (11.6)	40.1 (12.1)

[a]Data are presented as mean (SD).
[b]For SSI and VAS, higher numbers indicate worse scores; for SF-36, lower numbers indicate worse scores.
Abbreviations: HADS=Hospital Anxiety and Depression Scale, SF-36=36-item Short-Form Health Survey, SSI=Somatic Symptom Inventory, VAS=visual analog scale.

Table 4. Health-Related Quality of Life (SF-36) by HADS Diagnostic Categories at Baseline[a,b]

Category	Noncaseness	Mixed Anxiety-Depression	Depression Caseness	Anxiety Caseness	Comorbid Anxiety-Depression
Role-physical score	41.7 (9.8)	39.3 (9.3)	34.2 (9.9)	39.4 (10.1)	32.5 (9.8)
Social functioning score	40.6 (9.5)	33.9 (8.5)	29.7 (9.0)	32.6 (8.8)	24.9 (8.0)
Role-emotional score	37.2 (10.6)	31.5 (9.7)	25.3 (9.7)	31.0 (10.4)	22.6 (9.3)
Physical health summary score	48.8 (9.6)	48.7 (9.5)	45.5 (10.8)	49.1 (10.0)	44.5 (10.3)
Mental health summary score	36.4 (9.2)	27.7 (7.5)	22.5 (7.8)	25.9 (8.3)	17.6 (7.6)

[a]Data are presented as mean (SD). Normative mean (SD): 50 (10).
[b]Lower numbers indicate worse scores.
Abbreviations: HADS=Hospital Anxiety and Depression Scale, SF-36=36-item Short-Form Health Survey.

associated with normalization of symptomatic and HRQoL variables at 6 months' follow-up (Table 6), which provides some validation of the definition of remission used.

Baseline factors associated with remission at 6 months' follow-up. For the baseline caseness for depression category, a lower VAS overall pain severity score, a lower age, being married, working for pay, and a lower number of previous episodes of depression were associated with greater odds of achieving remission (Figure 1).

For the baseline caseness for anxiety category, a lower SSI nonpainful somatic subscore, a higher educational level, a shorter duration of the current episode of depression, and a lower number of previous episodes of depression were associated with greater odds of achieving remission (Figure 2).

For the baseline caseness for comorbid anxiety-depression category, a lower baseline score on the HADS-A, a lower VAS overall pain score, working for pay, a lower number of previous episodes of depression, and the absence of a comorbid chronic medical condition were associated with greater odds of achieving remission (Figure 3).

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Tables 5A-C. Still Caseness and Remission Proportions at
3 and 6 Months' Follow-Up for the Caseness Depression
Category at Baseline[a,b]

A.

Follow-Up	Still Caseness (D+A+, D+A–, D+A?)	Remission (D–A–)
3 Months	35.2	34.8
6 Months	25.4	50.2

B.

Follow-Up	Still Caseness (D+A+, A+D–, A+D?)	Remission (D–A–)
3 Months	44.8	24.9
6 Months	33.3	40.4

C.

Follow-Up	Still Caseness Case D (D+A–, D+A?)	Case A (A+D–, A+D?)	Comorbid (D+A+)	Remission (D–A–)
3 Months	8.4	15.8	30.6	22.5
6 Months	6.6	11.4	20.1	40.6

[a]Data are presented as %.
[b]D–A– (noncaseness); D+A–, D+A? (caseness for depression);
 D–A+, D?A+ (caseness for anxiety); and D+A+ (caseness for
 comorbid anxiety-depression).

DISCUSSION

In this naturalistic sample of patients with a clinical diagnosis of depression whose physician had decided to commence antidepressant treatment, only 66.4% of enrolled patients were probable cases for depression on the basis of self-rating on the HADS, while 74.1% of patients were probable cases for anxiety. When looking at "pure" caseness using the diagnostic criteria, 10.6% were probable cases for depression only and 18.2% were probable cases for anxiety only. This finding suggests that, in daily clinical practice, physicians do not always make a differential diagnosis between depressive disorders and anxiety disorders when they start an antidepressant treatment and that anxiety was a stronger predictor of enrolling a patient in treatment than depression. The percentage of probable cases for depression was lower in the patients enrolled by GPs (59.8% vs 72.5%), while the percentage of probable cases for anxiety was similar between GPs and psychiatrists (75.6% vs 72.7%). Surprisingly, 11.0% of the enrolled patients were neither cases for depression nor anxiety (with only minor differences between patients enrolled by GPs and psychiatrists: 12.3% vs 9.9%).

The appropriateness of the prescription of antidepressants has been questioned previously.[2] A Finnish primary care study[20] showed that psychotropic medication was prescribed to 70% of patients with mental disorder symptoms (when a wider definition than a formal diagnosis was used) and to 13% of patients with no sign of mental disorder. It has been shown that physicians use methods other than formal *DSM-IV* or *ICD-10* criteria to make prescription decisions.[2] Our finding that the percentage of

Table 6. Somatic Symptom Severity and HRQoL at 6 Months
Follow-Up in Patients Who Achieved Remission (n = 1,225)[a]

Measure	Mean (SD)
Somatic symptom severity score	
SSI pain	1.5 (0.5)
SSI somatic	1.3 (0.3)
VAS overall pain	14.7 (19.5)
SF-36 bodily pain	52.7 (9.3)
HRQoL (SF-36) score [b]	
Role-physical	48.9 (7.6)
Social functioning	49.1 (7.5)
Role-emotional	46.9 (8.1)
Physical health summary	52.0 (7.4)
Mental health summary	48.2 (7.5)

[a]Remission was defined as D–A–, independent of caseness status at
 baseline.
[b]Normative mean (SD) for SF-36.
Abbreviations: HRQoL = health-related quality of life, SF-36 =
 36-item Short-Form Health Survey, SSI = Somatic Symptom
 Inventory, VAS = visual analog scale.

noncase subjects receiving an antidepressant is slightly higher in GP-treated patients than in psychiatrist-treated patients confirms previously published data.[21]

Caseness for comorbid anxiety-depression was found to be slightly lower (52.6% vs 58.9%) in patients enrolled by GPs compared to patients enrolled by psychiatrists. Published figures of depression and anxiety comorbidity vary between 39% in an Australian general population sample[22] and 59% in a German general population sample,[23] and between 51% and 62% (comorbidity also included alcohol abuse) in depressed outpatient samples.[24,25]

The lowest scores on SSI pain symptoms and VAS overall pain severity domains and the least impairment on the SF-36 bodily pain subscale at baseline were found in the noncaseness and the mixed anxiety-depression patients (with subthreshold symptoms), with intermediate scores in the depression or anxiety caseness patients and the highest scores (reflecting greatest impairment) in those with comorbid anxiety-depression. This finding confirms that patients suffering from depressive disorders as well as patients suffering from anxiety disorders have more painful physical symptoms.[26–29]
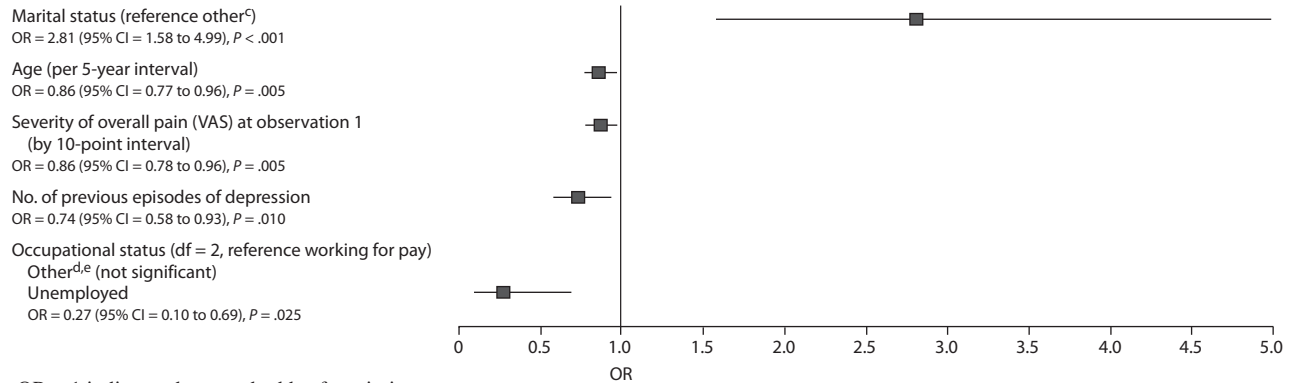
An interesting finding is that the nonpainful somatic symptoms (as assessed with the SSI) show a similar pattern, suggesting that their relationship to depression and anxiety is similar to that for the painful physical symptoms. This finding corroborates recently published results that the scores on the painful SSI items (eg, headaches, pains in lower back, soreness in muscles, neck pain, and pain in joints), as well as the scores on the nonpainful SSI items (eg, feeling fatigued, not feeling to be in good physical health, not feeling well, feeling weak, heavy feelings in arms and legs, hands and feet not warm enough) are all significantly increased in patients with major depression.[30]

HRQoL scores varied substantially across diagnostic categories at baseline. The 1 exception to this observation was that the mean physical aspect of HRQoL (SF-36 PCS) was never more than 1 SD below population norms.

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Figure 1. Baseline Characteristics Associated With Categorical Status at 6 Months' Follow-Up[a,b]

Patients were cases for depression at baseline (but were not A+) and were noncases for both depression and anxiety at 6 months' follow-up
n = 258 (maximum possible n = 283)

Marital status (reference other[c])
OR = 2.81 (95% CI = 1.58 to 4.99), P < .001

Age (per 5-year interval)
OR = 0.86 (95% CI = 0.77 to 0.96), P = .005

Severity of overall pain (VAS) at observation 1
  (by 10-point interval)
OR = 0.86 (95% CI = 0.78 to 0.96), P = .005

No. of previous episodes of depression
OR = 0.74 (95% CI = 0.58 to 0.93), P = .010

Occupational status (df = 2, reference working for pay)
  Other[d,e] (not significant)
  Unemployed
OR = 0.27 (95% CI = 0.10 to 0.69), P = .025

[scale: 0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 — OR]

[a]An OR < 1 indicates decreased odds of remission.
[b]Country not statistically significant (P = .252) but included in the model. Data from Norway were pooled with those from Sweden and Ireland with the United Kingdom to avoid problems of quasi separation during the modeling.
[c]Other includes divorced, legally separated, widowed, partner (living separately), and no relationship.
[d]Other includes retired, student, voluntary work, and keeping house (full-time).
[e]Other also significantly different from unemployed (OR = 2.58; 95% CI = 1.00 to 6.62).
Abbreviations: OR = odds ratio, VAS = visual analog scale.

Figure 2. Baseline Characteristics Associated With Categorical Status at 6 Months' Follow-Up[a,b]

Patients were cases for anxiety at baseline (but were not D+) and were noncases for both depression and anxiety at 6 months' follow-up
n = 433 (maximum possible n = 460)
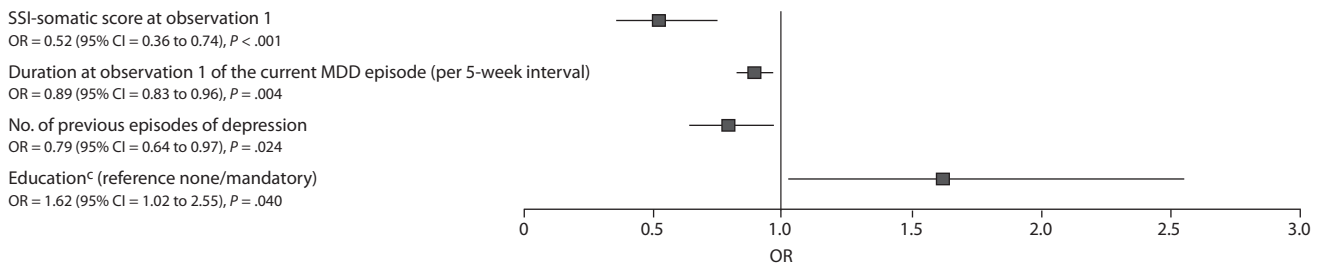
SSI-somatic score at observation 1
OR = 0.52 (95% CI = 0.36 to 0.74), P < .001

Duration at observation 1 of the current MDD episode (per 5-week interval)
OR = 0.89 (95% CI = 0.83 to 0.96), P = .004

No. of previous episodes of depression
OR = 0.79 (95% CI = 0.64 to 0.97), P = .024

Education[c] (reference none/mandatory)
OR = 1.62 (95% CI = 1.02 to 2.55), P = .040

[scale: 0 0.5 1.0 1.5 2.0 2.5 3.0 — OR]
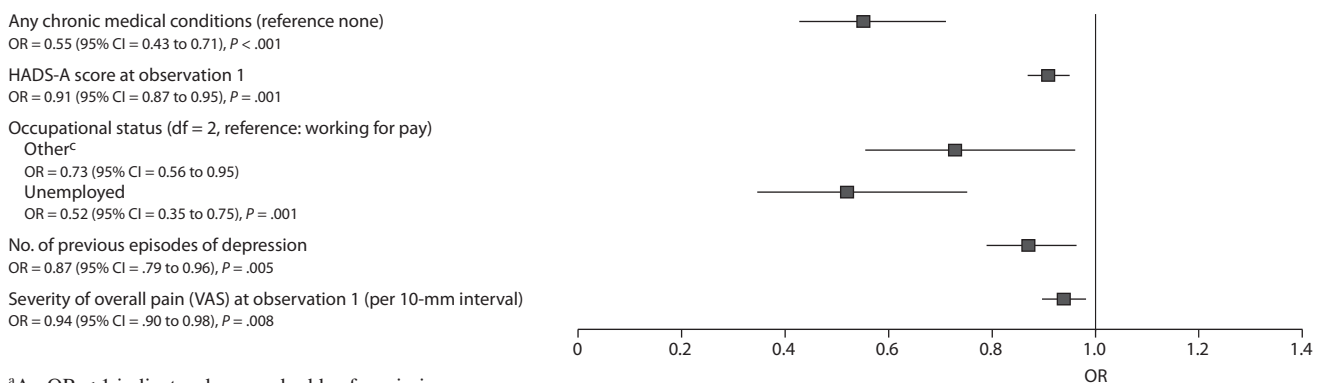
[a]An OR < 1 indicates decreased odds of remission.
[b]Country not statistically significant (P = .211) but included in the model.
[c]Education includes further, university, and postgraduate education.
Abbreviations: MDD = major depressive disorder, OR = odds ratio, SSI = Somatic Symptom Inventory.

Figure 3. Baseline Characteristics Associated With Categorical Status at 6 Months' Follow-Up[a,b]

Patients were cases for anxiety and depression at baseline and and were noncases for both depression and anxiety at 6 months' follow-up
n = 1,359 (maximum possible n = 1,481)

Any chronic medical conditions (reference none)
OR = 0.55 (95% CI = 0.43 to 0.71), P < .001

HADS-A score at observation 1
OR = 0.91 (95% CI = 0.87 to 0.95), P = .001

Occupational status (df = 2, reference: working for pay)
  Other[c]
  OR = 0.73 (95% CI = 0.56 to 0.95)
  Unemployed
  OR = 0.52 (95% CI = 0.35 to 0.75), P = .001

No. of previous episodes of depression
OR = 0.87 (95% CI = .79 to 0.96), P = .005

Severity of overall pain (VAS) at observation 1 (per 10-mm interval)
OR = 0.94 (95% CI = .90 to 0.98), P = .008

[scale: 0 0.2 0.4 0.6 0.8 1.0 1.2 1.4 — OR]

[a]An OR < 1 indicates decreased odds of remission.
[b]Country was statistically significant (P < .001).
[c]Other includes retired, student, voluntary work, and keeping house (full-time).
Abbreviations: HADS-A = Hospital Anxiety and Depression Scale-Anxiety, OR = odds ratio, VAS = visual analog scale.

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However, the emotional component (SF-36 MCS) was far below population norms in all diagnostic categories. It is remarkable that, even in the noncaseness patients, this score was 1.5 SDs below population norms, which suggests that these help-seeking patients do present with substantial impairment of their emotional HRQoL despite not fulfilling screening criteria for anxiety or depression.

The comorbid for anxiety-depression category had significant impairment of SF-36 MCS (more than 2 SDs below population norms), confirming previously published results of significant levels of functional impairment in this subgroup.[31,32] The present analysis also confirms that patients with caseness for comorbid anxiety-depression have the poorest emotional HRQoL, as their MCS was more than 3 SDs below population norms (and more than 20% lower than caseness for depression or caseness for anxiety subjects). A recent Australian study using the SF-12[23] also showed that comorbid major depression and generalized anxiety disorder had a 20% lower mental health score than pure generalized anxiety disorder or pure major depression.

The follow-up data on symptomatic outcome (remission/still caseness) for the 3 diagnostic categories (caseness for depression, caseness for anxiety, and caseness for comorbid anxiety-depression) provide some interesting findings. The study illustrates that a longer duration of treatment (6 months vs 3 months) results in a better symptomatic outcome (about 15% higher remission rates). This finding is consistent with the results of a previous study that found remission rates after 6 months of treatment to be 28.6% higher than after 2 months of treatment.[33]

There is ongoing debate about whether outcomes among patients with depression and substantial anxiety symptoms are poorer than those among patients with depression without anxiety symptoms.[34] Part of the debate is probably due to the fact that different definitions of *anxious depression* were used in the articles. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study was designed to be relevant to clinicians by including patients more typical of outpatient practice and found that, when looking at outcomes in nonanxious and anxious depression, remission rates were 33.4% and 22.2%, respectively; remission rates in patients without or with comorbid generalized anxiety disorder were 29.5% and 21.2%, respectively.[35,36] These differences are well in line with the 10% difference in remission rates between caseness for depression subjects and caseness for comorbid anxiety-depression subjects in our sample.

It is also noteworthy that the SF-36 mental health score also dramatically improved after 6 months of treatment (about 30%) in noncaseness for depression or noncaseness for anxiety subjects at baseline.

The regression models assessing which baseline characteristics are associated with 6-month outcomes also show some clinically relevant findings, mostly in line with the findings of STAR*D.[36] First, baseline depression severity as measured by the HADS-D was not significantly associated with remission at 6 months, although other more indirect measures of depression severity (like number of previous episodes or duration of current episode) were. Baseline anxiety severity as measured with the HADS-A was significantly associated with remission at 6 months but only for the caseness for comorbid anxiety-depression subjects.

Second, baseline somatic symptom severity was significantly associated with remission at 6 months. Overall, both painful and nonpainful somatic symptoms were highly correlated, suggesting that they could be regarded as 1 symptom cluster. The presence of chronic medical conditions was also associated with remission at 6 months but only for the caseness for comorbid anxiety-depression subjects.

Third, sociodemographic factors (lower age, a higher educational level, working for pay, and being married) were associated with better outcomes. These findings are clinically important, since neither pharmacotherapy nor psychotherapy can modify them.

The main limitation of the present study is that all results are based on patient-rated scales and that HADS-based diagnostic categories were constructed in order to reflect more standard diagnostic categories. However, the outcome and the regression models investigating the association between baseline variables and outcome closely reflect published data of studies in which more standard diagnostic categories were used.

In conclusion, these results indicate that physicians do not always differentiate between anxiety and depressive symptoms when making a clinical diagnosis of depression. Most enrolled patients had significant emotional-depressive and emotional-anxious symptoms, as well as significant nonpainful and painful somatic symptomatology at baseline. Clinical, symptomatic, and sociodemographic variables were associated with outcome in this study.

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