Anxiety and Depression Prevalence Rates in Age-Related Macular Degeneration

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Purpose. To estimate the prevalence rates of depression and anxiety in patients with wet age-related macular degeneration (AMD) and the relationship with visual acuity and to develop a simple algorithm for depression screening.

Methods. This cross-sectional, prospective, observational, multicenter study was performed in France, Germany, and Italy. Retina specialists at 10 centers per country each enrolled 12 consecutive patients with wet ARMD. Patients were stratified into four severity groups by using best eye (BE) and worst eye (WE) visual acuity (VA) thresholds (BE:VA 20/40 and WE:VA 20/200). Patients rated themselves on the Hospital Anxiety and Depression Scale (HADS). Analysis of variance was performed to estimate the effect of VA severity levels on HADS scores adjusted on age, gender, and country.

Results. Patients (females 60%) were recruited, with a mean age of 77 years and 2.3 years' disease duration. Mean BE:VA at inclusion was 0.49 logMar (logarithm of the minimum angled of resolution) and WE:VA 1.0 logMar. The prevalence of severe depression increased from 0% (BE:VA $\geq$ 20/40+WE:VA $\geq$ 20/200) to 7.6% (BE:VA $<$ 20/40+WE:VA $<$ 20/200), whereas anxiety was unrelated to VA loss. Moreover, total depression scores were strongly associated with VA severity ($P = 0.006$), but not total anxiety scores ($P = 0.840$). Responses to two HADS items ("I still enjoy things I used to enjoy"; "I can enjoy a good book or radio or television program") identified 95% of severely to moderately depressed patients.

Conclusions. Self-rated depression in patients with AMD was associated with VA severity level. It should, therefore, be relatively easy for ophthalmologists to implement the screening procedure and refer identified patients to psychiatrists for proper assessment and treatment. (*Invest Ophthalmol Vis Sci.* 2007;48:1498–1503) DOI:10.1167/iovs.06-0761

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Supported by an unrestricted grant from Alcon France SA, Rueil-Malmaison, France. Alcon France SA employed GB, but the authors had no financial or other conflicts of interest relating to Alcon Laboratories or directly relevant to the contents of this study. AA, FB, and JAS have participated in clinical trials unrelated to this study and financed by Alcon Laboratories.

Submitted for publication July 6, 2006; revised November 15, 2006; accepted February 19, 2007.

Disclosure: **A. Augustin**, None; **J.A. Sahel**, None; **F. Bandello**, None; **R. Dardennes**, None; **F. Maurel**, None; **C. Negrini**, None; **K. Hieke**, None; **G. Berdeaux**, None

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Progressive vision loss due to age-related macular degeneration (AMD) can severely impair quality of life and is often associated with depression (prevalence approximately 30%), and so constituting a major source of disability.[1,2] Accordingly, if such patients were treated as a whole, with a special focus on depression when symptoms are persistent, ophthalmologists may improve their patients' quality of life.[3]

Although most retina specialists have psychiatry in their training, an in-depth assessment of anxiety-depression is not an appropriate task for them. Instead, however, a simple screening process may increase their awareness of a possible depressive illness and help them to refer suspected cases to psychiatrists.

The Structured Clinical Interview (SCID) for the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), is a standard instrument for diagnosing depression, but it involves a structured clinical interview, and certain items may be difficult for some retina specialists to assess (e.g., suicide; abnormal, morbid thoughts; and morbid preoccupation with worthlessness).[4] The SCID was used by Brody et al.[5,6] who reported a baseline depression prevalence rate of 23.8% in patients with advanced AMD. Casten et al.[7] observed a depression prevalence rate of 43.0% when the SCID was used in elderly patients with advanced AMD. Thus, depressive disorder is a significant problem for elderly patients with advanced macular degeneration, but it has been little investigated in Europe.

Depression rating scales more specific to AMD have also been used. The Hospital Anxiety and Depression Scale (HADS: a 14-item, self-administered scale validated in all major European languages) was used by Zigmond and Snaith[8] and Miskala et al.[9] in submacular surgery trials, but few patients with AMD (2%–4%) reported definite anxiety or depression.[8,9] When HADS diagnoses were compared with those made with the SCID, reports gave a specificity ranging from 71% to 92% and from 78% to 96% for a HADS threshold score of 8.[10] The Center for Epidemiologic Studies-Depression (CESD) scale is a self-administered, 20-item questionnaire.[11] that was used by Rovner et al.[12,13] in 51 patients with bilateral AMD. Depression scores were correlated with vision-specific disability, general physical disability, and visual acuity. The depression prevalence rate was 33.0% (19.9%–47.0%), approximately twice that in the community at large. The HADS and CESD are both self-administered, and their contents are close to everyday speech, but the HADS is shorter than the CESD, and it evaluates anxiety and depression on two orthogonal axes. Both instruments were designed as screening tools, and scores higher than threshold identify patients who ought to be evaluated psychiatrically to confirm or exclude psychopathology.

Data concerning the effects of unilateral and bilateral AMD on anxiety–depression prevalence are confusing. In the trial by Miskala et al.[9] of patients with AMD treated by submacular surgery, the HADS indicated a higher rate of definite anxiety with unilateral compared with bilateral AMD, but no such trend was observed with depressive symptoms. Higher anxiety with unilateral AMD could be explained by apprehension

TABLE 1. AMD Degree of Severity Definition

AMD Classification	Definition
Mild	Unilateral exudative AMD VA of same eye <0.4
Moderate	Bilateral AMD (at least one eye exudative) VA of both eyes <0.4
Severe	Bilateral AMD (at least one eye exudative) VA of at least one eye ≤0.1

VA is expressed in logMar units converted to decimals.

about future vision loss, whereas patients with bilateral AMD may have become more reconciled. However, these observations were not confirmed by Childs et al.,[14] who also used the HADS. In contrast, when Dong et al.[15] pooled the baseline data of the two previous submacular surgery studies, they found that median anxiety and depression scores were both one scale point less in unilateral than in bilateral AMD. The finding was consistent with that in Rovner et al.,[12,13] who found high depression prevalence rates in patients with bilateral AMD using the CESD.

Our survey had the following three goals: (1) to estimate the prevalence rates of depression and anxiety in patients with AMD in three European countries; (2) to study the relationship between depression rates and visual acuity, taking into account unilateral and bilateral AMD; and (3) to develop a simple algorithm for depression screening.

MATERIALS AND METHODS

The MICMAC (MICro-economics of MACular disease) study was conducted in France, Germany, and Italy, according to a multicenter, cross-sectional design that was planned to include a total of 360 patients (120 per country).

Investigators

Ten specialized retinal disease centers were selected in each country. Enrolled centers were required to adhere to study demands by monitoring or treating at least 60 patients per annum, by making patients' medical files available for audit purposes, and by devoting the time needed to achieve quality. One investigator was identified at each center and subsequently instructed in study procedures by the local clinical research assistant. Institutional Review Board IRB)/Ethics Committee approval was obtained, and the study was conducted in compliance with the Declaration of Helsinki.

Patients

Each center screened 12 consecutive patients presenting with exudative AMD (predominantly classic, subfoveal, choroidal neovascularization identified on the basis of patients' notes, fundus photographs, and fluorescein angiograms). Patients at each center were recruited according to AMD severity (i.e., four mild, four moderate, and four severe at each center (Table 1). This stratification was to optimize the statistical power of tests when evaluating associations between severity of disease and parameters such as comorbidity prevalence rates.

Patients aged 50 years or older with AMD were included if they visited a center, for any reason, during the enrollment period; had a clinical record at the center that contained all critical information required by the study; were able to complete the HADS, either personally or with help from a caregiver; and gave their written consent. Patients were excluded from the study if they had dry AMD, impaired visual acuity not due to AMD, or mental disability or were participating in another study or clinical trial.

Data Collection

Data collection included clinical and sociodemographic data, obtained from the patient directly or the medical record, concerning age, gender, inclusion and noninclusion criteria, history of AMD, ocular and general comorbidity, clinical status, AMD risk factors, best corrected visual acuity of both eyes at diagnosis and currently, and previous treatments. Responses to the HADS, available in French, German, and Italian, were also collected.[9,10,16] The HADS is a reliable, validated, self-administered 14-item scale designed for screening purposes.[17] Items are rated 0 to 3 and take just a few minutes to complete. Seven items related to anxiety assess feelings of tension, tendency to worry unnecessarily, and apprehensive anticipation. Seven items related to depression assess enjoyment of usual activities, sense of humor de-

TABLE 2. Least-Square Means of 14 HADS Items

HADS Dimensions	VA Severity Levels BE>20/40 WE≥20/200 *n* = 91	BE≥20/40 WE<20/200 *n* = 46	BE<20/40 WE≥20/200 *n* = 113	BE<20/40 WE<20/200 *n* = 86	*P*
Anxiety					
I feel tense or "wound-up"	1.361	1.323	1.294	1.468	0.60
I get a sort of frightened feeling as if something awful is about to happen	1.207	1.139	1.237	1.360	0.71
Worrying thoughts go through my mind	1.387	1.407	1.472	1.539	0.77
I can sit at ease and feel relaxed	1.074	0.972	1.069	1.050	0.91
I get a sort of frightened feeling like "butterflies" in the stomach	0.888	0.818	0.871	0.895	0.97
I feel restless as if I have to be on the move	1.189	1.095	1.328	1.065	0.30
I get sudden feelings of panic	0.692	0.680	0.701	0.774	0.91
Depression					
I still enjoy the things I used to enjoy	0.624	0.545	0.863	0.958	0.02
I can laugh and see the funny side of things	0.750	0.731	0.856	1.025	0.17
I feel cheerful	0.887	0.898	0.836	0.999	0.63
I feel as if I am slowed down	1.095	1.389	1.441	1.521	0.01
I have lost interest in my appearance	0.490	0.600	0.509	0.743	0.20
I look forward with enjoyment to things	0.840	0.957	0.891	1.208	0.15
I can enjoy a good book or radio or television program	0.579	0.519	1.205	1.107	0.01

Data are adjusted for gender, age, and country for analysis of variance ($N = 336$).

TABLE 3. Least-Square Means of HADS Anxiety and Depression Total Scores

HADS Dimensions	VA Severity Levels: BE>20/40 WE≥20/200 *n* = 91	BE≥20/40 WE<20/200 *n* = 46	BE<20/40 WE≥20/200 *n* = 113	BE<20/40 WE<20/200 *n* = 86	*P*	German HADS Data (Mean Score)
Anxiety	7.800	7.435	7.975	8.151	0.840	6.24
Depression	5.468	5.892	6.488	7.633	0.006	6.10

Data are adjusted for gender, age and country, for analysis of variance ($N = 336$), and comparable historical HADS data for a general German population, matched in age and sex ratio.

pressed mood, and optimistic attitude. Total depression and anxiety scores range from 0 to 21 in each case, with total scores ≤7 considered asymptomatic, scores of 8 to 10 possibly or borderline symptomatic, and scores ≥11 definitively symptomatic.[9] Investigators helped patients if requested, checked responses for completeness and reminded patients of omitted items, while accepting that omissions could be deliberate. In addition, patients completed three self-administered quality-of-life and utility scales, not reported herein.

Statistical Analysis

The factorial structure of the HADS was validated by principal component analysis with varimax rotation, as it has not been used widely in patients with wet AMD. Cronbach's α was calculated for each score and values >0.7 supported good internal validity.[18]

Visual acuity was dichotomized as best eye VA (BE:VA) and worst eye VA (WE:VA), measured in logMAR (logarithm of the minimum angle of resolution) units and converted into decimals. A threshold of 20/40 applied to BE:VA and 20/200 to WE:VA.[19] Patients were then grouped into four severity levels, as follows: (1) best acuity (BE:VA ≥ 20/40; WE:VA ≥ 20/200); (2) intermediate acuity (BE:VA ≥ 20/40; WE:VA < 20/200); and (3) intermediate acuity (BE:VA ≥ 20/40; WE:VA < 20/200); and (4) worst acuity (BE:VA < 20/40; WE:VA < 20/200).

HADS scores of the four VA severity groups were compared by analysis-of-variance. Least-square means were calculated and adjusted on country, age, and sex distribution. In addition, HADS scores in the general population (Germany only) were used to generate historical control data for subjects of the same age and gender.[20]

Classification and Regression Tree (CART) techniques were used to develop algorithms for depression screening.[21] Two target populations were identified (severely depressed and severely or moderately depressed).

Analyses were restricted to patients who completed all HADS questions (completers) so as to minimize sample fluctuations (e.g., validation analysis, regression analysis, CART). Two populations were compared (completers and the overall population) to search for bias selection.

Statistical analyses were performed with commercial software (SAS software, ver. 9.1; SAS Institute, Cary, NC), and tests were two-sided with α fixed at 5%. No adjustment was made for test multiplicity.

RESULTS

Twenty-two centers were recruited (10 in France, 5 in Germany, and 7 in Italy). In total, 360 patients were enrolled (France 120: 33%; Germany 126: 35%; and Italy 114: 32%). The mean age was 77 years, 59.6% were female, 58.5% were married, and 52.0% lived in towns. The average interval between AMD diagnosis and study inclusion was 2.3 years. Frequent, classic wet AMD lesions (≥50%) occurred in 54% of WE and 19% of BE cases. The incidence of BE:VA > 20/40 was 40% and of WE:VA ≤ 20/200, 38.3%. Best corrected binocular VA > 20/40 was retained by 34% of patients. Major risk factors for AMD were identified as follows: arterial hypertension (50.5%), heart disease (23.5%), smoking (17.0%), dyslipidemia (13.5%), hypermetropia (12.0%), AMD family history (9.0%), and severe myopia (3.5%). Eye comorbidities were mainly cataract with no surgery (20.2% of patients), glaucoma (10.5%), and ocular hypertension (10.5%).

The HADS was completed in full by 336 of 360 patients (93.3%), representing France 96.7%, Germany 95.2%, and Italy 87.7%. The 336 patients who entered the analysis did not differ from the 24 patients excluded because of age, BE:VA or WE:VA, disease duration, gender, or total HADS scores.

The principal components analysis identified only two axes, which agrees with the factorial structure described by Moorey et al.[16] The seven depression items project on axis 1 and the seven anxiety items on axis 2. Depression accounted for 37.8% of the variance and anxiety for 9.4%. Cronbach's α for all was greater than 0.7 (i.e., anxiety 0.81 and depression 0.78).

Table 2 presents least-square mean values of the seven HADS anxiety items and seven depression items according to BE:VA and WE:VA severity levels, after adjusting on age, gender, and country. All but two anxiety scores exceeded unity, but no score was significantly associated with WE:VA or BE:VA severity. By contrast, three depression items were significantly associated with disease severity—that is, "I still enjoy the things I used to enjoy" ($P < 0.02$), "I feel as if I am slowed down" ($P < 0.01$), and "I can enjoy a good book or radio or television program" ($P < 0.01$). Patients with both eyes severely affected (BE:VA < 20/40+WE:VA < 20/200) had higher scores on depression items than those with less severe VA loss.

Table 3 presents total least-square mean scores for the HADS anxiety and depression items, according to BE:VA and WE:VA severity. Total anxiety scores were not significantly related to increasing VA severity. The mean anxiety score for BE:VA < 20/40 (8.06) was greater than the equivalent score (6.24) for the German population. By contrast, total depression scores were strongly associated with VA severity ($P = 0.006$)

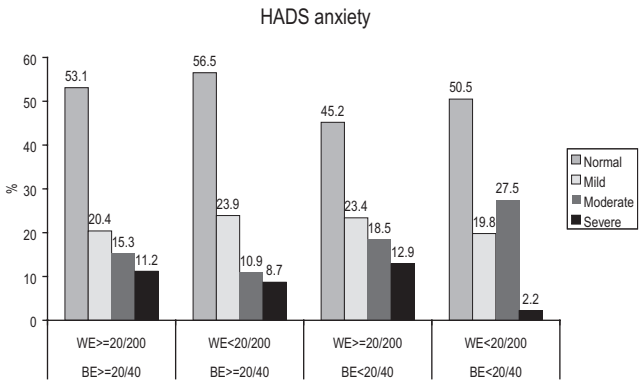

FIGURE 1. HADS anxiety scores classified as normal, mild, moderate, or severe, according to BE:VA and WE:VA severity levels ($N = 336$).

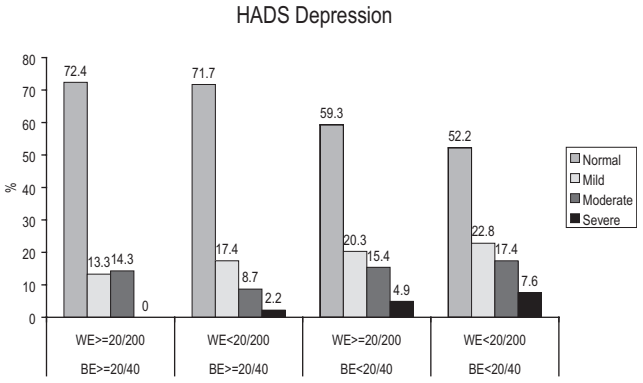

FIGURE 2. HADS depression scores classified as normal, mild, moderate, or severe, according to BE:VA and WE:VA severity levels (N = 336).

and the mean depression score for BE:VA < 20/40 (7.06) exceeded that of the German population (6.10).

Figure 1 shows distributions of anxiety scores for the total study population with respect to increasing VA severity. The prevalence of severe+moderate anxiety showed no trend across the four VA severity levels (sequence: 26.5%, 19.6%, 31.4%, and 29.2%). Severe anxiety, reported by 9.2% (31/336) of the patients, also showed no trend across VA severity levels. In total, 101/336 patients (30.1%) met the criterion for definite clinical anxiety (score, ≥11).

Figure 2 shows distributions of depression scores. The prevalence of severe+moderate depression scores generally increased across the four VA severity levels (sequence: 14.3%, 10.9%, 20.3%, and 25.0%). Severe depression was reported by 3.9% (13/360) of patients and increased almost linearly from 0.0% to 7.6%. In total, 60 of 336 patients (17.9%) met the criterion for definite clinical depression (score, ≥11).

Figure 3 shows the results of a CART analysis aimed at identifying items critical to severe depression (rated 3). In total, 13 patients (13/336: 3.9%) had total HADS depression scores ≥15 and were severely depressed. Eleven of them (84.6%) no longer enjoyed things as they had previously (item 1), but 12 (3.7%) of 323 nondepressed patients, and 2 (15.4%) of 13 depressed patients were misclassified on this item. However, the addition of item 3, "not feeling cheerful," successfully identified 11 (47.8%) of 23 patients with severe depression.

Figure 4 provides CART results identifying a broader group of patients with moderate or severe depression. In total, 60 patients (60/336: 17.9%) had moderate or severe depression based on total HADS depression scores (threshold score, ≥11). However, item 2, "not laughing and seeing the funny side of things," identified 59 patients with depression, but misclassified 131 (47.5%) of 276 nondepressed patients and 1 (1.6%) 60 depressed patients. The addition of item 7, "unable to enjoy a good book or radio or television program" identified 12 (15.4%) of 78 further patients with depression. Thus, items 2 and 7 together identified 57 (95.0%) of 60 patients with moderate or severe depression, but misclassified 55 (41.2%) of 131 nondepressed patients.

DISCUSSION

More than 90% of our patients in three European countries completed not only the HADS, but also three more complex self-rated instruments (NEI-VFQ-25, MacDQoL and HUI) not reported here.[22–24] Indeed, the HADS was developed specifically to identify depression and anxiety among inpatients of general hospitals and clinics, for subsequent evaluation by a mental health professional.[9] Items that can also result from physical disorders were excluded (i.e., symptoms such as dizziness, headache, insomnia, anergia, and fatigue).

More than 100 depression measures are available, and many can be self-administered.[25] Shumway et al.[26] examined the cognitive complexity of the 15 most widely used self-reported depression measures and among them the HADS was considered easy to read, with few linguistic problems. It has been validated by >70 studies and used by >1400 clinical and epidemiologic studies.[10] Therefore, the self-reported HADS seemed ideally suited to retinal specialist practice, where time is limited and primarily devoted to eye examinations—the more so as new AMD treatments become available.[27–29]

Our survey showed that patients with wet AMD and BE: VA < 20/40 had higher HADS total depression and anxiety scores than a comparable sample of the German population. However, only the total depression score was related to AMD severity. The absence of a relationship between HADS total anxiety scores and AMD severity was consistent with the limited variance explained by axis 2 and may explain the instability of axis 2, which could have been split into two axes.

Our prevalence rate for definite clinical depression was 17.9% (60/336) and the total rate for severe depression, 3.9% (13/336). The latter rate was similar to the depression prevalence rates of 2% and 4% reported by two submacular surgery trials in which the HADS was administered to patients of similar age and VA severity.[9,14] By contrast, our prevalence rate for definite clinical anxiety (30.1%; 101/336) was much higher than that after submacular surgery (9.5%).[8,9] The discrepancy may be explained by patient differences or intensive follow-up after surgery.

In comparison with other depression scales used in AMD, our prevalence rate for "definite depression" (17.9%) was below prevalence rates determined by the CESD (33%) and SCID (24.8% and 43.0%).[5,6,12,13] Several factors may explain these higher rates of depression (e.g., worse BE:VA, recent fellow-eye VA loss, or depression due to concomitant physical disorders).[30,31]

The submacular surgery studies, cited earlier, contrasted unilateral and bilateral AMD depression rates. Our approach was different. We used thresholds, as reported by Berdeaux et al.[19] in a previous study of vision-related quality of life in AMD. The factorial structure of HADS in our study was very similar to that of Moorey et al.,[16] except that we limited our factors to two. Accordingly, we were able to apply established rules for

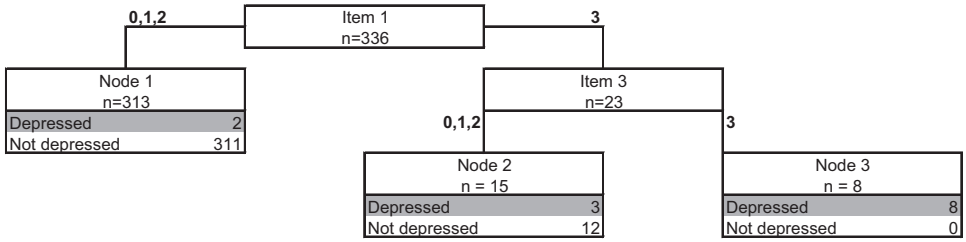

FIGURE 3. Classification and regression tree. Targeted variable: severe depression score. Item 1: "I still enjoy the things I used to enjoy" (0: definitely as much; 1: not quite so much; 2: only a little; 3: hardly at all). Item 3: "I feel cheerful" (0: most of the time; 1: sometimes; 2: not often; 3: never).

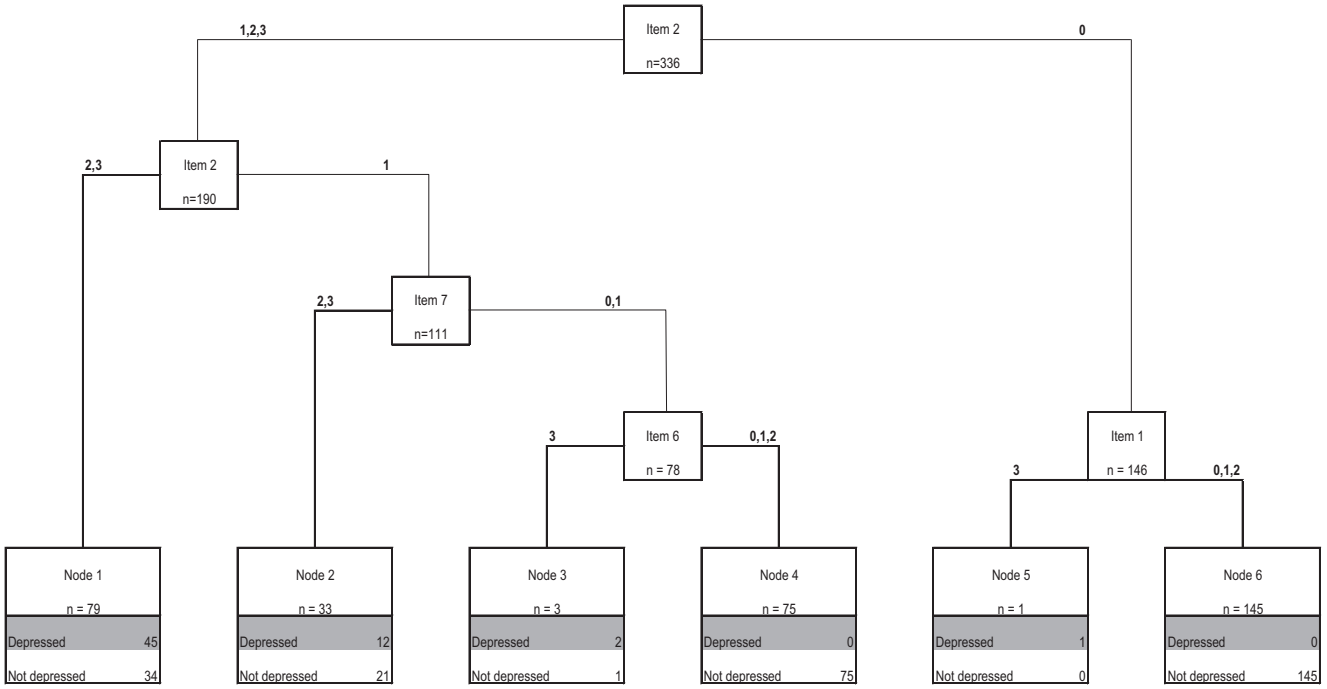

FIGURE 4. Classification and regression tree. Targeted variable: severe or moderate depression scores. Item 1: "I still enjoy the things I used to enjoy" (0: definitively as much; 1: not quite so much; 2: only a little; 3: hardly at all). Item 2: "I can laugh and see the funny side of things" (0: as much as I always could; 1: not quite so much; 2: definitely as much now; 3: not at all). Item 6: "I look forward with enjoyment to things" (0: as much as I ever did; 1: rather less than I used to; 2: definitively less than I used to; 3: hardly at all). Item 7: "I can enjoy a good book or radio or television program" (0: often; 1: sometimes; 2: not often; 3: very seldom).

classifying depression and anxiety, and these we applied to four levels of VA severity. This approach was more sensitive, and it enabled us to demonstrate a clear association between AMD severity and depression prevalence rates. Thus, global VA appears to be more predictive of depression in AMD than a division into unilateral and bilateral disease.

Moreover, the CART analysis shows that responses given to just two HADS items ("I still enjoy things I used to enjoy" and "I can enjoy a good book or radio or television program") may be used to identify up to 95% of depressed patients with severe or moderate depression. Two different items ("I still enjoy things I used to enjoy" and "I feel cheerful") appeared to identify a smaller proportion of patients with severe depression. Such abbreviations of the HADS would further simplify the tasks of retina specialists.

Our survey has certain limitations. First, the comparison of HADS scores, produced by patients with AMD, was restricted to a population of German subjects. Thus, on pooling data across three European countries, we assumed that the HADS was adjusted for country during its validation. Second, though we adjusted for country, the sample size from each country was small for an accurate determination of prevalence rates. Third, the cross-sectional nature of our design was suited to prevalence estimates, only. Prospective data collection, comparing populations, would allow an estimation of incidence rates at different stages of AMD, from diagnosis to legal blindness. Fourth, because depression symptoms were relatively infrequent, we could not dichotomize our sample to estimate the sensitivity and specificity of CART classifications. A further sample of patients with wet AMD is needed to validate the depression screening algorithm. Fifth, the cross-sectional nature of our experimental design did not allow us to follow up patients; hence, we do not know if patients were monitored for anxiety or depression. Also, the resources used to care for anxiety and depression were not collected. More data are needed to determine whether CNV patients are adequately diagnosed and treated for anxiety and depression disorders.

Depression severely diminishes quality of life and stands as the fourth major cause of disability worldwide.[32,33] Several studies demonstrate that severe depression worsens the prognosis of physical illnesses, such as breast cancer, cardiovascular disease, and diabetes.[34–36] By analogy with these physical disorders, treatment of depression should improve the prognosis of patients with eye diseases.[37] Such treatment has included education in a self-management program, which reduced psychological distress and prevented depression in patients with AMD.[5,6]

In conclusion, this study adds to the mounting evidence that self-rated assessment on appropriate rating scales is a useful and time-saving procedure to identify patients with anxiety or depression. Patients with scores above threshold may then be referred to psychiatrists. It should be relatively easy for ophthalmologists to implement this procedure with patients with AMD. Moreover, it appears that ophthalmologists may be able to screen depressed patients with AMD by asking them to rate two simple statements.

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APPENDIX

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