Psychological Disturbance in Graves Ophthalmopathy

Marjan Farid, MD; Anne-Catherine Roch-Levecq, PhD; Leah Levi, MBBS; Barbara L. Brody, MPH; David B. Granet, MD; Don O. Kikkawa, MD

Objective: To study mood disturbance in Graves ophthalmopathy.

Methods: Forty-eight patients (mean age, 55 years; 40 women and 8 men) with Graves ophthalmopathy from a university-based referral center were classified into two groups, 24 with moderate/severe disease (study group) and 24 with negligible/mild disease (control group). The groups were matched with regard to demographic and medical characteristics. All participants completed a mood survey to assess differences in degree of emotional distress.

Main Outcome Measure: The Profile of Mood States survey, a 65-item self-reported inventory designed to assess emotional distress, was the primary outcome measure. A total mood disturbance score was assigned by summing the scores derived on the 6 subscales of the survey—tension, depression, vigor, confusion, fatigue, and anger.

Results: Analysis of variance revealed that patients with moderate/severe Graves ophthalmopathy showed significantly greater emotional distress than patients with mild/negligible Graves ophthalmopathy on the Profile of Mood States mean total score ($P<.001$). Additionally, patients who had disfigurement (proptosis) as the predominant clinical feature had significantly elevated emotional distress compared with the control group ($P=.01$), whereas no significant difference was detected between the control group and patients with diplopia as the predominant clinical feature ($P=.20$).

Conclusion: Patients with moderate to severe Graves ophthalmopathy have significant mood disturbance, especially when disfiguring signs are predominant. We propose that evaluation of the psychological burden of the disease should be considered in routine follow-up and in decisions regarding treatment.

Arch Ophthalmol. 2005;123:491-496

Author Affiliations:
Departments of Ophthalmology (Drs Farid, Roch-Levecq, Levi, Granet, and Kikkawa and Ms Brody), Neurosciences (Dr Levi), and Family and Preventive Medicine (Ms Brody) and the Thyroid Eye Center (Drs Levi, Granet, and Kikkawa), University of California, San Diego. Dr Farid is now with the Department of Ophthalmology, University of California, Irvine.
Financial Disclosure: None.

GRAVES OPHTHALMOPATHY (GO) is an extrathyroidal manifestation of an autoimmune inflammatory disease that is associated with disfiguring proptosis, lid retraction, pain, redness, periorbital swelling, double vision, exposure keratitis, and sometimes even blindness.[1-3] Although the exact mechanism and pathogenesis of GO continue to be elucidated, studies point to possible cross-reactivity between the thyrotropin receptor–stimulating immunoglobulins and the thyrotropin receptor antigens expressed on orbital fibroblasts as the cause of the ophthalmopathy.[4,5] Discrete eye signs and symptoms are seen in 30% to 45% of patients, whereas clinically overt orbitopathy is present in 5% to 10% of patients with Graves hyperthyroidism.[1] Supportive medical therapy or observation only is needed for approximately 74% of patients; these patients fall into the category of mild ophthalmopathy. For patients with moderately severe active disease, a period of waiting for stabilization or spontaneous improvement precedes consideration of surgical treatment.[6] Surgical treatment may be both functional (involving muscle surgery for correction of double vision) and reconstructive (involving orbital decompression or lid surgery for proptosis or lid retraction, respectively).

Currently, the outcomes of GO and treatment, including surgical evaluations, are mostly assessed with biological measures such as the NO SPECS classification used in most previous studies of GO.[7] The NO SPECS classification artificially combines different parameters of the disease and has been criticized.[3] While biological measures are vital and provide valuable information to the physician, they often correlate poorly with functional capacity and perceived health as experienced by the patient.[8] Furthermore, the psychological burden of the disease on the patient is not routinely discussed by the clinician in the evaluation for treatment.

In 1992, a joint committee of thyroid associations recommended that self-assessment of the eye condition by the pa-

tient be used in evaluation of treatment.[9] It is well accepted that visual impairment in general causes substantial impairment in daily functioning and well-being.[10,11] Furthermore, psychological and psychiatric assessments of patients with other ophthalmic diseases have revealed significant emotional distress and depression associated with vision loss.[12-16] Several groups have reported that the effects of thyroid eye disease on physical and psychological functioning have a significant impact on a patient's health-related quality of life.[17-21] This decrease in the patient's daily functioning and perception of health in general has been shown to persist even many years after diagnosis and treatment.[22] Terwee et al[23-25] (1998, 1999, 2001) further developed and validated a disease-specific quality-of-life questionnaire for patients with GO (the GO-QOL), designed to address visual functioning and perceived psychosocial consequences as a result of the patients' changed appearance. Although health-related quality-of-life assessments are valuable for determining the effects of treatment for GO, few studies have looked at clinically significant psychological impairment related to the degree of disfigurement and dysfunction from the disease.

Egle et al[26] (1999) found increased frequency of symptoms of anxiety and depression in patients with thyroid-associated orbitopathy compared with the normal population. The same group also reported a general decrease in perceived quality of life in these patients.[21] The hyperthyroid state itself is associated with increased prevalence of anxiety and depression even after remission[27,28]; however, the added psychological effects from decreased visual functioning and disfigurement in GO as compared with patients with underlying Graves disease have not been reported.

Evaluation of the changes in a patient's mood as a result of worsening symptoms may alter treatment plans and result in earlier surgical intervention or perhaps a delay if psychological impairment is severe. Therefore, the physician must be aware of the emotional components of the patient's illness when making decisions regarding treatment. At the Thyroid Eye Center, University of California, San Diego, we observed that patients with GO were often severely emotionally affected by the physical consequences of their disease; that is, patients with severe disfigurement seemed to be much more psychologically disturbed than patients with few or no manifest signs.

In this study we aimed to measure mood disturbance in patients with moderate to severe GO as compared with patients with negligible to very mild GO, thereby controlling for the underlying autoimmune disease while measuring the prevalence of psychological disturbance resulting from the dysfunction and disfigurement caused by moderate to severe GO. Psychological distress was assessed by the Profile of Mood States (POMS), a disease-independent psychological survey that has been widely used in clinical and experimental research and has well-documented reliability and validity.[29-31] We predicted that patients affected with moderate to severe GO symptoms would exhibit higher levels of mood disturbance than patients with negligible to mild GO symptoms.

PARTICIPANTS

Participants were recruited from the patient population base of the Thyroid Eye Center at the University of California, San Diego. Consecutive patients coming in for an office visit over a 6-month period (April through September 2001) were asked to participate. Participants completed a mood survey and health-related questionnaire along with an informed consent form that had been approved by the university's Institutional Review Board andEthics Committee. A total of 152 surveys were distributed, and 74 (49%) were completed and returned. Forty-eight (65%) of these patients met the following inclusion and exclusion criteria: (1) diagnosis of GO confirmed at the Thyroid Eye Center; (2) no other unstable eye disease; (3) currently taking no current antidepressant, antianxiety, or mood-stabilizing medications; (4) euthyroid at time of evaluation based on a recent thyrotropin value; and (5) comprehension of the English language adequate to complete the mood survey.

Clinical data were obtained by chart review and included exophthalmometry measurements, eye motility measurements using a −4 to +4 scale in degree of ductions, degree of lagophthalmos, margin reflex distance measurements, degree of lid/periorbital edema, and tonometer readings at primary gaze and upgaze. Seventeen patients (23%) were excluded because they were currently taking antidepressant medications, 3 patients (4%) because of concomitant glaucoma, and 6 patients (8%) because there were no recent clinical eye measurements.

The study group consisted of 24 patients with moderate to severe GO symptoms, and the control group consisted of 24 patients with negligible to mild GO symptoms. Patients in both groups were individually matched based on age, sex, and ethnicity and were group matched based on socioeconomic status, marital status, and clinical history. Moderate to severe GO was defined as proptosis greater than 22 mm in either eye and/or significant extraocular movement (EOM) restriction greater than −1.5 in any direction of gaze and in either eye. The study group was further divided into two subgroups based on whether their predominant clinical signs consisted of proptosis (proptosis >22 mm and EOM restriction <−1) or muscle involvement (EOM restriction >−1.5 and proptosis <21 mm).

Ten patients each were in the predominant proptosis and predominant strabismus subgroups. All patients in the muscle restriction subgroup had diplopia in primary gaze. Each of these subgroups was compared with the control group. Four patients were excluded from the secondary analysis because they had both a high degree of proptosis and a high degree of EOM restriction. Negligible or mild GO was defined as proptosis of 21 mm or less in both eyes, EOM restriction of −1 or less in both eyes, no lagophthalmos, no lid or periorbital edema, margin reflex distance of 6 mm or less in both eyes, and no significant rise in intraocular pressure on upgaze. Graves ophthalmopathy was diagnosed based on history and clinical examination findings. Most patients had a previous systemic diagnosis of Graves disease. For some patients the diagnosis was confirmed by computed tomographic scan and/or thyroid function tests, and in some patients other ocular diseases that might have mimicked their symptoms (ie, myasthenia gravis) were ruled out.

MEASURES

Profile of Mood States

The Profile of Mood States (POMS)[29] is a 65-item self-reported symptom inventory designed to assess emotional distress during the previous week. The participant responds to each

item on a 5-point Likert scale ranging from "not at all" to "extremely." There are 6 subscales (tension/anxiety, depression/dejection, vigor/activity, confusion/bewilderment, fatigue/inertia, and anger/hostility) and a total score (summation of the 6 subscales). The vigor/activity scale was reverse-scored so that higher scores indicate greater mood disturbance for all scales. Seven items were not used in calculation of the scores. Total individual scores ranged from 0 to 232. High scores indicate high level of emotional distress. The POMS does not include somatic symptoms that might be confounded with physical illness. The POMS has been widely used for assessing psychological distress in various clinical and experimental research and has well-documented reliability and validity in adult and elderly populations.[30,31]

Health-Related Questionnaire

Clinical and demographic characteristics were obtained by a health-related questionnaire. Information was obtained about medical and psychiatric history, current medications, previous treatment with radioactive iodine, previous eye surgery, and current eye symptoms, such as pain or double vision. In addition, information was obtained about age, ethnicity, marital status, living arrangements, education, and principal occupation. The principal occupation and education of the subject and/or the primary household provider was used in the Hollingshead Two-Factor Index of Social Position to assign an occupation score to each subject.[32]

STATISTICAL ANALYSIS

Statistical analyses were conducted using Statistica for Windows, version 5.5 (StatSoft, 1999; Tulsa, Okla). Unpaired t and χ^2 tests were used to detect any difference in demographic and socioeconomic factors. Analyses of variance (ANOVAs) were used to test for any difference between groups. A 1-way ANOVA was performed on the POMS total score to test for any difference between the study groups and the control group, and a repeated-measure ANOVA was performed on the 6 subscales. An ANOVA was also used to compare each of the two subgroups with the control group. The assumptions of normality and homogeneity of variance between the groups were respected. The Tukey honestly significant difference test was used for the subgroup post hoc analysis.

The differences between groups were examined using planned comparisons. With the sample size of this study, there was a power of 0.90 to detect a difference of 1 SD (ie, 30 points difference; a large effect size)[29] between groups on the primary outcome measure, which was the total score on the POMS.

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE SAMPLE

The mean age of the participants was 55 years (range, 19-94 years), with an SD of 17.6 years (**Table 1**). There were 41 white patients, 5 of Asian origin, 1 of Hispanic origin, and 1 African American. Twenty-eight (58%) of the participants were married. Socioeconomic status, determined on the basis of education and occupation of the subject and/or primary household provider, was as follows: level 1 (major business or professional), 25% (n=12); level 2 (medium business or minor professional), 44% (n=21); level 3 (skilled craftsperson, cleri-

Table 1. Demographic and Clinical Characteristics of Participants With Graves Ophthalmopathy

	Study Group (n = 24)	Control Group (n = 24)	Significance
Mean (SD) age, y	54.2 (16.7)	56.2 (18.4)	$t_{46} = 0.4$, $P = .69$
Sex, No. (%)			
Female	20 (83)	20 (83)	$\chi^2_1 = 0.2$, $P = .65$
Male	4 (17)	4 (17)	
No. (%) white	22 (92)	19 (79)	$\chi^2_1 = 0.2$, $P = .65$
Hollingshead Two-Factor Index			
Level 1	6 (25)	6 (25)	
Level 2	10 (42)	11 (46)	
Level 3	3 (13)	2 (8)	$\chi^2_4 = 1.36$, $P = .85$
Level 4	5 (21)	4 (17)	
Level 5	0 (0)	1 (4)	
Marital status, No. (%)			
Single/widowed/divorced	11 (46)	9 (38)	$\chi^2_1 = 0.34$, $P = .56$
Married	13 (54)	15 (62)	
Prior radioactive iodine therapy, No. (%)			
Yes	9 (38)	11 (46)	$\chi^2_1 = 0.34$, $P = .56$
No	15 (62)	13 (54)	
Prior orbital/lid/ muscle surgery, No. (%)			
Yes	14 (58)	12 (50)	$\chi^2_1 = 0.34$, $P = .56$
No	10 (42)	12 (50)	

cal worker), 10% (n=5); level 4 (semiskilled worker), 19% (n=9); and level 5 (unskilled worker), 2% (n=1). Twenty participants (42%) reported that they had had previous radioactive iodine therapy for hyperthyroidism. Twenty-six participants (54%) reported that they had had previous orbital, lid, or eye muscle surgery for thyroid ophthalmopathy. Duration of disease from time of diagnosis ranged from 2 months to over 10 years in both groups; however, many patients in both groups reported having symptoms and signs of the disease for months to years prior to diagnosis. There was no significant difference in any of the above measures between the study group and the control group ($P>.05$) (Table 1).

There was no significant difference in clinical and demographic characteristics between the patients who met the inclusion criteria and those who did not. There was also no significant difference in age or sex between those who did vs did not respond to the survey.

COMPARISON OF MODERATE/SEVERE AND MILD/NEGLIGIBLE GO GROUPS

The ANOVA on the primary outcome measure, POMS, showed that the study group experienced significantly greater emotional distress than the control group (**Table 2**). Overall, participants in the study group reported significantly elevated emotional distress on the POMS total score compared with participants in the control group, ($P<.001$). Significant differences were seen in 5 of the 6 subscales, with the exception being the tension-anxiety subscale ($F_{1,46}=3.88$, $P=.055$). There was no significant interaction between the subscale scores and the groups.

Table 2. Profile of Mood States (POMS) Total and Subscale Scores in the Study and Control Groups	Mean (SD)		Difference Between Groups*	
	Study Group (n = 24)	Control Group (n = 24)	$F_{1,46}$	P
POMS total score	87.5 (45.5)	48.4 (29.2)	12.58	<.001
POMS subscale score				
Tension-anxiety	14.1 (8.7)	9.6 (7.0)	3.88	.055
Depression-dejection	17.6 (14.2)	8.3 (8.1)	7.77	.008
Anger-hostility	12.6 (10.9)	6.5 (6.5)	5.67	.02
Vigor-activity	20.3 (5.8)	12.7 (6.8)	17.31	<.001
Fatigue-inertia	12.7 (7.6)	5.7 (5.3)	13.82	<.001
Confusion-bewilderment	10.3 (6.3)	5.7 (4.5)	8.39	.006

*Evaluated using analysis of variance.

Table 3. Profile of Mood States (POMS) Total and Subscale Scores in the Proptosis and Muscle Restriction Subgroups and the Control Group*	Control Group (n = 24)	Proptosis Subgroup (n = 10)	Muscle Restriction Subgroup (n = 10)
POMS total score	48.4 (29.2)	97.8 (50.1)	77.1 (36.2)
POMS subscale score			
Tension-anxiety	9.6 (7.0)	15.8 (8.2)	11.6 (8.7)
Depression-dejection	8.3 (8.1)	20.2 (15.9)	15.3 (12.8)
Anger-hostility	6.5 (6.5)	15.1 (11.1)	8.9 (10.5)
Vigor-activity	12.7 (6.8)	20.6 (6.3)	20.6 (5.2)
Fatigue-inertia	5.7 (5.3)	13.5 (7.8)	12.7 (7.4)
Confusion-bewilderment	5.7 (4.5)	12.6 (6.8)	8.0 (4.1)

*Values are mean (SD).

COMPARISON OF SUBGROUPS WITH MILD/NEGLIGIBLE GO GROUP

One-way ANOVA on the POMS total score showed that the proptosis subgroup experienced significantly greater emotional distress than the control group ($F_{2,41}$=7.12, P=.002). The Tukey honestly significant difference test showed that the proptosis subgroup reported significantly more emotional distress than the control group on all subscales of the POMS (P=.01). There was no significant difference between the muscle restriction subgroup and the control group (P=.20) (**Table 3**). A repeated-measure ANOVA on the 6 subscales did not reveal any significant interaction between the subscale scores and the groups. There was no significant difference in age, sex, ethnicity, socioeconomic status, marital status, or clinical history between the proptosis and muscle restriction subgroups.

COMMENT

In GO, disfigurement and diplopia have been shown to have a significant impact on the patient's health-related quality of life.[18-22] In our study, patients with moderate to severe signs and symptoms demonstrated, in addition, a significant psychological depression in mood on a widely accepted psychological outcome measure. The present study demonstrates that patients who have noticeable proptosis and/or who have functionally limiting double vision have significant feelings of depression, anger, fatigue, confusion, and reduced vigor compared with patients who have very mild or negligible symptoms. Accordingly, psychological assessments should be considered in routine care for such patients, and referral for psychological intervention should be made appropriately. Awareness of a possible severe psychological impairment in patients with GO is important in the ophthalmic practice, where routine follow-up of these patients often occurs. It might be helpful to refer these patients for further psychological evaluation as appropriate or perhaps to add a mental health care professional to the multidisciplinary team caring for these patients.

When patients with GO were separated into those with predominantly disfiguring signs and those with predominantly functional deficits, we found that it was the disfiguring aspect of the disease that accounted for much of the emotional distress. The progressive disfigurement of GO is increasingly recognized as an indication for orbital decompression surgery. Many believe, however, that due to the operative risks it is only warranted when vision is threatened. In skilled hands, major complications such as visual loss are rare. Diplopia may occur as a complication but is treatable with subsequent strabismus surgery.[33] In light of the concomitant physical and psychological disability caused by GO, treatment should be individualized, and perhaps a lower threshold for reconstructive surgery should be considered in appropriate cases.

Other potential mechanisms may link severity of eye disease in GO with neuropsychiatric disease. There have been reported cases of encephalopathy as well as psychiatric disease that may be related to the presence of thyroid-related autoantibodies.[34,35] Although thyrotropin receptor antibodies have been shown to directly correlate with clinical features of GO,[4] the exact relationship of these antibodies to encephalopathy or central nervous system–mediated mood disturbance has not been established. Further studies of mood in patients with GO and levels of thyroid-related autoantibody titers would be needed to assess this relationship.

The GO-QOL, developed by Terwee et al,[23-25] has been shown to be an effective, disease-specific tool for assessing perceived health-related quality of life in patients with GO. On a clinical level, it may provide valuable information to the physician for constructing an individualized treatment plan for each patient and monitoring the effects of treatment. The POMS, on the other hand, measures specific mood disturbance independent of medical and physical conditions and may therefore provide a standard measure of mood in GO for research purposes. Furthermore, the POMS utilizes 65 simple 5-point responses to single-word adjectives, can be completed in 5 minutes, and requires only a seventh-grade education for comprehension. As such, it provides a clear and simple measure for the study of emotional distress in patients with eye dis-

ease. A similar method has been used in studies on the psychological consequences of age-related macular degeneration.[12,13,15] These studies found a strong main effect of status; that is, a significant difference between scores on the POMS of patients diagnosed as clinically depressed and those of patients diagnosed as not clinically depressed by the Structured Clinical Interview for *DSM-IV* Axis I Disorders ($P<.001$). The sensitivity of the POMS and the classification according to the Structured Clinical Interview for *DSM-IV* Axis I Disorders were correlated ($P<.001$).[13] The present study may represent another step toward a systematic approach to the investigation of psychological impairment in ophthalmic diseases.

A clinical diagnosis of depression or anxiety is made based on *DSM-IV* criteria, and although only a few studies have used both the POMS and *DSM-IV*–based criteria to assess depression in research populations,[36,37] there have been no reports correlating POMS scores with clinical diagnosis of psychiatric disease. No claims of clinical psychiatric disease can be made based on the present study.

Although there was a 49% response rate to the initial 152 surveys distributed, demographic analysis revealed no difference in age or sex between the responders and the nonresponders. There were equal numbers of patients with severe and mild GO in the response group, which is likely representative of the spectrum of patients with GO. Furthermore, there is no reason to believe that patients with greater emotional distress responded at a higher or lower rate, and our response group showed a wide range of mood disturbance.

The results of this study account for only a small sample of patients with GO and cannot be generalized to all patients with GO. However, this study does verify the clinical observations made in a university-based tertiary referral practice. Larger, multicenter studies with tighter inclusion/exclusion criteria, such as controlling for previous surgical intervention or radiation therapy, are needed to better study mood disturbance in all subpopulations of patients with GO. The sample of patients in our study was predominantly female, and although Graves disease affects women 5 to 10 times more frequently than men,[38] there may a difference in presentation between men and women that will need to be explored in future studies.

Graves ophthalmopathy is a debilitating disease associated with a significant psychological burden, especially when disfiguring signs are predominant. The emotional impact of the disease should be evaluated routinely and should be taken into consideration when making management decisions. While psychological evaluations may be beyond the scope of an ophthalmology practice, appropriate referral should be made to a mental health care professional. A lower threshold for surgical intervention in patients with significant GO-related mood disturbances might have a significant benefit in quality of life for selected patients. Further research is needed to fully evaluate GO-related mood disturbance and its impact on surgical intervention.

Correspondence: Don O. Kikkawa, MD, Department of Ophthalmology, University of California, San Diego, 9415 Campus Point Dr, La Jolla, CA 92093-0946 (kikkawa @eyecenter.ucsd.edu).

REFERENCES

1. Burch HB, Wartofsky L. Graves' ophthalmopathy: current concepts regarding pathogenesis and management. *Endocr Rev*. 1993;14:747-793.
2. Weetman AP. Thyroid-associated eye disease: pathophysiology. *Lancet*. 1991;338: 25-28.
3. Wiersinga WM, Prummel MF. An evidence-based approach to the treatment of Graves' ophthalmopathy. *Endocrinol Metab Clin North Am*. 2000;29:297-319.
4. Gerding MN, van der Meer JWC, Broenink M, Bakker O, Wiersinga WM, Prummel MF. Association of thyrotropin receptor antibodies with the clinical features of Graves' ophthalmopathy. *Clin Endocrinol (Oxf)*. 2000;52:267-271.
5. Bahn RS. Understanding the immunology of Graves' ophthalmopathy: is it an autoimmune disease? *Endocrinol Metab Clin North Am*. 2000;29:287-296.
6. Fatourechi V. Medical treatment of Graves' ophthalmopathy. *Ophthalmol Clin North Am*. 2000;13:683-691.
7. Werner SC. Modification of the classification of the eye changes of Graves' disease. *Am J Ophthalmol*. 1977;83:725-727.
8. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. *JAMA*. 1995;273:59-65.
9. Pinchera A, Wiersinga WM, Glinoer D, et al. Classification of eye changes of Graves' disease. *Thyroid*. 1992;2:235-236.
10. Salive ME, Guralnik J, Glynn RJ, Christen W, Wallace RB, Ostfeld AM. Association of visual impairment with mobility and physical function. *J Am Geriatr Soc*. 1994;42:287-292.
11. Scott IU, Schein OD, West S, et al. Functional status and quality of life measurement among ophthalmic patients. *Arch Ophthalmol*. 1994;112:329-335.
12. Williams RA, Brody BL, Thomas RG, Bandeen-Roche K, Enger C, Folstein MF. The psychological impact of macular degeneration. *Arch Ophthalmol*. 1998; 116:514-520.
13. Brody BL, Roch-Levecq A-C, Gamst AC, Maclean K, Kaplan RM, Brown SI. Self-management of age-related macular degeneration and quality of life: a randomized control study. *Arch Ophthalmol*. 2002;120:1477-1483.
14. Rovner BW, Casten RJ, Tasman WS. Effects of depression on vision function in age-related macular degeneration. *Arch Ophthalmol*. 2002;120:1041-1044.
15. Brody BL, Gamst AC, Williams RA, et al. Depression, visual acuity, comorbidity, and disability associated with age-related macular degeneration. *Ophthalmology*. 2001;108:1893-1901.
16. Scott IU, Schein OD, Feuer WJ, Folstein MF, Bandeen-Roche K. Emotional distress in patients with retinal disease. *Am J Ophthalmol*. 2001;131:584-589.
17. Bartley GB, Fatourechi V, Kadrmas EF, et al. Long-term follow-up of Graves' ophthalmopathy in an incident cohort. *Ophthalmology*. 1996;103:958-962.
18. Gerding MN, Terwee CB, Dekker FW, Koornneef L, Prummel MF, Wiersinga WM. Quality of life in patients with Graves' ophthalmopathy is markedly decreased: measurement by the Medical Outcomes Study instrument. *Thyroid*. 1997;7: 885-889.
19. Ljunggren JG, Torring O, Wallin G, et al. Quality of life aspects and costs in treatment of Graves' hyperthyroidism with antithyroid drugs, surgery, or radioiodine: results from a prospective, randomized study. *Thyroid*. 1998; 8:653-659.
20. Terwee CB, Dekker FW, Prummel MF, Wiersinga WM. Graves' ophthalmopathy through the eyes of the patient: a state of the art on health-related quality of life assessment. *Orbit*. 2001;20:281-290.
21. Kahaly GJ, Hardt J, Petrak F, Egle UT. Psychosocial factors in subjects with thyroid associated ophthalmopathy. *Thyroid*. 2002;12:237-239.
22. Terwee CB, Wakelkamp I, Tan S, Dekker F, Prummel MF, Wiersinga W. Long-term effects of Graves' ophthalmopathy on health-related quality of life. *Eur J Endocrinol*. 2002;146:751-757.
23. Terwee CB, Gerding MN, Dekker FW, Prummel MF, Wiersinga WM. Development of a disease specific quality of life questionnaire for patients with Graves' ophthalmopathy: the GO-QOL. *Br J Ophthalmol*. 1998;82:773-779.
24. Terwee CB, Gerding MN, Dekker FW, Prummel MF, van der Pol JP, Wiersinga WM. Test-retest reliability of the GO-QOL: a disease-specific quality of life questionnaire for patients with Graves' ophthalmopathy. *J Clin Epidemiol*. 1999; 52:875-884.
25. Terwee CB, Dekker FW, Mourits MP, et al. Interpretation and validity of changes in scores on the Graves' ophthalmopathy quality of life questionnaire (GO-QOL) after different treatments. *Clin Endocrinol (Oxf)*. 2001;54:391-398.

26. Egle UT, Kahaly GJ, Petrak F, et al. The relevance of physical and psychosocial factors for the quality of life in patients with thyroid-associated orbitopathy (TAO). *Exp Clin Endocrinol Diabetes*. 1999;107(suppl 5):S168-S171.

27. Fahrenfort JB, Wilterdink AML, van der Veen EA. Long-term residual complaints and psychosocial sequelae after remission of hyperthyroidism. *Psychoneuroendocrinology*. 2000;25:201-211.

28. Harsch I, Paschke R, Usadel KH. The possible etiological role of psychological disturbances in Graves' disease. *Acta Med Austriaca*. 1992;19(suppl 1):62-65.

29. McNair DM, Lorr M, Droppleman LF. *POMS Manual: Profile of Mood States (Revised)*. San Diego, Calif: Educational and Industrial Testing Service; 1992.

30. Nyenhuis DL, Yamamoto C, Luchetta T, Terrien A, Parmentier A. Adult and geriatric normative data and validation of the Profile of Mood States. *J Clin Psychol*. 1999;55:79-86.

31. Kaye JM, Lawton MP, Gitlin LN, et al. Older people's performance on the Profile of Mood States (POMS). *Clin Gerontol*. 1988;7:35-56.

32. Hollingshead AB. *Two Factor Index of Social Position*. New Haven, Conn: Hollingshead; 1957.

33. Lyons CJ, Rootman J. Orbital decompression for disfiguring exophthalmos in thyroid orbitopathy. *Ophthalmology*. 1994;101:223-230.

34. Seo SW, Lee BI, Lee JD, et al. Thyrotoxic autoimmune encephalopathy: a repeat positron emission tomography study. *J Neurol Neurosurg Psychiatry*. 2003; 74:504-506.

35. Othman SS, Abdul Kadir K, Hassan J, Hong GK, Singh BB, Raman N. High prevalence of thyroid function test abnormalities in chronic schizophrenia. *Aust N Z J Psychiatry*. 1994;28:620-624.

36. Hosaka T, Aoki T. Depression among cancer patients. *Psychiatry Clin Neurosci*. 1996;50:309-312.

37. Patten CA, Gillin JC, Golshan S, Wolter TD, Rapaport M, Kelsoe J. Relationship of mood disturbance to cigarette smoking status among 252 patients with a current mood disorder. *J Clin Psychiatry*. 2001;62:319-324.

38. Tunbridge WMG, Evered DC, Hall R, et al. The spectrum of thyroid disease in a community: the Whickham survey. *Clin Endocrinol (Oxf)*. 1977;7:481-493.

Notice to the Authors of Reports From Clinical Trials

The *Journal of the American Medical Association* (*JAMA*) and the *Archives of Ophthalmology* function as an editorial consortium.

With one submission and one set of reviews, your clinical trial manuscript will be considered for publication in both *JAMA* and the *Archives of Ophthalmology*.

Submit your paper to the journal of your choice according to the appropriate "Instructions for Authors" and the following guidelines will apply:

1. If your manuscript is accepted by *JAMA*, it will be considered for an editorial or commentary in *JAMA*. Your abstract will also be published in the *Archives of Ophthalmology* with a commentary or editorial.

2. If your manuscript is accepted by the *Archives of Ophthalmology*, it will be considered for an editorial or commentary in the *Archives of Ophthalmology*. Your abstract will also be considered for publication in *JAMA*.