

# Evaluation and characterization of generalized anxiety and depression in patients with primary brain tumors

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To determine clinical and sociodemographic factors that are associated with major neuropsychiatric illnesses among brain tumor patients, we administered a modified version of the Brief Patient Health Questionnaire and a demographic data form to 363 adult neuro-oncology patients. Responses were analyzed to assess for associations between demographic variables, clinical variables, and symptoms consistent with diagnoses of generalized anxiety disorder and/or depression. Multivariate logistic regression analyses showed that female gender was associated with the presence of symptoms of anxiety, depression, and combined anxiety and depression. Lower WHO tumor grade classifications, lower education level, and a history of psychiatric illness also emerged as important predictors of symptoms consistent with anxiety and/or depression. Marital status and presence of past/current medical illness trended toward being significantly associated with depression alone. Patient use of psychiatric medication was not associated with any study variables. Results of the present study suggest several hypotheses to test with neuro-oncology patients in further longitudinal analyses, which would benefit from the inclusion of a wider range of neuropsychiatric symptoms in conjunction with neurocognitive and functional impairment variables. *Neuro-Oncology* 10, 171–181, 2008 (Posted to *Neuro-Oncology* [serial online], Doc. D06-00088, Feb-

ruary 26, 2008. URL <http://neuro-oncology.dukejournals.org>; DOI: 10.1215/15228517-2007-057)

Keywords: anxiety, depression, neuropsychiatric symptoms, primary brain tumor

An estimated 41,130 new cases of primary benign and malignant brain tumors were diagnosed in 2004. The American Cancer Society found that the incidence of primary *malignant* brain and central nervous system tumors in 2005 was 18,500 new cases.<sup>1</sup> To date, the overwhelming majority of the research conducted on brain tumor patients centers on issues of patient survival. However, for many brain tumor patients, quality of life is affected by a number of illnesses related to their cancer treatment and diagnosis, including clinical depression and generalized anxiety disorder, yet few published studies document the presence of comorbid psychiatric diagnoses among brain tumor patients in a manner consistent with the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition<sup>2</sup> (*DSM-IV*).

Published reports have demonstrated that a substantial percentage of general oncology patients report anxiety and depressive symptoms. A study published by McDaniel et al. in 1995<sup>3</sup> found that up to one-half of cancer patients experience symptoms that would qualify them for a clinical diagnosis of depression. Although not as extensively studied as depression in cancer populations, anxiety also has been shown to be prevalent among oncology patients. In a study by Skarstein et al.<sup>4</sup> using the Hospital Anxiety and Depression Scale (HADS), 13% of 568 patients had diagnosable anxiety.

Received May 31, 2006; accepted June 7, 2007.

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Failing to adequately treat depression and other psychiatric symptoms in these patient populations can compromise overall health and quality of life.

The physiologic and functional impact of a brain tumor diagnosis may result in more specific neuropsychiatric, cognitive, and behavioral manifestations. In a prospective study published in 1999, using HADS, Pringle et al.<sup>5</sup> found that 30% of patients with intracranial neoplasms suffered from anxiety and 16% from depression. In a more recent study of 598 patients with high-grade glioma,<sup>6</sup> depression was reported to be very common in the preoperative and postoperative periods, but percentages of depressed patients differed considerably between physician reports and patient reports: physicians reported depression in 15% of patients, whereas 93% of patients reported symptoms consistent with depression. Depression also appears to be related to survival time in brain tumor patients.<sup>6</sup> In a study of 75 patients with solitary primary brain tumors reported by Mainio et al.,<sup>7</sup> patients with low-grade glioma who were depressed had significantly shorter median survival times after surgery than did those who were not. This difference was not found in depressed versus nondepressed patients with either benign tumors or high-grade gliomas.<sup>7</sup>

Depressive symptoms often accompany increased irritability or anxiety. Anxiety may result from situational fear related to diagnosis and prognosis or may be directly related to the effects of the tumor. Neurocognitive changes are also common and can include attention deficits, memory loss, and delirium or dementia. These changes may induce or worsen neuropsychiatric symptoms, as well as behavioral disturbances, in brain tumor patients.

Few studies exist with well-defined psychiatric treatments, for well-defined symptom clusters, or for formal psychiatric diagnoses associated with brain tumors. In this study, we catalogued and described the presence of anxiety and depressive symptoms in a large clinic sample of patients with primary brain tumors. The instruments we employed were brief, yet sensitive and specific, and importantly, were designed for use by health care providers who may not have specific training in psychiatric diagnosis. The present study employed a modified form of a commonly used screening instrument, the Primary Care Evaluation of Mental Disorders (PRIME-MD), which has been used to identify specific mental disorders using diagnostic criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, third revised edition (*DSM-III-R*),<sup>8</sup> and *DSM-IV*. The validity and utility of the PRIME-MD have been studied in primary care settings; Leopold et al.<sup>9</sup> reported that agreement was “moderate bordering on excellent,” with respect to any diagnosis, between the PRIME-MD and the Structured Clinical Interview for *DSM-III-R* in the 53 patients who received both interviews.

The PRIME-MD has been modified and shortened into a two-page questionnaire, the Brief Patient Health Questionnaire (Brief PHQ), that can be self-administered or read to the patient quickly and effectively at a regularly scheduled clinic visit.<sup>10</sup> Studies have shown that the Brief PHQ is also a valid and reliable tool in

obtaining diagnostic psychiatric criteria in primary care settings.<sup>11</sup> The present study used a modified version of the Brief PHQ to establish the presence of symptoms consistent with diagnoses of generalized anxiety disorder and depression in a large clinic sample of primary brain tumor patients.

## Materials and Methods

### Sample and Procedure

Researchers enrolled and obtained consent from 363 subjects older than 18 years by approaching all patients scheduled for an adult neuro-oncology clinic visit who were determined to be relatively intact cognitively by the treating physician during routine neurologic exam. Interested participants were asked to complete two study questionnaires, one of which pertained to demographic information. Patients were free to withdraw from the study at any time, and all patient information was protected to maintain strict anonymity in accordance with the guidelines of the Institutional Review Board of Duke University Medical Center (DUMC).

### Design and Measures

The present study used a cross-sectional design. All participants were administered two study measures, a modified version of the Brief PHQ (hereafter referred to as the Modified Brief PHQ) and a demographic data form, on the day of their clinic visit before being seen by the health care providers. The original PHQ contained seven questions, five of which were designed to assess and/or diagnose the level of depression, generalized anxiety, and stress of the patient being surveyed. The Modified Brief PHQ consisted of the three questions on the Brief PHQ pertaining to (1) depression, (2) generalized anxiety, and (3) the use of any medications to treat these illnesses. The depression scale consisted of nine items that correspond to the *DSM-IV* criteria of major depressive disorder (e.g., little interest or pleasure in doing things; feeling down, depressed, or hopeless) that were rated on a four-point Likert-type scale as having occurred in the past 2 weeks (0 = not at all to 3 = nearly every day). The generalized anxiety scale consisted of seven items conforming to *DSM-IV* criteria for generalized anxiety disorder (e.g., feeling nervous, anxious, on edge, or worrying a lot about different things) that were rated on a three-point Likert-type scale as having occurred in the past 4 weeks (0 = not at all to 2 = more than half the days). Scoring of the depression and anxiety scales consisted of summing responses to items. A third question on the Modified Brief PHQ asked respondents to indicate if they were “taking medicine for anxiety, depression, or stress” in a yes/no format. The information obtained from the demographic form was age, gender, ethnicity, marital status, education level, date of diagnosis, tumor location, tumor diagnosis, WHO tumor grade, and mode of treatment.

Individuals were classified into groups based on their

responses on the Modified Brief PHQ. Individuals with a score of >3 on items pertaining to generalized anxiety according to *DSM-IV* criteria were classified as having generalized anxiety disorder. For responses pertaining to depression, individuals with a score of >5, including a self-report of either anhedonia or feeling depressed, were classified as depressed. The following patient groups were used in analyses for associations: anxiety only (GAD), depression only (DEP), anxiety and depression (GAD & DEP), and neither syndrome (NEITHER). Chart review was also performed to assess patient history of recurrent tumor and occurrence of past and current medical illnesses. Past/current medical illness was defined as previous cardiac events, hypertension, diabetes mellitus, hyperlipidemia or hypercholesterolemia, significant renal disease requiring dialysis, and/or history of other cancer. History of psychiatric illness was defined as having been treated for a psychiatric condition in the past with medication, psychotherapy, or psychiatric admission.

### Statistical Analysis

The relationships between various clinical and demographic factors (gender, marital status, education, time from diagnosis, tumor grade, tumor site, past/current medical illness, and recurrent disease) and the presence of generalized anxiety disorder, depression, or a combination of anxiety and depression were tested individually using chi-square and Fisher's exact tests. All clinical and demographic variables that showed statistically significant associations with anxiety, depression, or both at the 0.25 level in these univariate analyses were candidate variables for a multivariate logistic model that assessed their joint effects on outcome. A backward elimination approach to logistic regression was used to find a reduced multivariate model. A significance level of 0.10 was used to remove a factor from analysis. Chi-square and Fisher's exact tests were also used to assess the relationship between various clinical and demographic factors and the presence of generalized anxiety disorder, depression, or a combination of anxiety and depression among patients who were and were not receiving psychiatric medication.

Tests with a *p* value less than 0.05 were considered statistically significant. Statistical analyses were conducted by the DUMC Cancer Center Biostatistics Unit using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

## Results

### Demographics and Diagnoses of Anxiety and Depression

Demographic data are presented in Table 1. Generally, participants tended to be male, diagnosed with glioblastoma multiforme, married, and Caucasian and to have a college degree. The initial analysis of the study sample showed that, according to the responses on the Modified Brief PHQ, 41% had current depression and 48% had

current generalized anxiety disorder, with only 5% of the study population carrying a previous diagnosis of a psychiatric illness.

Results of chi-square and Fisher's exact tests examining relationships between individual clinical and demographic factors and generalized anxiety disorder and depression are summarized in Table 2. Analysis of variance was used to assess the effect of age on the presence of anxiety, depression, or both. In Table 2, data are grouped by patients having any generalized anxiety disorder (GAD and GAD & DEP groups), no generalized anxiety disorder (DEP and NEITHER groups), any depression (DEP and GAD & DEP groups), and no depression (GAD and NEITHER groups). Results showed that gender, tumor grade, and previous psychiatric history were significant predictors of a diagnosis of anxiety. Women were more likely than men to be anxious ( $p = 0.030$ ), as were patients with lower WHO tumor grade classifications compared with those with higher grade disease ( $p = 0.0013$ ) and patients with a history

**Table 1.** Demographic characteristics ( $n = 363$ ; mean age  $\pm$  SD,  $43.7 \pm 11.4$  years)

Variable	n (%)
Gender	
Female	154 (42)
Male	209 (58)
Diagnosis	
Anaplastic astrocytoma	99 (27)
Glioblastoma multiforme	144 (40)
Anaplastic oligodendroglioma	23 (6)
Other	97 (27)
Marital status	
Single	57 (16)
Married	276 (76)
Divorced	20 (6)
Separated	5 (1)
Widowed	5 (1)
Ethnicity	
Caucasian	345 (95)
African American	12 (3)
Hispanic	1 (<1)
Asian	1 (<1)
American Indian	2 (1)
Other	2 (1)
Education	
<High school	11 (3)
High school diploma	50 (14)
Some college	93 (26)
College degree	144 (40)
Graduate degree	64 (18)
Not recorded	1 (<1)
Previous psychiatric illness	19 (5)
Current anxiety	174 (48)
Current depression	150 (41)

**Table 2.** Univariate analyses relating clinical and sociodemographic predictors to the diagnosis of generalized anxiety and depression

Variable	<i>n</i>	Any GAD ( <i>n</i> = 174)	No GAD ( <i>n</i> = 189)	<i>p</i> Value	Any DEP ( <i>n</i> = 150)	No DEP ( <i>n</i> = 213)	<i>p</i> Value
Gender							
Male	209	90 (43%)	119 (57%)	0.030	76 (36%)	133 (64%)	0.031
Female	154	84 (55%)	70 (45%)		74 (48%)	80 (52%)	
Mean age (SD)		42.5 (10.6)	44.9 (12.1)	0.049	43.5 (11.0)	43.9 (11.8)	0.776
Marital status							
Single	57	31 (54%)	26 (46%)	0.280	25 (44%)	32 (55%)	0.057
Married	276	125 (45%)	151 (55%)		109 (39%)	167 (61%)	
Divorced	20	12 (60%)	8 (40%)		10 (50%)	10 (50%)	
Separated	5	4 (80%)	1 (20%)		5 (100%)	0	
Widowed	5	2 (40%)	3 (60%)		1 (20%)	4 (80%)	
Education							
<High school	11	7 (64%)	4 (36%)	0.404	7 (64%)	4 (36%)	0.038
High school diploma	50	24 (48%)	26 (52%)		25 (50%)	25 (50%)	
Some college	93	51 (55%)	42 (45%)		45 (48%)	48 (52%)	
College degree	144	64 (44%)	80 (56%)		54 (38%)	90 (72%)	
Graduate degree	64	28 (43%)	36 (57%)		19 (30%)	45 (70%)	
Not recorded	1	0	1 (100%)		0	1 (100%)	
Time from diagnosis							
<3 months	17	8 (47%)	9 (53%)	0.999	9 (53%)	8 (47%)	0.578
3–12 months	105	51 (49%)	54 (51%)		46 (44%)	59 (56%)	
13–24 months	98	47 (48%)	51 (52%)		41 (42%)	57 (58%)	
>24 months	143	68 (48%)	75 (52%)		54 (38%)	89 (62%)	
WHO tumor grade							
I	6	2 (33%)	4 (67%)	0.0013	1 (17%)	5 (83%)	0.032
II	57	38 (67%)	19 (35%)		32 (56%)	25 (45%)	
III	126	64 (51%)	62 (48%)		43 (35%)	83 (65%)	
IV	162	61 (38%)	101 (62%)		69 (43%)	93 (57%)	
Not recorded	4	4 (100%)	0		3 (75%)	1 (25%)	
Brain not primary <sup>a</sup>	8	5 (62%)	3 (38%)		2 (25%)	6 (75%)	
Tumor site							
Right hemisphere	170	82 (48%)	88 (52%)	0.987	65 (38%)	105 (62%)	0.351
Left hemisphere	158	75 (47%)	83 (53%)		72 (46%)	86 (54%)	
Other <sup>b</sup>	35	17 (49%)	18 (50%)		13 (37%)	22 (61%)	
Past/current medical illness <sup>c</sup>							
Yes	96	52 (54%)	44 (45%)	0.190	47 (49%)	49 (51%)	0.091
No	267	122 (46%)	145 (54%)		103 (39%)	164 (61%)	
Recurrent disease <sup>d</sup>							
Yes	89	44 (49%)	45 (51%)	0.807	40 (45%)	49 (55%)	0.458
No	274	130 (47%)	144 (53%)		110 (40%)	164 (60%)	
Ethnicity							
White	345	166 (48%)	179 (52%)	0.813	144 (42%)	201 (58%)	0.625
Nonwhite	18	8 (44%)	10 (56%)		6 (33%)	12 (27%)	
Previous psychiatric illness <sup>e</sup>							
Yes	19	14 (74%)	5 (26%)	0.032	14 (74%)	5 (26%)	0.007
No	344	160 (47%)	184 (53%)		136 (40%)	208 (61%)	

Abbreviations: Any GAD, GAD, and GAD & DEP groups combined; No GAD, DEP, and NEITHER groups combined; Any DEP, DEP, and GAD & DEP groups combined; No DEP, GAD, and NEITHER groups combined.

<sup>a</sup>Brain not primary indicates that brain cancer was not the primary diagnosis or that the brain tumor was the result of metastasis.

<sup>b</sup>Other included diagnoses such as bilateral tumor location.

<sup>c</sup>Past/current medical illness included previous cardiac events, hypertension, diabetes mellitus, hyperlipidemia, hypercholesterolemia, significant renal disease requiring dialysis, and/or history of other cancers.

<sup>d</sup>Recurrent disease indicates tumor growth > 25% on MRI.

<sup>e</sup>History of psychiatric illness was defined as having been treated for a psychiatric condition in the past with medication, psychotherapy, or psychiatric admission.

of psychiatric problems ( $p = 0.032$ ). Gender, education, tumor grade, and previous psychiatric history were significant predictors of a diagnosis of depression. Women were more likely to be depressed ( $p = 0.031$ ), as were less educated patients ( $p = 0.038$ ), patients with lower WHO tumor grade classifications compared with those with higher grade disease ( $p = 0.032$ ), and patients with a history of psychiatric problems ( $p = 0.007$ ). Marital status and past/current medical illness trended toward being significant predictors of a diagnosis of depression: married individuals were less likely to be depressed than were unmarried individuals ( $p = 0.057$ ), and patients with past/current medical illness were more likely to be depressed than were those without ( $p = 0.091$ ). When considering the combined diagnoses of generalized anxiety disorder and depression, again, neuropsychiatric symptoms were more common in women than in men (data not shown).

Table 3 summarizes the relationships of factors across the GAD, DEP, GAD & DEP, and NEITHER groups; analyses also compared patients with no history of psychiatric illness with those who did have such a history. Univariate analyses were conducted comparing the four patient groups (NEITHER, GAD, DEP, and GAD & DEP) as well as a dichotomous grouping of GAD & DEP versus NEITHER, GAD, and DEP combined. In both the four-group and dichotomous analyses, significant relationships were found for gender, tumor grade, and previous psychiatric history. Patients with grade I or II tumors had a greater tendency to have anxiety and depression than did those with grade III or IV tumors. Women and patients with a history of psychiatric problems were also more likely than their counterparts to be depressed and anxious.

In order to assess the relative importance of predictors for probable diagnoses of generalized anxiety disorder, depression, and the combination of anxiety and depression, a series of logistic regression analyses were performed. Variables that were significant predictors of a psychological diagnosis at the 0.25 level of significance in univariate analyses were candidate predictors in multivariate analyses. The results of these analyses are presented in Table 4. Patients with grade IV disease had significantly less anxiety than did patients with grade I or II disease (odds ratio [OR] = 0.361; 95% confidence interval [95% CI], 0.203–0.641). There was a trend for patients with grade III disease also to have less anxiety than patients with grade I or II disease (OR = 0.582; 95% CI, 0.321–1.055;  $p = 0.075$ ). The relationship between anxiety and gender as well as previous psychiatric history also trended toward statistical significance: men were 33.5% less likely to have a diagnosis of anxiety than were women (OR = 0.665; 95% CI, 0.432–1.022), and patients with a history of psychiatric illness were more likely than others to have anxiety (OR = 2.781; 95% CI, 0.959–8.066).

For depression, multivariate logistic regression analyses showed that men had a 36% lower risk (OR = 0.638; 95% CI, 0.414–0.983) than did women. Compared with patients with less than a college education, patients with a graduate degree were significantly less likely to have

depression (OR = 0.454; 95% CI, 0.242–0.854). A history of psychiatric problems was also associated with a significantly greater risk of current depression.

Consistent with previous findings, men were less likely to have combined anxiety and depression (OR = 0.47; 95% CI, 0.302–0.747). In addition, individuals with a graduate-level education were less likely to be depressed than were those with less than a college-level education. A significant relationship was also found between tumor grade and the presence of both depression and anxiety: patients with grade III or IV disease were about half as likely to have both depression and anxiety as were patients with lower grade tumors.

### Use of Psychiatric Medication for Treatment

A total of 205 patients had symptoms that were consistent with depression, anxiety, or both. Among this group, only 44% were taking a psychiatric medication at the time of the study. Psychiatric medication use also differed across the anxiety and depression groups. In the GAD group, 69% were receiving no psychiatric medication, while 74% of the patients in the DEP group and 45% of those in the GAD & DEP group were receiving no psychiatric medication. Univariate analyses were performed to test for significant relationships between clinical or demographic variables and diagnosis of generalized anxiety disorder or depression among patients receiving and not receiving psychiatric medications (Table 5). These analyses detected no statistically significant relationships.

## Discussion

The present investigation expands upon previous work conducted with patients with brain tumors with regard to neuropsychiatric comorbidities. It provides new insights and contrasts in the areas of prevalence, demographic trends, and impact of psychiatric treatment. In particular, this study showed a 60% greater prevalence of generalized anxiety disorder and a more than two-fold higher prevalence of depression than reported in at least one previous study.<sup>12</sup> Other published studies indicate a high prevalence of self-reported depressive symptoms in brain tumor patients.<sup>6</sup> The difference between our results and those of Pelletier et al.<sup>12</sup> may reflect our patients' having a higher prevalence of neuropsychiatric symptoms due to the higher number of complex cases seen in our major tertiary specialty care center or our use of different assessment instruments. Our results are consistent with the high rate of symptoms of depression noted in Litofsky et al.'s study.<sup>6</sup> This may be because both our study and Litofsky et al. used a measure that is highly consistent with *DSM-IV* criteria.

Descriptive statistical analyses included in this study may offer some evidence of trends with regard to prevalence of anxiety and depression based on demographic or treatment variables. These trends can inform more effective detection and intervention for neuropsychiatric illnesses and concerns for patients with primary brain

**Table 3.** Univariate analyses relating clinical and sociodemographic predictors to having a diagnosis of generalized anxiety, depression, or both generalized anxiety and depression

Variable	<i>n</i>	NEITHER ( <i>n</i> = 158)	GAD ( <i>n</i> = 55)	DEP ( <i>n</i> = 31)	GAD & DEP ( <i>n</i> = 119)	<i>p</i> Value <sup>a</sup>
Gender						
Male	209	97 (46%)	36 (17%)	22 (11%)	54 (26%)	0.008 (0.002)
Female	154	61 (40%)	19 (12%)	9 (6%)	65 (42%)	
Mean age (SD)		44.7 (1.9)	41.4 (11.1)	45.5 (12.9)	43.0 (10.4)	0.189
Marital status						
Single	57	20 (35%)	12 (21%)	6 (11%)	19 (33%)	0.358 (0.130)
Married	276	128 (46%)	39 (14%)	23 (8%)	86 (31%)	
Divorced	20	7 (35%)	3 (15%)	1 (5%)	9 (45%)	
Separated	5	0	0	1 (20%)	4 (80%)	
Widowed	5	3 (60%)	1 (20%)	0	1 (20%)	
Education						
<High school	11	3 (27%)	1 (9%)	1 (9%)	6 (54%)	0.426 (0.110)
High school diploma	50	20 (40%)	5 (10%)	6 (12%)	19 (38%)	
Some college	93	33 (35%)	15 (16%)	9 (10%)	36 (39%)	
College degree	144	69 (48%)	21 (15%)	11 (8%)	43 (30%)	
Graduate degree	64	32 (50%)	13 (20%)	4 (6%)	15 (23%)	
Not recorded	1	1 (100%)	0	0	0	
Time from diagnosis						
<3 months	17	6 (35%)	2 (12%)	3 (18%)	6 (35%)	0.514 (0.958)
3–12 months	105	43 (41%)	16 (15%)	11 (10%)	35 (33%)	
13–24 months	98	40 (41%)	17 (17%)	11 (11%)	30 (31%)	
>24 months	143	69 (48%)	20 (14%)	6 (4%)	48 (34%)	
WHO tumor grade						
I	6	4 (67%)	1 (17%)	0	1 (17%)	0.002 (0.027)
II	53	16 (29%)	9 (16%)	3 (5%)	29 (51%)	
III	131	58 (45%)	25 (20%)	4 (3%)	39 (31%)	
IV	162	77 (48%)	16 (10%)	24 (15%)	45 (28%)	
Not recorded	4	0	1 (25%)	0	3 (75%)	
Brain not primary <sup>b</sup>	8	3 (38%)	3 (38%)	0	2 (25%)	
Tumor site						
Right hemisphere	170	76 (45%)	29 (17%)	12 (7%)	53 (31%)	0.760 (0.737)
Left hemisphere	158	66 (42%)	20 (13%)	17 (11%)	55 (35%)	
Other <sup>c</sup>	34	16 (44%)	6 (17%)	2 (6%)	11 (31%)	
Past/current medical illness <sup>d</sup>						
Yes	96	33 (34%)	16 (17%)	11 (11%)	36 (38%)	0.180 (0.250)
No	267	125 (47%)	39 (15%)	20 (7%)	83 (31%)	
Recurrent disease <sup>e</sup>						
Yes	89	39 (43%)	10 (16%)	6 (9%)	34 (31%)	0.441 (0.210)
No	274	119 (44%)	45 (11%)	25 (7%)	85 (38%)	
Ethnicity						
White	345	149 (43%)	52 (15%)	30 (9%)	114 (33%)	0.947 (0.799)
Nonwhite	18	9 (50%)	3 (17%)	1 (6%)	5 (28%)	
Previous psychiatric illness						
No	344	154 (45%)	54 (16%)	30 (9%)	106 (31%)	0.014 (0.0016)
Yes	19	4 (21%)	1 (5%)	1 (5%)	13 (68%)	

Abbreviations: NEITHER, did not meet criteria for generalized anxiety or depression; GAD, generalized-anxiety-only group; DEP, depression-only group; GAD & DEP, generalized anxiety and depression group.

<sup>a</sup>*p* Values outside of parentheses refer to the four patient groupings (NEITHER, GAD, DEP, and GAD & DEP), whereas *p* values within parentheses refer to a dichotomous grouping (GAD & DEP group vs. a combined group of NEITHER, GAD, and DEP).

<sup>b</sup>Brain not primary indicates that brain cancer was not the primary diagnosis or that brain tumor was the result of metastasis.

<sup>c</sup>Other included diagnoses such as bilateral tumor location.

<sup>d</sup>Past/current medical illness included previous cardiac events, hypertension, diabetes mellitus, hyperlipidemia, hypercholesterolemia, significant renal disease requiring dialysis, history of psychiatric illness, and/or history of other cancers.

<sup>e</sup>Recurrent disease indicates tumor growth >25% on MRI.

<sup>f</sup>History of psychiatric illness was defined as having been treated for a psychiatric condition in the past with medication, psychotherapy, or psychiatric admission.

**Table 4.** Summary of final reduced multivariate models using logistic regression to predict the presence of generalized anxiety, depression, and generalized anxiety and depression (1 degree of freedom)

	<i>B</i>	Pr > Chi-Square <sup>a</sup>	Odds Ratio	95% Wald Confidence Limits	
				Lower	Upper
<b>Anxiety</b>					
Intercept	0.739	0.008			
Male	-0.408	0.063	0.665	0.432	1.022
WHO grade III	-0.541	0.075	0.582	0.321	1.055
WHO grade IV	-1.020	0.0001	0.361	0.203	0.641
Previous psychiatric history	1.023	0.060	2.781	0.959	8.066
<b>Depression</b>					
Intercept	0.135	0.208			
Male	-0.449	0.042	0.638	0.414	0.983
College degree vs. < college degree	-0.441	0.066	0.644	0.403	1.029
Graduate degree vs. < college degree	-0.789	0.014	0.454	0.242	0.854
Previous psychiatric history	1.334	0.013	3.795	1.317	10.940
<b>Anxiety and depression</b>					
Intercept	0.466	0.122			
Male	-0.745	0.001	0.475	0.302	0.747
College degree vs. < college degree	-0.423	0.092	0.655	0.400	1.072
Graduate degree vs. < college degree	-0.687	0.045	0.503	0.257	0.986
WHO grade III or IV	-0.649	0.018	0.523	0.305	0.895

<sup>a</sup>Probability for Wald's chi-square.

tumors. The five key variables associated with development of generalized anxiety disorder and depression in primary brain tumor patients are gender, marital status, level of education, tumor grade, and past/current medical illness. These factors and differences in the use of psychiatric medication for treatment are discussed below.

### Gender

Sixty percent of the women in our sample reported symptoms consistent with diagnoses of generalized anxiety disorder and depression. This finding is consistent with epidemiologic studies of depression that have shown a higher prevalence of depression in women.<sup>13</sup> Various biologic, sociologic, and psychological explanations for this phenomenon have been proposed.<sup>14-16</sup> Other epidemiologic studies suggest that, in addition to psychosocial factors, physiologic factors (including times of change in estrogen levels) may make depression more likely in a vulnerable subgroup of women.<sup>17</sup> However, the higher prevalence of depression among women than among men may be representative of some other key factors. For example, women may be more likely than men to actively communicate their emotions freely and therefore admit to symptoms of neuropsychiatric illness.

The study also showed that women were significantly more likely than men to have both anxiety and depression; in general, women may be more affected by the interplay between factors in the development of depression and anxiety. In principle, the high co-occurrence of anxiety and depression may reflect a number of scenarios: (1) simple, high coincidence of two conceptually

and phenotypically distinct disorders; (2) some causal relationship between distinct disorders; (3) a dimensional structure for relevant symptoms that is substantially similar for the two disorders; or (4) a combination of shared and unique features for the two constructs.<sup>18</sup>

### Marital Status

Approximately 25% of the study participants were unmarried at the time of the study. Although not statistically significant, there was a trend toward a greater prevalence of depression among unmarried participants than among married participants. Published research has documented similar trends of fewer psychiatric symptoms among married cancer patients, suggesting that married individuals with cancer may have improved overall health habits, less delay in seeking medical care when symptomatic, and/or greater social support.<sup>19</sup> These factors may result in improved prognosis and ability to cope with medical and social stressors. Ultimately, the lower prevalence of depressive symptoms among married cancer patients has been found to correlate with improved cancer survival as both an independent and a dependent predictor.<sup>20</sup>

### Level of Education

Individuals with at least some college-level education were much less likely than those with no college education to have anxiety, depression, or both. Subjects with a higher educational background may be more aware of their physical and psychological needs, resulting in higher rates of use of health care resources.<sup>21</sup> Higher

**Table 5.** Cross-tabulation of patient characteristics and diagnoses of generalized anxiety and depression stratified by use of psychiatric medications

Variable	No Psychiatric Medication Used				Psychiatric Medication Used			
	<i>n</i>	GAD, DEP, GAD & DEP ( <i>n</i> = 115)	NEITHER ( <i>n</i> = 129)	<i>p</i> Value	<i>n</i>	GAD, DEP, GAD & DEP ( <i>n</i> = 90)	NEITHER ( <i>n</i> = 29)	<i>p</i> Value
Gender								
Male	156	69 (44%)	87 (56%)	0.233	53	43 (81%)	10 (19%)	0.283
Female	88	46 (52%)	42 (48%)		66	47 (71%)	19 (29%)	
Marital status								
Single	41	23 (56%)	18 (44%)	0.312	16	14 (88%)	2 (12%)	0.312
Married	187	85 (45%)	102 (55%)		89	63 (71%)	26 (29%)	
Divorced	10	4 (40%)	6 (60%)		10	9 (90%)	1 (10%)	
Separated	2	2 (100%)	0		3	3 (100%)	0	
Widowed	4	1 (25%)	3 (75%)		1	1 (100%)	0	
Education								
<High school	8	5 (63%)	3 (37%)	0.259	3	3 (100%)	0	0.664
High school diploma	32	16 (50%)	16 (50%)		18	14 (78%)	4 (22%)	
Some college	56	32 (57%)	24 (23%)		37	28 (76%)	9 (24%)	
College degree	101	45 (45%)	56 (55%)		43	30 (70%)	13 (30%)	
Graduate degree	46	17 (37%)	29 (63%)		18	15 (83%)	3 (17%)	
Not recorded	1	0	1 (100%)		0	0	0	
Time from diagnosis								
<3 months	11	6 (55%)	5 (45%)	0.771	6	5 (83%)	1 (17%)	0.528
3–12 months	72	35 (49%)	37 (51%)		33	27 (82%)	6 (18%)	
13–24 months	66	33 (50%)	33 (50%)		32	25 (78%)	7 (22%)	
>24 months	95	41 (43%)	54 (57%)		48	33 (69%)	15 (31%)	
WHO tumor grade								
I	6	2 (33%)	4 (67%)	0.542	0	0	0	0.501
II	31	19 (61%)	12 (39%)		25	22 (85%)	4 (15%)	
III	84	38 (45%)	46 (55%)		43	30 (71%)	12 (29%)	
IV	114	50 (44%)	64 (56%)		48	35 (73%)	13 (27%)	
Not recorded	3	3 (100%)	0		1	1 (100%)	0	
Brain not primary <sup>a</sup>	6	3 (50%)	3 (50%)		2	2 (100%)	0	
Tumor site								
Right hemisphere	114	56 (49%)	58 (51%)	0.777	55	38 (68%)	18 (35%)	0.176
Left hemisphere	106	49 (46%)	57 (54%)		52	43 (83%)	9 (17%)	
Other <sup>b</sup>	24	10 (42%)	14 (58%)		12	9 (82%)	2 (18%)	
Past/current medical illness <sup>c</sup>								
Yes	53	29 (55%)	24 (45%)	0.211	43	34 (79%)	9 (21%)	0.511
No	191	86 (45%)	105 (55%)		76	56 (74%)	20 (26%)	
Recurrent disease <sup>d</sup>								
Yes	55	23 (42%)	32 (58%)	0.443	34	27 (79%)	7 (21%)	0.641
No	189	92 (49%)	97 (51%)		85	63 (74%)	22 (26%)	
Ethnicity								
White	220	110 (48%)	120 (52%)	0.151	115	86 (75%)	29 (25%)	0.571
Nonwhite	14	5 (36%)	9 (64%)		4	4 (100%)	0	
Previous psychiatric illness								
No	239	111 (46%)	128 (54%)	0.191	105	79 (75%)	26 (25%)	0.257
Yes	5	4 (80%)	1 (20%)		14	11 (79%)	3 (21%)	

Abbreviations: GAD, generalized-anxiety-only group; DEP, depression-only group; GAD & DEP, generalized anxiety and depression group; NEITHER, did not meet criteria for generalized anxiety or depression.

<sup>a</sup>Brain not primary indicates that brain cancer was not the primary diagnosis or that brain tumor was the result of metastasis.

<sup>b</sup>Other included diagnoses such as bilateral tumor location.

<sup>c</sup>Past/current medical illness included previous cardiac events, hypertension, diabetes mellitus, hyperlipidemia, hypercholesterolemia, significant renal disease requiring dialysis, history of psychiatric illness, and/or history of other cancers.

<sup>d</sup>Recurrent disease indicates tumor growth >25% on MRI.



education also may lead to greater objective knowledge and understanding of prognosis and may be associated with having the financial resources to support treatment. Although level of education often correlates with socioeconomic level, this study did not directly assess income and/or occupational status. Therefore, this study is limited in its ability to determine whether the higher prevalence of anxiety and depression symptoms among individuals without a college education suggests that socioeconomic concerns, such as increased financial stressors, restrictions on disability and health insurance, and difficulties in navigating a complex medical system, may result in greater psychological distress.

This does not, however, explain the reverse findings in reference to education level among those with depression. Individuals with at least some college education or higher actually showed a *greater* tendency toward depression. This suggests that the complex interplay between anxiety and depression—psychologically, socially, or physiologically—affected the DEP and GAD groups uniquely and requires further exploration and replication as part of a longitudinal study.

### *Tumor Grade*

This study showed a significant relationship between tumor grade and psychological symptoms, with individuals with lower tumor grades exhibiting a higher risk of neuropsychiatric illness. In multivariate analyses, this trend was statistically significant for the presence of anxiety (OR = 0.361; 95% CI, 0.203–0.641). However, this study did not record the effect of neurocognitive impairment, presumably due to the neoplasm and treatment, on awareness of disease state or concept of disease-related mortality, which are factors that may have had a significant impact on expression of neuropsychiatric symptoms. Future studies should use multi-informant reports (e.g., family members, caregivers) together with clinician-based assessment to determine the role of such impairment in these findings.

### *Past/Current Medical Illness*

Although the findings were not statistically significant, there was a trend for patients with past/current medical illness to be more likely to be depressed than those without. Twenty-six percent of individuals in this study had a chronic disease or previous diagnosis of psychiatric illness; of these, 66% reported symptoms of neuropsychiatric illness, or 17% of the entire study population. Published studies have shown a correlation between certain demographic variables and individuals with chronic disease who develop depression. Peyrot and Rubin<sup>22</sup> found gender, level of education, and marital status to be risk factors for the development of depression in patients with diabetes and found that overall levels of psychological disturbance were higher in this population than in study populations without significant chronic disease. This suggests that the subset of patients with chronic disease or a previous diagnosis of psychiatric illness in the present study may have had a predisposition for psychiatric

illness unrelated to their tumor that was exacerbated by the diagnosis of an intracranial neoplasm. Our results support Peyrot and Rubin's observation that a subset of brain tumor patients may have a predisposition for psychiatric illness associated with the presence of comorbid medical illness. Our findings may simply reflect an increased concern or sadness regarding life expectancy that a tumor diagnosis and/or chronic disease can carry or, alternatively, a physiologic relationship between other chronic diseases, brain tumor pathophysiology, and/or cancer treatment that influences the development of anxiety and depressive symptoms. Both are hypotheses to be tested in future studies.

### *Differences in Use of Psychiatric Medication for Treatment*

A sizable proportion of all the patients studied (56%) had generalized anxiety disorder or depression; however, only 44% of these patients received any type of medication for anxiety or depression. This may reflect (1) failure to accurately diagnose and treat depression or generalized anxiety disorder, (2) hesitance among physicians regarding diagnosing neuropsychiatric illness among brain tumor patients, or (3) inadequate assessment of brain tumor patients on follow-up visits. It is also possible that the seemingly low prevalence of psychiatric medication use may be related to our limited knowledge of the number of patients referred for psychotherapy, the number of patients whose symptoms were of short duration and self-limited, and inaccuracies related to patient self-report in use of psychiatric medications.

Use of pharmacologic treatment varied across the different categories of neuropsychiatric illness. Patients with symptoms of both generalized anxiety disorder and depression showed the highest percentage use of pharmacotherapy at 55%, followed by anxiety only at 31% and depression only at 26%. This indicates either that physicians are better able to elicit and act on symptoms in patients with both diagnoses or that these patients are more likely to communicate their mental and emotional concerns when confronted with both anxiety and depression. In general, these findings are consistent with a call for improvements in the quality of treatment for serious mental illness in all health care sectors.<sup>23</sup> Among those individuals with anxiety or depression, the finding that just 44% reported being on medication for neuropsychiatric symptoms suggests that patients may receive insufficient treatment and management of their symptoms, further elucidating the importance of research into the appropriate psychiatric and psychological interventions needed for patients with brain tumors.

### *Sources of Error*

A major strength of this study is its ability to analyze a very large study population of diverse patients with primary brain tumors during a 2-year period. The most important weakness is that the data were obtained using an abbreviated measure based on diagnostic criteria for psychiatric diagnoses; this process only approximates

comprehensive clinical and objective assessment of neuropsychiatric symptoms and lacks the validity offered by a more comprehensive multi-informant approach. Self-reported symptomatology is a crude criterion for “caseness,” which may have low positive-predictive power for psychiatric diagnosis. Symptom-based rates generally are higher than those obtained by clinical diagnosis.<sup>22</sup> In addition, patients with a history of depression or other previous psychiatric illnesses were not excluded, although the effect of this variable was assessed. Future studies may benefit from oversampling patients with previous psychiatric illness to better understand the impact of this variable on development of neuropsychiatric symptoms secondary to diagnosis and treatment of a primary brain tumor.

### Practice Implications

Symptoms of depression and/or anxiety may not be revealed in the clinical setting through simple physician–patient interaction. Implementation of easily administered assessment tools may allow medical caretakers to readily address neuropsychiatric illnesses that can significantly affect therapy, compliance, and overall quality of life. Pelletier et al.<sup>12</sup> found that the presence of depressive symptoms was the single most important independent predictor of quality of life, and Litofsky et al.,<sup>6</sup> in a large sample of patients with high-grade glioma, found that survival was shorter and medical complications were higher for depressed patients than for nondepressed patients. Therefore, the care of brain tumor patients and other patients with potentially terminal illnesses requires a comprehensive approach that provides a method for

assessing and evaluating patients’ psychological, behavioral, and social concerns. This knowledge allows the patient care team to better address a patient’s emotional concerns or fears and any potential barriers to treatment that could directly affect patient quality of life.

The results of this study are being used to develop follow-up studies aimed at treating symptoms of anxiety and depression found in this patient population in an effort to improve the level of functioning and quality of life. Such studies will involve use of psychotropic drugs to treat such syndromes as depression, anxiety, cognitive impairment, behavioral disturbance, or other neuropsychiatric symptoms in patients with brain tumors. Other future studies will involve a psychoeducational and/or psychotherapeutic intervention to better address clinical neuropsychiatric symptoms and improve patients’ coping skills.

Additionally, the present study reveals the importance of studying the severity and duration of anxiety and depression symptoms in a longitudinal design. The high rates of anxiety and depression noted in the present study, which appeared largely untreated, at least by medication, highlight the importance of longitudinal assessment and follow-up with patients with brain tumors regarding neuropsychiatric illness, perhaps more frequently than the usual oncology clinical follow-up.

### Acknowledgments

We thank Henry S. Friedman and Sandra Tourt-Uhlig for their contributions to this project.

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