Pharmacologic Treatment of Anxiety Disorders in 1989 Versus 1996: Results From the Harvard/Brown Anxiety Disorders Research Program

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Objective: This article reports on the pharmacologic treatment of patients diagnosed with generalized anxiety disorder (GAD) enrolled in a naturalistic long-term study of anxiety disorders, with enrollment in 1989 through 1991 and follow-up in 1996.

Method: 711 patients were enrolled in the study during 1989–1991. At intake, 167 patients met DSM-III-R criteria for GAD; at 1996 follow-up, 103 patients met these criteria. The patients were divided into 3 groups by diagnosis: GAD alone (N = 18 at intake, N = 11 at follow-up), GAD comorbid with another anxiety disorder (N = 84 at intake, N = 52 at follow-up), and GAD comorbid with Research Diagnostic Criteria–defined major depressive disorder, with or without another anxiety disorder (N = 65 at intake, N = 40 at follow-up). The groups were evaluated at intake and follow-up on whether they received medication and the types of medication they received.

Results: Nearly one third of patients in the 1989–1991 sample were not receiving any medication for treatment of their anxiety disorder; in 1996, 27% of patients still were receiving no medication. There was a decrease in benzodiazepine treatment and an increase in antidepressant treatment in 1996 for GAD patients who did not have comorbid depression or another anxiety disorder.

Conclusion: The finding of one quarter to one third of patients with GAD receiving no medication is consistent with previous observations of undertreatment of depression. The findings on medication type suggest a shift in the type of medications being prescribed for treatment of GAD from exclusive benzodiazepine treatment to the combination of benzodiazepine and antidepressant treatment.

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Benzodiazepines have been the primary pharmacologic treatment for anxiety for more than 30 years.[1–3] Despite the often chronic and recurrent nature of anxiety disorders, long-term benzodiazepine treatment of anxiety as a symptom remains controversial, probably due to the possible development of side effects and physiologic dependence.[4] The long-term benzodiazepine treatment of anxiety disorders such as panic, phobias, and obsessive-compulsive disorder (OCD) appears less controversial. Benzodiazepines have well-demonstrated efficacy for panic disorder and various phobic states including social phobia and agoraphobia.[5,6] With the advent of selective serotonin reuptake inhibitors (SSRIs) and other relatively nontoxic antidepressants that have demonstrated therapeutic efficacy for these anxiety disorders, prescribing patterns have begun to shift so that antidepressant treatment has now replaced benzodiazepine treatment for the long-term management of these disorders.[7–13]

Generalized anxiety disorder (GAD), the term applied to the typical experience of persistent anxiety symptoms (e.g., tension, worry, apprehension, autonomic hyperactivity, jitteriness), is often associated with other DSM-IV

anxiety-spectrum disorders such as panic disorder and phobias of various kinds. Recent data from the Harvard/Brown anxiety disorders program found that, of patients with a lifetime diagnosis of GAD, 48% had an additional diagnosis of panic with agoraphobia, 33% had social phobia, and 21% had simple phobia.[14] Surveys have suggested that "pure" GAD is actually relatively rare, occurring in only 1.63% of surveyed patients.[1,15]

In addition to the frequent comorbidity of GAD and other anxiety disorders, patients with GAD also frequently meet diagnostic criteria for major depressive disorder (MDD).[16] In one study,[15] 46% of patients with GAD had a history of comorbid major depression. In another sample, 29% of outpatients with a principal diagnosis of GAD suffered from concurrent major depression or dysthymic disorder.[17] A third sample of outpatients reported that 34% of patients with GAD had a history of major depression but did not have concurrent major depression.[18]

This article reports on the pharmacologic treatment of 3 groups of patients diagnosed with GAD enrolled in a naturalistic long-term study of anxiety disorders, the Harvard/Brown Anxiety Disorders Research Program. The first group of patients had GAD alone and were selected to represent the typical anxious patient without panic or phobias. The second group had GAD mixed with another anxiety disorder such as panic disorder or agoraphobia and represents the typical comorbid anxiety patient. In the third group, all patients also had MDD in addition to GAD alone or in combination with another anxiety disorder.

METHOD AND DATA ANALYSIS

Enrollment of patients from 11 sites began in 1989 and lasted through 1991. Patients were at least 18 years of age at the time of the study, participated voluntarily, and signed a written consent form. Exclusion criteria included organic brain syndrome, a history of schizophrenia, or current psychosis.

Subject recruitment, diagnosis, and statistical methodology have been described elsewhere.[14,15,19] In brief, patients were recruited through private patient referrals, individual therapists, and advertisement, as well as through confidential chart review. An initial comprehensive evaluation assessed lifetime history of anxiety disorders by using selected items from a number of rating scales including the Structured Clinical Interview for DSM-III-R Patient Version[20] and the Schedule for Affective Disorders and Schizophrenia-Lifetime Version.[21] Anxiety disorders were diagnosed according to DSM-III-R, and affective disorders were diagnosed by Research Diagnostic Criteria.[22] Interviews were conducted by experienced clinical interviewers who were rigorously trained and closely supervised. Follow-up interviews were conducted at 6-month intervals for the first 2 years and then annually thereafter. Data on types of medication used were obtained for the week after initial enrollment and at follow-up 5 to 7 years later.

Table 1. Diagnoses at Intake and at Follow-Up[a]

	1989–1991 Intake (N = 167)		1996 Follow-Up (N = 103)	
Diagnosis	N	%	N	%
GAD alone	18	10.8	11	10.7
GAD with another anxiety disorder	84	50.3	52	50.5
GAD with MDD, with or without another anxiety disorder	65	38.9	40	38.8

[a]Abbreviations: GAD = generalized anxiety disorder, MDD = major depressive disorder.

Sample

A total of 711 patients enrolled in the study between 1989 and 1991; 167 met strict diagnostic criteria for GAD. Of these 167 patients with GAD, 102 (61%) had either GAD alone or with another anxiety disorder but without MDD (Table 1). Of these 102, 18 patients had GAD alone, and 84, the largest group, had GAD plus additional anxiety diagnoses such as panic disorder, simple or social phobia, or OCD. An additional 65 patients had MDD as well as GAD, with or without another anxiety disorder. At the 1996 follow-up, 103 patients had active GAD. Eleven patients had GAD alone, and 52 had GAD together with another anxiety disorder, for a total of 63 patients with GAD and an additional anxiety disorder, but no MDD; 40 patients had MDD as well as GAD, with or without an additional anxiety disorder. Of these 103 patients in the 1996 cohort, 48 were patients from the original 1989/1991 GAD sample who continued to meet criteria for GAD at 1996 follow-up. These 48 patients either did not recover from the initial GAD episode or recovered and were relapsing at the time of the 1996 follow-up. In 1996, 55 patients met criteria for GAD that was not present at enrollment. There were no differences in diagnosis or demographic characteristics between the 48 original enrollees and these 55 follow-up patients, so they were included together in the 1996 follow-up cohort.

RESULTS

Medication Versus No Medication

Medication received during the first week after enrollment and at the 1996 follow-up is shown in Table 2. There were only 3 GAD-alone patients in the 1989/1991 cohort and 2 GAD-alone patients in the 1996 cohort who received no medication, so these GAD-alone patients were combined with the patients who had GAD plus another anxiety disorder. In the 1989/1991 cohort, one third of the 102 patients who had GAD alone or with another anxiety disorder but without depression (N = 34) received no medication, and 26% of patients with an anxiety disorder

Table 2. Medication Versus No Medication at Intake and Follow-Up[a]

	Received Medication		No Medication	
Diagnosis	N	%	N	%
GAD with or without another anxiety disorder				
1989/1991 (N = 102)	68	67	34	33
1996 (N = 63)	46	73	17	27
GAD with MDD with or without another anxiety disorder				
1989/1991 (N = 65)	48	74	17	26
1996 (N = 40)	37	92	3	8

[a]Abbreviations: GAD = generalized anxiety disorder, MDD = major depressive disorder.

Table 3. Types of Medication Prescribed at Intake and at Follow-Up: Patients Diagnosed With Generalized Anxiety Disorder Only

	1989–1991 Intake (N = 18)		1996 Follow-Up (N = 11)	
Medication	N	%	N	%
No medication	3	17	2	18
Benzodiazepine alone	11	61	4	36
Antidepressant alone	4	22	1	9
Benzodiazepine + antidepressant	0		4	36

plus MDD (N = 17) also received no medication. In 1996, the percentage of GAD patients with additional anxiety disorders but without MDD who received no medication decreased slightly to 27% (N = 17). However, the proportion of all patients in 1996 with a diagnosis of both GAD and MDD who received no medication dropped dramatically from 26% (N = 17) in 1989/1991 to 8% (N = 3) in 1996.

The 48 patients who were diagnosed with GAD at both intake and 1996 follow-up allowed for a comparison of medication treatment over time in the same patient. Approximately one third (N = 15; 31%) of these patients with anxiety disorders received no medication at 1989/1991 intake, but this proportion declined to 15% (N = 7) in 1996. This increase in the proportion of patients who were receiving medication in 1996 compared with 1989/1991 for their anxiety disorder was significant (McNemar Cochran-Mantel-Haenszel test = 5.33, df = 1, p = .02).

Types of Medication Prescribed

Next, the types of medication received by GAD patients with or without another anxiety disorder were determined, and, again, those who also had MDD were separately examined. Types of medication prescribed for patients with comorbid GAD and anxiety disorders or comorbid GAD and MDD did not differ significantly between 1989/1991 and 1996. Types of medications prescribed for patients with GAD alone, however, changed during the years of treatment (Table 3). As might be expected in 1989/1991, the majority (N = 11; 61%) of patients who had GAD alone were treated with only a benzodiazepine; virtually all benzodiazepine recipients took alprazolam or clonazepam. This percentage declined to 36% (N = 4) in 1996. Use of antidepressants by GAD-alone patients increased from 1989/1991 to 1996. Antidepressants were prescribed for 22% of patients (N = 4) with GAD alone in the 1989/1991 group, and no patients who had GAD alone received a benzodiazepine plus an antidepressant. In 1996, 45% (N = 5) of GAD-alone patients received an antidepressant, whereas only 36% (N = 4) were prescribed a benzodiazepine without an antidepressant.

DISCUSSION

Although the number of patients is small, this study indicates that nearly one third of patients in 1989/1991 and 27% in 1996 who had an anxiety disorder without MDD were receiving no medication at the time of enrollment in this study. The finding that one quarter to one third of the sample of nondepressed patients with an anxiety disorder who sought treatment for anxiety were unmedicated as recently as 1996 is consistent with survey data suggesting that the percentage of Americans who were receiving long-term benzodiazepine treatment in the mid-1990s (1.65%) was far less than the approximately 25% lifetime prevalence rate of serious anxiety disorders in the United States.[23] These data are also consistent with the Medical Outcomes Study,[24] which reported 59% of depressed outpatients using neither an antidepressant nor a minor tranquilizer during a 6-month period in 1986. Undermedication has similarly been observed for depression: inadequate treatment defined as either no treatment or inadequate doses ranges as high as 67%,[25–28] leading a consensus conference panel to conclude that "there is overwhelming evidence that individuals with depression are being seriously undertreated."[29(p333)]

Our findings further suggest that medications were used more frequently for treatment of patients who met criteria for an anxiety disorder with and without comorbid MDD in 1996 compared with 1989/1991. Among GAD patients without comorbid anxiety or MDD, there was also a decline in treatment with benzodiazepines alone and an increased use of antidepressants in combination with benzodiazepines.

CONCLUSIONS

The conclusions of this study are limited by the small number of patients. Nevertheless, the data suggest that, as recently as 1996, significant numbers of patients with anxiety disorders were receiving no medication as part of their treatment program. Patients with anxiety who are also depressed, but who seek treatment for anxiety, are

more likely to receive medication, and patients with GAD are increasingly likely to receive antidepressants in conjunction with a benzodiazepine.

Recent reports suggest that SSRIs and other antidepressants are becoming the drugs of first choice for the treatment of panic and phobic disorders as well as OCD[7,30]; paroxetine has been approved for social anxiety disorder, and venlafaxine extended release has been approved for the treatment of GAD. Further studies will be necessary to determine whether benzodiazepines or antidepressants will be the preferred treatment for GAD.

Drug names: alprazolam (Xanax and others), clonazepam (Klonopin and others), paroxetine (Paxil), venlafaxine (Effexor).

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