Double-Blind, Placebo-Controlled Trial of Two Doses of Abecarnil for Geriatric Anxiety

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We studied the tolerability and efficacy of abecarnil, a new partial benzodiazepine agonist, for short-term relief of anxiety in geriatric patients. After a 1-week placebo lead-in, 182 outpatients (mean ± SD age = 68.3 ± 5.8; range, 59–85 years) were randomly assigned in a double-blind, parallel-group design to high-dosage abecarnil (7.5–17.5 mg daily), low-dosage abecarnil (3.0–7.0 mg daily), or placebo for 6 weeks of acute treatment followed by abrupt discontinuation and a 2-week follow-up. During the acute treatment period, the discontinuation rate from adverse events was greater for the group treated with high-dosage abecarnil (44%) than for the groups treated with low-dosage abecarnil (14%) or placebo (12%). The most frequently reported side effects associated with abecarnil were drowsiness and insomnia. For the acute treatment period, low-dosage abecarnil was superior to placebo in reducing anxiety at Weeks 2–4 and 6, and was statistically significantly superior to high-dosage abecarnil at Weeks 4–6. More than half of the placebo group showed at least moderate global improvement at Weeks 3 and 6. One week after abrupt discontinuation of abecarnil, the placebo-treated group had less anxiety than did both groups treated with high-dosage and low-dosage abecarnil. The most commonly reported symptoms of withdrawal were headache and insomnia. These data indicate that abecarnil, at dosages ranging from 3.0 to 7.0 mg daily, is better tolerated and more efficacious for the short-term treatment of anxiety in geriatric patients than are higher dosages of 7.5 to 17.5 mg daily. Abrupt discontinuation of abecarnil at either dosage range causes definite rebound symptoms within the first week after withdrawal. These data also suggest that treatment with placebo offers at least moderate relief of anxiety in many elderly patients.

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Epidemiologic surveys confirm the general clinical impression that symptoms of anxiety disorders are common among the elderly. Approximately 10% of elderly persons suffer from phobic disorders, making these the second most common psychiatric disorder in persons 65 or older, after cognitive impairment.[1] The prevalence of generalized anxiety disorder varies from 0.7% to 7.1%, and most cases begin before age 65.[1] The National Survey of Psychotherapeutic Drug Use[2] found total anxiety to be slightly higher in people 65 years or older (10.2%) than in all age groups combined (9.9%). Total anxiety rates for samples of elderly patients range from 0.7%[3] to 18.6%,[4] largely varying because of methodologic differences among studies.[5]

Despite the prevalence of anxiety in old age, several factors complicate both its recognition and its treatment. Physical symptoms of anxiety may be mistakenly interpreted as resulting from the various chronic medical illnesses that are so common in old age. The medications used to treat these illnesses generally result in polypharmacy and drug-drug interactions that may lead to increased adverse reactions.[6] Age-related physiologic changes[7] also contribute to wide dosage ranges and sensitivity to side effects.

Pharmacotherapy is probably the most common treatment approach to anxiety in geriatric patients,[8] and the benzodiazepines traditionally have been the first choice among anxiolytics.[9] For older patients, agents that have

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short half-lives are recommended because they do not cause the cumulative toxicity that often occurs with agents that have long half-lives. Although benzodiazepines are safe and effective for anxiety in geriatric patients, the age-related physiologic changes, multiple medical illnesses, and polypharmacy make elderly persons sensitive to the adverse effects associated with benzodiazepines, such as confusion, ataxia, and sedation. Studies of newer anxiolytic drugs that have potentially more favorable side-effect profiles, therefore, are especially relevant for geriatric age groups.

Abecarnil is a relatively new chemical entity that has demonstrated safety and efficacy in young adults who have generalized anxiety disorder. The compound is a beta carboline that has partial agonistic properties at certain subtypes of benzodiazepine receptors, where it shows high affinity. Although previous studies in young adults indicate abecarnil's tolerability and efficacy in those patients,[10] investigations focusing on elderly patient populations are lacking. To address this issue, we compared the tolerability and efficacy of two dosage ranges of abecarnil and placebo for the short-term relief of anxiety in geriatric patients.

METHOD

Patients

Subjects were outpatients between 60 and 85 years old who had suffered for at least 1 month from symptoms of anxiety that were serious enough for them to seek medical treatment with pharmacotherapy. To participate in the study, subjects were required to meet several inclusion criteria at the end of the screening period, including six or more symptoms of anxiety and a score on the Covi Anxiety Rating Scale that was greater than their score on the Raskin Depression Rating Scale. Subjects also were required to have a total score on the Hamilton Rating Scale for Anxiety (HAM-A)[11] of 18 or more and scores of 2 or more on the anxious mood and tension items at both the beginning and end of the screening period.

A score of 24 or less on the Mini-Mental State Examination[12] was used to exclude volunteers who had cognitive impairment. A score of 19 or more on the 21-item Hamilton Rating Scale for Depression (HAM-D)[13] and a score of 2 or more on the depressed mood item at the beginning and end of the screening period were used to exclude depressed patients. Other reasons for exclusion were a significant physical illness within 1 month of the study's initiation; any medical condition that could alter mental status; a current diagnosis or history of organic mental disorder, alcohol or other drug abuse, a psychotic disorder, or bipolar disorder; or a current diagnosis of major depressive disorder. Patients who had had a diagnosis within 6 months of the study's initiation of panic disorder, obsessive-compulsive disorder, social phobia, or other psychiatric conditions, or any other medical conditions associated with anxiety-like symptoms that could interfere with the study, were also excluded. In addition, patients who required concomitant medication that had anxiolytic properties and those who were undergoing concurrent psychotherapy were excluded from participation.

Study Design

The study used a double-blind, placebo-controlled, parallel-group design and was conducted at 11 participating clinical sites. After a 1-week screening period during which placebo was administered, subjects were randomly assigned to treatment with high-dosage abecarnil (7.5–17.5 mg daily), low-dosage abecarnil (3.0–7.0 mg daily), or placebo for 6 weeks of acute treatment (study Weeks 1 through 6). The dosage of medication could be increased or decreased during Weeks 1 and 2, but not by more than 2.5 mg/day for the high-dosage group or by more than 0.5 mg/day for the low-dosage group. Thereafter, the dosages were kept fixed, except that one additional dosage reduction was allowed. After Week 6, medication was abruptly discontinued, and patients were followed for an additional 2 weeks while they were given placebo (study Weeks 7 and 8).

The HAM-A and the Clinical Global Impression (CGI) scales were administered weekly to assess efficacy. Tolerability was assessed through weekly adverse-event reporting. The Physician Withdrawal Checklist[14] was used to determine symptoms that emerged after the abrupt withdrawal of treatment. Interrater-reliability training was provided to investigators from all 11 participating sites prior to their beginning the study.

Statistical Analyses

Two-way analysis of variance/covariance was used to assess between-treatment differences for continuous and interval-scaled variables, and chi-square or Cochran-Mantel-Haenszel tests were used for nominal variables. For this report, the primary measures of efficacy were the HAM-A total score and the CGI Global Improvement score. Efficacy analyses were performed on the intent-to-treat data set, which included evaluations from all patients who had been randomly assigned to treatment and who were given at least one dose of the assigned treatment and had a subsequent treatment rating.

Both last-observation-carried-forward (LOCF) and observed-cases (OC) analyses were performed for the intent-to-treat pool. A two-way fixed-effects analysis of variance with effects for treatment, center, and treatment-by-center interaction was used to analyze the efficacy data. The dependent variables were changes from baseline, and baseline scores were included as covariates. Pairwise comparisons between treatment groups were performed with t tests. Supplemental nonparametric analyses using rank-transform methods were applied to assess the

Table 1. Frequently Reported Adverse Events During Acute Treatment Period (%)

	Abecarnil 7.5–17.5 mg (N = 61)		Abecarnil 3.0–7.0 mg (N = 64)		Placebo (N = 57)	
Event	Total	Severe	Total	Severe	Total	Severe
Any event	97[a]	39	84	23	70	16
Drowsiness	61[a]	11	31[a]	3	12	0
Dizziness	28	5	20	2	19	2
Nausea	25[a]	2	11	3	9	0
Insomnia	25[a]	11	22[a]	13	7	4
Fatigue	20	2	11	0	12	0
Headache	20	2	25	5	19	2

[a]p < .05, drug vs placebo.

robustness of the parametric models. All comparisons were performed using two-tailed tests at the .05 level of significance.

RESULTS

Patient Population

In total, 184 patients were randomly assigned to treatment (high-dosage abecarnil, N = 61; low-dosage abecarnil, N = 65; and placebo, N = 58). Of the 184, 182 (high-dosage abecarnil, N = 61; low-dosage abecarnil, N = 64; and placebo, N = 57) were given at least one dose of study drug and had at least one subsequent safety evaluation. The mean ± SD age of the subjects was 68.3 ± 5.8 years (range, 59–85 years); 48% were women, and 93% were Caucasian. The treatment groups did not differ significantly in age, sex, or race. The mean duration of their symptoms of anxiety was 70.5 months. The mean ± SD scores for anxiety and depression levels at baseline were: HAM-A total = 22.7 ± 4.7 and HAM-D total = 11.9 ± 3.3. No significant differences were found between treatment groups in these measures at baseline.

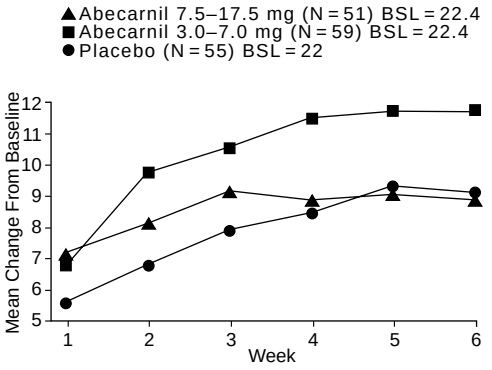
Acute Treatment Period

Subjects in the high-dosage abecarnil group were less likely to complete the study than those in the low-dosage group (51% vs. 78%, p = .014) or the placebo group (51% vs. 74%, p < .001). Moreover, the high-dosage group had a significantly (p < .001) higher discontinuation rate because of adverse events (44%) than did either the low-dosage group (14%) or the placebo group (12%). A relatively high rate of adverse events during the acute treatment period was observed in all treatment groups; 97% of the high-dosage abecarnil group experienced an adverse event of some sort, and drowsiness, nausea, and insomnia were more likely to occur in that group than in the placebo group (Table 1). In the low-dosage abecarnil group, only drowsiness and insomnia were reported more frequently than in the placebo group.

The LOCF analysis using the HAM-A total score as the primary efficacy measure indicated that low-dosage abecarnil was significantly superior to placebo in reducing anxiety at Weeks 2 through 4 and Week 6 and significantly superior to high-dosage abecarnil at Weeks 4 through 6 (Figure 1). The high-dosage abecarnil group did not differ significantly from the placebo group in the HAM-A total score at any time during the acute treatment period (Figure 1). For the OC analysis using the HAM-A total score as the primary efficacy measure (data not shown), low-dosage abecarnil was statistically significantly superior to placebo at Weeks 2 through 4 and superior to high-dosage abecarnil at Week 6 of the acute treatment period. The OC analysis using the HAM-A total score also indicated no significant differences between the high-dosage abecarnil and placebo groups.

Results using the CGI global improvement score as the primary efficacy measure indicated a similar response pattern (Table 2). For the LOCF analysis, low-dosage abecarnil was statistically significantly superior to placebo at Week 2 and Weeks 4 through 6. For the OC analysis, low-dosage abecarnil was superior to placebo at Weeks 2, 4, and 5. For both the LOCF and OC analyses, high-dosage abecarnil was no more efficacious than placebo at any time during the 6 weeks of acute treatment. The response patterns were similar if we compared the percentages of subjects who experienced at least moderate improvement using the CGI global improvement measure (Table 3). Also notable is the relatively high placebo-response rates, which increased over the 6-week treatment period to as high as 50.9% on the LOCF analysis and 61.5% on the OC analysis (Table 3).

Figure 1. Mean Change From Baseline for the Hamilton Rating Scale for Anxiety Total Score During the 6-Week Acute Treatment Period (LOCF Analysis)†



ABHI vs PLAC	.162	.192	.303	.726	.872	.895
ABLO vs PLAC	.228	.002**	.018*	.012*	.061(*)	.046*
ABHI vs ABLO	.787	.078(*)	.207	.036*	.047*	.038*

†A positive change from baseline indicates improvement.
Abbreviations: LOCF = last observation carried forward; ANOVA = analysis of variance; ANCOVA = analysis of covariance; ABHI = high-dosage abecarnil (7.5–17.5 mg/d); ABLO = low-dosage abecarnil (3.0–7.0 mg/d); PLAC = placebo.
(*) = p < .10; * = p < .05; ** = p < .01; *** = p < .001: based on two-way ANCOVA/ANOVA.
Figures below graph indicate p values for group comparisons.

Table 2. Mean Change From Baseline in Clinical Global Improvement Score During the 6-Week Acute Treatment Period (LOCF and OC Analyses)[a]

	Abecarnil High Dosage[b]		Abecarnil Low Dosage[b]		Placebo		Abecarnil High Dosage[b] vs Placebo (p value)		Abecarnil Low Dosage[b] vs Placebo (p value)	
Study Week	LOCF	OC	LOCF	OC	LOCF	OC	LOCF	OC	LOCF	OC
1	6.6	6.6	6.7	6.7	6.3	6.4	.46	.50	.15	.17
2	6.7	6.7	7.4	7.4	6.6	6.5	.71	.54	.007	.004
3	7.2	7.5	7.4	7.5	7.0	7.1	.43	.24	.15	.27
4	6.9	7.1	7.8	8.0	6.8	7.0	.61	.75	.003	.006
5	6.9	7.7	7.9	8.2	7.0	7.4	.77	.40	.014	.02
6	7.0	7.8	7.9	8.3	7.0	7.6	.92	.55	.014	.054

[a]Results from analysis of variance/covariance; higher mean indicates greater improvement; LOCF = last observation carried forward; OC = observed cases.
[b]Abecarnil high dosage = 7.5–17.5 mg/d; abecarnil low dosage = 3.0–7.0 mg/d.

Table 3. Percentage of Subjects Showing at Least Moderate Improvement on the Clinical Global Impression Global Improvement Score During the 6-Week Acute Treatment Period (LOCF and OC Analysis)[a]

	Abecarnil High Dosage[b]		Abecarnil Low Dosage[b]		Placebo		Abecarnil High Dosage[b] vs Placebo (p value)		Abecarnil Low Dosage[b] vs Placebo (p value)	
Study Week	LOCF	OC	LOCF	OC	LOCF	OC	LOCF	OC	LOCF	OC
1	33.3	33.3	30.5	30.5	25.5	25.9	.32	.37	.52	.59
2	39.2	40.4	57.6	58.6	36.4	38.0	.76	.74	.008	.008
3	56.9	63.4	55.9	56.4	50.9	55.3	.53	.47	.51	.78
4	54.9	61.5	66.1	71.2	45.5	50.0	.34	.28	.025	.034
5	51.0	61.3	64.4	71.7	49.1	56.4	.89	.65	.11	.15
6	51.0	64.5	67.8	79.1	50.9	61.5	.98	.78	.07	.07

[a]Cochran-Mantel-Haenszel statistics blocked for center; LOCF = last observation carried forward; OC = observed cases.
[b]Abecarnil high dosage = 7.5–17.5 mg/d; abecarnil low dosage = 3.0–7.0 mg/d.

Table 4. Mean Change From Baseline for the Hamilton Rating Scale for Anxiety Total Score During the 2-Week Follow-Up Period After Abrupt Discontinuation (OC Analysis)[a]

Study Week	Statistic	Abecarnil High Dosage[b]	Abecarnil Low Dosage[b]	Placebo	Abecarnil High Dosage[b] vs Placebo (p value)[c]	Abecarnil Low Dosage[b] vs Placebo (p value)[c]
1	N	42	52	43		
	Baseline mean	22.5	22.2	22.4	< .001	< .001
	Mean change	3.4	5.0	10.5		
2	N	30	38	28		
	Baseline mean	22.0	22.4	22.1	.15	.38
	Mean change (adj)[d]	9.0	10.1	11.6		

[a]Results from analysis of variance/covariance; positive change indicates improvement; OC = observed cases.
[b]Abecarnil high dosage = 7.5–17.5 mg/d; abecarnil low dosage = 3.0–7.0 mg/d.
[c]p Values are related to mean change.
[d](Adj) indicates that means were adjusted for baseline values.

Two-Week Follow-Up Period After Abrupt Discontinuation

According to the HAM-A total score, the placebo group had significantly less anxiety than the high-dosage abecarnil group at Week 1 during the follow-up period (Table 4). The placebo group also had significantly less anxiety than the low-dosage abecarnil group at Week 1.

For several symptoms on the Physician Withdrawal Checklist, incidence rates for new or worsened symptoms during the follow-up period were significantly higher for the high-dosage abecarnil group than for the placebo group. These rebound symptoms were less frequent in the low-dosage abecarnil group (Table 5).

DISCUSSION

These data indicate that abecarnil, at dosages ranging from 3.0 to 7.0 mg daily, is safe and efficacious for treatment of anxiety in geriatric patients and is better tolerated and more efficacious than higher dosages of 7.5 to 17.5

Table 5. Incidence Rates (%) on the Physicians' Withdrawal Checklist for New or Worsened Symptoms During the Follow-Up Period After Abrupt Discontinuation

	Abecarnil 7.5–17.5 mg/d (N = 34)		Abecarnil 3.0–7.0 mg/d (N = 51)		Placebo (N = 43)	
Symptom	Total	Severe	Total	Severe	Total	Severe
Headache	50[a]	0	35	8	5	0
Insomnia	44[a]	21	41[a]	20	14	5
Agitation	41[a]	15	27	10	19	9
Anxiety	35[a]	18	20	12	9	5
Appetite loss	35[a]	6	27	2	12	5
Flu-like symptoms	35[a]	9	27	0	12	5
Difficulty concentrating	32[a]	15	16[a]	4	2	2
Tremor	24[a]	3	18[a]	2	2	0
Poor coordination	24[a]	6	14	0	5	0
Confusion	18[a]	0	6	0	2	2
Depersonalization	15[a]	0	0	0	0	0

[a]$p < .05$, drug vs placebo.

mg daily. Moreover, the patients' response emerged within the first weeks of treatment and was sustained throughout the 6-week treatment period. Placebo alone also resulted in at least moderate global improvement in symptoms of anxiety at Weeks 3 and 6 for more than 50% of patients. Abrupt discontinuation of abecarnil at either dosage range caused definite rebound symptoms within the first week after withdrawal. Taken together, our results suggest that abecarnil may be a useful alternative to benzodiazepines in many anxious elderly patients. Further studies using benzodiazepines that have short half-lives, buspirone, or both as comparator compounds would help clarify the potential role of this new partial benzodiazepine-receptor agonist.

Several methodologic issues deserve comment. We performed multiple statistical testing, which could lead to the conclusion that our findings are not statistically significant if adjusted for these multiple comparisons. Such adjustments, however, are generally considered overly conservative and increase the possibility of incorrectly accepting the null hypothesis. We did use the conservative approach of two-tailed tests. Moreover, similar response patterns were observed with several outcome variables, and the results held up with the more conservative LOCF analyses.

Patients in this study had multiple symptoms of anxiety that had lasted an average of 70.5 months for the current episode. Not all patients in this study met criteria for generalized anxiety disorder; thus, these findings cannot be extrapolated to that condition. Possibly, abecarnil is most useful in patients who have milder symptoms of anxiety rather than in those who have a more severe anxiety disorder. Further studies would help to determine its efficacy in generalized anxiety disorder and would assess the role played in treatment response by previous exposure to benzodiazepines, age at onset, and medical comorbidity.

Mental conditions tend to present as heterogeneous syndromes in geriatric patients. For example, in major depression, previous studies indicated differences between subgroups of elderly depressed patients according to their age at the onset of their first depressive episode. Patients who had a late onset had a lower frequency of family history of depression but higher frequencies of cerebral atrophy, medical comorbidity, and deep white-matter hyperintensities on magnetic resonance imaging scans.[15] Similar forms of heterogeneity are likely with anxiety in geriatric patients. Studies focusing on homogeneous subgroups may clarify the specificity of response to abecarnil and other anxiolytic drugs.[16]

The abrupt discontinuation of medication caused a definite withdrawal syndrome that was most severe in the high-dosage treatment group. The low-dosage group experienced fewer symptoms of withdrawal. Studies that focus on tapering schedules necessary to avoid these symptoms of withdrawal would assist clinicians to eliminate these unpleasant effects. Moreover, comparisons with the withdrawal syndromes observed with the use of benzodiazepines would be useful in determining these drugs' relative tapering requirements.

Responses to placebo in this study were high and increased over the 6-week treatment period to 50.9% for the LOCF analysis and 61.5% for the OC analysis. Numerous factors can contribute to a placebo response, including a spontaneous remission, "conditioning" from prior treatment benefits, the duration of follow-up visits, the treatment setting, the duration and severity of the illness, the therapeutic alliance, and the expectations of the patient as well as the clinician.[17] High placebo-response rates may contribute such a high level of "background noise" that pharmacologic drug effects are no longer significant. Despite the large response to placebo and the moderate sample size in our study, we observed significant drug effects.

In summary, our results support the use of abecarnil at dosages ranging from 3.0 to 7.0 mg daily for the treatment of elderly patients who have multiple symptoms of anxiety. Further studies will determine the tapering schedule necessary to avoid the withdrawal syndrome observed after abrupt discontinuation of the drug. Additional studies also are needed to compare the efficacy and safety of this new compound with those of currently available anxiolytics such as benzodiazepines that have short half-lives and buspirone.

Drug names: buspirone (BuSpar)

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