Abecarnil for the Treatment of Generalized Anxiety Disorder: A Placebo-Controlled Comparison of Two Dosage Ranges of Abecarnil and Buspirone

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Background: The development of effective and well-tolerated anxiolytic agents is an area of critical clinical importance. Abecarnil, a beta carboline, is a partial benzodiazepine-receptor agonist that has demonstrated promise as an anxiolytic agent. In this study, we examine the efficacy, safety, and discontinuation-related effects of abecarnil, buspirone, and placebo in the acute and long-term treatment of patients who have generalized anxiety disorder. ***Method:*** This is a double-blind, placebo-controlled study of two dosages of abecarnil and buspirone. In total, 464 patients were randomized. After a placebo run-in week, patients entered a 6-week double-blind treatment period, followed by an optional 18-week maintenance period for treatment responders. After abrupt discontinuation of the acute or maintenance treatment, patients entered a 3-week placebo-substitution follow-up period. Treatment response was assessed with the Hamilton Rating Scale for Anxiety and the Clinical Global Impressions (CGI) Scale. ***Results:*** Compared with placebo, abecarnil showed significant anxiolytic activity early in the treatment period, particularly in the high-dosage group, though these differences did not maintain statistical significance at the end of the trial. Buspirone was associated with a slower onset of action and better symptom relief than placebo after 6 weeks of therapy. Withdrawal symptoms emerged in patients who abruptly discontinued abecarnil (particularly at the higher dosage) only in those receiving a longer duration of treatment. ***Conclusion:*** The results of this study need to be understood in the context of a high placebo-response rate, which hampers the ability to demonstrate significant drug-placebo differences. This study suggests that abecarnil may be an effective anxiolytic agent; further attention is warranted to assess its spectrum of clinical effectiveness.

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Although the benzodiazepines have long been the mainstay of treatment of generalized anxiety disorder (GAD), interest has been increasing in the use of other classes of agents for the treatment of affected patients. The search for non-benzodiazepine alternatives for the treatment of GAD has been spurred in part by concerns about physical dependence, abuse potential, and discontinuation-related withdrawal symptoms associated with benzodiazepine agents. Antidepressants were long considered effective for panic disorder, but on the basis of Klein's observation[1] that imipramine was less effective for non–panic-related anxiety, tricyclics were considered relatively ineffective for generalized anxiety. However, in 1986 Kahn et al.[2] demonstrated that imipramine was more effective than placebo and chlordiazepoxide in patients who had "anxiety neurosis," including those suffering from GAD; this anxiolytic effect was independent of its antidepressant effect.

Recently, Rickels and Schweizer[3] compared imipramine (mean dosage = 143 mg/day), trazodone (mean dosage = 255 mg/day), and diazepam (mean dosage = 26 mg/day) in a randomized, double-blind, controlled, 8-week trial for GAD. Diazepam-treated patients demonstrated the most improvement during the first 2 weeks of

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treatment, whereas imipramine-treated patients showed somewhat better anxiolytic efficacy, achieving statistical separation from diazepam by Weeks 6 to 8. Trazodone had comparable efficacy with that of diazepam. Approximately 73% of the imipramine-treated patients, compared with 69% of those given trazodone, 66% of those given diazepam, and 47% of those given placebo, demonstrated moderate-to-marked improvement by study completion. Although the patients treated with the antidepressants experienced higher rates of side effects, attrition rates were the same in all treatment groups. In addition to imipramine, other non-benzodiazepine agents, including the azapirone buspirone, have demonstrated efficacy comparable to that of the benzodiazepines (i.e., alprazolam, lorazepam, oxazepam, and clorazepate) in treating GAD.[4–7]

Abecarnil, a beta carboline, is a partial benzodiazepine-receptor agonist that has demonstrated promising results in the treatment of GAD.[8] Studies in animals using the benzodiazepine antagonist flumazenil suggested that abecarnil was associated with milder withdrawal symptoms than are associated with diazepam.[9] This article presents results from a double-blind, placebo-controlled study of the safety, efficacy, and discontinuation-related effects of two dosage ranges of abecarnil, buspirone, and placebo in the acute and long-term treatment of patients who have GAD.

METHOD

Study Design

After a week of single-blind placebo run-in, patients entered a double-blind, 6-week acute treatment period. For treatment responders, this was followed by an optional 18-week maintenance period, in which they were given the same drug they had taken during the acute treatment period. After the abrupt discontinuation of medication at the end of acute or maintenance treatment, patients entered a 3-week placebo substitution follow-up period.

At the start of the acute treatment period, patients were randomized to receive high-dosage abecarnil (7.5–22.5 mg/day), low-dosage abecarnil (3.0–9.0 mg/day), buspirone (15–45 mg/day), or placebo. The dosage of medication was gradually increased during the first 2 weeks of active treatment so that patients were given a minimum of 1 capsule (i.e., 7.5 mg, high-dosage abecarnil; 3.0 mg, low-dosage abecarnil; 15 mg, buspirone) three times per day by Day 15. After Day 15, the dosage was kept fixed (except that one dosage reduction was allowed), but continued use of a minimum dosage, as above, was required for the patients to remain in the study during the acute treatment period.

After completing the 6-week acute treatment period, patients judged to be doing well (i.e., responders) could enter an optional 18-week maintenance period in which investigators were encouraged to continue patients on the same dosage, although dosages could be adjusted if necessary.

At the completion of the 6-week acute treatment period, or at any time during the maintenance treatment period, patients who discontinued or completed the double-blind study phase entered a 3-week, single-blind follow-up period consisting of abrupt discontinuation with placebo substitution.

Assessments

Assessments were performed at the initial (screening) visit, after 1 week of placebo washout at baseline, and weekly thereafter during the 6 weeks of acute treatment. Assessments were also made at Weeks 8, 10, 12, 16, 20, and 24 during the maintenance treatment period and weekly during the 3-week follow-up period after abrupt discontinuation and placebo substitution. Screening assessment of each patient included collection of demographic, medical, and psychiatric information, laboratory assessments, electrocardiogram, and physical evaluation. Vital signs were taken throughout the study. The Physicians' Withdrawal Checklist[10] was administered at baseline, at the end of the acute and maintenance treatment periods, and weekly during the discontinuation period. For the purposes of this article, treatment response was assessed with the 14-item Hamilton Rating Scale for Anxiety (HAM-A)[11] and the Clinical Global Impressions (CGI) Scale.[12]

Study Population

Patients were outpatients who had GAD, as defined by the DSM-III-R and as diagnosed according to the Structured Clinical Interview for the DSM-III-R.[13] Eligible patients had a total score of ≥ 20 on the HAM-A and a score of at least 2 on the anxious mood item. Patients were required to have a Raskin Depression Scale score[14] that was less than or equal to that of their Covi Anxiety Scale score[15] and a Hamilton Rating Scale for Depression (HAM-D)[16] score of < 20. Patients were between the ages of 18 and 65. Women of childbearing potential were using medically accepted birth-control methods and had a negative pregnancy test prior to study entry. All patients were medically acceptable as determined by physical, laboratory, and neurologic examinations, and all provided written informed consent prior to study entry. Patients had been free of all psychotropic medication for at least 1 week prior to study entry and had not been treated with therapeutic doses of neuroleptics, tricyclic antidepressants, or monoamine oxidase inhibitors for at least a month. Patients had a negative urine screen for drugs of abuse and for benzodiazepines prior to study entry.

Exclusion criteria included a current diagnosis of or a history of bipolar illness, organic mental syndromes, schizophrenia or other psychotic disorders, or seizure disorders. Patients who had a current diagnosis of

Table 1. Demographic Characteristics

Characteristic	Abecarnil High[a]	Abecarnil Low[a]	Buspirone	Placebo
N	115	116	115	112
Mean age (y)	41.3	38.0	37.0	39.2
Men	43.8	37.7	39.3	41.1
Women	40.1	38.2	35.2	37.8
Sex [N (%)]				
Male	36 (31)	49 (42)	50 (43)	46 (41)
Female	79 (69)	67 (58)	65 (57)	66 (59)
Marital Status [N (%)]				
Single	30 (26)	31 (27)	35 (30)	36 (32)
Married	57 (50)	51 (44)	58 (50)	52 (46)
Separated	4 (3)	4 (3)	7 (6)	5 (4)
Divorced	24 (21)	29 (25)	15 (13)	19 (17)
Widowed	0 (0)	1 (1)	0 (0)	0 (0)
Mean duration of present episode (mo)	78.3	83.9	75.4	69.1
Onset from first episode (y)	11.8	10.9	11.6	11.6

[a]Abecarnil high = abecarnil 7.5–22.5 mg/d; abecarnil low = 3.0–9.0 mg/d.

Table 2. Patients' Severity of Illness at Baseline

Variable	Abecarnil High[a]	Abecarnil Low[a]	Buspirone	Placebo
N	115	116	115	112
Covi Anxiety Scale total	9.9	10.0	9.8	10.1
Hamilton Rating Scale for Anxiety total	25.2	25.4	24.4	25.1
Hamilton Rating Scale for Depression total	13.9	13.2	13.4	13.2
Raskin Depression Scale total	5.5	5.6	5.8	5.5
CGI Severity of Illness	4.3	4.3	4.2	4.3

[a]Abecarnil high = abecarnil 7.5–22.5 mg/d; abecarnil low = abecarnil 3.0–9.0 mg/d.

Table 3. Disposition of Patients

				Reasons for Attrition					
	Entered	Completed[a]		Adverse Events		Study Drug Ineffective		Other	
Group	N	N	%	N	%	N	%	N	%
Abecarnil high[b]	115	73	63[c,d]	30	26[e,f]	3	3	9	8
Abecarnil low[b]	116	86	74	12	10	3	3	15	13
Buspirone	115	76	66	22	19[g,h]	2	2	15	13
Placebo	112	85	76	11	10	7	6[i]	9	8
Total	458	320	70	75	16	15	3	48	10

[a]Completed acute study period.
[b]Abecarnil high = abecarnil 7.5–22.5 mg/d; abecarnil low = abecarnil 3.0–9.0 mg/d.
[c]$p < .05$, abecarnil high vs placebo.
[d]$p < .1$, abecarnil high vs abecarnil low.
[e]$p < .005$, abecarnil high vs placebo.
[f]$p < .01$, high abecarnil vs abecarnil low.
[g]$p < .06$, buspirone vs placebo.
[h]$p < .1$, buspirone vs abecarnil low.
[i]$p < .1$, buspirone vs placebo.

major depressive disorder, panic disorder, obsessive-compulsive disorder, social phobia, personality disorder, or psychoactive-use disorder were also excluded. In addition, patients undergoing concurrent psychotherapy, behavioral therapy, or cognitive therapy could not participate in the study.

Statistical analyses were performed with analysis of variance (ANOVA) and Cochran-Mantel-Haenszel statistics for categorical data appropriate to the measure under evaluation.

RESULTS

Patient Population

In total, 464 patients were randomized into the study and were given study drug. Six patients did not return for any postbaseline evaluations. The reasons for discontinuation are presented in the section on attrition below. All of the remaining 458 patients who took study drug returned for at least one posttreatment safety evaluation, and their data were included in the safety analysis. Of these 458 patients, 451 had at least one efficacy evaluation.

Demographic characteristics are summarized in Table 1. No statistically significant differences occurred across the four treatment groups for any of the baseline variables except for the distribution of ages. The largest percentages of patients were distributed within the following age ranges for each of the treatment groups: high-dosage abecarnil, 41–50 years (39%); low-dosage abecarnil, 31–40 years (31%); buspirone, 31–40 years (36%); and placebo, 18–30 years (30%).

No significant differences were found among the treatment groups in baseline evaluations of anxiety, depression, or overall CGI Severity of Illness scores. According to the CGI Severity of Illness Scale, patients were moderately to markedly ill at the start of treatment (Table 2).

Attrition

Table 3 gives the number of patients who completed 6 weeks of the study and the reasons for treatment discontinuation (attrition) in those who dropped out before study completion. Significantly fewer patients completed high-dosage abecarnil treatment than did those treated with placebo. More patients in the high-dosage abecarnil group reported adverse events that led to study discontinuation than those in the low-dosage abecarnil or placebo groups.

Dosage Ranges

The study was designed with a flexible dosage schedule, but patients needed to be taking a minimum of 3.0 mg/day in the low-dosage abecarnil group, 7.5 mg/day in the high-dosage abecarnil group, and 15 mg/day in the buspirone group. The mean dosage at Week 6 for the high-dosage abecarnil group was 13.4 mg/day and, at Week 24, 14.1 mg/day. For the low-dosage abecarnil group, the mean dosages were 7.2 mg/day at Week 6 and 7.6 mg/day at Week 24. For buspirone-treated patients, the mean dosages were 33.8 mg/day at Week 6 and 31.5 mg/day at Week 24.

Table 4. Percentages of Patients Reporting Adverse Events That Differed Significantly Between Treatment Groups

Adverse Event	ABHI[a] (N = 115)	ABLO[a] (N = 116)	BUSP[a] (N = 115)	Placebo (N = 112)
Any event	96[b,c]	81	86	80
Miscellaneous	12	9	5[c]	16
Throat discomfort	0[c]	3	2	6
Abdominal discomfort	9	5[b,c]	17	14
Appetite increased	1[c]	1[c]	3	6
Dysmenorrhea	3	3[c]	2[c]	9
Central nervous system	91[b,c]	73[c]	77[c]	57
Drowsiness	45[b,c]	27[c]	17	14
Dizziness	21[b]	16[b]	35[c]	13
Fatigue	17[b]	10	5	9
Lack of concentration	11[b,c]	8[c]	3	1
Confusion	7[c]	4	2	1
Coordination, difficult	6[c]	3	1	0
Ataxia	5[c]	1	1	0

[a]ABHI = abecarnil 7.5–22.5 mg/d; ABLO = abecarnil 3.0–9.0 mg/d; BUSP = buspirone 15.0–45.0 mg/d.
[b]$p < .05$, abecarnil vs buspirone.
[c]$p < .05$, vs placebo.

Adverse Events

Table 4 displays the percentages of patients who reported adverse events that differed significantly between treatment groups at any time during the study. Abecarnil-treated patients, particularly those given the high dosage, experienced more central nervous system effects, including drowsiness, dizziness, fatigue, confusion, and problems with concentration and coordination than did the patients given placebo and typically more than those given buspirone, with the exception of dizziness, which was reported more commonly with buspirone therapy.

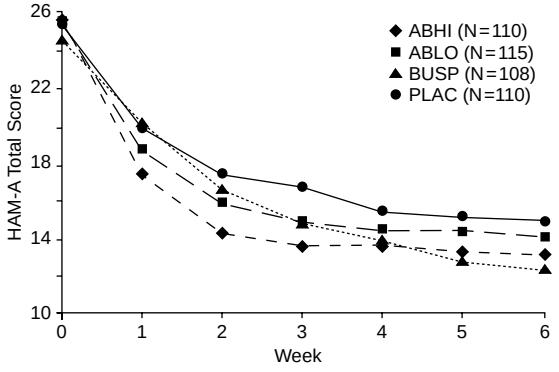
Clinical Outcome

Figure 1 presents the results for the total HAM-A score in the last-observation-carried-forward (LOCF) analysis. Compared with placebo, abecarnil showed significant anxiolytic activity after 1 week of treatment in both dosage groups; patients in the high-dosage abecarnil group experienced the most improvement. Results obtained from the available-patients (decreasing N) analysis were similar (data not shown).

Results from LOCF and completer analyses of CGI Severity of Illness and Improvement scores demonstrated early statistically significant improvement for abecarnil compared with placebo at Weeks 1–3 ($p < .05$), particularly for those in the high-dosage group, but these differences from placebo did not maintain statistical significance at the end of the trial.

The results of this study need to be evaluated with the understanding that more than 50% of the placebo-treated patients demonstrated at least moderate improvement at the treatment endpoint (LOCF) (Figure 2). This high placebo-response rate hampers the ability to demonstrate statistically significant effects of both active treatments.

Figure 1. Hamilton Rating Scale for Anxiety Total Score: LOCF, Acute Treatment Period†



p Values for each weekly assessment are as follows:

Comparison	Week 1	2	3	4	5	6
ABHI vs PLAC	.001***	0***	0***	.046*	.036*	.059(*)
ABLO vs PLAC	.047*	.031*	.017*	.198	.353	.259
BUSP vs PLAC	.413	.811	.113	.296	.067(*)	.043*

(*) = $p < .10$; * = $p < .05$; *** = $p < .001$
†Abbreviations: LOCF = last observation carried forward; ABHI = high-dosage abecarnil (7.5–22.5 mg/d); ABLO = low-dosage abecarnil (3.0–9.0 mg/d); BUSP = buspirone (15.0–45.0 mg/d); PLAC = placebo.

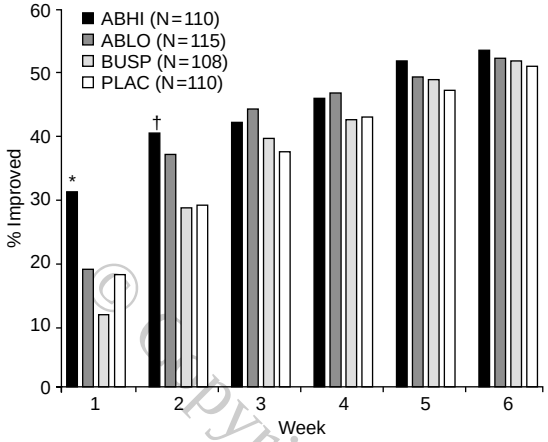
Follow-Up Period

When patients discontinued treatment abruptly during study Weeks 6–24, they entered a mandatory 3-week placebo follow-up period. The percentages of patients who experienced the emergence of three or more new symptoms on the Physicians' Withdrawal Checklist after abrupt discontinuation of double-blind therapy are given in Figure 3 for three population groups: those treated for as long as 6 weeks, those treated between 7 and 12 weeks, and those treated between 13 and 24 weeks. As the figure clearly shows, the emergence of discontinuation (withdrawal) symptoms appears to be highly influenced by duration of treatment: significant differences in withdrawal symptoms between abecarnil-treated and placebo-treated patients are present only after 12 to 24 weeks of therapy.

DISCUSSION

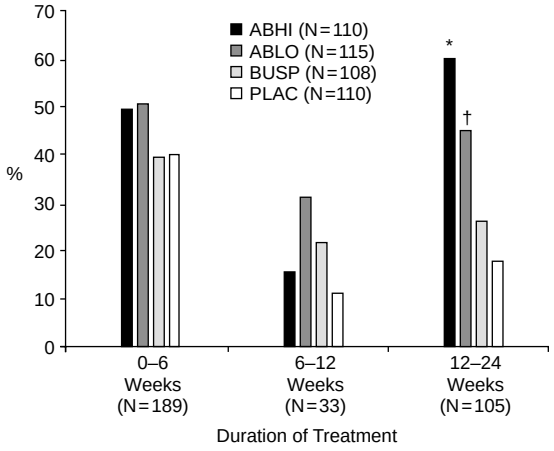
In this prospective, randomized, double-blind, placebo-controlled trial, abecarnil, particularly at higher dosages (7.5–22.5 mg/day), demonstrated early anxiolytic activity. Assessment of the full spectrum of its efficacy was hampered somewhat by a dramatically high rate of response to placebo in this study. Abecarnil was generally well tolerated; 10% to 26% of patients discontinued treatment because of adverse events, which was comparable with the discontinuation rate associated with buspirone (19%). Withdrawal symptoms emerged in patients who abruptly discontinued from treatment with abecarnil

Figure 2. Percentages of Patients Who Demonstrated Moderate or Marked Improvement (LOCF Analysis) During the Acute Treatment Period‡



*p < .05 vs placebo.
†p < .10 vs placebo.
‡Abbreviations: LOCF = last observation carried forward; ABHI = high-dosage abecarnil (7.5–22.5 mg/d); ABLO = low-dosage abecarnil (3.0–9.0 mg/d); BUSP = buspirone (15.0–45.0 mg/d); PLAC = placebo.

Figure 3. Percentages of Patients Who Had Three New Symptoms During the Discontinuation Period (Physicans' Withdrawal Checklist)‡



*p < .01 vs placebo.
†p < .10 vs placebo.
‡Abbreviations: ABHI = high-dosage abecarnil (7.5–22.5 mg/d); ABLO = low-dosage abecarnil (3.0–9.0 mg/d); BUSP = buspirone (15.0–45.0 mg/d); PLAC = placebo.

(particularly at the higher dosage) after a longer duration of treatment (3 to 6 months). Treatment with buspirone was associated with a slower onset of action but significantly better relief of symptoms than placebo after 6 weeks of therapy.

Results from this study suggest that abecarnil may be an effective anxiolytic agent. Further attention is warranted to assess its spectrum of clinical effectiveness, its use in acute and long-term treatment, strategies to minimize discontinuation-related symptoms, and its interaction with other anxiolytic medications and cognitive-behavioral therapies.

Drug names: alprazolam (Xanax), buspirone (BuSpar), chlordiazepoxide (Librium and others), clorazepate (Tranxene), diazepam (Valium and others), flumazenil (Romazicon), imipramine (Tofranil and others), lorazepam (Ativan and others), oxazepam (Serax and others), trazodone (Desyrel and others).

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