A Double-Blind Evaluation of the Safety and Efficacy of Abecarnil, Alprazolam, and Placebo in Outpatients With Generalized Anxiety Disorder

R. Bruce Lydiard, Ph.D., M.D., James C. Ballenger, M.D., and Karl Rickels, M.D., for the Abecarnil Work Group

In a placebo-controlled, multicenter study, 180 male and female outpatients, ages 18–65, with DSM-III-R generalized anxiety disorder, were treated with abecarnil (a partial benzodiazepine agonist), alprazolam, or placebo for 4 weeks. This was followed by a rapid (1-week) taper, during which patients were assessed for any taper-related symptoms. All patients were identified via a structured clinical interview for DSM-III-R and randomly assigned to one of the three treatment groups. More than 70% of each treatment group completed the study. In the acute-treatment phase, both abecarnil and alprazolam showed evidence for efficacy that was significantly better than that of placebo. Both active agents were tolerated well. After the swift taper, a significantly greater number of taper-related symptoms occurred in the alprazolam-treated group than in the abecarnil-treated group, which was not different than in the placebo-treated group. Additionally, less residual improvement followed the taper in the alprazolam-treated and the placebo-treated groups. These data indicate that the partial benzodiazepine agonist abecarnil may be useful as a safe, effective, short-term treatment for anxiety. Theoretical and practical implications of these findings are discussed.

(J Clin Psychiatry 1997;58[suppl 11]:11–18)

Anxiety disorders are among the most prevalent medical disorders in the general population. It has been estimated that as many as 17% of individuals in the United States will suffer from an anxiety disorder at some point. These disorders collectively constitute a significant public health problem. Untreated anxiety continues to be a major source of work and social disability for many affected individuals. Further, it appears that additional disorders are more likely to occur in individuals who already suffer from a psychiatric disorder.[1]

Over the past two decades, there have been great advances in our ability to treat anxiety disorders, including generalized anxiety disorder (GAD).[2] The benzodiazepines (BZs), which exert their anxiolytic effects via potentiation of the effects of gamma-aminobutyric acid (GABA), have traditionally been the mainstay for the treatment of GAD. However, the therapeutic efficacy of the BZs is offset to some extent by the occurrence of physical dependence and withdrawal symptoms after longer-term use; other adverse effects such as ataxia, sedation, and memory disturbance; and concern about abuse potential.

Intense interest in the BZ-GABA receptor complex of the central nervous system (CNS) has provided exciting new avenues for advances in the development of therapeutic agents.[3] New knowledge about the subtypes of the BZ receptors in the CNS and the periphery has contributed significantly to our understanding of the biology of anxiety. The subsequent characterization of a family of pharmacologic agents that exert markedly different effects at the BZ-GABA receptor complex is a direct outgrowth of the basic research in this area over the past decade.

The spectrum of agents that have been shown to exert effects at the BZ-GABA receptor complex ranges from agents such as clonazepam or diazepam, which are "full agonists," to "inverse agonists" at the other end of the spectrum.[4] Full agonists produce anxiolysis, sedation, ataxia, muscle relaxation, and memory impairment (see Figure 1). If given chronically, the full agonists such as clonazepam, alprazolam, and diazepam also produce

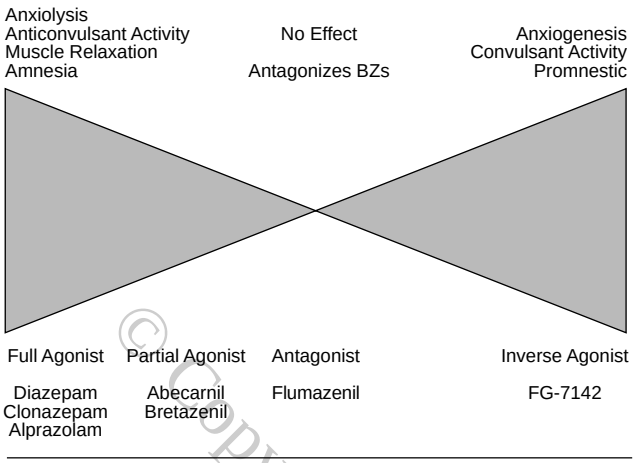
From the Institute of Psychiatry, Medical University of South Carolina, Charleston.

Presented at the 20th Collegium Internationale Neuropsychopharmacologicum symposium titled "A New Concept in the Treatment of Anxiety," held June 23–27, 1996, in Melbourne, Australia. The symposium was made possible by an educational grant from Schering AG.

Participating investigators included Bernard Beitman, M.D. (Columbia, Mo.), Robert L. DuPont, M.D. (Rockville, Md.), Roberto Dominguez, M.D. (Miami, Fla.), Peter P. Roy-Byrne, M.D. (Seattle, Wash.), Walton T. Roth, M.D. (Palo Alto, Calif.), James C. Ballenger, M.D. (Charleston, S.C.), R. Bruce Lydiard, Ph.D., M.D. (Charleston, S.C.), Karl Rickels, M.D. (Philadelphia, Pa.), and Scott Woods, M.D. (New Haven, Conn.)

Reprint requests to: R. Bruce Lydiard, Ph.D., M.D., Institute of Psychiatry, Medical University of South Carolina, 171 Ashley Avenue, Charleston, SC 29425.

Figure 1. The Spectrum of Benzodiazepine-Receptor Ligands



physical dependence: abrupt discontinuation after their chronic administration frequently precipitates a withdrawal syndrome. Inverse agonists, at the other end of the spectrum, are anxiogenic, can cause seizures, and may be promnestic. Neutral BZ receptor antagonists, such as flumazenil, which occupy the BZ receptor but exert no pharmacologic effects, lie roughly midway between the full agonists and the inverse agonists on this pharmacologic spectrum.

One of the strategies in developing anxiolytics that exert their effects via the BZ receptor has been to look for compounds that exert anxiolytic properties but have some advantages over the existing agents. Partial BZ agonists have been identified as a promising group of agents in this regard. These agents are potentially effective anxiolytics and have possibly less risk for dependence/withdrawal, sedation, ataxia, and other unwanted effects. As shown in Figure 1, these partial agonists are on the anxiolytic end of the spectrum between the full agonists and the neutral antagonist flumazenil. This group includes abecarnil, a beta-carboline that has partial BZ agonistic properties. It is of interest that there are partial agonists across the spectrum from full agonists to inverse agonists.

Abecarnil is a novel compound that has a high affinity for BZ receptors. It has been shown to possess potent anxiolytic and anticonvulsant activity in preclinical studies, and it exhibits the characteristics of a potentially useful clinical agent with partial BZ agonistic properties. Preliminary safety and early efficacy studies in humans have indicated that the agent appears to be safe in dosages of up to 90 mg/day, with side effects typical of BZ-like anxiolytics (dizziness, fatigue, unsteady gait) appearing in a dose-related fashion. A subsequent multicenter study[5] confirmed that abecarnil showed therapeutic effects in patients who had GAD at dosages in the range of 3–9 mg/day. Most importantly, dosages in this range exhibited significant anxiolytic effects but no significant withdrawal symptoms after abrupt discontinuation after 3 weeks of treatment.

A placebo-controlled comparison of abecarnil versus alprazolam in the treatment of GAD was designed to assess the longer-term comparative efficacy of abecarnil as well as the profile of symptoms emerging in patients who received 4 weeks of treatment followed by a rapid 1-week taper.

METHOD

The overall study design was multicenter, double blind, and placebo controlled. Patients who had DSM-III-R GAD[6] were randomly assigned to the abecarnil (3.0 mg/day to 9.0 mg/day), alprazolam (1.5 mg/day to 4.5 mg/day), or placebo treatment groups. The study had a 4-week, double-blind treatment period and a 1- to 2-week medication-tapering period. Patients were evaluated weekly.

Flexible dosing schedules were used, so that the dosages were adjusted by the investigators according to efficacy and side effects. The number of patients expected to complete the study was 180, and these were evenly divided among the three treatment groups. Patients who discontinued for reasons unrelated to the pharmacologic effects before they completed at least 2 weeks of double-blind treatment and the required evaluations were replaced.

Patient Sample Characteristics

All patients gave written informed consent to the procedures after a thorough explanation of the study requirements and purpose had been given to them. Patients were male or female outpatients between the ages of 18 and 65 who had a current diagnosis of DSM-III-R GAD.[6] The diagnostic evaluation was completed via the Structured Clinical Interview for DSM-III-R (SCID).[7]

The DSM-III-R diagnostic criteria included unrealistic or excessive anxiety and worry (apprehensive expectation) about two or more life circumstances for a period of 6 months or longer, during which the individual was bothered more days than not by these concerns. In addition, at least 6 of 18 associated symptoms were required to be present. These included motor tension items (trembling, twitching or feeling shaky, muscle tension, aches or soreness, restlessness, easily fatigued); autonomic overactivity items (shortness of breath or smothering sensations, palpitations or tachycardia, sweating or cold clammy hands, dry mouth, dizziness or light-headedness, nausea, diarrhea or other abdominal distress, flushes—hot flashes—or chills, frequent urination, trouble swallowing or "lump in throat"); and vigilance and scanning items (feeling keyed up or on edge, exaggerated startle response, difficulty concentrating or "mind going blank" because of anxiety, trouble falling or staying asleep, irritability). Patients were required to be free of any psychotropic medication for at least 1 week and for at least 1 month for therapeutic doses of

neuroleptics or antidepressants. Patients who had other psychiatric disorders that were not likely to interfere with the objectives of the study were allowed to enroll.

Individuals who had a history of psychosis, mania, current major depression, substance abuse (within 6 months), or other Axis I disorders believed likely to interfere with the objectives of the study were excluded. Any patients who had been receiving anxiolytics for less than 4 weeks were required to undergo a 1-week period during which no evidence of withdrawal was apparent. Individuals who had been taking anxiolytics (equivalent to 20 mg/day of diazepam or 3 mg/day of alprazolam) for more than 4 weeks had their dosages tapered gradually, in keeping with good clinical practice, and also were observed for emergence of withdrawal prior to study entry. Patients were allowed to take 500 mg of chloral hydrate for sleep during the study as long as it was not taken for more than 2 consecutive days and it was not taken the evening before the study visit. Patients who had taken any investigational drug within the 30 days immediately preceding admission to the study were excluded.

Women of childbearing potential were required to use medically accepted birth-control methods, have a negative pregnancy test, and give written assurance that they were not planning to become pregnant.

Patients were required to be in good medical health, with no contraindications to taking study medication and not known to suffer from other medical conditions that have been associated with anxiety-like symptoms such as hyperthyroidism. Their current health status was confirmed by medical history, physical examination, ECG, neurologic examination, and clinical laboratory tests. Patients who had a positive urine screen test for drugs of abuse were excluded.

Efficacy and Safety Assessments

Clinical assessment tools included the Hamilton Rating Scale for Anxiety (HAM-A),[8] Raskin Depression Rating and Covi Anxiety Scales,[9] Clinical Global Impression (CGI) Scale,[10] Hopkins Symptom Checklist,[11] and Physicians' Withdrawal Checklist.[12] Patients were required to have a score of 18 or more on the HAM-A scale at the point of randomization and to have a score on the Covi Anxiety Scale that was equal to or higher than that on the Raskin Depression Rating scale.

Medication Dosage Schedule

All study medication was prepared as identical capsules containing 1.0 mg abecarnil, 0.5 mg alprazolam, or placebo. Dosages were titrated to 1 capsule t.i.d. by Study Day 4, and 2 capsules t.i.d. by Study Day 8, and a maximum of 3 capsules t.i.d. by Study Day 15. Clinicians were allowed to adjust the patients' dosage in a flexible fashion or to withhold a dosage increase on the basis of efficacy, tolerability, and clinical judgment. However, to remain in the study, patients were required to take at least 1 capsule b.i.d., and every effort was made to treat each patient with a minimum of 1 capsule t.i.d.

At the end of Study Week 4 (Day 28), patients had their daily dosage reduced. This reduction took place over a period of either 1 or 2 weeks. Initially, patients had their dosage reduced by 1 capsule per day. At 50% reduction, the investigator or study coordinator called the patient and determined the patient's clinical status. If the medication tapering was proceeding without incident, it was continued at a rate of 1 capsule per day; if significant symptoms emerged, the tapering was reduced by 50% and extended for up to 1 additional week.

Safety Evaluations

Safety evaluations included physical examination, ECGs, and laboratory tests, as well as a review of adverse events throughout the study. Patients were asked about any adverse event that had occurred since their last visit, and these were followed through the course of the study. Additionally, the Physicians' Withdrawal Checklist, which is used to detect and assess symptoms of BZ withdrawal, was administered weekly and during and after the tapering period. In total, 36 symptoms covering five areas (gastrointestinal, mood, motor, convulsions/psychosis, and somatic problems) were assessed and were rated from absent (0) to severe (4).

Statistical Analysis

The primary goals of this study were to assess further the efficacy of abecarnil vs. placebo in patients who have GAD and to compare the efficacy of abecarnil with that of alprazolam, an agent that has documented efficacy in GAD. In this study, abecarnil was to be considered superior to placebo if there were a statistically significant difference ($p < .05$, two-tailed) on change in HAM-A score from baseline and a significantly better CGI Severity of Illness or Global Improvement score. The primary efficacy analyses were performed on the intent-to-treat population (i.e., those patients who were randomized, took at least one dose of study medication, and had a subsequent rating).

Data will be presented in two ways: (1) observed cases (OC), which indicates data from all patients who were rated at the evaluation time presented, and (2) last-observation-carried-forward (LOCF), in which the last rating score for any patient who dropped out of the study prior to completion is entered for each subsequent potential visit.

A two-way, fixed-effects analysis of covariance model with effects for treatment, center, and treatment by center was used in the efficacy analysis. Dependent variables were the changes from baseline (Day 0). For the efficacy variables, change from baseline indicates positive scores for improvement. Baseline variables were used as covariates in the analysis.[13] If assumptions for the analysis of

Table 1. Summary of Demographic Characteristics

Characteristic	Treatment Group Abecarnil (N = 67)	Alprazolam (N = 63)	Placebo (N = 62)
Mean age (y)	39.5	44.0	42.7
Men	37.0	41.2	44.3
Women	41.3	47.3	41.5
Sex [N (%)]			
Male	28 (42)	34 (54)	27 (44)
Female	39 (58)	29 (46)	35 (56)
Mean weight (lb)			
Men	180.7	181.1	183.9
Women	151.2	141.9	150.3
Marital status [N (%)]			
Single	22 (33)	12 (19)	18 (29)
Married	32 (48)	31 (49)	27 (44)
Separated	5 (7)	2 (3)	2 (3)
Divorced	7 (10)	17 (27)	15 (24)
Widowed	1 (2)	1 (2)	0 (0)
Mean duration of current episode (mo)	92.6	73.6	98.7
Onset from first episode (y)	15.0	16.9	15.3

Table 2. Mean Investigator-Rated Behavioral Rating Scale Results at Baseline

Variable	Treatment Group Abecarnil (N = 67)	Alprazolam (N = 63)	Placebo (N = 62)	Mean Score
Raskin Depression Scale total	4.9	5.0	5.0	5.0
Covi Anxiety Scale total	9.3	9.6	9.3	9.4
Hamilton Anxiety Scale total	24.3	24.1	24.8	24.4
CGI Severity of Illness item	4.2	4.3	4.3	4.2

covariance were not met, analysis of variance was performed. Unweighted means (SAS Type III Sums of Squares using PROC GLM) were used in the analysis. These analyses of variance/covariance were performed each week during the acute treatment period and at the taper. Comparisons were made on the basis of pairwise t tests (SAS least-squares means) using the pooled-error term from the analysis of variance/covariance. When the assumptions of the analysis of covariance were met, adjusted mean changes rather than observed mean changes were compared.

All tests were two tailed. All p values were reported on the basis of reported SAS Type III Sums of Squares. Categorical analyses were determined a priori and were performed on CGI responders, defined as those patients who had a rating of much improved (2) or very much improved (1) vs. the proportion of patients who had no improvement or whose condition worsened from baseline. The Mantel-Haenszel test,[14] controlling for centers, was applied in a pairwise manner to assess differences between treatments.

Table 3. Mean Dosage and Mean Number of Capsules Taken by Week During Acute Treatment Period

Treatment Group	Week 1	Week 2	Week 3	Week 4
Abecarnil	2.5 mg (2.5 caps)	5.0 mg (5.0 caps)	6.7 mg (6.7 caps)	7.4 mg (7.4 caps)
Alprazolam	1.2 mg (2.3 caps)	2.0 mg (3.9 caps)	2.6 mg (5.1 caps)	2.6 mg (5.3 caps)
Placebo	– (2.4 caps)	– (5.1 caps)	– (7.2 caps)	– (8.0 caps)

RESULTS

The demographic and other relevant characteristics of the treatment samples are shown in Table 1. The abecarnil-treated group was significantly younger than the alprazolam-treated and placebo-treated groups for all patients and for the subgroup of male patients (means ranged from 37.0 to 44.3 years). The subgroup of female abecarnil-treated patients was 1.5 inches shorter than the other groups (data not shown). There were no other significant demographic differences at baseline.

All patients met the DSM-III-R criteria for GAD. The baseline ratings for each patient group (see Table 2) reflect at least moderate illness in each treatment group. Each patient group had at least some depressive symptoms. There were no differences between the treatment groups on these clinical ratings at baseline.

Study Medication Dosage

The mean dosages of study medication (identical capsules containing 1 mg abecarnil, 0.5 mg alprazolam, or placebo) at each week of the study are shown in Table 3. The mean duration of treatment during the acute phase for the abecarnil-treated group was 27.3 days; for the alprazolam-treated group, 27.0 days; and for the placebo-treated group, 26.4 days. There were no significant differences between groups in duration of treatment.

Dropouts and Adverse Events

In the abecarnil-treated group, 53 (79.1%) of the randomized subjects completed all 4 weeks; corresponding numbers for the alprazolam-treated group were 45 (71.4%) and for the placebo group, 45 (72.6%). Of the patients who entered the tapering period after the 4-week acute period, 69% of the abecarnil-treated patients, 79% of the alprazolam-treated patients, and 78% of the placebo-treated patients completed the 1-week tapering schedule.

No deaths or serious adverse events occurred.

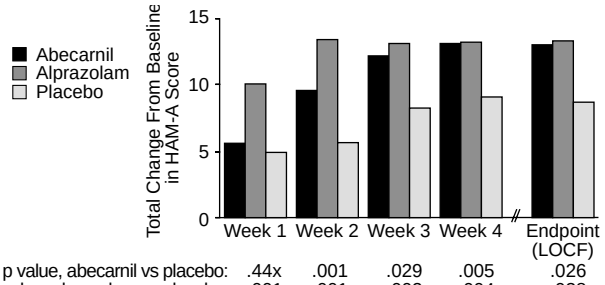
Table 4 shows the adverse events reported by the three treatment groups during the study. The adverse events were predominantly related to the central nervous system. The most frequently reported adverse event was drowsiness, which was reported statistically significantly more frequently ($p < .05$) by the alprazolam-treated group (63%) than by the abecarnil-treated group (25%), whose

Table 4. Adverse Events[a]: Incidence Rates (%) by Treatment Group During Acute Treatment Period

	Abecarnil (N = 67)		Alprazolam (N = 63)		Placebo (N = 62)	
Event	Total	Severe	Total	Severe	Total	Severe
Any event	66[b]	16	92[c]	27	71	15
Miscellaneous	10	0	8	2	8	0
Musculoskeletal	7	4	5	2	8	0
Backache, pain	3	3	2	2	0	0
Muscle spasm	1	1	0	0	2	0
Sciatica	1	1	0	0	2	0
Cramps	1	1	0	0	0	0
Cardiovascular	7	1	0	0	5	0
Gastrointestinal	25	1	13	0	19	0
Nausea	15[b]	0	3	0	8	0
Taste, abnormal	1	1	0	0	2	0
Appetite loss, anorexia	0[b]	0	8	2	0	0
Central nervous system	58[b]	12	89[c]	24	53	10
Drowsiness	25[b]	1	63[c]	11	18	0
Headache	18	4	14	2	19	2
Fatigue	10	1	5	2	6	2
Dizziness	9	1	21	0	11	0
Lack of concentration	6	0	3	2	5	0
Irritability	6	1	2	0	2	2
Lethargy	6	1	11	0	2	0
Depression	4	3	3	2	0	0
Insomnia	4	1	5	2	8	2
Incoherence	1	1	0	0	0	0
Fogginess	1	1	0	0	0	0
Ataxia	0[b]	0	10[c]	2	0	0

[a]Events for which there was an incidence of at least 5% for abecarnil, or there was a significant difference between two groups (drug-drug or drug-placebo), or at least 1% of abecarnil-treated patients reported the event as severe.
[b]$p < .05$, abecarnil vs alprazolam.
[c]$p < .05$, drug vs placebo.

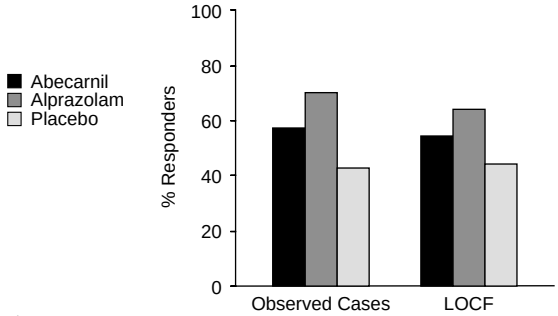
Figure 2. Hamilton Rating Scale for Anxiety (HAM-A) Score for the Three Treatment Groups (Observed Cases) at Weeks 1–4*



p value, abecarnil vs placebo:	.44x	.001	.029	.005	.026
p value, alprazolam vs placebo:	.001	.001	.002	.004	.038

*Endpoint includes all patients with at least one evaluation at study exit (completion or last visit). p Values at bottom indicate between-group differences after significant two-way ANOVA/ANCOVA.

Figure 3. Clinical Global Impression (CGI) Ratings at Week 4 for Observed Cases and All Subjects Entered With Last Observation Carried Forward (LOCF)*



p value, abecarnil vs placebo:	.107	NS
p value, alprazolam vs placebo:	.040	.05

*Subjects rated as much improved (2) or very much improved (1) were considered responders.

rate was not statistically significantly different than that in the placebo-treated group (18%) for this variable. Headache and fatigue were the next most commonly reported symptoms, but these were not significantly different between groups. Abecarnil appeared to be associated with significantly more nausea (15%) than was alprazolam (3%) or placebo (8%). The overall frequency of reported adverse events was higher in the alprazolam-treated group (92%) than in the abecarnil-treated group (66%), which did not differ from placebo (71%).

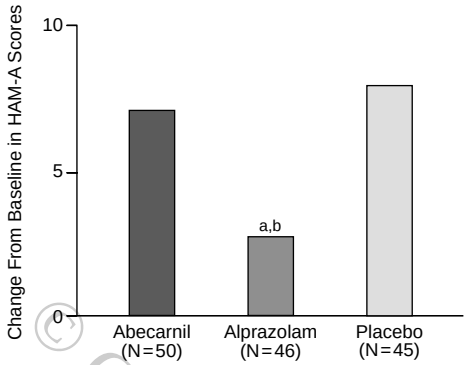
Acute Treatment Outcomes

The effects of treatment on the total HAM-A scores are displayed in Figure 2. Statistically significant differences occurred by Week 1, with the alprazolam-treated group achieving significantly more reduction in HAM-A scores than the other two groups. By Week 2, a statistically significant difference was found between the abecarnil-treated and placebo-treated groups. At Weeks 3 and 4, there were differences between both drugs and placebo, but no drug-drug differences. The study endpoint (LOCF) ratings summary is consistent with the observed-cases data. Both abecarnil and alprazolam were statistically significantly more effective than placebo in reducing symptoms of anxiety in patients who had GAD over the initial 4-week treatment period.

The percentages of patients in each treatment group who had CGI ratings of much improved (2) or very much improved (1) at Week 4 are shown in Figure 3. In the observed cases, alprazolam was statistically significantly better than placebo ($p < .04$), but abecarnil was not statistically significantly better than placebo. For this variable in the LOCF analysis at Week 4, a statistically significantly greater percentage of responders was found in the alprazolam-treated group than in the placebo-treated group ($p < .05$), but no statistically significant difference was found between the abecarnil-treated group and the placebo-treated group.

In sum, both abecarnil and alprazolam showed greater efficacy than placebo in reducing anxiety in symptomatic outpatients who had DSM-III-R GAD. The onset of action

Figure 4. HAM-A Total Scores*



*No differences between abecarnil-treated and placebo-treated patients were noted, but alprazolam-treated patients had significantly less residual reduction in HAM-A scores than did placebo- or abecarnil-treated patients.
[a]p < .001 vs placebo.
[b]p < .03 vs abecarnil.

Table 5. Clinical Global Impression Improvement Scores 1 Week After the Rapid-Tapering Phase

Measure	Abecarnil (N = 50)	Alprazolam (N = 45)	Placebo (N = 45)
CGI Improvement (mean score)	5.0	4.3[a]	5.0

[a]p < .03, alprazolam vs placebo.

of alprazolam appeared earlier, and the degree of response was significantly greater on some measures than that seen with abecarnil. However, more adverse effects also were reported during the acute treatment phase by patients treated with a low-to-moderate dosage (average 2.6 mg/day) of alprazolam than by patients treated with abecarnil.

Tapering Period

After the 4-week acute treatment phase, patients were tapered off study medication at the rate of 1 capsule per day. As previously noted, the majority of subjects who entered the tapering phase (69% of the abecarnil-treated, 79% of the alprazolam-treated, and 78% of the placebo-treated patients) completed the 1-week tapering schedule. Figure 4 shows the HAM-A total scores for each treatment group 1 week after completing the rapid (i.e., 1-week) tapering schedule. As shown in this figure, the residual change from baseline in the HAM-A total score in the alprazolam-treated group (3.2) was significantly less than in either the abecarnil-treated (8.5) or placebo-treated (9.5) groups.

In addition, the post-tapering CGI-improvement ratings (see Table 5) indicate that despite significant improvement during the acute phase, the alprazolam-treated group retained significantly less improvement 1 week post-tapering than did the abecarnil-treated and placebo-treated groups, which were not different from each other.

Table 6. Physicians' Withdrawal Checklist: Incidence Rates (%) for New or Worsened Symptoms During and After the Tapering Phase

	Abecarnil (N = 58)		Alprazolam (N = 52)		Placebo (N = 49)	
Symptom	Total	Severe	Total	Severe	Total	Severe
Nausea	29[a]	3	27[a]	4	10	2
Appetite loss	22[b]	0	44	4	8	0
Diarrhea	14	0	21	6	8	0
Dysphoric mood	28[a]	12	48[a]	19	12	4
Anxiety	16[a]	10	19[a]	10	2	2
Irritability	14	9	17	10	8	0
Insomnia	28	16	38	12	20	2
Bad dreams	16	2	31	4	16	6
Fatigue	16	3	25	13	12	6
Muscular jerking, fasciculations	14	0	29	6	16	0
Poor coordination	12[b]	0	31[a]	4	2	0
Agitation	10[b]	3	27	13	14	6
Headache	24	9	35	13	22	4
Flu-like symptoms	22	2	29[a]	2	10	2
Feeling weak	19	0	15	4	22	0
Dizziness	16[b]	0	37[a]	10	14	2
Muscle aches	16[b]	0	33	8	18	4
Loss of interest in sex	14	2	27[a]	8	10	2
Diaphoresis	12	0	19	2	8	0
Tremor	12[b]	3	31[a]	10	6	0
Palpitations	12	2	19	4	10	0
Tinnitus	9	0	13	2	6	0
Increased acuity to sound, smell, touch	12[b]	3	33[a]	0	14	0
Photophobia	9	3	17	4	8	2
Metallic taste	5	0	12	0	4	0
Paresthesia	3[b]	0	23	6	10	0
Perceptual distortions	2[b]	0	17[a]	4	2	0
Difficulty expressing thoughts	19	3	33[a]	2	14	0
Confusion	14	0	29	2	12	0
Difficulty concentrating	12	5	27	13	12	4
Depersonalization and derealization	7[b]	0	23[a]	0	6	0
Paranoid reactions	7	0	17[a]	0	2	0

[a]p < .05, active drug vs placebo.
[b]p < .05, abecarnil vs alprazolam.

The Physicians' Withdrawal Checklist was used during and after the tapering phase to assess the effects of rapid (1-week) discontinuation of study medication. New symptoms that emerged or symptoms that worsened during the tapering period were recorded. Table 6 shows the taper-related symptoms in the three treatment groups. During the taper period, abecarnil-treated patients differed statistically significantly from placebo-treated patients in three symptoms: nausea, dysphoric mood, and increased anxiety. These three, as well as several other symptoms, also occurred statistically significantly more frequently in the alprazolam-treated group than in the placebo-treated group.

DISCUSSION

This study supports the effectiveness of the use of abecarnil for the treatment of GAD in symptomatic outpatients, and it found fewer associated side effects and withdrawal symptoms than with the use of alprazolam. Alprazolam appeared to have a statistically significant effect earlier in the study and greater effects on more outcome measures than did abecarnil, possibly because of the relatively low dosage of abecarnil used. The most important finding was that after a rapid (1-week) tapering off of study medication, notable clinical differences were observed between the two active agents. Alprazolam was, as expected, a highly effective anxiolytic. However, after as few as 4 weeks of treatment, notable withdrawal symptoms were observed during the rapid taper and follow-up observation periods. In contrast, abecarnil, which also showed anxiolytic effects at the dosage used, was associated with much fewer withdrawal symptoms during the tapering-off period and less rebound anxiety. Abecarnil also was less likely than alprazolam to cause adverse effects during acute treatment. No differences occurred in any adverse effects or in the overall frequency of reported adverse effects between the abecarnil-treated (66%) and placebo-treated (71%) groups during acute treatment. In contrast, alprazolam was associated with significantly more sedation and ataxia than was either abecarnil or placebo and with significantly more reported events (92%) at what would be considered a moderate therapeutic dosage (average 2.6 mg/day) during the acute treatment phase.

This study has several practical implications. Abecarnil, a partial BZ agonist, has been shown to be effective, at least in the short term, for the treatment of GAD. After 4 weeks of treatment, abecarnil (in contrast with alprazolam) caused only a few clinically significant withdrawal effects when dosage was tapered swiftly over 1 week. These findings suggest that abecarnil has a clinical advantage over alprazolam for the short-term treatment of anxiety. In addition, the therapeutic effects of abecarnil appeared to be sustained beyond the period of treatment and tapering. Even after effective short-term treatment, a residual therapeutic benefit was still evident after the taper was completed, as evidenced by the improvement over baseline.

The design of this study—rapid withdrawal over 1 week as opposed to abrupt discontinuation of treatment—has allowed for an examination of the clinical usefulness of a new agent such as abecarnil in a more real-life situation. The data support the relative ease of discontinuation of abecarnil after 4 weeks of treatment, in contrast with the standard BZ comparator, alprazolam. The reason for the difference found in the number and intensity of taper-related symptoms between abecarnil and alprazolam is unclear. Previous studies in patients who had GAD have indicated that more than 50% of subjects who discontinued diazepam after 6 weeks of treatment subsequently remained symptom free for at least 3 months[15]; other studies with BZs also have indicated some residual improvement after short-term (4-week) treatment in anxious patients.[16]

It may be that either pharmacokinetic or pharmacodynamic differences inherent to the agents used in the different studies, as well as possible differences in the patient populations, are important variables. Because abecarnil is a partial agonist, it may reduce the degree or speed of the development of physical dependence relative to that with full agonist compounds. Some preclinical studies have suggested intriguing hypotheses about a possible novel mechanism of action. According to data from animal studies, it appears that the partial BZ agonists produce fewer changes in GABA function than full agonists do when they are given chronically. Gallager et al.[17] treated rodents with diazepam in a chronic administration regimen and administered a single dose of the pure antagonist flumazenil. This single exposure resulted in a reversal of BZ-induced dorsal raphe GABA-receptor subsensitivity and a restoration of the anticonvulsant effects of diazepam. Further, the reversal of tolerance to the anticonvulsant effects persisted for 7 days after the single dose of flumazenil, even after diazepam was continued. In another study, Hernandez et al.[18] compared the effects of chronic administration to rats of diazepam, a full BZ agonist; RO-16-6028, a partial BZ agonist; and the neutral antagonist flumazenil. They found that the development of changes in GABA-receptor function that typically accompany chronic treatment with BZ (i.e., GABA receptor subsensitivity and loss of anticonvulsant efficacy of BZ) were most pronounced with diazepam, intermediate with the partial agonist, and absent with flumazenil.

These and other studies suggest that partial BZ agonists such as abecarnil, in clinically therapeutic doses, may carry a lower risk for the development of physical dependence and withdrawal. Since these agents lie between the full agonists and the neutral antagonists on the spectrum of BZ-receptor ligands, it may be that a unique receptor effect allows for anxiolytic effects but prevents or reduces the degree of development of significant physical dependence, at least over the short term. These findings from preclinical studies are consistent with the findings of the current study, which found that abecarnil had a significant anxiolytic effect with a more gradual onset than the full agonist alprazolam, had minimal withdrawal after a rapid taper, and had continued residual therapeutic effects after discontinuation.

The data reported here indicate that newer agents such as abecarnil may be quite useful for short-term management of anxiety, with good tolerability during treatment and minimal withdrawal symptoms after a swift taper. Future research should also be directed toward exploring whether compounds such as abecarnil, with potentially novel receptor mechanisms, may prove to be useful in the

long-term management of chronic anxiety disorders. The current study, for example, suggests that the intermittent use of a partial BZ agonist such as abecarnil could possibly allow for better treatment of chronic anxiety disorders such as GAD. Future research efforts should provide useful information on the usefulness of these new compounds as well as allow for exploration of new treatment strategies such as intermittent treatment of chronic anxiety disorders.

Drug names: alprazolam (Xanax), chloral hydrate (Noctec), clonazepam (Klonopin), diazepam (Valium and others), flumazenil (Romazicon).

REFERENCES

1. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8–19
2. Brawman-Mintzer O, Lydiard RB. Psychopharmacology of anxiety disorders: treatment resistance. Psychiatr Clin North Am 1996;3:31–88
3. Breier A, Paul SM. The GABA-A/benzodiazepine receptor: implications for the molecular basis of anxiety. J Psychiatr Res 1990;24:91–104
4. Haefly W, Martin JR, Schoch P. Novel anxiolytics that act as partial agonists at benzodiazepine receptors. Trends Pharmacol Sci 1990;11:452–456
5. Ballenger JC, McDonald S, Noyes R, et al. The first double-blind, placebo-controlled trial of a partial benzodiazepine agonist abecarnil (ZK 112-119) in generalized anxiety disorder. Psychopharmacol Bull 1991;27: 171–179
6. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised. Washington, DC: American Psychiatric Association; 1987
7. Spitzer R, Williams J, Gibbon M, et al. Structured Clinical Interview for DSM-IIIR. Washington DC: American Psychiatric Press; 1990
8. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–55
9. Lipman RS. Differentiating anxiety and depression in anxiety disorders: use of rating scales. Psychopharmacol Bull 1982;18:69–77
10. Guy W. ECDEU Assessment Manual for Psychopharmacology, revised. Rockville, Md: National Institute of Mental Health; 1976. US Dept Health, Education, and Welfare publication (ADM) 76–338
11. Derogatis LR, Lipman RS, Rickels K, et al. The Hopkins Checklist (HSCL): a self-report symptom inventory. Behav Sci 1974;19:1–15
12. Rickels K, Schweizer E, Case G, et al. Long-term therapeutic use of benzodiazepines, I: effects of abrupt discontinuation. Arch Gen Psychiatry 1990; 47:899–907
13. SAS Institute, Inc. SAS Procedures Guide for Personal Computers, version 6 edition. Cary, ND: SAS Institute; 1985
14. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22:719–748
15. Rickels K, Case WG, Downing RW, et al. One-year follow-up of anxious patients treated with diazepam. J Clin Psychopharmacol 1986;6:32–36
16. Rickels K, Fox IL, Greenblatt DJ, et al. Clorazepate and lorazepam: clinical improvement and rebound anxiety. Am J Psychiatry 1988;145:312–317
17. Gallager DW, Heninger K, Heninger G. Periodic benzodiazepine antagonist administration prevents benzodiazepine withdrawal symptoms in primates. Eur J Pharmacol 1986;132:31–38
18. Hernandez TD, Heninger C, Wilson MA, et al. Relationship of agonist efficacy to changes in GABA sensitivity and anticonvulsant tolerance following chronic benzodiazepine ligand exposure. Eur J Pharmacol 1989;170: 145–155