0145-6008/00/2405-0666$03.00/0
ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

Vol. 24, No. 5
May 2000

Pharmacological Treatments for Alcoholism: Revisiting Lithium and Considering Buspirone

Jan Fawcett, Howard M. Kravitz, Marcella McGuire, Michael Easton, Jeffrey Ross, Vincent Pisani, Louis F. Fogg, David Clark, Michael Whitney, Glenda Kravitz, Javaid Javaid, and Gregory Teas

Objective: Previous research has suggested that both lithium and buspirone could lessen alcoholics' desire to drink as well as reduce the actual amounts of alcohol consumed. The purpose of this study was to compare lithium and buspirone monotherapy with placebo on outcomes of abstinence, alcohol quantity consumed, treatment retention and compliance, and medication side effects.

Methods: We conducted a randomized, double-blind, placebo-controlled, three-arm parallel group, clinical trial that compared lithium and buspirone with placebo in 156 alcohol-dependent men.

Results: Study retention rates for the three treatment groups at 3 and 6 months, respectively, were 61% and 46% for lithium, 44% and 27% for buspirone, and 52% and 38% for placebo (p = NS, for 3 and 6 months). Overall abstinence rates were 28% and 19% at 3 and 6 months, respectively. However, mean daily quantities of alcohol consumed and percentage of drinking days decreased significantly ($p < 0.0001$) over time in all treatment groups. Differential improvement was seen only for the decrement in quantity consumed in the buspirone group, compared with the placebo group, but only at a trend level ($p = 0.07$). According to pill counts, compliance did not differ significantly among the treatment groups.

Conclusions: These results do not support the hypothesis that either lithium or buspirone, compared with placebo, produces differential reductions in alcohol consumption. The results suggest the need to enhance treatment retention to maximize outcomes.

Key Words: Alcoholism, Psychopharmacotherapy, Lithium, Buspirone, Depression.

A MAJOR GOAL of pharmacological research in the treatment of alcoholism is to develop safe and effective interventions to increase sustained abstinence during and after treatment and to lessen relapse drinking. An increasing number of agents appear promising with regard to their capacity to affect alcohol consumption, as evidenced by the growing body of literature on pharmacotherapies for alcohol dependence published particularly in the last 5 years (Anton, 1996; Garbutt et al., 1999; Gorelick, 1993; Litten and Allen, 1993; Moncrieff and Drummond, 1997; Sass et al., 1996; Schaffer and Naranjo, 1998).

However, few controlled clinical trials of lithium, and none involving the serotonergic agent buspirone, had been published at the time we began the study that we report herein. Our group has been involved in the evaluation of lithium carbonate for the treatment of patients with alcohol dependence since the early 1980s, and we initiated the current study with lithium and buspirone in 1990.

The two largest double-blind, placebo-controlled clinical trials of lithium in the treatment of alcoholism were conducted by Fawcett et al. (1987) and Dorus et al. (1989). Fawcett et al. (1987) evaluated 122 alcoholic men after inpatient alcohol treatment. Subjects who maintained a minimal lithium blood level of 0.4 mmol/liter or more, compared with both placebo-treated subjects and those failing to maintain this minimal blood level, had significantly higher abstinence rates (Fawcett et al., 1984, 1987). Depressive symptoms or a diagnosis of depression did not affect outcome. Because a measurable placebo was not used in this study, it was not possible to separate, with certainty, a lithium effect from a compliance effect. In contrast, Dorus et al. (1989) evaluated 457 male alcoholic outpatients in a multicenter Veterans' Affair Cooperative Study. They reported no differences in abstinence rates, reductions in the number of days spent drinking, or reduction in depressive symptom severity between the lithium or placebo groups for either depressed or nondepressed subjects. The controversy that these two large trials engendered with regard to lithium's efficacy was a sufficiently compelling rationale for undertaking this replication study. No subsequent controlled trial involving lithium has been published since the completion of these two major studies more than a decade ago.

From the Departments of Psychiatry (J.F., H.M.K., M.M., M.E., J.R., V.P., L.F.F., D.C., M.W., G.K.) and Preventive Medicine (H.M.K.), Rush-Presbyterian-St. Luke's Medical Center, Rush Medical College of Rush University (J.F., H.M.K., M.E., J.R., V.P., L.F.F., D.C.), and the Department of Psychiatry (J.J.), University of Illinois at Chicago, Chicago; and the Alexian Brothers Medical Center (G.T.), Elk Grove, Illinois.

Received for publication August 5, 1999; accepted March 10, 2000.

This study was supported by National Institute on Alcohol Abuse and Alcoholism Grant AA07645.

Reprint requests: Howard M. Kravitz, DO, MPH, Rush Institute for Mental Well-Being, 1725 West Harrison Street, Suite 955, Chicago, IL 60612.

Buspirone, an azapirone compound with serotonergic activity (5-HT_{1A} partial agonist), is marketed as an anxiolytic and has been shown to have antidepressant effects (Robinson et al., 1990). Preliminary data indicated that buspirone reduced the desire to drink as well as the actual amounts of alcohol consumed (Sussman, 1994). Recent efforts to examine buspirone's efficacy for the treatment of alcoholism were based primarily on its clinical effects and its lack of cross-tolerance with alcohol. Animal studies have shown that buspirone decreases ethanol consumption, and preliminary clinical research suggests that buspirone is associated with decreased drinking parameters in chronic alcoholics (Bruno, 1989; Sellers et al., 1985). Studies in alcohol-dependent subjects, particularly those with anxiety disorders, are somewhat contradictory but suggest that buspirone has some advantage over placebo (Bruno, 1989; Kranzler et al., 1994; Tollefson et al., 1992).

Malec et al. (1996b) and Garbutt et al. (1999) have reviewed five published controlled trials (Bruno, 1989; Kranzler et al., 1994; Malcolm et al., 1992; Malec et al., 1996a; Tollefson et al., 1992) that assess buspirone's efficacy in the treatment of alcohol dependence. Comorbid mood and anxiety disorders have complicated the interpretation of the outcomes of these studies. Malec et al. (1996b) concluded that buspirone's main effect was on the associated psychopathological symptoms and treatment retention rather than on alcohol consumption. More recently, George et al. (1999) found no difference in days to relapse between subjects treated with buspirone or placebo.

In this study, we examined the effectiveness of lithium carbonate and buspirone for the treatment of alcoholism in a double-blind randomized and placebo-controlled design. We attempted to resolve the question of whether subjects treated with lithium or buspirone, compared with subjects treated with a placebo pill, could demonstrate a higher rate of abstinence, lower amounts of alcohol consumed, or longer treatment retention in a program of low intensity support. We hypothesized that subjects assigned to either of the two active treatments would (1) more successfully maintain abstinence, and (2) consume less alcohol than subjects who received placebo. Because dropout rates of approximately 50% or more (Bolotova et al., 1977; Florenzano et al., 1982; Kline et al., 1974; Merry et al., 1976) and noncompliance (Gordis et al., 1989) have been major concerns, we considered study retention a primary outcome.

METHODS

Subjects

We recruited male alcohol-dependent volunteers between 1991 and 1995 for this 6-month, double-blind, placebo-controlled clinical trial of lithium and buspirone. All subjects gave their verbal and written informed consent to participate after the procedures had been thoroughly explained by study staff. The study procedures followed institutional guidelines and were approved by the Human Investigation Committee of Rush-Presbyterian-St. Luke's Medical Center.

All study candidates were recruited as outpatient volunteers from responses to public information, direct advertising, hospital referrals, and our inpatient and outpatient alcoholism rehabilitation programs. Enrollment and follow-up activities occurred at three sites, i.e., two community hospitals and a tertiary care medical center. Candidates were screened with a two-stage process that involved telephone, followed by face-to-face, interviews. Females were excluded from entry as study subjects because of the possible harmful effects of lithium carbonate on pregnant women and because of the relatively low prevalence rate of alcohol-dependent women available at the recruitment sites.

Exclusion criteria consisted of unstable medical conditions, psychiatric symptoms that required immediate treatment (e.g., psychosis, and suicidal or homicidal behavior), a nonalcohol substance dependence diagnosis (except nicotine dependence) within the 6 months preceding study entry, clinically significant drug abuse within the 4 months preceding study entry, and current disulfiram use. (We did not exclude one subject diagnosed with comorbid cocaine dependence who tested negative for all drugs at baseline screening and during treatment.) Study candidates who used naltrexone or other medications known to affect alcohol consumption, which were not in general use for this indication at the time the study began, were excluded.

Study candidates also were required to successfully complete at least two of three tests on a pretreatment neurocognitive functioning screening battery. Neurocognitive functioning was assessed with the Shipley Institute of Living Scale (Shipley, 1940), the Symbol Digit Modalities Test (Smith, 1973), and the Trailmaking Test (Parts A and B) (Leckliter and Matarazzo, 1989; Reitan, 1958). IQ estimates were derived from the conversion table developed by Paulson and Lin (1970) for the transformation of Shipley raw total scores into estimates of Wechsler Adult Intelligence Scales scores (Wechsler, 1981). Candidates who failed two or more of these tests were excluded from study participation.

Altogether, 373 of 549 study candidates were excluded from participation. The three largest categories of nonparticipants were men who did not show up for the face-to-face interview ($n = 116$; 31%), or who decided that they were not interested in the study ($n = 109$; 29%), or who failed the neurocognitive test battery ($n = 85$; 23%). Nine percent ($n = 32$) were excluded because comorbid medical problems and 8% ($n = 31$) were excluded for miscellaneous reasons. One subject who did not meet criteria for current alcohol dependence was inadvertently enrolled; his data were excluded from all data analyses.

All subjects received a comprehensive history and physical examination, an electrocardiogram, and laboratory tests (including urinalysis, urine toxicology, complete blood count, thyroid battery, liver enzymes, renal function, and electrolytes). Candidates who were determined to be ineligible to participate were referred to appropriate treatment services.

Procedure

A total of 175 men between 21 and 60 years of age who met DSM-III-R (American Psychiatric Association, 1987) criteria for alcohol dependence within 6 months of study entry and who had completed detoxification were randomized to placebo or one of the two active treatments, either lithium or buspirone. Baseline assessments took place before the random assignment to a drug therapy condition and were completed within 1 to 4 weeks. Subjects requiring detoxification were referred for treatment and then reevaluated for study entry after acute medical management was no longer needed. Subjects could begin study medication after 5 days of abstinence, which was determined by self-report and Breathalyzer results. Subjects were tested for breath alcohol at least once during the screening period.

Diagnostic Assessment. Lifetime and recent diagnoses of alcohol dependence and other nonalcohol substance use disorders (including duration and severity), and other past and current axis I psychiatric disorders were made by using the Structured Clinical Interview for DSM-III-R (SCID) (Spitzer et al., 1991, 1992). Subjects also were rated on the Global Assessment of Functioning Scale (Goldman et al., 1992; Jones et al., 1995), a modified version of the Global Assessment Scale (Endicott et al., 1976).

Experienced psychiatric nurses who completed extensive training on the use of the study instruments conducted all clinical evaluations. SCID interviewers were trained by experienced clinicians who, themselves, were trained according to the standards established for the National Institute of Mental Health Collaborative Psychobiology of Depression Study. They met with the trainers at 2-week intervals to review audiotaped interviews and the SCID reports. At the meetings, cases were discussed and group ratings were made on diagnoses and Global Assessment of Functioning Scale scores. With regard to sensitive measures such as the SCID suicide item, all raters had to demonstrate perfect agreement. Formal interreliability scores are not available.

Other Measures of Psychopathology. The Beck Depression Inventory (Beck et al., 1961) and the Beck Anxiety Inventory (Beck et al., 1988) were administered at baseline and follow-up visits throughout the study. Social and occupational impairment was assessed at baseline with the self-rated Social Adjustment Scale (Weissman and Bothwell, 1976; Weissman et al., 1981).

Measurement of Drinking. Subjects were asked about drinking or drug use for the period of 30 days before baseline assessment, and for the period between each clinic visit. If a subject failed to show up for follow-up, the nurse attempted to contact him by telephone. Available significant others were interviewed to confirm the self-report data. Drinking was recorded for any time period in which either the subject or his informant reported drinking. Because this information was collected at follow-up visits rather than in a day-by-day diary format, these data are not directly comparable with those derived from the Time-Line Follow-Back (Sobell et al., 1980) and may be subject to recall and reporting bias. The Time-Line Follow-Back was not the standard method for recording drinking data when we began study intake.

The indicators measured included frequency of drinking days, quantity consumed on drinking days, and drug use since last visit. Alcohol consumption was quantified as standard ethanol units (SEUs) according to a standard formula (1 SEU = 1 oz of spirits = 4 oz of wine = 12 oz of beer) (Sobell et al., 1980).

Nonabstinence was defined as the first episode of drinking, however brief or limited, after the start of treatment. Nonabstinence was determined by the presence of alcohol in the blood or by urine alcohol screen, or by any self- or informant (e.g., significant other) report of drinking behavior. We combined all available sources into a single indicator variable for whether a subject drank, with the assumption that the most negative report was the most accurate, to maximize the probability of detecting drinking behavior (Fuller et al., 1988). Drinking during the treatment phase did not result in automatic study exclusion.

Alcohol and Drug Screens. Subjects with and without a history of drug abuse were routinely and randomly tested for the presence of alcohol and drugs. At baseline and at 6-month review visits, standard laboratory blood alcohol levels and a urine toxicology battery were obtained. During follow-up (weekly during the first month and every other week for the next 5 months), research nurses obtained Breathalyzer and blood samples to assess alcohol use. Follow-up alcohol and drug monitoring was performed by using the Ontrack® Abuscreen (Roche, Nutley, NJ) urine toxicology kits and Breathalyzer.

Medication Dosage. Study medication was dispensed in capsules containing either 300 mg of lithium carbonate, 10 mg of buspirone, or placebo. Initially, subjects were prescribed one capsule daily, which was increased to one capsule twice daily after 3 days. Thereafter, the dose was increased every fourth day by one capsule until they reached a dose of two capsules twice daily. Our maximum daily dose of buspirone, 40 mg/day, equaled the mean maximal daily dosage Kranzler and Meyer (1989) prescribed in their earlier study that involved a high-anxiety subgroup of alcohol-dependent inpatients.

Management of side effects was addressed through a standard protocol. If a subject experienced clinically significant side effects, the dose was decreased; the minimal allowable dose to remain in the study was two capsules daily. If side effects did not remit, the study physician evaluated the subject, and, if indicated, the study medication was discontinued. Dose changes in response to side effects were made by the blinded investigator (M.E.).

Compliance Monitoring. Subjects kept a medication diary that was reviewed at each visit along with pill counts. Subjects were considered compliant if there was evidence that they took at least 80% of their prescribed doses since the previous visit.

Samples of blood for lithium and for buspirone were collected at each visit, beginning after 1 week of medication. A nonblinded physician (J.R.) monitored all lithium levels and adjusted doses as needed to prevent toxicity and to achieve an optimal blood level of 0.4 to 1.0 mmol/liter, in accordance with results from our earlier study (Fawcett et al., 1987). Buspirone treatment compliance was followed by measuring, in blood, its major metabolite, 1-(2-pyrimidinyl)piperazine, by high-performance liquid chromatography with ultraviolet detection, as described by Diaz-Marot et al. (1989). Subjects who received buspirone did not undergo dose adjustments once a target dose of 20 mg twice daily was achieved except as needed to control side effects. To preserve the double blind, the nonblinded physician advised random dose adjustments for subjects who received placebo.

The nonblinded physician did not reveal group assignments to study personnel and had no clinical responsibilities during the course of the study. We did not routinely ask, at the end of each subject's treatment, whether the subject or clinical rater had a guess as to the subject's random assignment to buspirone, lithium, or placebo.

Psychosocial Treatment and Support. Supportive interventions were administered to all subjects at the time of their follow-up visits (described below) by research nurses who were trained to deliver the supportive intervention in a standard manner. The individual therapeutic intervention consisted of encouragement to maintain abstinence and supported the subjects' efforts to achieve this. The research nurse inquired, in general, about how the subject was doing and, more specifically, focused on drinking behavior. Although nondirective, the research nurse gave advice where appropriate. Relapse was addressed in a supportive manner and with encouragement for the subject to resume abstinence. Subjects also were encouraged to attend Alcoholics Anonymous (AA) meetings.

Follow-Up Data Collection. Clinical research nurses interviewed subjects about their medication compliance and side effects, drinking and drug status, medical visits, adherence to other prescribed treatments and attendance at self-help meetings, and mood at each follow-up visit. Visits were weekly for the first 2 weeks, biweekly through the third month, and then monthly for the last 3 months of the clinical trial. When subjects failed to return for follow-up appointments, they received three telephone calls followed by a letter of concern. If no contact was made, the subject was dropped from the study.

Data Analysis

Our intent-to-treat data set consists of 156 subjects who (1) completed the SCID depression and alcohol use disorders modules, (2) were randomized to treatment, (3) received at least one treatment dose, and (4) returned for at least one postbaseline follow-up assessment. Our criteria required that subjects remain in treatment for at least 1 week to be included in these analyses, because we presumed that the therapeutic effects of the study medications would be delayed.

The three treatment groups were compared on baseline sociodemographic and clinical variables by using χ^2 and Fisher's exact tests on categorical variables, analysis of variance on continuous variables, and nonparametric tests on nonnormally distributed continuous variables (Agresti and Finlay, 1986.). Post hoc comparisons were performed if exploratory analyses indicated a need to determine which groups differed and the extent to which they differed.

Treatment effects on the time to first drink and the time to dropout were analyzed by using survival analysis methods (Lee, 1992.). Dropout was analyzed by using the Kaplan-Meier method and survival curves were compared with the log rank test. Time to first drink was analyzed by using Cox regression. We counted subjects as abstinent for the amount of time that they had participated if they were removed from the treatment study

because of protocol violation or if they discontinued treatment before drinking again. They were not excluded from the analysis despite dropping out before the end of the study (Fuller, 1991). Other investigators have considered abstinent dropouts as treatment failures at the time of termination, with the assumption, as a worst case scenario, that their date of first return to drinking was the date of dropout (Dorus et al., 1989; O'Malley et al., 1996); we considered this option as too conservative.

We used random-effects regression models to examine the effects of treatment on quantity of alcohol consumed and percentage of days drank (Hedeker and Gibbons, 1997). This method permits the analysis of data on subjects who are not measured at the same number of time points by averaging over their missing data patterns. Three time point variables (random effects) were constructed for these repeated-measures analyses, i.e., time 0, the end of the 1-month pretreatment baseline period (n = 156); time 1, months 1 through 3 (n = 155); and time 2, months 4 through 6 (n = 79).

Comorbid depression may predict relapse drinking and confound the assessment of alcohol treatment efficacy (Greenfield et al., 1998; Hasin and Nunes, 1998; Mason et al., 1996). Therefore, we conducted secondary analyses on study retention by stratification, on the SCID, of the current depression status in the Kaplan-Meier analysis and on the drinking outcome variables by adding depression status as a covariate in the random-effects and Cox regression models.

Statistical analyses were conducted by using the Statistical Package for the Social Sciences (SPSS for Windows, Release 6.0; SPSS, Chicago, IL) and MIXREG (Hedeker and Gibbons, 1996). Sample sizes for these analyses varied because of missing data. The α level was set to 0.05 for statistical significance, and results are reported as two-tailed tests of hypotheses unless otherwise specified. Trend levels for significance ($0.05 < p < 0.1$) also are reported in the case of clinically meaningful findings. Data are presented as mean ± 1 SD values unless otherwise specified.

RESULTS

Baseline Group Differences

The 156 men comprising the intent-to-treat sample did not differ significantly from the 19 men who either dropped out of treatment before completion of at least one post-baseline assessment (n = 14) or did not complete the mood disorders module of the SCID (n = 5) on any comparisons of pretreatment sociodemographic, drinking, or other clinical characteristics (all $p > 0.10$).

Table 1 shows that the three treatment groups did not differ significantly on sociodemographic characteristics or baseline cognitive functioning. The buspirone group drank nonsignificantly larger amounts on a smaller percentage of days in the 30 days before study entry, thus drinking heavier on drinking days (Kruskal-Wallis χ^2 = 5.94; df = 2; p = 0.051).

A SCID current mood disorder was diagnosed in 49% (76 of 156); but the three groups did not differ significantly. SCID anxiety disorders were diagnosed in 8% (n = 13); 5 of 13 had comorbid depressive and anxiety disorders. Although current anxiety disorders were most prevalent in the lithium-treated group (χ^2=10.54; df = 2; p = 0.005), buspirone-treated subjects had the highest mean baseline Beck Depression Inventory (F = 2.77; df = 2, 151; $p <$ 0.07) and Beck Anxiety Inventory (F = 3.47; df = 2, 150; p = 0.03) scores.

Treatment Retention and Attrition

Of the 156 subjects, 82 (53%) completed the first 3 months and 59 (38%) completed the 6-month therapeutic trial. Ten subjects were withdrawn for administrative (i.e., protocol) reasons, nine in the first 3 months. The most frequent reason was violation of the double blind (e.g., opening the medication capsule to determine its contents) (n = 5); four of these five subjects drank before leaving the study. Other reasons for termination included requiring antidepressant treatment for depression (n = 2); suffering a myocardial infarction (n = 1); taking disallowed medication (disulfiram, n = 1; this subject also drank); and discontinuing study medication (n = 1).

According to Kaplan-Meier analysis, at the end of 3 months, the lithium group had a nonsignificantly higher retention rate (lithium, 61%; placebo, 52%; buspirone, 44%; log rank test = 4.00; df = 2; p = 0.14). After 6 months, the lithium group still had the highest retention rate (lithium, 46%; placebo, 38%; buspirone, 27%; log rank test = 5.56; df = 2; p = 0.06), which was significant only among nondepressed subjects (log rank test = 7.31; df = 2; $p < 0.03$). The nondepressed lithium (45%; log rank test = 6.95; df = 1; p = 0.008) and placebo (45%; log rank test = 3.21; df = 1; p = 0.07) groups, compared with the nondepressed buspirone group (16%), had higher retention rates.

Compliance

The percentages of prescribed doses taken were recorded at each follow-up visit. Because the intervals between assessments were not equal, and to account for missing data, weighted mean daily doses were computed. Although the study protocol allowed a maximum of four capsules daily, subjects who acknowledged taking more accounted for reported mean doses beyond the upper limit.

Adjusted average compliance was 88 ± 12% and did not differ significantly between treatment groups. The three groups took a similar average number of capsules daily, approximately 3.3 ± 0.7 (Kruskal-Wallis χ^2 = 0.70; df = 2; p = 0.70). Mean daily doses for the two active treatment groups were as follows: lithium, 982 ± 181 mg (range of mean daily doses = 575-1214 mg/day; blood level = 0.63 ± 0.23 mmol/liter); and buspirone, 33 ± 7 mg (range of mean daily doses = 18–43 mg/day; 1-(2-pyrimidinyl)piperazine blood level = 0.44 ± 0.34).

Drug Treatment Effects

Abstinence. Only 44 subjects (28%) were abstinent through 3 months, and 29 (19%) completed the 6-month study and remained abstinent. The three treatment groups did not differ significantly in the proportions abstinent at 3 (χ^2 = 3.13; df = 2; p = 0.21) or 6 months (χ^2 = 1.22; df = 2; p = 0.54).

The Cox regression analysis for time to first drink showed a significant treatment group-by-depression interaction (likelihood ratio test = 10.11; df = 2; p = 0.006),

Table 1. Baseline Demographic and Clinical Characteristics of 156 Alcohol Dependent Subjects

	Lithium (Li)	Buspirone (B)	Placebo (P)	p
No. of subjects	56	48	52	
Sociodemographics				
Mean (± SD) age, y	41.0 (8.0)	38.8 (8.3)	40.0 (7.8)	NS
Race/ethnicity, *n* (%)				NS
White	48 (86)	41 (85)	42 (81)	
African American	5 (9)	4 (8)	2 (4)	
Hispanic	3 (5)	2 (4)	8 (15)	
Asian	0	1 (2)	0	
Marital status, *n* (%)				NS
Married	26 (46)	16 (33)	23 (44)	
Separated/divorced/widowed	12 (21)	12 (25)	17 (33)	
Never married	12 (21)	14 (29)	8 (15)	
Cohabiting	6 (11)	6 (13)	4 (8)	
Mean (± SD) education, y	13.9 (2.2)	14.0 (2.1)	13.7 (2.1)	NS
Mean (± SD) IQ[a]	116.4 (4.8)	114.9 (5.7)	116.4 (5.3)	NS
Employed, *n* (%)	46 (82)	38 (79)	40 (77)	NS
Median annual income range[b]	$40–49,000	$30–39,000	$40–49,000	NS
Drinking				
Mean (± SD) age first met alcohol dependence criteria, years	20.5 (6.5)	19.5 (4.8)	20.0 (3.6)	NS
Mean (± SD) pretreatment drinking, 30 days before study entry				
Percentage of days drank in 30 days prestudy	75 (28)	67 (30)	72 (30)	NS
SEUs (standard ethanol units) per day	10.9 (6.1)	13.5 (10.4)	11.2 (8.1)	NS
SEUs per drinking day	16.0 (9.4)	20.4 (11.8)	15.1 (7.7)	0.05[c]
Symptom ratings				
Mean (± SD) Baseline Beck Depression Inventory[d]	10.7 (8.5)	14.5 (9.5)	11.6 (6.9)	<0.07[e]
Mean (± SD) Baseline Beck Anxiety Inventory[f]	7.8 (7.7)	11.9 (9.2)	9.0 (6.9)	0.03[g]
Mean (± SD) Global Assessment of Functioning Scale score[h]	50.1 (11.2)	48.2 (9.7)	52.2 (11.2)	NS
Mean (± SD) Social Adjustment Scale overall score[a]	0.93 (0.43)	0.93 (0.34)	0.95 (0.33)	NS
DSM-III-R current mood[i] and anxiety[j] diagnoses, *n* (%)				
Major depression	15 (26.8)	12 (25.0)	16 (30.8)	
Dysthymia	1 (1.8)	2 (4.2)	2 (3.8)	
Double depression[k]	2 (3.6)	3 (6.3)	3 (5.8)	
Depression NOS[l]	5 (8.9)	6 (12.5)	9 (17.3)	
Panic disorder	0	1 (2.1)	0	
Phobias (social or simple)	5 (8.9)	0	0	
Obsessive–compulsive disorder	1 (1.8)	0	0	
Generalized anxiety disorder	3 (5.4)	0	0	
Posttraumatic stress disorder	2 (3.6)	0	0	
Anxiety NOS[l]	1 (1.8)	1 (2.1)	1 (1.9)	

[a] Data missing for two subjects.
[b] Data missing for four subjects.
[c] Kruskal-Wallis $\chi^2 = 5.94$; $df = 2$, $p = 0.05$; [B > P].
[d] Data missing for two subjects.
[e] $F = 2.77$; $df = 2, 151$; $p < 0.07$.
[f] Data missing for three subjects.
[g] $F = 3.47$; $df = 2, 150$; $p = 0.03$; [B > L; $p = 0.05$].
[h] Data missing for one subject.
[i] Depressive disorders [*n* (%): lithium = 23 (41%); buspirone = 23 (48%); placebo = 30 (58%)]; $\chi^2 = 3.00$; $df = 2$; $p = 0.22$.
[j] Anxiety disorders [*n* (%): lithium = 10 (18%); buspirone = 2 (4%); placebo = 1 (2%); two lithium-treated subjects had two anxiety disorders]; $\chi^2 = 10.41$; $df = 2$; $p = 0.005$.
[k] Major depression plus dysthymia.
[l] Not otherwise specified.

which indicates that a depressive disorder at the beginning of treatment may be a moderator of treatment effect. Among depressed subjects, the hazard ratio for drinking again was two times higher in the lithium group than in the placebo group (hazard ratio = 2.03; Wald test = 4.18; $df = 1$; $p = 0.04$). Among nondepressed subjects, the hazard

Table 2. Alcohol Consumption: Quantity and Percentage of Days Drank

Drinking outcome	SEUs per day (± SD) [*n*]		
	Lithium	Buspirone	Placebo
Pretreatment baseline	10.9 ± 6.1 [56]	13.5 ± 10.4 [48]	11.2 ± 8.1 [52]
Months 1–3	0.69 ± 1.0 [55]	0.97 ± 1.7 [48]	0.81 ± 1.5 [52]
Months 4–6	0.64 ± 1.3 [34]	0.25 ± 0.45 [18]	0.39 ± 1.0 [27]
Percent days drank (± SD) [*n*]			
Pretreatment baseline	75 ± 28 [56]	67 ± 30 [48]	72 ± 30 [52]
Months 1–3	10 ± 15 [55]	7 ± 10 [48]	8 ± 14 [52]
Months 4–6	10 ± 17 [34]	4 ± 7 [18]	6 ± 14 [27]

ratio for drinking again was two times higher in the buspirone group compared with the placebo group (hazard ratio = 2.23; Wald test = 4.75; $df = 1$; $p = 0.03$).

Drinking: Quantity and Frequency. Data for the continuous drinking variables "SEUs per day" and "percent days drank" were aggregated for the 30 days of pretreatment and across all follow-up visits for which these data were available, to get averages for the two variables at pretreatment and at months 1 through 3 and 4 through 6 for each subject. These data were analyzed by using random-effects regression.

Table 2 shows the distribution of the two drinking outcome measures by treatment group assignment. Compared with the placebo-treated subjects, buspirone- but not lithium-treated subjects had a higher average SEU intake pretreatment ($z = 2.04$; $p = 0.04$). After controlling for this baseline treatment group difference, the time effect is significant for the quantity of alcohol consumed. During treatment, the average trend across time in number of SEUs consumed daily decreased significantly among placebo-treated subjects ($b = -6.09$; $z = -8.96$; $p < 0.0001$). The mean difference in trend lines for the average SEUs consumed by active drug-treated relative to placebo-treated subjects shows that the improvement across time was greater for the buspirone-treated but not the lithium-treated subjects, but only at a trend level for significance ($b = -1.85$; $z = -1.81$; $p = 0.07$). At the next step, we examined the joint significance of the depression-related model term. The baseline depression status and the interaction of treatment and time with depression status were not significantly related to mean SEU consumption above the influences of treatment group, time, and the group-by-time interaction (likelihood ratio $\chi^2 = 10.48$; $df = 6$; $p > 0.10$).

For the outcome of average percentage of days drank, there were no statistically significant baseline differences among treatment groups. As shown in Table 2, the time effect was significant with regard to the decrement in the average percentage of days drank during treatment ($b = -0.37$; $z = -12.54$; $p < 0.0001$). However, the treatment group-by-time interaction test indicated that neither active treatment was significantly more effective than placebo. Addition of the baseline depression status and the interaction of treatment and time with depression status also did not reveal any statistically significant differential treatment effects (likelihood ratio $\chi^2 = 12.00$; $df = 6$; $p > 0.05$).

Among the 87 subjects who drank during the first 3 months, 57 (66%) would be considered heavy drinkers and averaged at least five drinks per drinking day. The three groups did not differ significantly in the proportion of subjects who resumed heavy drinking or in the average amount consumed per drinking day (9.4 ± 6.9 SEUs).

Concomitant Treatment

In addition to the supportive psychosocial intervention provided at follow-up visits for all subjects, a little more than half ($n = 80$; 51%) of the sample attended AA meetings while they participated in the study. Proportionally fewer placebo-treated subjects (37%), compared with subjects in the two active treatment groups (lithium, 60%; buspirone, 58%), attended at least one AA meeting ($\chi^2 = 6.65$; $df = 2$; $p < 0.04$). Among AA attendees, the three groups did not differ significantly in the average number of meetings attended weekly ($F = 1.31$; $df = 2,77$; $p = 0.28$).

Screening for Alcohol and Drug Use

Of 136 subjects tested at least once (range = 1–10), 23 had at least one positive test (17.4%; placebo, $n = 10$; buspirone, $n = 4$; lithium, $n = 9$). Our rate of positive drug screens during treatment was 7.2% (57 of 783 tests). Subjects admitted all 23 positive tests for alcohol before the results were available for confirmation, which suggests some credibility of self-reported drinking and abstinence.

Medication Side Effects and Discontinuation

Side effects were reported by 90 (58%) subjects and ranged from 44% (23 of 52) on placebo to 61% (34 of 56) on lithium and 69% (33 of 48) on buspirone ($\chi^2 = 6.47$; $df = 2$; $p < 0.04$). Compared with placebo-treated subjects, a significantly higher proportion of buspirone- ($\chi^2 = 5.14$; $df = 1$; $p = 0.02$) but not lithium- ($\chi^2 = 2.32$; $df = 1$; $p = 0.13$) treated subjects experienced side effects. Only three subjects discontinued medication specifically because of side effects (two on buspirone and one on lithium). The most commonly reported groups of side effects were neurological (particularly dizziness; $n = 33$) and gastrointestinal ($n = 33$). The former group was the only one reported significantly more frequently by subjects who received one of the active medications ($\chi^2 = 40.1$; $df = 2$; $p < 0.00001$), i.e., 52% ($n = 25$) of subjects who received buspirone

compared with 10% ($n = 5$) of subjects who received placebo ($\chi^2 = 19.5$; $df = 1$; $p = 0.00001$). Gastrointestinal symptoms were reported more frequently by lithium-treated subjects ($n = 17$; 30%), but the difference among treatment groups was not statistically significant ($\chi^2 = 4.55$; $df = 2$; $p = 0.10$).

DISCUSSION

The results of this therapeutic trial fail to confirm the major hypothesis that active medications in comparison with placebo treatment would produce meaningful reductions in the amounts of alcohol drunk and improve treatment retention in groups of male alcohol-dependent volunteers. Active pharmacotherapy was associated with limited therapeutic benefits. To some extent, our findings reveal the opposite effect. Although the buspirone group, as a whole, consumed a trend level less alcohol than the placebo group did over the course of treatment, nondepressed subjects treated with buspirone had the lowest study retention and abstinence rates. Moreover, lithium was less effective than placebo in reducing alcohol consumption among depressed subjects.

These results could be attributed to random fluctuation. A second plausible explanation is that nondepressed buspirone-treated subjects may have dropped out earlier because of initial medication side effects. A third alternative is whether the presence or absence of depression should be considered in pharmacotherapy treatment matching. This possibility has been suggested by Mason et al. (1996) and Greenfield et al. (1998) but not by the earlier data of Dorus et al. (1989) or us (Clark and Fawcett, 1989; Fawcett et al., 1987). A larger sample is needed to test this hypothesis.

Overall, our results are consistent with the results of previous syntheses of data from randomized controlled trials on the efficacy of pharmacotherapies for maintaining abstinence in alcohol-dependent patients. Specifically, Garbutt et al. (1999) found that all positive findings with lithium were limited to studies that did not control for comorbid depression. Malec et al. (1996b) concluded that buspirone's main effect in the treatment of alcoholism is on associated psychopathological symptoms rather than on alcohol consumption per se.

Ours is the first randomized controlled trial to specifically examine buspirone's efficacy for alcohol-dependent subjects with comorbid depression. Previous mean buspirone doses ranged from 20.5 to 52.5 mg/day (Malec et al., 1996b), compared with a mean dose of 33 mg/day in our study. One may suggest that our subjects may not have received an adequate trial. Although our subjects had a mean blood level of 0.44 ng/ml, there is no published literature on treatment samples with which to compare this level. Furthermore, 69% reported side effects, which may have limited further dose increments.

Our study was limited by our relatively high dropout rate, leading to incomplete ascertainment of outcomes. In terms of treatment attrition, our total dropout rates were 47% and 62% at the end of 3 and 6 months, respectively. Our high rate of attrition may reflect, among the possible contributory factors, both the relative infrequency of our supportive intervention and the nonspecific nature of this therapy. Although the intervention may have helped some subjects maintain abstinence and forestalled earlier dropping out, others may have required more intensive supportive interventions. Dropouts because of medication side effects, as in other similar clinical trials (Garbutt et al., 1999), was low (2%).

Our high dropout rates may reflect the severity of our subjects' alcohol dependence and resistance to treatment. Consistent with this notion, Anton et al. (1999) suggested that the findings from their 12-week study of cognitive behavioral therapy plus either naltrexone or placebo for DSM-III-R–diagnosed alcohol-dependent men and women, which included a 83% retention rate, may have limited capability of generalization because of the more favorable characteristics of their sample (e.g., no comorbidity and less severe dependence), which they selected to minimize the type II error rate. Almost half of our subjects had comorbid depression at baseline, and a little more than half received AA treatment during the course of the study. Others have reported study retention of less than 70%. Review of a few of the major treatment studies of the past decade indicates that sample characteristics must be considered, especially the independent and joint contributions to low retention rates of depression, severity of alcohol dependence, and study duration. Mason et al. (1996) conducted a 6-month study of desipramine for alcohol-dependent patients with or without a DSM-III-R diagnosis of major depression; overall, only 31.4% completed the study. Project MATCH subjects completed 8.3 to 9.3 weeks of the 12-week trial and 66% to 68% of scheduled treatment sessions (Project Match Research Group, 1997); they did not indicate the percentage of Diagnostic Interview Schedule-diagnosed cases of depression in their sample. In the combined analysis of O'Malley and Volpicelli's 12-week naltrexone versus placebo trials (O'Malley et al., 1995), discontinuation rates of 34% and 44% from the naltrexone and the placebo groups, respectively, were reported; their samples had "no (other) significant psychiatric disease."

These data also reconfirm conclusions from our original study that treatment compliance per se is associated with improved outcomes. Garbutt et al. (1999) observed that the effect of compliance on outcome measures rarely has been analyzed. However, staying in treatment itself may have a significant effect on symptomatic drinking. Whether this represents greater motivation on the part of these subjects or is simply the effect of adhering to treatment and performing newly learned behaviors is unclear. It seems evident that dropout reduction is an outcome that requires attention in any alcohol treatment strategy. In addition, greater focus should be placed on improving patient com-

pliance with the fundamental components of their treatment.

Although this was not a study of treatment versus nontreatment, in general, subjects in all three treatment groups improved despite our inability to demonstrate an overall effect of lithium or buspirone on alcohol consumption. It is possible that our supportive intervention was therapeutic in its contribution to the reduced symptomatic drinking. Because all subjects received this intervention, we cannot control for its effect. However, the apparent significant effects of psychosocial treatment highlight the importance of using placebo-controlled trials to evaluate the efficacy of any pharmacotherapy for alcoholism.

One might wonder why the results of this study were different than our earlier study, which showed a delayed time to the onset of drinking in the group treated with lithium carbonate compared with placebo (Fawcett et al., 1987). The previous study was undertaken in subjects who were hospitalized for treatment, stabilized, and started on medication about 7 days before discharge; the dropout rate was lower in this study than in the present study. One conclusion that can be drawn from these results and from the literature is that dropout is very important in interpreting the outcomes of these sorts of studies. It is unclear if different results that were obtained were attributable to substantive differences or differential dropout rates. Until the motivation for patients who choose to drop out of studies is better understood, it will be difficult to interpret results from these types of studies. In the present study, medications may have been ineffective to control drinking because the uncontrolled drinkers may have dropped out prematurely, before realizing its therapeutic benefits.

It is important to emphasize that, despite finding no clear advantage for pharmacotherapies over placebo, various study limitations may have contributed to the negative results and masked any potential advantages for the treatment conditions that we tested. We have already discussed the potential limitations of attrition or high dropout rates and attendant biases in ascertaining outcome. By producing smaller cell sizes, dropouts reduce the power to detect differences in outcomes. However, before conducting this study, we calculated that 42 subjects per treatment group were needed to achieve a power of 0.80 with the type I error rate set at 0.05. Another possible source of bias concerns the double blind. We mentioned that a few subjects opened their study capsules; however, we have no way to determine whether others did the same. Indeed, this could be a problem with any clinical trial in which study medications are dispensed in capsule form. Perhaps of greater concern is the fact that an undetermined number of subjects in any clinical trial figure out the identity of their treatment, particularly if placebos are included (Greenberg and Fisher, 1989).

Finally, the negative findings from our study are instructive. They have major implications for treatment and further study. Further analyses of the present database may provide clues to strategies for reduction of the number of dropouts, enhancement of compliance, and maximization of outcomes.

ACKNOWLEDGMENT

The authors thank Dr. Robert Zadylak, and the staff members (who are too numerous to mention individually) at Rush-Presbyterian-St. Luke's Medical Center, Alexian Brothers Medical Center, and Christ Community Hospital for their help in subject recruitment and for their diligence in conducting all aspects of patient care.

REFERENCES

Agresti A, Finlay B (1986) *Statistical Methods for the Social Sciences.* 2nd ed. Dellen Publishing, San Francisco.

American Psychiatric Association (1987) *Diagnostic and Statistical Manual of Mental Disorders.* 3rd ed, revised. American Psychiatric Association, Washington, DC.

Anton RF (1996) Neurobehavioral basis for the pharmacotherapy of alcoholism: Current and future directions. Alcohol Alcohol (Suppl. 1) 1:43–53.

Anton RF, Moak DH, Waid R, Latham PK, Malcolm RJ, Dias JK (1999) Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics: Results of a placebo-controlled trial. Am J Psychiatry 156:1758–1764.

Beck AT, Epstein N, Brown G, Steer RA (1988) An inventory for measuring clinical anxiety: Psychometric properties. J Consult Clin Psychol 56:893–897.

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J (1961) An inventory for measuring depression. Arch Gen Psychiatry 4:561–571.

Bolotova ZN, Polotnikov AG, Barv AM (1977) Lithium treatment in alcoholic patients. Zh Nevropatol Psikhiatr 77:1235–1237.

Bruno F (1989) Buspirone in the treatment of alcoholic patients. Psychopathology (Suppl. 1) 22:49–59.

Clark DC, Fawcett J (1989) Does lithium carbonate therapy for alcoholism deter relapse drinking? Recent Dev Alcohol 7:315–328.

Diaz-Marot A, Puigdellivol E, Salvatella C, Comellas L, Gassiot M (1989) Determination of buspirone and 1-(2-pyrimidinyl)piperazine in plasma by high-performance liquid chromatography. J Chromatogr 490:470–473.

Dorus W, Ostrow DG, Anton R, Cushman P, Collins JF, Schaefer M, Charles HL, Desai P, Hayashida M, Malkerneker U, Willenbring M, Fiscella R, Sather MR (1989) Lithium treatment of depressed and nondepressed alcoholics. JAMA 262:1646–1652.

Endicott J, Spitzer RL, Fleiss JL, Cohen J (1976) The Global Assessment Scale: A procedure for measuring overall severity of psychiatric disturbance. Arch Gen Psychiatry 33:766–771.

Fawcett J, Clark DC, Aagesen CA, Pisani VD, Tilkin JM, Sellers D, McGuire M, Gibbons RD (1987) A double-blind, placebo-controlled trial of lithium carbonate therapy for alcoholism. Arch Gen Psychiatry 44:248–256.

Fawcett J, Clark DC, Gibbons RD, Aagesen CA, Pisani VD, Tilkin JM, Sellers D, Stutzman D (1984) Evaluation of lithium therapy for alcoholism. J Clin Psychiatry 45:495–499.

Florenzano R, Feuerhake O, Retamal P, Venegas F, Yazigi C, Palma MI (1982) Ensayo terapeutico de carbonato de litio en pacientes alcoholicos ambulatorios. Rev Med Chile 110:1071–1074.

Fuller RK (1991) Assessment of treatment outcome. Alcohol Alcohol Suppl 1:519–522.

Fuller RK, Lee KK, Gordis E (1988) Validity of self-report in alcoholism research: Results of a Veterans Administration cooperative study. Alcohol Clin Exp Res 12:201–205.

Garbutt JC, West SL, Carey TS, Lohr KN, Crews FT (1999) Pharmacological treatment of alcohol dependence: A review of the evidence. JAMA 281:1318–1325.

George DT, Rawlings R, Eckardt MJ, Phillips MJ, Shoaf SE, Linnoila M (1999) Buspirone treatment of alcoholism: Age of onset, and cerebrospinal fluid 5-hydroxyindolacetic acid and homovanillic acid concentrations, but not medication treatment, predict return to drinking. Alcohol Clin Exp Res 23:272–278.

Goldman HH, Skodol AE, Lave TR (1992) Revising Axis V for DSM-IV: A review of measures of social functioning. Am J Psychiatry 149:1148–1156.

Gordis E, Fuller RK, Hewitt BG (1989) Alcoholism treatment research: New directions for an old problem. JAMA 262:1680–1681.

Gorelick DA (1993) Pharmacological treatment. Recent Dev Alcohol 11:413–427.

Greenfield SF, Weiss RD, Muenz LR, Vagge LM, Kelly JF, Bello LR, Michael J (1998) The effect of depression on return to drinking: A prospective study. Arch Gen Psychiatry 55:259–265.

Greenberg RP, Fisher S (1989) Examining antidepressant effectiveness: Findings, ambiguities and some vexing puzzles, in *The Limits of Biological Treatments for Psychological Distress: Comparisons with Psychotherapy and Placebo* (Fisher S, Greenberg RP eds), pp 1–38. Erlbaum and Associates, Hillsdale, NJ.

Hasin DS, Nunes EV (1998) Comorbidity of alcohol, drug, and psychiatric disorders: Epidemiology, in *Dual Diagnosis and Treatment. Substance Abuse and Comorbid Medical and Psychiatric Disorders* (Kranzler HR, Rounsaville BJ eds), pp 1–30. Marcel Dekker, New York.

Hedeker D, Gibbons RD (1996) MIXREG: A computer program for mixed-effects regression analysis with autocorrelated errors. Comput Methods Programs Biomed 49:229–252.

Hedeker D, Gibbons RD (1997) Application of random-effects pattern-mixture models for missing data in longitudinal studies. Psychol Methods 2:64–78.

Jones SH, Thornicroft G, Coffey M, Dunn G (1995) A brief mental health outcome scale: Reliability and validity of the Global Assessment of Functioning (GAF). Br J Psychiatry 166:654–659.

Kline NS, Wren JC, Cooper TB, Varga E, Canal O (1974) Evaluation of lithium therapy in chronic and periodic alcoholism. Am J Med Sci 268:15–22.

Kranzler HR, Burleson JA, Del Boca FK, Babor TF, Korner R, Brown J, Bohn MJ (1994) Buspirone treatment of anxious alcoholics: A placebo-controlled trial. Arch Gen Psychiatry 51:720–731.

Kranzler HR, Meyer RE (1989) An open trial of buspirone in alcoholics (letter). J Clin Psychopharmacol 9:379–380.

Leckliter N, Matarazzo JD (1989) The influence of age, education, IQ, gender, and alcohol abuse on Halstead-Reitan Neuropsychological Test Battery performance. J Clin Psychol 45:484–512.

Lee ET (1992) *Statistical Methods for Survival Data Analysis.* 2nd ed. John Wiley, New York.

Litten RZ, Allen JR (1993) Reducing the desire to drink: Pharmacology and neurobiology. Recent Dev Alcohol 11:325–344.

Malcolm R, Anton RF, Randall CL, Johnston A, Brady K, Thevos A (1992) A placebo-controlled trial of buspirone in anxious inpatient alcoholics. Alcohol Clin Exp Res 16:1007–1013.

Malec E, Malec T, Gagne MA, Dongier M (1996a) Buspirone in the treatment of alcohol dependence: A placebo-controlled trial. Alcohol Clin Exp Res 20:307–312.

Malec TS, Malec EA, Dongier M (1996b) Efficacy of buspirone in alcohol dependence: A review. Alcohol Clin Exp Res 20:853–858.

Mason BJ, Kocsis JH, Ritvo EC, Cutler RB (1996) A double-blind, placebo-controlled trial of desipramine for primary alcohol dependence stratified on the presence or absence of major depression. JAMA 275:761–767.

Merry J, Reynolds CM, Bailey J, Coppen A (1976) Prophylactic treatment of alcoholism by lithium carbonate: A controlled study. Lancet 2:481–482.

Moncrieff J, Drummond DC (1997) New drug treatments for alcohol problems: A critical appraisal. Addiction 92:939–947.

O'Malley SS, Croop RS, Wroblewski JM, Labriola DF, Volpicelli JR (1995) Naltrexone in the treatment of alcohol dependence: A combined analysis of two trials. Psychiatr Ann 25:681–688.

O'Malley SS, Jaffe AJ, Chang G, Rode S, Schottenfeld R, Meyer RE, Rounsaville B (1996) Six-month follow-up of naltrexone and psychotherapy for alcohol dependence. Arch Gen Psychiatry 53:217–224.

Paulson MJ, Lin T-T (1970) Predicting WAIS IQ from Shipley-Hartford scores. J Clin Psychol (Suppl.) 26:453–461.

Project MATCH Research Group (1997) Matching alcoholism treatments to client heterogeneity: Project MATCH posttreatment drinking outcomes. J Stud Alcohol 58:7–29.

Reitan RM (1958) Validity of the Trailmaking Test as an indicator of organic brain damage. Percept Mot Skills 8:271–276.

Robinson DS, Rickels K, Feighner J, Fabre LF, Gammans RE, Shrotriya RC, Alms DR, Andary JJ, Messina ME (1990) Clinical effects of the 5-HT_{1A} partial agonists in depression: A composite analysis of buspirone in the treatment of depression. J Clin Psychopharmacol (Suppl.) 10:67S–76S.

Sass H, Soyka M, Mann K, Zielgansberger W (1996) Relapse prevention by acamprosate: Results from a placebo-controlled study on alcohol dependence. Arch Gen Psychiatry 53:673–680.

Schaffer A, Naranjo CA (1998) Recommended drug treatment strategies for the alcoholic patient. Drugs 56:571–585.

Sellers EM, Naranjo CA, Forgie L, Lawrin M (1985) The effects of buspirone, trazodone, and zimelidine on voluntary ethanol consumption in laboratory animals. Report prepared by the Bristol Myers Company, Princeton, NJ.

Shipley WC (1940) A self-administering scale for measuring intellectual impairment and deterioration. J Psychol 9:371–377.

Smith A (1973, revised 1982) *Symbol Digit Modalities Test.* Western Psychological Services, Los Angeles.

Sobell MB, Maisto SA, Sobell LC, Cooper AM, Cooper TC, Sanders B (1980) Developing a prototype for evaluating alcohol treatment effectiveness, in *Evaluating Alcohol and Drug Abuse Treatment Effectiveness, Recent Advances* (Sobell LC, Sobell MB, Ward E eds), pp 129–150. Pergamon Press, New York.

Spitzer RL, Williams JBW, Gibbon M, First MB (1991) *Structured Clinical Interview for DSM-III-R.* Patient edition. American Psychiatric Association, Washington, DC.

Spitzer RL, Williams JBW, Gibbon M, First MB (1992) The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. Arch Gen Psychiatry 49:624–629.

Sussman N (1994) The uses of buspirone in psychiatry. J Clin Psychiatry Monogr 12:3–19.

Tollefson GD, Montague-Clouse J, Tollefson SL (1992) Treatment of comorbid generalized anxiety in a recently detoxified alcoholic population with a selective serotonergic drug (buspirone). J Clin Psychopharmacol 12:19–26.

Wechsler D (1981) *Manual for the Wechsler Adult Intelligence Scale-Revised.* The Psychological Corporation, San Antonio, TX.

Weissman MM, Bothwell S (1976) Assessment of social adjustment by patient self-report. Arch Gen Psychiatry 33:1111–1115.

Weissman MM, Sholomskas D, John K (1981) The assessment of social adjustment: An update. Arch Gen Psychiatry 38:1250–1258.