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Testing Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (The COMBINE Study): A Pilot Feasibility Study

The COMBINE Study Research Group

Background: Medications (such as naltrexone and acamprosate) as well as behavioral therapies have been previously reported to be effective in the reduction of alcohol intake and to prevent relapse drinking. However, the efficacy of using several medications alone or together in combination with behavioral therapies has not been widely investigated. The purpose of this study was to evaluate the feasibility of this combined therapy approach to apply it to a larger scale multisite clinical trial. Outcome focused on recruitment, retention, adherence to study parameters and medication, physical complaints, and physiologic toxicity.

Methods: At 11 sites, 108 individuals with alcohol dependence were randomized in a double blind fashion to receive placebo, naltrexone, or acamprosate alone or in combination. In addition, some individuals were randomized to receive Medical Management (MM) provided by a health care practitioner alone or in combination with an enhanced behavioral intervention, Combined Behavioral Intervention (CBI), delivered by a trained therapist. A final group received CBI alone without pills. All participants were treated and assessed for a maximum of 16 weeks.

Results: The attendance at therapy and research visits, and medication adherence and tolerability were good with no statistical differences between the medication or behavioral intervention groups. Over 75% of participants completed the week-16, end of study, assessment and the average medication adherence (percent of total pills taken) was about 65%. The level and types of physical complaints were not unexpected and similar among the medication and placebo groups. There were no group differences in liver or kidney toxicity. Importantly, the combination of naltrexone and acamprosate did not present significantly more physical complaints than either alone.

Conclusions: Sufficient numbers of alcohol dependent participants can be recruited and retained in a relatively sophisticated outpatient trial combining medications and behavioral interventions. Participant adherence to the trial protocol including medication regimens was at acceptable levels. Physical complaints and organ toxicity were within expected and acceptable levels. Based on these results a larger scale study utilizing these methodologies appears feasible.

Key Words: Alcoholism, Pharmacotherapy, Behavioral Therapy, Naltrexone, Acamprosate.

THE COMBINE Study is a federally funded multisite randomized controlled clinical trial comparing two medications (naltrexone and acamprosate) and their combination in the context of two behavioral treatments (Medical Management with or without Combined Behavioral Intervention). An additional treatment condition will also be used to evaluate the effect of pill taking by comparing the effectiveness of an enhanced alcohol relapse prevention intervention, Combined Behavioral Intervention (CBI) with no pill ingestion compared to CBI with pill taking and Medical Management (MM). The rationale, goals, study design, assessments, and statistical approaches to outcome variables are detailed in the accompanying article (The COMBINE Study Research Group, 2003).

The overall goal of the COMBINE Study is to examine whether there are any differences in outcome when medications, thought to be effective in their own right, are combined with each other or with an enhanced behavioral intervention (CBI). Ancillary goals are to compare the effectiveness of the medications against each other or when combined with the enhanced behavioral intervention. The rationale for evaluating these issues derives from both scientific and practical concerns. For instance, the most effective studies with naltrexone appear to use a relapse-prevention-based therapeutic approach such as cognitive behavioral therapy (e.g., Anton et al., 1999), which in and of itself is an effective treatment (Project MATCH, 1998). However, this type of intervention requires specific training and may be more expensive to deliver than self-help ap-

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proaches (e.g., Alcoholics Anonymous attendance) or medication-based medical management approaches. On the other hand, acamprosate has not been evaluated with specific behavioral interventions in mind and appears to promote abstinence across a variety of such therapies found in common practice (Mason, 2001). It is unclear which medication is best, how much extra benefit these medications might provide if an enhanced behavioral intervention were used concomitantly, and, finally, whether combining medications would provide any more benefit than either one alone. The latter question addresses an issue salient in other areas of medicine (such as in hypertension, infectious disease, and depression) in which combinations of medications, often working through different biological mechanisms, are additive in effecting a treatment response.

While the scientific goals and hypotheses of the COMBINE study appear clear and well-justified, concerns existed during the planning phase of the study about practical and medical issues such as: 1) subject recruitment and acceptance of the protocol, 2) coordination of treatment and research aspects of the protocol by study sites, 3) adherence to medication, 4) adherence to research visits and study completion, 5) adverse events (physical complaints) of the medications – especially with the combined naltrexone/acamprosate dosing, and 6) effects of the medications (especially the combined medication group) on physiologic functions, i.e., liver and kidney toxicity. While an earlier study (Mason et al., 2002) and an initial pilot study conducted by our group (Johnson et al., 2003) addressed concerns number 5 and 6 in well-controlled inpatient settings over a short period of time (several weeks), the other concerns could only be addressed in the population targeted for the main trial, i.e., treatment-seeking outpatients. Moreover, while the earlier study results did not indicate significant medical or toxicological concerns, only an extended dosing period under more naturalistic conditions (ambulatory alcoholics ingesting other medication during access to alcohol) could adequately address these issues.

Of particular concern was the subjects' willingness to participate in a clinical trial requiring multiple treatment and research assessments while taking 8 pills per day over a 16-week period. There was also concern about whether the inclusion of a no-pill "CBI-only" treatment condition would adversely affect overall recruitment and retention, specifically in that condition. Therefore, in addition to medication tolerance and toxicity, subject recruitment and retention were of ultimate concern. Modifications in the main trial protocol would have to be considered if data suggested that any of these concerns were of sufficient magnitude to undermine the feasibility of the study. Therefore, it was decided to perform a second pilot study not only to inform the design of the main trial, but also to allow sites to become completely familiar with the research and therapeutic procedures to be utilized in the main trial. Reported here are the findings of that pilot study with results focused on recruitment, adherence, and tolerability of the study treatments.

METHODS

Rationale and Study Design

Since one goal of this study was to familiarize staff with all parameters of the main trial, as well as to completely evaluate subject acceptability, all the procedures to be utilized in the main trial including the assessments, treatments, and medication dosing were similar to that detailed in the accompanying article (The COMBINE Study Research Group, 2003). The primary exception was that subjects were informed at the outset that this was a "pilot study" and also that there would be no follow-up after the full 16 weeks of treatment. In the main trial, assessments are planned at 26, 52, and 68 weeks after the initiation of treatment. Also, in this pilot study, subject assignment to the combined active medication group was double that of the other groups to better observe tolerability and/or toxicity, if any existed. In the main trial, currently underway, randomization to all treatment conditions will be equal.

Subject Recruitment and Assessment

Subjects were recruited by advertisements and from clinical referrals at all 11 participating study sites. They received assessments as detailed in the accompanying paper, including the following domains: 1) History/Physical and Physiologic Assessment, 2) Laboratory Measurements, 3) Adverse Events, 4) Drinking Levels, 5) Alcohol and Drug Involvement, 6) Motivation, 7) Craving, 8) Psychological/Assessment, 9) Social Support, 10) Quality of Life, 11) Therapy Compliance and Process Measures. The initial assessment battery was expected to take about 4 hr to complete but during this study it was determined that the battery took an average of about 6 hr to complete. To ease subject and staff burden, the number of assessments was reduced to those now appearing in the chart in the accompanying article (The COMBINE Study Research Group, 2003). The revised assessment battery took, on average, about 4.75 hr to complete.

In this report, we will focus on the baseline demographics, salient drinking parameters obtained from the Form 90 (Tonigan et al., 1994, Miller, 1996), Alcohol Dependence Scale (Skinner and Horn, 1984), Obsessive Compulsive Drinking Scale (Anton et al., 1996), and DrinC (Miller et al., 1993), research adherence (weeks of data collection, inactive status checklist), medication adherence (pill count form), dose reductions (SAFTEE), and side effects (SAFTEE) (Levine and Schooler, 1986).

An attempt was made to obtain data regarding the number of individuals that were screened by phone or in person prior to randomization. However, because of site variability on what constituted a "screened individual," this number (N = 495) was only an approximation. All in-person screened individuals signed an informed consent form (approved by the IRB at each site and accompanied by a certificate of confidentiality issued by NIAAA) prior to receiving any study-specific assessments. Individuals were required to maintain a minimum of 4 days of abstinence prior to being randomized to a specific treatment condition. During these 4 days, subjects typically visited the center several times where they were breathalyzed prior to the assessments. Blood and urine samples were sent to a central laboratory (Quintiles Laboratories) for analysis of key organ function parameters and the presence of proscribed drugs (e.g., cocaine, opiates).

The inclusion and exclusion criteria were the same as those detailed for the main trial (The COMBINE Study Research Group, 2003). All individuals needed to meet the DSM-IV criteria for alcohol dependence. Subjects needed to have been drinking a minimum of 14 drinks (females) or 21 drinks (males) on average per week over a consecutive 30-day period in the 90-day period prior to initiation of abstinence. They also needed to have two or more days of heavy drinking (defined as 4 drinks for females and 5 drinks for males) during that time, with the last drink being within 21 days of randomization to treatment.

Important exclusion criteria included a recent history of other substance abuse or dependence (other than nicotine or cannabis), serious psychiatric disorder requiring specific pharmacological intervention, unstable medical conditions (including liver function tests more than 3 times

normal), and having received either study medication within the past 30 days.

Treatment Conditions

After assessment, subjects were randomized to one of nine conditions (cells) at each study site by a preassigned and blinded randomization code as indicated in Fig. 1. It can be seen that subjects in one cell (termed "cell 9") received no study medication (active or placebo) but only CBI therapy. This cell was included to check for effects of pill taking on the outcome achievable with CBI alone.

Since one of the primary goals of this Pilot study was to assess the tolerability and safety of the combined medications, the number of people randomized to the cells receiving both acamprosate and naltrexone was twice as large as the cells receiving only one or no medication.

All subjects except those in the CBI-only group received 8 pills a day. The naltrexone dose was increased in steps over a one week time period and given as two pills each day as follows: one placebo and one containing 25 mg on days 1 through 4, one placebo and one containing 50 mg on days 5 though 7. On day 8 through day 112 (16 weeks), two pills, each containing 50 mg (total dose of 100 mg) were given. Acamprosate was given from day one through day 112 (16 weeks) as two 500 mg pills three times per day (total dose of 3 g per day). Identical placebos for each of the medications were given in a similar fashion for the placebo group although the naltrexone and its placebo looked different from the acamprosate and its placebo. Each subject (except those in the CBI-only group) took up to 8 pills a day of active medication or placebo from day 8 till day 112 of the study. If a subject experienced intolerable side effects, health care providers (physicians and/or nurses) who provided the Medical Management therapy had the option of reducing the study medication by the following scheme: 1) the acamprosate (or placebo) pills were reduced to one in the morning and one in the afternoon with two at night; 2) if there was no improvement in adverse symptoms after three days, the naltrexone (or placebo) pills could be reduced to only one pill in the morning. If the study drug dose was reduced, attempts were made to increase it back to full dosage within several weeks.

Treatment and Assessment Durations and Frequencies

All subjects receiving study medication received up to 9 Medical Management (MM) appointments (weeks 0, 1, 2, 4, 6, 8, 10, 12, and 16) scheduled with a health care provider (physician or nurse). At this visit, the SAFTEE assessment was performed, pill counts were obtained, more medication dispensed (except at week 16), and MM counseling (including a drinking assessment and support for abstinence) was provided. If a subject discontinued taking the medication because of an adverse event, medical monitoring (termed "Medical Attention") was substituted for Medical Management at the specified visits. Subjects who received CBI had a maximum of 20 sessions over a total of 16 weeks of treatment study participation. Those subjects in the CBI-only condition were also seen by a health care professional at baseline and at weeks 4, 8, 12, and 16 for the sole purpose of reviewing the laboratory results. While research assistants assessed drinking history and craving as required in the main protocol on the Medical Management visit days, these outcome variables were not analyzed for this feasibility study and are not subsequently reported here. On weeks 8 and 16, a longer assessment was performed, as required by the main protocol. A complete blood count, as well as liver and kidney function, were evaluated at baseline, weeks 4, 8, 12, and 16.

RESULTS

Study Population

The screening, recruitment, and randomization numbers for the study are given in Fig. 1. The number of individuals screened is a conservative estimate since at many sites individuals are prescreened by various systems and these individuals are not counted as undergoing a formal screening visit. The main reasons for study exclusion at the formal screening session were 1) taking exclusionary medications (24%) 2) opiate and other drug dependence (17%) 3) having other exclusionary DSM IV psychiatric diagnoses (13%) and 4) not drinking within the prestudy time window for participation (12%). Of the people actively screened, 108 individuals met inclusion criteria, were randomized to one of the treatment conditions, and received at least one dose of medication or one CBI treatment session. As can be seen in Fig. 1 there were about twice as many individuals (N = 36) assigned to the combined acamprosate-naltrexone

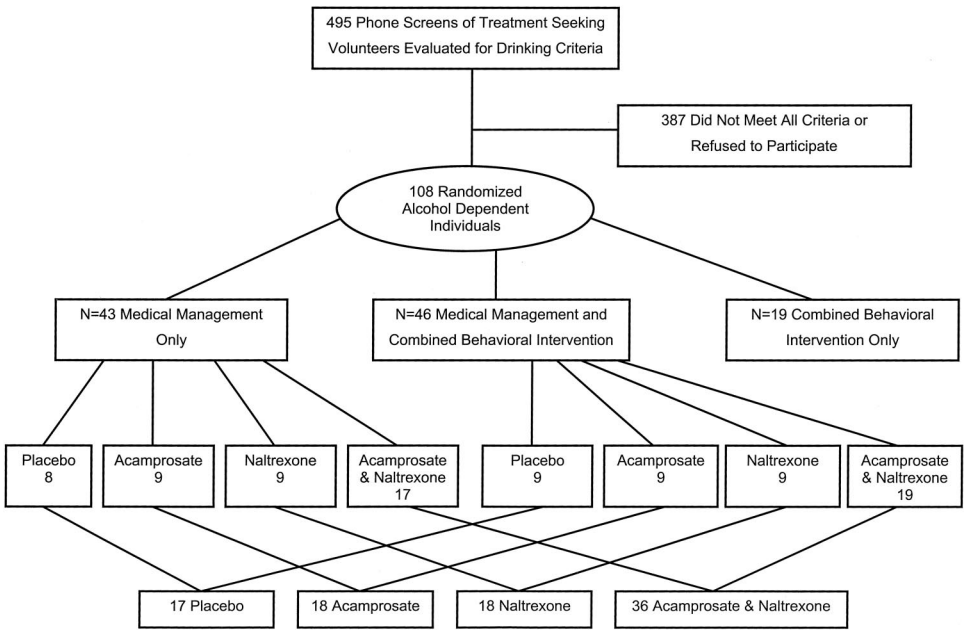

Fig. 1. COMBINE Study Feasibility Pilot Screening and Randomization Scheme.

medication condition in which the most concern for tolerability and safety existed. Essentially the subject distribution among the cells occurred as planned.

The demographic characteristics and significant drinking parameters of the study participants are presented in Table 1. The sample exhibited good representation of both genders and minorities. The average age in the early 40's is consistent with other published alcohol treatment studies. About 40% of the subjects were married and 70% were employed. There were no significant differences across the treatment groups on any key demographic parameter.

Overall, study participants drank on about 75% of the pretreatment study days and consumed about 13 drinks per drinking day. Alcohol problem severity was, on average, in the moderate range based on the ADS, OCDS, and DrinC scores. These variables were similar across all groups with the only significant difference ($p < 0.01$) being the Obsessive-Compulsive Drinking Scale score that was lower in the CBI-only group. While this variable and a few others suggested lower severity in the CBI only group this was felt to be due solely to chance and to be clinically insignificant, given the similarity on most other measures including the drinking intensity and frequency.

Research Adherence

Of the 108 individuals randomized to the study treatment, 34 (31%) did not complete all 16 weeks of treatment. The reasons for treatment noncompletion were as follows: 10 were lost to follow-up, 9 were dissatisfied with treatment, 2 wanted alternative medications, 2 had a time conflict, 1 needed more intensive treatment and 10 had no known reason given.

Key study performance parameters are provided in Table 2. Overall, about three quarters of the subjects provided end point data at week 16 of the study (some individuals who had dropped out earlier provided week 16 data). This did not differ significantly between treatment groups.

Medication Adherence

Subjects assigned to the medication groups (all but the CBI-only group) took about 65% of the total possible pills, defined as the number of total pills that could have been taken over the total 112 days of the study (based on pill-count reconciliation of dispensed versus returned medication at each visit). The median percent adherence (i.e., 50% of subjects took more and 50% took less) ranged from 55–81% across groups. There were no significant differences among the medication groups. Importantly, none of

Table 1. Baseline Demographics and Drinking Measures of Alcohol Dependent Individuals by Treatment Group Assignment

Patient Characteristics	Placebo ($n = 17$)	Acamprosate ($n = 18$)	Naltrexone ($n = 18$)	Acamprosate + Naltrexone ($n = 36$)	CBI Therapy Only ($n = 19$)
Age mean[a]	38 (6.5)	42 (11.1)	41 (7.3)	44 (10.4)	43 (11.2)
% Minority	17.6	22.2	16.7	27.8	21.1
% Male	76.5	66.7	77.8	80.6	63.2
% Married	35.3	44.4	38.9	47.2	36.8
% Employed	70.6	77.8	55.6	75.0	68.4
Alcohol Dependence Score (ADS)[a]	20 (8.7)	16 (7.5)	21 (8.2)	17 (8.5)	15 (7.4)
OCDS Score**[a]	17 (6.9)	15 (6.5)	17 (6.1)	14 (6.5)	10 (5.6)
Drinking Consequences (DRINC)[a]	58 (24.8)	48 (25.6)	57 (26.1)	54 (28.4)	39 (18.5)
Percent Days Drinking[a]	68 (20.7)	80 (19.8)	81 (22.1)	73 (29.1)	75 (27.9)
Drinks per Drinking Day[a]	15 (11.8)	13 (10.2)	16 (10.8)	11 (6.3)	10 (9.9)

The range of the various rating instruments are as follows: ADS (range 0–47), OCDS (range 0–56) and DrinC (range 0–150). Standard Drinks are considered to be approximately 12 oz. of beer, 1.5 oz. of spirits, or 5 oz. of wine.

[a] Mean (SD).

** Overall $p < 0.01$.

CBI, combined behavioral intervention.

Table 2. Treatment, Research, and Medication Adherence by Treatment Assignment

	By Medication Assignment				By Therapy Assignment		
	Placebo ($n = 17$)	Acamprosate ($n = 18$)	Naltrexone ($n = 18$)	Acamprosate + Naltrexone ($n = 36$)	CBI Only ($n = 19$)	MM Only ($n = 43$)	MM CBI ($n = 46$)
Treatment completion	76%	67%	56%	67%	79%	60%	72%
Research adherence							
% Completed[a] wk 8	82%	83%	83%	86%	84%	84%	85%
% Completed[a] wk 16	76%	78%	78%	72%	79%	79%	72%
Medication adherence							
Mean adherence[b]	66%	67%	59%	69%	N/A	61%	71%
Median adherence	72%	81%	55%	81%	N/A	60%	85%*
% Subjects with dose reduction	18%	33%	28%	33%	N/A	37%	22%

[a] Completed = having outcome data available for that visit.

[b] Percent of total possible meds taken out of 112 days expected dosing.

* $p < 0.03$ MM only vs. MM + CBI.

N/A, not applicable; MM, medical management; CBI, combined behavioral intervention.

Table 3. Percent of Alcohol Dependent Subjects with Salient Adverse Events by Medication Treatment*

	Placebo (n = 17)	Acamprosate (n = 18)	Naltrexone (n = 18)	Acamprosate + Naltrexone (n = 36)
Nausea	47%	18%	56%	33%
Vomiting	18%	12%	22%	8%
Diarrhea	59%	59%	56%	75%
Abdominal pain	12%	6%	22%	31%
Increased appetite	18%	35%	28%	11%
Decreased appetite	35%	29%	33%	22%
Headache	35%	47%	39%	56%
Dizziness	12%	35%	11%	22%
Fatigue	18%	53%	50%	33%
Nervousness	35%	41%	56%	44%
Insomnia	35%	59%	39%	42%
Somnolence	18%	47%	17%	36%
Depression	18%	29%	28%	31%
Itching	6%	24%	11%	6%
Rash	0%	12%	0%	6%
Increased libido	0%	12%	0%	0%
Decreased libido	0%	24%	17%	14%

* No overall difference between the treatment groups (Fisher's Exact Tests).

the active medication groups were significantly less compliant than the placebo group, and the combined acamprosate-naltrexone group adherence was equal to, or better than, placebo or either of the two medications ingested alone. However, the median compliance was significantly ($p < 0.03$) better for those subjects who received the combined CBI+MM intervention (85%) than those that received MM only (60%).

Dose Reduction

There were a number of subjects who requested or required a dose reduction as allowed by the protocol. While only 18% of the placebo group received a dose reduction, about one-third of those on active medication had a dose reduction. However, there was no overall significant difference between the groups (Fishers Exact $p = 0.7$). There were no significant differences between any of the active medication groups. In particular, the combined acamprosate-naltrexone group had a similar number of dose reductions as the groups receiving either medication alone. While a slightly higher percentage of subjects required a dose reduction in the MM alone group (37%), this was not significantly different from the subjects in the MM + CBI group (22%).

Adverse Events

The most salient symptoms that have been reported by others to be related to naltrexone (Anton et al., 1999; Croop et al., 1997; Kranzler et al., 2000; O'Malley et al., 1992; Volpicelli et al., 1992) or acamprosate (Paille et al., 1995; Pelc et al., 1997) include nausea, diarrhea, headache, and fatigue. However, a total of 17 (13 in addition to the four above) symptoms were systematically recorded in our study. Physical complaints and symptoms endorsed by the study participants are given in Table 3. It can be seen that a large number of placebo-treated subjects reported numerous physical symptoms during the study. While there is some variability of the percentage of subjects reporting these symptoms during treatment, there were no meaningful observable differences overall among the treatment groups. There is some suggestion that more subjects taking the combination of acamprosate and naltrexone reported diarrhea, and that more subjects taking any medication compared to placebo experienced fatigue and decreased libido. However, none of these observations were statistically significant. Overall, the number of individuals reporting any side effect was similar across all treatment groups. Importantly, there is no suggestion that the subjects taking combined acamprosate-naltrexone reported any more side effects than the other groups including the placebo-treated group. One subject in the naltrexone group and one subject in the acamprosate group could not tolerate the medication because of adverse effects. Importantly, no subject discontinued medication in the combined naltrexone-acamprosate group due to adverse effects.

Table 4. Baseline and Week 16 Liver and Kidney Function Parameters

	Baseline		Week 16	
Lab Measures	Mean	SD	Mean	SD
ALT (6-37 IU/L)*				
Placebo	50.1	25.00	41.1	29.40
Acamprosate	25.5	11.22	26.3	17.08
Naltrexone	47.4	31.34	41.1	27.27
Acamprosate + Naltrexone	29.9	14.89	31.7	19.35
AST (10-36 IU/L)*				
Placebo	38.1	19.67	29.3	11.45
Acamprosate	25.0	8.22	26.0	7.79
Naltrexone	43.6	27.46	32.6	13.54
Acamprosate + Naltrexone	28.3	14.93	28.7	13.93
Bilirubin (0.2-12 mg/L)*				
Placebo	0.4	0.18	0.4	0.13
Acamprosate	0.5	0.17	0.5	0.39
Naltrexone	0.5	0.25	0.6	0.24
Acamprosate + Naltrexone	0.4	0.20	0.4	0.19
BUN (4-24 mg/dl)*				
Placebo	13.3	3.39	12.8	4.31
Acamprosate	14.3	5.06	15.5	4.72
Naltrexone	13.0	4.37	14.4	3.78
Acamprosate + Naltrexone	14.6	4.44	13.5	3.96
Creatinine (0.4 + 1.2 mg/dl)*				
Placebo	0.8	0.19	0.8	0.18
Acamprosate	0.9	0.16	0.9	0.17
Naltrexone	0.9	0.21	0.9	0.20
Acamprosate + Naltrexone	0.9	0.15	0.9	0.16

* normal range.

Liver and Kidney Function Laboratory Measures

Since naltrexone is metabolized by the liver and acamprosate is excreted essentially unchanged by the kidney, there should theoretically be no interactive organ toxicity generated by the combination of these medications. However, the only way to be confident was to evaluate this directly under natural conditions (with exposure to relapse drinking, other medications, regular diet variations, etc.) Table 4 provides the baseline and week 16 values of key liver and kidney function lab tests. Values obtained at week

4, 8, and 12 were quite similar to those obtained at week 16. Therefore, for ease of presentation, only baseline and week 16 values are shown. As can be seen, there was some variation of liver enzyme levels (ALT, AST) between the treatment groups at baseline. Despite this, within-group (baseline to week 16) differences were small and clinically insignificant. In general, the mean bilirubin level in each treatment group remained stationary during treatment. Between-group differences were small and insignificant. Similar results were obtained for both BUN and creatinine levels.

However, one naltrexone subject experienced a greater than 5-fold elevation in liver enzymes (both AST and ALT) during treatment, which led to medication discontinuation. This person had both relapsed to heavy drinking and had tested positive for hepatitis C. In addition, one acamprosate subject, one placebo subject, and two additional naltrexone subjects all had some liver enzyme elevation (greater than 3 times but less than 5 times normal) during the course of the study. There were no liver function test elevations in the combined acamprosate-naltrexone group that met this criterion.

DISCUSSION

This COMBINE Study pilot indicates that subjects can be recruited, assessed, treated, and retained in the study as designed. The medications were generally well tolerated and adherence to medication was within expectation for alcohol treatment trials (for examples see (Anton et al., 1999; Krystal et al., 2001; O'Malley et al., 1992; Pelc et al., 1997; Sass et al., 1996)). Importantly, the combination of psychosocial treatments (MM plus CBI) and medications (acamprosate and naltrexone) showed similar acceptability as either modality alone.

Specifically, the time commitment of meeting with a health care professional (MM) and a therapist (CBI), although ostensibly more burdensome than meeting with only one person, did not cause more treatment dropout or less research completion. Conversely, it appeared that more people complied with medication in the CBI+MM group.

Of note, those subjects receiving CBI-only without any study medication (no pill group) showed similar treatment retention and research adherence to the therapy groups receiving some study medication. This was of interest since the recruitment for the study generally emphasized the medication aspects of the trial. Many subjects volunteered because they had about an 8 in 10 chance of getting some pills and a 2 in 3 chance of getting "active medication." This implies that, in general, subjects recruited for this trial accepted the general expectation that behavioral therapy alone could be helpful to them.

Of equal importance was the reasonably high level of medication adherence. Although subjects were required to take 8 pills per day in 3 divided doses, the medication adherence was reasonable and consistent with other alcohol relapse prevention pharmacotherapy clinical trials. Given the complex nature of dosing two separate medications multiple times per day, blister packs, rather than electronic cap monitoring for example, was deemed the only practical, reliable, and acceptable method of medication delivery. While our measure of adherence levels could have been somewhat inflated by the sole use of pill counts, there was no systematic bias based on medication assignment. This was evidenced by similar recorded pill counts in all groups, including the combined active medication group. While there was some suggestion that active medication groups required more dosage reductions than the placebo group, this was not significantly different for single versus combined medication groups. Very few individuals dropped out of the study because of intolerable side effects, and there were no significant differences in any reported side effects between placebo and active medication groups, including the combined medication group.

In general, there were few observable medication group differences in liver and kidney function over the course of the study. While a few individuals did experience an increase in liver enzyme levels during the course of treatment, they were too few to suggest an overall pattern worthy of concern at this time. However, this finding does indicate the need to closely monitor liver function in clinical trials of alcoholics who receive medications metabolized by the liver (Allen et al., 1997; Croop et al., 1997). A recent report of hepatoxicity in patients receiving high dose naltrexone and nonsteroidal anti-inflammatory agents highlights this fact (Kim et al., 2001). In the main trial, currently under way, liver function monitoring is occurring on a routine basis.

The results of this study, while supportive of the feasibility of the main COMBINE Study, should not be overinterpreted in regards to the safety, tolerability, and acceptability of these therapies at this time. The sample size, while adequate for a preliminary study, is certainly not large enough to support substantive conclusions. Also, it must be remembered that the sites conducting this study had highly motivated and well-trained research and treatment staff. Subjects were screened carefully and had high expectations of participating in a "state-of-the-art" treatment trial with previously reported efficacious medications and behavioral treatments. Therefore, it could be assumed that the methods employed were carried out under highly favorable conditions. Nevertheless, the data are informative. The data generated on the safety and tolerability of the medication combination is consistent with the results of a smaller, more tightly controlled COMBINE pilot inpatient study (Johnson et al., 2003) and an earlier drug interaction study (Mason et al., 2002). The emphasis on medication compliance in the MM treatment likely contributed to the relatively high medication adherence, and the combined use of MM and CBI did not interfere with retention. Subjects were willing and able to undergo about 5 hr of baseline assessment and 16 weeks of treatment whether or not they received study medication. All of the above suggest that the main COMBINE Study, which is currently in progress, will have a high probability of achieving its goals.

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