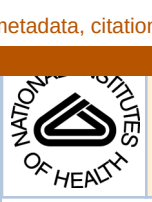

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RELATIONSHIP BETWEEN MEDICATION ADHERENCE AND TREATMENT OUTCOMES: THE COMBINE STUDY

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Abstract

Background—Within the alcoholism field, there is mounting evidence supporting an important relationship between medication adherence and drinking outcomes. Little is known however, about the complex relationships between medication and treatment variables and drinking outcomes. The present paper reports on the differential impact of medication adherence and treatment factors on drinking outcomes. Data derived from the COMBINE Study was used to investigate the interrelationships between medication adherence, combination treatments and drinking outcomes.

Methods—Twelve hundred and twenty-six patients were randomized to one of eight different combination treatments involving two medications - naltrexone and acamprosate and placebo, and two behavioral treatments - medical management (MM) and combined behavioral intervention (CBI). Two primary drinking outcomes were percent days abstinent (PDA) and time to first heavy drinking day. Medication adherence was defined as a proportion that reflects the number of pills taken by the maximum number of pills expected to be taken over the course of the trial. A generalized linear mixed model was used to estimate the effects of adherence on PDA while proportional hazards model was used to examine similar co-variate effects on time to first heavy drinking day.

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Data presented in this report were collected as part of the multisite COMBINE trial sponsored by the National Institute on Alcohol Abuse and Alcoholism, in collaboration with the COMBINE Study Research Group. The Combine study was supported by National Institute on Alcohol Abuse and Alcoholism (NIAAA) Cooperative Agreements U10AA11715, 11716, 11721, 11727, 11756, 11768, 11773, 11776, 11777, 11783, 11787, 11799, and 11773 and by career scientist awards K05AA014715, K05AA00133, K24DA022288 and K23AA00329. A full listing of the staff of the COMBINE Study can be found at http://www.cscc.unc.edu/combine/.

Results—Concerning time to first heavy drinking day, a significant three-way interaction was found between medication adherence, CBI and naltrexone (p=0.0160). Within the MM only plus placebo group (no CBI), significant differences were found in "recovery" (i.e., no heavy drinking days) rates between *adherers* and *noadherers* (40% vs. 10%, p<0.0001). Such differences became nonsignificant (p = .12) when CBI was introduced into the relationship. CBI did not add any such advantage to naltrexone-treated patients.

Conclusions—CBI might serve a protective function for *nonadherers* in the placebo group; the median relapse time was reduced when these *nonadherers* were exposed to the alcohol specialty intervention. CBI offered little additional benefit to *nonadherers* in the naltrexone group. Among *nonadherers in* the naltrexone group, relapse rates appear to be more a function of inadequate exposure to the active medication and less influenced by CBI.

Keywords

Naltrexone; Acamprosate; Medication Adherence; Combined Behavioral Intervention (CBI); Medical Management (MM)

INTRODUCTION

Within the alcoholism field, there is mounting evidence supporting an important relationship between medication adherence and treatment outcomes (Chick, et al., 2000; Pettinati, 2006; Volpicelli et al., 1997; Weiss, 2004; Zweben and Zuckoff, 2002). Pharmacotherapy that is proven for its therapeutics in reducing acute withdrawal symptoms and/or urges to drink alcohol or use of other drugs is effective when patients adhere to the prescribed medical regimen. In addition, behavioral treatment employed in combination with medication can facilitate medication adherence. Behavioral therapy can be used to address patient concerns related to adverse reactions to the medication while improving coping skills, building supportive relationships for taking medication for chronic conditions, and strengthening motivation to change (Carroll, 1997). These factors are not only relevant to improving medication adherence but to sustaining the benefits of change as well.

More is known about the impact of medication adherence on treatment outcome in naltrexone studies than in acamprosate trials (Pettinati, 2006). Specifically, several placebo-controlled naltrexone studies have demonstrated a significant relationship between good adherence to medication and behavioral treatment regimens and successful treatment outcomes (Baros et al., 2007; Cramer et al., 2003; Onken et al., Volpicelli et al., 1997; Oslin et al., in press). For example, Volpicelli et al., (1997) tested the efficacy of naltrexone in an alcohol dependent population and discovered significant differences in outcomes between those who took their medication regularly and those who did not; medication-adherent patients had a 14% relapse rate in contrast to 50% in the nonadherent group. These authors also found significant differences between naltrexone and placebo patients in drinking outcomes *only* among patients that took their medication regularly. Placebo-adherent patients had a relapse rate of 50% in comparison to 25% of the naltrexone-adherent group. In contrast, among individuals with low medication adherence, no significant differences were observed between naltrexone and placebo patients on drinking measures. These differences in outcomes between placebo and naltrexone-treated patients appeared to be moderated by medication adherence.

Similar findings have been reported by Cramer and her colleagues (2003). These researchers found that pill adherence was a better predictor of drinking outcomes than naltrexone treatment in the first 13 weeks of treatment. Similar findings have been reported by Fuller et al., (1986) in their study testing the effects of disulfiram on alcohol dependent patients.

Fuller et al., (1986) found no significant differences in abstinence rates between placebo and active medication conditions but did find a significant relationship between pill adherence (i.e., active and inactive medications) and drinking outcomes in the total sample. Together these findings on medication adherence rates might explain why discrepancies in outcomes have been reported across naltrexone trials (Kranzler et al., 2000).

Other studies have reported a significant interaction between medication adherence, behavioral therapy and treatment outcomes. Baros et al., (2007) tested the combined efficacy of behavioral treatment and naltrexone and found a doubling in the effect size of the medication by therapy interactions when the analysis was performed only on the subgroup of naltrexone-adherent patients. Among those receiving naltrexone and cognitive behavioral therapy (CBT), the likelihood of decreasing drinking was greater if patients took their study medication as prescribed. Improved outcomes were typically observed in the sample population with 80% adherence to the prescribed medication.

It should be noted that there may are a number of individual and contextual factors that may further moderate the relationship between medication adherence and treatment outcome in a trial involving behavioral and/or pharmacological therapies (see e.g., Moos et al., 2002; Moos & Moos, 2003; Joe, et al., 1991).). In medical programs, low medication adherence rates has been shown to be more damaging for patients with chronic disorders such as hypertension and diabetes than those with acute disorders (Weiss, 2004). In substance use programs, adherence to methadone (as defined by dosage level) may be further moderated by patient satisfaction, prior treatment history, patient motivation, early program involvement and the kinds and amounts of services received in the first 3 months of treatment (Joe, et al, 1991; Simpson, et al., 1997; Zang et al., 2003). Further, in substance use programs which involve behavioral treatments, the relationship between treatment adherence and outcome may be moderated by such matters as outcome expectancies of patients, inadequate planning and a poor working alliance between therapist and patient (Moos, 2005) In other words, medication adherence, albeit important, may interact with a variety of circumstances and conditions to produce different outcomes.

To have a better understanding of the nature of relationship between medication adherence and outcomes, more rigor is required to investigate the topic. Most studies of adherence lack sufficient power to test the complex relationships between medication adherence, treatment variables and drinking outcomes. Outcome studies typically report medication adherence rates, but rarely do they report comparisons between patients with good vs. poor medication adherence across different kinds of treatment modalities. Thus, much more needs to be known about the differential impact of medication adherence on alcohol patients involved with different medications and behavioral treatments. The present paper reports on the findings on the relationship between medication adherence and drinking behavior in a large scale, multi-site, combined medication and behavioral treatment, namely, the National Institute on Alcohol Abuse and Alcoholism's COMBINE Study.

METHODS

The COMBINE Study Design

The COMBINE Study tested combinations of two medications, naltrexone and acamprosate and two behavioral treatments, low-intensity medical management (MM) and moderately intensive combined behavioral intervention (CBI). A total of 1383 patients were randomized to one of nine treatment conditions after 4 days of abstinence and followed up at 68 weeks post randomization. Eight of the cells involved a medication/placebo and behavioral treatment combinations. A ninth cell involved CBI only (no pills).

The overall aim of the current study was to test whether differences in medication adherence rates across the 8 treatment combinations would yield different drinking outcomes. It was hypothesized that higher medication adherence rates across the various treatment combinations would produce better drinking outcomes in the study group. In line with the aforementioned objective, only patients who received medication or placebo equivalents were included in the analysis. The CBI only, no-pill condition (cell 9) was excluded in the analysis of the findings on analysis of medications adherence.

The study sample was comprised of 1226 patients in the 8 medication/placebo (i.e., 8 cells) conditions. All patients that received study medication or placebo were also assigned to MM. Approximately 38% (465) of the 1226 patients that received study medication/placebo also received CBI (along with MM). Table 1 lists the eight medication/placebo treatment combinations along with the CBI only condition. To be eligible, individuals had to meet DSM-IV criteria for alcohol dependence and be seeking treatment; those individuals who were medically unstable, had serious psychiatric problems, or were drug dependent in the past 6 months were excluded. (For a full description of the methodology employed in the COMBINE Study see Pettinati et al., 2005).

Behavioral Treatments

Medical Management (MM) was primarily focused on enhancing medication adherence and providing support for achieving abstinence (Pettinati et al., 2004)). MM was derived from brief interventions that have been employed opportunistically as stand-alone treatments in nonspecialty health care settings, or as behavioral platforms for pharmacotherapies. Many of the components of brief interventions were adopted for MM in the COMBINE trial. To enhance the ecological validity of this primary care type model, except for the initial session which averaged 45 minutes, MM sessions were kept to an average of 20 minutes in duration. Patients were expected to attend 9 MM sessions over 16 weeks. The content of the sessions was focused on relaying alcohol-related information, facilitating medication adherence, managing medication side effects, actively referring to Alcoholics Anonymous (AA), and in general, providing support for abstinence.

Combined Behavioral Intervention (CBI) was comprised of three effective components of behavioral interventions – i.e., motivational enhancement therapy (MET) cognitive-behavioral therapy (CBT) and twelve-step facilitation (TSF) (Miller, 2004). CBI involved some degree of flexibility in session attendance dependent upon treatment goals and progress. Patients could attend as many as 20 sessions over 16 weeks with each session averaging 50 minutes. To enhance the applicability of the combined behavioral intervention (CBI), a variety of “pull-out” procedures were developed. These procedures addressed sundry clinical issues which often arise over the course of treatment such as no-shows, cancellations or missed appointments, medication nonadherence and everyday hardships (housing, financial, and legal problems). Also, different modules were designed to address patient difficulties in a number of areas such as communication problems, psychiatric symptoms and other problems. Attendance at mutual support groups such as Alcoholics Anonymous (AA) was supported particularly for those who lacked abstinence-related support. Patients were asked to identify a supportive significant other (SSO) and were encouraged to bring the SSO to the sessions. Motivational interviewing strategies and techniques were employed in all components of CBI.

Assessment Measures

Two primary drinking outcomes were percent days abstinent (PDA) and time to first heavy drinking day, defined as 5 or more drinks for men and 4 or more drinks for women per day. Drinking outcomes were derived from the Form 90 (Miller et al., 1996) administered at

baseline and the Timeline- Followback (Sobell and Sobell, 1996) administered during the 16-week treatment period. These two instruments assess daily drinking. Summary scores are derived from the daily drinking record to provide temporal drinking practices (i.e., episodic, binge and steady drinking).

The COMBINE research protocol was focused on achieving maximum exposure to the medication and placebo equivalents. The extent to which patients ingested the full dose of the medications or placebo equivalents comprised the definition of medication adherence. Patients were expected to take 8 pills daily (100 mg. of naltrexone and/or 3,000 mg. of acamprosate or the placebo equivalents) for 112 days or 896 pills during the treatment phase of the study. Patients were assigned a proportion that reflected the number of pills taken by the maximum number of pills expected to be taken over the course of the trial. Thus a patient ingesting 800 pills over the course of the treatment would have had an exposure rate of 800/896 or 0.89. Dose reductions were allowed if side effects persisted or were recurrent. However, patients were returned to the expected dosage when side effects disappeared or were reduced.

Adherence was computed from the pill count records for 1226 patients randomized to the 8 medication conditions. Individuals who were nonadherent to the medication or who withdrew from the study had all available information used in the computation of adherence so that proportions of the full protocol dose varied from 0.0 to 1.0. For purposes of testing and interpreting the effects of medication adherence on treatment outcomes, we categorized patients as adherent or nonadherent depending upon whether they had taken 80% or more of the maximum number of pills during treatment. An 80% cut-off point for medication adherence has been employed in clinical trials of naltrexone and other medications (Baros et al., 2007; Chick, et al., 2000; Osterberg and Blaschke, 2005; Pettinati et al., 2000).

Exposure to the behavioral treatments was defined by the amount of session attendance. The session check list for MM and CBI was used to measure adherence to treatment visits. Individuals were expected to attend on average 9 MM sessions and between 12 to 16 CBI sessions over the 16-week treatment period.

Treatment withdrawal or drop-out was measured differently for the behavioral treatments (MM and CBI). Individuals missing 3 consecutive MM or CBI sessions or not attending any CBI or MM sessions for a period of one month were considered drop-outs in the study. Patients categorized as drop-outs were treated as relapsed (i.e., returning to heavy drinking) in the data analysis. Treatment attendance was monitored by the COMBINE Coordinating Center (CC).

Statistical Analysis

As mentioned earlier, this report is based on 1226 patients randomized to the 8 medication/ treatment combinations. A generalized linear mixed model was used to estimate the effects of the study treatments on differences in PDA over time. A mixed linear modeling strategy is suited to the variable number of repeated measurements obtained for each subject while adjusting for adherence covariates and the 3-way factorial design of study treatments. The effect of the three treatment factors (i.e., acamprosate, naltrexone and CBI) on time to first heavy drinking day was assessed with a proportional hazards model. Adjustments were made for baseline PDA, adherence status, and clinical site for all two- and three-way interactions with treatment effects. The statistical methods employed were identical to those reported earlier (Anton et al., 2006) which followed a pre-specified approach to analyzing the primary drinking outcomes. Exploratory analysis was evaluated at the nominal $p = 0.05$ level of significance.

RESULTS

Patient Characteristics

A total of 1226 patients comprised the total study population (69% men and 31% women). Of this sample, 42% were married and the average age of the group was 44 years. A sizeable proportion (23%) of the patients were categorized as ethnic minorities (i.e., 8% African-American, 11% Latino and 4% Other). The majority of individuals had at least a high school education (69%). Baseline data on alcohol consumption revealed the following: (1) the mean number of heavy drinking days in the 30 days prior to treatment was 19.6; (2) the mean number of drinks per drinking day was 12.6; and (3) the percentage of days drinking was 75%. Except for one finding, there were no significant differences in the 76 pretreatment characteristics that were compared across various treatment combinations (Anton et al., 2006); there was small but significant difference in the number of alcohol dependence symptoms between MM and MM+CBI conditions (5.6 vs. 5.4 symptoms, respectively, $p < 0.05$). Given the number of comparisons made, it is conceivable that the latter finding might be spurious. (For a full description of the sample, see Anton et al., 2006).

Medication Adherence by Medication Condition

In general, data from this study show that the combination medication (acamprosate and naltrexone) conditions had significantly lower adherence rates than the placebo condition (See Table 2 below). Overall, individuals receiving acamprosate + naltrexone consumed fewer pills than those in the placebo group (64.9% vs. 76.2%, of the expected dose of 896 pills, $p<0.01$). These differences were consistent across both MM only and MM + CBI conditions. In addition, adding acamprosate to naltrexone appeared to result in lower adherence rates than providing naltrexone alone; significant differences were found between the combination medication condition (acamprosate and naltrexone) and the naltrexone alone condition (64.9% vs. 72.2%, respectively ($p = 0.01$). Moreover, significant differences were found between acamprosate and placebo conditions. (69.7% vs. 76.2%, respectively, $p< 0.05$) but not between the naltrexone and placebo conditions (ns). Finally, it should be important to note that individuals who failed to take their medication regularly were more likely to stop or withdraw from the medication completely. Thus, mean adherence rates to the expected dosage was 36.1 % for *withdrawers* in contrast to 90.02 % for *nonwithdrawers* ($p= 0.001$).

Medication Adherence by Behavioral Treatment Modality

In examining the relationship of behavioral treatments to medication adherence, we initially compared medication adherence between those receiving MM alone and those receiving the more intensive alcohol specialty treatment (i.e., CBI + MM). Contrary to prior expectations, we found that adding CBI to MM did not produce better results than those patients receiving only the MM behavioral intervention; that is, both MM only and MM+CBI were equally effective in sustaining a commitment to the medication regime. In the MM only vs. MM +CBI conditions, mean adherence to the full medication regime was 71.8% vs. 69.8%, respectively (ns).

We also conducted another analysis examining whether sessions attendance was related to medication adherence. As expected, there was a highly significant association found in medication adherence rates (≥ 80% maximum dose exposure) between individuals attending at least 7 MM or MM+CBI sessions and those that did not. Approximately 75% of the high treatment attendees ((7 or more sessions) in both behavioral treatments (i.e., MM only and MM+CBI) were categorized as medication adherent (≥ 80% maximum dose exposure) ($p<0001$). In contrast, 25% of low treatment attendees in both behavioral treatments were placed in the medication adherent category ($p<0001$).

In addition, rates of withdrawal from medications were not significantly different between MM only and MM+CBI (37% vs. 34%, respectively, ns). Thus, patients were just as likely to take their pills regardless of whether they were assigned to only a low intensity, nonspecialty treatment (MM) or to an additional moderately intensive, alcohol specialty treatment (MM+CBI). Of interest is whether CBI session attendance improved or reduced MM session attendance. The findings show that there were no significant differences in MM session attendance between MM only and MM+CBI patients. Mean number of MM sessions attended for MM only patients was 7.44 vs. 7.65 for the MM+CBI patients (ns). Consequently, participating in CBI did not enhance or impede MM attendance.

Medication Adherence and Primary Drinking Outcome: PDA and Time to First Heavy Drinking Day

To examine the effects of medication adherence on PDA across all treatment combinations we employed a generalized linear mixed model adjusting for baseline PDA and clinical site. As indicated earlier, patients were also categorized as adherent or nonadherent depending upon whether they had taken 80% or more of the full dose medication or placebo during treatment. Results of these analyses can be found on Table 3.

As in other medication trials, nonadherents to the study medication did more poorly than adherents. At the end of week 16, mean PDA for adherent patients was 82% vs. 72% for nonadherent patients ($p<0.0001$). Further, in adjusting for the maximum dose adherence (i.e., ≥ 80% of the pills) we discovered a medication by therapy interaction. As observed on Table 3, a significant interaction was found between naltrexone and CBI with the naltrexone/no CBI group (i.e., MM only) having the highest mean PDA (79.84%) and the placebo/no CBI group having the lowest PDA (73.93%) at week 16 ($p= 0.01$). No other interactions were significant. These data are very consistent with our primary intent- to- treat outcome analysis where a similar interaction was found (See Anton et al., 2006).

To examine the relationship between medication adherence and time to first heavy drinking day, we employed a proportional hazards regression model adjusting for site and baseline PDA with placebo+MM as the reference group. For clinical interpretation, we classified patients (i.e., the numbers and proportions) as having relapsed if they had one or more heavy drinking days during treatment. To conduct a more parsimonious analysis, so that no assumptions would be required for medication adherence, we only included patients who had complete data on treatment delivery and drinking (e.g., Timeline Follow Back) at the end of 16 weeks ($n = 1147$).

Results of these analyses can be found on Table 4. As with PDA, the risk was significantly reduced if patients remained adherent (80% or more maximum dose adherence) to the active or inactive medication (H.R. 0.439, CI 0.319–0.605, $p<.0001$). These data also show a relationship between adherence and the behavioral treatment modality. As in the primary outcome paper (Anton et al., 2006), there was a significant main effect for naltrexone for the time to first heavy drinking day. The reduction of risk for relapse was enhanced when patients remained adherent to the study medication. The relapse hazard ratio was 0.476 (CI 0.340–0.666, $p< .0001$) for patients who were adherent to naltrexone in contrast to those who were adherent to the placebo. The table also shows a main effect that almost reaches significance for acamprosate ($p= .06$). However, what we are likely seeing are the positive effects of adherence to treatment in general, since patients that received both active naltrexone and active acamprosate were also included in the acamprosate main effect group due to the factorial design.

Of major interest is the three-way significant interaction between medication adherence, naltrexone and CBI ($p = 0.016$). With regard to time to first heavy drinking day, medication

adherence, CBI and naltrexone appear to have a differential impact on the study population. The reduction of risk for relapse appears to be dependent upon whether the patients were medication adherent, received CBI and/or naltrexone.

The figures below (1a, 1b, 2a, and 2b) illustrate how to interpret clinically the three-way interaction between naltrexone, medication adherence and CBI. The figures give the probabilities of not returning to heavy drinking at various time periods over the 16-week treatment period. These probabilities are expressed as cumulative proportions (i.e., percentages) in these figures.

In Figure 1a, we examined differences in drinking outcomes between *adherers* and *nonadherers* who were not assigned to an active medication (no naltrexone or double placebo) and an intensive treatment condition (MM only). These data revealed that the probability of not returning to heavy drinking (i.e., nonrelapse) is higher for *adherers* than *nonadherers* in this assignment category. More specifically, 10% of the *nonadherers* who were not assigned to both an active medication condition and a more intensive treatment modality (i.e., received double placebo and MM only) had not relapsed (i.e., had no heavy drinking days) by the end of the study. In contrast, 40% of *adherers* in MM only and placebo condition were placed in this remitted or recovering category ($p<0.001$). In short, the "recovery" rate among *adherers* in the MM only, placebo condition was quite striking when compared to the *nonadherers in the same condition.* Thus in the absence of both CBI and naltrexone (MM only with double placebo or no naltrexone), adherence seems to be one of the factors in decreasing the overall hazard of relapse.

In Figure 1b we investigated differences in drinking outcomes between *adherers* and *nonadherers* who were assigned to a double placebo (i.e., no active medications or no naltrexone) condition and a more intensive treatment condition (CBI). Unlike patients in Figure 1a, all patients in Figure 1b *received CBI* along with MM. These data show that the probability of maintaining sobriety (i.e., no heavy drinking days) for nonadherent placebo patients was higher if they received CBI than if they did not. More precisely, in the absence of an active medication but in the presence of CBI, differences in recovery rates (i.e. no heavy drinking days) between *adherers* and *nonadherers* is less pronounced than the patients in Figure 1a. Among patients receiving placebo + CBI, approximately 25% of the *nonadherers* (<80% of the full dose) had not resumed heavy drinking by the end of the 16 week treatment period whereas 35% of *adherers* (≥ 80% of the full dose) in the same condition (i.e., double placebo and CBI) were placed in the non-relapsed category ($p = .12$, ns). In other words, differences between *adherers* and *nonadherers* to the inactive medication condition became non-significant when CBI was introduced into the relationship thereby suggesting that exposure to CBI may decrease the risk of relapse secondary to pill nonadherence.

Figures 2a and 2b compare the recovery patterns between nonadherent and adherent among patients receiving an active medication (naltrexone). In Figure 2a, naltrexone-treated patients were assigned to MM only whereas their counterparts in Figure 2b received MM +CBI. Overall, these two figures demonstrate that the probability of recovery (i.e., returning to heavy drinking) essentially remained the same whether or not they were assigned to the more intensive treatment condition (i.e., CBI).

Figure 2a shows that in the absence of CBI, the amount of exposure to naltrexone seemed to make a significant difference in decreasing the risk of relapse over the 16-week treatment period. At the end of 16 weeks, the percentage of *adherers* that maintained sobriety (i.e., having no heavy drinking days) was almost double that of *nonadherers* (42% vs. 22%, $p= 0.022$). Figure 2b shows that there is almost no change in drinking outcomes (i.e., relapse to

heavy drinking) between *adherers* and *nonadherers* when exposed to CBI; differences in relapse rates between these two groups remained virtually the same as in Figure 2a despite the exposure to CBI (39% vs. 21%), p = 0.026). In brief, adding CBI did not have an impact on the relapse rates relative to the no CBI group among naltrexone-treated patients,

In summary, among patients receiving placebo, the rates of change in drinking behavior between *adherers* and *nonadherers* appear to differ in accordance with the presence and absence of CBI. The highest rates of relapse to heavy drinking was found in the placebo group unless they were exposed to CBI, which then lowered (mediates non-adherence to pills) the relapse rates. Among naltrexone-treated patients, the magnitude of change between naltrexone adherers and nonadherers remained essentially the same whether or not patients were exposed to CBI. Such findings suggest that differences in outcomes between *adherers* and *nonadherers* may be related to the amount of exposure to the active medication (naltrexone) and are less influenced by CBI.

DISCUSSION

This paper examined the relationship between medication adherence and drinking outcomes at 16 weeks, the time period between treatment entry and treatment completion. More specifically, we addressed whether there were differences in medication adherence rates across 8 medication/behavioral treatment combinations. We also investigated whether there were differences in medication adherence between the two behavioral treatment modalities (i.e., combined behavior intervention (CBI) + medical management (MM) vs. MM only). Additionally, we examined whether differences in medication adherence rates across the 8 combinations were associated with differences in drinking outcomes. Answers to these questions were expected to further our understanding of the interrelationship between medication adherence and treatment outcome

Data revealed significant differences in pill taking adherence rates between the combination medications (naltrexone + acamprosate) and the double placebo conditions. Similarly, significant differences in pill taking adherence rates were found between acamprosate + naltrexone placebo and the double placebo conditions but not between the naltrexone + acamprosate placebo and the double placebo conditions. Also, significant differences in pill taking adherence rates were revealed between the combination medications (naltrexone + acamprosate) and the naltrexone + acamprosate placebo conditions. These findings were consistent across behavioral treatments.

Individuals that received acamprosate only exhibited prominent side effects and lower adherence rates than the double placebo group. Consequently, it would seem that adding acamprosate to naltrexone lowered the adherence rates of patients assigned to this combination medication condition. The higher number of reported side effects in the combination conditions could account for these differences. For example, nausea was present in 42.4% of the combination group (acamprosate and naltrexone) in contrast to 21.2% in the placebo conditions (p = 0.05) (Ciraulo, 2007). Similar findings were observed with regard to other adverse effects such as vomiting and diarrhea (p = 0.05) (Ciraulo, 2007). These findings are comparable with other drug trials where pill adherence rates are typically higher for patients in the placebo than in the active medication groups (Osterberg and Blaschke, 2005).

Moreover, those patients who failed to take their medication regularly were also more likely to stop their medication completely. This is important to note since those who stopped taking their medication were also more likely to resume drinking than those who continued taking the medication until the end of treatment; the average PDA for medication

withdrawers was 65.9% in contrast to 80.7% among *nonwithdrawers* ($p<0.0001$). These findings are in agreement with Rohsenhow and her colleagues (2000) who found that a higher severity of side effects such as nausea and vomiting predicted nonadherence among naltrexone-treated patients and might also contribute to poorer drinking outcomes in an alcohol-dependent population.

Concerning the relationship between medication adherence and behavioral treatments, the more intensive, specialty treatment CBI, did not perform better than the less intensive, primary care type MM approach. There were no significant differences in both adherence and medication discontinuance rates between MM alone or in combination with CBI. Such findings are consistent with other alcohol medication trials involving naltrexone (Baros et al., 2007; Oslin et al., in press). Baros et al., (2007) found no significant differences in medication adherence rates between the more intensive cognitive behavioral therapy (CBT) and the less intensive motivational enhancement therapy (MET). Similarly, Oslin et al., (in press) in testing the effects of naltrexone among alcohol patients assigned to behavioral interventions of varying intensities (e.g., compliance enhancement (CE), doctor only and cognitive behavioral therapy, found no significant differences between the three contrasting behavioral approaches in facilitating medication adherence.

As expected, high medication adherence fared better than low medication adherence with regard to PDA and time to first heavy drinking day. With regard to PDA, we found a significant interaction between naltrexone and CBI with the naltrexone/MM only group having the highest PDA and the placebo/MM only having the lowest PDA. These results are comparable to the COMBINE Study primary intent-to-treat outcome findings (Anton et al., 2006). As in the current paper, the results of the main outcome paper show PDA highest in the naltrexone/no CBI (i.e., MM only) group (80.6%) and the lowest for the placebo/no CBI group (75%, $p = 0.0009$). In short, drinking outcomes (i.e., PDA) of the COMBINE study did not change when pill taking adherence status was introduced into the analysis, thereby strengthening the conclusions drawn from the main outcome paper.

With respect to first heavy drinking day, a significant three-way interaction was found between medication adherence, CBI and naltrexone. Lower relapse rates appeared to be dependent upon whether the patient was adherent to medication and received naltrexone or CBI. Within the placebo group, CBI seems to have had a beneficial impact on decreasing the odds of returning to drinking among patients nonadherent to pill taking. In the presence of CBI, the recovery (non-relapse) period for patients who were nonadherent to placebo was extended. CBI may have provided these nonadherent patients with an increased level of support that resulted in a reduction in heavy drinking. Other components of CBI such as increasing coping skills to deal with cravings or drink refusal strategies, providing optimism for change and enhancing self-efficacy might have been useful in extending the recovery period.

In contrast, among naltrexone-treated patients, CBI demonstrated no significant additional benefit beyond what was produced by exposure to the active medication in the context of medical management. Unlike the placebo group, ongoing adherence to the study medication may have helped to reduce the likelihood of relapse with CBI providing minimal additional benefit. The findings on the three-way interaction indicate that effects of medication on outcomes are moderated by both medication and CBI, such that CBI provides a buffer for nonadherence in the placebo but not in the medication condition.

In interpreting the results on the three-way interaction, consideration should be given to why CBI did not have a noticeable impact on naltrexone-treated patients. MM was primarily designed to maximize and support pill taking adherence. Consequently, maximum dose

medication adherence rates were relatively high across MM treatment combinations. Thus, it is conceivable that since MM had a strong focus on adherence, it may have caused a "ceiling effect" on this outcome variable such that any additional work on adherence via CBI may be less potent or observable. It is also conceivable that CBI inadvertently helped these naltrexone-treated patients to be less concerned about not taking or stopping the medication. CBI emphasizes decision-making responsibilities and promotes self-efficacy on the part of patients. Such an approach may have indirectly empowered or allowed patients to stop taking the medication if they felt it was not working (i.e., experiencing side effects).

It is not clear which components of CBI have benefited or not benefited nonadherent patients. A process analysis aimed at examining mechanisms of action associated with CBI and medication adherence might provide further understanding of how this treatment modality impacts on alcohol patients (Stout, 2007).

In summary, high medication adherents fared better than low medication adherents across all combinations. CBI seemed to have a beneficial impact on nonadherents in the placebo condition raising the issue of whether CBI may serve as a cushion or have a protective function for nonadherent, placebo patients. On the other hand, adherence to naltrexone provided a significant increase in time to relapse. However, CBI did not add any such advantage to naltrexone-treated patients.

The current study adds to the growing literature (see e.g., O'Malley et al., 2003; Garbutt et al., 2005) supporting the use of a primary care approach as a behavioral platform for pharmacotherapy with alcohol dependent patients. It confirms the findings of the primary COMBINE Study report (Anton et al. 2006) which showed MM to be beneficial for a sizeable proportion of patients regularly taking naltrexone. However, the MM approach was utilized in a clinical trial. Consequently, other factors, unrelated to the treatment approach (e.g., conducting an extensive assessment battery, repeated contact with research staff, and follow-up visits) could account for the positive findings (Clifford et al., 2007). Thus, MM will need to be adapted to "real world" medical settings like primary care clinics, to determine the feasibility and utility of the approach.

In conclusion, there are several new treatment strategies for alcohol dependent patients, involving pharmacotherapies, behavioral interventions, or the combination. The success of these treatments is strongly tied to good patient medication adherence and visit attendance at behavioral interventions. In studies like the COMBINE study, where medication adherence rates and session attendance rates are high, treatment outcomes reported for the total study group in an intent to treat analysis, as previously reported, were not substantially altered by a retrospective analyses that considered medication adherence. However, in clinical practice these issues must be considered.

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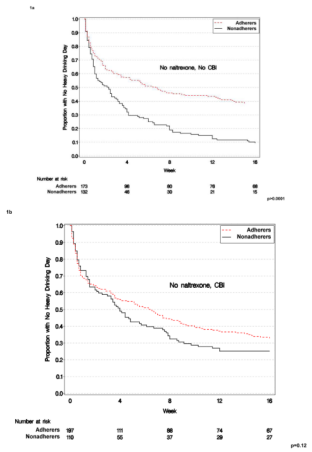

Figure 1.

Figure 1a & 1b. Cumulative proportion of Patients with No Heavy Drinking Days during treatment between Adherers and Nonadherers: No Naltrexone (placebo Naltrexone) by Combined Behavioral Intervention (CBI) therapy groups

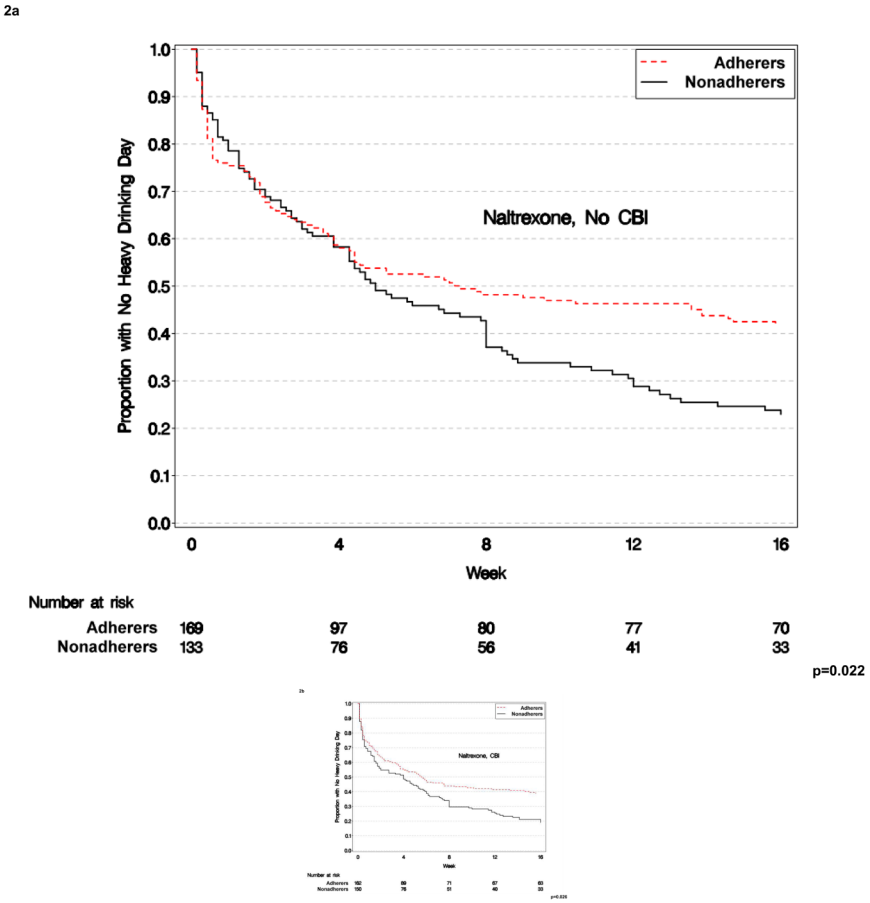

Figure 2.

Figure 2a and 2b. Cumulative proportion of Patients with No Heavy Drinking Days during treatment between Adherers and Nonadherers: Naltrexone by Combined Behavioral Intervention (CBI) therapy groups

Table 1

Treatment Group Combinations (1383 Randomized Patients)

	Placebo (N)	Acamprosate (N)	CBI only (no pills) (N)
Medical Management Only (n=607)			
Placebo	153	152	
Naltrexone	154	148	
Medical Management + Combined Behavioral Intervention (CBI) (n=619)			
Placebo	156	151	
Naltrexone	155	157	
CBI only (no pills)			157

Table 2

Comparison of Pill Adherence Rates between Medication/Treatment Combinations (N = 1224)[++]

Medication group	MM Only Mean % (SD)	MM+CBI Mean % (SD)	Total for Medication Group Mean % (SD)
Placebo Naltrexone/ Placebo Acamprosate (n= 309)	75.6 (31.7)	76.8 (31.2)	76.2 (31.4)
Naltrexone/ Placebo Acamprosate[a] (n= 307)	72.1 (34.1)	72.3 (32.6)*	72.2 (33.3)**
Acamprosate/ Placebo Naltexone[b] (n= (303)	65.4 (34.1)**	74.1 (30.7)**	69.7 (32.7)*
Naltrexone + Acamprosate[b] (n= 305)	65.8 (35.6)**	64.1 (34.6)***	64.9 (35.0)***

[++] Two observations were missing in these data

MM = Medical Management

CBI = Combined Behavioral Intervention

[a] Significance levels reflect comparisons with naltrexone + acamprosate

[b] Significance levels reflect comparisons with placebo

* $p < 0.05$;

** $p = 0.01$;

*** $p < 0.01$

Table 3

Tests of Percent Days Abstinent (PDA) at Baseline and Week 16 Adjusted for Full Dose Adherence: Naltrexone X Combined Behavior Intervention (CBI) Interaction (N=1226)

	Baseline Mean	s.e.	Week 16 Adjusted Mean	s.e.
Naltrexone/CBI (n=312)	25.34	1.405	76.48	1.44
Naltrexone/No CBI (n=302)	26.59	1.433	79.84	1.46
No Naltrexone/CBI (n=307)	25.08	1.460	77.81	1.51
No Naltrexone/No CBI (n=305)	24.68	1.432	73.93	1.47

CBI = Combined Behavior Intervention

All differences are statistically significant at $p = 0.01$

Table 4

Main Effects and Interactions for Comparisons between Treatment Combinations to Placebo*

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio (95% CIs)
Baseline PDA	0.003	0.001	5.87	0.01	1.00 (1.00–1.01)
Main effects					
Adherent	−0.823	0.163	25.47	<.0001	0.44 (0.32–0.61)
Acamprosate	−0.287	0.150	3.65	0.06	0.75 (0.56–1.01)
Naltrexone	−0.742	0.171	18.83	<.0001	0.48 (0.34–0.67)
CBI	−0.715	0.180	15.72	<.0001	0.49 (0.34–0.70)
Two-way interactions					
Acamprosate × Naltrexone	0.234	0.146	2.57	0.11	1.26 (0.95–1.68)
Naltrexone × CBI	0.775	0.221	12.35	0.0004	2.17 (1.41–3.35)
Acamprosate × CBI	0.177	0.146	1.46	0.23	1.19 (0.90–1.59)
Adherent × Acamprosate	0.119	0.147	0.01	0.93	1.01 (0.76–1.35)
Adherent × Naltrexone	0.552	0.208	7.04	0.008	1.76 (1.55–2.61)
Adherent × CBI	0.718	0.209	11.81	0.001	2.05 (1.36–3.09)
Three-way interactions					
Adherent × Naltrexone × CBI	−0.709	0.294	5.80	0.016	0.49 (0.28–0.88)

PDA = Percent Days Abstinent

CBI = Combined Behavioral Intervention

* Employing proportional hazard model for time to first heavy drinking day, adjusting for site, baseline PDA, full dose adherence and treatment effects; included all patients with complete treatment data at the end of treatment (n = 1147).