

# Medication Compliance Feedback and Monitoring in a Clinical Trial: Predictors and Outcomes

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## ABSTRACT

**Objective:** The objective of this study was to demonstrate the utility of continuous monitoring and enhancement of medication compliance during a long-term clinical trial, predictors of compliance, and relationships to drinking outcomes.

**Methods:** Alcohol-dependent patients enrolled in a multicenter VA cooperative study were randomly assigned to once-daily naltrexone (NTX) for 3 or 12 months (short-term or long-term NTX) or placebo for 12 months of treatment. All medications were dispensed in bottles with medication event monitoring (MEMS, AARDEX, Union City, CA) caps with a microprocessor that recorded openings as presumptive doses. Patients were trained to develop personal cues as dosing reminders. Monthly feedback sessions included review of compliance data and cues.

**Results:** There were no significant differences among short-term NTX, long-term NTX, and placebo (209 each

groups in measures of compliance. Overall compliance rates were  $71\% \pm 31\%$  of doses for the first 13 weeks and  $43\% \pm 33\%$  of doses over 52 weeks. Some doses were taken during  $83\% \pm 27\%$  of the first 13 weeks. Higher medication compliance predicted fewer drinks per drinking day ( $P = .02$ ) throughout follow-up and a lower percentage of drinking days ( $P = .002$  during the first 13 weeks) with no significant effect for treatment group.

**Conclusions:** The feedback and monitoring programs were important features to demonstrate that lack of treatment effect was not a result of poor compliance. Medication compliance data supported the internal validity of the trial by demonstrating that good compliers had better outcomes, irrespective of treatment with NTX or placebo. The MEMS feedback methodology is feasible for use in multicenter trials.

**Keywords:** alcoholism, clinical trial, compliance, medication, naltrexone.

## Introduction

One of the most important concerns for clinical trial designers is how well patients will comply with the protocol for the duration of follow-up. Inadequate or unequal compliance with the study medication regimen by patients in one or all randomized groups can affect the results of the trial. Some patients stop taking the study medication immediately after randomization, other continue to attend follow-up visits but discontinue the study medication, and others might take the medication erratically thereby receiving a lower dose than planned. All of these concerns were addressed during the planning of an 18-month trial to evaluate naltrexone (NTX ReVia, DuPont

Pharmaceuticals, Wilmington, DE) as a treatment for alcohol dependence. The population to be enrolled was expected to be poor compliers with study medication, follow-up visits, and overall persistence in the study. Previous multicenter trials with alcohol-dependent patients revealed that medication compliance was a significant factor in drinking outcomes for medication and placebo groups, irrespective of the type of treatment [1–4]. In contrast, studies of NTX have shown that higher compliance was associated with improved outcomes only among the NTX-treated groups [5–7].

The main outcomes for this trial were 1) relapse to heavy drinking during the first 13 weeks; 2) drinks per drinking day; and 3) days drinking during 52 weeks of follow-up. The primary intention-to-treat analysis demonstrated that naltrexone was not superior to placebo treatment for any of the three end points [8]. Secondary analyses demon-

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strated that patients who were more compliant with medication had better outcomes whether they took naltrexone or placebo. Analyses of covariance, with one covariate taken at a time, showed that medication compliance, attendance at counseling sessions, and attendance at Alcoholics Anonymous meetings had strong effects on the drinks per drinking day and number of days drinking that were independent of naltrexone treatment [8].

Anticipating low medication compliance in this chronically alcohol-dependent population, we had used every feasible method to engage and maintain patients in the study to adequately evaluate the drug [8]. A program to promote compliance was included in the trial to avoid differences in compliance rates among groups and to reduce treatment dropouts so we could test the drug's effectiveness adequately [9,10]. Data describing medication compliance throughout the 52-week follow-up were available to explore predictors of medication compliance and the relationships between compliance and treatment outcomes. This report describes rates of compliance, patient characteristics predictive of compliance, and associations between compliance and alcohol use during the trial using the records of medication dosing throughout the 52-week trial.

## Methods

### Protocol

Alcohol-dependent patients who signed consent forms were enrolled in a study of the efficacy of NTX versus placebo at 15 Department of Veterans Affairs Medical Centers (VA) hospitals over a 2-year period. Patients were randomly assigned to three groups of equal size. Institutional review boards at each center and an independent data safety monitoring board monitored the project.

The double-blind study included three treatment groups: long-term, 50 mg of naltrexone for 12 months; short-term, 50 mg of naltrexone for 3 months followed by masked crossover to placebo for 9 months; or placebo for 12 months, all once daily. All patients were given individual counseling using a modified 12-step approach (Twelve Step Facilitation Treatment, TSFC) adapted for this clinical trial [11,12]. Evaluations were performed at baseline, monthly for 12 months, and quarterly through month 18. Monthly assessments included a review of drinking, medication usage, and compliance feedback, using MEMS data, and standardized counseling. The timeline follow-back system [13] was used to obtain drinking histories at every follow-up visit. Compensation was provided only for

time to attend monthly visits to collect data, but not to take the medication or attend counseling sessions. Patients who discontinued study medication or counseling were asked to continue to participate in monthly assessments to provide drinking data.

The Obsessive-Compulsive Drinking Scale (OCDS) was completed at baseline for use as a covariate in analyses [14]. Fourteen questions cover obsessive and compulsive aspects of drinking (e.g., frequency of thoughts, ability to divert thoughts, ability to resist urges to drink). Higher scores, with a range of 0 to 82 indicate a more severe drinking disorder.

### Eligibility Criteria

Subjects were diagnosed as alcohol dependent by DSM-IV criteria [15] with no comorbid Axis I diagnosis requiring psychotropic medication, nor a comorbid substance abuse/dependence diagnosis. They were veterans, 18 years or older with recent drinking to intoxication (heavy drinking two times in at least 1 week in the 30 days before screening). All subjects were outpatients and sober by examination for 5 days before randomization.

### Compliance Enhancement

All patients participated in the Medication Usage Skills for Effectiveness Program (MUSE-P) [9,10]. The standardized program has been effective in enhancing medication compliance among patients with chronic schizophrenia and chronic mood disorders [10]. Medication was provided in bottles with microelectronic monitor caps (MEMS, purchased from APREX, division of AARDEX, Union City, CA) that recorded the date and time of each opening and showed the number of hours elapsed since the previous opening. The feedback system was a discussion between the site research coordinator and patient focused on development of personalized cues for self-reminders and maintenance of the once daily regimen. Data on the previous month's dosing were shown to the patient when the MEMS cap was downloaded to a computer at each monthly visit to demonstrate self-efficacy. MEMS data were accumulated for 12 months for each patient for use in efficacy analyses.

### Analyses

Compliance with the once-daily study medication was defined as the number of days on which the bottle was opened divided by the number of days in that period. Intention-to-treat analyses used the protocol-defined denominators of 13 and 52 weeks. Additional analyses were based on the number of

days until the patient discontinued the medication, no doses after that day. Medication compliance was assessed as overall rates of taking one dose daily or compliance rate. The window for 13 and 52 week follow-up was  $\pm 15$  days.

Treatment efficacy variables were: percentage of days drinking, number of drinking days reported during that period divided by the number of days during that period for which data are available; drinks per drinking day, total number of drinks reported during the period divided by the number of days on which one or more drinks were reported; and time to relapse, number of days from randomization until relapse where relapse is defined as the first episode of a heavy drinking day with six or more drinks/drinking occasion for men and four or more for women.

The primary efficacy analysis was based on intention to treat. Secondary analyses were planned for an “as-treated” basis as well as analyses based on compliance with the treatment regimen. Analyses of variance (ANOVA) and chi-square were performed. The PROC REG procedure from SAS with backward elimination of nonsignificant variables was used for multivariate analyses. Multivariate analyses were based on summary variables for 13- and 52-week data.

## Results

### Baseline Characteristics

We randomly assigned 627 alcohol-dependent veterans into three equal groups of 209 subjects (placebo and short-term and long-term naltrexone). Table 1 lists demographic characteristics at baseline. There were no statistically significant differences among the groups in demographic characteristics or in measures of alcoholism severity [8].

### Compliance With Study Medication

*Intention to treat.* Patients took study medication on  $71\% \pm 31\%$  of days during the first

13 weeks and  $43\% \pm 33\%$  of days during the entire 52-week trial. Patients took some medication, at least one dose weekly, for  $51\% \pm 36\%$  of weeks for the full year. Compliance rates were not significantly different among the NTX and placebo treatment groups (Table 2). Figure 1 depicts the patterns of treatment persistence. By the end of 52 weeks of follow-up, 48% of patients continued to take study medication.

*As treated: censoring postdiscontinuation data.* Limiting analyses to the period until patients either discontinued taking doses or completed the study provided a view of compliance patterns among patients while they were engaged in the treatment program. Mean duration of treatment was  $44 \pm 12$  weeks before discontinuation. Patients took  $72\% \pm 29\%$  of medication during the year, while they wanted to participate (Table 2).

*If treated: censoring nonparticipant data.* Another method for evaluating rates of compliance was to include only patients who took doses for a minimum of 14 days, thereby eliminating patients who clearly did not want to participate in the treatment program. The cohort included 87% (548 of 627) of the total randomized population. They took doses for mean  $74\% \pm 29\%$  during the first three months and  $44\% \pm 33\%$  of doses, taking at least one dose weekly for 52% of weeks over 12 months (Table 2).

### Use of Compliance Techniques

Half of the patients (58%) reported that the digital displays on the MEMS cap were useful: number of hours since the bottle was last opened and number of openings today. Selection of a reminder cue was considered useful by 85% of patients (Table 3). Three-fourths of patients selected a morning time to take their once-daily tablet. Half of the doses (57%) were taken within the dose window, with a range of 1 hour before or after the selected dose time. These data did not change appreciably over weeks 13 to 52 (Table 4).

**Table 1** Demographic characteristics at baseline

Characteristic	Long-term NTX	Short-term NTX	Placebo
Number of subjects	209	209	209
Age (years)	$49.3 \pm 10$	$48.5 \pm 10$	$49.5 \pm 10$
Percent male	97.1	97.6	99.5
Education (years)	$13.2 \pm 2$	$13.3 \pm 2$	$13.2 \pm 2$
OCDS scores	$20.1 \pm 12$	$20.8 \pm 12$	$20.4 \pm 12$
No. drinks per drinking day in previous 90 days	$13.1 \pm 8$	$14.1 \pm 9$	$13.0 \pm 7$
Percentage of drinking days in previous 90 days	$65.9 \pm 30$	$68.3 \pm 29$	$65.6 \pm 29$

Abbreviation: NTX, naltrexone.

**Table 2** Compliance (percentage of days taking study medication) for 13 and 52 weeks

	NTX	Long-term NTX	Short-term NTX	Placebo	All <sup>§</sup>	Weeks with some treatment
<b>13 weeks</b>						
N	356 of 418			173 of 209	529 of 627	
No. of days in study	89 ± 27			88 ± 27	89 ± 27	
Intention to treat (%) <sup>*</sup>	72 ± 31			70 ± 31	71 ± 31	83 ± 27
As treated (%) <sup>†</sup>	80 ± 25			79 ± 25	80 ± 25	93 ± 18
If treated (%) <sup>‡</sup>					74 ± 29	84 ± 26
<b>52 weeks</b>						
N		185 of 209	190 of 209	185 of 209	560 of 627	
No. of days in study		223 ± 134	225 ± 136	221 ± 132	223 ± 134	
Intention to treat (%) <sup>*</sup>		44 ± 34	43 ± 33	42 ± 33	43 ± 33	51 ± 36
As treated (%) <sup>†</sup>		72 ± 29	72 ± 29	72 ± 29	72 ± 29	85 ± 27
If treated (%) <sup>‡</sup>					44 ± 33	52 ± 36

<sup>\*</sup>Intention to treat: based on the expected duration of treatment (91 days for 13 weeks or 365 days for 52 weeks); N = 529 for 13-weeks' N = 560 for 52-weeks.

<sup>†</sup>As treated: based on the number of days before discontinuation of medication (or completion of the study); N = 529 for 13 weeks' N = 560 for 52 weeks.

<sup>‡</sup>If treated: censoring patients who took study medication for ≤14 days: N = 513 for 13 weeks; N = 548 for 52 weeks.

<sup>§</sup>No significant differences across groups.

Abbreviation: NTX, naltrexone.

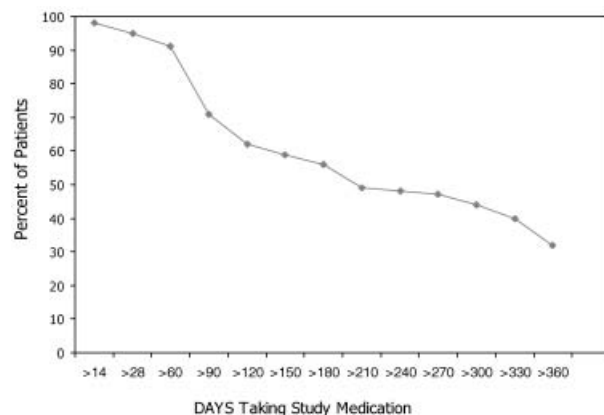
### Predictors of Medication Compliance

Examining the correlations between patient characteristics and compliance rates, multivariate analyses of the intention-to-treat population showed that higher 52-week compliance rates were found among patients who had low OCDS scores ( $P = .005$ ) and a low percentage of drinking days ( $P = .009$ ) before enrollment. Patients who had a family member willing to be interviewed and those who took medication for other medical disorders were better compliers than those without those attributes. Compliance was 50% when there was family member support, and 39% if not ( $P = .0001$ ). Compliance was 47% if patient took other medication, and 38% if not ( $P = .003$ ). The coefficients indicate that for an increase of 10 points in OCDS, medication compliance drops 3.4%. An increase in percentage of drinking days of 10%

leads to a drop in compliance of 1.3%. These were small in magnitude. Only OCDS and family support were significantly related to outcomes at 13 weeks.

### Predictors of Treatment Outcomes

Higher medication compliance predicted fewer drinks per drinking day ( $P = .02$ ) throughout follow-up and a lower percentage of drinking days ( $P = .002$  during the first 13 weeks), whereas naltrexone treatment had no effect. Higher baseline OCDS also predicted more drinking days ( $P = .03$ ). An increase of 10% in medications compliance would be associated with a decrease of 0.3 drinks per drinking day during 52-week follow-up. The same increase in compliance is related to a decrease of one percentage point in percentage of drinking days. Using medication compliance both as a continuous variable and as a categorical variable ( $\geq 50$ ,  $\geq 70$ , and  $\geq 90$ % compliance) as a covariate with treatment, no relationships were found for any of the outcomes at 13 or 52 weeks.



**Figure 1** Proportion of patients continuing to take study medication during 1 year of follow-up.

### Discussion

These data demonstrated that alcohol-dependent patients who volunteered to participate in this 52-week medication treatment program adequately complied with the once-daily regimen. Compliance with the study medication was significantly correlated with improved outcome, but unrelated to naltrexone treatment. The primary and secondary outcomes have been reported previously, as the basis for this report on additional analyses undertaken to better understand the study results. Continuous electronic compliance measurement provided data throughout follow-up for analyses by

**Table 3** Usefulness (%) of medication compliance reminders

	13 weeks	52 weeks
MEMS (frequency selected)		
Cap is a reminder	59	58
Cue is a reminder	85	85
Cue usefulness (frequency of use)		
Clock time	67	68
Meal time	9	7
Daily activity	18	16
Other	6	9

rate or by follow-up interval. Without these data, critics could have charged that compliance rates differed among treatment groups, that NTX adverse effects had caused patients to discontinue treatment, or that inadequate amounts of NTX were taken to assess outcomes. We used the continuous compliance records for these analyses to generate hypotheses that could be evaluated in future studies.

#### Internal Validity of the Clinical Trial

Continuous electronic compliance-monitoring methodology has been demonstrated to be superior to counting returned tablets because patients could appear to be better compliers by not returning unused tablets [16,17]. MEMS data could be reviewed to determine that the patient opened the bottle at the planned time to remove a dose. Previous experience has shown that patients do not open the MEMS cap at the appropriate time day after day simply to appear to have taken a dose [10]. As demonstrated again in this trial, patients simply stop taking the medication when they decide not to continue. MEMS data revealed that few subjects stopped and restarted medication or took tablets sporadically. Most subjects who discontinued treatment simply stopped taking the tablets, at which point we considered them discontinuers. Naltrexone is known to occupy mu receptors for several days, with an 18-hour terminal half-life of the active

metabolite, 6- $\beta$ -naltrexol [18]. This gives some support to the adequacy of taking several doses per week.

#### Compliance Enhancement Method

Other reports have demonstrated that medication compliance can be enhanced in studies of treatment for alcoholism. For example, Sullivan et al. [19] used several indirect measures to estimate compliance rates ranging from 78% to 97%. They used stringent selection and reinforcement methods to achieve high rates of compliance. In our trial, we used the same eligibility criteria as in other naltrexone trials. The additional method employed to enhance medication compliance was the inclusion of the MUSE-P medication feedback program. Our research coordinator saw the patient once a month for data collection, MEMS data download, and feedback. The review of MEMS data took only a few minutes, including review of cues. We postulate that the MUSE-P was equivalent to low-intensity motivational enhancement. It was focused exclusively on taking the medication daily, not on suggesting that the medication would reduce drinking. Patients knew that naltrexone was not an aversive treatment like disulfiram. They were told that it was not a cure, but was thought to reduce craving. The development of a cue was a successful intervention because the majority of doses were taken within the time frame, or dose window, selected by the individual. This finding suggests the usefulness of this simple intervention to improve compliance.

#### Compliance with Medication for Other Medical Disorders

The adequacy of daily compliance rates and duration of treatment persistence can be demonstrated by comparisons to other medical disorders. A review of studies in which hypertensive patients were prescribed a once-daily medication showed an

**Table 4** Compliance rates by schedule

Compliance with selected dose time	13 weeks				52 weeks			
	% Choosing window	Doses taken as planned* (within dose window)		% Choosing window	Doses taken as planned* (within dose window)			
		N	%		N	%		
Morning dose (3 am to <12 pm)	75	16,040	61	76	39,134	57		
Afternoon dose (12 pm to <5 pm)	7	1,220	52	6	2,911	51		
Evening dose (5 pm to <8 pm)	6	870	47	6	1,801	43		
Bedtime dose (8 pm to <3 am)	12	2,152	59	12	5,804	55		
All dose times	100	20,282	59	100	49,650	56		

\*Dose window was 1 hour before to 1 hour after the dose time selected by the patient. Determination of morning, afternoon, evening, or bedtime dosing was based on the time selected for the dose allowing windows to overlap two periods.

average compliance rate of 76%, with a wide range of 53% to 85%. Nevertheless, 56% of people prescribed medication to control blood pressure discontinued in 6 months. A study showed that 28% of insulin-dependent diabetes patients obtained less than the prescribed amount of insulin [20]. Persistence with oral diabetes medication also was poor, with only 18% of patients continuing to take acarbose for 1 year [21].

Thus, taking 71% of doses during the first 13 weeks, and 43% of doses over 52 weeks appears to have been reasonable. Persistence with treatment for 1 year by 48% of patients demonstrated a high commitment to the medication program.

### *Predictors of Medication Compliance*

The second aspect of these analyses was to determine whether patient characteristics could be used to predict medication compliance. A series of analyses was undertaken including multiple baseline characteristics and instrument scores to look for significant predictors of high medication compliance. Four issues were weakly predictive of higher compliance in these models. High OCDS scores indicating high levels of obsessiveness and compulsiveness for drinking, and a higher percentage of drinking days predicted lower medication compliance rates. Roberts et al. [22] demonstrated that higher OCDS scores indicated low resistance and control, high obsession, and high interference of drinking with life. Addiction severity and drinks per drinking day were significantly correlated with OCDS scores. Nevertheless, in their population, high OCDS scores, and high number of drinks per drinking day, predicted earlier relapse to heavy drinking. Among the other predictors of medication compliance, we interpret the predictive value of having a significant other person willing to be interviewed as a sign that the patient had some support for participation in this treatment trial. Finding that use of any other medication for a medical disorder predicted compliance suggests that the patient's health beliefs supported medical interventions.

### *Medication Compliance as a Predictor of Drinking Outcomes*

Fuller et al. [1,23] demonstrated a result similar to ours in a study of disulfiram and placebo. No differences were seen between treatments, but treatment compliers had better success than non-compliers. This finding would have been expected

for disulfiram because it is an aversive treatment, but aversion cannot explain the results with placebo. Lithium also was found to be ineffective for treatment [2,24]. The compliance result was confirmed in a VA study of lithium that showed significant differences in drinking between compliers and noncompliers without an effect for lithium [3,4]. Our results parallel these earlier trials.

### *Medication Compliance in Other Naltrexone Trials*

Unlike the other studies that demonstrated better NTX efficacy among high compliers, we found no differences between NTX and placebo treatments at any compliance rate. Three previous naltrexone trials assessing medication compliance found efficacy for the drug among patients who took the largest amount of medication. Volpicelli et al. [5] reported that naltrexone improved relapse rates and number of drinking days only among patients who took more than 90% of medication, by pill count, with no difference in craving. Namkoong et al. [6] found better outcomes among patients who had higher rates of compliance with the study medication in a placebo-controlled trial using electronic monitoring. Rohsenow et al. [7] reported that medication compliance, based on urinary riboflavin measurement, was higher among patients who believed that the medication would help them stop drinking, but not based on commitment to abstinence or self-efficacy about abstinence. They also found higher compliance rates among patients with strong urges to drink, based on a laboratory model. Better compliance has been found among patients who believed that the medication would help them stay sober [7,25], but not among those who were committed to abstinence [7]. Medication compliance rates during the first 13 weeks were almost as high in this trial, 71% of doses, as in the short term study that also used MEMS (80%) [6]. Among those continuing, medication was taken for mean 44 weeks during the year of treatment.

Our analyses demonstrated better control of drinking among higher compliers, but no effect of treatment. Namkoong et al. [6] used a median split, at 87% compliance by MEMS, to determine two groups taking naltrexone as high and low compliers. The higher compliance group did significantly better on abstinence and never relapsed during treatment. Volpicelli et al. [5] used pill counts and self-reports to measure compliance instead of electronic monitoring. They found significantly better outcomes among patients taking more than 90% of naltrexone doses than in the placebo

group or among lower compliers that we did not replicate.

### Summary

The medication feedback and monitoring programs were important features to demonstrate that lack of treatment effect was not due to poor compliance. Medication compliance data supported the internal validity of the trial by demonstrating that good compliers had better outcomes, irrespective of treatment with NTX or placebo. The computer-based feedback methodology is feasible for use in multicenter trials, whereas the simple cue-development program might be transferable to routine clinical practice.

This study was Supported by the Department of Veterans Affairs, Medical Research Service, Cooperative Studies Program. Naltrexone (ReVia) was provided by Du Pont Pharmaceuticals.

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