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What Happens When People Discontinue Taking Medications? Lessons from COMBINE

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Abstract

Aims—We use intensive longitudinal data methods to illuminate processes affecting patients' drinking in relation to the discontinuation of medications within an alcohol treatment study. Although previous work has focused on broad measures of medication adherence, we focus on dynamic changes in drinking both before and after patients discontinue.

Design—We conducted secondary data analyses using the COMBINE study, focused on participants who discontinued medications prior to the planned end of treatment. Using an interrupted timeseries analysis, we analyzed drinking in the weeks before and after discontinuation and also studied outcomes at the end of the COMBINE follow-up.

Participants—We describe the sub-sample of COMBINE participants who discontinued medications (n=450), and compare them to those who were medication adherent (n=559) and to those who discontinued but had substantial missing data (n=217).

Measurements—The primary outcomes were percent days abstinent (PDA) and percent heavy drinking days (PHDD). Medication adherence data were used to approximate the date of discontinuation.

Findings—For many patients, an increase in drinking starts weeks before discontinuation (PDA: $F(1,4803) = 19.07$, $p < .001$; PHDD: $F(1,4804) = 8.58$, $p = .003$) then escalates at discontinuation (PDA: $F(1,446) = 5.05$, $p = .025$; PHDD: $F(1,446) = 4.52$, $p = .034$). Among other effects, the amount of change was moderated by the reason for discontinuation (e.g., adverse event; PDA: $F(2,4803) = 3.85$, $p = .021$; PHDD: $F(2,4804) = 5.36$, $p = .005$) and also whether it occurred in the

first or second half of treatment (PDA: $F(1,4803) = 5.23$, $p = .022$; PHDD: $F(1,4804) = 8.79$, $p = .003$).

Conclusions—The decision to stop medications appears to take place during a weeks-long process of disengagement from treatment. Patients who discontinue medications early in treatment or without medical consultation appear to drink more frequently and more heavily, though there may be opportunities for clinical intervention. These data also support the use of sophisticated imputation strategies for missing data in preference to the practices now in common use.

Introduction

In randomized medication trials, the duration of treatment is usually fixed. However, in most trials patients depart from the planned medication regimen for both anticipated and unanticipated reasons. Absent other sources of bias, as long as departures from the ideal medication schedule are not greatly different across drug and placebo arms, the validity of the drug-placebo comparison is not threatened (1). However, even if medication and placebo arms are balanced with regard to adherence, a better understanding of the circumstances under which people stop medications, and the implications for clinical outcome, are important for improving the delivery of medications and other interventions. There is an extensive literature on medication adherence in addictions (2–6). Overall, this research has reinforced the conclusion that more adherence is associated with better outcomes, but that strong, well-replicated predictors of adherence are rare. While these findings are useful, patients' choices to continue or terminate medication occur through a complex interactive process that research has only begun to examine.

The purpose of this paper is to use intensive longitudinal data methods to help illuminate some of the dynamic processes that may affect patients' choices to stop medications. In particular, this paper focuses on the relationship between drinking and medication use. How drinking relates to stopping medications is important both for clinical and research reasons. Clinically, there is the question of whether stopping medications is a cause or an effect of increased drinking. If a person stops medications, is a resumption of problem drinking inevitable, or is there reason to hope that further intervention might be successful? From a research perspective, patients who stop medications often are removed or drop out of research follow-up (7, 8).

Stopping medications is usually considered only from the perspective of adherence; from that point of view, stopping is unequivocally bad because of the failure to achieve the full desired dosage for the full planned time. However, in clinical practice, patient and clinician decisions to continue vs. stop medications are determined by ongoing cost-benefit calculations that are largely unobservable, but are affected by drinking during treatment as well as the interactions between patient and clinician (9).

Although methods to maximize adherence have been extensively studied (6, 10), there have been no quantitative process studies on a fine time scale of the relationships between drinking and medication discontinuation. For example, there is a widespread belief that patients who discontinue treatment often do so in anticipation of increasing their drinking (11), but we lack data on how often this is true (patients may stop medications because they

feel they are cured), nor do we know how quickly drinking accelerates (when it does) after the last medication dose.

Indeed, to our knowledge, only one study has examined such timing (12). In that study, of patients who were both non-adherent to medication and resumed drinking, nearly two-thirds reported that their relapse occurred prior to discontinuing medication, suggesting that, in the majority of cases, relapse could be a determinant of future non-adherence. Of the remaining one-third, nearly equal proportions either discontinued their medications first (suggesting that some patients may relapse because they stopped taking efficacious medications) or engaged in both activities at roughly the same time (suggesting reciprocal causality or the presence of a third factor affecting both activities). While helpful in understanding the potential causal direction of the relationship between medication non-adherence and drinking, these results provide only a static picture of relationships and do not quantify how much drinking changes around the time that non-adherence occurs.

What happens when people discontinue medications is also important for research methodology, yet direct inquiry on this question is lacking. Instead, many investigators of addiction trials believe that discontinuing medications is a prelude to a resumption or escalation of substance use, resulting in the common practice of imputing a return to baseline drinking when there is missing drinking outcome data (e.g., 11). However, such an approach almost certainly leads to biased effect estimates and standard errors (13). In other studies, participants have been dropped from research follow-up when they have stopped taking medications (e.g., 7). Such approaches can lead to inaccurate conclusions about trial results.

In this paper, we have taken advantage of the fact that in the COMBINE study, patients who discontinued or were taken off study medication were followed for outcome as long as possible using the Form 90 to capture daily drinking data (14). The COMBINE data provide us with a valuable opportunity to study drinking both before and after medications were discontinued. These analyses should help to inform clinical efforts to respond adaptively to patients' needs. The detailed longitudinal data available in COMBINE also can inform us about the appropriate handling of missing outcome data within large medication trials, because patients who drop out of treatment also tend to drop out of research follow-up visits even if these are attempted.

Methods

For a detailed description of the COMBINE study, please see (15–17). Briefly, COMBINE investigators randomized 1,383 newly abstinent participants to nine groups to assess whether supplementing medications with a behavioral intervention would improve drinking outcomes over monotherapies. Over a 16-week period, patients were assigned to one of four medication conditions: placebo only, naltrexone only, acamprosate only, and naltrexone + acamprosate, either with or without the combined behavioral intervention (CBI), resulting in four medication regimens $\times$ two CBI regimens or eight different groups. The final group received CBI only, with neither placebo nor active medication; the current analyses ($n=1226$) omit this cell ($n=157$). The dosages of naltrexone and acamprosate were 100 mg/

day, and 3,000 mg/day, respectively. Those receiving CBI could attend up to 20 sessions; the CBI treatment protocol was standardized and supervised across study sites (18).

Pill count data were used to estimate medication use. These data were captured for 7–10 days every other week. Since a full calendar of medication use was not available, we used interpolation to estimate it during short gaps in the count data. We defined “discontinued” medications as a minimum of 7 successive days with no medication taken and no subsequent resumption of medication. In preliminary analyses, we found that the probability that a person who interrupted medications would subsequently resume medications dropped substantially if the interruption lasted more than 7 days. We did not consider participants who discontinued medications in the final planned week (week 16) to have discontinued their medications early. We compared these subgroups (i.e., full adherence [$n=559$] vs. discontinued meds [$n=667$]) on baseline characteristics and treatment assignment. To study the dynamic processes before and after medication discontinuation, we focused analyses on those who discontinued prematurely. For inclusion in our pre-post change (PPC) analyses, we required participants to have at least two weeks of non-missing drinking data before and after the week of discontinuation; this reduced the sample from 667 to 450 cases. From the Inactive Status Form (ISF), the reasons for discontinuation were grouped into three categories: (1) adverse events, (2) the patient choose to discontinue, and (3) no recorded reason for discontinuation.

Statistical Methods

We used descriptive statistics (means, standard deviations, and frequencies) to describe the cases that did or did not discontinue medications prematurely, and t-tests and chi square tests to compare the two samples. Our two primary dependent variables were weekly percent days abstinent (PDA) and percent heavy drinking days (PHDD). Because both measures were skewed, we used an arcsine transformation for PDA and a log transformation for PHDD ($\log(1 + \text{PHDD})$) to improve normality, reducing the skewness of both measures.

To study changes in drinking before and after medications were discontinued, we computed drinking measures for a span of 13 weeks centered on the week of medication discontinuation, extending them up to 6 weeks before and after that week. In the dynamic analyses, these data were analyzed by hierarchical linear modeling (HLM) for repeated measures, with time points nested within subjects, using PROC MIXED in SAS 9.3. These are interrupted timeseries analyses, with one timeseries for each participant, centered on the time of medication discontinuation; we adopted a Toeplitz pattern for cross-time covariances. The analysis was designed to study time trends in drinking related to medication discontinuation by including a linear term for time (termed “Week”) to capture secular changes in drinking not specifically related to discontinuation (i.e., expected to continue both before and after discontinuing medications), and a binary term (termed pre-post change [PPC]) that was coded 1 for time points before discontinuation and 0 afterwards to capture changes in drinking on or after discontinuation. The PPC term is central since it tells us how much change in drinking is associated with the change in medication status, and the interactions that involve it tell us how much this change depends on other variables.

Following previous research, we created another binary term (termed Early Discontinuation) that classified each patient as having discontinued “early” if medications were discontinued in weeks 1–8 (coded 1) vs. “late” if discontinued in weeks 9–15 (coded 0). To test for effects of treatment on changes in drinking before and after medication discontinuation, we introduced three binary terms: one for each medication, naltrexone and acamprosate (coded 1 for active medication vs. 0 for placebo), and a third term for CBI therapy (coded 1 for CBI plus medication management vs. 0 for medication management only). We tested for interactions between these treatment terms and both PPC and Early Discontinuation to determine whether the effect of PPC was moderated by the time at which subjects discontinued medication.

To parallel the results of the main COMBINE outcome analysis (15) we also included an interaction term for the naltrexone-by-CBI interaction to capture the treatment combination with the largest treatment effect according to the main paper, and the interaction of that term with PPC to explore whether the effect of PPC was more evident in this treatment combination. We employed a backwards elimination procedure to trim unneeded variables from our statistical models, while maintaining hierarchy (i.e., we retained non-significant main effect terms in the model if they were involved in a statistically significant interaction). The alpha level for inclusion was .05.

Finally, to determine the long-term outcome for participants who discontinued medication early, we conducted a general linear model analysis of PDA and PHDD for the last week of treatment (week 16). We did not covary for baseline individual differences in our analyses since the focus of our analyses is on within-subject change, and the only significant difference found between those who discontinued vs. did not discontinue medications was a minor age difference (see Table 1).

Results

The baseline characteristics for the patients who did/did not discontinue medications are given in Table 1 (for a full analysis of medication adherence in COMBINE see (18)). Of the 12 variables compared, three showed inter-group differences that were statistically significant at $p < .05$: assignment to active naltrexone or acamprosate and age. Patients who discontinued medications early were more likely to have been assigned either of the active medications than those who completed medication and were on average about two years younger. The higher rate of discontinuing medication among those receiving active medication may be due to medication side effects. Approximately 54% of patients discontinued their medications ($n = 667$). Of patients who discontinued, 127 (19%) were taken off medications by COMBINE staff because of adverse effects, 288 (44%) discontinued per patient choice, and 252 (37%) discontinued but with no data on reason for discontinuing. Many of the patients for whom the reason for discontinuing medication was unavailable did so late in the study (e.g., weeks 13–15).

The results of the analyses of the patients for whom we have adequate data before and after medication discontinuation are presented in Table 2. For both outcomes, there were statistically significant linear changes in drinking that occurred before discontinuation of

medications (i.e., Week), as well as dynamic changes occurring at the time that medications were discontinued (i.e., PPC).

While there was variation across individuals, on average an increase in drinking started weeks before medications stopped, and drinking continued to increase afterwards, at a rate not greatly different from the earlier rate of change. However, the main effects for (1) why medication was stopped, (2) whether medication stopped early vs. late in treatment, and (3) the magnitude of the PPC can best be described in the context of the interactions that involve these variables. Our analysis focuses around the changes that happened near in time to when participants stopped taking medications (i.e., PPC), so the interactions that involve this variable are especially important. (See Figures 1 and 2.) One important interaction was that involving the effect of PPC as a function of early vs. late medication discontinuation (Early Discontinuation). Patients who discontinued medication early in treatment experienced a 14% decrease in absolute PDA between pre- and post-discontinuation, as compared to only a 5.5% decrease among patients who discontinued medication late. For PHDD, patients who discontinued medication early in treatment experienced a 4% increase between pre- and post-discontinuation, as compared to only a 1.4% decrease among patients who discontinued medication late. In addition, the participants who discontinued late in treatment exhibited greater PDA change than those who discontinued early.

The magnitude of PPC was also significantly moderated by the reported reason that medication was discontinued. The largest change in drinking occurred among those who discontinued medications by their own choice; for these patients, PDA decreased by 14% pre- to post-discontinuation, vs. a 10% decrease for those for whom there was no recorded reason for discontinuing, vs. a 3% decrease for those discontinuing owing to an adverse event. Patients who discontinued on their own increased PHDD by 4% vs. 2% for the no-reason-recorded category and less than 1% for discontinuing for an adverse event. In addition, those who chose to discontinue on their own exhibited the least abstinence, followed closely by those for whom we had no data on reason for stopping, with those stopping because of adverse events having the highest levels of abstinence. In addition, the COMBINE treatments were associated with different drinking patterns. Patients who received placebo medication and only medication management rather than medication management plus CBI, drank more than the other three groups for both PDA and PHDD outcomes (Figures 3 and 4).

The results of analyses of end-of-treatment drinking in Table 3 partially confirmed the primary COMBINE outcome analyses (15) in that there was a naltrexone by CBI interaction, along with main effects for naltrexone and CBI, for PHDD, while for PDA there was only a naltrexone main effect. Reason for discontinuing was a strong predictor for both outcomes: compared to participants with unknown reasons for discontinuing medications, participants who decided on their own to stop medications exhibited higher levels of drinking at week 16, followed by participants who stopped because of adverse events. Discontinuing medications early in the study was a predictor of less frequent abstinence, but did not predict PHDD.

Our primary analyses, which focused on change near the time that medications were discontinued, necessarily required having non-missing drinking data both before and after the discontinuation time. Of the 667 cases who discontinued, there were 217 who had too much missing drinking data for our purposes. Comparisons between this group and the 450 who were in the primary analyses resulted in one small difference among 18 background variables (patients with missing data averaged less than 2 years older; see Supplementary Online Content). There were also no significant differences between these groups on baseline drinking, but there were highly significant differences in drinking in the last month of treatment. The missing data group exhibited less PDA ($t(582)=19.85$, $p<0.0001$) and more PHDD ($t(582)=18.20$, $p<0.0001$); see Supplementary Online Content for details. By the last month of follow-up, however, the difference in PDA became non-significant, though the difference in PHDD remained significant ($t(480)=18.20$, $p = 0.01$).

Discussion

There were changes in drinking around the time that patients stopped taking medications, but these typically started before medications were discontinued and continued progressively thereafter. These data suggest that the decision to discontinue medications takes place during a usually extended (weeks-long) process of disengagement from treatment. This implies that there is a window of opportunity for clinical intervention, perhaps for alternative treatment if the patient does not wish to continue medications. Interventions to improve adherence were part of the COMBINE treatment protocol, which may help to account for the number of patients who stopped and restarted medications more than once.

The modest improvement in drinking for some patients who were taken off medication for adverse events seems to represent a clinical opportunity, even if only during the week when medications end. Implementing a clinical intervention for these individuals could help them remain on a healthier path. Not surprisingly, the patients who stopped medications on their own initiative did badly, especially those who stopped early in treatment. Such patients may be poorly motivated, demoralized, or unprepared for the demands of a rigorous treatment protocol. Perhaps no professional intervention could reach all of these patients, but at least some doors should be left open to encourage their return to of treatment. Clinical policies favorable to patient admission of relapse and/or continued alcohol use could serve to improve dialogue between provider and patient, and perhaps prevent discontinuation.

As suggested in earlier research, there were differences between patients who discontinued early in treatment and those who did so later, with those who discontinued earlier showing higher levels of drinking by week 16, although their drinking levels are lower around the time they discontinued. As noted above, this may be due to a combination of motivation and/or burden effects. Treatment also affected patients' drinking. Patients who took only placebo medications and did not receive CBI (i.e., those not receiving an active therapy other than medication management) had higher drinking levels than those who received CBI and/or active medication, a pattern similar to that seen in the overall outcome analyses for COMBINE. As shown in Figures 3 and 4, treatment effects do not seem to disappear suddenly when medication stops, but rather dissipate gradually. This gradual dissipation, in

conjunction with the protective effect that CBI seems to have, indicates that there may be another period of opportunity for the treatment team to offer patients alternatives to help maintain treatment gains. Other data (not shown) indicate that most patients who stopped medications and who received CBI also stopped CBI within one to two weeks of discontinuing medication.

These data have implications for research methodology. Although there were instances of major relapses near the time of medication discontinuation, this is not the norm. Thus, continued research follow-up of persons who discontinue medications for any reason is indicated. Similarly, imputation methods such as return to baseline drinking or immediate heavy drinking are not empirically supported in view of overall gradual change after discontinuing medication. (These and other single-imputation methods are deprecated for multiple statistical reasons as well (13).) Because progressive change seems to be normative when patients leave treatment, it appears feasible to devise regression methods using data prior to study dropout to estimate more accurately what the missing values should be. Furthermore, because we know that overall there is a gradual rather than abrupt increase in drinking after medications are discontinued, it would be feasible to conduct sensitivity analyses in which a progressive per-week or per-month increase in drinking could be imputed for each patient from the end of their drinking data forward. This method, described as the pattern mixture model approach, was suggested in an National Research Council report on missing data in clinical trials (19, pages 88–89). These analyses would indicate how rapid an increase in drinking would be required to compel a revision in major study conclusions.

Limitations/Caveats

The results from COMBINE, a complex, large-scale study, may not generalize to all treatment outcome studies. The primary outcome data we have are self-reported drinking levels, which are subject to biases, as suggested by the different long-term drinking patterns for clients who exhibited some missing drinking data. The number of cases for whom no reason was reported for medication discontinuation is another limitation. While the majority of these cases stopped late in the intervention period, making the specific reason for their discontinuation less important, knowing more about why people make these choices would be useful both for researchers and for clinicians.

Future Directions

Future research on the processes associated with terminating medications and research participation should focus on the multiple, interacting factors leading to a decision to end treatment, and the circumstances under which some treatment dropouts subsequently re-enter formal or informal treatment systems. Although logistical challenges make such research difficult, the success of the COMBINE study in obtaining drinking outcome data after treatment dropout demonstrates that such research is feasible, and could contribute much to our understanding of new ways to intervene or re-intervene with such patients. Others have examined typologies of substance users (20), potentially related to medication adherence. Such an approach is beyond the scope of this manuscript, where we focused on general trends rather than individual differences.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Predicted Percent of Days Abstinent Before and After Discontinuation of Medications, By Time of Discontinuation and Reason for Discontinuation ^a

^a Predicted values from the model in Table 2 were estimated in the transformed scale and transformed back to the original scale for this graph. “Early” and “Late” refer to discontinuation in the first vs. second half of planned treatment. “AE” = adverse event, “S Choice” = discontinuation at the request of the patient. “Unknown” = no reason for discontinuation was recorded.

Figure 2. Predicted Percent Heavy Drinking Days Before and After Stopping Medications, by Time of Stopping and Reason Stopped ^a

^a Predicted values from the model in Table 2 were estimated in the transformed scale and transformed back to the original scale for this graph. “Early” and “Late” refer to discontinuation in the first vs. second half of planned treatment. “AE” = adverse event, “S Choice” = discontinuation at the request of the patient. “Unknown” = no reason for discontinuation was recorded.

Figure 3. Predicted Percent of Days Abstinent Before and After Stopping Medications, by Naltrexone and CBI Treatment a

^a Predicted values from the model in Table 2 were estimated in the transformed scale and transformed back to the original scale for this graph. “MM” = medication management, “CBI” = COMBINE Behavioral Intervention, “Nalt” = active naltrexone.

Figure 4. Predicted Percent Heavy Drinking Days Before and After Stopping Medications, by Naltrexone and CBI Treatment ^a

^a Predicted values from the model in Table 2 were estimated in the transformed scale and transformed back to the original scale for this graph. “MM” = medication management, “CBI” = COMBINE Behavioral Intervention, “Nalt” = active naltrexone.

Table 1

Baseline Variable Comparison of COMBINE Patients Who Completed vs. Discontinued Medication Treatment

	Completed Medication	Discontinued Medication		
Variable	% or Mean (Std)	% or Mean (Std)	Test	p
Gender (% female)	30%	31%	$\chi^2(1)=0.173$	0.68
Married	44%	46%	$\chi^2(1)=0.330$	0.57
Employed full time	64%	59%	$\chi^2(1)=2.677$	0.10
Minority	19%	20%	$\chi^2(1)=.008$	0.93
Naltrexone	47%	53%	$\chi^2(1)=5.238$	0.022
Acamprosate	46%	53%	$\chi^2(1)=5.377$	0.020
CBI Therapy	50%	51%	$\chi^2(1)=0.020$	0.89
Age	45.3 (10.3)	43.5 (10.0)	$t(1224)=3.09$	.002
Years of Education	14.7 (2.8)	14.5 (2.7)	$t(1201)=1.58$	0.11
SCID Alcohol Dependence Score	5.09 (1.20)	5.20 (1.14)	$t(1224)=1.61$	0.11
BL % of Days Abstinent	24.1 (24.2)	26.2 (25.7)	$t(1224)=1.45$	0.15
BL % Heavy Drinking Days	66.8 (27.9)	64.5 (29.0)	$t(1224)=1.35$	0.18
N	559	667		

Table 2

Type III Tests for Effects Around Medication Discontinuation On Transformed Percent Days Abstinent and Percent Heavy Drinking Days^a

Predictor	PDA			PHDD		
	Coef	F	P	Coef	F	p
Intercept	1.194	F(1,445)=1089.66	<.001	1.137	F(1,443)=65.61	<.001
Week	-0.010	F(1,4803)=19.07	<.001	0.028	F(1,4804)=8.58	0.003
PPC	-0.013	F(1,446)=5.05	0.025	0.050	F(1,446)=4.52	0.034
Naltrexone	0.094	F(1,4803)=5.27	0.022	0.054	F(1,4804)=3.70	0.054
CBI Therapy				-0.184	F(1,4804)=0.84	0.361
Reason=AE	-0.123	F(2,4803)=2.29	0.10	0.458	F(2,4804)=4.37	0.013
Reason=S Choice	-0.071			0.412		
Reason=Unk	0 (ref)			0 (ref)		
Early Stop	0.122	F(1,4803)=4.97	0.026	-0.340	F(1,4804)=3.66	0.056
PPC*Reason=AE	0.071	F(2,4803)=3.85	0.021	-0.373	F(2,4804)=5.36	0.005
PPC*Reason=S Choice	-0.038			0.108		
PPC*Reason=Unk	0 (ref)			0 (ref)		
PPC*Early	-0.079	F(1,4803)=5.23	0.022	0.390	F(1,4804)=8.79	0.003
Naltrexone*CBI				0.606	F(1,4804)=5.48	0.019

^aType III tests for each variable covary for all the other effects in the model. The predictors were coded: Week (-6 to +6); PPC (1 for time points before medication discontinuation [weeks -6 to -1], 0 for week of discontinuation onward); Naltrexone (0 for placebo medication, 1 for active medication), CBI therapy (0 for medication management only, 1 for CBI plus medication management), Reason (3 categories coded 0 for absent and 1 for present, with Reason = unknown as the reference level); and Early Stop (1 for clients who stopped in weeks 1-8 and 0 for clients who stopped in weeks 9-15). All interactions were computed as products of the coded variables.

Table 3

Type III Tests for Effects at Week 16 on Transformed Percent Days Abstinent and Percent Heavy Drinking Days^a

Predictor	PDA			PHDD		
	Coef	F	P	Coef	F	P
Intercept	1.036	F(1,578)=283.25	<.001	1.740	F(1,578)=71.06	<.001
Naltrexone	0.195	F(1,578)=5.86	0.016	-0.787	F(1,578)=12.73	<.001
Acamprosate	0.029	F(1,578)=0.02	0.88	-0.161	F(1,578)=1.08	0.30
CBI Therapy	0.136	F(1,578)=2.90	0.09	-0.594	F(1,578)=6.90	0.009
Reason=AE	-0.095	F(2,578)=7.69	<.001	0.115	F(2,578)=4.38	0.013
Reason=S Choice	-0.131	F(1,578)=		0.525		
Reason=Unk	0 (ref)			0 (ref)		
Early Stop	-0.161	F(1,578)=9.03	0.003	0.308	F(1,578)=2.99	0.08
Naltrexone*CBI	-0.166	F(1,578)=3.24	0.07	0.902	F(1,578)=8.52	0.004

^aType III tests for each variable covary for all the other effects in the model. The predictors were coded: Naltrexone and Acamprosate (0 for placebo medication, 1 for active medication), CBI therapy (0 for medication management only, 1 for CBI plus medication management), Reason (3 categories coded 0 for absent and 1 for present (AE = Adverse Event, S Choice = patient choice), with Reason = Unk (unknown) as the reference level); and Early Stop (1 for clients who stopped in weeks 1–8 and 0 for clients who stopped in weeks 9–15). All interactions were computed as products of the coded variables.