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Early Abstinence in Cocaine Pharmacotherapy Trials Predicts Successful Treatment Outcomes

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Abstract

There is a robust relationship between early and later abstinence in smoking cessation, but that relationship has not been explored among other substances of abuse. To assess whether early abstinence during treatment, as opposed to baseline abstinence, predicted later abstinence among cocaine dependent patients, data from two randomized double-blind controlled clinical pharmacotherapy trials were analyzed. Similar to the findings in the smoking cessation literature, results indicate that abstinence in the first two weeks of pharmacotherapy predicted later in-trial abstinence. This finding has implications for both treatment research and for clinical practice, suggesting that patients who do not respond early in treatment may need a more intensive intervention.

1. Introduction

The available literature on smoking cessation documents a robust relationship between early and later abstinence. Studies done in community samples of self-quitters (i.e. Garvey, Bliss, Hitchcock, Heinhold & Rosner, 1992) for example, demonstrate that it is the first weeks of a cessation attempt when relapse risk is the highest, with the relative risk decreasing the longer abstinence is sustained. Kenford et al. (1994) described results from two independent randomized clinical trials on active and placebo transdermal nicotine replacement therapy. Participants were assessed before, during, and following six to eight weeks of patch therapy, and predictors of smoking status at the end of therapy and six-month follow-up were sought. Commonly investigated baseline characteristics such as the Fagerstrom Tolerance Questionnaire scores (Fagerstrom & Schneider, 1989), number of cigarettes smoked per day, years smoked, breath carbon monoxide (CO) levels, and plasma cotinine and nicotine levels, as well as during-treatment nicotine withdrawal levels, failed to predict smoking status at end-of-treatment and follow-up. In contrast, smoking status during the first two weeks of treatment, especially in the second week, was a robust predictor of smoking status at end-of-treatment and six-month follow-up in both studies. Based on their findings, Kenford et al. (1994) proposed two rules for predicting abstinence outcomes: 1) Any smoking during weeks one and two of treatment predicted short and longer-term failure, and 2) Abstinence during weeks one and two predicted short and longer-term success.

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Laboratory studies of smoking abstinence have provided further evidence of the relationship between early and later abstinence. Heil, et al. (2004) found that failure to abstain during early study periods where subjects could earn incentives for abstinence led to failure to abstain during later periods where abstinence was required for earning incentives.

Taken together, these studies described above underscore the fundamental importance of establishing abstinence in the initial weeks of a cessation effort. What has not been fully explored is whether this relationship between early and later abstinence is true for abused stimulants, most notably cocaine.

Studies exploring the relationship between early and later abstinence in cocaine treatment have focused on abstinence in treatment compared to abstinence post-treatment. Higgins and colleagues (2000) have shown that achieving a period of continuous abstinence during cocaine treatment is associated with significantly greater odds of being abstinent at 12-month post-treatment follow-up. Further, the results show that the odds for post-treatment abstinence increase with each one-week increase in continuous abstinence (defined by both urine drug screens and self-report) during treatment (O.R. =1.14, CI = 1.09–1.20, p=.001). However, Higgins and colleagues do not provide data on where in the treatment period abstinence occurs. As such, published data on the “first two weeks of a quit attempt” during cocaine treatment that could be used to parallel the findings in the smoking literature is not available.

Prior cocaine research does show a link between baseline abstinence and later in-treatment abstinence (Alterman 1996, 1997;Ehrman, 1998; Kampman, 2002). In those studies, patients who presented with cocaine-positive urines during baseline had less abstinence during pharmacotherapy trials for cocaine dependence. In addition, the patients with the least baseline abstinence also failed to engage in treatment and had higher attrition rates than did individuals who were abstinent at baseline. In those studies, abstinence throughout the trial was compared to baseline abstinence without regard to what happened during the early period of treatment. As such, no conclusions about the relationship between baseline and early abstinence can be made from those studies.

More recently, investigators have examined the impact of abstinence in the week prior to randomization on subsequent abstinence in a double-blind pharmacotherapy trial (Levin et al., 2008). Defining baseline cocaine use as negative only if all baseline urines were cocaine-negative, the investigators found that among patients without co-morbidities, those who were cocaine-negative at baseline actually showed increased probability of cocaine use during the course of the study, while those who were cocaine-positive at baseline showed decreased probability of cocaine use during the same period. This somewhat surprising finding suggests that further investigation of the relationship between early abstinence and later abstinence during cocaine trials is warranted.

Recently, studies have examined what impact abstinence during a placebo lead-in period has on later in-treatment abstinence (Bisaga et al., 2005; Bisaga et al., 2006). In those studies, prior to randomization to either pharmacotherapy or placebo, patients undergo a single-blind placebo lead in period of one or two weeks. During that period, patients receive manual-guided psychotherapy. Results from a double-blind study of gabapentin and relapse-prevention therapy revealed that patients able to provide at least two cocaine-negative urines during a two-week placebo lead-in period had better rates of abstinence during the trial (Bisaga et al., 2005). Although that study includes only 50 patients, the findings dovetail nicely with the above findings regarding baseline cocaine abstinence and treatment outcome. In addition, the outcome from the larger trial revealed no medication effects (Bisaga et al., 2006).

Having a placebo lead-in during which to assess early abstinence is not always feasible. In addition, providing psychosocial treatment during that placebo lead-in means that patients are

not still in baseline as it has been defined in the above trials, but are also not yet receiving a full course of treatment. As such, it may be difficult to generalize the above findings to the majority of pharmacotherapy trials, which are conducted without such a lead-in period.

Therefore, in order to test whether the relationship between the first two weeks of a quit attempt, operationally defined as the first two weeks of medication in a trial of pharmacotherapy for cocaine dependence, and later abstinence mirrors that found in the smoking cessation literature, and to explore how baseline and early abstinence are related, we analyzed aggregate data from two double-blind randomized placebo-controlled pharmacotherapy trials conducted here at the Treatment Research Center.

2. Materials and Methods

Data from two randomized double-blind placebo-controlled pharmacotherapy trials conducted here at the Treatment Research Center (TRC) were included in the analysis. One study focused on amantadine, propranolol and their combination for cocaine dependence (AMPRO). The other focused on naltrexone, disulfiram and their combination for cocaine dependence (DISULF). In each trial, urine samples were gathered three times per week and analyzed for benzoylecgonine. In the AMPRO study, there were no overall significant effects of either drug alone or the combination (Kampman et al., 2006). Among highly adherent patients, Propranolol had better retention and AB rates. In the DISULF study, abstinence from cocaine as measured by cocaine-negative urines and days of self-reported abstinence from cocaine or alcohol did not differ between placebo and any of the medication groups (Pettinati, et al., 2008).

As there were no medication effects on cocaine abstinence in either study, for purposes of these analyses, all patients in both studies were included without regard to treatment group assignment. Cocaine abstinence was measured using urine benzoylecgonine (BE). The BE cutoff for determining whether a sample was positive for cocaine was 300 ng/ml in both studies.

In each trial the first two weeks were screening weeks where no pharmacotherapy or other (e.g., psychosocial) treatment was provided. It is important to note for our purposes here that during those screening weeks, patients were not required to achieve abstinence from cocaine. In fact, continued use in the baseline screening was a prerequisite for randomization in the AMPRO trial as patients were required to provide at least one cocaine-positive urine during the screening period in order to be randomized into that study. The next two weeks of the studies (Weeks 3 and 4 of the trials) were the initial weeks of pharmacotherapy. As these two weeks are the first weeks of full treatment, we viewed them as being analogous to the first two weeks of a quit attempt in smoking cessation trials like those mentioned above, and refer to that period as “early abstinence”. For purposes of examining later abstinence, we looked at abstinence in weeks 7 and 8 as a point-prevalence measure of later in-trial abstinence. Weeks 7 and 8 were chosen as they represent a midpoint for in-trial abstinence, and as they are approximately four weeks after the start of treatment. We also examined continuous abstinence for the entire later portion of the trial, excluding the screening and early abstinence phases, leaving weeks five of the trial and beyond included as percent of cocaine-negative samples.

We first examined abstinence in Weeks 3 and 4, both as individual weeks and as a composite of the two weeks in relation to abstinence in weeks 7 and 8. Correlations of the two abstinence measures revealed that there was a linear relationship between providing at least two cocaine-negative urine samples in Weeks 3 and 4, and achieving any abstinence in Weeks 7 and 8. For this reason, the remaining analyses focus on those patients able to provide at least two cocaine-negative urine samples during weeks 3 and 4.

Stepwise regression analyses were then conducted to examine whether early abstinence was a significant predictor of later point-prevalence and continuous abstinence. Baseline severity

measures, baseline cocaine use, demographic variables, craving scores, observational measures, and early abstinence measures were included in the analyses (see Table 2 for complete list of variables used).

3. Results

Correlations between early abstinence and later abstinence are shown in Table 3. Baseline abstinence (prior to medication) and early abstinence were correlated for only the DISULF study.

Stepwise regression analyses of the whole data set revealed that abstinence in the first two medicated weeks was a significant predictor of abstinence in weeks 7 and 8 as was gender and early abstinence, while abstinence in weeks 3 and 4, alone and with composite craving in week 3 were predictors of percent cocaine-negative urines during the studies (Table 4). Analyses of the two studies separately revealed that only abstinence in weeks 3 and 4 was a predictor of later abstinence in the AMPRO study. In the DISULF study, abstinence in weeks 3 and 4, alone and with gender predict abstinence in weeks 7 and 8, while abstinence in weeks 3 and 4 is the sole predictor of percent cocaine-negative urines. In the DISULF trial men had better cocaine abstinence outcomes than did women (Pettinati et al., 2008).

We then analyzed the early abstinence data to see whether there were any patterns that emerged in the early abstinence data that accounted for this relationship between early and later abstinence. What we were most curious about was whether sustained early abstinence showed a stronger relationship to later abstinence than did sporadic abstinence. Results indicated that patterns of early abstinence varied widely at the lower levels of early abstinence (e.g., two or three abstinences in weeks three and four), and less so at higher levels of early abstinence (e.g., four or five abstinences), most likely due to the restricted range of possible combinations at the higher levels. In our clinical experience, it takes roughly three days of cocaine abstinence to meet the 300 ng/ml benzoylecgonine threshold in our qualitative sampling methods. Thus, two cocaine-negative urines approximate six to eight days of cocaine abstinence, meaning no use for 50% of the two week early medication phase.

4. Discussion

From the studies analyzed here, it appears that abstinence during the first two weeks of medication in cocaine pharmacotherapy trials is at least partially analogous to the first two weeks of a quit attempt in smoking cessation trials. In the cocaine trials, the ability to provide at least two cocaine-negative urines during the first two weeks of medication predicted later abstinence during the trials. As noted above, cocaine-negative urines is equivalent to approximately one week of abstinence from cocaine, suggesting that one week of abstinence may be a minimum threshold for later success in cocaine dependence treatment. This does not need to be a week as defined as seven consecutive days, but instead seven days in total.

Limitations to this study include the heterogeneous admission requirements for each study which could account for some of the differences we see in early abstinence. AMPRO allowed but did not require co-occurring alcohol dependence, while DISULF required co-occurring alcohol and cocaine dependence. As there was no follow-up period for these studies, we cannot compare our results here to those of Higgins et al., (2000) to determine whether we see the same pattern of within and post treatment abstinence that has been shown in prior analyses of cocaine data. Were we able to look at early and later in trial abstinence and post-treatment abstinence, we might be able to make stronger parallels to findings from the smoking cessation literature.

Although measures such as the ASI were not predictive in this sample, it is likely that baseline patient characteristics may account for some portion of the variability in abstinence rates achieved and sustained across time. That said, it also seems plausible that individual differences fail to offer a complete explanation for the relationship between initial and later abstinence.

It is well-documented, for example, that the intensity of nicotine withdrawal and craving decreases and abstinence self-efficacy increases over time within individual smokers during a period of sustained abstinence. Smoking urges decrease in an orderly manner across the initial month of smoking abstinence, and less intense urges are associated with a lower risk for relapse (Doherty, Kinnunen, Militello & Garvey 1995). It is hypothesized that such dynamic changes during an initial period of abstinence might directly lower relapse risk, independent of pre-study individual differences (Higgins et al., 2000). Similar factors may be at work in cocaine abstinence, such that decreases in use fuel decreased craving, making future use less likely.

That early abstinence predicts later abstinence among cocaine patients regardless of study or of treatment group assignment suggests that the best treatment outcomes will stem from engendering abstinence in the greatest number of patients at the start of a clinical trial. Adaptive designs, where patients are assessed at set time points and those failing to respond have their treatment “adapted” in hopes of promoting better outcomes, could be used to promote early abstinence (c.f., Murphy 2005 for review). The data presented here suggest that the best points for assessment and treatment modifications would be after two weeks of a given medication in a pharmacotherapy trial.

Were early abstinence as a response to medication to be used in adaptive designs, the assessment time points would have to be based on the titration schedule of the medication or the time to known full efficacy. Our findings regarding early abstinence may have implications for clinical treatment as well as clinical trials. Perhaps patients unable to achieve any abstinence in the first weeks of outpatient treatment should be referred to a more intensive treatment, such as that available on an in-patient basis, or should be provided with additional incentives for initiating abstinence such as those available through contingency management interventions (see Higgins, Heil & Lussier, 2004 for review).

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References

Alterman AI, Kampman K, Boardman CR, Cacciola JS, Rutherford MJ, McKay JR, Maany I. A cocaine-positive baseline urine predicts outpatient treatment attrition and failure to attain initial abstinence. Drug Alcohol Depend 1997;46(1–2):79–85. [PubMed: 9246555]

Alterman AI, McKay JR, Mulvaney FD, McLellan AT. Prediction of attrition from day hospital treatment in lower socioeconomic cocaine-dependent men. Drug Alcohol Depend 1996;40(3):227–33. [PubMed: 8861401]

Bisaga A, Aharonovich E, Garawi F, Levin FR, Rubin E, Raby WN, Nunes EV. A randomized placebo-controlled trial of gabapentin for cocaine dependence. Drug Alcohol Depend 2006;81(3):267–74. [PubMed: 16169160]

Bisaga A, Aharonovich E, Garawi F, Levin FR, Rubin E, Raby WN, Vosburg SK, Nunes EV. Utility of lead-in period in cocaine dependence pharmacotherapy trials. Drug Alcohol Depend 2005;77(1):7–11. [PubMed: 15607836]

Doherty K, Kinnunen T, Militello FS, Garvey AJ. Urges to smoke during the first month of abstinence: relationship to relapse and predictors. Psychopharmacology 1995;119(2):171–8. [PubMed: 7659764]

Fagerstrom KO, Schneider NG. Measuring nicotine dependence: a review of the Fagerstrom Tolerance Questionnaire. J Behav Med 1989;12:159–182. [PubMed: 2668531]

Garvey AJ, Bliss RE, Hitchcock JL, Heinold JW, Rosner B. Predictors of smoking relapse among self-quitters: a report from the Normative Aging Study. Addict Behav 1992;17(4):367–77. [PubMed: 1502970]

Gourlay SG, Forbes A, Marriner T, Pethica D, McNeil JJ. Prospective study of factors predicting outcome of transdermal nicotine treatment in smoking cessation. Br Med J 1994;309:842–846. [PubMed: 7950614]

Heil SH, Alessi SM, Lussier JP, Badger GJ, Higgins ST. An experimental test of the influence of prior cigarette smoking abstinence on future abstinence. Nicotine Tob Res 2004;6(3):471–9. [PubMed: 15203781]

Higgins ST, Badger GJ, Budney AJ. Initial abstinence and success in achieving longer-term cocaine abstinence. Exp Clin Psychopharmacol 2000;8(3):377–386. [PubMed: 10975629]

Higgins ST, Heil SH, Badger GJ, Mongeon JA, Solomon LJ, McHale L, Bernstein IM. Biochemical verification of smoking status in pregnant and recently postpartum women. Exp Clin Psychopharmacol 2007;15(1):58–66. [PubMed: 17295585]

Higgins ST, Heil SH, Plebani Lussier J. Clinical implications of reinforcement as a determinant of substance use disorders. Annual Review of Psychology 2004;55:431–461.

Kampman KM, Dackis C, Lynch KG, Pettinati HM, Tirado C, Gariti P, Sparkman T, Atzram M, O'Brien CP. A double-blind, placebo-controlled trial of amantadine and propranolol for the treatment of cocaine dependent patients with severe cocaine withdrawal symptoms. Drug and Alcohol Dependence 2006;85(2):129–137. [PubMed: 16697124]

Kampman KM, Volpicelli JR, Mulvaney F, Rukstalis M, Alterman AI, Pettinati H, Weinrieb RM, O'Brien CP. Cocaine withdrawal severity and urine toxicology results from treatment entry predict outcome in medication trials for cocaine dependence. Addict Behav 2002;27(2):251–60. [PubMed: 11817766]

Kenford SL, Fiore MC, Jorenby DE, Smith SS, Wetter D, Baker TB. Predicting smoking cessation: who will quit with and without the nicotine patch. JAMA 1994;271:589–593. [PubMed: 8301790]

Levin FR, Bisaga A, Raby W, Aharonovich E, Rubin E, Mariani J, Brooks DJ, Garawi F, Nunes EV. Effects of major depressive disorder and attention-deficit/hyperactivity disorder on the outcome of treatment for cocaine dependence. Journal of Substance Abuse Treatment 2008;34(1):80–9. [PubMed: 17574796]

Murphy SA. An experimental design for the development of adaptive treatment strategies. Statistics in Medicine 2005;24:1455–1481. [PubMed: 15586395]

Pettinati HM, Kampman KM, Lynch KG, Xie H, Dackis C, Rabinowitz AR, O'Brien CP. A double blind, placebo-controlled trial that combines disulfiram and naltrexone for treating co-occurring cocaine and alcohol dependence. Addictive Behaviors 2008;33:651–667. [PubMed: 18079068]

Yudkin PL, Jones L, Lancaster T, Fowler GH. Which smokers are helped to give up smoking using transdermal nicotine patches? Results from a randomized, double-blind, placebo-controlled trial. Br J Gen Pract 1996;46(404):145–8. [PubMed: 8731618]

Table 1

Included Studies

STUDY NAME	N	PATIENT POPULATION	BRIEF DESCRIPTION	OUTCOME
Amantadine and Propranolol (Kampman et al., 2006) **AMPRO**	199	Cocaine dependent, alcohol co-dependence allowed if med-free detox	10-week double-blind trial with 4 groups; Amantadine 300 mg/day Propranolol 100 mg/day Amantadine + Propranolol Placebo	No overall significant effect of either drug alone or the combination. Among highly adherent patients, Propranolol had better retention and AB rates.
Naltrexone and Disulfiram(Pettinati et al., 2008) **DISULF**	208	Cocaine and alcohol dependence	14-week double-blind trial with 4 groups; Disulfiram 250 mg/day Naltrexone 100 mg/day Disulfiram + Naltrexone Placebo	Abstinence from cocaine as measured by cocaine-negative urines and days of self-reported abstinence from cocaine or alcohol did not differ between placebo and any of the medication groups

Table 2

Variables Included in Step-wise Regression Analyses

Severity[*β]	**Demographics**[β]	**Craving**	**Observations**[β]	**Early Cocaine Abstinence**
Medical Critical Score	Gender	Cocaine Selective Severity Assessment (CSSA)[β]	Interviewer Severity Rating	Urine benzoylecgonine (BE) screens for weeks 3 & 4
Alcohol Critical Score	Employment Critical Score[*]	Baseline composite craving		Urine BE screens for week 3
Drug Critical Score		Week 1 composite craving		Urine BE screens for week 4
Legal Critical Score		Week 2 composite craving		Baseline urine BE screens[β]
Family Critical Score		Week 3 composite craving		
Psychiatric Critical Score		Week 4 composite craving		

[*] Taken from the Addiction Severity Index

[β] Baseline Measure

Table 3

Correlations Between Early and Later Cocaine Abstinence

		Wks 3 & 4 AB	Wks 7 & 8 AB	% AB Wks 5-end
ALL DATA	Wks 3 & 4 AB	----	.45*	.48*
	Wks 7 & 8 AB		----	.87*
	% AB Wks 5-end			----
AMPRO	Wks 3 & 4 AB	----	.30*	.28*
	Wks 7 & 8 AB		----	.75*
	% AB Wks 5-end			----
DISULF	Wks 3 & 4 AB	----	.43*	.49*
	Wks 7 & 8 AB		----	.85*
	% AB Wks 5-end			----

*p≤.01

Table 4

Summary of Stepwise Regression Analyses for All Data

Study	Later Cocaine Abstinence	Variable	B	SE B	β
ALL DATA	Weeks 7 and 8				
		Weeks 3&4 AB	.758	.107	.517**
		Weeks 3&4 AB	.727	.107	.495**
		Gender	−.745	.353	−.154*
	Percent Cocaine-Negative				
		Weeks 3&4 AB	.102	.015	.511**
		Weeks 3&4 AB	.095	.015	.475**
		Week 3 composite craving	−.013	.006	−.152*
AMPRO	Weeks 7 and 8				
		Weeks 3&4 AB	.661	.213	.409**
	Percent Cocaine-Negative				
		Weeks 3&4 AB	.086	.031	.372**
DISULF	Weeks 7 and 8				
		Weeks 3&4 AB	.865	.146	.537**
		Weeks 3&4 AB	.836	.143	.519**
		Gender	−.948	.441	−.191*
	Percent Cocaine-Negative				
		Weeks 3&4 AB	.117	.019	.554**

*p<.05,

** p<.01

Note: For ALL DATA

R^2 =.267, for Weeks 7 and 8 Step 1, ΔR^2 =.023 for Step 2 (ps <.05)

R^2 =.262 for Percent Cocaine-Negative Step 1, ΔR^2 =.022 for Step 2 (ps <.05)

For DISULF

R^2 =.288, for Weeks 7 and 8 Step 1, ΔR^2 =.036 for Step 2 (ps <.05)