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Study Blinding and Correlations Between Perceived Group Assignment and Outcome in a Cocaine Pharmacotherapy Trial

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Abstract

While much research has suggested that the integrity of the blind is compromised in psychotropic drug trials, little research has been conducted on blinding in substance abuse trials. The current study examines the integrity of the blind in an outpatient pharmacotherapy trial investigating the effectiveness of amantadine and propranolol in treating cocaine addiction. Results suggest that neither nurses (N=174, kappa = 0.08, p=0.22) nor participants (N=163, kappa = 0.09, p=0.26) could accurately predict treatment assignment. Furthermore, nurses' perceptions of treatment assignment were significantly related to trial completion, medication compliance and cocaine use—results that may have training implications for medical personnel.

Keywords

Experimental design; blinding; cocaine; pharmacotherapy

The present study examines the integrity of the blind in a placebo-controlled study investigating the effectiveness of amantadine and propranolol for cocaine addiction. We sought to answer two questions: 1) Can subjects and clinicians correctly identify medication assignment? 2) Are subject and experimenter opinion regarding medication assignment related to outcome?

Originally formulated in the 18th century as a tool for detecting fraud, the double blind technique is now viewed as an essential tool in controlling for experimenter and subject bias.^{1,2} In a meta-analysis of 250 clinical trials, Schulz et al. (1995) estimated that unblinded trials found effect sizes on average 17% greater than blinded trials, suggesting a substantial influence of experimenter and subject bias in unblinded trials.³ Further studies have isolated the influence of subject and investigator bias, indicating that the effects of subject and experimenter bias may often outweigh the effects of the procedure being tested.^{4–6}

Though it appears that both experimenter and subject opinions can affect study outcomes, few clinical trials report blinding efficacy.⁷ This is particularly problematic in light of recent findings indicating the unintentional unblinding of much research claiming to be “double-blind.”^{7–9} For instance, Fergusson et al. (2002) reported that, of a random sample of 191 general medicine and psychiatric trials, only 15 trials reported on blinding efficacy, and, of these, 9 reported that blinding was imperfect.⁹ Unblinding (often due to side effects of medication) is thought to occur particularly frequently in trials of psychotropic drugs.¹⁰

While numerous studies have been conducted on the integrity of the blind in pharmacotherapy trials,^{7–10} little headway has been made in the area of substance abuse. However, blinding efficacy in nicotine replacement therapy trials has been examined, and nicotine replacement trials have been judged very difficult to effectively blind.¹¹ These studies raise questions as to whether clinical pharmacotherapy trials with a substance dependent population may be difficult to effectively double-blind. Since unblinded members of the placebo group may be more prone to drop out¹² and cocaine dependent individuals already show particularly high attrition rates in drug treatment programs,^{13,14} it is essential that we investigate the integrity of the blind in cocaine pharmacotherapy studies.

Methods

Subjects

The subjects in the original study were 199 DSM-IV cocaine dependent men and women between the ages of 18 and 60. Subjects dependent on alcohol in addition to cocaine were also admitted if cocaine was the primary dependency. Subjects with other dependencies, except nicotine addiction, were excluded. Other psychiatric exclusion criteria included psychosis, dementia and the use of other psychotropic medications.

Only subjects who completed the “Treatment Opinion Form” at the final study visit are included in these analyses (form and participants described below).

Procedures

As this study reports on secondary analyses, only relevant sections of the procedures from the main trial are discussed here. A complete description of the study procedures can be found in the main paper.¹⁵ Subjects were treatment-seeking cocaine users recruited through advertisements in the local media. After reviewing and signing informed consent subjects entered a 10-week trial, including a two-week baseline phase and an eight-week randomized medication phase.

Subjects in the full trial were randomly assigned to either propranolol (n = 49), amantadine (n=50), the combination of amantadine and propranolol (n=50), or placebo (n=50). All subjects were prescribed the same number of capsules regardless of group or week of treatment. There was no significant difference in medication adherence rates among the four groups: placebo 50%, propranolol 54%, amantadine 53%, amantadine and propranolol 52% ($\chi^2 = 0.167$, $p = 0.98$). All participants also received twice-weekly individual cognitive-behavioral therapy. Urine toxicology screens were obtained at screening and 3 times weekly thereafter with samples analyzed qualitatively (≥ 300 ng/ml of benzoylecgonine was considered positive).

Medication Compliance—Medication compliance was measured by nurses each week during medical management sessions, via self-report and returned pill blister packs. Subjects who took at least 80% of the medication prescribed to them were judged to be medication compliant. Medication adherence of 80% or more is a commonly used standard for optimal medication adherence in pharmacotherapy trials in general and specifically in addiction pharmacotherapy trials.^{16,17}

The Treatment Opinion Form—The treatment opinion form, completed by both the subject and nurse, was administered at the end of medication visit during week 10. The form consisted of four multiple choice questions: 1) What treatment do you think you are receiving? 2) How confident of this rating are you? 2) If you feel that you are receiving

active medication, do you feel that it has been helpful to you? 4) What do you feel has been the greatest benefit to you from taking active medication?

We analyzed the first question on this form, designating members of the “perceived placebo” group as those who thought (or whose nurses thought) they were taking only placebo and the “perceived active medication” group as those who reported believing that they belonged to any of the other three conditions (amantadine, propranolol, or amantadine +propranolol).

Treatment Completion—Treatment completers were defined as subjects who attended the end-of-study visit within the final week of treatment. If participants failed to attend this visit or attended the final study visit outside of the study window, they were considered non-completers and excluded from the analysis.

Results

Statistical Analysis

Participants in the present study were those participants in the original amantadine propranolol study who completed or whose nurses completed the “Treatment Opinion Form.” Participants were composed of two groups: 152 participants (76% of the original sample) who completed the Treatment Opinion Form and 173 participants (87% of the original sample) whose nurses completed the form. In most cases, the nurse completed the Treatment Opinion Form if the participant completed the form; therefore the demographics of these groups of subjects are very similar. Participants for whom a Treatment Opinion Form was completed did not differ significantly in demographics and baseline substance use from those for whom a Treatment Opinion Form was not completed. See table 1 for a more complete description of participants in the present study.

Treatment Opinion (Subject)

Participants who believed they were taking placebo differed significantly only in racial makeup from participants who believed they were taking active medication (see table 1). We did not find that subjects were able to accurately guess their treatment condition (see table 2). The observed rate of agreement was 65.64% (7.98% correctly guessed placebo, and 57.67% correctly guessed active treatment), but was not significantly higher than the agreement rate of 62.31% expected by chance ($\kappa=0.08$, $p=0.26$). We note that this value of κ is in the range described as *slight agreement* by Landis and Koch (1977), and *poor agreement* by Fleiss (1981).^{18,19} An examination of the rates of misclassification showed no significant difference between the rate of participants misclassifying themselves as placebo versus the rate of misclassification as active treatment (McNemar Chi-square = 0.29, $p=0.59$).

We found one significant difference between the perceived active and perceived placebo groups. There was a significant effect of study completion (see table 3). Participants who believed they were receiving placebo were significantly less likely to complete the study than those who believed they were receiving active medication. There were no significant differences between the groups in terms of the percent of clean urines (as determined by the urine drug screen), medication compliance (percent of medications taken of those prescribed), and number of therapy visits attended.

Treatment Opinion (Nurse)

There were no significant differences in terms of baseline substance use and demographics between subjects whose nurses believed they were taking placebo vs. active medication (see

table 1). As with the participants themselves, the nurses were not able to accurately guess the participants' treatment condition (see table 2). The observed rate of agreement was 53.44% (14.94% correctly guessed placebo, and 38.51% correctly guessed active treatment), but was not significantly higher than the agreement rate of 49.43% expected by chance ($\kappa=0.08$, $p=0.22$). Again, this value of κ would be interpreted as *slight* or *poor* agreement. An examination of the rates of misclassification showed significant differences in the rate of the two types of misclassification (McNemar's Chi-square = 25.00, $p<0.0001$). Of the 81 incorrect guesses, 63 (77.78%) were errors in classifying participants who received active treatment as placebo participants, so the nurses appear to have incorrectly guessed placebo at much higher rates than active treatment.

We found several significant effects related to the nurses' perceptions. Subjects whose nurses believed they were taking active medications were significantly more likely to complete the study, take at least 80% of their medication, and produce clean urines than subjects whose nurses believed they were taking placebo (see table 3).

Correlation between Practitioner and Subject Forms

The observed agreement between the participant and nurse guesses was 58.97%, which was significantly higher than the agreement rate of 50% expected by chance ($\kappa=0.18$, $p=0.01$). However, the value of κ again falls in the range of *slight* or *poor* agreement. An analysis of the discordances between participant and nurse showed that disagreements were significantly more likely to involve the nurse guessing placebo and the participant guessing active treatment (McNemar Chi-square = 22.56, $p<0.001$).

Discussion

The present study examines the integrity of the blind in a placebo-controlled substance abuse treatment trial, investigating whether study subjects and nurses can correctly identify medication assignment and if subject and practitioner opinion regarding medication assignment are related to outcome. Our most noteworthy finding is that neither nurses nor subjects were able to accurately guess participants' treatment assignment. While inconsistent with similar research in nicotine dependence,¹¹ these data suggest that the integrity of the blind may be maintained in cocaine dependence treatment trials, at least those involving amantadine and propranol.

The second question examined by this paper investigated the relationship between perceived treatment group and outcome. Participants whose nurses believed were taking active medications were more likely to complete the trial, be medication compliant, and produce cocaine negative urines, independent of the actual medication assignment. The causal direction of this relationship is impossible to disentangle in the current study: we do not know whether opinion of treatment group assignment influences outcome, outcome influences opinion of group assignment, or whether other factors influence both treatment opinion and outcome. Furthermore, we did note a correlation between nurse and subject opinion of group assignment. It is also possible that practitioners and subjects influence one-another's opinions, adding to the complexity of the association.

Despite this complexity, there are practical implications of this research. As related research indicates that experimenter bias influences outcome,⁴ nurses should be trained to avoid drawing conclusions about treatment group assignment, since these opinions may influence participant outcome. Furthermore, it seems that nurses base their judgments on study outcomes, regardless of probability, whereas participants appear to be more optimistic and, in fact, realistic about their chances of being prescribed active medication. In this trial participants were 3 times as likely to be taking active medication than only placebo, a fact

which the participants seem to take into account and nurses appear to ignore. If nurses are influencing participants' opinion and nurses have a pessimistic and unrealistic outlook on treatment group assignment, participant retention may be unnecessarily influenced and jeopardized. Educating the practitioners about their (and their subjects') inability to accurately guess treatment assignment might help decrease experimenter bias.

The only outcome correlated with subject opinion was study completion (whether subjects attended the final visit within the visit window). We might assume that participants who thought they were taking placebo were less motivated to complete treatment. Until the actual causal pathway is elucidated, research subjects might be educated about the lack of a relationship between actual and perceived group assignment to mitigate high dropout rates.

Conclusion

This study provides encouraging initial data regarding blinding in illicit substance abuse trials. The current authors hope that these optimistic findings regarding blinding will inspire future substance use investigators to incorporate reports of blinding efficacy into cocaine pharmacotherapy publications. Though our analysis of opinion and outcome suggests some interesting associations, the relationships discussed here are strictly correlational. Further research is required before we can draw any conclusions regarding possible causal influences of subject opinion or study outcome.

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Table 1
Comparison of perceived treatment groups along demographics and baseline substance use

Variable	Subjects' Opinion			Nurses' Opinion		
	Perceived placebo	Perceived Active Medication	Significance	Perceived placebo	Perceived Active Medication	Significance
Mean Age	39.6	40.3	$p=0.61$	41.1	39.7	$p=0.18$
% black	71.8%	89.7%	$p<0.01$	81.3%	88%	$p=0.25$
Years of Education	12.47	12.76	$p=0.46$	12.9	12.5	$p=0.30$
% Male	66.7%	61.8%	$p=0.58$	69.8%	60.8%	$p=0.22$
# of days drinking past 30	4.8	5.77	$p=0.45$	5.8	6.9	$p=0.61$
# of days using cocaine past 30	17.34	14.7	$p=0.09$	16.4	14.6	$p=0.17$

Table 2
Subjects' and nurses' perception of group assignment compared to their actual group assignment

Actual Treatment	Subject Opinion			Nurse Opinion		
	Perceived Placebo	Perceived Active Medications	% Correct	Perceived Placebo	Perceived Active Medications	% Correct
Placebo	13	26	33%	26	18	59%
Propranolol	8	35	81%	24	20	45%
Amantadine	12	31	72%	20	23	53%
Amantadine + Propranolol	10	27	73%	19	23	55%
Total	43	119	65%	89	84	53%

Table 3

Relationship between perceived study group and study outcome

Variable	Subjects' Opinion		Nurses' Opinion		Statistics
	Perceived placebo (N=43)	Perceived Active Medication (N=119)	Perceived Placebo (N=89)	Perceived Active Medication (N=84)	
# study drops	22 (51%)	38 (32%)	42 (47%)	22 (26%)	$\chi^2=8.17$ $p=0.004$
80% meds	21 (49%)	69 (58%)	35 (39%)	56 (67%)	$\chi^2=11.2$ $p<0.001$
# Therapy Sessions attended	8.24	8.20	7.86	8.75	F=1.08 $p=0.30$
% Clean Urines	4.91%	9.69%	2.57%	13.48%	F=19.52 $p<0.001$