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Belief about Drug Assignment and Abstinence in Treatment of Cigarette Smoking using Nortriptyline

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Abstract

The purpose of this study was to assess the relationship of beliefs about drug assignment and abstinence status in two treatment studies using nortriptyline hydrochloride as an adjunct to smoking cessation. Smokers (N=345) drawn from two clinical trials were asked at the final follow-up (FFU) at 52-64 weeks whether they believed they had received active or placebo drug; responses were obtained from 76% of the sample (n=262). Biochemically verified abstinence was collected at end of treatment (EOT) and FFU. In both studies, participants were correct in guessing drug assignment. At FFU, belief about drug assignment was not related to abstinence for either active or placebo participants. Participants who received active drug and who were smoking at EOT were more likely to believe they had received placebo than active drug participants who were abstinent at EOT. There was no significant relationship between belief about drug and abstinence status for placebo participants at EOT. Baseline variables did not significantly predict correctness of drug identification. Participants who experienced drug side effects not easily attributable to nicotine withdrawal were more likely to identify their drug assignment as nortriptyline. We conclude that experience during the active treatment period, including side effects and treatment success, may be related to belief about drug assignment, that the field would be well served by at least two assessments of blindness in clinical trials, and that discrepancy between these findings and those studying NRT may be due to differences in dependent variables.

Introduction

The purpose of this study was to assess the relationship of participants' beliefs about drug assignment to abstinence status in two treatment studies using nortriptyline hydrochloride. Blinding is a cornerstone of randomized clinical trials in drug evaluation (Fergusson, Glass, Waring, & Shapiro, 2004; Gaudino & Herbert, 2005; Hrobjartsson & Gotzsche, 2003, 2004). Studies of pharmacotherapies for tobacco dependence have adhered to this tradition. Mooney et al. (Mooney, White, & Hatsukami, 2004) reported that 17 of 73 studies of nicotine replacement therapy (NRT) assessed blindness, and 12 of these reported that participants identified drug assignment at better than chance rates. Dar et al. (Dar, Stronguin, & Etter, 2005), studying NRT for smoking reduction, found that participants could identify drug, and that those who believed they were on active drug at the end of the study showed greater reduction in smoking than those who believed they were on placebo, independent of actual drug dose. These findings have implications, including the effect of beliefs about drug assignment on study outcome, and the potential usefulness of no treatment control conditions and of active placebos.

Most studies using nortriptyline have reported accuracy of either participant or staff perception of dose. All that have collected relevant data reported that active drug can be differentiated from placebo (Hall, Humfleet, Reus, Munoz, & Cullen, 2004; S. M. Hall et al., 2002; Hall et al., 1998; Prochazka, Kick, Steinbrunn, Miyoshi, & Fryer, 2004; Prochazka et al., 1998).

In the current study, we examined the relationship between belief about drug assignment and study outcome for nortriptyline. Like Dar et al. (Dar, Stronguin, & Etter, 2005), we explored the relationship between belief about drug and outcome. Dar et al.

evaluated changes in self-reported cigarettes per day. We studied biologically verified cigarette abstinence. We also examined baseline correlates of correct versus incorrect guessing, and of belief that one had active or placebo drug.

Nortriptyline is widely acknowledged as an effective treatment for tobacco dependence (Fiore, Bailey, Cohen, & al, 2000; Hughes, Stead, & Lancaster, 2005; Wagena, Knipschild, & Zeegers, 2005). It has distinct side effects, including dry mouth, weight gain, constipation and blurred vision, suggesting that accurate drug identification is likely; beliefs about drug could play a role in outcome. This is especially so since informed consent requires a description of potential side effects. Given this complex of clinically useful differences between placebo and active drug, a marked side effect profile, and knowledge of distinctive drug side effects conveyed via informed consent, the study of the relationship of beliefs about drug and outcome and the correlates of these beliefs in nortriptyline studies is of interest.

Method

The Original Studies

Data for the present study were drawn from two clinical trials. In the first, we compared 12 weeks of active versus placebo nortriptyline and cognitive behavioral therapy versus health education. Participants were assessed for biochemically confirmed abstinence at the end of treatment (EOT) (12 weeks), at 24 and 38 weeks, and at a final follow-up (FFU) 64 weeks from study start (Hall et al., 1998). In the second, we compared nortriptyline to sustained release bupropion to placebo, crossed with psychological intervention with medical management. We assessed participants at EOT (12 weeks), at 24 and 36 weeks, and at FFU 52 weeks from study start (S. Hall et al.,

2002). For the present set of analyses, we selected EOT (week 12) and the FFU (week 52 or 64) to study.

Dosing procedure for nortriptyline was consistent across studies. Dose was titrated to therapeutic levels for depression (50-150 ng/ml). Participants received nortriptyline hydrochloride 25 mg/d for 3 days. Dose was increased to 50 mg/d for 4 days. Serum levels were assessed at week 2; dose was increased to 75 mg/d if a therapeutic level had not been reached. At week 4, serum levels were assessed again and if necessary, drug dosage was increased to 100 mg/d. At week 6, serum levels were assessed to determine final dose. Whenever titration occurred for a participant receiving an active drug, medication was titrated for a yoked participant receiving placebo in the same cohort. Participants continued to receive the maintenance dose of medication until week 12, and medication was tapered during week 13. In the first study, the modal maintenance dose was 100 mg/day; in the second, the modal maintenance dose was 75 mg/day (n=26), but 100 mg/day (n=25) was almost as frequent. In both studies participants were considered abstinent if they reported not having smoked for seven days before the assessment, and self-report was verified by expired air carbon monoxide and serum cotinine.

We selected participants from each trial who were in those conditions that received either nortriptyline or placebo for a twelve week treatment period. This included all participants in the comparison of active versus placebo nortriptyline (N=199) from Hall et al. (Hall et al., 1998). From Hall et al. (S. Hall et al., 2002) those 146 participants who participated in either the nortriptyline or placebo treatment conditions were included. Participants who received bupropion were excluded. All participants had

completed a written informed consent approved by the University of California San Francisco Institutional Review Board.

At the final assessment for both studies (FFU), participants were asked whether they had received active or placebo drug. In the study comparing bupropion and nortriptyline (S. Hall et al., 2002), if they reported having received active drug, they were asked which drug they thought they had received, bupropion or nortriptyline.

Data Analysis Methods

In the analysis of the effects of belief about drug on outcome, the independent variables were participants' actual drug assignment (active versus placebo) and participants' belief about drug assignment (active versus placebo). The dependent variables were abstinence status at EOT and FFU (week 64 for study 1 and week 52 for study 2). To analyze the relationship of belief about drug assignment and abstinence data, we nested guesses within actual drug (Dar, Stronguin, & Etter, 2005; Marascuilo & Serlin, 1988). We used PROC CATMOD (SAS 9.13) due to the dichotomous nature of the dependent variable. We used all available data but did not record missing data as indicative of smoking.

Baseline variables were correlated with correctness of guess and of guessing placebo or active drug using point-biserial correlations. We also compared both groups (Correct Guess vs. Incorrect Guess and Guess Placebo vs. Guess Active) for differences in baseline variables using analysis of variance (ANOVA) for continuous variables and Chi-squares for categorical variables. Of the 13 potential side effects, we first determined the percentage of participants reporting each side effect. If the number

responding was greater than 10%, we determined the relationship of the side effects of nortriptyline to participants' belief about drug using Chi-square analyses.

Results

Seventy-six percent of participants (n=262) answered the questionnaire about perceived dose. Demographic, smoking behavior, and diagnostic characteristics of the sample by dose are described in Table 1. Comparisons with the entire combined sample (N=345) indicated that, of the 14 baseline variables, participants answering the belief question differed significantly from those who did not on age and number of years of regular smoking, two highly correlated variables (r =.89, p<.0001). Those answering the questionnaire were older ($\bar{x}$=41.71, SD=10.68) than those who did not ($\bar{x}$=36.90, SD=9.00; F(1,343)=13.75, p=.0002) and had smoked regularly for more years ($\bar{x}$=23.11, SD=10.87) than those not completing the questionnaire ($\bar{x}$=19.01, SD=9.88, F=(1, 340)=9.14, p=.0027).

Table 2 shows numbers and percentages of participants in each drug condition and their belief about drug assignment. As Table 2 indicates, the relationship between actual dose and belief about dose allowed us to reject the null hypothesis that dose and belief were unrelated at p<.05.

At FFU, beliefs were unrelated to FFU abstinence status for the entire sample (χ^2 (1,N=262) =.32, p=.572). FFU belief about drug was significantly correlated with EOT abstinence (χ^2 (1,N=241)=4.13, p<.0422), but this effect was not readily interpretable due to different outcomes for nortriptyline and placebo participants. Nortriptyline participants who, at FFU, believed they were on placebo were more likely to have been smoking at EOT than nortriptyline participants who believed they were on

active drug (χ^2 (1,*N*=241) =18.48, *p*<.0001). If participants were on placebo drug, their beliefs at FFU had no relation to smoking status at EOT (χ^2 (1,*N*=262) =1.17, *p*=.280).

Characteristics that Predict Identification of Drug Dose

None of the 14 baseline variables predicted correctness of guess. In the second study, participants were asked whether they believed they were on active drug, and if so, whether they were specifically on nortriptyline or bupropion. Sixteen participants (43.2%) who correctly guessed they were receiving active drug incorrectly guessed that they were receiving bupropion. Removing these participants from the analyses had no significant effect on the magnitude or direction of the correlations.

Of the potential side effects, seven (rash, difficulty urinating, racing heartbeat, swollen legs, chest pain, shortness of breath and sexual difficulties) occurred at frequencies ≤10% in the entire sample. Of the remaining side effects, dry mouth (χ^2=28.31, *df*=1, *p*<.0001; *OR*=4.45, *CI*[.95]=(2.52, 7.85)), lightheadedness (χ^2=4.90, *df*=1, *p*=.0286; *OR*=1.99, *CI*[.95]=(1.07, 3.72)), shaking hands (χ^2=4.53, *df*=1, *p*=.0436; *OR*=2.82, *CI*[.95]=(1.05, 7.59)) and blurry vision (χ^2=7.50, *df*=1, *p*=.0066; *OR*=6.16, *CI*[.95]=(1.42, 26.73)) were all associated with participants' belief they had received nortriptyline. Constipation (χ^2 (1,*N*=254) = 1.05, *p*=.305) and weight gain (χ^2(1,*N*=254) = .068, *p*=.7944) were not significantly associated with participants' beliefs about drug**.**

Discussion

Participants from two double-blinded clinical trials accurately identified whether they were on nortriptyline or placebo at final follow-up occurring 52 to 64 weeks from study start. Participants' belief about dose at final follow-up was not related to their abstinence status at final follow-up, however. Belief about drug dose at final follow-up

did relate to abstinence status at the end of active treatment but only for active drug participants. Active drug participants who believed they had been on placebo drug during treatment were more likely to have been smoking during drug treatment. This pattern suggests that participants use their outcome while on drug to formulate their beliefs about drug status. This is not a strong finding, however, since there was no relation for participants on placebo drug. Abstinence status at the final follow-up, the time point concurrent with the collection of data about beliefs, was not related to beliefs, possibly because by this point participants attributed success or failure to other factors.

Easily perceivable symptoms that participants probably had not experienced previously or that are not associated with quitting smoking appeared to be related to whether a participant identified drug as active or placebo. Other side effects, like weight gain and constipation, can be attributed to other causes especially when quitting smoking. Given the correlational nature of the study, however, alternate explanations are possible.

These data differ from the findings reported with NRT (Dar, Stronguin, & Etter, 2005), where reduction in number of cigarettes smoked at 6 months was related to belief about drug. There are several differences between the present study and that reported by Dar et al. (Dar, Stronguin, & Etter, 2005). First, the drugs differ in side effects. However, since nortriptyline has at least as distinctive a side effect profile as NRT, this does not seem to be a likely explanation for differences between the studies. Second, the studies differ in the length of time the drug was supplied, and the proximity of the query about participants' beliefs to drug use. We believe, however, the most likely explanation may be that the present study used biologically verified abstinence versus continued smoking as an outcome measure, while Dar et al. (Dar, Stronguin, & Etter, 2005) used

self-reports of number of cigarettes smoked. It is possible that quantitative self-reports are more easily influenced by subjective factors, including belief about drug, than biologically verified data. It would be of interest to replicate the findings of Dar et al. (Dar, Stronguin, & Etter, 2005) in a study of NRT treatment using biochemically verified abstinence as an outcome measure.

Recently, Rees, Wade et al.(Rees, Wade, Levy, John M. Colford, & Hilton, 2005) demonstrated that participants' belief about their experimental status may change over time, and suggest that such beliefs be monitored at least twice during any study. This methodology would allow a more definitive determination of the influence of beliefs about drug on behavioral outcomes.

One reviewer of this paper questioned that appropriateness of combining the two clinical trials used because the two studies differed in the probability of receiving active drug. That is, subjects in the second study were theoretically more likely to guess active drug (67%) than subjects in the first study (50%). However, this is not relevant to the nested analyses of abstinence and belief about drug, the primary analyses in this paper. In these analyses, we examined the abstinence status differences between those who guessed active and those who guessed placebo, not the probability of guessing the correct drug assignment versus actual drug assignment. It should also be noted that the two studies produced parallel results when the data were analyzed separately by study.

In summary, the present study is suggestive at best. It does, however, indicate directions for future research. These include the necessity for more sophisticated designs to study the effects of belief on outcome, potential differences as a function of dependent variables and, quite possibly, between drugs used.

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References

Dar, R., Stronguin, F., & Etter, J.-F. (2005). Assigned versus placebo effects in nicotine replacement therapy for smoking reduction in Swiss smokers. *Journal of Consulting and Clinical Psychology*(73), 350-353.

Fergusson, D., Glass, K. C., Waring, D., & Shapiro, S. (2004). Turning a blind eye: the success of blinding reported in a random sample of randomised, placebo controlled trials. *British Medical Journal, 328*(February 21), 328-423.

Fiore, M., Bailey, W. C., Cohen, S. J., & al, e. (2000). *Treating Tobacco Use and Dependence: Clinical Practice Guidelines* (Vol. June). Rockville MD: U. S. Department of Health and Human Services. Public Health Service.

Gaudino, B. A., & Herbert, J. A. (2005). Methodological issues in clinical trials of antidepressant medications: perspectives from psychotherapy outcome research. *Psychotherapy and Psychosomatics, 74*, 17-25.

Hall, S., Humfleet, G., Reus, V., Munoz, R., Hartz, D., & Maude-Griffin, R. (2002). Psychological intervention and antidepressant treatment in smoking cessation. *Arch Gen Psychiatry, 59*(10), 930-936.

Hall, S. M., Humfleet, G. L., Reus, V. I., Munoz, R. F., & Cullen, J. (2004). Extended nortriptyline and psychological treatment for cigarette smoking. *American Journal of Psychiatry, 161*(11), 2100-2107.

Hall, S. M., Humfleet, G. L., Reus, V. I., Munoz, R. F., Hartz, D. T., & Maude-Griffin, R. (2002). Psychological intervention and antidepressant treatment in smoking cessation. *Archives of General Psychiatry, 59*(October), 930-936.

Hall, S. M., Reus, V. I., Munoz, R., Humfleet, G., Frederick, S., & Triffleman, E. (1998). Nortriptyline and cognitive-behavioral therapy in the treatment of cigarette smoking. *Archives of General Psychiatry, 55*, 683-693.

Hrobjartsson, A., & Gotzsche, P. C. (2003). Placebo treatment versus no treatment. *Cochrane Database Systemic Review, (3)CD003974*.

Hrobjartsson, A., & Gotzsche, P. C. (2004). Placebo intervention for all clinical conditions. *Cochrane Database Systemic Review, 2004(3)*(CD003974).

Hughes, J. R., Stead, L. F., & Lancaster, T. (2005). Nortriptyline for smoking cessation: A review. *Nicotine Tob Res, 7*(4), 491-499.

Marascuilo, L. A., & Serlin, R. C. (1988). Statistical methods for the social and behavioral sciences. *A series of books in psychology*.

Mooney, M., White, T., & Hatsukami, D. (2004). The blind spot in the nicotine replacement therapy literature: Assessment of the double-blind in clinical trials. *Addictive Behaviors*(29), 763-684.

Prochazka, A. V., Kick, S., Steinbrunn, C., Miyoshi, T., & Fryer, G. E. (2004). A randomized trial of nortriptyline combined with transdermal nicotine for smoking cessation. *Arch Intern Med, 164*(20), 2229-2233.

Prochazka, A. V., Weaver, M. J., Keller, R. T., Fryer, G. E., Licari, P. A., & Lofaso, D. (1998). A randomized trial of nortriptyline for smoking cessation. *Arch Intern Med, 158*(18), 2035-2039.

Rees, J. R., Wade, T. J., Levy, D. A., John M. Colford, J., & Hilton, J. F. (2005). Changes in beliefs identifying unblinding in randomized controlled trials: a method to meet CONSORT guidelines. *Contemporary Clinical Trials, 26*(1), 25-37.

Wagena, E. J., Knipschild, P., & Zeegers, M. P. (2005). Should nortriptyline be used as a first-line aid to help smokers quit? Results from a systematic review and meta-analysis. *Addiction, 100*(3), 317-326.

Table 1
Baseline Variables by Actual Drug Condition

	Placebo	**Active**
Variable	$\bar{x}$ (***sd***)	$\bar{x}$ (***sd***)
Number of Participants	173	172
Age	40.7 (10.4)	40.4 (10.6)
Beck Depression Inventory	8.6 (6.9)	8.6 (7.3)
Profile of Mood States	28.0 (32.3)	29.8 (34.6)
Carbon Monoxide (ppm)[1]	25.7 (12.1)	25.1 (10.9)
Prior Quit Attempts	4.4 (7.4)	4.7 (7.6)
Usual Number of Cigarettes Smoked per Day	22.2 (8.8)	22.0 (10.3)
Number of Years Smoking Regularly	22.2 (10.5)	22.0 (11.1)
Variable	***n*** **(%)**	***n*** **(%)**
Female	92 (53.2)	83 (48.3)
Caucasian	146 (84.9)	151 (88.3)
Married/ With Partner	68 (39.5)	64 (37.4)
Previous History of MDD	58 (33.5)	56 (32.6)
Hollingshead Socioeconomic Status		
Highest	42 (24.6)	37 (22.3)
Lowest	0 (0.0)	1 (.6)
Educational Level Achieved		
High School Graduate or Less	16 (9.3)	17 (10.0)
Some College	66 (38.4)	51 30.0)
College Graduate	56 (32.6)	69 (40.6)
Graduate Degree	34 (19.8)	33 (19.4)

[1] ppm = parts per million

Table 2
Actual Dose by Perceived Dose

	Actual Dose		
Perceived Dose	Placebo	Nortriptyline	Total
Believed Placebo	*n*=61 45.86%	*n*=18 13.95%	*n*=79 30.15%
Believed Active	*n*=72 54.14%	*n*=111 86.05 %	*n*=183 69.85%
Total	*n*=133 50.76 %	*n*=129 49.24 %	*N*=262 100.00%

Chi-Square (*df*=1)=31.67,
p<.0001