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# Assigned Versus Perceived Placebo Effects in Nicotine Replacement Therapy for Smoking Reduction in Swiss Smokers

Reuven Dar
Tel Aviv University

Florencia Stronguin
Academic College of Tel Aviv–Yafo

Jean-Francois Etter
University of Geneva

In this report, the authors explore the relationships of perceived treatment to outcome in a large, placebo-controlled trial of nicotine replacement treatment for smoking reduction. In the original study (J. F. Etter, E. Laszlo, J. P. Zellweger, C. Perrot, & T. V. Perneger, 2002), which was conducted in French-speaking Switzerland, smokers were randomly assigned to receive nicotine, matching placebo products, or no intervention. At the end of the 6-month study, participants were asked to guess whether they had received nicotine or placebo. In the present analysis, the authors examined the difference in smoking reduction between those who believed they had received nicotine and those who believed they had received placebo. Regardless of actual treatment, smokers who believed they had received nicotine had significantly better outcome than those who believed they had received placebo.

Nicotine replacement therapy (NRT) has been used as an aid for smoking cessation for over 2 decades. A recent review of over 100 trials of NRT with follow-up periods from 6 months to 1 year (Silagy, Lancaster, Stead, Mant, & Fowler, 2003) concluded that NRT helps about 7% of smokers who would not have quit had they used a similar approach without NRT. This conclusion is based on placebo-control studies, which aim to control for smokers' expectations regarding the effects of nicotine (Brandon, Juliano, & Copeland, 1999; Frenk & Dar, 2000; Perkins, Sayette, Conklin, & Caggiula, 2003). The standard placebo-controlled design, however, may not control for the full range of potential placebo effects of NRT. Specifically, a recent review of placebo effects in smoking (Perkins et al., 2003) defined *placebo* as "the effect of expecting drug in the absence of pharmacological actions of the drug" (p. 696). This type of placebo effect is overlooked in the standard placebo-controlled design, as smokers' beliefs and expectations regarding their drug assignment are rarely assessed in controlled trials.

In the laboratory, participants' beliefs about their drug assignment can be manipulated and examined with the *balanced-placebo design* (Marlatt & Rohsenow, 1980), in which participants are randomly assigned to one of four conditions, corresponding to each combination of instructions (told drug or told no drug) and drug delivery (receiving or not receiving drug). Few laboratory studies have examined the short-term effects of instructions on response to NRT. Gottlieb, Killen, Marlatt, and Taylor (1987), for example, used the balanced-placebo design to examine the effects of instructions and nicotine gum on self-reported withdrawal symptoms during the 1st week of a quit attempt. Instructions that participants received nicotine reduced withdrawal, whereas nicotine by itself did not. In Hughes, Pickens, Spring, and Keenan's (1985) study, smokers trying to quit self-administered more nicotine gum than placebo gum when told they may receive either gum. However, when the placebo gum was described as a new nicotine gum with fewer side effects, or when the nicotine gum was described as a placebo gum with more side effects than the nicotine gum, participants did not self-administer the nicotine gum more than the inactive gum. These studies suggest that smokers' beliefs and expectations can influence the short-term effects of nicotine delivery devices. To date, however, no study to our knowledge has assessed the interaction between beliefs regarding drug assignment and outcome in long-term NRT trials.

The balanced-placebo design assumes that the instructions fully control participants' beliefs regarding their drug assignment. If this assumption is not verified, then the validity of this design for assessing placebo effects is jeopardized. In reality, there is often reason to doubt this assumption, especially when the studied drug, such as nicotine, has recognizable effects that are not fully reproduced by the placebo. For the same reasons, the assumption of blindness cannot be justified in placebo-controlled studies of NRT (e.g., Hughes & Krahn, 1985). This problem limits both the

Reuven Dar, Department of Psychology, Tel Aviv University, Tel Aviv, Israel; Florencia Stronguin, School of Behavioral Sciences, Academic College of Tel Aviv–Yafo, Tel Aviv, Israel; Jean-Francois Etter, Institute of Social and Preventive Medicine, Faculty of Medicine, University of Geneva, Geneva, Switzerland.

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Correspondence concerning this article should be addressed to Reuven Dar, Department of Psychology, Tel Aviv University, Tel Aviv 69978, Israel. E-mail: ruvidar@freud.tau.ac.il

balanced-placebo and the placebo-controlled designs' adequacy to fully assess the placebo effect of nicotine replacement products.

One partial solution to the limitations of the laboratory studies is to examine how smokers' beliefs about their drug assignment are associated with outcome in trials of NRT. On the one hand, this approach does not allow for causal inferences, as beliefs regarding drug assignment can be formed gradually and can be based on many factors, including the perceived difficulty in reducing smoking. On the other hand, beliefs regarding drug assignment are directly assessed rather than assumed to be controlled by instructions, so their validity is better established. In addition, this approach permits examination of the relationship between perceived drug condition and outcome over periods of many months and in natural settings.

In the present analysis, we set out to explore the relationships of actual and perceived drug condition to outcome in a large, placebo-controlled study of NRT for smoking reduction in heavy smokers (Etter, Laszlo, Zellweger, Perrot, & Perneger, 2002; hereafter *the original study*). In contrast to most placebo-controlled NRT studies, participants were asked at the conclusion of the study to guess whether they had received nicotine or placebo. This report presents a secondary analysis of the original study's data that uses these guesses to assess the placebo effects associated with perceived drug assignment. Specifically, in both the nicotine and the placebo conditions, we examined the difference in outcome between those who believed they had received nicotine and those who believed they had received placebo.

## Method

### *The Original Study*

Etter et al. (2002) conducted a randomized controlled trial with three arms—nicotine, placebo, and no treatment—in adult heavy smokers ($M$ = 30 cigarettes per day) who were not prepared to quit smoking. Participants ($N$ = 923) were recruited from the general population of French-speaking Switzerland between 1999 and 2001. Their mean age was 42.8 years, the mean level of education was 13.7 years, and the two genders were equally represented. Ethnic data were not collected, but the population of French-speaking Switzerland tends to be relatively homogeneous (largely Caucasian). Participants had to declare no intention to quit smoking in the next 6 months, but the participants had to be committed to try to reduce their daily cigarette consumption by half and to not use commercial NRT products during the study. They received follow-up questionnaires by mail 3 and 6 months after randomization. Participants received the treatment free of charge and were not paid. Possible side effects of the treatment were explained to them. All signed an informed consent and provided a health status questionnaire signed by their physicians. The study was approved by research ethics committees of the Swiss cantons of Geneva, Vaud, and Valais.

Participants received an information booklet after enrollment and after completion of the 3-month survey, which covered reasons and means for reducing cigarette consumption and included addresses of smoking cessation clinics. With each delivery of nicotine or placebo products, participants received a two-page information leaflet on these products. Participants in the nicotine group could choose among a nicotine transdermal patch (which contained 25 mg and delivered 15 mg of nicotine over 16 hr), a nicotine gum (which contained 4 mg and delivered 2 mg of nicotine), a nicotine inhaler (a plug that contained 10 mg and delivered 5 mg of nicotine; Nicorette, Pharmacia), or a combination of these. Participants in the placebo group could choose among matching placebo patches, gums, and inhalers. Participants in both the nicotine and placebo groups could switch between products or use several products at the same time. In both groups, participants received an initial package that contained a 5-day supply of each product (patch, gum, or inhaler). After testing the products, they ordered by mail the amount and type of product they needed. Subsequently, participants received nicotine or placebo products by mail every other week for 6 months. Nicotine and placebo products were sent to participants in unbranded packaging, similar in the two groups, labeled "nicotine or placebo." Thus, participants were not aware of the nature of the products they received. The investigators were aware of the nature of products mailed to participants but had no in-person contact with participants and only minimal (reactive) telephone contact. All documents sent by mail were identical in the nicotine and placebo groups.

### *Data Analysis*

As the goal of Etter et al.'s (2002) study was reducing smoking in smokers who were unwilling to quit, the main outcome in the original study was the reduction in the number of cigarettes smoked per day (CPD) at the end of the 6-month trial. In addition, in the 6-month follow-up survey, participants in the nicotine and placebo groups were asked to guess whether they had received nicotine or placebo during the study period ("In which group were you, in your opinion?"). In the present analysis, we examined how participants' beliefs regarding their group assignment, in addition to actual group assignment, related to reduction in CPD. The two independent variables in the analysis were actual group assignment (nicotine or placebo) and perceived group assignment (guessed nicotine, guessed placebo, or did not know). The data could not be analyzed with a factorial 2 × 3 analysis of variance (ANOVA), as the guesses and actual assignment were not independent. Therefore, we analyzed the data in a nested design, in which guesses were nested in actual assignment (Marascuilo & Serlin, 1988). This analysis yielded three effects: (a) the overall difference between placebo and nicotine, (b) the difference between the three perceived assignment responses (nicotine, placebo, do not know) among those who received nicotine, and (c) the difference between the three perceived assignment responses among those who received placebo. The latter two are similar to the main effects of one-way ANOVA in each of the drug conditions but use the combined error mean square, rather than the error mean square within each drug condition, to calculate the $F$ values (Marascuilo & Serlin, 1988).

## Results

### *Results of the Original Study*

Of the 923 participants, 879 (95%) returned the final questionnaire, with a median time of 196 days after randomization. At this point, 67% of the participants in the nicotine group and 57% in the placebo group used NRT or placebo products daily or occasionally, $\chi^2(1, N = 224) = 6.80$, $p = .01$. The average duration of use of the products was 120 days in the nicotine group compared with 98 days in the placebo group, $t(407) = 3.51$, $p < .001$. Among daily users, the type and amount of products used were similar in the nicotine and placebo groups. The mean reduction in CPD was 10.7 cigarettes in the nicotine group, 8.7 in the placebo group, and 4.9 in the control group ($p < .05$ for all pairwise differences).

### *Secondary Analysis of the Outcome: Perceived Versus Actual Group Assignment*

Of 534 participants, 491 (92%) responded to the item asking them to guess their drug assignment. As Table 1 shows, although guessing was related to actual group assignment, $\chi^2(2, N = 333) = 47.36$, $p < .001$, many participants, especially in the nicotine

group, did not guess correctly whether they had received nicotine or placebo. The mean change in CPD from baseline to the 6-month survey, as a function of actual and perceived group assignment, is presented in Table 2.[1] In the nested two-way ANOVA, the effect of the actual treatment (nicotine vs. placebo), which was significant in the original study, was no longer significant after adjusting the error term for guesses that regarded group assignment, $F(1, 485) = 0.43$, $p = .51$.[2] In contrast, the associations between smoking reduction and perceived treatment (guessed nicotine, guessed placebo, did not know) were significant both for those who received nicotine, $F(2, 244) = 6.33$, $p = .002$, and for those who received placebo, $F(2, 241) = 4.55$, $p = .011$. Scheffé contrasts showed that among those who received nicotine, as well as among those who received placebo, participants who guessed they had received nicotine had larger CPD reductions than those who guessed they had received placebo. In both treatment groups, the differences between those who believed they had received either nicotine or placebo and those who did not know were not statistically significant.

Table 2
*Mean Reduction in Cigarettes Smoked per Day as a Function of Actual and Perceived Treatment*

| Response | Received nicotine | Received placebo | Total (*N*) |
|---|---|---|---|
| Guessed nicotine | 14.0 | 13.8 | 13.9 |
| *SD* | 11.8 | 10.7 | 11.5 |
| CI | 11.8–16.2 | 10.6–16.9 | |
| *n* | 95 | 40 | 135 |
| Guessed placebo | 8.1 | 8.1 | 8.1 |
| *SD* | 10.2 | 9.6 | 9.7 |
| CI | 5.4–10.7 | 6.4–9.8 | |
| *n* | 65 | 133 | 198 |
| Did not know | 10.7 | 8.9 | 9.9 |
| *SD* | 10.5 | 10.5 | 10.5 |
| CI | 8.4–13.0 | 6.6–11.3 | |
| *n* | 87 | 71 | 158 |
| Total | 11.3 | 9.3 | 10.3 |
| *SD* | 11.2 | 10.2 | 10.7 |
| *n* | 247 | 244 | 491 |

*Note.* CI = 95% confidence intervals for group means.

### *Correlates of Erroneous Guessing*

In each treatment group, we used Bonferroni pairwise comparisons to compare the baseline measures of participants who guessed correctly with those who guessed incorrectly and those who were unable to guess. In the placebo group, those who falsely believed they had been receiving nicotine had significantly higher baseline Fagerström scores (Heatherton, Kozlowski, Frecker, & Fagerström, 1991) compared with those who guessed correctly (6.8 vs. 5.7, $p = .012$) and reported smoking their first cigarette in the morning approximately 15 min sooner (15.1 vs. 29.7, $p = .048$). In the nicotine group, in contrast, there was no difference between those who falsely believed they had received placebo and those who guessed correctly in either Fagerström scores (6.0 vs. 5.9, $p = .95$) or time to the first cigarette (24.2 min vs. 25.1 min, $p = 1.00$). Accuracy was not related in either group to having used NRT in the past, to participants' initial self-reported intention to reduce smoking, to the number of CPD, or to any demographic variables.

## Discussion

Etter et al. (2002) found that both nicotine and placebo treatments reduced cigarette consumption in heavy smokers who were not prepared to quit. Nicotine was only slightly more effective than placebo, however, whereas participants receiving either nicotine or placebo improved considerably more than participants who did not receive any treatment. Etter et al. concluded that "the reduction in cigarette consumption due to nicotine per se was relatively small" and that "treatment effectiveness was mostly attributable to a placebo effect" (p. 493). The present secondary analysis of the data elucidates these placebo effects by showing that reduction of smoking was strongly related to participants' beliefs about their drug assignment. Smoking reduction was larger in those who believed that they had received nicotine compared with those who believed they had received placebo, regardless of actual drug assignment. Moreover, after adjustment to perceived drug assignment, the association between actual drug assignment and smoking reduction was no longer statistically significant.

Our findings are consistent with the results of studies that have used a balanced placebo design (Gottlieb et al., 1987; Hughes et al., 1985), in which instructions about whether participants received nicotine or placebo, rather than actual drug condition, predicted smokers' immediate responses to NRT. In clinical trials, however, smokers' beliefs regarding their drug assignment are not manipulated but instead are formed during the study. As Etter et al. (2002) assessed these beliefs after 6 months of treatment, placebo effects in this study cannot be equated with effects of expectations. In addition to expectations, several alternative mechanisms could have accounted for the observed relationships between perceived treatment and smoking reduction. First, believing that one had received a placebo product may have decreased compliance or caused discouragement, which in turn, may have resulted in less

Table 1
*Participants' Guesses Regarding Whether They Received Nicotine or Placebo, Assessed at the 6-Month Follow-Up Survey*

| Response | Received nicotine | Received placebo |
|---|---|---|
| Guessed nicotine | | |
| % | 38.5 | 16.4 |
| *n* | 95 | 40 |
| Guessed placebo | | |
| % | 26.3 | 54.5 |
| *n* | 65 | 133 |
| Did not know | | |
| % | 35.2 | 29.1 |
| *n* | 87 | 71 |

*Note.* The 6-month follow-up survey data are from Etter et al.'s (2002) study, but are tabulated here in a different way.

[1] Note that the means of the two groups are slightly different than those reported in the original study, as Table 2 includes only those participants who responded to the item that asked them to guess their group assignment.

[2] Note that this is not due to lack of statistical power: A post hoc power analysis indicated that (with our sample sizes) this test had a power of nearly 0.8 for detecting a small effect of 0.25 and nearly 1.0 for detecting a medium effect of 0.5.

successful outcomes. Second, many participants who correctly guessed that they received placebo continued to use the products after 6 months, suggesting that the placebo products were reinforcing to users. Evidence from studies of the sensory factors involved in smoking (e.g., Rose, Behm, Westman, & Johnson, 2000) suggests that the oral stimulation provided by the placebo gum or inhaler may reduce craving and help smokers delay the next cigarette (Cohen, Britt, Collins, Al'Absi, & McChargue, 2001). A third mechanism that could account for the association between beliefs and cigarette consumption is that participants' deduced their beliefs regarding their drug assignment from their success in reducing smoking. Specifically, those who succeeded in reducing cigarette consumption may have attributed their success to having received nicotine, whereas those who did not succeed in reducing their cigarette consumption may have deduced that they had been given placebo.

Finally, Etter et al. (2002) relied exclusively on self-report in evaluating their results. Although this is clearly less desirable than relying on objective measures, it would have significantly affected the results only if the validity of reporting interacted with either actual or perceived drug assignment. In terms of the present analysis, participants who believed they had received nicotine may have overreported the amount of smoking reduction, either in response to experimental demands or because they were reluctant to admit that despite having received nicotine, they failed to reduce their cigarette consumption. Objective assessment of smoking reduction, with biochemical verification, could overcome this problem.

Regardless of how beliefs about drug assignment were formed, the present analysis underlines the importance of assessing these beliefs and their relationships to outcome (Hughes & Krahn, 1985) in NRT studies. More generally, our results are relevant to understanding and estimating placebo effects in other treatments. A recent review (Hróbjartsson & Gøtzsche, 2003) assessed the effects of placebo interventions by comparing the outcome of placebo and no-treatment conditions across a large range of health problems. The authors concluded that there was no evidence that placebo interventions in general have clinically important effects. This conclusion, however, is restricted to the definition of placebo as "control treatments with a similar appearance to the study treatments, but without their essential components" (Hróbjartsson & Gøtzsche, 2003, p. 2). Our results suggest that this conclusion cannot be generalized to the wider definition of placebo effects that involves patients' beliefs and expectations regarding the treatment (Perkins et al., 2003).

The present results are based on a very large sample with an exceptional follow-up rate. However, the extent to which they can be generalized to other populations, including to smokers who are committed to quit (rather than reduce) smoking, cannot be established. Future research should experimentally assess the impact of beliefs on the effect of NRT on smoking cessation in long-term cohort studies.

The main clinical implication of this article is that the potential effects of subjective beliefs concerning treatment assignment should be considered in the design of clinical studies. A principal mean to control for these effects is the systematic inclusion of no-treatment control groups in placebo-controlled studies. In addition, our results suggest that in future NRT studies, products designed to imitate the sensory and behavioral features of cigarettes should be compared with the presently available nicotine and placebo products.

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