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Effect of instructions and nicotine on smoking cessation, withdrawal symptoms and self-administration of nicotine gum

John R. Hughes, Suzy B. Gulliver, Geri Amori, Gina C. Mireault, and James F. Fenwick

Human Behavioral Pharmacology Laboratory, Departments of Psychiatry and Psychology, University of Vermont, 1 South Prospect Street, Burlington, VT 05401, USA

Abstract. Seventy-seven smokers quit smoking and were randomly assigned to a 3 × 2 design contrasting instructions (told received nicotine gum versus told received placebo gum versus not told which gum received) and receipt of nicotine (received nicotine gum versus received placebo gum). Both being told one received nicotine and actual receipt of nicotine increased the number of days abstinent and decreased the number of cigarettes smoked ($P<0.05$). Receipt of nicotine but not instructions appeared to influence withdrawal ($P=0.06$). Instructions but not receipt of nicotine appeared to influence craving ($P=0.08$), gum self-administration ($P=0.06$) and reported helpfulness of the gum ($P=0.02$). Neither nicotine nor instructions influenced side-effects. Instructions and nicotine interacted in several ways. For example, nicotine appeared to increase abstinence in the blind and told placebo conditions more than in the told nicotine condition ($P<0.05$). Our results suggest the effects of instructions and nicotine 1) are not mutually exclusive, 2) vary across dependent variables and 3) can interact such that instructions modify the therapeutic and subjective effects of nicotine.

Key words: Blindness – Expectancy – Nicotine gum – Reinforcement – Smoking cessation – Tobacco withdrawal

Instructions that one will receive a drug can produce physiological, behavioral and subjective changes similar to the pharmacological actions of the drug (Hull and Bond 1986; Marlatt and Rohsenow 1980). In some situations, instructional effects have been cited as the cause of presumed pharmacological effects (Marlatt and Rohsenow 1980). In other situations, instructions have been shown to interact with the pharmacological effect of a drug to increase or decrease the drug effect (Penick and Hinkle 1964; Penick and Fisher 1965).

Several studies have been cited as showing that instructions influence smoking (e.g., see Gritz 1980); however, only four studies have directly tested the effects of instructions on abstinence from smoking, withdrawal symptoms and use of nicotine gum (Fagerstrom and Storm 1981; Hughes et al. 1985, 1989b; Gottlieb et al. 1987). In terms of abstinence, two studies reported that instructing subjects they had received nicotine gum increased abstinence rates independent of nicotine content of the gum (Fagerstrom and Storm 1981; Gottlieb et al. 1987). In one of these studies the effect occurred only in the more dependent smokers (Fagerstrom and Storm 1981). In the other study the effect of instructions occurred with some measures of abstinence but not others (Gottlieb et al. 1987). One of these studies also reported that some withdrawal symptoms were diminished by being told one had received nicotine gum (Gottlieb et al. 1987).

Studies on gum self-administration found different results. In one study (Hughes et al. 1985) smokers had concurrent access to both nicotine and placebo gums and were given no instructions. Under these conditions, nicotine gum was self-administered at a rate much greater than placebo gum. However, when smokers were given instructions that suggested placebo gum contained nicotine and visa versa, nicotine gum was not self-administered at a rate greater than placebo. Thus, instructions and nicotine interacted such that instructions controlled whether nicotine content of the gum would or would not influence gum use. In a similar study, (Hughes et al. 1989b), smokers not trying to quit were given concurrent access to nicotine and placebo gums. Instructions and nicotine again interacted such that instructions that nicotine was available increased self-administration of nicotine gum but not self-administration of placebo gum.

The present study had two main purposes. One was to extend the prior work on the effects of instructions on abstinence and withdrawal symptoms by using 1) a no-instructions (i.e., blind) group as a control group and 2) several measures of each variable. A second purpose of the study was to replicate our prior findings on the interaction between instructions and nicotine on gum self-administration when subjects had access, not to both nicotine and placebo gums, but rather to only one gum. We hypothesized 1) both instructions and nicotine would influence smoking behavior, withdrawal and gum self-administration, and 2) instructions and nicotine would interact such that nicotine would serve as a reinforcer in the blind condition but as an aversive stimulus in the told placebo condition.

Subjects and methods

Subjects

Seventy-seven smokers who wished to stop were recruited from public service annoucements. To be included subjects must have been over 18 years old, have smoked at least

Offprint requests to: J. R. Hughes

ten cigarettes/day of at least 0.5 mg nicotine for at least 1 year, fulfilled DSM-III criteria for tobacco dependence (American Psychiatric Association 1981), and believe nicotine gum would relieve their withdrawal symptoms. Subjects were excluded if they had a contraindication to nicotine gum use (Hughes and Miller 1984), had psychiatric, emotional or drug abuse problems, were taking a psychoactive medication or had chewed nicotine gum before.

Design

The traditional balanced placebo design (Marlatt and Rohsenow 1980) contrasts instructions (told received drug versus told received placebo) with drug receipt (received drug versus received placebo). We modified this design by adding a third instructional set (called "Blind") in which subjects were not told which drug they received. Subject were randomly assigned to cells. Experimenters were blind to gum contents.

Procedure

At the first baseline session, subjects signed an informed consent document which listed the therapeutic and side-effects of nicotine gum and stated each subject had a 50/50 chance of receiving nicotine or placebo gum. Subjects were told they could or could not be told the contents of their gum. Subjects were not told they might be deceived.

At all sessions, subjects were counseled about smoking cessation for 15–30 min according to a previously described protocol (Hughes and Kottke 1986). At the baseline sessions, subjects were given a stop-smoking manual and viewed a 13-min slide/tape show to insure they received the correct rationale, expectancies and instructions about nicotine gum (Hughes and Miller 1984). Subjects were instructed to use the gum according to FDA-approved guidelines (Merrell Dow 1984); e.g., use as needed when the urge to smoke occurs. Subjects were not given guidelines about how much gum to use.

Subjects returned in 1 week for the second baseline session. At this session and thereafter subjects were seen individually to prevent comparison of gums, withdrawal symptoms, etc. At this session an envelope was opened which contained a card that stated whether the subject was to receive nicotine gum, placebo gum or was to not know what they were to receive. This card was shown to the subject. In reality, the gum may have contained either nicotine or placebo gum. Subjects were told to stop smoking and begin using the gum in the morning.

To insure that subjects in the told placebo group would sample the gum and to increase their motivation to try to quit they were told repeatedly, "You have been assigned to the placebo group. Our prior studies have shown that in some people chewing placebo gum does help them quit." Subjects were given a sheet to self-monitor their daily gum use and were told to return the filled and empty gum blisters at the next weekly session.

The third and fourth sessions occurred 1 and 2 weeks post-cessation. At these sessions, some subjects in the deceived groups noted the side-effects or efficacy of the gum were not as expected. Responses to such queries were developed a priori and emphasized the variability in responses to the gum across individuals and noted that, for matching purposes, the placebo gum did have side-effects similar to nicotine.

Subjects were debriefed upon their completion of the study. Deceived subjects were given nicotine gum to help them try to quit again. No subject objected to the deception.

Drug. The commercially available nicotine gum (Nicorette, 2 mg Merrell-Dow Pharmaceuticals) and a placebo gum which contained flavoring agents to mimic the taste and irritancy of nicotine gum were used. An error in assigning gums occurred such that in the blind group more subjects received placebo gum than nicotine gum; however, assignment to nicotine and placebo was still randomized and double-blind.

Measures

Smoking behavior. At the weekly post-cessation meetings, subjects stated the number of cigarettes and the number of days smoked since the last session. In addition, subjects designated someone to be an observer (usually a spouse, friend or fellow employee) who reported the subject's smoking status. The subjects also submitted a breath sample for carbon monoxide (CO) to verify smoking status (Hughes et al. 1976).

Four smoking variables were used: 1) proportion of subjects who smoked no cigarettes during the week, 2) proportion who smoked on 2 or fewer days/week, 3) number of days smoked/week and 4) number of cigarettes smoked/week. The second measure was included as many smokers reported smoking one or two cigarettes on 1 or 2 days of the week (see below). Abstainers were those whose carbon monoxide level was less than 10 ppm and whose observer verified their smoking status. The two subjects who failed to return after cessation were counted as smokers.

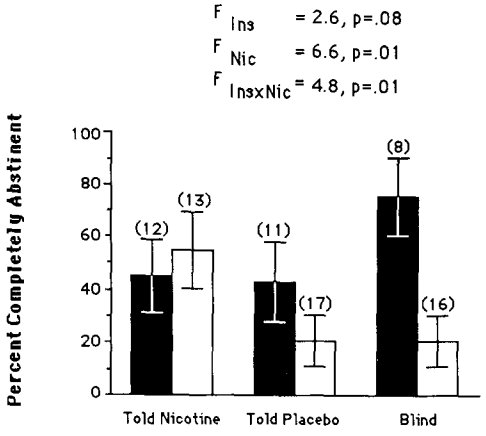
Withdrawal effects. Five withdrawal effects were measured: 1) self-reported withdrawal symptoms, 2) observer-rated withdrawal behaviors, 3) heart rate, 4) weight and 5) self-reported craving. These were taken at the baseline and abstinence sessions. The first two measures were scales validated in prior research (Hughes et al. 1984, 1989a; Hughes and Hatsukami 1986). Craving for tobacco was not included in these scales but was rated separately by a 100 mm visual analog scale. Heart rate was taken by manual palpation of the radial artery for 30 s.

Gum self-administration. Gums self-administered were inferred from the number of empty blisters in the packets returned each week. Prior work indicated this measure of self-administration to be sensitive to nicotine and instructional effects (Hughes et al. 1985, 1989b).

Self-reported gum effects. Side-effects from the gum were measured at both post-cessation weeks by summing a 14-item scale. Ratings of drug effects, drug liking, and helpfulness of the gum were taken at the end of the study and were measured by single item 1–5 scales.

Data analysis

A 3-way repeated-measures analysis of variance (ANOVA) for continuous measures and a similar log-linear model for dichotomous measures were run for each variable. These $3 \times 2 \times 2$ ANOVAs had instructions (told nicotine versus told placebo versus blind) and drug (received nicotine ver-



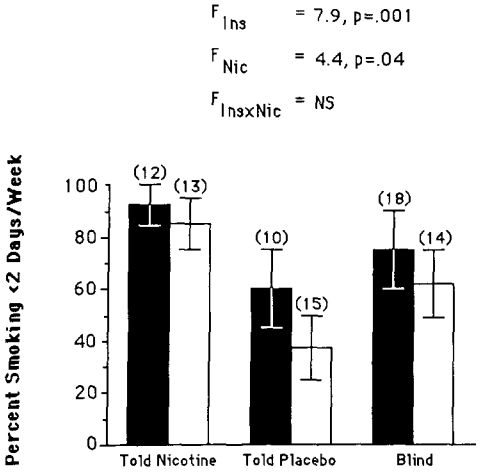
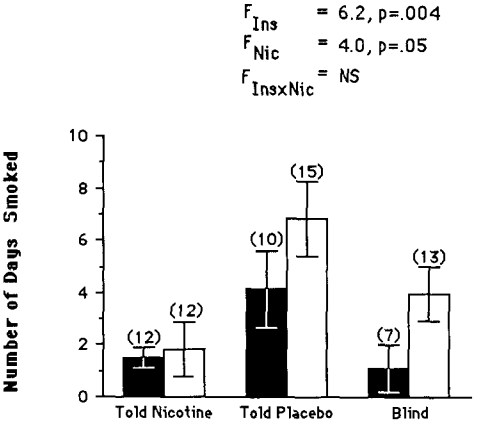


Fig. 1. Abstinence by instruction and drug group (*open bars* = placebo, *solid bars* = nicotine; sample sizes in parenthesis). The results are cumulative across weeks 1 and 2.



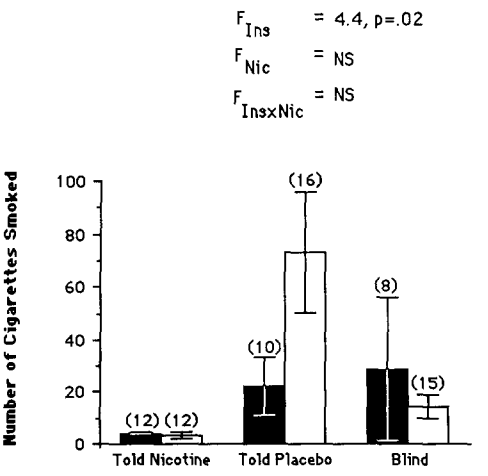


Fig. 2. Smoking behavior by instruction and drug group (*open bars* = placebo, *solid bars* = nicotine; sample sizes in parenthesis). The results are cumulative across weeks 1 and 2.

sus received placebo) as grouping factors and time (1st week versus 2nd week of abstinence) as the repeated factor. Post-hoc testing used Duncan's multiple comparisons procedure.

Results

Subject characteristics

Subject characteristics were similar to those in prior studies and those of population-based samples of smokers (Shopland and Brown 1985): i..e., age = 40.1 years (SD = 10.7), 52% were men, 99% completed high school, 55% were professionals, cigarettes/day = 29.0 (SD = 10.2), duration of smoking = 21.8 years (SD = 11.7), nicotine yield of cigarette = 0.70 mg (SD = 0.28), number of prior quit attempts = 3.6 (SD = 3.2) and Fagerstrom Tolerance Score = 6.0 (SD = 1.8). These characteristics did not differ across groups.

Internal validity checks

At the end of the trial 29% of subjects stated they never thought they were deceived, 63% considered deception but were unsure and 8% believed they were deceived. These figures did not differ across instructional or drug groups. The prevalence of considering deception in the instructional groups was not greater than that for the non-instructed (blind) groups.

Abstinence for smoking

Receipt of nicotine and instructions that one received nicotine increased most measures of abstinence ($P = 0.01$–0.08; Fig. 1). Post-hoc testing of the complete abstinence criteria indicated that the told nicotine instructions increased abstinence, the blind instructions had no effect, and the told placebo instructions decreased abstinence. Receipt of nicotine and instructions also decreased most measures of smoking behavior ($P = 0.004$–0.05; Fig. 2). Post-hoc testing of both smoking behaviors indicated the told nicotine and blind groups were similar and smoked less than the told placebo group.

The effects of instructions and nicotine on the complete abstinence measure interacted ($P = 0.01$; Fig. 1). This interaction occurred in the 1st week and again in the 2nd week. Post-hoc testing of the interaction indicated the abstinence rates differed between nicotine and placebo group in the blind condition but not in the told nicotine told placebo groups. Similar interactions appeared to occur for the other smoking variables but these were not statistically significant.

Since one study reported instructional effects on smok-

ing behavior only in highly dependent smokers (Fagerstrom and Storm 1981), we divided subjects into high and low dependence groups using a median split of the Fagerstrom Tolerance Scale (Fagerstrom 1978) and looked for an instructions by dependence interaction. Smokers' level of dependence did not influence the instructions effect, nicotine effect or their interaction.

Three a priori planned sets of analyses examined the contribution of the individual instructional groups to the main effect of instructions via $2 \times 2 \times 2$ ANOVAs similar to the main analyses. The first analyses compared the told nicotine and told placebo groups; i.e., as in the classical balanced placebo design. The previously described main effect for instructions occurred again with all the smoking behavior variables ($F > 4.6$, $P < 0.03$). A trend for the previously described instructions by nicotine interaction with the complete abstinence measure also occurred ($F = 2.9$, $P < 0.09$).

The second set of planned analyses compared the told nicotine and blind groups. Since the blind group serves as a neutral control group, these analyses indicated the positive effects of being told one is receiving nicotine. Instructions that one received nicotine appeared to increase the probability of smoking for less than 2 days/week ($F = 3.7$, $P < 0.06$) but did not influence the other three smoking cessation variables. The previously described instructions by nicotine interaction again occurred with complete abstinence ($F = 10.1$, $P < 0.002$).

The third set of planned analyses compared the told placebo and blind groups. These analyses indicated the negative effects of being told one is receiving placebo. Instructions that one received placebo decreased the probability of smoking less than 2 days/week ($F = 5.8$, $P < 0.02$) and the number of days smoked ($F = 4.5$, $P < 0.04$) but not the other two abstinence variables. The instructions by nicotine interaction with complete abstinence did not occur.

Withdrawal effects

To examine effects on withdrawal, we used only smokers who stopped smoking. As with most smoking trials, many subjects smoked a few cigarettes on a few days post-cessation. Since prior work suggested smoking a few cigarettes does not influence withdrawal symptoms (Hughes and Hatsukami 1986) or gum self-administration (Hughes et al. 1985), we did not exclude subjects who smoked a total of less than ten cigarettes on 2 or fewer days/week. Using this criteria, 50 of the 77 subjects remained. Of these 50 subjects, 25 smoked no cigarettes. Among the remaining 25 subjects, the median number of cigarettes smoked during the entire 2 weeks post-cessation was 3.0. The modal total number of cigarettes over the 2 weeks was 1.5.

We also used only withdrawal symptoms valid in the present sample of subjects. Initial analyses documented increases in self-reported withdrawal, observer-rated withdrawal and weight, and decreases in heart rate with cessation ($F > 3.6$, $P < 0.05$). Surprisingly, craving did not increase with abstinence but rather decreased ($F = 8.5$, $P < 0.01$).

Analysis of withdrawal variables was similar to the ANOVA described for smoking behavior, except baseline values were used as covariates. Post-hoc comparisons of the various pairs of instructional sets were not run due to the small sample sizes per cell ($n = 7$–16). Item-by-item analyses of the withdrawal scales were not also run, as the resultant number of statistical tests would be quite large and we feared false positive results.

Neither nicotine or instructions had main effects on self-reported withdrawal, observed withdrawal, heart rate or weight. However, a marginal nicotine by time interaction occurred with self-reported withdrawal ($F = 3.8$, $P = 0.06$). Although small cell sizes prevented post-hoc testing, inspection of the results suggested the increase in withdrawal symptoms in the 1st week post-cessation differed little between nicotine and placebo (Nic $= +2.1$, Pl $= +3.2$), but by the 2nd week no withdrawal was occurring among subjects on nicotine (Nic $= -0.6$) whereas withdrawal persisted among subjects on placebo (Pl $= +2.6$).

Nicotine had no influence on craving. A marginal instructions effect occcured ($F = 2.7$, $P = 0.08$). Instructions that one received nicotine produced slightly less craving ($x = 24.5$) than instructions that one received placebo gum ($x = 35.0$) or no instructions ($x = 40.3$) ($F = 2.7$, $P = 0.08$). An instructions by nicotine interaction did not occur.

Gum self-administration

Nicotine and instructions might change gum self-administration simply because they affect smoking behavior. This is because gum use typically only occurs when smokers are abstinent; thus, any increase in the rate of abstinence by nicotine or instructions should be accompanied by increased gum use.

In contrast, nicotine and instructions might change gum self-administration, not due to their therapeutic effects, but rather because they influence the reinforcing effects of gum among abstinent smokers. To more clearly assess the influence of instructions and nicotine on reinforcing effects only, we analyzed gum self-administration data only for the 48 abstinent subjects.

Among abstinent subjects, there was no significant main effect for nicotine on gum self-administration, a marginal main effect for instructions ($F = 3.0$, $P = 0.06$) and a week by instructions interaction ($F = 7.8$, $P = 0.002$). Again, due to small sample sizes, post-hoc tests were not feasible. Inspection of the means suggested that in the 1st week post-cessation, gum use did not differ in the told nicotine and told placebo groups (Gum used/week, told Nic $= 45.8$, told Pl $= 42.8$) but in the 2nd week gum use was greater in the told nicotine group than in the told placebo group (told Nic $= 52.6$, told Pl $= 33.8$).

A non-significant interaction ($P > 0.10$) suggested that in the told nicotine group, nicotine gum was self-administered *more* than placebo gum (no. of gums/2 weeks: Nic $= 107.0$, Pl $= 89.6$), but in the told placebo group and blind groups, nicotine gum was self-administered *less* than placebo gum (no. of gums/2 weeks for the told placebo group: Nic $= 67.3$, Pl $= 91.2$; for the blind group: Nic $= 105.2$, Pl $= 119.3$). This trend occurred in both the 1st and 2nd weeks.

Self-reported effects of gum

Self-reported effects were analyzed only for abstinent subjects. Neither nicotine nor instructions influenced self-reported side-effects. Instructions that one received nicotine gum increased self-rated drug effect ($P = 0.02$; Fig. 3) and

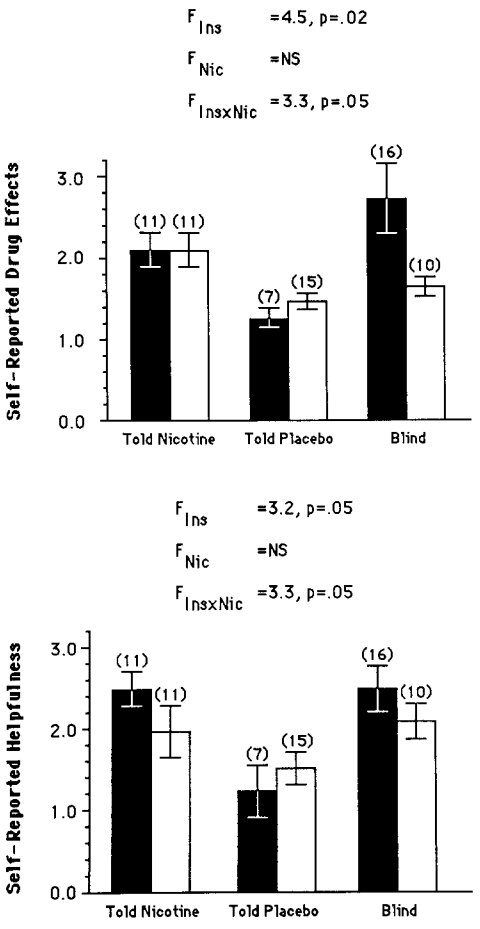


Fig. 3. Self-reported drug effect and helpfulness by instruction and drug group (*open bars* = placebo, *solid bars* = nicotine; sample sizes in parenthesis). The results are the average of weeks 1 and 2. ■ Nicotine; □ placebo

helpfulness of the gum ($P=0.05$) but not drug liking. Nicotine did not influence self-rated drug effects, helpfulness or liking. An instructions by nicotine interaction also occurred ($P=0.05$) such that the nicotine content of the gum increased self-reported drug effect in the blind condition but not in the told nicotine or told placebo conditions.

Dicussion

Abstinence and smoking behavior

Our abstinence and smoking behavior results replicate two prior studies (Fagerstrom and Storm 1981; Gottlieb et al.1987) that found instructions influenced abstinence from cigarettes. Instructions significantly decreased the number of days abstinent and decreased the number of cigarettes. Instructions had somewhat smaller effects on percent completely or partially abstinent. In some respects, our results are more robust than these prior findings. Unlike Fagerstrom and Storm (1981) our effect of instructions was not limited to the more dependent smokers. Unlike Gottlieb et al. (1987), we found that instructions effected all abstinence measures and occurred in both week 1 and week 2 post-cessation.

The addition of a non-instructions group allowed us to test the effects of instructions more specifically than did prior studies. Our results suggest both negative effects from instructions that one will receive placebo and positive effects from instructions that one will receive nicotine. In prior studies using the traditional balanced placebo design, instructional effects have been attributed solely to the positive effects of being told one will receive drug. Our results suggests one cannot assume this without a no-instructions group.

Withdrawal effects

Our withdrawal results are discordant with the single prior study (Gottlieb et al. 1987). In our study, instructions appeared to influence craving but not withdrawal. Conversely, Gottlieb et al. (1987) found that instructions influenced withdrawal but not craving. Two explanations for this discrepancy are plausible. First, our results may represent false positives because our sample size was smaller than that of Gottlieb et al. (1987). Second, the results of Gottlieb et al. (1987) may represent false negatives because they did not report that their withdrawal measures were valid and they found main effects for instructions in only some of the subscales of withdrawal at only some of the time points.

Gum self-administration

Again, our results are discordant with Gottlieb et al. (1987). In our study, instructions appeared to influence gum self-administration but this did not occur in Gottlieb et al. (1987). Two possible reasons for this discrepancy are 1) we denied the possibility of deception, and 2) Gottlieb et al. (1987) asked subjects to use ten pieces of gum/day. This latter instruction may have made gum use an insensitive dependent variable.

We also found a non-significant trend that instructions can cause nicotine to serve as either a reinforcer (i.e., self-administered more than placebo) or an aversive stimulus (i.e., self-administered less than a placebo). Although this finding was not statistically significant, we would note the effect 1) was large (Fig. 2), 2) occurred in both the 1st and 2nd weeks, 3) was predicted a priori from previous work (Hughes et al. 1985, 1989b) and 4) is believable. The effect is believable in that when subjects are told they are receiving nicotine gum, the stimulus effects are probably labeled as indicators of therapeutic efficacy whereas when told they received placebo, the same stimulus effects are labeled as side-effects.

Theoretical significance

A recent review concluded that interactions between instructions and drug effects are rare (Hull and Bond 1986). However, our data suggest instructions and nicotine interacted such that nicotine controlled not just the magnitude of a nicotinic effect, but whether a therapeutic, reinforcing or subjective effect of nicotine would even occur. Such demonstrations of interactions between instructions and drug effects are important in that they cannot be explained by traditional theories of expectancy or placebo effects, as those theories usually state the pharmacological effects of drugs are unimportant.

Significance to human psychopharmacology research

Our study provides an example of the importance of instructions to human psychopharmacology research in that

it compared drug effects under instructional sets similar to those in experimental trials (i.e., some subjects were not told whether they received active drug or placebo) and under instructional sets similar to those in therapeutic settings (i.e., some subjects were told they received active drug). As described above, nicotine appeared to increase quit rates, and perceived drug effects under "experimental" instructions but not under "therapeutic" instructions. One explanation of this result is that the stimulus effects of nicotine may be important to subjects in an experiment in that they indicate whether the subject is on active drug or placebo. On the other hand, when patients in a clinic are told they are receiving nicotine gum, the same stimulus effects are not perceived as providing any new information and thus have little effect on cessation.

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