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Smoking History, Instructions and the Effects of Nicotine: Two Pilot Studies

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HUGHES, J R , G STRICKLER, D KING, S T HIGGINS, J W FENWICK, S B GULLIVER AND G MIREAULT *Smoking history, instructions and the effects of nicotine Two pilot studies* PHARMACOL BIOCHEM BEHAV **34**(1) 149–155, 1989 —In Study 1, ten never-smokers, ten ex-smokers and nine current smokers received nicotine (2 mg) and placebo gum hourly for 4 hours on 2 consecutive days in a randomized, double-blind, cross-over protocol Dysphoria from nicotine was greatest in never-smokers, intermediate in ex-smokers, and least in current smokers ($p<0$ 05) On the third day, subjects were given concurrent access to the same gums and told to chew ad lib Across all subjects, nicotine was an aversive stimulus (i e , self-administered less than placebo) Nicotine was avoided most in never-smokers, intermediate in ex-smokers and least in current smokers ($p<0$ 05) Study 2 used a similar protocol and compared the nine current smokers in Study 1 who were not told they would receive nicotine with eight informed smokers, i e , smokers told they would receive nicotine Although nicotine appeared to be a reinforcer more often in the informed smokers than in the uninformed smokers (63% vs 22%), this result was not statistically significant Our results suggest 1) past drug history can influence the stimulus effects of nicotine and 2) the effects of instructions on the response to nicotine may be less in experimental settings than in therapeutic settings

Drug history Drug self-administration Expectancy Instructions Nicotine Smoking Reinforcement Tobacco Tolerance

SEVERAL factors control the stimulus effects of nicotine (3, 6, 11). This article reports studies of the effect of past and present smoking history (Study 1) and instructions (Study 2) on the physiological and subjective responses to and preference for nicotine and placebo in humans.

STUDY 1 EFFECT OF PAST SMOKING HISTORY

Past and present drug history influences the response to several drugs (38). In nonhumans, prior exposure to nicotine can produce tolerance to nicotinic effects many weeks later (28, 30, 35, 36) In humans, *present* smoking influences the response to nicotine; e g , smokers and nonsmokers differ in their heart rate response to nicotine (25). The effect of *past* smoking history, i.e., comparing the effect of nicotine between never-smokers and ex-smokers, has not been studied in humans.

METHOD

Subjects

Subjects were recruited by advertisements which stated, "Gum chewers wanted for a study on the use of gums to deliver medications " To be included, subjects must have chewed gum at least weekly and had never chewed nicotine gum. Subjects who had a history of psychiatric or drug abuse problems, might be pregnant or had a contraindication to nicotine gum (22) were excluded

Potential subjects were asked about their present and past alcohol, tobacco, caffeine and drug use to minimize their knowing that they were divided into groups by smoking status alone Ten never-smokers (NS) and ten ex-smokers (ES) were chosen from the eligible subjects NS had never smoked daily for >2 weeks. ES had smoked >10 cigarettes/day for >1 year and had been abstinent for >1 year. Nine current smokers (CS) served as a control group (one CS dropped out at the start of the experiment) Current smokers presently smoked >10 cigarettes/day for >1 year To prevent confounding the effects of the experimenter-delivered nicotine via nicotine gum and subject-delivered nicotine via tobacco, CS were required to abstain from smoking overnight. Smoking status among the groups was confirmed at the first session by breath carbon monoxide (17) Subjects were unaware

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they were chosen on the basis of their smoking history

Instructions

All subjects read and signed an informed consent document that gave the following rationale for the study

> "Many times patients do not take their medications due to side-effects When medication is placed in a gum rather than a capsule or tablet, patients can control how much medicine they receive by how hard they chew the gum Thus, patients could also control how many side-effects they would have and, hopefully, be more likely to take medicine This study tests how easy or difficult it is for people to chew gum as a way to take medication "

The document also stated

> "Smoking, coffee drinking and alcohol use interact with many drugs, thus, if you smoke or drink coffee or alcohol, you will have to abstain overnight before each testing day and during the time you use gum, i e , for 5 hours on the first 2 days and for 9 hours on the third day "

The consent form stated that subjects could receive a stimulant (amphetamine, caffeine, and nicotine were given as examples), a tranquilizer (alcohol and Valium were given as examples) or a placebo The behavioral effects and side-effects of all these drugs and the side-effects of chewing the stiff gum were listed. A previous study indicated that among smokers instructions that one is receiving nicotine can influence whether nicotine will serve as a reinforcer (23) We did not know what effect instructions of receipt of nicotine would have on NS and, more importantly, on ES, thus, we believed it best to not directly tell subjects they would receive nicotine However, as noted above, subjects were informed that nicotine was one of the drugs they might receive

Ethics

Since NS and ES would be exposed to nicotine in the study, it could be hypothesized that the experiment could prompt these subjects to begin or resume using tobacco or nicotine gum We believed the probability of this outcome was minimal because 1) there have been no reports of abuse of nicotine gum by NS or ES, 2) the gum has several unpleasant side-effects, and 3) the onset of psychoactive effects is relatively slow (13, 16, 22) In addition, 4) the duration of exposure in this study would be short, and 5) subjects were not directly told that they would receive nicotine In addition, a previous study reported that experimental administration of tobacco did not induce ES to relapse to smoking (8) Even so, the consent form explicitly stated that if any subject feared use of one of these drugs listed would lead to dependence, they should not enter the study None of the NS, ES or CS dropped out for this reason

Three months after the study we contacted the subjects and debriefed them as to the contents of the gums they took and the real purpose of the study At the time of this follow-up we could reach 13 of the 20 NS and ES (many were summer students who could not be found in the fall) None of the 13 were using nicotine gum or tobacco

Design

The study used a modification of the procedure of Johanson, deWit and colleagues (5) and consisted of two consecutive periods 1) an exposure period and 2) a test of preference for nicotine Each of these tests was run as a randomized, double-blind, placebo-controlled trial The exposure period insured subjects had experienced the effects of nicotine gum before the preference test

Drug

Commercially available 2 mg nicotine gum and an inert placebo (Nicorette, Lakeside Pharmaceuticals, Merrell Dow, Inc) were used The placebo contained flavoring agents to match the taste and irritancy of nicotine

Test of Physiological/Subjective Response to Nicotine

This period consisted of a two-day cross-over trial with exposure to nicotine and placebo gums At the initial session, subjects reported to the lab at 7 to 10 a m and completed a standard Triangle Taste Test (1) comparing nicotine and placebo gums according to the protocol we used in a previous study (23) This was to insure that subjective ratings during the drug exposure period and self-administration during the preference testing period were not due to a taste preference for nicotine among ES or S

Subjects then completed the bipolar form of the Profile of Mood States (POMS) and a short form of the Addiction Research Center Inventory (ARCI) The POMS is a 72-item questionnaire which gives scores for composed/anxious, agreeable/hostile, elated/depressed, confident/unsure, energetic/tired and clear-headed/confused scales (27) The short form of the ARCI is a 49-item questionnaire which gives scores for sedation (PCAG), euphoria (MBG), dysphoria and psychomimetic changes (LSD), and amphetamine-like effects (BG and AG) (10) We used only the first three scales as these appear to be the scales most sensitive to the effects of nicotine (Henningfield, personal communication) Both the POMS and the ARCI have been shown to be sensitive to the effects of nicotine gum (20,29) Subjects also had their sitting blood pressure and pulse taken using a random-zero sphygmomanometer (37) and palpitation of the radial artery for 30 seconds

Subjects were randomly assigned in a double-blind manner to receive nicotine or placebo gum on the first day Subjects were given a sheet of four gums labeled Gum A and instructed to chew one piece each hour They were told to chew the gum according to the FDA-approved instructions, i e , chew each piece slowly for 30 minutes Subjects were also told to not change their daily activity level and to abstain from alcohol, caffeine, tobacco and large meals for the next 4 hours Subjects were given POMS and ARCI forms to complete one hour after they began each gum They also had a designated observer (usually a friend or relative) sign a form verifying they had taken the gum and filled out the forms as directed

Subjects returned to the lab one hour after their last gum, turned in their empty gum sheets and gave a breath sample for CO analysis Subjects' blood pressure and pulse were taken as before Subjects rated how much they liked the drug from 1 = disliked a lot to 5 = liked a lot They filled out a questionnaire about whether they thought the gums reminded them of alcohol, caffeine, marijuana, tobacco or placebo They also indicated whether they believed they received a stimulant, tranquilizer or placebo (21)

The next day these procedures were repeated except subjects received a sheet of gums labeled Gum B which contained the gum not received on the first day

Test for Preference for Nicotine

On the third day, subjects reported again between 7 and 10 a m This time subjects were given two sheets of nine pieces of gum labeled Gum A and Gum B These contained the same drugs as during the physiological/subjective testing period and the

subjects were informed of this Subjects were instructed to 1) chew gum whenever they wished, 2) wait one hour between the start of each piece of gum, 3) use one gum from package A first and then one from package B, 4) after these first two pieces, use gum from either package, 5) chew at least one more gum after the first two pieces, 6) chew each piece for at least 15 minutes, 7) record the time and type (A or B) of each gum used, 8) not drink alcohol or smoke, and 9) maintain their normal level of caffeine intake and activity Subjects were told that use of the different gums would indicate to the experimenters the "acceptability" of the gums A breath sample was obtained as before Subjects returned 9 hours later The number of missing gums were counted and any discrepancies with the self-monitoring report resolved and subjects gave a breath sample At the end of the study, the Triangle Taste Test was repeated

If the subjects completed all study procedures according to their report, the report of their observer and their breath samples, they were paid The NS and ES were paid $50 and the CS $75 The CS were paid more due to their required abstinence from cigarettes, however, CS, NS and ES were unaware that the pay rate of CS differed from NS and ES

Data Analysis

The scores for the POMS and ARCI were entered into $3 \times 2 \times 4$ repeated measures ANCOVA with smoking history (NS vs ES vs CS) as a grouping factor and drug (nicotine vs placebo) and time (hours 1–4) as repeated factors and baseline scores at hour 0 as the covariate The heart rate and blood pressure analyses were entered into a 3×2 ANCOVA with smoking history and drug as grouping factors and baseline scores as the covariate The drug-liking and drug-effects scores were entered into a similar 3×2 ANOVA without the covariate as baseline scores Ratings of each gum as an active substance (i.e , alcohol, caffeine, marijuana, tobacco or placebo) and as a stimulant (i e , stimulant as tranquilizer or placebo) were compared between nicotine and placebo by 2×2 McNemar's chi-square test.

To evaluate preference for nicotine, a preference ratio (PR) was calculated for each subject as the ratio of nicotine gums self-administered divided by total number of gums self-administered (23). Thus, self-administration of only nicotine gum would produce a PR of 1 0, of only placebo gum a PR of 0 0, and of equal amounts of each a PR of 0 5 This preference was compared across groups with a Kruskal-Wallis ANOVA (28) More specific tests for avoidance of nicotine and for any use of nicotine used Bartholomew's test for order (4).

RESULTS

Internal Validity

Among the subject characteristics, ES were the oldest, CS intermediate and NS the youngest, $F(2,26) = 5.3$, $p < 0\ 02$ (Table 1) There was also a nonsignificant trend for more women among CS However, neither age nor gender was related to physiological or subjective response to or preference for nicotine. The ES averaged 6.2 years (range 1 5–15 years) since they stopped smoking.

Neither NS, ES, or CS identified nicotine gum on the basis of taste at a rate greater than chance either before or after the study Both self-report and carbon monoxide data indicate all CS abstained as required. The preference data from one NS, a foreign student, was deleted as he misunderstood the instructions and intentionally self-administered equal amounts of nicotine and placebo gums

Physiological and Subjective Response to Nicotine

Heart rate was higher with nicotine gum than placebo (mean = 74 3 vs 71 8), $F(1,25) = 9\ 3$, $p < 0.005$, but the effect of nicotine did not interact with smoking status Nicotine did not produce a main effect or interaction on systolic or diastolic blood pressure No significant adverse effects to nicotine gum (e g , nausea) occurred in any group

TABLE 1

MEAN AND STANDARD DEVIATION FOR SUBJECT CHARACTERISTICS

	Study 1		Study 2	
	Never-Smokers (n = 10)	Ex-Smokers (n = 10)	Smokers (Uninformed) (n = 9)	Smokers (Informed) (n = 8)
Age	25 8 (2 7)	34 3† (7 5)	29 2 (6 4)	27 0 (6 8)
Men/Women	5/5	4/6	2/7	1/7
Cigarettes/day	—	20 5* (13 9)	24 7 (11 7)	30 3 (9 2)
Nicotine yield	—	—	0 90 (0 22)	0 79 (0 20)
Duration of smoking	—	7 5* (5 6)	10 1 (5 7)	12 8 (6 3)
Fagerstrom Score	—	—	6 3 (1 9)	5 0 (1 5)

*When smoking

†$p < 0\ 05$, ex-smokers > never-smokers and smokers

Nicotine produced a main effect to increase scores on the dysphoria scale of the ARCI, $F(1,234) = 7.3$, $p < 0\ 02$ (Fig 1) Nicotine and smoking status also interacted, $F(2,234) = 5\ 2$, $p < 0.02$, such that dysphoria from nicotine was greatest in NS, intermediate in the ES, and least in the CS There was no main effect for or interactions with time

Three post hoc analyses were done to clarify the smoking history by nicotine interaction. The first post hoc analysis indicated that on placebo gum the deprived CS had slightly greater dysphoria than the NS or ES but this difference was not statistically significant. The second post hoc analysis indicated that on nicotine gum NS had significantly more dysphoria than ES or CS, Duncans test, $p < 0.01$, and that the apparent difference between ES and CS was not statistically significant The third post hoc

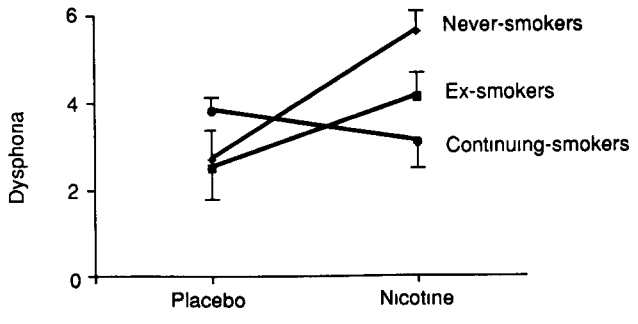

FIG 1 Mean and s e scores for the LSD (dysphoria) scale of the ARCI (16) Scores averaged across hours 1–4 and adjusted for baseline

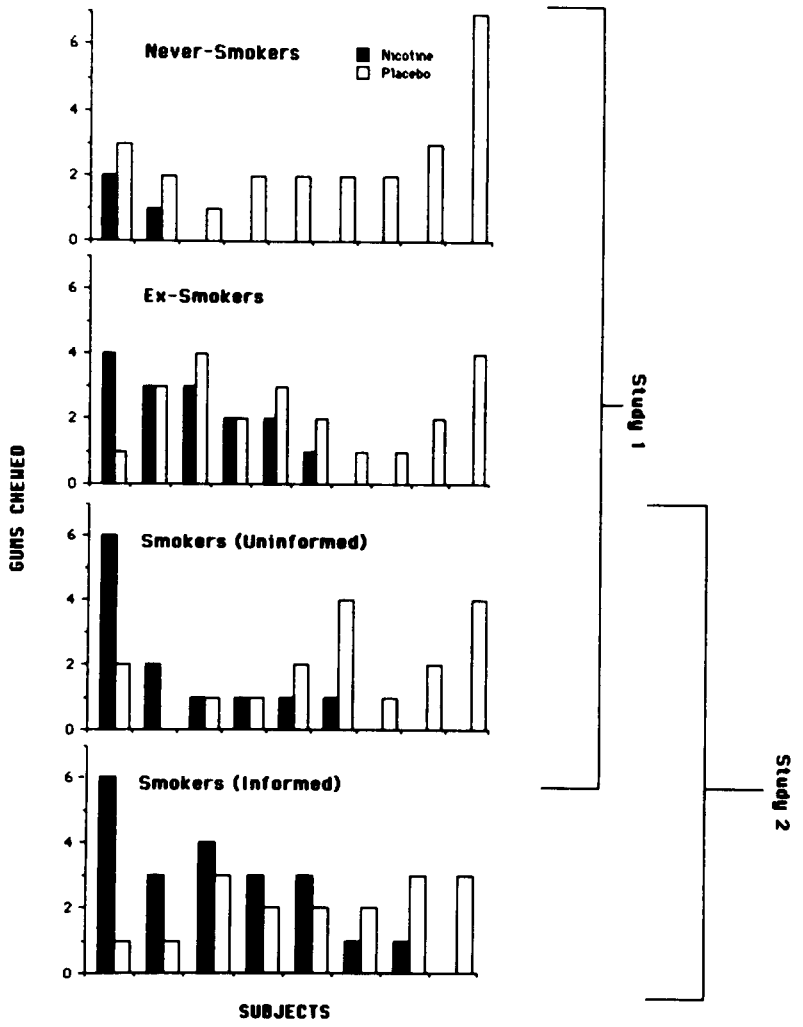

FIG 2 Number of gums self-administered on test day not including the required one piece of nicotine and placebo gums

analysis compared the nicotine-placebo difference scores across the three smoking history groups NS had an increase in dysphoria scores with nicotine (+3 0) that was significantly different from the smaller increase in ES (+1 5) and slight decrease in CS (−0 7), Duncan's test, $p<0$ 01 The effect of nicotine in ES and CS was not significantly different Among ES, self-reported dysphoria was not related to duration of abstinence

Nicotine did not produce a main effect or interaction on any of the POMS scales nor on the ARCI sedation or euphoria scales Nicotine also produced a main effect to decrease drug liking, $F(1,234)=26$ 0, $p<0$ 001, but nicotine and smoking status did not interact

Nicotine was more often rated as an active substance (i e , alcohol, caffeine, marijuana or tobacco) than placebo was rated as an active substance, $\chi^2(1)=22$ 6, $p<0$ 001 Twenty-two (76%) of subjects rated nicotine gum as an active substance and 4 (14%) rated placebo as an active substance Eight of the 29 subjects stated nicotine gum reminded them of tobacco

Nicotine gum was more often rated as a stimulant than placebo gum was rated as a stimulant, $\chi^2(1)=15$ 2, $p<0$ 001 Fourteen subjects (48%) rated nicotine as a stimulant, 9 (31%) rated it as a tranquilizer and 4 (20%) rated it as placebo or don't know One subject (5%) rated placebo as stimulant, 6 (21%) rated it as a tranquilizer and 22 (74%) rated it as a placebo or don't know

The ratings of active drug vs placebo, ratings of similarity to tobacco and stimulant vs tranquilizer ratings did not differ across smoking history groups

Preference for Nicotine

Across all three groups, three subjects preferred nicotine gum (i e , chewed more nicotine than placebo gum), four subjects showed no preference and twenty-one preferred placebo gum The cumulative preference ratio (PR) across all three groups was 30/94 (0 32) which is significantly less than the expected 47/94 (0.50), binomial test, $p<0$ 05 The mean and (standard error) for the PR for NS was 0 08 (0 05), for ES was 0 30 (0 09) and for SS was 0 36 (0 12) This apparent trend was not statistically significant in the Kruskal-Wallis ANOVA of PRs

Subjects were then classified by whether they avoided nicotine (i e , self-administered less nicotine than placebo gum) Among NS, all nine avoided nicotine gum Among ES, one preferred nicotine gum, two had no preference, and seven avoided nicotine gum (Fig 2). Among ES, avoidance of nicotine was not related to

duration of abstinence Among CS, two preferred nicotine gum, two had no preference and five avoided nicotine gum. Thus, 100% of NS, 70% of ES, and 55% of CS avoided nicotine gum, Bartholomew's test for order, NS>ES>CS, $\chi^2=4.9$, $p<0.05$.

In terms of chewing any nicotine gum (after the required one piece), seven NS (70%) did not chew any nicotine gum compared with four ES (40%) and three CS (33%), Bartholomew's test, NS>ES>CS, $\chi^2=4\ 2$, $p<0.05$

DISCUSSION

Never-smokers reported the most dysphoria from nicotine, ex-smokers were intermediate, and current smokers reported the least dysphoria from nicotine This result is consistent with prior findings both for nicotine and other drugs and for humans and nonhumans. In terms of nicotine, although no prior studies have systematically examined the effect of past and present use of nicotine on subjective effects from nicotine, several studies have anecdotally noted that injectable nicotine is more unpleasant to nonsmokers than smokers (12, 24, 25) In terms of other drugs, morphine produces more dysphoria in those without a history of morphine use than in those with a past history of morphine, i e , postaddicts (26), or those with a present history of morphine use, i e., continuing addicts (10) In terms of nonhumans, past history of exposure to a drug can influence the discriminative effects (supposedly a measure of subjective effects) of that drug (31).

Never-smokers avoided nicotine the most, ex-smokers were intermediate, and current smokers avoided nicotine the least. This result is consistent with the dysphoria results. It is also consistent with findings with nicotine and other drugs in humans and nonhumans. In terms of nicotine, again no direct data are available, but one small study reported IV nicotine was avoided by a nonsmoker but self-administered by smokers (12). In terms of other drugs, one study found that a present history of greater alcohol use was related to preference for diazepam (deWit, personal communication). Finally, in terms of nonhumans, several studies have shown that both present and past history can have a significant influence on the reinforcing effects of a drug (38)

Although the results of the present study are consistent with prior findings, our results should be considered preliminary for three reasons 1) our sample size was small and thus, our statistical power to detect differences was low, 2) each subject was tested only once; thus, we have no data on reliability within a subject, and 3) the effect of history was not statistically significant in our major analysis (i.e., the Kruskal-Wallis ANOVA of PRs) but only with specific post hoc analyses.

One interpretation of our results is that the smoking history groups differed in their tolerance to the aversive effects of nicotine Tolerance to the effects of nicotine among current smokers is widely accepted (11, 24, 25, 30). Tolerance to nicotine among ex-smokers has not been reported.

Tolerance to nicotine among ex-smokers could be due to incomplete loss of acquired tolerance. Although prior studies have not examined tolerance years after cessation of nicotine, nonhuman studies indicate acquired tolerance to nicotine can persist for up to 3 months after cessation of nicotine (28, 30, 35, 36).

Tolerance among ex-smokers could also be genetically determined (14) With other drugs (e g., alcohol), tolerance to aversive effects appears to be genetically transmitted and related to increased risk of abuse (32) In nonhumans, genotype can control whether tolerance to tobacco occurs (2) In humans, indirect data suggest genetic tolerance to nicotine may occur in humans and be related to the risk of becoming a smoker (14). For example, adolescents vary in tolerance to the aversive effects from tobacco and those with fewer aversive effects appear to be more likely to become smokers (34). Finally, tolerance among ex-smokers could be due to passive exposure to smoke in utero or during childhood as ex-smokers are likely to have had parents that smoked. Infants of smokers have detectable levels of nicotine and its metabolites (9) Whether such exposure is sufficient to produce tolerance is unknown

Our results may be of clinical significance for at least two reasons First, our finding that never-smokers and ex-smokers self-administered less nicotine gum than placebo gum and rate nicotine gum as producing dysphoria suggests nicotine gum is aversive to both never-smokers and ex-smokers. This would suggest that if nicotine gum were used as a treatment for nonsmoking disorders (e g , aggression, dementia, ulcerative colitis) its abuse liability would be of little concern (15). However, the present study is not a completely adequate test of abuse liability as many drugs of abuse are initially aversive Second, ex-smokers appeared to have an increased tolerance to the aversive effects of nicotine. This increased tolerance may be a factor in the relative ease of relapse to smoking among ex-smokers (24)

STUDY 2 EFFECT OF INSTRUCTIONS

In Study 1, nicotine was not a reinforcer even among CS. However, the CS in Study 1 were not directly told that they would receive nicotine Prior studies suggest nicotine can serve as a reinforcer only when subjects know that nicotine is available (18,23). Thus, one hypothesis is that if CS had been told that they were receiving nicotine gum, nicotine would have served as a more robust reinforcer This hypothesis was tested in Study 2.

METHOD

A second group of ten CS were selected as before. One newly recruited CS dropped out after the first session due to time commitments. The remaining nine subjects underwent the same protocol as in Study 1 including the same informed consent. However, the experimental instructions for this group explicitly stated that Gums A and B could both be nicotine gum, could both be placebo gum, or one could be nicotine and the other placebo This group of smokers was labeled informed smokers (IS). The nine smokers in Study 1 were used as comparison group and labeled uninformed smokers (UIS) As described above, this group was told the gums could contain a stimulant, tranquilizer or placebo and nicotine was listed as a possible stimulant. However, these subjects were not explicitly told the gums contained either nicotine or placebo

RESULTS

Internal Validity

Subjects smoked between one and one and a half packs of moderately low-nicotine cigarettes for about 10 years (Table 1) Their Fagerstrom scores for dependence were below the cutoff for dependent smokers (i.e , 7) (7) and were somewhat lower than that seen in withdrawal clinics (19). None of these characteristics differed between UIS and IS

Neither UIS or IS identified nicotine gum on the basis of taste at a rate greater than chance either before or after the trial. Self-report and carbon monoxide data indicate one IS appeared to have smoked during the study. His data were deleted leaving nine UIS and eight IS who participated

Physiological and Subjective Response to Nicotine

Heart rate was higher with nicotine gum than placebo (mean =

76 8 vs 73 6), F(1,15) = 8 6, $p<0$ 01 The effect of nicotine did not interact with instructional group Nicotine did not produce a main effect or interaction on systolic or diastolic blood pressure

Nicotine did not produce a main effect or interaction on any of the POMS scales nor on the ARCI sedation or dysphoria scales On the ARCI euphoria scale, nicotine, instructional group and time interacted such that euphoria from drug increased with cumulative doses in the IS but decreased in the UIS, F(1,125) = 4 1, $p<0$ 02 Nicotine did not produce a main effect nor interact with instructional group to decrease drug liking

Nicotine gum was more often rated as an active substance than placebo, $\chi^2(1) = 5$ 2, $p<0$ 05 Ten subjects (63%) rated nicotine gum as active and three (19%) rated placebo gum as active Seven of the 17 smokers reported nicotine gum reminded them of tobacco

Nicotine gum was more often rated as a stimulant than placebo gum, $\chi^2(1) = 7$ 6, $p<0$ 01 Eight subjects (50%) rated nicotine as a stimulant, none rated it as a tranquilizer and 8 (50%) rated it as a placebo or don't know One subject (6%) rated placebo gum as a stimulant, none rated it as a tranquilizer, and 15 (94%) rated it as a placebo or don't know Surprisingly, the ratings of active vs placebo, similarity to tobacco, and stimulant vs tranquilizer did not differ between instructional groups

Preference for Nicotine

As stated in Study 1, the mean and (standard error) preference ratio (PR) for UIS was 0 36 (0 12) For the IS the mean PR was 0 50 (0 10) This apparent difference was not statistically significant via a Mann-Whitney test (33)

Among the UIS, two of the nine preferred nicotine gum to placebo gum, two had no preference and five avoided nicotine Among the IS, five of eight preferred nicotine gum and three avoided nicotine. The apparently greater incidence of preference for nicotine gum among IS than UIS (63% vs 22%) was not statistically significant via Fishers exact test (33)

DISCUSSION

Our results were in the hypothesized direction (i e , greater preference in IS than UIS) and appeared of substantial magnitude (i e , 63% of IS vs 22% of UIS preferred nicotine gum), however, in the absence of statistical confirmation, the most conservative interpretation of our results is that we have failed to replicate our two earlier studies that found instructions modify the reinforcing effects of nicotine (18,23)

Our failure to replicate could be due to our small sample sizes and resultant low power On the other hand, we found a significant instructional effect in one prior study with samples of 10 subjects/condition (23) In addition, the magnitude of the effect in the present study is less than that of our prior two studies For example, in our earlier work, instructions controlled whether nicotine would or would not serve as a reinforcer (23) or whether nicotine would serve as a reinforcer or a punisher (18) In the present study, nicotine appeared to only modify the degree to which nicotine served as a reinforcer

One possible reason for our failure to replicate is differences in the potency of the instructional sets between the present study and our prior studies In the two earlier studies, deceived subjects were given instructions to make them believe nicotine gum contained no drug (i e , a placebo) In the present study, deceived subjects were given instructions that nicotine gum contained, not a placebo, but rather a nonnicotine psychoactive drug (i e , stimulant, tranquilizer or placebo) Perhaps the contrast between being told one will receive nicotine gum vs being told one will receive placebo gum is a more "potent" instructional manipulation than the contrast between being told one will receive nicotine gum vs being told one will receive a nonnicotine drug

Another possible reason for our failure to replicate is that the present study took place in an experimental setting, whereas our former studies took place in therapeutic settings Instructional effects could be more potent in a therapeutic setting because individuals have been reinforced for instruction following in therapeutic settings to a greater extent than in the few experimental settings they have experienced

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