Original investigation

Reinforcement Enhancing Effects of Nicotine Via Patch and Nasal Spray

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Abstract

Introduction: Confirming preclinical findings, nicotine in humans (via smoking) enhances reinforcement from nondrug rewards. Recent demonstration of similar effects with nicotine via e-cigarettes suggests they may also occur when using nicotine replacement therapies (NRT).

Methods: Effects of nicotine via NRT patch or nasal spray were assessed on responding reinforced by music, video, or monetary rewards, or for no reward (control). Nontreatment seeking smokers ($N = 31$) participated in three virtually identical experimental sessions, each following overnight abstinence ($CO \leq 10$ ppm). In a fully within-subjects design using a double-dummy procedure, these sessions involved: (1) nicotine patch (Nicoderm 14 mg) plus placebo spray, (2) placebo patch plus nicotine spray (Nicotrol, 2×1 mg/trial), or (3) placebo patch plus placebo spray. Session order was counter-balanced.

Results: Relative to placebo, reinforced responding due to nicotine via spray or patch was greater for video reward (both $p < .01$) but not for music reward (both $p > .10$). Similar results for NRT spray and patch confirms preclinical findings indicating no difference between fast and slow nicotine delivery, respectively, on reinforcement enhancing effects. Withdrawal relief was unrelated to these effects of nicotine via NRT on nondrug reinforcement.

Conclusions: Nicotine from NRT has some reinforcement enhancing effects in humans, possibly in a manner consistent with nicotine via e-cigarettes but not tobacco smoking. Our findings could suggest differential dose-dependency of available rewards to enhanced reinforcement by nicotine. Such effects may help contribute to the efficacy of NRT for aiding smoking cessation, but more research focusing on dose-dependency of these nicotine actions is needed.

Implications: Acute nicotine from smoking enhances reinforced responding for nondrug sensory rewards. Yet, nonsmoked nicotine, including from NRT medications of patch and nasal spray, may act more selectively across rewards, perhaps due to lower dosing exposure. Our results suggest that nicotine via NRT enhances responding for visual (video) reward, but not from auditory (music) reward, just as in prior results using e-cigarettes. Withdrawal relief from NRT was unrelated to reinforced responding, consistent with positive (and not negative) reinforcement from this nicotine. Further research evaluating the dose-response effects of nicotine may clarify differences in enhanced reinforcement depending on the type of available reward.

Introduction

Consistent with preclinical research,¹ studies with humans show that nicotine (via tobacco smoking) acutely enhances reinforcement from rewards unrelated to the availability of nicotine.² For example, after closely adapting procedures from rodent models on lever pressing for auditory or visual (tones, lights) stimuli in response to nicotine or saline,^{1,3,4} we consistently found that smoked nicotine enhanced responding in humans reinforced by sensory rewards⁵ of brief auditory (music) and visual (video) stimuli.^{6–8} Such responding did not differ between smoking behavior without much nicotine (ie, denicotinized cigarettes) versus no smoking, pointing to nicotine per se as critical, separate from simple smoking behavior. Specificity of these smoked nicotine effects was also suggested by a lack of enhancement in responding for a nonsensory reward, money, or for a no reward control condition.

Because these acute effects of smoked nicotine were also partly found with e-cigarettes,⁹ a nonsmoked product, nicotine intake regardless of method of administration likely has reinforcement enhancing effects in humans (as in the preclinical research¹). Moreover, other research shows that recent abstinence from nicotine reduces, and subsequent resumption of smoked nicotine use (as well as bupropion) reinstates, reinforced responding for nondrug rewards in a manner that is not related to withdrawal or its relief, respectively (which might suggest negative reinforcing effects).^{10,11} Such findings confirm rapid loss of those positively reinforcing nicotine effects early upon making a quit attempt, as would be expected and comparable to preclinical findings of removing nicotine administration in nondependent animals.¹² Consequently, nicotine replacement therapy (NRT) products, FDA-approved to help smokers quit,¹³ may also have reinforcement enhancing effects. Conceivably, such effects could potentially help explain, at least in part, the efficacy of NRT in aiding smoking cessation.

The current study assessed reinforcement enhancing effects of nicotine from NRT patch and from NRT nasal spray, each versus placebo patch and spray. The procedures we earlier developed and evaluated with nicotine via tobacco or electronic cigarettes^{2,6,8,9} were also used here to test nicotine via the NRT patch and spray products, facilitating comparisons with that earlier research. We hypothesized that responding reinforced by auditory (music) and visual (video) stimuli, but not by money or no reward control, would be enhanced by the two active NRT patch and NRT spray conditions, relative to the single placebo (patch and spray) condition.

Methods

Participants

Participants ($N = 31$; 14 men, 17 women) were adults who smoked ≥ 10 cigarettes per day for at least 1 year and met DSM-V criteria for nicotine dependence.¹⁴ All were nontreatment seekers participating only for monetary payment. Respective mean ($\pm$ SD) smoking characteristics were 15.2 ± 4.2 cigarettes/day and 5.2 ± 1.4 on the Fagerstrom Test of Nicotine Dependence (FTND).¹⁵ They were 33.7 ± 8.5 years of age, and mostly self-identified as Caucasian (71.0%), with 25.8% African American, and 3.2% more than one ethnicity. Men and women did not differ on any of these characteristics. All were given a physical exam by study physician to ensure they were healthy, including no contraindications to use of NRT by patch or spray, and not pregnant (women of child-bearing age). Also, those currently being treated for any serious psychological problems (eg, psychosis, major depression) were excluded, as were those with recent exposure to NRT products or e-cigarettes.

NRT and Placebo Patch and Nasal Spray Products

Active NRT

NRT products were selected specifically to equate their expected levels of nicotine exposure at the point of testing. Transdermal nicotine (TN) was administered via Nicoderm 14 mg patch, which produces peak plasma nicotine levels of about 15 ng/mL approximately 3 hours after administration,^{16,17} the point at which session task responding began following patch application (see Procedures). To ensure stability, the patch was applied to the participant's upper arm or back and supported there with cloth tape. We selected the 14 mg patch because that level of blood nicotine is comparable to the level from intermittent 2 mg dosing via nasal spray nicotine (NS) with Nicotrol (0.5 mg/spray, typically two sprays per 1 mg dosing), based on past research¹⁸ and confirmed in our prior study with this same patch and spray dosing procedure.¹⁷ As with blood nicotine levels in our prior study, comparing nicotine via intermittent 2 mg spray versus 14 mg patch,¹⁷ two consecutive administrations of the NS (ie, four sprays, or 2 mg per dosing) presented every 20 minutes in 1 hour should produce plasma nicotine levels of about 14 ng/mL, similar to the 14 mg patch. (A very similar pattern of administering intermittent 2 mg NS produced a mean concentration of 16 ng/mL in an early study.¹⁹)

Placebo

Placebo patches similar in appearance (from 1–800 patches; Salt Lake City UT) were also taped to the subject's upper arm or back, just as with the 14 mg nicotine patch and as in our past studies.²⁰ The placebo nasal spray condition contained no nicotine but did have a very small amount of capsaicin (as in food grade pepper extract) in saline to mimic the brief nasal irritation from Nicotrol. This placebo spray (studied under IND #26872) has also been used frequently in our previous studies.^{17,21}

Reinforcement Task

As in our prior studies of acute nicotine effects on enhancing non-drug reinforcement,² reinforced responding was assessed with a simple computer task ("Applepicker"²²). In brief, participants use arrow keys on the keyboard to move a cursor around a "field" shown on a monitor, pressing a button (one response) whenever the cursor lands on one of the "tree" icons to look for "apples." The number of such responses required to find an "apple" (and earn one unit of the designated reinforcer; see below) constitutes the reinforcement schedule, which is a progressive ratio incrementing by 50% after each completed ratio (ie, PR50%), starting with FR10.

The four 15-minute task trials per session differed in the single reward type made available on each trial. These rewards were presented over the session in counter-balanced order between participants, with that same order used across sessions for the same participant. Also as in our prior research, the available reward types (and unit of each earned reinforcer) were: (1) music (playing 30 seconds of preferred music through headphones), 2) video (playing 30 seconds of preferred video, shown in separate window of monitor), (3) money (counter on monitor incrementing by \$0.10), and (4) no reward (control for nonspecific responding). Each reward's delivery occurred immediately upon completing each ratio. Details for obtaining and verifying the content for each reward, and confirming their comparable reinforcing efficacy, are described elsewhere.^{2,8,11} In brief, the specific music and video rewards were identified individually during the introductory session to ensure that they would be similarly efficacious for participants in subsequent study sessions. Participants provided their own preferred music and identified

preferred video from clips available online (usually comedy routines). They then listened to or watched portions of their music tracks and video clips, rating each (0–100 visual-analog scale, VAS) for “liking.” Those rated >75 were used as available “rewards” for those designated music or video trials in the subsequent experimental sessions. Personalizing these reward items ensures each is clearly reinforcing for that individual (in contrast to assuming the same music and video rewards will be comparably reinforcing in all participants).

Very importantly, participants were instructed to work on the task only as long as they wanted more of the designated reward type. All were told they could stop responding before the end of each 15-minute task period and simply rest quietly or read the available magazines (intentionally of minimal interest to avoid being alternative reinforcers). “Earnings” for each respective reward trial averaged 3.8 minutes of music, 3.7 minutes of video, and \$0.74 for money, or just over seven reinforcers for each reward trial, demonstrating comparable reinforcing efficacy²³ as expected. Mean ($\pm$ SE) durations of responding per 15-minute trial were 8.5 ± 0.7 minutes for music, 7.7 ± 0.5 minutes for video, 8.7 ± 0.8 minutes for money, consistent with the comparable earnings and reinforcing efficacy for each above, and 2.8 ± 0.4 minutes for no reward. These durations show that the point of maximal reinforcing efficacy for each reward was reached well before the end of each trial.

Procedure

At the introductory visit, prospective participants provided written informed consent, identified preferred music and video rewards (see above), and learned the Applepicker task (without access to rewards) to become familiar with it. They later received a physical exam by physician to verify eligibility for study enrollment. Then, they completed three subsequent 2-h experimental sessions following overnight abstinence and differing only in the active (TN, NS) versus placebo patch/spray condition in effect: (1) TN patch + placebo spray, (2) placebo patch + NS spray, or (3) placebo patch + placebo spray. Thus, the three NRT conditions comprised active TN only, active NS only, or double placebo (ie, combined active TN + NS was never administered). The order of these TN, NS, and placebo conditions across sessions was counter-balanced between subjects. Participant compensation for completing the entire study was \$200.

Study Sessions

On each of the three study days, participants first came in for a brief morning initial visit at least 3 hours before the scheduled experimental session testing TN, NS, and placebo effects on reinforced responding. These visits were to provide confirmation of abstinence as instructed, verified by expired-air CO ≤ 10 ppm²⁴ via Breathco CO monitor (Vitalograph, Lenexa, KS), followed by application of the patch condition designated for that day's testing session (TN for one session, placebo patch for two sessions). This procedure allowed sufficient time to reach peak absorption of nicotine from TN in that patch condition upon subsequent arrival to each testing session at least 3 hours later (mid-day). At arrival to the mid-day testing session, CO ≤ 10 ppm was again assessed to confirm continued abstinence, and participants completed the MNWS nicotine withdrawal measure.²⁵

Then, testing of reinforced responding for the different rewards began with the designated available reward identified at the start of each trial. Before each trial, participants were administered four sprays from NS (on one session) or from placebo (on two sessions). Trials lasted 20 minutes each, to provide 2 minutes for controlled administration of sprays, completion of the 15-minute task period,

and 3 minute for brief rest until the next trial. The MNWS withdrawal measure was again assessed at the end of each session to gauge differences due to TN, NS, and placebo conditions. Finally, to check success of blinding to the NRT/placebo conditions, all were asked at the end of each session whether the patch, and separately the spray, contained “nicotine,” “placebo,” or “don't know.” This study protocol was approved by the University of Pittsburgh Institutional Review Board.

Data Analyses

All analyses were conducted using IBM SPSS 24.0. Generalized estimating equations (GEE) with a normal probability distribution and independent correlation structure were used to analyze the main dependent measure of trial behavior reinforced by rewards (number of task responses). Two participants had missing data for the number of responses on one trial each (music reward during the placebo condition and money reward during the nicotine patch condition) due to a computer malfunction. Preliminary analyses found no effects of NRT/placebo condition order, or main effect of sex or interaction of sex $\times$ NRT/placebo condition, on responding across sessions. We also found no significant effects of reward orders on responding across trials within sessions. Finally, as expected given our prior research comparing active versus placebo patch and spray, mean correct identification of the product's nicotine content did not significantly exceed the chance rate of 50%, as correct guesses were 48% for TN patch, and 54% for NS spray.

The primary analysis involved two within-subjects factors: NRT condition (TN, NS, placebo) and type of reward trial (music, video, money, nothing). A priori GEE's were conducted separately for each reward, to test differences between the placebo versus TN or NS conditions (isolating nicotine effects per se). Effects of nicotine were expected to be significant for music and video rewards, and not significant for monetary reward or no reward, based on prior studies of acute nicotine effects via tobacco smoking.^{2,6,8} Pairwise comparisons of the estimated marginal means were used to follow up significant main effects. An exploratory analysis was also conducted to test for any effect of withdrawal relief on responding across rewards and NRT conditions. This additional analysis added within-session change in withdrawal (change from baseline to end of session) to the variables included in the primary analysis as a within-subjects covariate. Withdrawal was also examined using repeated-measures analysis of variance (RM ANOVA), with NRT conditions (3) and time of assessment (2; baseline, end of session) as within-subjects factors. Significant effects in the RM ANOVA were followed up with planned contrasts.

Results

NRT and Reinforcing Value of Rewards

Overall reinforced responding was significantly influenced by the main effect of reward type, Wald χ^2 (3 df) = 79.67, $p < .001$, as responding was comparable across the three rewards and far more than for the no reward control trial (as expected). Consistent with the durations of responding and number of rewards earned (see Methods section), the estimated mean ($\pm$ SE) number of responses per reward were 590.9 (± 55.1) for music, 557.6 (± 55.1) for video, 612.0 (± 67.8) for money, and 160.3 (± 25.3) for no reward. Total responding varied significantly by NRT condition, Wald χ^2 (2 df) = 12.03, $p < .01$, with more responding during both active NRT conditions relative to the placebo condition.

More importantly, the NRT $\times$ reward interaction was also significant, Wald χ^2 (6 df) = 15.34, $p < .05$, indicating varying patterns of responding for the rewards across nicotine conditions. Estimated mean ($\pm$ SE) nicotine-induced responding (ie, the mean difference in responding between each NRT condition vs. placebo) for the music, video, and money rewards is shown in Figure 1. In the a priori GEE's conducted separately for each reward, there was a main effect of NRT condition on reinforced responding for video reward, Wald χ^2 (2 df) = 14.04, $p < .01$. Responding was higher after NS versus placebo, $\beta = 158.10$, 95% CI = [48.63, 267.56], Wald χ^2 (1 df) = 8.01, $p < .01$, and after TN versus placebo, $\beta = 188.23$, 95% CI = [89.71, 286.74], Wald χ^2 (1 df) = 14.02, $p < .001$, while the NS versus TN conditions did not differ from each other, $\beta = 30.13$, 95% CI = [-40.45, 100.70], $p = .40$. These comparisons indicated that nicotine intake per se from NRT spray and patch enhanced reinforced responding for video reward.

Unexpectedly, and contrary to all our prior smoked nicotine studies (but consistent with our study of nicotine via e-cigarettes),^{2,9} there was no main effect of NRT condition on responding for music reward, Wald χ^2 (2 df) = 2.98, $p = .23$. Also contrary to any of our prior nicotine studies was a difference in responding for the monetary reward due to NRT conditions, Wald χ^2 (2 df) = 6.80, $p < .05$. Responding for money was greater after NS versus placebo, $\beta = 109.77$, 95% CI = [24.89, 194.66], Wald χ^2 (1 df) = 8.01, $p < .01$, but, as expected, not due to TN versus placebo, $\beta = 50.42$, 95% CI [-49.38, 150.22], $p = .32$. Finally, however, the main effect of NRT

condition on the low level of responding for the no reward control was not significant, Wald χ^2 (2 df) = 4.24, $p = .12$, as routinely found in our prior research.²

Withdrawal Relief from NRT and Reinforced Responding for Rewards

We also examined differences in withdrawal relief due to the NRT conditions. As anticipated, the NRT condition $\times$ time interaction was significant, $F(2, 60) = 4.85$, $p < .05$. Withdrawal at baseline [which did not differ by condition, $F(2, 60) = 0.71$, $p = .50$] declined significantly by the end of session for NS (24.6 ± 4.0 to 12.7 ± 2.6 , respectively) and TN (20.4 ± 3.3 to 15.5 ± 2.4), but not following the placebo condition (22.1 ± 3.4 to 20.3 ± 2.9), as expected. To directly test whether this withdrawal relief could have influenced the reinforced responding results, perhaps suggesting negative (rather than positive) reinforcing effects of NRT, the primary analyses were repeated including the withdrawal change score as a covariate. Change in withdrawal had no significant effect on responding, Wald χ^2 (1 df) = 0.67, $p = .41$. Similarly, controlling for change in withdrawal did not change any parameters or effects reported above.

Discussion

Results were partly consistent with prior research,⁸ as reinforced responding for video reward was significantly enhanced by nicotine, via NRT spray or patch compared to the placebo spray/patch condition. Consequently, this reinforcement enhancing effect specific to a visual sensory reward from video was due to acute nicotine intake per se from NRT products, and not from behavioral effects of simply using a nasal spray or patch. To our knowledge, this is the first demonstration of reinforcement enhancing effects of nicotine in humans via NRT medication and one of only two on nicotine from a source other than cigarette smoking. Although speculative, enhancing reinforcement from video reward could partly help explain some of the efficacy of NRT spray and patch for quitting smoking, especially since smoking is commonly done while engaged in reinforcing "leisure" activities.²⁶⁻²⁸ Moreover, because visual rewards comprise well over half the nearly 6 h/day U.S. adults typically spend on leisure activities (eg, 3 hours watching TV, 0.5 hour with games or video on computer),²⁹ enhancement of visual sensory reward due to nicotine via NRT would be expected to attenuate most of the loss of reinforcement when trying to remain abstinent from smoking while engaged in such activities, thereby reducing chances of lapsing in those situations.

Our prior research on reinforcement enhancing effects of nicotine via tobacco smoking or electronic cigarettes may help guide future studies to understand the pattern of NRT results we observed here. As noted, these effects of nicotine spray or patch were not found for responding reinforced by the music reward, contrary to hypotheses and to our prior studies manipulating nicotine intake from tobacco smoking. In those studies, smoked nicotine enhanced reinforcement from both video and music sensory rewards, but not from money (nonsensory) or the no reward control.^{6,8} However, we subsequently found that nicotine from e-cigarettes enhanced reinforcement from the video reward, but not from music (or from money or no reward), relative to responding from placebo or no e-cigarettes,⁹ just as in this study with NRT spray and patch. Because the amount of nicotine intake from intermittent e-cigarette administration was likely more modest than via intermittent tobacco smoking, those results could suggest differential sensitivity to dose of nicotine's reinforcement

Figure 1. GEE estimated mean $\pm$ SE nicotine-induced responding for each available reward, by active NRT conditions ($N = 31$). Values reflect the mean difference between each respective NRT condition versus placebo. Responding for video reward, but not music, was significantly increased by the nicotine spray and patch, relative to the placebo condition. Nicotine spray also increased responding for money relative to placebo. ** $p < .01$ and *** $p < .001$ for comparison with placebo condition.

enhancing effects depending on the type of reward made available by responding. In other words, the nicotine dose-dependent curve for increasing reinforced responding may be shifted to the left (ie, greater sensitivity) for video (and other?) reward compared to music reward. In the current study, consequently, the more modest nicotine dosing obtained from the intermittent Nicotrol spray or the 14 mg Nicoderm patch, relative to that from intermittent tobacco smoking, may have been sufficient to increase responding for video reward but not music reward. Notably, recent research with rodents has shown enhanced responding for a visual reinforcer after very low nicotine dosing, regardless of speed of administration,³⁰ consistent with the notion that reinforced responding for video reward here may be enhanced by doses lower than those required to enhance responding for music reward.

Perhaps also relevant is our prior study showing that highly preferred, but not moderately or less preferred, music reward was enhanced by nicotine from a full cigarette, but not by intake from a half cigarette or less.⁷ Another potential influence may be individual differences, as the neural basis of individual differences in reward sensitivity to music has been identified,³¹ suggesting the same dose of nicotine may likely enhance reinforced responding for music in some smokers but not others. These observations raise the question of what amount of nicotine intake is needed to enhance reinforcement from which types and magnitudes of rewards, and in those with which individual difference characteristics. Nicotine's effects on striatum may be relevant to explaining potentially greater sensitivity to nicotine across reward types, as visual rewards may differentially activate striatum compared to other available rewards.^{32–34} Further research that explicitly manipulates a range of nicotine doses before testing, such as via 21 mg or even higher dose patches³⁵ as well as carefully controlled dosing by other means,³⁶ would be necessary to confirm this possible explanation for the pattern of nicotine results across types of reward in these studies with nonsmoked nicotine products of e-cigarettes and NRT.

Also consistent with preclinical studies^{1,3,30} was that the speed of nicotine uptake did not appear to differentially influence reinforced responding for nondrug rewards, as findings were generally the same for nicotine rapidly administered by spray or very slowly by patch, compared to the placebo spray/patch condition. Thus, differential speed of nicotine delivery from spray versus patch did not affect our results for responding reinforced by most of the available rewards. Yet, we did see greater responding for money due to nicotine from NRT spray but not patch, the first time we have ever seen a nicotine effect on monetary reinforcement.² Because smoked or e-cigarette (or patch) nicotine has not been shown to increase responding for money, dose or delivery speed is unlikely to be relevant here. In sum, results here require replication and parametric study to determine if nicotine may reliably increase responding for a broader array of nonsensory (money) rewards, and what magnitude of such rewards would be necessary.

Strengths of the study include the first direct test, to our knowledge, of the reinforcement enhancing effects of nicotine in humans from NRT medications. Use of matching non-nicotine (placebo) spray and patch aided comparison due to nicotine intake per se from NRT administration. Assessment of withdrawal relief due to NRT conditions allowed us to verify that nicotine's negatively reinforcing effects did not appear relevant to explaining its effects on enhancing reinforcement from the rewards. We also confirmed smoking abstinence before each session, and equal reinforcing efficacy across the three rewards available for responding on separate trials. In terms of

limitations, we do not have data on plasma nicotine levels after NRT spray or patch administration to confirm dose and speed of nicotine delivery, but such plasma concentrations from our prior study with these same spray and patch administration procedures showed virtually identical levels,¹⁷ as noted previously. The generalizability of our findings to clinical effects of NRT may be limited due to study here of smokers not seeking treatment. These volunteers were tested for practical and ethical considerations given the within-subjects design, and due to the brief use of each product over several hours rather than over days and weeks in those attempting to quit smoking.

In any case, these findings extend prior results with tobacco and electronic cigarettes to partly confirm specificity of reinforcement enhancing effects of nicotine per se in humans, using FDA-approved NRT medications. Combined with prior studies of nicotine via smoking or via e-cigarettes, this study points to differential dose-response effects of nicotine on enhancing reinforcement between types of sensory reward (video vs. music). If confirmed in future research carefully manipulating dosing, results could further help explain why adhering to regimens of regular use of higher dose NRT products improves success with abstaining from cigarette smoking.^{37,38} Specifically, NRT use would limit loss of these reinforcement enhancing effects of nicotine after attempting to quit tobacco,² although such use also very clearly blunts withdrawal symptoms that foster relapse.³⁹ Research should also expand testing to other types of nicotine-containing NRT products that may enhance non-drug reinforcement in humans (eg, lozenge, inhaler, gum), as well as other nonmedicinal products, especially those with high doses (eg, hookah), and to evaluating the conditions under which this occurs.

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Declaration of Interest

None declared.

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