Original Investigation

Mood, nicotine, and dose expectancy effects on acute responses to nicotine spray

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Abstract

Introduction: We recently showed effects of nicotine dose and nicotine expectancy on some responses to cigarette smoking, with generally no influence of induced mood on these effects. The present study extended this line of research to Nicotrol nasal spray, to determine whether formulation (spray vs. smoking) alters responses.

Methods: Smokers abstained overnight before each of two virtually identical sessions, involving negative or positive mood induction. They were randomized to one of five groups, four comprising the 2×2 balanced placebo design, varying actual and expected dose of nicotine in the nasal spray, and the fifth group a no-spray control. Dependent measures included self-reported affect, craving, withdrawal, and spray ratings of “liking” and “how much nicotine.” Analyses were limited to those whose nicotine expectancies were manipulated successfully ($N = 48$).

Results: The following results matched those from our smoking study: expecting nicotine increased liking; expected, but not actual, nicotine dose increased dose perception; neither actual nor expected nicotine dose had much influence on affect or withdrawal; and mood had no influence on these effects. However, both actual and expected nicotine dose decreased craving in response to spray, contrary to our prior study with smoking.

Discussion: Formulation made little difference in some effects of nicotine and expectancies, but other effects differed by formulation. Some of these findings, particularly for craving reduction, may have implications for enhancing the acute therapeutic effects of nasal spray and, perhaps, other medications in smokers trying to maintain abstinence after quitting.

Introduction

A major nonpharmacological influence on responses to drug use is the user's expectations about what he or she will experience when using the substance, formally termed “response expectancies” (Kirsch, 1997). Response expectancies are determined substantially by “stimulus expectancies” or the belief that one is consuming a substance that contains a drug or no drug (Kirsch, 1997; Perkins, Sayette, Conklin, & Caggiula, 2003). A procedure often used to manipulate stimulus expectancies is the “balanced placebo design” (BPD; Marlatt & Rohsenow, 1980). In the BPD, participants are assigned to one of the four combinations of actual (given drug vs. given no drug) and expected (expecting drug vs. expecting no drug) drug content of the substance they receive, for a 2×2 between-subjects manipulation. Using this approach, we found that expectancy for nicotine influenced cigarette reward and the perceived nicotine content of that cigarette more than the actual nicotine dose in the cigarette (Perkins et al., 2008a).

Nonpharmacological factors other than expectancies also may influence responses to substance use. In the same study (Perkins et al., 2008a), we found that the physical act of inhaling cigarette smoke, in the absence of actual or expected nicotine, acutely relieved craving. This nonexpectancy influence may result from unconditioned responses to sensory smoke stimuli or from conditioned responses unmediated by expectancies (Rose, 2006). To add further complexity, these influences may not be static but can be modulated further by acute situational factors, such as the smoker's mood (Brandon, Juliano, & Copeland, 1999; Sayette, Loewenstein, Kirchner, & Travis, 2005). Nicotine is commonly believed to be more reinforcing during negative mood due to its ability to alleviate negative affect (NA) (Kassel, Stroud, & Paronis, 2003). However, in our study (Perkins et al.,

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2008a), we found no influence of negative versus positive mood on the effects of actual or expected nicotine, although negative mood increased smoking reinforcement regardless of actual or expected nicotine.

In the present study, we sought to determine whether these various nonpharmacological and pharmacological effects observed in our earlier study with cigarette smoking, an abused form of nicotine, extend to nicotine delivery via nasal spray (Nicotrol), a novel medicinal form of the drug used as a nicotine replacement therapy (NRT). Differences between findings with nasal spray in the present study versus cigarette smoking in our prior study could provide important information on how nonpharmacological influences on responses to nicotine intake vary by formulation (Juliano & Brandon, 2004; Moerman, 2002). Such influences also could be exploited in smoking cessation treatment to enhance therapeutic effects of NRT.

Methods

Participants

Participants were 97 young adults (53 men, 44 women) who smoked at least 10 cigarettes per day for at least 1 year and had no prior experience with Nicotrol nasal spray. They were recruited from the surrounding community and were paid for their participation. After providing informed consent, participants completed measures of smoking and health history to verify eligibility. Mean (*SE*) characteristics were as follows: age of 28.7 (1.0) years, nicotine yield of preferred brand of 0.95 (0.02) mg, smoking rate of 16.0 (0.5) cigarettes/day, and score of 3.9 (0.2) on the Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991). Ethnicity of the sample was 78.4% White, 13.4% Black, 3.1% Asian, and 2.1% American Indian or Alaska native, with the rest more than one ethnicity.

Negative and positive mood induction procedure

The mood induction procedure has been described in detail elsewhere (Conklin & Perkins, 2005; Perkins et al., 2008a). Briefly, this procedure altered an existing mood manipulation technique (Goodwin & Sher, 1993), involving the combination of pictorial slides from the International Affective Picture System (Lang, Ohman, & Vaitl, 1988) and mood-congruent classical music. Slides were presented for 12 s each as musical selections played. Only one or the other mood type was presented on a given day (negatively valenced slides and music for negative mood induction, positively valenced slides and music for positive mood induction), following an adaptation period involving neutrally valenced slides and music.

Nasal sprays

The active spray was Nicotrol nasal spray (1.0 mg nicotine; Pfizer Inc.), and the placebo spray contained capsaicin to match the sensory irritating effects of Nicotrol but with no nicotine (see Perkins, Jacobs et al., 2004; Perkins, Lerman, Keenan, Fonte, & Coddington, 2004). Arterial nicotine levels rise quickly after spray delivery and peak within 5 min (Gourlay & Benowitz, 1997).

Dependent measures

Affect, craving, and withdrawal. Affect was assessed with the Diener and Emmons (1984) Mood Scale, yielding positive affect (PA) and NA scores. Craving was assessed with the four-item version (Carter & Tiffany, 2001) of the Questionnaire on Smoking Urges (Tiffany & Drobes, 1991). Nicotine withdrawal was assessed by the scale developed by Hughes, Gust, Skoog, Keenan, & Fenwick (1991).

Spray reward and nicotine perception. The reward value, or "liking," of the spray was assessed using an item asking, "How much do you like the spray?" Perception of nicotine content was assessed with an item asking, "How high in nicotine is this spray?" (This item was different from the expectancy measure, which offered only a dichotomous choice; see below.)

Check of manipulation of nicotine expectancy

After their initial exposure to the nasal spray (see procedure below), participants in the spray groups were asked to circle on a form either "yes" or "no" to a question asking, "Do you think this spray contains nicotine?" This dichotomous choice measure was similar to that used in our prior study of expectancy in cigarettes (Perkins et al., 2008a) and was designed to determine whether participants believed the instructions they were given about the nicotine content of the nasal spray. During analyses, we also related responses to this question to scores on the 20-item Balanced Inventory of Desirable Responses–Impression Management scale (BIDR-IM; Paulhus, 1991), a measure of socially desirable responding, which participants completed during screening. This comparison enabled us to determine whether participants' self-reported belief in dose instructions captured their true beliefs about the spray or simply reflected demand characteristics of the study (i.e., subjects' desire to respond in the way they believe the experimenter wants).

Procedure

Procedures mirrored those of our prior study with smoking (Perkins et al., 2008a) to facilitate comparison of results between studies. Participants engaged in two sessions, each preceded by overnight (>12 hr) smoking abstinence, confirmed by an expired-air carbon monoxide level of less than 10 ppm. Sessions differed only by the mood induction condition, positive or negative. Participants were randomly assigned to one of five groups, either a no-spray control condition ($n = 14$, 7 men and 7 women) or one of the four expected or actual nicotine dose conditions in the 2×2 BPD: expected nicotine/given nicotine ($n = 18$, 10 men and 8 women), expected nicotine/given no nicotine ($n = 22$, 12 men and 10 women), expected no nicotine/given nicotine ($n = 25$, 14 men and 11 women), and expected no nicotine/given no nicotine ($n = 18$, 10 men and 8 women). Group assignment remained the same for both sessions, although participants were not told this. Randomization called for assignment of more subjects to the groups involving conflicting expected versus actual dose conditions because of the likelihood that fewer in these groups would believe the dose instructions and, thus, hold the intended expectancies (Perkins et al., 2008a). Analyses of expectancy effects are limited to those subjects whose expectancies were manipulated successfully.

At each session, participants first rested quietly and completed baseline measures of affect, withdrawal, and craving. They were then presented with neutral mood slides and neutral music for 4 min, followed by the mood induction condition assigned for that day, either negative or positive slides and music, for 4 min. Repeat assessment of affect, withdrawal, and craving was obtained (post-mood induction 1 [PI1]). Those assigned to the four nasal spray groups were presented with the designated spray (nicotine vs. no nicotine) and, depending on group assignment, were given the following dose instructions via computer screen:

Participants in the “expected nicotine” groups were informed: “You will be using a nicotine spray product designed to help people quit smoking” and “that contains nicotine.” Participants in the “expected no nicotine” groups were informed: “You will be using a placebo spray that is not expected to help people quit smoking” and “that contains no nicotine.” Participants in the spray groups then received two sprays, one in each nostril (spray exposure period). Two sprays of the Nicotrol bottle deliver the recommended dose of 1.0 mg nicotine. Two minutes later, participants rated the spray for reward and nicotine perception and completed the dichotomous item assessing the manipulation of nicotine expectancy. For all five groups, the negative or positive mood induction then continued for 4 min, followed by final assessment of affect, withdrawal, and craving (post-mood induction 2 [PI2]). This study was approved by the University of Pittsburgh Institutional Review Board.

Data analyses

Affect, craving, and withdrawal measures were assessed at three timepoints: baseline; PI1, before spray exposure; and PI2, after spray exposure (PI2). Changes across timepoints determined the effects of mood induction alone (baseline to PI1) and of brief spray exposure during one mood or the other (PI1 to PI2). Spray reward and nicotine perception were assessed once, just after spray exposure. All analyses were collapsed across sex to conserve statistical power for analyses of primary interest and because our prior study of BPD effects with smoking found no interactions with sex (Perkins et al., 2008a). We first examined whether the mood manipulation worked by conducting an analysis of variance (ANOVA) on the change in affect from baseline to PI1 as a function of negative versus positive mood (i.e., within subjects). We also examined the success of the expectancy manipulation by identifying those participants in each of the four spray groups who believed the instructions designated for their group, based on their response to the manipulation check item described previously. Subsequent analyses were limited to those who believed their dose instruction on both days (i.e., whose nicotine expectancies were manipulated successfully). This was done because BPD effects (the separate and combined influences of actual and expected nicotine dose) cannot be examined clearly without successful manipulation of expectancies about drug dose (Hull & Bond, 1986; Martin & Sayette, 1993). Otherwise, varying dose instructions has little meaning.

Then we addressed the three main questions of interest (in the context of negative vs. positive mood): (a) What are the simple effects of nasal spray use (without actual or expected nicotine) versus no spray on affect, withdrawal, and craving? (b) Among those who use a nasal spray, what are the effects of actual and expected nicotine intake (i.e., the BPD) on these

measures? (c) Among those who use a nasal spray, what are the effects of actual and expected nicotine intake on spray reward and nicotine perception? To address the first question, we used ANOVA to compare responses from pre- to post-spray exposure (PI1 to PI2) for the group who both believed and received no nicotine in the spray (i.e., absence of both actual and expected nicotine) with those for the no-spray controls. Mood context was a within-subjects factor. The second question, on affect-related responses to the BPD manipulations, was analyzed via ANOVAs involving the four spray groups. The between-subjects factors were nicotine expectancy and actual nicotine, whereas the within-subject factors were time (PI1 to PI2) and mood. Because our focus here was on acute responses to spray, only interactions involving time were of interest. We hypothesized the existence of interaction effects of time with actual nicotine and with nicotine expectancy and that these effects would be greater under negative versus positive mood. Similar ANOVAs were performed to address the third question, the effects of the BPD on spray reward and nicotine perception as a function of mood, except there was no within-subjects factor of time since these measures were obtained just once. We hypothesized the existence of main effects of actual and expected nicotine and interactions of each with mood.

Results

Check of manipulations

Mood. In the ANOVAs of change from baseline to PI1 due to negative versus positive mood, the mood $\times$ time interaction was significant for all measures: $F(1, 94) = 39.68, 67.60$, and 23.94 , for NA, PA, and withdrawal, respectively (all $p < .001$), and $F(1, 94) = 6.34, p < .05$, for craving. We found no differences among the groups in these responses to mood induction prior to nasal spray exposure. Thus, the mood induction manipulation was successful in producing different levels of NA and PA.

Nicotine expectancy. The percentages of those in the four spray groups who responded on the expectancy check measure in a manner consistent with dose instructions (i.e., “believers”) during negative and positive mood, respectively, and the resulting sample sizes in the analyses, were as follows: expected nicotine/given nicotine, 78% and 78% ($n = 11$); expected no nicotine/given no nicotine, 89% and 83% ($n = 13$); expected nicotine/given no nicotine, 55% and 64% ($n = 9$); and expected no nicotine/given nicotine, 84% and 64% ($n = 15$). The vast majority of subjects in three of the groups believed their instructions, the same as in our prior study of nicotine expectancy due to mood induction using cigarettes (Perkins et al., 2008a). However, only about 60% of those told they were receiving a nicotine spray but given the spray without nicotine believed their dose instructions, compared with 72.5% of those in this condition in our prior study (Perkins et al., 2008a). The present results demonstrate the challenge of executing the full BPD for nicotine via nasal spray. As stated, only those whose expectancies were congruent with their dose instructions on both days were included in the subsequent analyses. Comparisons between those who did versus did not believe their dose instructions showed no differences in cigarettes per day, $F(1, 64) < 1$; FTND score, $F(1, 64) = 1.39$, nonsignificant (ns); nicotine yield of preferred brand, $F(1, 64) < 1$; or score on the social desirability measure, the BIDR-IM, $F(1, 64) = 1.12, ns$. Thus, belief in dose instructions did not

appear to be systematically related to characteristics that might influence responses to nicotine or expectancy.

Question 1: Effects of spray use versus no spray as a function of mood

Responses to negative and positive mood induction on affect, withdrawal, and craving are shown in Figure 1 for all five groups. In addressing the first question, we compared responses for the group who both believed and received no nicotine in the spray (i.e., absence of both actual and expected nicotine; $n = 13$) with those for the no-spray controls ($n = 14$). We found no significant differences in responses between these two groups, suggesting that the simple sensory effects of nasal spray use, without actual or expected nicotine, did not influence these responses.

Question 2: Effects of actual and expected nicotine on responses as a function of mood

As shown in Figure 1, there were no interaction effects of time with either actual nicotine or expectancy, or with both (i.e., triple interaction), on affect. An effect of mood $\times$ time was observed for withdrawal, $F(1, 40) = 9.86, p < .01$, but not for craving, as withdrawal decreased over time under positive ver-

sus negative mood induction. Yet craving, but not withdrawal, was influenced by the interactions of time $\times$ nicotine, $F(1, 40) = 8.62, p < .005$, and time $\times$ expectancy, $F(1, 40) = 4.13, p < .05$. Actual nicotine and expectancy each decreased craving after nasal spray exposure, regardless of mood (Figure 1). No other interactions were significant.

Question 3: Effects of actual and expected nicotine on reward as a function of mood

As shown in Figure 2, spray reward (liking) was increased by nicotine expectancy, $F(1, 40) = 12.60, p < .001$, but decreased by actual nicotine, $F(1, 40) = 5.36, p < .05$. Nicotine perception ("how much nicotine") was similarly increased by nicotine expectancy, $F(1, 40) = 79.29, p < .001$, but only marginally increased by actual nicotine, $F(1, 40) = 3.24, p < .10$ (Figure 2). No other effects, including those of mood, were significant for reward or perception.

Discussion

Several findings from the present study were consistent with our prior study of mood, nicotine, and expectancy effects in cigarette smoking (Perkins et al., 2008a). First, expecting nicotine

Figure 1. Mean negative and positive affect, withdrawal, and craving in all five groups across timepoints during negative mood induction (top) and positive mood induction (bottom). Shown here are only those participants within the four spray groups who believed their dose instructions and, thus, whose dose expectancies were manipulated successfully, under both mood conditions ($N = 48$). As noted in the text, expectancy for nicotine (a, $p < .05$) and actual nicotine (b, $p < .005$) significantly decreased craving regardless of mood, but no other effects were observed, including between the no-spray group and the group receiving and expecting the no-nicotine spray. BL, baseline; PI1, post-mood induction 1 (before spray exposure); PI2, post-mood induction 2 (after spray exposure).

Figure 2. Mean (SE) ratings of “liking” (spray reward) and “how much nicotine” (dose perception) after brief spray exposure, as a function of actual (given) and expected nicotine dose. Main effects of expectancy were seen for both measures (both $p < .001$), whereas the main effect of actual nicotine ($p < .05$) was significant only for liking.

increased liking of nasal spray in the present study, as it did via smoking. Second, as with smoking, neither actual nor expected nicotine dose had much influence on affect or withdrawal following brief spray exposure (see Figure 1). Third, as in our smoking study, nicotine expectancy, but not actual nicotine, significantly increased perception of nicotine via spray (see Figure 2). Fourth, mood had little influence on these effects in either study, suggesting that mood per se may not be a contextual factor that alters nicotine expectancy effects, although other methods of manipulating mood should be examined to determine the breadth of this conclusion (Brandon et al., 1999; Copeland, Brandon, & Quinn, 1995). Finally, we found that manipulating nicotine expectancies that conflict with the actual nicotine dose administered was at least as difficult with nasal spray compared with cigarette smoking (Perkins et al., 2008a).

However, a few findings differed by formulation. Contrary to the effects of smoking without nicotine or expectancy (vs. no smoking) in our prior study, mere spray use without nicotine or expectancy (vs. no spray) did not attenuate craving (see Figure 1). This finding suggests that stimuli accompanying smoking but not nasal spray acutely relieve some symptoms, either because of qualitative differences in the smoke versus spray stimuli or because of conditioned responses to smoking stimuli that are absent with nasal spray use in smokers naive to the spray. Second, expecting nicotine, as well as actual nicotine, acutely decreased craving in response to spray (see Figure 1), contrary to our prior smoking study but somewhat consistent with a BPD study of smoking during a stressor (Juliano & Brandon, 2002). Such expectancies could be exploited in smokers using NRT to alleviate craving and, perhaps, aid cessation (Fucito & Juliano, 2007; Juliano & Brandon, 2004). Third, liking was decreased by actual nicotine in spray (see Figure 2); in our prior study, liking was increased by actual nicotine in cigarettes.

Strengths of the present study included the close similarity between its procedures and those of our prior smoking study, the robust mood induction procedure, analyses of only those subjects whose dose expectancies were manipulated successful-

ly, and use of Nicotrol, the commercially available nasal spray NRT, to increase the clinical applicability of our findings. This study also had several limitations. First, the number of participants whose expectancies were manipulated successfully proved to be small, compromising statistical power. Consequently, although many of our findings were consistent with prior studies of smoking, involving much larger samples, some of our null results could be due to inadequate power. Second, the timing of the reward and perception measures, as well as the expectancy manipulation check, was 2–3 min after the nasal spray exposure, just before rather than after peak arterial levels (Gourlay & Benowitz, 1997). Third, only one spray administration was provided, and the effects of nicotine and dose expectancy may differ with more extended nasal spray exposure, as subjects adapt to the aversive effects and acquire conditioned responses to spray use. Fourth, our participants were smokers not trying to abstain from smoking with the use of NRT, and responses to nasal spray nicotine may be greater in smokers who are trying to quit permanently (Perkins, Stitzer, & Lerman, 2006; Perkins et al., 2008b).

In conclusion, although formulation made surprisingly little difference in some acute effects of nicotine and expectancies, manipulations of actual and expected nicotine dose influenced craving during nasal spray administration in the present study but not during cigarette smoking in our prior study. Yet, in the absence of actual or expected nicotine, spray use had no influence on craving, unlike with smoking. Mood had little influence on these responses regardless of nicotine formulation. Not clear is whether these differences are inherent in the formulations or could be minimized with repeated exposure to the spray and adaptation to its aversive sensory effects, as smokers adapt to aversive effects of smoking with continued experimentation as teens (Eissenberg & Balster, 2000). These results, particularly for craving, may have implications for improving acute symptom relief in smokers abstaining with the use of NRT. Future research in larger samples should explore whether these effects vary with other NRT formulations, as well as with more extended NRT use and in smokers attempting to quit permanently (Fucito & Juliano, 2007).

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Declaration of Interests

None declared.

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