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# Pulmonary Delivery of Nicotine Pyruvate: Sensory and Pharmacokinetic Characteristics

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The aim of this study was to evaluate pharmacokinetic and subjective responses to a prototype nicotine pyruvate (NP) aerosol generation system. In nine healthy adult daily cigarette smokers, plasma nicotine levels and subjective responses were assessed after double-blind administration of 10 inhalations of: NP (10 μg/puff, 20 μg/puff, and 30 μg/puff); Nicotrol/Nicorette nicotine vapor inhaler (NV) cartridge; and placebo (room air). Plasma nicotine concentrations increased to a significantly greater extent after inhalations of 20 μg/puff or 30 μg/puff NP (by 5.0 ± 3.4 ng/ml and 8.3 ± 3.1 ng/ml) than after placebo and NV conditions. Satisfaction ratings were higher for all NP conditions than for placebo, and harshness/irritation was lower for the NP 20 condition than for the NV control condition. Pulmonary function showed no adverse changes. These results demonstrate that NP inhalations produce rapid increases in plasma nicotine concentrations, provide satisfaction and are well tolerated. At the 20 μg/puff dose, peak nicotine concentrations were higher than with the Nicotrol/Nicorette nicotine vapor inhaler cartridge. Further trials of this promising nicotine inhalation technology are warranted to assess its safety and efficacy in smoking cessation treatment or harm reduction approaches.

*Keywords:* nicotine, smoking cessation, tobacco, aerosol, pyruvic acid

The annual death toll from diseases caused by smoking is estimated to be 440,000/year in the United States (*Smoking-attributable mortality*, 2008) and 5 million/year worldwide (Ezzati & Lopez, 2003). Smoking cessation leads to a substantial reversal of the risks borne by smokers (Kenfield, Stampfer, Rosner, & Colditz, 2008; Papathanasiou et al., 2007), and thus, smoking cessation treatment assumes a primary role in the prevention of smoking related disease. However, current smoking cessation treatments have limited effectiveness. Long-term (>1 year) abstinence rates are often less than 25%, despite the advent of new pharmacotherapies such as varenicline and bupropion (Fant, Buchhalter, Buchman, & Henningfield, 2009; Fiore et al., 2008). Nicotine replacement therapy (NRT) continues to be one of the mainstays of smoking cessation treatment (Schnoll et al., 2009), and is the only pharmacotherapy

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approved for over-the-counter (OTC) sales. Nonetheless, long term success rates in an OTC setting remain low, typically less than 10% (Hughes, Shiffman, Callas, & Zhang, 2003).

To overcome the limited effectiveness of NRT, it will be necessary to recognize and address a major shortcoming of current NRT products; that is, these products do not provide smokers with rapid absorption of nicotine in conjunction with the unique respiratory tract sensory cues accompanying nicotine inhalation. These inhalational cues, along with the delivery of nicotine, are of primary importance in effectively relieving smokers' craving for cigarettes (Rose, 1988). Indeed, nicotine administered without airway sensory cues only slightly suppresses craving for cigarettes (Rose, Behm, Westman, & Johnson, 2000; Rose, Behm, Westman, Bates, & Salley, 2003). Moreover, blockade of airway sensations during cigarettes smoking markedly reduces the relief of craving after inhaling cigarette smoke (Rose, Tashkin, Ertle, Zinser, & Lafer, 1985; Rose, Westman, Behm, Johnson, & Goldberg, 1999). Conversely, presentation of airway sensory cues has been shown to reduce craving for cigarettes and facilitate smoking cessation (Rose & Hickman, 1987; Westman, Behm, & Rose, 1995).

Current forms of NRT, however, fail to provide these important inhalational components of cigarette smoking, thereby limiting their efficacy as cessation therapies. For example, the nicotine nasal spray, although it is a rapid-acting NRT, lacks the inhalational cues of cigarette smoke, and has aversive irritating properties; these deficiencies, along with restrictions in access because of prescription requirements, have impeded widespread acceptance by smokers. Similarly, the nicotine vapor inhaler, while simulating the behavioral components of smoking and presenting some sensory cues resembling those of cigarette smoke, provides a much lower dose of nicotine, which is slowly absorbed through the buccal mucosa without reaching the lung in significant amounts (Lunell, Bergstrom, Antoni, Langstrom, & Nordberg, 1996; Lunell, Molander, Ekberg, & Wahren, 2000; Schneider, Olmstead, Franzon, & Lunell, 2001).

Thus, there is a gap in the field of current NRT products that could be filled with a rapid-acting, lung delivery nicotine inhaler having acceptable sensory properties. Such an inhaler, which does not deliver other toxic smoke constituents, could hold great promise for assisting smokers in breaking their addiction to cigarettes, as well as reducing the harm associated with cigarette smoking. This study reports the completion of the first step in establishing the feasibility of a novel approach to nicotine replacement therapy that delivers nicotine to the lung by inhalation (Rose, Rose, Turner, & Murugesan, 2008). This approach stems from our discovery that nicotine vapor when combined with the vapor of pyruvic acid, a weak organic acid normally present in all living cells, forms a stream of submicron airborne particles consisting of nicotine pyruvate (NP) salt. Unlike other existing approaches to generating a nicotine aerosol, no combustion, heat or propellant is necessary to produce the nicotine containing particles. Measurements conducted in our laboratory prior to human testing showed that a greater amount of nicotine can be delivered in standard 35-ml puffs than with nicotine vapor alone. Additionally, it was anticipated that NP aerosol would avoid the irritation associated with inhalation of pure nicotine base (Caldwell et al., 2009; Lee, Gerhardstein, Wang, & Burki, 1993), for two reasons: (1) the near-neutral pH of NP was expected to attenuate the irritating effect of pure nicotine base (Armitage & Turner, 1970; Lux & Frecker, 1988); and (2) the small diameter of the NP particles should result in their deposition over the large surface area of the lung rather than being concentrated in a small region of the trachea, which can elicit irritation and cough (Huchon, 1990; Katz, Schroeter, & Martonen, 2001; Usmani, Biddiscombe, & Barnes, 2005). Lung deposition is difficult to achieve using metered dose inhalers or dry powder delivery systems, having particle sizes well above 1 μm. To gain alveolar entry and deposition of particles with consequent rapid absorption, we speculated particles would need to be similar in size to cigarette smoke particles (<1 μm). Particles of the NP aerosol have an average mass median aerodynamic diameter (MMAD) of 0.62 μm, as estimated by cascade impactor measurements (unpublished data), small enough to be almost totally inhaled deep into the lung, ensuring rapid absorption.

Pyruvate, as sodium pyruvate, has been inhaled at a dose of 0.65 mg pyruvate per day to treat chronic obstructive pulmonary disease (Votto, Bowen, Barton, & Thrall, 2008), and in this study 0.76 mg in total was used per subject. Pyruvate is rapidly metabolized, and it was unlikely that inhalation in such doses would alter the physiological level of 0.44 mg/100 ml blood (Landon, Fawcett, & Wynn, 1962). The acute risk profile of NP was thus assumed to be similar to that of nicotine alone.

This study was an initial investigation in which 9 smokers were exposed to several doses of NP aerosol administered by inhalation, and an active control condition, the Nicotrol/Nicorette nicotine vapor (NV) inhaler cartridge, as well as an inactive placebo (air). Venous plasma nicotine levels and subjective responses were assessed. The study had three main aims: (1) to determine whether NP inhalation would produce higher and more rapid boosts in plasma nicotine concentrations than the control conditions; (2) to evaluate the efficacy of NP inhalations relative to the control conditions in providing satisfaction and alleviating subjective withdrawal symptoms (e.g., craving reduction); and (3) to evaluate the safety and tolerability of acute NP administration, based on subjective reports or airway irritation and objective measurement of pulmonary function using spirometry.

## Materials and Methods

### Study Design

This was a preliminary, double-blind, placebo controlled, crossover evaluation of the effects of inhaling NP aerosol on plasma nicotine concentrations, subjective relief of smoking withdrawal symptoms and indices of tolerability and safety. Because the primary pharmacokinetic end point was defined as the *increase* in plasma nicotine in the first 5 min, immediately after the tenth puff, one condition could feasibly be

studied every 50 min. This design was consistent with the distributional half life of nicotine (9 min; Feyerabend, Ings, & Russell, 1985), and with the expectation that maximum plasma levels per dose inhaled would be relatively low, minimizing carryover effects.

A prototype aerosol delivery system was assembled, loaded, and calibrated to deliver successively to each participant five different conditions during the morning of the study day, a different condition administered every 50 min. Three of the conditions involved administering the NP test medications: either 10 μg, 20 μg, or 30 μg of NP per 35 ml puff. In the remaining two conditions, approximately 10 μg of nicotine per puff was supplied from a Nicotrol/Nicorette inhaler cartridge (the active control), or room air was supplied (the inactive control or placebo). To minimize the likelihood of adverse events, the NP doses were presented in ascending order from 10 μg to 20 μg to 30 μg per puff, whereas the control conditions were arranged in a counterbalanced sequence alternating with the 3-sequence block of NP conditions.

### Test Medications

Pyruvic acid of 97% purity was obtained from Sigma-Aldrich Inc. (St. Louis, MO/USA) and stored at 4 °C. Nicotine free base USP with a claimed 99.5% purity, retested at the Center for Nicotine and Smoking Cessation Research (CNSCR) at Duke University, was also stored at 4 °C. For operation of the NP delivery system, all constituents needed to be at room temperature. The prototype components were loaded with NP 10, 20, or 30 or with the NV cartridge at the CNSCR and tested for stability before shipping for assembly at the study site at Christchurch Clinical Studies Trust (CCST), Christchurch, New Zealand. The NV cartridges were purchased in the United States and shipped to New Zealand. When assembled before use, the seal around the cartridge was punctured in order to allow nicotine vapor to be released. CCST staff was trained in the inhalation procedures by means of detailed training diagrams and instructions, as well as a site visit from CNSCR (by coauthor TM).

### Puff Delivery Apparatus

Measured dose inhalations were delivered by an electric powered motorized syringe pump and 60-ml syringe connected to a 3-way valve. The pump was timed to draw in 35-ml room air over 2 s and then expel the air out through the aerosol delivery system for each condition and every puff. The subject inhaled through the same mouthpiece for all puffs and conditions. In the placebo condition, when the participant puffed on the mouthpiece, air was inhaled through an empty tube, which contained a cigarette filter to provide draw resistance. Before each inhalation, while the motorized syringe pump drew in air, the subject exhaled into room air. When the pump expelled air into the delivery system the subject inhaled the measured 35-ml volume through the mouthpiece, and completed the inspiration from room air, followed by a 5-s breath hold before exhaling into the room air. A total of 10 puffs were taken at 30-s intervals, requiring a total of 5 min.

The motorized syringe system and the known dose in each prototype were first tested without human subjects to measure the average nicotine delivery per puff over 10 puffs of 35 ml. In these tests, particulate matter or nicotine vapor was collected by filtration through a Cambridge 44-mm diameter high-efficiency filter contained in a holder. These samples were shipped on ice and analyzed at Duke CNSCR using Gas Chromatography (Agilent GC-HP6890 series with Nitrogen Phosphorus Detector (Agilent Technologies Inc. Santa Clara, CA). Based on five determinations for each condition, the three NP aerosol conditions were found to deliver an average of 10.3 μg/puff ($SD$ = 1.66), 23.7 μg/puff ($SD$ = 3.39), and 33.0 μg/puff ($SD$ = 0.63) of nicotine. These conditions will be referred to below as "NP 10," "NP 20," and "NP 30," respectively. Based on three determinations, the nicotine vapor condition ("NV") delivered 9.1 μg/puff ($SD$ = 0.64), which agrees to within 10% of the value reported previously (Schneider et al., 2001).

### Aerosol Generation Apparatus

The delivery system used to generate the NP aerosol (Figure 1) consisted of a cylindrical translucent Teflon tube outer housing (11 cm long, 11-mm inside diameter [ID], and 13-mm outside diameter [OD]) containing three elements arranged in a series. The first component, where the airstream entered (distal to the mouth), consisted of a porous polypropylene/polyethylene filter loaded with 140 μl of pyruvic acid. The second component consisted of a Teflon washer (11-mm OD), having one, two, or three cylindrical openings (3.5-mm ID) that allowed air to flow through the washer. Depending on the nicotine dose condition, the number of openings that contained a nicotine-loaded membrane (60 μl Nicotine base) versus empty openings were either: 0 loaded/3 empty (placebo), 1 loaded/1 empty (NP 10), 1 loaded/0 empty (NP 20), or all three loaded with nicotine (NP 30). These configurations were derived empirically based on benchtop measurements of nicotine deliveries from the system. The loading was accomplished by inserting a piece of nicotine-loaded membrane (nonwoven polyester membrane with an expanded PTFE membrane backing, 6 cm long and 8 mm wide) into a 3-mm ID, 3.5-mm OD and 6 cm long, thin walled, clear Teflon tube (a support to hold the membranes in place), which was then inserted into the designated openings. The ID of the tube with inserted membrane was approximately 2 mm and 60 μl of nicotine base was added to the membrane. The third component (proximal to the mouth end) consisted of a 2 cm long segment of a charcoal cigarette filter. The first and second components were spaced 1 cm apart and the second and third components were separated by 1 cm. As air entered the distal end of the device, pyruvic acid vapor was entrained by the airstream. Subsequently, the air stream passed through the nicotine loaded membrane and the nicotine vapor reacted with the pyruvic acid vapor to form NP particles. As

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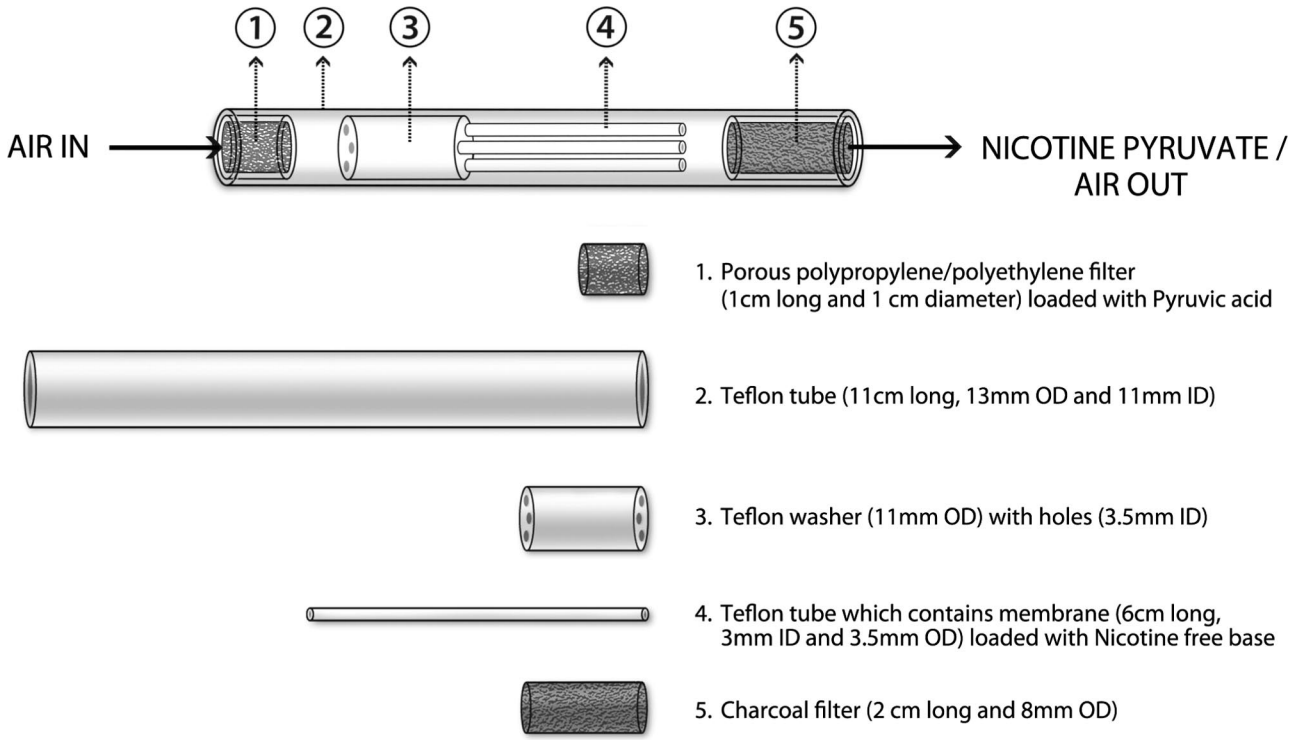


*Figure 1.* Nicotine pyruvate aerosol generation system.

these particles passed through the charcoal filter, excess vapor of pyruvic acid or nicotine was adsorbed or absorbed, along with approximately 20% of the particles. The remaining particle stream exited the filter for inhalation by the research participant.

## Screening

Participants were recruited from the Christchurch, New Zealand area by word of mouth advertising and from a database of volunteers. Eighteen subjects were screened by a medical practitioner and 10 met requirements for study participation, after blood tests, ECG, and smoking history. Nine of these were enrolled in the study. The Fagerström test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991) was also administered.

**Inclusion criteria.** Subjects, male or female, age 18 to 65 years of age, had to be current smokers of at least 10 regular brand cigarettes daily, and with an exhaled CO of 10 ppm or more, to confirm current smoker status, with pulmonary function (KoKo Digidoser spirometer Model 323200, Pulmonary Data Services, Louisville, CO) values Forced Expiratory Volume ((FEV1) and Forced Expiratory Flow (FEF) 25–75) at least 75% of the normal values predicted for that individual based on age, gender, and height. None smoked menthol brands.

**Exclusion criteria.** Pregnant women and nursing mothers were excluded, along with subjects with serious cardiac, respiratory, psychiatric, or other serious disease, particularly cardiac rhythm disorders and abnormally high or low blood pressure, urinary evidence of illegal drugs or excess breath alcohol, and recent or current use of other nicotine or tobacco products.

## Study Day Procedure

In accordance with the tenets of the Declaration of Helsinki, and following receipt of approval from the New Zealand Ministry of Health, from its Upper South B Regional Ethics Committee and its Standing Committee on Therapeutic Trials, informed consent was obtained from nine healthy volunteers, who were admitted to the clinic overnight, abstaining from tobacco or nicotine while at the clinic. On the study day, a baseline expired air carbon monoxide reading $<15$ ppm confirmed abstinence from smoking. Volunteers were studied during a 5 1/2 hour morning session presenting five conditions at 50-min intervals, taking 10 puffs of 35 ml after baseline measurements at the start of each condition. Prior to these five experimental conditions, a practice condition presented air inhalations.

**Plasma nicotine responses.** In each condition, 5 ml of blood was withdrawn 5 min before inhalation, and at 0, 1, 2, 5, 10, 20, and 30 min after the tenth puff. Each sample was immediately placed on ice, centrifuged within 30 min at 4 °C and aliquoted into separate plasma samples, stored at $-70$ °C, and later shipped on dry ice for analysis at Environmental Science and Research, Porirua, New Zealand. Laboratory staff at ESR Porirua were blinded to the sequence of medication codes. Plasma nicotine concentrations were quantified by gas chromatography coupled with mass spectropho-

tometer (GC/MS). Values below the limit of quantification (2 ng/ml) were estimated as half of that limit (Duval & Karlsson, 2002). For one subject, over 50% of the samples had insufficient volume, and therefore this subject was omitted from data analysis of plasma nicotine concentrations. Among the remaining eight subjects, four samples could not be assayed because of insufficient volume, and for these samples nicotine concentrations were estimated by linear interpolation based on values at adjacent time points.

**Subjective responses.** Responses were elicited on a Likert-type scale with responses ranging from 1 to 7 (1 = *not at all*, 7 = *extremely*). The following questionnaires were administered:

The ***smoking withdrawal symptom reports*** (9 questions on an abbreviated version of the Shiffman-Jarvik withdrawal questionnaire (Shiffman & Jarvik, 1976) were elicited 5 min before inhalations began, and again 5 to 10 min after the last (tenth inhalation) in each condition. The answers were scored to give composite answers for craving (urges to smoke, miss a cigarette, and crave a cigarette), negative affect (calm vs. tense, irritable), arousal (wide awake, able to concentrate), and hunger.

An ***inhalation evaluation questionnaire*** (19 questions) was completed 5 to 10 min after the tenth inhalation, and the answers scored for ratings of satisfaction ("satisfying," "taste good"), psychological reward ("calm you down," "help you concentrate," "more awake," "reduce your hunger," and "less irritable"), nausea/dizziness, enjoyment of sensations in the throat and chest, and craving reduction, which was based on "Do (the puffs) immediately reduce your craving for cigarettes?" (Cappelleri et al., 2007) The strength of sensations were scored separately for the strength of puffs on tongue, in nose, back of throat, windpipe, and chest, estimated nicotine yield and similarity to the usual brand of cigarettes. Spirometry (FEV1 and FEF 25–75, best of 3 readings) was repeated after all conditions had been completed.

## Data Analysis

The original analysis plan in the protocol specified a small number of a priori comparisons of interest and no correction for multiple comparisons. However, to achieve a more comprehensive understanding of the results, we conducted a more complete set of comparisons that incorporated a correction for multiple testing to limit Type I error. The Holm's correction procedure for multiple testing at the 0.05 alpha significance level was adopted, which has been shown to be more powerful than the traditional Bonferroni adjustment, while still providing equivalent protection against Type I error (Aickin & Gensler, 1996). To limit the number of statistical comparisons, a series of conditionalized comparisons (Keppel, 1982) were conducted to evaluate efficacy and tolerability of the NP conditions relative to the control conditions. For the analysis of plasma nicotine concentrations, the immediate increase in nicotine concentration from the preinhalation baseline to the first postinhalation time point (5 min) was first compared between placebo and each of the three active NP dose conditions. Because the placebo was known to contain no nicotine, one-tailed paired tests were used in these comparisons. As reported below, the NP 20 and NP 30 dose conditions were the only doses found to be superior to placebo. Thus, in follow-up analyses, only these two doses were compared to the active NV condition, using two-tailed tests with Holm's $p$ value correction and $\alpha = .05$.

Three outlying values were identified in the pre-to-post inhalation nicotine boost: all three showed decreases in nicotine concentrations after inhalation, one subject's value decreasing by 6.9 ng/ml (5.6 *SD*s from the mean of the other subjects) in the NP 10 condition, one decrease of 2.5 ng/ml (3.4 *SD*s from the mean) in the NP 30 condition, and one decrease of 3.3 ng/ml in the NV condition (6.2 *SD*s from the mean). The results will be presented excluding these outliers from the analysis of plasma nicotine values; however, a sensitivity analysis showed that exclusion of these values did not affect the conclusions regarding the statistical significance of comparisons between conditions.

For subjective measures related to efficacy, including satisfaction and relief of withdrawal symptoms, paired $t$ tests were first conducted comparing each of the three active NP dose conditions with the placebo control group. Two-tailed tests (with Holm's correction) were used in these comparisons as it was not known in which direction any detectable differences between NP and other conditions would be found. For example, an aversive taste conceivably would result in the NP aerosol being rated worse than placebo. In follow-up analyses, NP doses showing superiority over placebo were compared to the active NV control condition. For measures of tolerability (e.g., harshness/irritation), only those doses of NP that showed evidence of efficacy relative to placebo (NP 20 and NP 30) were compared against the NV active control condition, again using a two-tailed alpha criterion of 0.05 with a Holm correction.

When presenting the outcomes of hypothesis testing we will first present *corrected p* values, which take into account the Holm correction (uncorrected $p$ values will follow in parentheses). Unless explicitly noted, all $p$ values refer to two-tailed tests. A number of other secondary variables not directly related to hypotheses about efficacy or tolerability (e.g., strength of respiratory tract sensations, estimated nicotine yield) were tabulated for descriptive purposes (paired $t$ tests with uncorrected $p$ values only are reported for these exploratory comparisons).

# Results

## Subjects

Nine smokers (7 men, 2 women) participated in the study; they reported smoking an average of 13.5 cigarettes/day ($SD = 2.85$) and had a mean FTND score of 5.2 ($SD = 1.3$), indicating moderate nicotine dependence. Participants' mean age was 27.4 years ($SD = 7.99$), and they reported having smoked an average of 8.9 years ($SD = 7.8$). Expired air carbon monoxide at the screening session averaged 20.3 ppm ($SD = 13.4$). After overnight abstinence, at the begin-

ning of the experimental session, expired air CO averaged 7.2 ppm ($SD$ = 2.9). Mean body weight was 78.1 kg ($SD$ = 21.8).

### Plasma Nicotine Results

F2 Figure 2 presents the plasma nicotine concentrations in all conditions and at all time points. Baseline-corrected values are depicted, obtained by subtracting the preinhalation baseline values from the values at each postinhalation time point (baseline values did not differ across conditions, mean values ranging from 1.0–2.7 ng/ml). As the graph shows, the NP 20 and NP 30 dose conditions yielded rapid increases in nicotine levels, which were apparent at the 5 min time point, immediately after completion of the inhalations. Statistical comparisons confirmed that the NP 20 and NP 30 conditions produced higher nicotine concentrations than placebo: For the NP 20 condition, the mean increase in nicotine concentration was 5.0 ($SD$ = 3.4) ng/ml (difference from placebo = 4.8 ng/ml), $t(7) = 4.85$, $p$ (one-tailed) = .007 (uncorrected $p = .0035$) for the comparison versus placebo. For the NP 30 condition, the mean increase in nicotine concentration was 8.3 ($SD$ = 3.1) ng/ml (difference from placebo = 8.0 ng/ml), $t(6) = 7.56$, $p$ (one-tailed) = 0.0004 (uncorrected $p = .00015$) for the comparison versus placebo. Follow-up comparisons also showed that the NP 20 and NP 30 dose conditions produced significantly higher plasma peak nicotine concentrations than the active NV control condition: for the NP 20 condition, the mean difference from NV in nicotine concentrations was 4.7 ng/ml, $t(6) = 3.31$, $p = .016$ (uncorrected $p = .016$); for the NP 30 condition, the mean difference from NV was 6.6 ng/ml, $t(5) = 5.94$, $p = .004$ (uncorrected $p = .002$).

### Puff Ratings

T1 Table 1 depicts the subjective ratings of the rewarding effects of inhalations. All three NP dose conditions were rated as significantly more satisfying than placebo: for the composite scale, $t(8) = 3.01$, $p = .017$ (uncorrected $p = .017$) for NP 10; $t(8) = 3.19$, $p = .026$ (uncorrected $p = .013$) for NP 20; $t(8) = 3.25$, $p = .036$ (uncorrected $p = .012$) for NP 30. Subsequent comparisons with the NV condition showed only nonsignificant trends for the three NP doses to be rated higher. Ratings of immediate craving reduction showed a significant difference between the NP 20 dose condition and placebo: $t(8) = 3.36$, $p = .03$ (uncorrected $p = .01$). A follow-up comparison with the NV condition did not reach statistical significance. Comparisons between active NP conditions and placebo on ratings of psychological reward did not reach statistical significance.

Although not the focus of hypotheses in the present study, descriptive statistics for other subjective ratings are also presented in Table 1 (which lists only uncorrected $p$ values for uniformity). Airway sensations following inhalation of NP were generally reported throughout the respiratory tract. Estimated nicotine content also showed higher values in the nicotine conditions relative to placebo.

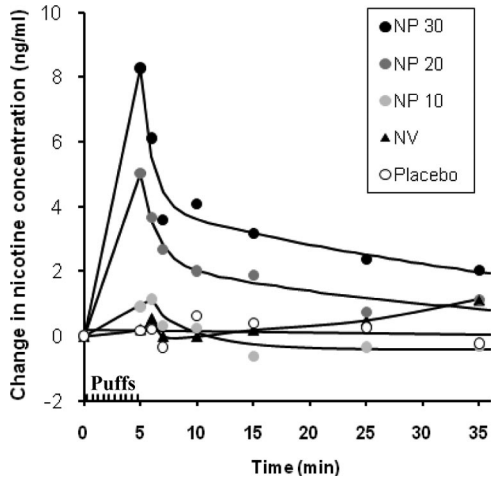


*Figure 2.* Change in plasma nicotine concentration over time relative to preinhalation baseline for the five experimental conditions. After baseline, the first measurement was 5 min after the first puff, at the end of the tenth puff.

### Withdrawal Relief

Table 1 (bottom) also displays the change in the craving rating scale of the withdrawal questionnaire from pre- to postinhalations. The NP 20 dose condition showed a marked reduction in craving relative to placebo: $t(8) = 3.51$, $p = .024$ (uncorrected $p = .008$). The NP 10 condition also showed a significant difference from placebo: $t(8) = 2.89$, $p = .04$ (uncorrected $p = .02$). The comparisons with the NV condition, however, did not reach significance. Other withdrawal symptoms scales showed no significant effects of condition.

### Tolerability

There were no significant adverse reactions to any of the conditions. Of the nine subjects, one had headache after exposure to the NP 10 condition; one other subject had headache and one subject reported loose stool, but these instances preceded exposure to any of the inhalation conditions. Out of the 45 sets of 10 inhalations, mild cough occurred during 19 of the exposures: 15 coughs (among 5 subjects) in the NP 10 condition, 5 coughs (2 subjects) in the NP 20 condition, 12 coughs (6 subjects) in the NP 30 condition, 8 coughs (5 subjects) in the NV condition, and 1 cough (1 subject) after the room air placebo.

Based on assessments of efficacy described above (e.g., increases in plasma nicotine), the NP 20 and NP 30 dose conditions were the only conditions demonstrating superiority over the NV control condition. Therefore, a statistical comparison of harshness/irritation ratings was conducted between each of the two NP conditions and NV, which showed the NP 20 condition to be significantly less harsh/irritating than the NV condition: $t(8) = 3.09$, $p = .03$ (uncorrected $p = .015$).

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Table 1
*Subjective Evaluation of Puffs on 7-Point Scale, and p Values (Uncorrected) for Comparisons With Placebo and Nicotine Vapor Inhaler Cartridge (NV)*

| | NP 10 | NP 20 | NP 30 | NV | Placebo |
|---|---|---|---|---|---|
| Question | | | | | |
| Did you enjoy the sensations in your mouth and throat? | 1.44 (0.73) | 2.44 (1.51) | 1.67 (1.00) | 1.56 (0.88) | 2.89 (1.54) |
| *p* value vs. placebo | 0.026 | — | — | 0.042 | — |
| *p* value vs. NV | — | 0.052 | — | — | 0.042 |
| Did they immediately reduce your craving for cigarettes? | 2.00 (0.87) | 2.89 (1.36) | 2.56 (1.01) | 2.22 (1.20) | 1.67 (1.32) |
| *p* value vs. placebo | — | 0.01 | — | — | — |
| *p* value vs. NV | — | — | — | — | — |
| How high in nicotine? | 3.11 (1.45) | 3.56 (1.42) | 3.22 (1.64) | 4.00 (1.73) | 1.67 (1.12) |
| *p* value vs. placebo | 0.032 | 0.001 | 0.001 | 0.007 | — |
| *p* value vs. NV | — | — | — | — | 0.007 |
| How similar to your cigarette? | 2.33 (1.50) | 3.22 (1.64) | 2.89 (1.54) | 2.22 (1.20) | 2.11 (1.69) |
| *p* value vs. placebo | — | 0.03 | — | — | — |
| *p* value vs. NV | — | — | — | — | — |
| How harsh or irritating? | 3.11 (1.96) | 3.22 (1.92) | 4.11 (1.69) | 4.78 (1.86) | 1.22 (0.67) |
| *p* value vs. placebo | 0.04 | 0.015 | 0.0005 | 0.0006 | — |
| *p* value vs. NV | 0.09 | 0.015 | — | — | 0.0006 |
| How harsh or irritating on tongue? | 2.00 (1.00) | 2.11 (2.03) | 2.89 (2.21) | 3.11 (2.15) | 1.11 (0.33) |
| *p* value vs. placebo | 0.009 | — | 0.028 | 0.015 | — |
| *p* value vs. NV | — | — | — | — | 0.015 |
| How harsh or irritating in nose? | 1.56 (0.73) | 1.33 (0.71) | 1.89 (1.05) | 1.78 (0.97) | 1.11 (0.33) |
| *p* value vs. placebo | — | — | 0.043 | 0.022 | — |
| *p* value vs. NV | — | 0.035 | — | — | 0.022 |
| How harsh or irritating back of mouth and throat? | 4.11 (2.03) | 3.11 (1.54) | 4.00 (1.80) | 4.78 (1.86) | 1.56 (0.73) |
| *p* value vs. placebo | 0.013 | 0.008 | 0.001 | 0.001 | — |
| *p* value vs. NV | — | 0.008 | — | — | 0.001 |
| How harsh or irritating in windpipe? | 2.67 (1.41) | 3.00 (1.73) | 3.67 (2.00) | 3.89 (1.76) | 1.67 (0.71) |
| *p* value vs. placebo | — | 0.029 | 0.009 | 0.002 | — |
| *p* value vs. NV | 0.09 | 0.009 | — | — | 0.002 |
| How harsh or irritating in chest? | 2.22 (0.83) | 2.78 (2.11) | 3.33 (2.18) | 2.67 (1.66) | 1.22 (0.44) |
| *p* value vs. placebo | 0.017 | 0.054 | 0.021 | 0.021 | — |
| *p* value vs. NV | — | — | — | — | 0.021 |
| Composite scores | | | | | |
| Nausea and dizziness | 1.28 (0.44) | 1.78 (1.15) | 2.11 (1.22) | 1.67 (0.83) | 1.28 (0.56) |
| *p* value vs. placebo | — | — | 0.01 | — | — |
| *p* value vs. NV | — | — | — | — | — |
| Psychological reward | 1.93 (0.74) | 2.53 (1.03) | 2.18 (0.86) | 2.13 (0.83) | 1.69 (0.74) |
| *p* value vs. placebo | — | — | — | — | — |
| *p* value vs. NV | — | — | — | — | — |
| Satisfaction | 2.61 (1.05) | 3.17 (1.37) | 2.72 (0.94) | 2.00 (0.71) | 1.89 (1.22) |
| *p* value vs. placebo | 0.012 | 0.013 | 0.017 | — | — |
| *p* value vs. NV | — | — | — | — | — |
| Change in craving | −0.44 (0.87) | −0.85 (1.03) | −0.29 (0.84) | −0.59 (0.86) | 0.41 (0.80) |
| *p* value vs. placebo | 0.02 | 0.008 | 0.13 | 0.03 | — |
| *p* value vs. NV | — | — | — | — | — |

*Note.* Unless indicated, values are *M* (*SD*). NP 10 = 10 μg/puff of nicotine pyruvate; NP 20 = 20 μg/puff of nicotine pyruvate; NP 30 = 30 μg/puff of nicotine pyruvate.

## Safety Assessment

Indices of pulmonary function showed no significant changes from the beginning of the experimental session to the end (Table 2). T2

Table 2
*Spirometry Results on Study Day (Best of 3 Readings)*

| | FEV1 (liters) | FEF 25 75 (liters/s) |
|---|---|---|
| Before inhalations | 3.87 (3.2–4.32) | 3.89 (2.70–5.65) |
| After inhalations | 3.92 (3.23–4.36) | 3.98 (2.95–5.5) |
| After/before | 1.01 (0.97–1.03) | 1.03 (0.90–1.13) |

*Note.* Values are mean (range). FEV1 = forced expiratory volume in one second; FEF = forced expiratory flow.

## Discussion

The findings confirm that NP inhalation at the NP 20 and NP 30 dose conditions produced rapid increases in plasma nicotine concentrations assessed after inhalations ended, relative to the placebo and active nicotine vapor control conditions. Although blood samples were not collected during the 10 inhalations of each condition, the first postinhalation sample showed that blood levels had already reached significant levels, averaging over 8 ng/ml in the NP 30 condition, indicative of rapid pulmonary absorption of nicotine. This result is consistent with particle size measurements showing that the mass median aerodynamic diameter is approximately 0.6 μm (unpub-

lished data), comparable to that of cigarette smoke (Hinds, 1978), and readily able to reach the alveoli of the lung.

The absence of detectable peak nicotine concentrations in the NV and NP 10 dose conditions is not surprising in view of the low total dose of nicotine (0.1 mg) delivered in these two conditions. In contrast, a typical cigarette dose of approximately 1 mg nicotine typically produces venous plasma nicotine peaks of 10 to 15 ng/ml (Benowitz, Porchet, & Jacob, 1990). At roughly one tenth of this dose, the NV and NP 10 dose conditions would only have yielded peaks of $<2$ ng/ml, close to the detection threshold of the assay method used. Our results thus confirmed the prediction that a nicotine aerosol delivery system can deliver a higher dose than a vapor delivery system.

Subjective ratings suggested that all doses of NP were moderately satisfying to smokers, yielding higher ratings of satisfaction than placebo. There were trends for ratings to exceed those of the NV condition, but these did not reach statistical significance. Craving reduction, assessed by the prepost puffing change in the craving scale of the Shiffman-Jarvik questionnaire, was greater for the NP 10 and NP 20 conditions than for placebo. The NP 20 condition was also rated higher than placebo for ratings of how much puffs "immediately reduced your craving." However, none of the NP conditions was significantly different from the NV condition. With respect to harshness/irritation, NP at the 20 μg/puff dose was rated significantly less irritating than the nicotine vapor condition; this finding was likely to be the result of the mildly acidic pH of the NP particles along with their small aerodynamic size, resulting in dispersion of particles over the large surface area of the lung.

Thus, tolerability of the NP aerosol was excellent, and there were no significant adverse events. Pulmonary function measurements also showed no changes from the beginning to the end of the session, supporting the acute safety of NP inhalation at the doses used in this study. Future studies will be needed to assess the safety and tolerability of extended use of a NP delivery system, and to evaluate its usefulness in promoting abstinence from cigarettes smoking.

The results of the present study may also be compared with those of a recently published pilot study of a metered dose inhaler system (Caldwell et al., 2009). In that study, smokers were asked to inhale 10 "puffs" from a metered dose inhaler delivering nicotine in an ethanol/hydrofluroalkane propellant, using a spacer device attached to facilitate pulmonary deposition. Two dose conditions, 50 μg/puff and 100 μg/puff, were tested, and peak plasma nicotine concentrations averaged 12.5 ng/ml and 9.4 ng/ml, respectively. In contrast to the present study results, there was a slight delay of approximately 5 min after inhalations until peak levels were reached. Inhalations were "reasonably well tolerated," although one of 10 subjects could not complete the high dose condition because of coughing. Ratings of satisfaction, craving and several other subjective responses were comparable to those reported after NP inhalation. However, initial inhalations from the metered dose inhaler often triggered coughing, and while harshness/irritation was not explicitly rated, enjoyment of airway sensations received the lowest possible median rating of 1 on a 7-point scale (range = 1–2) versus a median value of 3 (range = 1–5) for the NP 20 condition, suggesting greater enjoyment of the NP 20 condition. The present method is also advantageous in not requiring propellants or cumbersome spacer devices.

Although the technology evaluated in this study was not presented as a commercial product, in principle the technology could be incorporated into a device that can provide a smoker with a supply of nicotine, conveniently accessible on demand. One can envision two main applications of this type of lung delivery nicotine inhalation system. First, this technology may have promise as an adjunct to smoking cessation treatment. By providing rapid nicotine delivery along with many of the rewarding effects of nicotine inhaled in cigarette smoke, a lung delivery nicotine inhaler could prove more effective than current NRT in weaning smokers off of cigarettes. In this application, the ultimate goal would be to wean smokers gradually off of nicotine altogether. While inhaled nicotine is likely to be more addictive than some forms of NRT (e.g., patch), it may nonetheless prove to be less difficult to relinquish than cigarettes, for the following reasons: (1) it would not deliver many of the nonnicotine compounds that are contained in cigarette smoke, such as monoamine oxidase inhibitors (Fowler et al., 1996a, 1996b) and acetaldehyde, which are thought to potentiate the addictive properties of nicotine (Cao et al., 2007); (2) the dose could be set to a range lower than that obtained from most cigarette brands, and the inhaler could be used to supplement slow-acting forms of NRT. In this scenario, the inhaler would be used as a "rescue" or relapse prevention treatment to address breakthrough craving occurring during use of standard slower-onset NRT products such as patch, gum or lozenge; and (3) the sensory qualities might be engineered to be less appealing than cigarettes, while still sufficiently acceptable to promote efficacy.

A second application of this nicotine inhalation technology could be for long term nicotine replacement, to be used by smokers who would otherwise relapse to smoking; this approach would be analogous to methadone maintenance, which has been demonstrated to be an effective treatment of heroin addiction (Strain, Stitzer, Liebson, & Bigelow, 1994). In this harm reduction scenario, ex-smokers would continue to receive the perceived benefits of nicotine while minimizing the risk of disease from combustion and pyrolysis products, including nitrosamines, polycyclic aromatic hydrocarbons, carbon monoxide and numerous other toxic substances contained in tobacco smoke. Accumulating evidence suggests that some smokers may be using cigarettes to self medicate a variety of psychiatric disorders, including depression, anxiety, attention-deficit/hyperactivity disorder (ADHD) and schizophrenia. A major challenge for future research will be to identify smokers who are good candidates for long term nicotine maintenance. For these smokers, long term use of nicotine replacement may indeed be warranted if they will not otherwise quit smoking. If the nicotine inhalation technology evaluated in this study continues to prove more acceptable and efficacious than current forms of NRT, it could have enormous potential for improv-

ing public health. The potential for reducing cigarette related harm was noted by Sumner (2003), who stated: "Even if used very broadly, clean inhaled nicotine might reduce public health problems as much as a very successful tobacco control programme."

This study had a number of strengths as well as limitations. Strengths included the repeated measures design (which provided greater sensitivity than a between-groups comparison), subject and experimenter blinding, and precise control over nicotine dosing using machine-controlled puff volume and timed breath hold. Additional strengths included the measurement of both pharmacokinetic and subjective responses, as well as the use of an active control condition (NV) in addition to the placebo control. Limitations included the small sample size and short duration of exposure. In addition, blood sampling began after the completion of inhalations, limiting the precision with which the rate of rise in plasma nicotine concentrations could be assessed.

In summary, the results of this study indicate that the novel technology employed to generate nicotine containing particles for inhalation has promise as a potentially more effective form of nicotine replacement. The pharmacokinetic and subjective data demonstrated that this technology can be used to administer nicotine by the pulmonary route for rapid absorption, coupled with acceptable sensory qualities, to provide subjective satisfaction and relief of craving. Further controlled trials of this technology are warranted to fully assess its safety and efficacy in aiding smokers to relinquish cigarettes and thereby avoid the deadly diseases caused by smoking.

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## Correction to Rose et al. (2010)

In the article "Pulmonary Delivery of Nicotine Pyruvate: Sensory and Pharmacokinetic Characteristics," by Jed E. Rose, James E. Turner, Thangaraju Murugesan, Frédérique M. Behm, and Murray Laugesen (*Experimental and Clinical Psychopharmacology,* 2010, Vol. 18, No. 5, pp. 385-394), some the descriptors in Table 1 (p. 391) were incorrectly denoted as "harsh or irritating," instead of "strong." The following table contains the correct terms.

Table 1
*Subjective Evaluation of Puffs on a 7-Point Scale, and p Values (uncorrected) for Comparisons With Placebo and Nicotine Vapor Inhaler Cartridge (NV)*

| | NP 10 | NP 20 | NP 30 | NV | Placebo |
|---|---|---|---|---|---|
| Question | | | | | |
| Did you enjoy the sensations in your mouth and throat? | 1.44 (0.73) | 2.44 (1.51) | 1.67 (1.00) | 1.56 (0.88) | 2.89 (1.54) |
| *p* value vs. placebo | *0.026* | — | — | *0.042* | — |
| *p* value vs. NV | — | *0.052* | — | — | *0.042* |
| Did they immediately reduce your craving for cigarettes? | 2.00 (0.87) | 2.89 (1.36) | 2.56 (1.01) | 2.22 (1.20) | 1.67 (1.32) |
| *p* value vs. placebo | — | *0.01* | — | — | — |
| *p* value vs. NV | — | — | — | — | — |
| How high in nicotine? | 3.11 (1.45) | 3.56 (1.42) | 3.22 (1.64) | 4.00 (1.73) | 1.67 (1.12) |
| *p* value vs. placebo | *0.032* | *0.001* | *0.001* | *0.007* | — |
| *p* value vs. NV | — | — | — | — | *0.007* |
| How similar to your cigarette? | 2.33 (1.50) | 3.22 (1.64) | 2.89 (1.54) | 2.22 (1.20) | 2.11 (1.69) |
| *p* value vs. placebo | — | *0.03* | — | — | — |
| *p* value vs. NV | — | — | — | — | — |
| How harsh or irritating? | 3.11 (1.96) | 3.22 (1.92) | 4.11 (1.69) | 4.78 (1.86) | 1.22 (0.67) |
| *p* value vs. placebo | *0.04* | *0.015* | *0.0005* | *0.0006* | — |
| *p* value vs. NV | *0.09* | *0.015* | — | — | *0.0006* |
| How strong on tongue? | 2.00 (1.00) | 2.11 (2.03) | 2.89 (2.21) | 3.11 (2.15) | 1.11 (0.33) |
| *p* value vs. placebo | *0.009* | — | *0.028* | *0.015* | — |
| *p* value vs. NV | — | — | — | — | *0.015* |
| How strong in nose? | 1.56 (0.73) | 1.33 (0.71) | 1.89 (1.05) | 1.78 (0.97) | 1.11 (0.33) |
| *p* value vs. placebo | — | — | *0.043* | *0.022* | — |
| *p* value vs. NV | — | *0.035* | — | — | *0.022* |
| How strong in back of mouth and throat? | 4.11 (2.03) | 3.11 (1.54) | 4.00 (1.80) | 4.78 (1.86) | 1.56 (0.73) |
| *p* value vs. placebo | *0.013* | *0.008* | *0.001* | *0.001* | — |
| *p* value vs. NV | — | *0.008* | — | — | *0.001* |
| How strong in windpipe? | 2.67 (1.41) | 3.00 (1.73) | 3.67 (2.00) | 3.89 (1.76) | 1.67 (0.71) |
| *p* value vs. placebo | — | *0.029* | *0.009* | *0.002* | — |
| *p* value vs. NV | *0.09* | *0.009* | — | — | *0.002* |
| How strong in chest? | 2.22 (0.83) | 2.78 (2.11) | 3.33 (2.18) | 2.67 (1.66) | 1.22 (0.44) |
| *p* value vs. placebo | *0.017* | *0.054* | *0.021* | *0.021* | — |
| *p* value vs. NV | — | — | — | — | *0.021* |
| Composite scores | | | | | |
| Nausea & dizziness | 1.28 (0.44) | 1.78 (1.15) | 2.11 (1.22) | 1.67 (0.83) | 1.28 (0.56) |
| *p* value vs. placebo | — | — | *0.01* | — | — |
| *p* value vs. NV | — | — | — | — | — |
| Psychological reward | 1.93 (0.74) | 2.53 (1.03) | 2.18 (0.86) | 2.13 (0.83) | 1.69 (0.74) |
| *p* value vs. placebo | — | — | — | — | — |
| *p* value vs. NV | — | — | — | — | — |
| Satisfaction | 2.61 (1.05) | 3.17 (1.37) | 2.72 (0.94) | 2.00 (0.71) | 1.89 (1.22) |
| *p* value vs. placebo | *0.012* | *0.013* | *0.017* | — | — |
| *p* value vs. NV | — | — | — | — | — |
| Change in craving | −0.44 (0.87) | −0.85 (1.03) | −0.29 (0.84) | −0.59 (0.86) | 0.41 (0.80) |
| *p* value vs. placebo | *0.02* | *0.008* | *0.13* | *0.03* | — |
| *p* value vs. NV | — | — | — | — | — |

*Note.* Unless indicated, values are *M* (*SD*). For each variable, the first italicized line lists *p* values for comparisons with placebo and the second italicized line lists *p* values for comparisons with NV. Dashes indicate non significant comparisons.

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