Airway Sensory Replacement Combined With Nicotine Replacement for Smoking Cessation*

A Randomized, Placebo-Controlled Trial Using a Citric Acid Inhaler

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Study objective: This study was conducted to determine if the combination of airway sensory replacement and nicotine replacement improves 10-week smoking abstinence rates over nicotine replacement alone.

Design: Double-blind, randomized, placebo-controlled trial.

Setting: Outpatient research clinic.

Participants: One hundred healthy volunteers who smoked at least one pack of cigarettes per day and desired to quit smoking.

Interventions: Subjects received either citric acid (n=41) or lactose placebo (n=59) inhalers to cope with smoking urges for 10 weeks. All subjects received self-help materials and nicotine patches for 6 weeks. Return visits were at weeks 1, 4, 6, and 10. Abstinence was defined as zero cigarettes smoked since the quit date verified by exhaled carbon monoxide ≤8 ppm at all return visits. Inhaler effects were measured by a standardized questionnaire.

Measurements and results: The primary outcome of continuous abstinence at the end of the 10-week treatment period was 19.5% (95% confidence interval [CI]=7.4 to 31.6%) for the citric acid group vs 6.8% (95% CI=0.4 to 13.2%) for the lactose group (p=0.05). Relief from craving and short-term abstinence increased as airway sensations from the inhaler also increased. Abstinence at 10 weeks for subjects receiving strong airway sensations from the inhalers was 33.3% (95%CI=14.5 to 52.1%). At 6 months, there was no difference in abstinence between the treatment groups (0% vs 5.1%, p=0.20).

Conclusions: When combined with the nicotine patch, the citric acid inhaler improved 10-week smoking abstinence over lactose inhaler. The combination of airway sensory replacement and nicotine replacement may prove beneficial for smoking cessation.

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Key words: citric acid; nicotine patch; smoking cessation

Cigarette smoking is a complex addiction based on pharmacologic and behavioral dependencies. To address these dependencies, most comprehensive smoking cessation programs include nicotine replacement and behavioral counseling.1 Nicotine replacement provides the pharmacologic need for nicotine while behavioral counseling assists in breaking the associations between situational cues and smoking. Despite many advances in this treatment approach, the success of comprehensive treatment programs at 1 year is only about 10%.1,3

This traditional approach to smoking cessation may have met with limited success because it does not address the airway sensations from smoking as one of the dependencies of smoking.4,5 In the same way that intravenous alcohol cannot provide the same taste as an orally consumed alcoholic beverage, nicotine replacement cannot provide the enjoyable airway sensations of cigarette smoke. Because the airway sensations have always been linked to the nicotine effect, smokers may gauge their nicotine intake according to these airway sensations.6 If nicotine is provided without the airway sensations, smokers may not realize that they are receiving nicotine, and may begin smoking again to receive the airway sensations that they have come to associate with the nicotine effect.

An alternative approach to smoking cessation treatment is to provide the usual nicotine replacement and nicotine tapering therapy while also providing nicotine-free airway sensory replacement. In addition to the mild craving reduction afforded by nicotine replacement, the airway sensory replacement may further reduce craving for cigarettes and other withdrawal symptoms. In previous work from our laboratory, non-nicotine inhalers have been...
shown to be successful in reducing craving for cigarettes, and improving 3-week smoking abstinence when used by themselves.7-10 Building on this model of combining nicotine and airway sensory replacement, and by using a placebo inhaler to control for the oral and manual components of smoking, we hypothesized that a citric acid inhaler combined with the nicotine patch would improve 10-week smoking abstinence rates over a placebo inhaler combined with the nicotine patch.

METHODS

Subjects

Through local newspaper advertisements, we recruited healthy volunteers who expressed a strong desire to quit smoking and who smoked at least one pack per day of cigarettes of a brand delivering at least 0.3 mg nicotine by Federal Trade Commission analysis. We included subjects only if they were 25 to 60 years, and were determined to be healthy by screening history and pulmonary function testing. We excluded subjects with a history of skin allergies, asthma, FEV1 less than 60% of predicted, major psychiatric disorders requiring medication, alcohol or drug abuse, and current pregnancy. Subjects with upper respiratory tract infection within 10 days were deferred until their illness had resolved. Informed consent approved by local institutional review boards was read and signed by each subject prior to enrollment. The study was conducted at the Durham (NC) Veterans Affairs Medical Center from June 1992 to June 1993. Monetary incentives were not given for participation.

Design

Using computer-generated simple randomization, subjects were assigned to either active (citric acid) or placebo (lactose) inhalers. The randomization and outcome assessment were conducted in double-blind fashion.

Inhalers: The inhaler was a hollow, cigarette-sized tube with an air dilution system at the proximal end and a measured dose of ground citric acid (USP) or lactose in the distal end. The citric acid condition was 50% citric acid and 50% lactose. Because a baffle near the proximal end of the mouthpiece filtered out large particles, the inhaler delivered particles approximately 10 to 20 μm in size. The amount of ingredient per puff could be regulated by rotating a sleeve that covered dilution holes at the proximal end of the inhaler. Roughly 100 puffs could be obtained from the inhaler with one 100-mg refill cartridge. The inhalers were provided for 10 weeks after the quit date, with up to three refills per day.

Nicotine Patches: In a regimen previously shown to be effective, nicotine patches (Habitrol, Ciba-Geigy, Edison, NJ) were used for a 6-week period: 21 mg/24 h for 4 weeks, 14 mg/24 h for 1 week, and 7 mg/24 h for 1 week.11

Clinic Visits: Subjects reported five times to the research clinic over the first 10-week period. At baseline, subjects completed baseline questionnaires, including the Fagerstrom Tolerance Questionnaire and a smoking motivation questionnaire.12,13 Subjects were provided a self-help manual14 and were instructed to begin wearing the nicotine patches on the morning of their quit date, on the hairless area of the chest and sides of the body. Subjects were advised to puff on the inhalers just like a cigarette to cope with urges to smoke. At the end of each day, subjects recorded number of cigarettes smoked, number of uses of the inhaler, number of puffs per typical inhaler use, and whether they wore the nicotine patch. Subjects completed a withdrawal questionnaire at the end of day 1 (the quit date). At each follow-up visit, subjects were given inhaler refills and nicotine patches and completed questionnaires. At the 4-week visit, subjects were instructed to wear one 14-mg/24 h patch per day for 1 week, then one 7-mg/24 h patch per day for 1 week. Subjects returned to the clinic at the end of 10 weeks for checking of vital signs and carbon monoxide levels. All of the follow-up visits lasted about 15 to 30 min. During these visits, the subjects had very little interaction with other participants, and only brief (<5 min) encouragement or suggestions provided by the study staff.

Outcomes

Smoking Abstinence: Abstinence was assessed by self-report and exhaled carbon monoxide. During the first 6 weeks, the number of cigarettes smoked was recorded by the subjects on diaries at the end of each day. Exhaled carbon monoxide levels were measured at the end of 1 week, 4 weeks, 6 weeks, 10 weeks, and 24 weeks (BreathCO, Vitalograph, Lenexa, Kansas). Those who successfully abstained from smoking for 10 weeks were contacted by telephone at 24 weeks to determine smoking abstinence rates.

Inhaler Effects Questionnaire: Airway sensations, relief from craving, help in refraining from smoking, and puff enjoyment were rated on a seven-point ordinal scale ranging from 1 ("not at all") to 7 ("extremely"). The sensations of the inhaler were rated separately for the tongue, nose, mouth/throat, windpipe, and chest. Previous studies have shown a medium strength cigarette (Marlboro Light) to produce a 3.7 (SD=1.4) strength rating for the mouth and throat on this scale. Within this study, the test-retest reliability of the mouth/throat rating comparing mouth/throat sensations at the end of day 1 to the end of week 1 revealed a Spearman’s rho of 0.81 (p=0.0001).

Withdrawal Symptoms: Relief from craving, help in refraining from smoking, and puff enjoyment were rated on a seven-point ordinal scale ranging from 1 ("not at all") to 7 ("extremely"). A modification of a questionnaire derived and validated by Shiffman and Jarvis15 was also used. Instructions for the 83 items were worded: “Circle the number that most accurately reflects how you felt today” scored on a scale from 1 ("not at all") to 7 ("extremely").

Safety: Blood pressure, pulse, weight, pulmonary function test results, and adverse effects were recorded at every visit. Adverse effects were assessed by self-administered open-ended questionnaires.

Statistical Analysis

Sample Size: The sample size of 100 subjects had 70% power to detect the difference between abstinence rates at the end of treatment (10 weeks) of 10% and 30% (two-sided alpha=0.05).

Smoking Abstinence: Abstinence was defined as zero cigarettes smoked since the quit date, verified by exhaled carbon monoxide levels ≤8 ppm at the return visits.16,17 Using an intention-to-treat analysis, the primary outcome was percent continuous abstinence at the end of the 10-week treatment period, compared between treatment groups using the x² statistic. Other secondary abstinence outcomes were as follows: percent abstinence at 4 weeks, 6 weeks, and 24 weeks using the x² statistic at each time point. Outcomes were also tested in a multivariable logistic model to adjust for baseline differences between the two treatment groups. All p values are two-tailed.

Inhaler Effects Questionnaire: The means of individual items were compared between treatment groups using t tests.

Withdrawal Symptoms: The means of relief from craving, help in refraining from smoking, and puff enjoyment were compared between treatment groups using t tests. The modified Shiffman-Jarvik questionnaire was analyzed using six subscales corresponding to craving, negative affect, arousal, somatic symptoms, appetite, and habit. The subscale scores (the mean of the individual items) were compared between the treatment groups using
repeated measures analysis of variance in abstinent subjects only.

Safety: Change from baseline in blood pressure, pulse, FEV₁,
FVC, FEV₁/FVC ratios, and adverse effects were compared be-
tween treatment groups using Student’s t test, Fisher’s exact test,
or the χ² test as appropriate.

RESULTS

Subjects

Of 229 smokers responding to advertisement, 100 subjects were enrolled in the study and assigned to treatment groups. Of the 128 who did not enroll, reasons were “decided not to participate” (n=34), chronic medical or psychiatric illness (n=19), smoked less than one pack per day or nicotine content of cigarette <0.3 mg (n=17), illicit drug use (n=13), history of asthma or FEV₁ <60% predicted (n=11), age >65 years (n=9), skin problems (n=6), or other (n=19).

At baseline, the resulting treatment groups were significantly different for the mean number of cigarettes smoked per day, mean number of years smoked, and mean exhaled carbon monoxide concentration (Table 1). These characteristics all were higher for the active treatment group. Baseline blood pressure, pulse, and weight were similar between treatment groups.

Smoking Abstinence

Two subjects (one each in the citric acid and lactose groups) reported smoking zero cigarettes since the quit date, but had an exhaled carbon monoxide of ≥8 ppm, so were counted as smoking in the analysis. The primary outcome of abstinence at 10 weeks for the citric acid group was 19.5% vs 6.8% for the lactose group (p=0.05, adjusted p=0.06). (Table 2). Secondary outcomes of abstinence at 4 and 6 weeks for the citric acid and lactose groups were 36.6% vs 18.6% (adjusted p=0.02) and 34.1% vs 11.9%, respectively (adjusted p=0.004). Most of the relapses occurred during the first 2 weeks after the quit date (Fig 1). The secondary outcome of abstinence at 24 weeks (14 weeks after the intervention was discontinued) for the active and placebo groups was 0% vs 5.1% (adjusted p=0.37).

Inhaler Effects Questionnaire

Airway sensations in the nose, throat, windpipe, and chest were significantly stronger for the citric acid group than for the lactose group at the end of the quit date. The mean sensations for the citric acid group and lactose groups for the “tongue” was 3.57 vs 3.15 (p=0.31), “nose” 1.63 vs 1.11 (p=0.016), “mouth/throat” 4.71 vs 2.28 (p=0.0001), “windpipe” 2.97 vs 1.73 (p=0.002), and “chest” 2.2 vs 1.32 (p=0.003). Baseline predictors of “mouth/throat” sensation were the smoking motivation habit scale (p=0.004) and the smoking motivation craving scale (p=0.02): subjects with higher habit and craving scores had higher “mouth/throat” sensations at the end of the quit day.

Withdrawal Symptoms

On the quit date, relief from craving was higher in the citric acid group than in the lactose group (citric acid mean=2.86, lactose mean 2.23, p=0.05). Help in refraining from smoking and puff enjoyment were not significantly different between treatment groups.

A dose-response relationship was observed when the airway sensations from the inhalers were compared with the inhaler effects combining treatment groups (Table 3). Stronger throat sensations were associated with more “craving relief” and more “help in refraining from smoking.” As shown in Figure 2, abstinence rates were higher for subjects who received stronger throat sensations from either the citric acid inhaler or placebo plus nicotine patch.

Table 1—Baseline Subject Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Active (n=41)</th>
<th>Placebo (n=59)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr, mean (SD)</td>
<td>42.6 (7.8)</td>
<td>40.1 (8.2)</td>
<td>0.12</td>
</tr>
<tr>
<td>Female gender, %</td>
<td>63.4</td>
<td>74.6</td>
<td>0.23</td>
</tr>
<tr>
<td>Race, white, %</td>
<td>87.8</td>
<td>91.5</td>
<td>0.74</td>
</tr>
<tr>
<td>Cigarettes smoked per day</td>
<td>34.7 (11.1)</td>
<td>28.9 (9.6)</td>
<td>0.007</td>
</tr>
<tr>
<td>No. of years smoked</td>
<td>25.3 (6.6)</td>
<td>21.8 (8.1)</td>
<td>0.027</td>
</tr>
<tr>
<td>Age of initiation of smoking, yr</td>
<td>17.4 (3.1)</td>
<td>17.6 (2.5)</td>
<td>0.76</td>
</tr>
<tr>
<td>Fagerstrom score</td>
<td>6.9 (1.8)</td>
<td>6.6 (1.6)</td>
<td>0.36</td>
</tr>
<tr>
<td>Exhaled carbon monoxide, ppm</td>
<td>42.7 (15.1)</td>
<td>35.6 (15.6)</td>
<td>0.027</td>
</tr>
<tr>
<td>Some education beyond 12th grade, %</td>
<td>82.9</td>
<td>91.5</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Table 2—Continuous Smoking Abstinence Rates*

<table>
<thead>
<tr>
<th>Group</th>
<th>4 wk†</th>
<th>6 wk†</th>
<th>10 wk†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citric acid inhaler</td>
<td>36.6</td>
<td>34.1</td>
<td>19.5</td>
</tr>
<tr>
<td>+ nicotine patch, % (n=41)</td>
<td>18.6</td>
<td>11.9</td>
<td>6.8</td>
</tr>
<tr>
<td>Placebo inhaler</td>
<td>18.6</td>
<td>11.9</td>
<td>6.8</td>
</tr>
<tr>
<td>+ nicotine patch % (n=59)</td>
<td>18.6</td>
<td>11.9</td>
<td>6.8</td>
</tr>
</tbody>
</table>

*No cigarettes smoked since the quit date, verified by exhaled carbon monoxide ≥8 ppm at return visits.
†Secondary outcomes: adjusted p=0.02 at 4 weeks, p=0.004 at 6 weeks.
‡Primary outcome: unadjusted p=0.05 comparing citric acid with placebo groups, adjusted p=0.06.
Continuous Smoking Abstinence
Citric Acid Inhaler and Nicotine Patch vs. Lactose Inhaler and Nicotine Patch

![Graph showing abstinence rates over time]

There were no significant differences between abstinent subjects in the citric acid and lactose groups in nicotine withdrawal subscales of "craving," "arousal," "negative affect," "appetite," "habit," or "somatic symptoms."

**Safety**

There were no significant differences in systolic blood pressure, diastolic blood pressure, pulse, or weight between the treatment groups. The most common adverse effects were headache (23% of subjects), itching or burning at the patch site (13%), and sleep disturbances (12%). There were no significant differences between the treatment groups for adverse effects. "Cough" or "shortness of breath" occurred in 9.8% of the citric acid group and in 3.3% of the lactose group (p=0.22).

Pulmonary function testing revealed no significant change from baseline through week 10 between treatment groups. There was no association between amount of inhaler use and change in pulmonary function.

One subject in the placebo group complained of a cough with phlegm production 15 min after using the inhaler and discontinued use of the inhaler after 9 days. This subject was a 42-year-old man who smoked 25 cigarettes per day, and had baseline FVC of 5.78 (104% of predicted), FEV1 of 4.56 (102% of predicted), and FEV1% of 78.9% (99% of predicted). He had a 15% reduction in FVC, FEV1, and FEV1% from baseline at two of four follow-up visits. The cough promptly resolved after he discontinued using the inhaler.

**Table 3—Inhaler Mouth/Throat Sensations and Inhaler Effects***

<table>
<thead>
<tr>
<th>Mouth/Throat Sensation</th>
<th>Both Inhaler Groups</th>
<th>Citric Acid Inhaler</th>
<th>Lactose Inhaler</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Craving Relief1</td>
<td>Help Refrain From Smoking1</td>
<td>Craving Relief</td>
</tr>
<tr>
<td>7</td>
<td>4.0±1.8</td>
<td>4.8±1.7</td>
<td>3.8±1.9</td>
</tr>
<tr>
<td>6</td>
<td>2.6±1.3</td>
<td>3.3±1.7</td>
<td>2.6±1.3</td>
</tr>
<tr>
<td>5</td>
<td>3.4±1.7</td>
<td>3.8±1.5</td>
<td>3.4±1.9</td>
</tr>
<tr>
<td>4</td>
<td>3.0±1.7</td>
<td>3.2±2.0</td>
<td>2.4±1.5</td>
</tr>
<tr>
<td>3</td>
<td>2.1±0.8</td>
<td>2.9±1.5</td>
<td>2.0±0.8</td>
</tr>
<tr>
<td>2</td>
<td>2.5±1.2</td>
<td>3.4±1.8</td>
<td>2.5±2.3</td>
</tr>
<tr>
<td>1</td>
<td>1.5±0.8</td>
<td>2.5±1.8</td>
<td>1.0±0.0</td>
</tr>
<tr>
<td>Total</td>
<td>2.8±1.7</td>
<td>3.3±1.9</td>
<td>2.5±1.7</td>
</tr>
</tbody>
</table>

*Data shown are means±SD. "Mouth/throat sensations" measured on a scale from 1 to 7. "Craving relief" and "help refrain from smoking" measured on a scale from 1 ("not at all") to 7 ("extremely"). Data from day 1 and week 1 were combined. Seven observations had missing data.

1p<0.0001 for the association between mouth/throat sensations and "craving relief."

1p=0.03 for the association between mouth/throat sensations and "help refrain from smoking."
**Study Adherence**

**Dropouts:** In the citric acid group 100% of subjects returned at 1 week, 90.2% at 4 weeks, 78.0% at 6 weeks, and 70.7% at 10 weeks. In the lactose group, 94.9% of subjects returned at 1 week, 79.7% at 4 weeks, 66.1% at 6 weeks, and 61% at 10 weeks. There was no statistically significant difference between dropout rates between the treatment groups at any time point.

**Inhaler Use:** The inhaler was not used at all by five subjects: four in the lactose group, one in the citric acid group. Use of the inhaler (duration of use, number of uses, and number of puffs per use) was not significantly different between the two treatment groups. The mean duration of inhaler use was 15.4 days (SD=18.8). On the quit date, the mean number of uses was 7.7 (SD=6.4; range, 1 to 38 uses) and the mean number of puffs per use was 4.7 (SD=3.2; range, 1 to 20 puffs per use). The use of the inhaler decreased over time such that at the end of 2 weeks, the mean number of uses was 4.8 (SD=3.4; range, 1 to 15) and the mean number of puffs per use was 7.8 (SD=9.3; range, 1 to 35). At the end of weeks 1, 2, 6, 8, and 10, the proportion of subjects still using the inhalers was 51%, 32%, 14%, 7%, and 2%, respectively.

Among the subjects who remained abstinent at 10 weeks, six subjects used the inhaler daily with tapering of use over time, and five subjects used the inhaler intermittently, often with several days of nonuse between days of use.

**Nicotine Patch Use:** Compliance with the 6-week nicotine patch treatment period measured at weeks 1, 4, and 6 was similar for both citric acid and lactose groups: 100% vs 89.8%, 87.8% vs 79.7%, and 70.7% vs 55.9% (p=0.14 at 6 weeks).

**Subject Blinding:** Subjects were asked if they thought they had received active or placebo inhalers at the 10-week visit. Both groups were slightly more likely to know which group they were in than by chance alone (50%): for the 57 respondents, 69.6% (95% confidence interval [CI]±19%) of the citric acid group thought they had received active powder, 67.6% (95% CI±16%) of the lactose group thought they had received placebo powder.

**Discussion**

In this randomized controlled trial, the combination of a citric acid inhaler with the nicotine patch increased smoking abstinence over placebo inhaler and the nicotine patch during 10 weeks of inhaler use, but not at the 6-month follow-up. Because the placebo inhalers controlled for the oral and handling factors associated with the act of smoking, this improvement in abstinence was most likely due to the airway sensations provided by the inhalers.

In previous studies without nicotine replacement, citric acid delivery systems were shown to decrease craving for cigarettes and promote abstinence during a short-term treatment period of 3 weeks.\(^6\)\(^8\) We hypothesized that the citric acid inhaler of the present study would improve the efficacy of the nicotine patch by reducing craving for cigarettes even further. This hypothesis was supported by the association of airway sensations with immediate relief from craving, but was not reflected on the average daily withdrawal craving questionnaire. These findings may mean that the continuous nicotine delivery from the patch relieved craving due to nicotine withdrawal while the citric acid inhalers relieved peaks of...
craving. When examining the inhaler use among subjects who were successful at 10 weeks, many subjects used the inhalers in an intermittent fashion, so it is likely that the inhaler was also used as a relapse prevention tool, to avert relapse during times of "craving crisis."

The rationale for the 10-week duration of the inhaler intervention was to decrease craving for cigarettes during the first part of the cessation attempts. Because the inhaler may have also functioned as a relapse prevention tool, and relapses still occur after 10 weeks, the duration of inhaler treatment may have been too brief to expect an improvement in abstinence at 24 weeks. Indeed, 24-week abstinence was no longer higher in the citric acid group than the placebo group. In two smoking cessation trials using the nicotine inhaler and nasal spray for smoking cessation, the inhaler treatment period lasted from 6 to 12 months.\textsuperscript{18,19} In the nasal spray study, 43% of those who were abstinent from smoking in the active spray group were still using the spray at 12 months. If the mechanism of inhaler effect is as a relapse prevention tool, then further studies with a longer inhaler treatment period are needed to determine the effect of the inhalers over a 6-month period.

The low success rates of 0% and 5.1% at 6 months may be a result of differences in subject characteristics and abstinence definition. In this study conducted in North Carolina, the subjects had baseline carbon monoxide levels higher than most studies involving the nicotine patch. Designing the study to reflect what often occurs in medical practice, we used a relatively brief duration of nicotine patch treatment of 6 weeks, and minimal behavioral counseling. Because early slips back to smoking are associated with long-term relapse and we used a 6-month abstinence outcome, we strictly defined abstinence as: zero cigarettes smoked from the quit date. Many other studies allow for a 1- to 2-week grace period before counting these subjects as having a relapse to smoking.\textsuperscript{2,20} In a previous study at our site involving the nicotine patch alone, the abstinence rates at the end of the 6-week nicotine patch treatment period, allowing for slips in the first 2-week period, were 29.5% for the active patch vs 8.8% for the placebo patch.\textsuperscript{11} However, using the strict abstinence definition of zero cigarettes smoked from the quit date, the 6-week abstinence rates were 17.9% (95% CI=9.4 to 26.5%) for the active patch group and 7.5% (95% CI=1.7 to 13.3%) for the placebo patch group. Reexamining the current study's 6-week strict abstinence rates of 34.1% (95% CI=19.6 to 48.7%) for the citric acid inhaler and 11.9% (95% CI=3.6 to 20.1%) for the lactose inhaler, the lactose group rate from the current study (11.9%) is comparable to the active patch group from the previous study (17.9%), and the citric acid group rate (34.1%) is higher than the active patch group rate (17.9%).

The inhalers were well tolerated in this study, which restricted their use to healthy volunteers screened by medical questionnaire and spirometry. One subject in the lactose inhaler group required termination of treatment because of temporary respiratory side effects (1% total dropout rate). Because of the risk of bronchospasm, these dry aerosol inhalers should probably be avoided in smokers with clinically significant obstructive airways disease until further studies are conducted in patients with lung disease.

The therapeutic potential of the inhalers may have been limited by the current inhaler design. The most significant problem of particle agglomeration could be improved by a metered-dose inhaler that controls the particle size and puff delivery more precisely. Because subjects desired a range of strength of airway sensations, an inhaler design that allows adjustment of sensation strength (or inhalers containing different sensation strengths) may lead to better subject titration and improved success.

The citric acid inhaler may have several advantages over inhalers that contain nicotine. These inhalers may allow for the dissociation of the reward of nicotine from the act of smoking, thereby leading to extinction of the conditioned reinforcement of airway sensations over time.\textsuperscript{6} Additionally, citric acid inhalers appear to have no addictive potential.

In summary, the combination of airway sensory replacement and nicotine replacement significantly improved 10-week smoking abstinence rates beyond placebo inhaler and nicotine replacement, but this improvement was not sustained to 6 months. In the future, citric acid inhalers may fill an important gap in smoking cessation therapy by providing the airway sensations that smokers expect when they are trying to quit.

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