Nicotine Blood Levels and Short-term Smoking Reduction with an Electronic Nicotine Delivery System

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***Objectives*: To evaluate nicotine delivery from the NJOY® King Bold Electronic Nicotine Delivery System (ENDS) and its short-term potential for smoking reduction or cessation. *Methods*: One week of ad libitum use was followed by measurements of plasma nicotine, heart rate, and craving and withdrawal after 12 hours of nicotine abstinence in 25 adult smokers not interested in quitting. *Results*: After 5 minutes of use, blood nicotine levels increased by a mean of 3.5 ng/mL ($p < .001$), heart rate increased, and craving was reduced by 55%. Cigarettes per day were reduced by 39% during the test week, and perceptions of use for reduction or cessation were positive. *Conclusions*: The NJOY® King Bold ENDS delivers nicotine and led to short-term smoking reduction.**

***Key words*: nicotine delivery, electronic cigarette, smoking cessation**

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Cigarette smoking remains a major public health problem in the United States, with 19% of the adult population (43.8 million) continuing to smoke.[1] Approximately 52% of smokers attempt to quit smoking each year,[1] but success rates for those quitting on their own are only about 4% at one-year.[2] Currently available FDA-approved short-acting nicotine replacement products (gum, lozenge, inhaler, and nasal spray) typically double the chances of success,[3] but long-term quit rates are still modest. Theoretically, products that more closely approximate cigarettes in their sensory characteristics and speed of nicotine delivery might increase rates of success.

Over the past several years, the use of electronic nicotine delivery systems (ENDSs), commonly known as e-cigarettes, has dramatically increased[4] because these systems have the potential to deliver significant levels of nicotine and mimic many of the sensory characteristics of cigarettes (eg, realistic puffing and inhalation, taste, a "hit" or scratchiness in the back of the throat, and a visible mist that closely resembles smoke). Puffing on an ENDS activates the battery that heats and aerosolizes a solution containing nicotine, propylene glycol, and/or vegetable glycerin, along with flavorings.

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Smoking machine studies of the particle size and other properties of the aerosol suggest that ENDS products may deliver at least some nicotine directly to the pulmonary system, thereby permitting rapid absorption. In contrast, the approved short-acting NRT products deliver nicotine to the oral or nasal mucosa, where absorption is much slower. However, the few published human pharmacokinetic studies of ENDS products have shown wide variation in nicotine delivery. Inexperienced users of some of the early-generation ENDS products achieved nicotine levels similar to those reached with placebo or with a nicotine inhaler.[5,6] In contrast, experienced users of the later-generation larger sized ENDS products with higher-voltage batteries achieved nicotine levels similar to those reached by smoking a conventional cigarette.[7] One study showed that with experience, users learned to alter their puff topography (ie, they learned to take longer puffs) to increase the amount of nicotine they absorbed from the device.[8]

Several studies and clinical trials have shown that ENDS can reduce nicotine craving and withdrawal symptoms and may be useful as an aid for smoking reduction or cessation.[5-7,9-13] One of the largest studies (N = 300) of ENDS use in smokers who were not interested in quitting showed promising rates of reduction and cessation at the end of one year, but did not find differences between the active and placebo ENDS.[14] That study suggests that the sensory aspects of ENDS may have some benefit on their own, whereas its authors hypoth-

esize that the low dose of nicotine delivered by this early generation ENDS may not have been sufficient.

Due to the wide variability in nicotine delivery, knowledge of the nicotine pharmacokinetics of an ENDS, after allowing the subjects to gain experience with the product, may be useful in deciding whether to go forward with larger scale studies of reduction or cessation.

The current study tested the latest version of ENDS from NJOY, Inc: the 26 mg NJOY® King Bold in a sample of smokers not currently interested in quitting. The primary objective was to evaluate the acute effects of using the ENDS, after 12 hours of nicotine abstinence, on nicotine blood levels, heart rate, breath carbon monoxide (CO), and perceived levels of cigarette craving and withdrawal, and after gaining one week's experience with the product. Secondary objectives were to evaluate the effects of the one-week trial period on use patterns, cigarette consumption and perceptions of the product as a pilot for a larger study for reduction and cessation.

METHODS

Trial Design

This was an open-label, noncomparative study conducted at one site at Los Angeles Clinical Trials, Burbank, CA. The study and the informed consent form were approved by Essex IRB, Lebanon, NJ.

Subjects

Subjects were recruited from the study site's database and from the community through advertisements. Eligibility was determined through a telephone screen and a screening visit in which smoking history, medical history, and concomitant medications were documented; blood pressure and heart rate were recorded; end-expired breath carbon monoxide (CO) was measured; and a urine specimen for a dipstick test for the presence of drugs of abuse was obtained. Inclusion criteria were as follows: age 18-65 years; general good health; body mass index between 18 and 35 kg/m^2; smoking of at least 10 factory-produced cigarettes per day for the previous year; and CO level >10 ppm. Exclusion criteria were as follows: pregnancy or lactation; current abuse of drugs other than tobacco; use of any prescription psychiatric or opioid medications within 14 days; use of an ENDS within the previous 14 days; use of nicotine replacement products within the previous 30 days; desire to attempt to reduce or quit smoking within the next 30 days; or consumption of alcohol less than 24 hours before visit 3. Subjects were compensated $300 for completing all 3 visits.

Study Product

The ENDSs used were NJOY® King Bold (NJOY, Inc., Scottsdale, AZ) and were provided to the subjects free of charge by the manufacturer. Externally, these ENDSs resemble conventional cigarettes; but internally, they contain a lithium battery, a heater unit, an integrated circuit, and a wick surrounded by a cotton wad containing 0.5 mL of nicotine solution (Figure 1). These ENDSs are neither rechargeable nor refillable; rather, they are disposable. The nicotine solution contains approximately 26 mg of nicotine. The nicotine is dissolved in 2 excipients, namely propylene glycol USP and glycerol USP, both present at approximately 40%. The balance of the solution consists of a variety of flavoring agents, each of which is present at less than 0.2% and has received the Flavor Extracts and Manufacturers Association (FEMA) classification as Generally Recognized as Safe (GRAS) for use in food products,[15] although their safety in inhaled products has not been confirmed. In addition, one NJOY® King Bold style contained menthol. According to the manufacturer, some of the sensory improvements over prior versions consist of size (the same length and diameter as a traditional "king" cigarette), light weight, paper feel, flexible length (rather than a metal tube), soft tip, a realistic light tip that burns along a portion of the length of the device, and flavoring that is intended to appeal to customers in the United States.

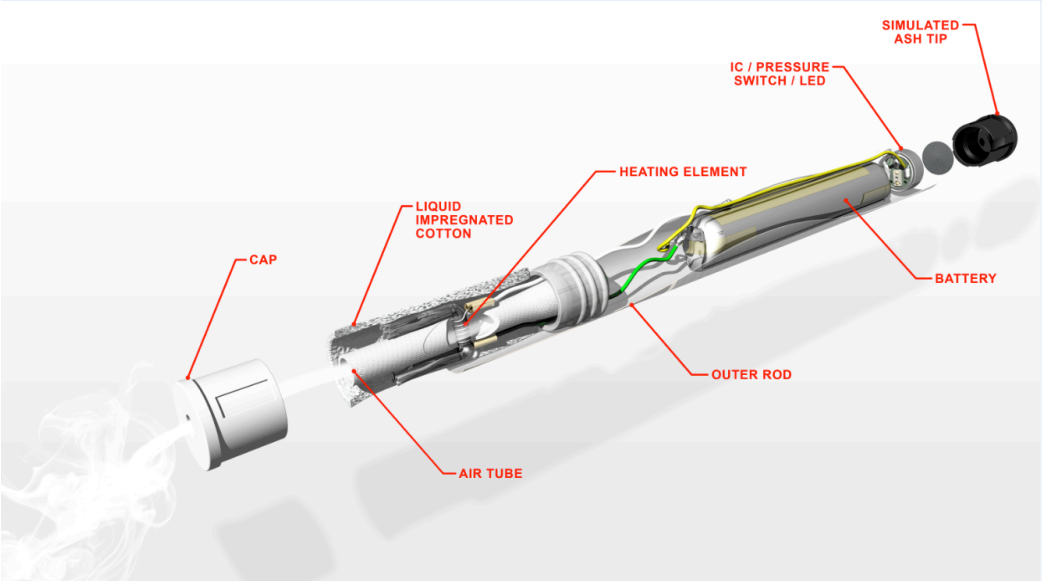
Study Visits and Procedures

The study consisted of 3 clinic visits at one-week intervals. The screening visit (visit 1) was scheduled after 12 noon to ensure that breath CO levels, as measured with a Micro$^+$™ Smokerlyzer® (Bedfont—Maidstone, Kent, UK), would be approaching steady state for the day. Along with the health assessments, smoking and ENDS history were recorded and the Fagerström Test for Nicotine Dependence (FTND) was administered.[16] Subjects who passed the screening visit were asked to return to the clinic within 21 days for the training visit (visit 2), which could occur at any time during the day. At the end of visit 1, subjects were provided with a diary on which to record the number of conventional cigarettes they smoked each day over the following week, providing a more accurate baseline measure than the retrospective data collected at visit 1.

At visit 2, the diary was returned and the subjects were instructed on the use of the ENDS, after which they were allowed to use the product on an ad libitum basis for 20 minutes while in the clinic. Subjects were given a 10-day supply of the ENDS. This supply was intended to last until visit 3, which was scheduled for 7 days later but could occur up to 10 days later. Depending on preference, subjects received either menthol or nonmentholated ENDS.

The subjects were instructed to start using the ENDS on the day after visit 2 and to use them as often as they like (ad libitum) during the following week. No specific instructions on reducing traditional cigarettes were given. At the end of the visit, subjects were supplied with daily diaries to record the number of cigarettes and puffs off the ENDS at the end of each day. A small manual counter was

Figure 1
The NJOY® King Bold



Courtesy of NJOY, Inc;, Scottsdale AZ

provided for keeping track of ENDS puffs. Subjects were instructed to reset the counter to 0 at the end of each day.

Visit 3 was scheduled for 7 days after visit 2. Subjects were instructed to abstain from all forms of nicotine (including tobacco products) for 12 hours before the visit. They were also instructed to abstain from food and caffeinated beverages for one hour before the visit. The visit started at either 7:30 AM or 10:30 AM. At visit 3, the subject's diary of cigarette and ENDS usage was collected and the subjects completed a questionnaire of their perceptions of the ENDS. Subjects were eligible to continue with the testing procedures if their breath CO level was less than 10 ppm (verifying 12-hour abstinence from cigarette use), and if their blood alcohol level was 0.00%, (verifying abstinence from alcohol) as measured by the Alco Sensor IV (Intoximeters, Inc, St. Louis, MO).

A 20-gauge catheter was inserted into the antecubital (large forearm) vein approximately 30 minutes before testing of the study product began. The ENDS dosage for the pharmacokinetic/pharmacodynamic testing consisted of 2 series of 10 puffs of the ENDS, with a 30-second inter-puff interval (IPI). The second series of puffs began one hour after the start of the first series. The puffs were taken from either a mentholated or a non-mentholated ENDS, depending on the subject's preference. A 4-mL blood sample was drawn into a lavender-top tube 5 minutes before and 5, 10, 15, and 30 minutes after the first puff of each series. The plasma samples were then sent to a central laboratory (LabCorp) for analysis of nicotine and cotinine by liquid chromatography/tandem mass spectrometry (LC/MS-MS).[17]

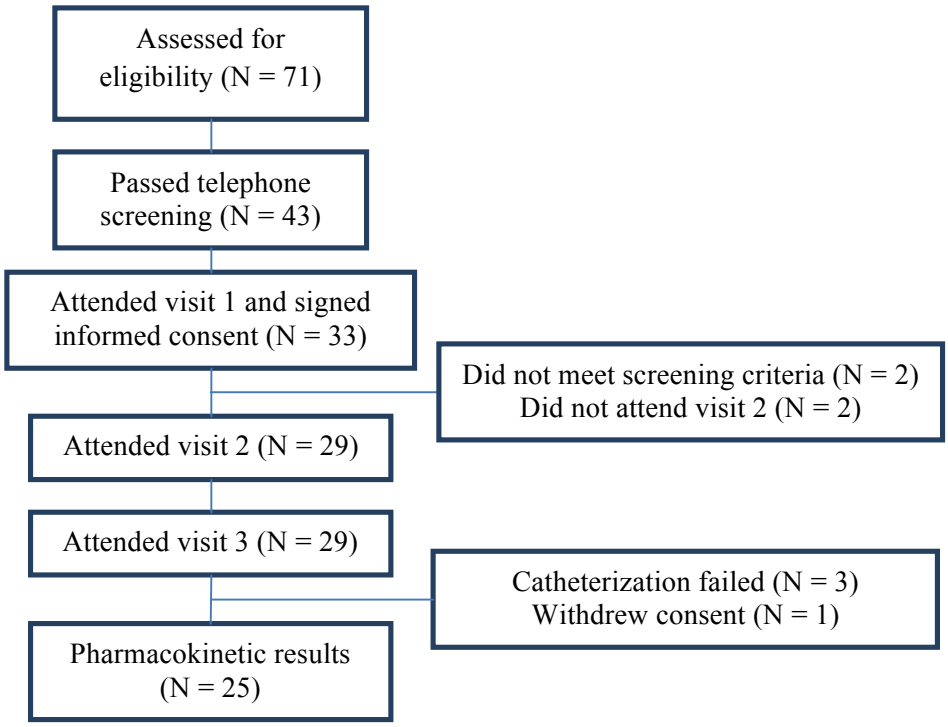
End-expired CO was measured 10 minutes before the first series of puffs (baseline), and again 12, 25, 35, and 50 minutes after the first puff of both testing series. Heart rate (beats/min) was recorded by the study staff at 20-second intervals beginning 5 minutes before the first puff of each visit and continuing for 35 minutes after each set of puffs. (DinaMap® Pro 300 with finger sensor, GE, Fairfield, CT).

Standardized self-administered scales for measuring perceived craving for cigarettes and symptoms of nicotine withdrawal were administered 2 minutes before, and 7, 20, and 40 minutes after product administration.

Measures

Craving assessment. This study used a self-administered 5-item subset of the Questionnaire of Smoking Urges (QSU) that, although not validated, has been used in previous publications.[18,19] Sample items are "I crave a cigarette right now" and "If it were possible I would smoke right now." Each item is a 100-mm visual analogue scale (VAS) from 0 (disagree) to 100 (agree). The subject draws a perpendicular line that intersects the 100–mm line at the point that best describes how he or she is feeling at that moment. A standardized ruler was used to measure the length of the line from 0 to the

Figure 2
Disposition of Subjects



point of intersection. The mean of the 5 items was used a single "Craving Score."

Withdrawal assessment. For the assessment of symptoms of nicotine withdrawal, the subjects completed a self-administered questionnaire that contained 4 items of the 15-item Minnesota Nicotine Withdrawal Scale (MNWS)[20]: (1) angry, irritable, frustrated; (2) anxious, nervous; (3) depressed mood, sad; and (4) difficulty concentrating. These items were selected because they were judged to be most likely to occur after only 12 hours of abstinence from nicotine. A similar subset was used for an earlier pharmacokinetic study of an ENDS product.[5] For each item, the subject circled a number that best described how he or she felt at that moment: 0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = severe. Each item was analyzed separately and not aggregated into a single "withdrawal score."

***Perception of* ENDS.** After the one-week trial period, subjects completed a 9-item self-administered questionnaire that rated their satisfaction with the ENDS. Three items compared "taste," "feel," and "look" of the ENDS with that of a traditional cigarette. Other items included "Delivers a high level of nicotine," "Reduces your craving for nicotine," "Ease of use," "Safety of using the product," "Would use to help cut back on smoking traditional cigarettes," and "Would use to help quit smoking traditional cigarettes." Each item was rated on a scale of 0 (not at all satisfied) to 6 (extremely satisfied)." Items for this pilot questionnaire were compiled from several studies of ENDS.[5,7]

Nicotine extraction from product. After the pharmacokinetic portion of the study, each subject's used ENDS units were sent to a laboratory (Global Laboratory Services, Wilton, NC) to determine the amount of nicotine that had been extracted during the 20 puff testing session. Each unit was disassembled and the remaining nicotine in the unit extracted with a solvent and measured by a gas chromatograph-flame ionization detector.

Statistical Analysis

Univariate statistics were calculated for all parameters at each time (mean, standard error of the mean, and median for continuous variables; median, minimum, maximum for scalar variables). Paired t tests were used to compare continuous variable pre- and post-puffing at each time. Measurements immediately prior to the first series of puffs were used as the baseline for calculating change during both puff series; thus, change values for the second series of puffs represent the cumulative effect of both puff series. Paired t tests were used to compare baseline and post-treatment

Table 1
Demographics and Baseline Characteristics

Sex, Male %	66%
Age, years, mean, (range)	43 (18-63)
Race, White, Asian, %	86%, 14%
Baseline cigarettes/day, mean, (SEM)	20.1 (1.28)
Smoking history, years, mean (SEM)	21.1 (2.46)
Carbon monoxide, ppm, mean (SEM)	18.5 (1.5)
Menthol smokers, %	24%
Number of previous quit attempts, median	3
History of ENDS use, %	55%
FTND[a], mean (SEM)	4.5 (0.4)

Note.
a FTND = Fagerström Test for Nicotine Dependence, a 0 to 10 scale, with higher scores indicating greater dependence.

values. All comparisons were 2-tailed, with a p-value of .05 considered to be statistically significant, with Bonferroni corrections applied to account for multiple comparisons.

According to the central laboratory (LabCorp), the limit of detection (LOD) and lower limit of quantification (LLOQ) for the analysis of plasma nicotine is 1 ng/mL. For baseline blood samples with "none detected" levels of nicotine (below the LLOQ), we assigned the value LLOQ/2 or 0.5 ng/ml.[21]

RESULTS

Subjects

Seventy-one candidates were assessed for eligibility through telephone screening. Of the 43 who passed the phone screening, 33 attended the in-person screening visit (visit 1) and signed the informed consent document. Two subjects did not meet the screening criteria at visit 1, and 2 others did not return for visit 2. The remaining 29 subjects attended all 3 visits. At visit 3, we were unable to obtain a steady flow of blood from 3 female subjects, and a fourth female subject decided that she did not want to continue after successful insertion of the catheter into the forearm vein, leaving 25 who completed all of the testing at visit 3 (Figure 2). The demographics and baseline characteristics for the 29 who completed visit 2 and attended visit 3 are presented in Table 1. Sixty-six percent of the subjects were male; 45% had never used an ENDS product, 48% had used fewer than 10 ENDS, and only 7% had used more than 10 in their lifetime.

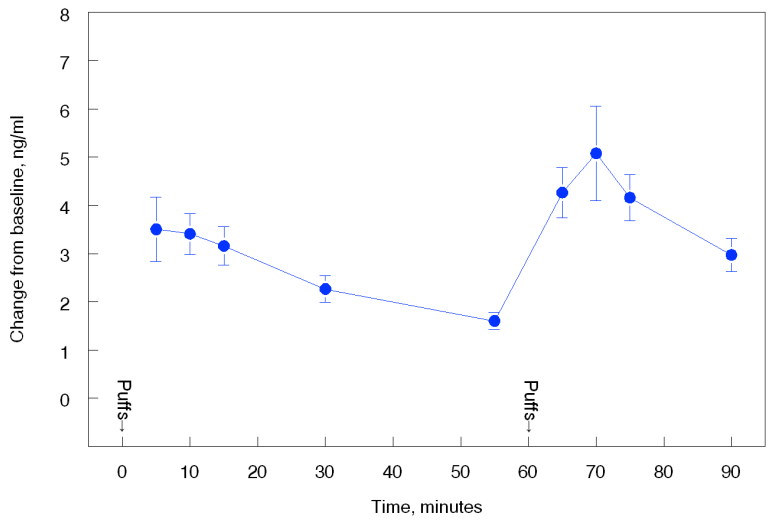
Pharmacokinetics and Pharmacodynamics

Nicotine blood levels. Sixteen subjects had no detectable plasma nicotine at baseline (quantified as 0.5 ng/mL, see statistical analysis section). The remaining 9 subjects had baseline levels ranging from 1.1 to 4.1 ng/mL. The pattern of rise and fall in nicotine levels after each series of ENDS puffs was similar for both groups. We present here data for the 16 subjects who had no detectable levels of blood nicotine at baseline, a sample that provides more reliable results for research and regulatory issues with regard to the response to nicotine delivery from an ENDS.

As Figure 3 shows, after one week of testing, the mean increase in blood nicotine was 3.5 ng/mL (SEM, 0.69 ng/mL; range, 0.8-8.5 ng/mL) approximately 30 seconds after the first series of 10 puffs, slowly declined to the 30-minute mark, increased again after the second series of puffs to a peak mean increase of 5.1 ng/mL (range, 1.1-7.1 ng/mL) 10 minutes after the first puff of the second series, and then gradually decreased to the 90-minute time point. Mean changes from baseline in nicotine blood levels were statically significant at all measurement times (paired t test, all $p < .002$). The correlation between the total amount of nicotine that subjects extracted from the ENDS during the 2 series of 10 puffs and their plasma nicotine levels was 0.67 at the 5-minute mark and 0.57 at the 65-minute mark, indicating that puff topography played a mediating role.

Heart rate. Baseline heart rate on the study day ranged from 48 to 86 beats/min, with a mean of 68 beats/min (SEM, 2.2 beats/min). Consistent with the nicotine blood levels, heart rate (Figure 4) increased through the 10-minute mark after the beginning of each series of puffs, then gradually declined towards baseline. Mean increases in heart rate 5 and 10 minutes after the first series of puffs were 2.4 and 5.3 beats/min, respectively, after which the mean heart rate increase declined to 0.8 beats/min. Mean changes following the second

Figure 3
Plasma Nicotine, Change from Baseline



Note.
Mean changes from baseline were statically significant at all times (paired t test, p < .002).

series of puffs were 2.0 and 4.8 beats/min after 5 and 10 minutes, respectively, followed by a decline to 2.6 beats/min. All increases in heart rate were statistically significant except at the last measurement (35 minutes) after the first series of puffs (paired t test; all p < .004).

Carbon monoxide. Breath CO levels did not rise after either series of puffs, thereby confirming that the heating of the nicotine solution did not result in combustion. Mean baseline CO levels were 3.5 ppm (SEM, 0.57 ppm), with a range of 0-9 ppm. The mean CO 2 hours later had declined to 3.08 ppm (SEM, 0.53 ppm). Only one subject had an increase as high as 2 ppm, which was within the margin of error of the CO monitor, between any 2 time points.

Craving. After 12 hours of abstinence from nicotine, baseline craving levels for most of the subjects were moderate to high (median, 76/100; range, 0-100). Figure 5 shows the median change in craving from baseline to each measured time point. Each series of ENDS puffs followed the same pattern, with craving reduced by the highest median percentage immediately after ENDS use (55.5%, series 1; 80.7%, series 2), followed by steady incremental increases in craving.

Withdrawal. After 12 hours of abstinence from nicotine, baseline scores for anger, depression, and lack of concentration were low and are not reported here. Anxiety was the only withdrawal symptom that at least 20% of the subjects rated as 3 or more on the 5-point scale at baseline. Anxiety declined considerably after the first series of puffs, with only one report as high as 2 on the 5-point scale at any subsequent time-point.

Use of ENDS and Cigarettes during the Practice Week

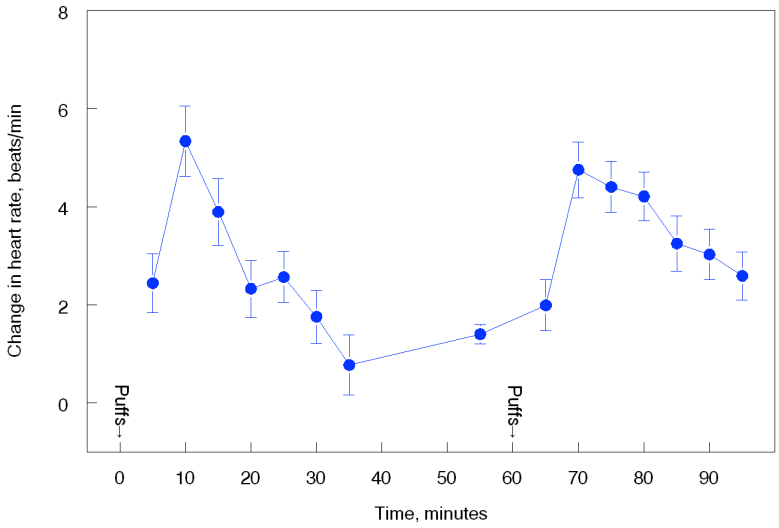
Use of ENDS. All of the subjects used the NJOY® King during the trial week, with all but 5 subjects using it every day. Mean daily puff usage varied widely (median, 59 puffs/day; range, 1.7-400 puffs/day). Only 2 subjects averaged more than 160 puffs per day (345 and 400 puffs/day, respectively).

Reduction in Cigarette Use. Mean daily cigarette smoking decreased from the baseline week to the trial week in 89% of subjects, with a mean reduction in cigarettes per day of 39%, a statistically significant change (paired t test, p < .001). Smoking was reduced by 50% or more in 32% of subjects. Four subjects reported no cigarette usage on the 6th day, the day before the testing day.

Subjects' Perceptions and Experiences

Perceptions of the ENDS. Subjects had generally favorable perceptions of the ENDS after the one-week trial period. Figure 6 shows the percentage of subjects with responses to the perception questionnaire in the categories of low (0-1), medium (2-4), and high (5-6) on the 7-point scale ranging from 0 for "not at all satisfied" to 7 for "extremely satisfied." More than 50% of subjects reported "high satisfaction" with features such as "easy to use," "looks like a traditional cigarette," and "safety of using product." Responses were mixed for compar-

Figure 4
Heart Rate, Change from Baseline

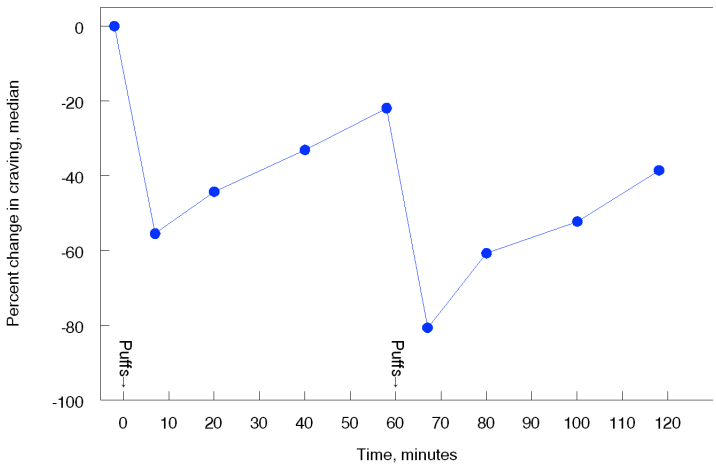


Note.
All changes from baseline were significant (paired t test, p < .004) except for 35 minutes after the first series of puffs.

isons of "taste" and "feel" of the ENDS with those of traditional cigarettes. Most subjects responded positively on questions regarding "delivers a high level of nicotine" and "reduces craving for nicotine."

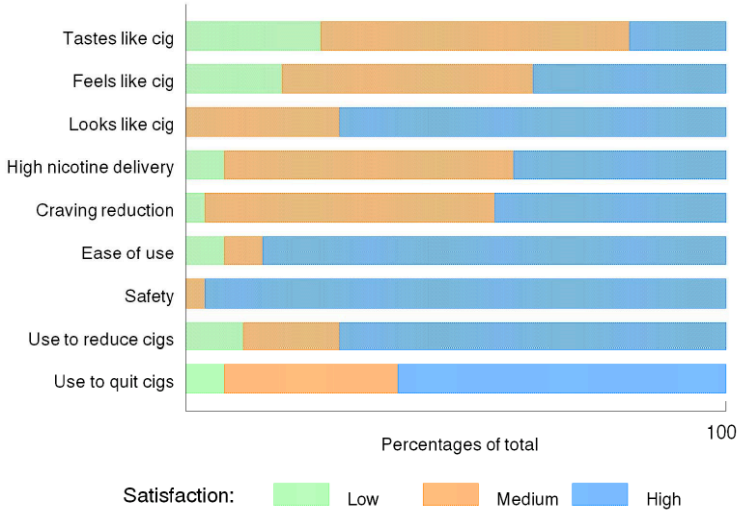
On the issue of future use, 72% responded in the "high satisfaction" category to the item "would help cut back on smoking," whereas 62% responded in the same category to the item "would use the prod-

Figure 5
Craving for Cigarettes, Change from Baseline



Note.
The craving score was the mean of the visual analog scale scores (0-100 mm) for a 5-item subset of the Questionnaire of Smoking Urges.

Figure 6
Perceptions of the NJOY® King ENDS after One Week of Use



Note.
Percentage of subjects with responses to the perception questionnaire in the categories of low (0-1), medium (2-4), and high (5-6) on the 7-point scale ranging from 0 for "not at all satisfied" to 7 for "extremely satisfied."

uct to help quit smoking."

Adverse events. The NJOY® Kings were well tolerated. Twelve subjects experienced a total of 15 adverse events (AE) during the one-week trial period. Twelve AEs were considered "probably related" to the ENDS; the most common of these AEs were local irritation of the mouth, throat, or airways, specifically throat irritation (7), followed by cough (2), dry throat (1), and burning sensation on lips (1). One subject experienced intermittent headaches. All of the subjects reported the AE's as "mild," with the exception of one subject who discontinued use after 2 days because of an AE of throat irritation, which was rated as moderate. Most of the local AEs resolved within the first few days of use as subjects became more familiar with the product.

Discussion

The purpose of this study was to assess the nicotine pharmacokinetics and user perception and satisfaction with the NJOY® King Bold electronic nicotine delivery system (ENDS) to determine its suitability for a larger-scale study of the efficacy and safety of the product as an aid to smoking reduction/cessation. In smokers with a week's worth of practice and12 hours abstinence from nicotine, 10 puffs from the ENDS over a 4.5-minute period resulted in acute increases in plasma nicotine and heart rate and a median 55% reduction in craving, suggesting a clinically significant nicotine boost. Although comparisons with other studies can only be suggestive, the 3.5 ng/mL nicotine boost at 5 minutes was larger than that reported for several earlier-model ENDS products but was less than 50% of that achieved by users of some custom ENDS kits (10 ng/mL) that have been shown to more closely approximate the boost from traditional cigarettes.[7] The nicotine boost from the ENDS product used in this study is probably greater than that from the nicotine inhaler, gum, or lozenge and similar to that from the fast-acting 2-mg nicotine mouth spray available in parts of Europe.[21]

Although increases in blood nicotine were observed in all subjects, there was considerable between-subject variability, particularly at the initial 5-minute mark (range, 0.8 to 8.5 ng/mL). This broad range suggested considerable individual variation in smoking topography, as confirmed by the correlation of 0.67 between nicotine boost at 5 minutes and the amount of nicotine that the subject extracted from the product through puffing during testing. Allowing the subjects to use the product ad libitum until satisfied, rather than on a fixed schedule of 10 puffs with an inter-puff interval of 30 seconds, might have resulted in reduced variability. It is also possible that even within the fixed schedule, the subjects were effectively titrating their dose to achieve a desired level of nicotine, albeit less than they would have received from smoking a traditional cigarette. As expected, end-expired breath CO did not increase after use of the ENDS, thereby confirming that no combustion had

taken place.

The practice week in this study not only provided the subjects with experience in using the product before the pharmacologic testing (only 7% had previously used more than 10 ENDS units in their lifetime), but it also provided pilot data on adverse events, use patterns, cigarette consumption, and product perceptions. The ENDS used in this study was well tolerated, with mild, transient throat irritation being the most commonly reported adverse event.

The subjects took a median of 59 puffs per day of the ENDS, which translates to roughly the same number of puffs as 6 cigarettes, slightly less than the mean reduction of 7 cigarettes per day (39%). Participants who volunteer to test an ENDS for one week would be expected to reduce their smoking to some degree, and short-term results are not predictive of future reduction or quitting; but the magnitude of reduction, including 4 subjects who had switched completely to the ENDS on the last day of testing, are promising signs. The reduction results were also similar to those reported at the end of the second week of the ECLAT study (which evaluated use of ENDS in smokers not interested in quitting).[14] Given the lack of a placebo control group, it is unclear how much of the reduction was due to nicotine delivery and how much to the sensory aspects of the ENDS. The ECLAT study did not find a difference between active and placebo groups in term of reduction, but the authors of that study suggested that the early-generation ENDS that they used might not have delivered sufficient nicotine to further augment the behavioral or sensory properties of the product.[14]

The participants' short-term perceptions of this ENDS were generally positive. Although these results are not predictive of long-term reduction or quitting, 72% reported high levels of satisfaction for "using to cut back on cigarettes," and 62% for "using to quit smoking cigarettes." High levels of satisfaction were also reported for "looks like a cigarette," "ease of use," and "safety." Other aspects of satisfaction with the product had greater variation in self-reported ratings, including the sensory items "tastes" or "feels" like a cigarette and the dependence items "delivers a high level of nicotine" and "reduces craving." These results suggest avenues for future product refinement.

As newer ENDS products that mimic the pharmacokinetics and sensory characteristics of cigarettes even more closely are developed, there could be multiple implications for tobacco users as well as for tobacco product regulators.[22] Historically, nicotine replacement products for smoking cessation have been tested to assure that they have low abuse liability due to concerns that primary addiction in nonsmokers might occur if "liking" is high and also out of concern that those who switch to the nicotine replacement product after quitting cigarettes might not be able to quit using the product. However, one also can argue that higher ratings of comparability to cigarettes might actually have public health value by enabling smokers to switch to and continue to use an ENDS product rather than a cigarette. Other public health factors include the short- and long-term health effects of using an ENDS, not only compared to quitting completely or using NRT, but to continued smoking. The fact that ENDS generate heat to aerosolize nicotine, eliminates many of the toxic constituents (eg tar and carbon monoxide) created by the combustion of tobacco in traditional cigarettes. A recent study of a sample of ENDS showed that the toxicant levels were orders of magnitude less than tobacco cigarettes, but more than in medicinal nicotine replacement products.[23] Further research is needed to inform the public health debate.

The current study has several limitations. First, the small sample of primarily Caucasian, primarily non-menthol smokers limits the study's generalizability. However, small sample sizes are common for pharmacokinetic studies, so the pharmacokinetic results remain highly relevant. Second, for this study we assumed that one week of practice would be sufficient for subjects to become "experienced users." Future studies could include pharmacokinetic and/or puff topography testing before and after a trial use period to quantify the effect of practice in using the device. Third, the one-week testing period was too short to support any conclusions about the ENDS product's long-term potential for smoking reduction or cessation. Nevertheless, the positive results of this study provide impetus to move forward with a larger study. Finally, longer-term studies of ENDS for smoking reduction/cessation should include a non-nicotine control group to assess the efficacy of nicotine above and beyond the sensory and behavioral aspects of ENDS—something that was not done in this short-term study.

These results suggest that this ENDS product delivered enough nicotine to suppress craving, was generally liked, resulted in few adverse events, and resulted in significant smoking reduction during a one-week trial. Nicotine delivery was comparable to that provided by some current FDA-approved nicotine replacement products. Thus, this ENDS has potential for use as an aid to smoking reduction and cessation, but larger trials of the product are needed. Toxicological research is also needed to assess whether ENDS deliver significant amounts of any potentially harmful substances besides nicotine, which is a relatively benign substance despite its primary role in dependence.

Human Subjects Statement

This study was approved by Essex IRB, Lebanon NJ on April, 1, 2013. Protocol Number NJ-001-LACT. The ClinicalTrials.gov Identifer is NCT01898169.

Conflict of Interest Statement

Dr Nides has received compensation from NJOY, Inc. and GlaxoSmithKline. Dr Leischow has re-

ceived compensation from GlaxoSmithKline, Pfizer, and Cypress Bioscience. Mr Simmons and Ms Bhatter have no conflict of interest to report.

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