Nicotine Exposure by Device Type among Adult Electronic Nicotine Delivery System Users in the Population Assessment of Tobacco and Health Study, 2015–2016

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ABSTRACT

Background: Previous studies have examined the characteristics of open and closed system electronic nicotine delivery system (ENDS) users, but population-level information on nicotine exposure among these users has not been available.

Methods: We analyzed nicotine biomarker and survey data from Wave 3 of the Population Assessment of Tobacco and Health (PATH) study collected from October 2015 to October 2016. We identified 277 exclusive ENDS users and 468 dual cigarette and ENDS users and analyzed concentrations of nicotine and its metabolites obtained from urine samples by device type and other characteristics, such as frequency of use and e-liquid flavor.

Results: Among exclusive ENDS users, open system users had higher levels of total nicotine exposure (TNE-2) than closed system users [8.8 μmol/g creatinine (95% confidence interval [CI] = 5.3–14.8 μmol/g vs. 2.0 μmol/g (95% CI = 0.7–5.4 μmol/g)]. However, TNE-2 concentrations were similar when open and closed system users were stratified as daily [26.4 μmol/g (95% CI = 20.1–34.7 μmol/g) vs. 27.1 μmol/g (95% CI = 16.4–44.9 μmol/g)] and nondaily [0.5 μmol/g (95% CI = 0.1–1.9 μmol/g) vs. 0.2 μmol/g (95% CI = 0.0–0.7 μmol/g)] ENDS users. Dual users generally had higher nicotine exposure than exclusive users.

Conclusions: Nicotine exposure was observed to be higher among exclusive open system ENDS users compared with closed system users, but levels were similar when users were stratified by frequency of use.

Impact: These results suggest that exclusive ENDS users with similar use patterns receive comparable levels of nicotine, regardless of whether they use open or closed system devices.

Introduction

More research is warranted to understand potential benefits and risks of high-nicotine electronic nicotine delivery systems (ENDS) to adult smokers and nicotine-naïve youth (1). Such devices could facilitate and prolong addiction, especially among young people; conversely, sufficient nicotine delivery from ENDS might help adult smokers transition from combustible tobacco product use. ENDS devices can vary widely from closed disposable or pod-based systems (such as "Juul") to open tank or modifiable systems (2). Our interest in this study is whether certain types of devices produce higher levels of nicotine exposure than others (3). Previous studies have used biomarker data to measure nicotine exposure among ENDS users (4–6), but we are unaware of large-scale population studies that have looked at nicotine biomarker levels by device category. In this study, we use the resources of the national Population Assessment of Tobacco and Health (PATH) Study to compare nicotine exposure among users of open (rechargeable and refillable) and closed (not rechargeable or uses prefilled cartridges) system ENDS devices in the United States.

Materials and Methods

This study used survey and biomarker data that were collected from October 2015 to October 2016 in Wave 3 of the PATH Study. The PATH Study is a nationally-representative longitudinal cohort study of the U.S. civilian, noninstitutionalized population of youth and adults aged 12 years and older. The study is sponsored by the Center for Tobacco Products of the Food and Drug Administration and the National Institute of Drug Abuse of the NIH and conducted by Westat. At Wave 1, a total of 32,320 adults aged 18 years and older completed survey interviews, and 78.4% or 28,148 of these participants were interviewed during Wave 3. At Wave 1, a stratified probability sample of 11,522 adults who were interviewed and provided a urine specimen was selected for biospecimen analyses. The sample was selected to ensure that respondents represented diverse tobacco product use patterns. Selected participants were asked for urine specimens after completion of the interview in each follow-up wave. At Wave 3, some 8,643 respondents provided a urine specimen that met the criteria for analysis. Detailed information on the PATH Study and its design and methods have been published previously (7).

The study analyzed data from current ENDS users, who reported current every day or someday use of "electronic nicotine products" and were asked a series of questions about their product use and the characteristics of the device that they used most of the time (8). These questions included whether the device was rechargeable, used cartridges, was refillable, and could have its voltage changed. Users were also asked whether the e-liquid used in the device contained nicotine as

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well as various flavors including tobacco, menthol or mint, clove or spice, fruit, chocolate, an alcoholic drink, a nonalcoholic drink, candy, desserts, or other sweets, or some other flavor. Respondents could select multiple flavors. In this analysis, we categorized e-liquid flavors as any tobacco flavor, any menthol or mint excluding tobacco flavor, and any fruit/sweet/spice/drink excluding tobacco, menthol, and mint.

Consistent with a previous analysis that examined the demographic and product use characteristics of adult ENDS users (8), we classified ENDS devices as open systems if they were rechargeable, did not use cartridges, and were refillable; and closed systems if they were either not rechargeable or were rechargeable and used cartridges. Current ENDS users were further classified as exclusive users if they reported currently not using cigarettes, filtered cigars, cigarillos, traditional cigars, pipes, hookah, smokeless tobacco, snus pouches, or dissolvable tobacco at all and not having used nicotine replacement therapy (NRT) products in the past three days. Current users were categorized as dual users if they reported also currently using cigarettes every day or some days, but none of the other listed tobacco products and not using NRT products in the past three days. This study focuses on exclusive ENDS users, given that dual users also receive nicotine exposure from cigarettes, but results for dual users are presented for comparison with those for exclusive users.

We analyzed data from the urinary nicotine panel of the Wave 3 Biomarker Restricted Use File (9), which contains concentrations for nicotine and its metabolites as well as the minor alkaloids anabasine and anatabine. Urine specimens were stored and analyzed by the National Center for Environmental Health of the Centers for Disease Control and Prevention (CDC), and the results presented here meet the standards for accuracy and precision of CDC's quality control and assurance program (10). The detailed laboratory procedure manual for the urinary nicotine biomarker panel is available online and presents measures of accuracy and precision including coefficients of variation for the analytes (11). Coefficients of variation for the biomarkers used in this analysis ranged from 3.48% to 7.42% for low concentrations and from 3.08% to 5.66% for high concentrations. Researchers have recommended the use of total nicotine equivalents, the sum of concentrations of nicotine and its metabolites, as the best measure of nicotine exposure (12). Cotinine and trans-3′-hydroxycotinine were analyzed for all samples, and their molar sum was calculated as TNE (Total Nicotine Equivalents)-2. Nicotine and five major metabolites were analyzed in samples with cotinine levels at or above 20 ng/mL, and their molar sum was calculated as TNE-6. We calculated mean biomarker levels by device type for nicotine and all of its available metabolites and mean TNE-2 levels by device type and other characteristics including frequency of use, quantity of use, and whether e-liquid contained certain flavors or nicotine. Geometric mean concentrations were calculated because of skewness in the data, and concentrations were adjusted for creatinine to account for differences in hydration. Individuals with creatinine values outside the normal range of 10–370 mg/dL were excluded from analyses. Imputed values equal to the limit of detection (LOD) divided by the square root of 2 were used when biomarker concentrations were below the LOD. Comparisons of biomarker levels between groups were conducted using linear regression analysis of participants' data with the logged biomarker concentration as the dependent variable and a group indicator variable and logged creatine concentration as independent variables (13). All analyses were conducted in SAS version 9.4 (14) using urinary biomarker weights and balanced repeated replication with Fay's adjustment of 0.3 to account for the complex survey design of the PATH Study. The use of Wave 3 cross-sectional biomarker weights ensured that the estimates were representative for current ENDS users who were in the U.S. civilian, noninstitutionalized adult population at Wave 1 and were in the United States and not incarcerated at Wave 3. Westat's Institutional Review Board approved the PATH Study design and protocol.

Results

Table 1 presents geometric mean biomarker concentrations by device type for exclusive and dual ENDS users. Among exclusive users, open system users were found to have higher levels of cotinine (563.0 vs. 118.6 μg/g creatinine), hydroxycotinine (990.4 vs. 238.2 μg/g),

Table 1. Urinary biomarker concentrations by tobacco use status and device type, 2015–2016.

	Exclusive users[a]		Dual users	
Urinary biomarker (concentration)	Open system ($n = 205$)[b] GM (95% CI)	Closed system ($n = 72$) GM (95% CI)	Open system ($n = 251$) GM (95% CI)	Closed system ($n = 217$) GM (95% CI)
Anabasine (μg/g creatinine)	0.8 (0.6–0.9)[c,d]	0.8 (0.5–1.4)[c,d]	4.7 (4.0–5.6)[e]	7.6 (6.3–9.2)
Anatabine (μg/g)	0.7 (0.5–0.9)[c,d]	0.6 (0.4–1.1)[c,d]	7.1 (5.8–8.8)[e]	12.7 (10.2–15.8)
Cotinine (μg/g)	563.0 (332.6–953.0)[e]	118.6 (44.7–315.0)	2,435.5 (2,091.4–2,836.2)	2,571.0 (2,082.8–3,173.8)
Cotinine *N*-oxide (μg/g)	146.6 (97.7–219.8)	112.7 (62.5–203.1)[c]	291.7 (259.0–328.6)	310.2 (257.0–374.3)
Hydroxycotinine (μg/g)	990.4 (588.6–1,666.4)[e]	238.2 (87.8–646.2)	3,866.8 (3,250.5–4,600.0)	4,452.9 (3,498.7–5,667.4)
Nicotine (μg/g)	584.4 (383.0–891.7)	357.4 (170.0–751.2)[c]	1,019.8 (848.8–1,225.3)[e]	1,490.3 (1,169.4–1,899.2)
Nornicotine (μg/g)	22.8 (17.0–30.7)	17.2 (9.8–30.4)[c]	48.8 (42.5–56.0)	63.1 (52.7–75.5)
Nicotine *N*-oxide (μg/g)	182.3 (123.1–269.9)	126.9 (65.1–247.5)[c]	308.8 (264.5–360.6)	379.4 (301.2–477.9)
Total nicotine equivalents - 2 (μmol/g)	8.8 (5.3–14.8)[e]	2.0 (0.7–5.4)[c]	35.3 (30.1–41.5)	40.1 (32.4–49.7)
Total nicotine equivalents - 6 (μmol/g)	29.5 (19.9–43.9)	19.3 (10.6–35.3)[c]	52.0 (46.1–58.6)	62.8 (53.4–73.9)

[a]Exclusive users reported current every-day or some-day use of electronic nicotine products, and dual users reported current every-day or some-day use of electronic nicotine products and cigarettes. Both groups reported not currently using filtered cigars, cigarillos, traditional cigars, pipes, hookah, smokeless tobacco, snus pouches, or dissolvable tobacco and not using nicotine replacement therapy products in the past 3 days.

[b]Devices were classified as open systems if they were rechargeable, did not use cartridges, and were refillable, and closed systems if they were either not rechargeable or were rechargeable and used cartridges.

[c]Estimate should be interpreted with caution because it has low statistical precision. It is based on a sample size of less than 50, or the relative SE of the estimate is larger than 30%.

[d]More than 40% of values were below the LOD.

[e]$P < 0.05$ for open and closed system users.

Table 2. TNE-2 concentrations for exclusive ENDS users by product and use characteristics, 2015–2016.

	Exclusive users		
Total nicotine equivalents - 2 (μmol/g creatinine)	**Overall GM (95% CI)**	**Open system ($n = 205$) GM (95% CI)**	**Closed system ($n = 72$) GM (95% CI)**
Frequency of ENDS use			
Every day ($n = 200$)	26.6 (21.7–32.6)	26.4 (20.1–34.7)	27.1 (16.4–44.9)[a]
Some day ($n = 77$)	0.3 (0.1–0.9)[a]	0.5 (0.1–1.9)[a]	0.2 (0.0–0.7)[a]
Quantity of ENDS used per day[b]			
<1 mL of e-liquid ($n = 36$)	—	16.5 (8.4–32.5)[a]	—
1+ mL of e-liquid ($n = 113$)	—	35.1 (27.8–44.3)	—
<1 product or cartridge ($n = 18$)	—	—	19.1 (7.9–46.0)[a]
1–3 products or cartridges ($n = 13$)	—	—	55.9 (34.8–89.9)[a]
4+ products or cartridges ($n = 5$)	—	—	21.4 (2.3–197.6)[a]
E-liquid flavor[c]			
Tobacco ($n = 59$)	6.1 (2.4–15.7)	7.0 (1.5–32.4)[a]	5.2 (1.8–14.7)[a]
Menthol or mint ($n = 49$)	5.9 (2.3–15.1)[a]	7.1 (2.2–22.9)[a]	3.9 (0.7–22.6)[a]
Fruit/sweet/spice/drink[d] ($n = 154$)	7.8 (4.4–13.8)	9.5 (5.2–17.2)	2.1 (0.3–13.7)[a]
E-liquid contains nicotine			
Yes ($n = 226$)	14.3 (9.8–20.8)	15.3 (9.3–25.0)	11.2 (5.4–23.2)[a]
No ($n = 48$)	0.2 (0.1–0.4)[a]	0.2 (0.1–0.8)[a]	0.1 (0.0–0.5)[a]
Device voltage can be changed			
Yes ($n = 159$)	13.6 (8.3–22.3)	13.5 (8.2–22.2)	15.9 (1.5–165.4)[a]
User changes voltage ($n = 119$)	13.5 (7.8–23.4)	12.5 (7.0–22.1)[e]	40.1 (15.4–104.3)[a]
No/don't know ($n = 101$)	2.6 (1.2–5.3)[a]	3.1 (0.9–10.5)[a]	2.0 (0.7–5.7)[a]

[a]Estimate should be interpreted with caution because it has low statistical precision. It is based on a sample size of less than 50, or the relative SE of the estimate is larger than 30%.
[b]Established every-day ENDS users were asked about the average number of products that they used each day. Users of devices that were not rechargeable or refillable were asked about the number of products that they used; users of devices with nonrefillable cartridges were asked about the number of cartridges; and users of devices with refillable cartridges, tanks, or modifiable systems were asked about the number of milliliters of e-liquid.
[c]Respondents could select multiple e-liquid flavors. Flavor use was categorized as any tobacco flavor; any menthol or mint, excluding tobacco flavor; and any fruit, sweet, spice, or drink, excluding tobacco, menthol, or mint.
[d]Response options included in this category were clove or spice, fruit, chocolate, an alcoholic drink (such as wine, cognac, margarita or other cocktails), a nonalcoholic drink (such as coffee, soda, energy drinks, or other beverages), and candy, desserts, or other sweets.
[e]$P < 0.05$ for open and closed system users.

and TNE-2 (8.8 vs. 2.0 μmol/g creatinine) compared with closed system users. Among dual users, closed system users had higher levels of anabasine (7.6 vs. 4.7 μg/g creatinine) and anatabine (12.7 vs. 7.1 μg/g) compared with open system users. Dual users generally had higher nicotine exposure than exclusive users, with TNE-2 concentrations of 35.3 and 40.1 μmol/g creatinine for open and closed system dual users.

As shown in estimates for exclusive users in **Table 2**, every day ENDS users had much higher nicotine exposure than some day users overall ($P < 0.001$), but TNE-2 concentrations were similar for open and closed system users when stratified by frequency of ENDS use ($P = 0.905$ for every day and 0.361 for some day users). Concentrations were also similar for users of various e-liquid flavor categories such as tobacco ($P = 0.801$), menthol or mint ($P = 0.505$), and fruit, sweet, spice, or drink ($P = 0.146$) by device type. TNE-2 levels increased with greater quantity of use for daily open system users ($P = 0.045$). ENDS users who reported using e-liquids with nicotine had much higher nicotine exposure than users who reported that their e-liquids did not contain nicotine ($P < 0.001$), although 14 of the 48 exclusive users who reported not using nicotine had TNE-2 concentrations above 1 μmol/g creatinine. In addition, ENDS users who reported that they could change the voltage on their device had higher nicotine exposure than those who reported that they could not or did not know if they could do so ($P < 0.001$). The small number of closed system users who said that they could and did change the voltage ($n = 8$) tended to have very high TNE-2 levels.

Supplementary Table S1 presents concentrations for nicotine and its metabolites for exclusive and dual users who reported that their e-liquid contained nicotine by device type and frequency of use. Among exclusive users, no differences were observed by device type when users were stratified by frequency of use. This pattern was also generally observed for dual users.

Discussion

This study analyzed nicotine exposure among users of open and closed system ENDS devices using PATH Study biomarker and survey data. Among exclusive ENDS users, higher levels of biomarkers such as TNE-2 were observed among open system users, but levels were similar when users were stratified by frequency of ENDS use. Adequate nicotine levels could help adults transition completely from use of combustible tobacco products, but high levels could contribute to addiction, especially among nicotine-naïve youth and young adults.

The results in this study are generally consistent with previous analyses of PATH Study biomarker data. Goniewicz and colleagues (15) analyzed Wave 1 data and found that exclusive e-cigarette users overall had a geometric mean TNE-2 concentration of 2.0 nmol/mg creatinine, which was very similar to the mean concentration found for closed system users in this study and less than the concentration for open system users. They also found that exclusive cigarette smokers had a mean TNE-2 concentration of 27.9 nmol/mg, which was similar to the results in this study for daily ENDS users, regardless of device type. Dual users in the Goniewicz and colleagues study had a mean TNE-2 concentration of 43.7 nmol/mg, which was

higher than the mean concentrations for exclusive cigarette smokers and e-cigarette users and was again consistent with our results.

Our results complement and perhaps elucidate previous findings on nicotine exposure by ENDS device type. We have found that open system users had higher overall nicotine exposure as measured by total nicotine equivalents, but that nicotine exposure was similar when users were stratified by daily and nondaily use, which could be a novel finding. Previous research has suggested that open system devices may be preferable in terms of nicotine delivery for ENDS users. For example, a small cross-over study published in 2015 found that current smokers may experience greater reduction in nicotine withdrawal symptoms when using refillable ENDS devices with tanks than when using rechargeable devices with cartridges (16). On the other hand, any differences in nicotine exposure during actual use could result from differences in product use, including frequency of use. A study of ENDS users conducted in 2014 found that open system users were both more likely than closed system users to use their product every day and to report that their device satisfied cravings (17), which seems consistent with our findings. Previous analysis of Wave 3 adult ENDS users similarly found that open system users were more likely to be daily ENDS users and former cigarette smokers than closed system users (8), and both of these characteristics could be related to increased nicotine delivery. Disentangling the relationship between device characteristics, nicotine exposure, and frequency of use among ENDS users thus remains a challenging task.

This study has certain limitations. First, survey data and urine samples were collected in 2015 and 2016. ENDS devices and use patterns tend to change fairly rapidly. Perhaps most importantly, JUUL, a rechargeable device that uses prefilled cartridges, has since come to dominate the ENDS market in the United States (18). Some studies have found that JUUL use tends to produce high levels of nicotine exposure, in part because of the product's high nicotine concentration in the form of a salt (6, 19, 20). These results and biomarker data from subsequent PATH Study waves will allow for analysis of changes in nicotine exposure among ENDS users over time. Second, information on some product use characteristics was limited or difficult to interpret. For example, daily ENDS users were asked about the quantity of ENDS products that they used per day, but the question varied by device type. Users of disposable devices were asked about the number of products that they used, users of devices with nonrefillable cartridges were asked about the number of cartridges they used, and users of devices with refillable cartridges, tanks, or modifiable systems were asked about the number of milliliters of e-liquid. Nicotine exposure among ENDS users may vary by other factors such as the specific device voltage or e-liquid nicotine concentration, but this information may not be available in the PATH Study or may be reported in different ways by participants. As noted in the tables, sample sizes for some groups were less than 50, and these estimates should therefore be interpreted with caution. Results for dual users by device category are difficult to interpret, given that these individuals also obtain nicotine from cigarettes. Results for dual users presented here are generally intended as standards of comparison for exclusive users. Finally, all information about ENDS use and devices was self-reported by PATH Study participants and not subject to independent verification.

That stated, the strengths of this study and the importance of its findings are considerable. By using PATH Study data, it has drawn upon the resources of a large, national study population that provided detailed information on product use and device characteristics as well as biospecimens for analysis. Consistent with suggestions from previous studies, it has found that open system ENDS users had higher nicotine exposure than closed system users, although the difference appears to have been largely the result of differences in frequency of use between daily and nondaily users. Dual users generally had higher nicotine exposure than exclusive ENDS users. Further investigation of this issue with subsequent waves of PATH Study data is merited, given the importance of ENDS use as a matter of public health.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the U.S. Department of Health and Human Services or any of its affiliated institutions or agencies.

Authors' Contributions

B.L. Rostron: Conceptualization, formal analysis, methodology, writing–original draft, writing–review and editing. **B. Coleman:** Conceptualization, writing–review and editing. **Y.-C. Cheng:** Methodology, project administration, writing–review and editing. **H.L. Kimmel:** Supervision, funding acquisition, project administration, writing–review and editing. **O. Oniyide:** Formal analysis, validation. **L. Wang:** Conceptualization, investigation, writing–review and editing. **C.M. Chang:** Conceptualization, supervision, writing–review and editing.

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