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E-cigarette Nicotine Dose and Flavor: Relationship with Appeal, Choice, and Tobacco Use Among Veterans with Comorbid Psychiatric Disorders

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Abstract

Background: Electronic cigarettes (EC) may aid some smokers in reducing combustible tobacco use. Smokers with psychiatric co-morbidities tend to have higher nicotine dependence and worse outcomes, so may particularly benefit from alternative cessation aids. EC characteristics, like nicotine level and flavor, may influence EC's appeal to smokers. Nicotine level may impact EC's efficacy in reducing combustible cigarette use.

Methods: Non-treatment-seeking cigarette smokers with medical/psychiatric co-morbidities rated 'liking' of ECs varying in nicotine level (12mg, 24mg) and flavor (menthol, 'slim'-tobacco, 'burley'-tobacco), during an open-label Choice Procedure. Smokers (N=43) chose ECs for a 4-week take-home-trial, and used EC and/or combustible cigarettes as they wished. Analyses examined ratings and choice by nicotine level and flavor, and the relationship between consistent take-home choice of 12mg versus 24mg baseline demographic/smoking characteristics, and outcomes (cigarettes/day, nicotine intake, motivation to quit smoking) during take-home-trial and one-month follow-up.

Results: Smokers who chose menthol-flavor, tobacco-flavor and/or 24mg nicotine e-liquids for the first take-home week rated these conditions as more 'liked' than alternative options, at baseline. Groups who chose 12mg versus 24mg throughout the take-home trial did not significantly differ on baseline characteristics, or smoking-related outcomes within the take-home trial, however, motivation to quit smoking increased more from baseline to one-month follow-up in choosers of higher nicotine (24mg) ECs.

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Conclusions: Associations between subjective ratings and subsequent choice support feasibility of open-label choice-procedures in EC trials. Access to 12mg or 24mg nicotine ECs was associated with reduced smoking, and 24mg ECs with increased motivation to quit smoking in smokers with medical/psychiatric co-morbidities.

Keywords

e-cigarettes; smoking; tobacco harm reduction; nicotine; flavor; psychiatric co-morbidities

1. Introduction

Electronic cigarettes (EC) may aid smoking reduction/cessation (e.g., (Buu, Hu, Piper, & Lin, 2018; Glasser, et al., 2017; Knight-West & Bullen, 2016)). In longitudinal trials, giving smokers take-home ECs reduces combustible cigarette use (Adriaens, Van Gucht, Declerck, & Baeyens, 2014; Nides, Leischow, Bhattar, & Simmons, 2014; Pacifici, et al., 2015; Pulvers, et al., 2016; Rohsenow, Tidey, Martin, Colby, & Eissenberg, 2018; Valentine, et al., 2017). EC may be especially promising in smokers with psychiatric comorbidities (Hefner, Valentine, & Sofuoglu, 2017; Prochaska, Das, & Young-Wolff, 2017), who begin smoking at an earlier age, consume more cigarettes, are more tobacco-dependent, and less likely to quit (Smith, Mazure, & McKee, 2014). We demonstrated that open-label choice and take-home access to 12mg or 24mg nicotine ECs was related to reduced smoking, increased readiness/motivation to quit, without changing a marker of nicotine intake (cotinine) in smokers with psychiatric co-morbidities (Valentine, et al., 2017). It is important to determine whether e-liquid nicotine level or flavor impact EC appeal, and whether nicotine level is associated with smoking outcomes, in smokers with psychiatric co-morbidities.

Higher nicotine level in ECs may improve their potential as smoking reduction/cessation aids. In cross-sectional surveys of EC users, use of higher e-liquid nicotine concentrations is associated with more reported alleviation of craving, satisfying ‘throat hit’ and efficacy as a smoking reduction/cessation aid (Etter, 2015, 2016). Among a sample of smokers who used ECs to quit smoking, 81% used ECs with >15mg nicotine to quit, 16% increased and none decreased their EC nicotine-level during the cessation attempt, while 65% decreased EC nicotine-levels after successful smoking-cessation (Farsalinos, Romagna, Tsiapras, Kyrzopoulos, & Voudris, 2013).

In the present study, smokers with mental illnesses sampled, rated, and selected e-liquids (varying by nicotine level and flavor) for an open-label, single-arm, take-home EC clinical trial. Primary outcomes for the overall sample are published (Valentine, et al., 2017). This secondary analysis examines relationships between subjective ratings and initial choice of e-liquids, and compares baseline characteristics and smoking-related outcomes between groups who consistently chose moderate (12mg) versus higher (24mg) nicotine e-liquids throughout the take-home trial.

2. Methods

Non-treatment-seeking smokers (> 5 cigarettes/day), age ≥ 18, with no current regular EC or smokeless tobacco use, unstable mental illness or medical disorders, were recruited by word-

of-mouth from VA Connecticut Healthcare System. All participants were veterans receiving care and had documented medical and psychiatric co-morbidities. The study was approved by the VA Connecticut Healthcare Human Subjects Subcommittee. Participants provided written informed consent and were paid for participation.

2.1 E-liquid sampling and choice procedure

E-liquids were made-to-order by Pace Engineering Concepts (Delafield, WI, USA) and all included propylene glycol (PG) to vegetable glycerin (VG) ratio of approximately 50PG:50VG. Flavors were 1) menthol (2.7% concentration (net wt. %)), 2) 'burley'-tobacco (robust), 3) 'slim'-tobacco (sweeter/lighter). Nicotine added to base liquids yielded nicotine concentrations of 12 or 24mg/ml (net wt. %).

In the open-label Choice Paradigm, participants were first given a brief tutorial on how to activate and puff on the EC. They then sampled each of the six e-liquid options (3 flavors*2 nicotine levels) in a set order and immediately after sampling a given e-liquid, asked to rate it on a single item visual analogue scale (VAS) labeled with 'hate it' (left), 'neutral' (middle), 'love it' right. After sampling all six, participants chose one or more e-liquids to take home for take-home week 1. They were then given the e-liquid(s) of their choice, all EC components, and given a hands-on tutorial on how to use the EC at home (e.g., charge, refill, adjust settings).

2.2 Four-Week EC Take-Home Trial

Participants were provided take-home ECs for the four-week trial and instructed to use the EC and/or their own combustible cigarettes as they chose. They were given their e-liquid(s) of choice, from 6 nicotine*flavor combination options. Participants returned weekly for assessment and e-liquid refills, and could alter e-liquid choices and/or request more than one take-home e-liquid. At the end of the four-week trial, ECs were collected. No study ECs or e-liquids were provided over the one-month follow-up.

2.3 Outcome measures

Subjective 'liking' of each e-liquid, assessed by a single visual analogue scale (VAS) ranging from 0 ('hate it') to 100 ('love it'), was collected during the sampling and choice procedure at baseline. Smoking heaviness (cigarettes per day (CPD)), nicotine intake (urine cotinine levels (ng/ml) (a nicotine metabolite)), and readiness/motivation to quit smoking (Contemplation Ladder Score (CLS (Biener & Abrams, 1991))) were measured at baseline, weekly during take-home trial, and one-month follow-up.

2.4 Data Analysis

We conducted the following exploratory analyses. First, impacts of nicotine level and flavor on subjective e-liquid VAS ratings were analyzed using a mixed-model including nicotine (12mg, 24mg), flavor (menthol, 'slim'-tobacco, 'burley'-tobacco) and their interaction as fixed-effects, and an unstructured covariance to model within-subject correlations. Second, to examine whether subjective e-liquid ratings related to initial choice of take-home e-liquid, participants were categorized by choice of flavor (menthol vs. tobacco) and nicotine level (12mg vs. 24mg) in week 1, and Wilcoxon rank-sum tests assessed whether choice-groups

differed in subjective ratings (average VAS for menthol or tobacco flavor, or 12mg or 24mg nicotine). Third, we compared baseline characteristics of those who consistently chose 12mg versus 24mg nicotine e-liquids throughout the 4-week trial, using chi-square/Fisher exact test or t-test. We then compared outcomes (CPD, cotinine, CLS) over time in the two nicotine-level-choice-groups using mixed-models. If needed, outcomes were log- or square-root-transformed to address skewness. Models included time (baseline (week 0), take-home trial (weeks 1–4), follow-up (week 8)), nicotine-choice (12mg vs. 24mg) and time*nicotine-choice interaction as fixed effects, and used an unstructured covariance. Omnibus tests were followed by planned post-hoc contrasts assessing changes in outcomes from baseline to a) end-of-take-home trial and b) follow-up, by nicotine-level-choice-group.

3. Results

Demographics and baseline smoking characteristics of participants in the take-home trial are in Supplemental Table 1. Briefly, participants were predominantly African American (67%), males (93%), reporting menthol as usual brand/type of cigarette (86%), and on average 57 years old smoking 16.5 CPD. Psychiatric disorders included PTSD (42%), depression (35%), anxiety disorders (16%), and alcohol (51%), cocaine (45%), and opioid (37%) use disorders, with the majority of participants meeting criteria for multiple disorders (for Consort Diagram and detailed demographics, see (Valentine, et al., 2017)).

3.1 Influence of Nicotine Level or Flavor on Subjective E-Liquid Ratings

VAS ‘liking’ scores were available for 48 out of 50 subjects who initiated the baseline session (284 scores in total) (Supplemental Figure 1). Nicotine*flavor interaction ($p=0.91$) and main effect of nicotine ($p=0.20$) were not statistically significant. A main effect of flavor was observed ($p=0.01$), with higher ‘liking’ of menthol than ‘slim’-tobacco (LS-mean 58.73 vs. 41.13, difference 17.6 (95% CI 6.43 to 28.78), $p=0.003$), or ‘burley’-tobacco (LS-mean 58.73 vs. 43.94, difference 14.79 (95% CI 1.62 to 27.95), $p=0.03$). ‘Burley’-tobacco versus ‘slim’-tobacco ratings were not significantly different ($p=0.57$).

3.2 Relationship Between Baseline Subjective Ratings and Initial Take-Home Choice

In week 1, 19 subjects chose menthol only and 22 chose tobacco-flavor only to take-home. ‘Liking’ VAS ratings of menthol EC were higher ($p<0.001$) amongst those who subsequently chose menthol in week 1 (median VAS=77.0; IQR= [67.5;87.0]) versus tobacco-flavor-choosers (45.5 [30.0;53.8]). Tobacco-flavor was rated higher ‘liking’ ($p=0.001$) amongst those who subsequently chose tobacco in week 1 (50.5 [39.9;66.4]) versus menthol-flavor-choosers (30.0 [14.8;43.0]). Differential preference for menthol over tobacco (menthol minus tobacco VAS) was higher ($p<0.001$) in menthol-choosers (45.3 [23.2;62.5]) than tobacco-choosers (−10.50 [−26.88;9.25]).

In week 1, 21 subjects chose 12mg nicotine only and 18 chose 24mg only for take-home (2 subjects chose both and were excluded from this analysis). ‘Liking’ ratings for 12mg nicotine did not significantly differ ($p=0.35$) between 12mg-choosers (53.0 [40.0;62.0]) versus 24mg-choosers (43.3 [39.5;55.7]). ‘Liking’ ratings for 24mg nicotine were higher ($p=0.04$) in 24mg-choosers (51.7 [47.3;62.8]) versus 12mg-choosers (44.0 [34.7;53.3]).

Differential preference for 12mg over 24mg (12mg minus 24mg VAS) was higher ($p=0.01$) in 12mg-choosers (7.33 [-6.33;16.7]) than 24mg-choosers (-6.67 [-16.00; -0.33]).

3.3 Baseline Characteristics and Smoking Outcomes Based on Nicotine Choice during Trial

Groups who chose 12mg (N=15) or 24mg (N=19) nicotine consistently throughout the 4-week take-home trial did not significantly differ on demographic or baseline smoking-related variables (Supplemental Table 1). Nine subjects who chose 12 and 24mg were excluded from these analyses. For the CPD outcome (log-transformed) there was a main effect of time ($F_{5, 23.6}=13.62$, $p<0.0001$), due to reduced smoking during/after trial, but no significant effect of nicotine-choice-group ($p=0.19$) or nicotine-choice-group*time interaction ($p=0.16$) (Figure 1A). For cotinine (square-root-transformed) there was a trend of higher cotinine levels in 24mg-choosers than 12mg-choosers (difference 7.3 (95% CI -0.1 to 14.7) on square-root-scale; $F_{1, 31.7}=4.02$, $p=0.05$; Figure 1B) but no significant effect of time ($p=0.51$) or nicotine-choice-group*time interaction ($p=0.31$). For CLS there was an effect of time ($F_{5, 26.9}=2.97$, $p=0.03$), due to increased readiness/motivation to quit across the trial, but no significant effect of nicotine-choice-group ($p=0.38$) or nicotine-choice-group*time ($p=0.53$) (Figure 1C).

Post-hoc comparisons between nicotine-choice-groups assessed change in outcomes from baseline to end-of-take-home-trial (week 4) or one-month follow-up (week 8) (Table 1). From baseline to end-of-take-home-trial or follow-up, there were significant reductions in CPD within each nicotine-choice-group, no significant change in cotinine levels within either nicotine-choice-group, and CLS significantly increased in 24mg-choosers only (by 1.90 to end-of-take-home-trial and 1.78 to follow-up). Nicotine-choice-groups did not significantly differ in degree of change from baseline to end-of-take-home-trial on these outcomes. From baseline to follow-up, a group difference reflected greater increases in readiness/motivation to quit (CLS) in 24mg-choosers versus 12mg-choosers (difference 2.01 (95% CI 0.05, 3.96), $p=0.04$).

4. Discussion

Subjective ratings were associated with subsequent initial take-home choice of flavor or nicotine level. Groups who chose 12mg vs. 24mg consistently throughout the take-home-trial did not significantly differ on baseline characteristics. Smoking decreases did not significantly differ between these nicotine-level-choice groups, cotinine did not significantly change, and readiness/motivation to quit smoking increased more from baseline to follow-up in the 24mg-choice-group.

Subjective ratings and choice behavior were associated. Greater 'liking' ratings were positively associated with subsequent initial (week 1) take-home choice for corresponding flavor and nicotine-levels, consistent with studies demonstrating correlations between subjective liking and drug use behavior (Comer, et al., 2008). In our sample of mostly menthol cigarette smokers, menthol-flavored EC were rated higher 'liking' than either tobacco flavor. However, a similar number of smokers chose tobacco-flavor versus menthol-

flavored EC for take-home, and some chose both flavors across take-home weeks, suggesting tobacco-flavored ECs appeal to some menthol-cigarette smokers.

Our findings of reduced smoking during the EC take-home trial in both nicotine-level-choice-groups, without parallel reductions in cotinine, is consistent with prior research. Longitudinal EC trials show reduced smoking following take-home EC access, with e-liquids containing a range of nicotine concentrations (personalized nicotine levels (Pacifi, et al., 2015)), (9–18mg (Wagener, et al., 2014)), (11mg (Goniewicz, et al., 2017)), (18mg (Adriaens, et al., 2014; Rohsenow, et al., 2018)), (24mg, except <9% receiving 12mg (Pulvers, et al., 2016)), (26mg (Nides, et al., 2014)), with some showing maintenance of nicotine exposure-indicators (cotinine) (Goniewicz, et al., 2017; Pacifi, et al., 2015; Pulvers, et al., 2016). Our trend nicotine-choice-level difference reflected slightly higher cotinine levels across all timepoints in 24mg-choosers, consistent with laboratory studies with controlled puffing protocols wherein smokers achieve progressively higher plasma nicotine levels with escalating e-liquid nicotine concentrations (Hiler, et al., 2017), and with moderate correlations between cotinine and self-reported usual e-liquid nicotine concentration amongst regular EC users (Etter, 2014). However, studies assessing nicotine-containing vs. no nicotine EC on smoking outcomes generally associate nicotine-containing ECs with better outcomes (lower desire to smoke, higher abstinence), but not statistically-significantly (Bullen, et al., 2013; Khoudigian, et al., 2016), and smokers on the nicotine-patch showed similar reductions in smoking if randomized to EC with no or higher (24mg) nicotine (Baldassarri, et al., 2018). Therefore, a similar reduction in smoking in 12mg-choosers and 24mg-choosers could be consistent with both conditions delivering sufficient nicotine to support smoking reduction/cessation, and/or reflect the fact that ECs efficacy as smoking reduction/cessation aides are not fully attributed to nicotine replacement effects.

Smokers who consistently chose 24mg vs. 12mg nicotine throughout the take-home trial reported a greater increase in readiness/motivation to quit from baseline to follow-up. These findings are consistent with studies of smokers given take-home ECs containing higher nicotine reporting increased motivation to quit (18mg (Rohsenow, et al., 2018) and self-efficacy to resist smoking (24mg (<9% used 12mg) (Pulvers, et al., 2016). Baseline characteristics did not significantly differ by nicotine-level-choice-groups, so are unlikely to explain this finding.

Limitations of this pilot included the relatively small sample size, open-label study design, limited e-liquid options, and predominantly male menthol-smoking sample. However, a Choice Paradigm ensured participants made informed choices, open-label take-home options increased external validity, and the sample with medical/psychiatric co-morbidities is understudied and has high clinical need of smoking reduction/cessation aids. The variety of psychiatric co-morbidities included in the sample, and fact that most participants met criteria for multiple co-morbidities, limited the ability to assess the effects of specific co-morbidities (e.g., depression or alcohol use disorder) on smoking outcomes in this sample, but this presents an important avenue for future research.

These preliminary findings validate use of Choice Procedures in EC trials and suggest ECs with moderate (12mg) or higher (24mg) nicotine levels can be appealing and effectively

reduce heaviness of smoking in individuals with psychiatric disorders. Higher nicotine levels may more effectively increase readiness/motivation to quit smoking.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Non-treatment-seeking cigarette smokers in clinical trial of electronic cigarettes (EC)
- Open-label choice of moderate or high nicotine take-home EC for one month
- Subjective EC 'liking' ratings at baseline related to subsequent take-home choice
- Similar reduction in smoking in groups choosing moderate or high nicotine EC
- Greater increase in motivation to quit smoking in group choosing high nicotine EC

Figure 1. Smoking Outcomes by Nicotine Level Choice.

Measures of (A) heaviness of smoking (combustible cigarettes per day (CPD)); (B) nicotine intake (cotinine, a nicotine metabolite); (C) readiness/motivation to quit combustible cigarette smoking (Contemplation Ladder Score (CLS)) are presented across all timepoints, including baseline, end of each take-home electronic cigarette week (EC wk1–4), and at 1 month follow-up (F/up). Data are presented as raw means with error bars representing standard error (SE). Groups that chose 12mg nicotine (grey solid lines, circles) versus 24mg nicotine (black solid lines, squares) consistently within the 4-week take-home trial were compared on these outcomes. Individuals who chose both 12 and 24mg nicotine EC within the take-home period were excluded from these analyses, but are presented for visual purposes only (grey dotted line, triangles).

Table 1.

Changes from Baseline to End-of-Trial or One-Month Follow-up in the Always-Chose-12mg (N=15) vs. Always-Chose-24mg (N=19) Groups

<i>A. Change: Baseline (Wk 0) to End of E-Cigarette Take-Home Trial (Wk 4)</i>		Always-Chose-24mg (N=19) ¹				Always-Chose-12mg (N=15) ¹				Difference (Always-24mg vs. Always-12mg) ¹			
Outcome	Measure ³	Estimate ²	Lower CI ²	Upper CI ²	p-value ²	Estimate	Lower CI	Upper CI	p-value	Estimate	Lower CI	Upper CI	p-value
Heaviness of Smoking	Cigarettes per Day (CPD)	-1.32	-1.84	-0.79	<.0001	-1.63	-2.23	-1.03	<.0001	0.31	-0.48	1.11	0.43
Nicotine Intake	Urine Cotinine	2.93	-4.90	10.76	0.45	3.53	-4.75	11.80	0.39	-0.60	-11.99	10.80	0.92
Motivation to Quit Smoking	Contemplation Ladder Score (CLS)	1.90	0.66	3.14	0.004	0.92	-0.49	2.33	0.19	0.98	-0.90	2.86	0.30
<i>B. Change: Baseline (Wk 0) to End of One-Month Follow-up (Wk 8)</i>		Always-Chose-24mg (N=19)				Always-Chose-12mg (N=15)				Difference (Always-24mg vs. Always-12mg)			
Outcome	Measure ³	Estimate	Lower CI	Upper CI	p-value	Estimate	Lower CI	Upper CI	p-value	Estimate	Lower CI	Upper CI	p-value
Heaviness of Smoking	Cigarettes per Day (CPD)	-1.02	-1.52	-0.51	0.0003	-0.75	-1.32	-0.17	0.01	-0.27	-1.04	0.50	0.48
Nicotine intake	Urine Cotinine	1.76	-7.52	11.03	0.70	6.55	-3.53	16.62	0.19	-4.79	-18.48	8.90	0.48
Motivation to Quit Smoking	Contemplation Ladder Score (CLS)	1.78	0.52	3.04	0.007	-0.23	-1.72	1.27	0.76	2.01	0.05	3.96	0.04

¹ Groups defined by those who consistently chose 24mg or 12mg nicotine e-liquids during the 4-week open-label take-home trial. Participants who chose both nicotine levels within a given week or across different weeks were excluded from these analyses. Statistics for Always-Chose-24mg or Always-Chose-12mg indicate whether there was a significant change from baseline to (A) end-of-trial or (B) follow-up within each group. Statistics for 'Difference (Always-24mg vs. Always-12mg)' indicate whether there is a significant group difference in the change score.

² Estimate, lower and upper limits of the 95% Confidence Interval (CI), and p-values presented from the mixed-model fits.

³ Measures were transformed prior to the analysis as follows: cigarettes per day (CPD) was log-transformed; urine cotinine was square root transformed; contemplation ladder score (CLS) was untransformed (raw).