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Acute effects of JUUL and IQOS in cigarette smokers.

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Abstract

Background: JUUL is an electronic cigarette that aerosolizes a nicotine-containing liquid, while IQOS heats tobacco to produce an aerosol. Both are marketed to smokers, but their effects have seldom been examined in this population.

Methods: Eighteen cigarette smokers (13 men) with no JUUL or IQOS experience completed a within-subject, laboratory study assessing nicotine delivery and subjective effects after controlled (10 puffs, ~30 sec interpuff interval) and *ad libitum* (90 min) use of JUUL, IQOS, or own-brand cigarettes (OB).

Results: JUUL increased mean plasma nicotine concentration significantly from 2.2 (SD=0.7) ng/ml to 9.8 (4.9) ng/mL after 10 puffs and to 11.5 (9.3) ng/mL after *ad libitum* use. IQOS increased mean plasma nicotine significantly from 2.1 (0.2) ng/mL to 12.7 (6.2) ng/mL after 10 puffs and to 11.3 (8.0) ng/mL after *ad libitum* use. OB increased mean plasma nicotine significantly from 2.1 (0.2) ng/mL to 20.4 (11.4) ng/mL after 10 puffs and to 21.0 (10.2) ng/mL after *ad libitum* use. Mean OB plasma nicotine concentration was significantly higher than JUUL and IQOS. OB increased expired CO concentration, but IQOS and JUUL did not. “Craving a cigarette/nicotine” and “Urges to smoke” were reduced significantly for all products following the directed bout.

Conclusions: Among smokers, JUUL and IQOS delivered less nicotine than cigarettes. Also, in this sample, IQOS and OB reduced abstinence symptoms more effectively than JUUL. Additional work with experienced JUUL and IQOS users is needed, as their nicotine delivery profiles and subjective experiences may differ.

Introduction

Electronic cigarettes (ECIGs) are a heterogeneous class of tobacco products that use a battery-powered element to heat a liquid to produce a nicotine-containing aerosol. “Pod-mod” ECIGs use replaceable reservoirs that combine the heating element with a liquid that often has a high concentration (50–60 mg/ml) of protonated nicotine (“nicotine salt”).

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Relative to freebase nicotine aerosol, protonated nicotine may be less aversive to inhale[1]. JUUL is a popular pod-mod device[2] that contains 69 mg/ml nicotine liquid, 94% in the protonated form[3]. While the tobacco industry has invested heavily in ECIGs[4], it also markets other types of electronic devices, such as heated tobacco products, that heat pressed tobacco (not a liquid) to produce an aerosol. One such product is "IQOS" that heats pressed tobacco rods ("HeatSticks" or "HEETS") to produce an aerosol that contains nicotine as well as some, but not all, of the non-nicotine toxicants in combustible cigarette smoke[5–7]. The effects of JUUL or IQOS in cigarette smokers are largely unknown, so this study compares the biomarkers and subjective effects of JUUL and IQOS to own brand combustible cigarettes in this population.

Method

The method for this VCU IRB-approved study was similar to that reported elsewhere[8, 9]. Briefly, community volunteers aged 18–55 who smoked ≥10 cigarettes daily and with expired air carbon monoxide (CO) ≥15 ppm at screening and who reported no JUUL or IQOS experience were recruited to complete three, ~4-hour, Latin-square ordered sessions that were each preceded by 12 hours of nicotine/tobacco abstinence (verified with CO ≤10 ppm and baseline plasma nicotine concentration <5.0 ng/mL[8,10]). Sessions differed by product used: JUUL (tobacco or mint flavor pod), IQOS (tobacco or menthol), or own brand cigarette (OB; JUUL and IQOS flavors were matched to OB). Four, sealed IQOS kits and "Amber Label" and "Green Label" "HeatSticks" were purchased via eBay in September, 2017. Five JUUL kits were purchased at a local tobacco store in Richmond, VA in February, 2018; additional "Virginia Tobacco" and "Cool Mint" JUUL pods were purchased at a local retailer from September, 2017 through June, 2019. All products were charged prior to the start of the study session as indicated by product labeling. Product use consisted of one 10-puff "directed" bout (30 second interpuff interval) and, after 25 minutes rest, a 90-minute *ad libitum* bout. Blood was sampled via a catheter placed in a forearm vein before and immediately after each bout, heart rate and blood pressure were monitored continuously (heart rate and blood pressure data not reported), and expired air CO (Vitalograph; Lenexa, KS) and subjective effects[10] were measured before and after each bout. Participants were compensated $100 after each session.

Blood plasma was analyzed for nicotine concentration[11] (LOQ=2 ng/mL) and values below the LOQ were replaced with 2 ng/ml[8–10]. Statistical analyses (repeated measures ANOVAs, with Huynh-Feldt corrections) were performed using IBM SPSS (Version 26.0). Post-hoc testing for significant condition (OB, JUUL, IQOS) by time (pre-directed, post-directed, pre-*ad lib*, post-*ad lib*) interactions and main effects of condition and time were analyzed using Holm-Sidak corrected *t*-tests.

Results

Participant Characteristics

Thirteen men and 5 women (8 Caucasian, 7 African-American, 3 other) completed the study. Participants' mean (SD) age was 36.8 (9.3) years and they reported smoking a mean of 16.4 (5.1) cigarettes/day for 11.7 (8.9) years. Fifty-six percent smoked menthol. The average

machine-smoked nicotine yield of participants' OB cigarettes was 0.94 (0.17) mg[12]. Mean exhaled CO at screening was 21.1 (6.6) ppm.

Biomarkers—There was a significant condition by time interaction for plasma nicotine [F(6,96)=7.08,p<.001]. As Table 1 shows, mean plasma nicotine concentration (N=17) increased significantly in all three conditions following the directed and the *ad libitum* bouts, relative to immediately before each bout (ts>4.25;ps<.05). Mean plasma nicotine was significantly higher in OB relative to JUUL and IQOS following both bouts (ts>3.06;ps<.05).

There was a significant condition by time interaction for CO [F(6,102)=48.79, p<.001]. As Table 1 shows, mean CO increased significantly for OB only after the directed bout and after the *ad libitum* bout (ts>5.87;ps<.05); no significant increases in CO were observed for JUUL or IQOS. Mean CO concentrations following the directed and the *ad libitum* bouts were significantly higher for OB relative to JUUL and IQOS (ts>4.68;ps<.05) .

Subjective effects—We examined each subjective measure (visual analog scale items and the Questionnaire of Smoking Urges-Brief Factors 1 and 2; QSU[13]) for evidence of suppression of tobacco/nicotine abstinence effects after each bout (N=17; see Table 1). Mean scores for "Craving a cigarette/nicotine" and "Urges to smoke" were reduced in all three conditions following the directed bout and, for OB and IQOS, were reduced following the *ad libitum* bout (ts>2.54;ps<.05). Mean scores for these two items were lower for OB relative to JUUL following the *ad libitum* bout (ts>2.83;ps<.05) and mean score for "Urges" was lower for OB relative to IQOS following the *ad libitum* bout [$t(16)$=2.14;p<.05]. Following the directed bout, mean scores for "Impatient" and "Irritable" were reduced for OB, JUUL, and IQOS (ts>2.35;ps<.05). Mean scores for "Anxious" were reduced following both bouts for OB and JUUL (ts>2.77;ps<.05). Mean scores for "Restless" were reduced for OB and IQOS following the directed bout (ts>3.06;ps<.05). Mean scores for "Difficulty concentrating" were reduced for JUUL following both bouts and were reduced for OB following the *ad libitum* bout only (ts>2.56;ps<.05). Mean scores for "Depression" were significantly reduced from baseline prior to the *ad libitum* bout in the IQOS condition [t(16)=2.69;p<.05]. Mean scores for "Pleasant" and "Satisfy" were higher for OB than for JUUL and IQOS following both bouts (ts>2.51;ps<.05). Mean scores for "Taste good" were significantly higher for OB than for JUUL following the directed bout, and was higher for OB than IQOS following the *ad libitum* bout (ts > 2.29; ps<.05).

Mean QSU Factor 1 scores were reduced for OB and IQOS following the directed bout and for OB, IQOS, and JUUL following the *ad libitum* bout (ts>2.78;ps<.05). Mean Factor 1 score was lower for OB relative to JUUL following the directed and *ad libitum* bouts (ts>2.51;ps<.05). Mean Factor 2 scores were reduced for OB and IQOS following the directed and *ad libitum* bouts (ts>2.81;ps<.05).

Discussion

This study is one of the first independent examinations of JUUL/IQOS nicotine delivery in cigarette smokers with no prior JUUL or IQOS experience and it shows that OB cigarettes

delivered more nicotine and suppressed tobacco/nicotine abstinence more effectively than JUUL or IQOS. JUUL delivered the least nicotine, in seeming contradiction to independent reports of its high nicotine yield with 4-sec puffs[3] and industry-sponsored reports of higher nicotine delivery with 3-sec puffs[14]. In the present study, the participants received no instructions regarding puff duration and, if they took ~2 second puffs as is typical of cigarette smokers[8,15], that shorter puff duration may explain the lower delivery reported here. Indeed, in a recent study, six experienced pod-mod users were able to obtain an average nicotine boost of 28.6 (9.8) ng/mL following 30 puffs over 10 minutes, with an average plasma nicotine concentration of 12.9 ng/mL at four minutes, consistent with the current results[16]. Taken together, these results concerning JUUL's nicotine yield and delivery highlight the need for continued work to characterize JUUL's nicotine delivery profile (especially in JUUL-experienced individuals) as well as the need for puff topography measurement for this and other novel tobacco products and how they may change over time with experience.

IQOS is not the first product to use an electrical element to heat pressed tobacco: an earlier product of similar design ("Accord") was marketed nearly two decades ago[17]. Relative to that earlier product, IQOS may deliver nicotine and suppress tobacco/nicotine abstinence effects more effectively[15,18]. A recent independent study investigating the acute effects of IQOS and a tank-style ECIG (18 mg/mL, 8 watt device) also found that combustible cigarettes suppressed tobacco abstinence symptoms more than ECIG or IQOS, although IQOS was more satisfying and provided more enjoyable throat sensations than ECIG[19]. Notably, Accord did not substitute for cigarettes in cigarette smokers[20] and the acceptability of IQOS as a cigarette substitute among long-term cigarette smokers is uncertain, as is its capacity to reduce the lethality of tobacco consumption[21–28]. Notwithstanding that uncertainty and dearth of data informing what impact on public health IQOS may have, IQOS is now available in the US market, after FDA review of a premarket tobacco product application.

As novel tobacco products grow in popularity, independent research examining their nicotine and other toxicant delivery is required to inform regulation, and that research must take into account changes in user behavior that might accompany greater experience with the product. Data generated in this manner can help inform policymakers who may be considering eliminating protonated nicotine and/or limiting the rate at which nicotine is emitted from tobacco products[29].

Disclosures and Acknowledgements

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Dr. Eissenberg is a paid consultant in litigation against the tobacco and electronic cigarette industry and is named on a patent for a device that measures the puffing behavior of ECIG users.

All of the authors have made significant contributions to this manuscript and have read and approved the final manuscript.

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What this paper adds:

1. JUUL and IQOS are tobacco products that use electronic heaters to create an aerosol for user inhalation.
2. Limited data are available on JUUL and IQOS nicotine delivery and abstinence symptom suppression among cigarette smokers.
3. The current study is one of the first independent studies of the acute effects and nicotine delivery profile of JUUL and IQOS in cigarette smokers.
4. JUUL and IQOS deliver less nicotine and reduce tobacco abstinence symptoms to a lesser degree than own-brand cigarettes in smokers naïve to JUUL and IQOS.

Table 1.

Means and Standard Deviations for Outcome Variables by Product Type.

	Own-Brand Cigarette								JUUL								IQOS							
	Pre-Directed		Post-Directed		Pre-Ad *Lib*		Post-Ad *Lib*		Pre-Directed		Post-Directed		Pre-*Ad Lib*		Post-*Ad Lib*		Pre-Directed		Post-Directed		Pre-*Ad Lib*		Post-*Ad Lib*	
Outcome Variables	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Plasma Nicotine[A]	2.1	0.2	**20.4**	11.4	**8.8**	3.6	**21.0**	10.2	2.2	0.7	**9.8**	4.9	**4.3**	1.8	**11.5**	9.3	2.1	0.2	**12.7**	6.2	**5.4**	1.7	**11.3**	8.0
CO[A]	5.2	2.4	**8.7**	2.5	**8.8**	2.8	**16.6**	7.0	5.5	2.4	**5.1**	2.3	5.3	2.4	**4.7**	1.9	5.3	2.0	4.9	1.8	**4.6**	1.8	**4.3**	1.4
QSU																								
Factor 1[B,C]	24.8	8.2	**13.2**	10.7	**21.2**	8.9	**11.5**	10.2	24.7	7.5	20.1	9.3	21.7	9.3	**17.8**	10.6	25.1	8.2	**16.0**	9.3	**20.4**	8.5	**14.4**	9.7
Factor 2[C]	11.7	8.3	**6.9**	7.4	9.7	7.4	**5.5**	7.6	10.3	8.3	8.1	7.8	9.5	7.5	6.5	7.2	12.5	8.4	**6.6**	7.8	**9.1**	8.6	**6.6**	8.9
HH																								
Anxious	46.3	32.5	**24.8**	30.6	**22.1**	22.8	**19.4**	27.5	42.8	31.9	**24.4**	31.8	**20.8**	30.1	**20.4**	27.0	44.5	34.9	28.4	33.9	**17.2**	27.2	28.4	32.6
Craving[A]	75.2	30.7	**34.9**	35.0	**55.2**	30.5	**25.5**	29.2	70.5	30.9	**49.3**	36.0	54.0	38.0	53.9	34.9	73.5	33.5	**42.9**	31.8	**53.8**	29.9	**36.2**	32.1
Depression[C]	21.4	28.3	9.8	16.8	11.5	21.5	8.8	13.6	15.1	20.9	8.8	16.6	8.1	17.0	8.2	16.3	20.5	26.1	15.1	22.6	**10.6**	20.1	11.5	21.7
Diff Concentrate[C]	28.2	26.4	18.5	20.4	18.1	20.8	**10.4**	18.1	37.6	30.1	**17.3**	19.9	**15.5**	22.5	**17.8**	25.8	30.0	31.9	24.4	29.9	16.8	20.6	18.9	27.0
Drowsy	35.2	25.0	28.7	26.1	24.9	24.3	23.4	26.9	33.8	28.2	21.4	24.6	25.9	31.1	25.3	27.0	31.9	33.9	29.4	26.5	23.4	24.6	27.4	29.8
Hunger	39.9	22.7	31.9	24.4	34.8	25.9	39.8	30.7	43.2	29.8	35.6	33.3	39.5	35.9	58.4	29.0	43.0	35.5	30.2	25.5	37.7	29.0	53.2	31.9
Impatient[C]	42.1	28.3	**23.9**	27.3	**26.9**	29.3	**25.5**	28.2	41.0	30.6	**25.9**	31.0	31.4	28.9	31.8	30.5	51.4	31.0	**25.1**	30.9	**29.7**	30.3	**27.2**	27.0
Irritable[C]	37.4	31.0	**14.9**	17.2	**14.1**	16.0	**14.6**	22.0	34.5	31.1	**18.4**	22.1	**15.4**	22.3	15.1	26.4	38.7	33.3	**19.8**	26.3	**16.8**	21.0	**16.8**	24.1
Restless[A]	40.8	29.4	**19.7**	24.8	27.7	27.2	**21.5**	28.1	30.2	25.5	26.9	25.9	**17.9**	25.7	24.7	27.6	38.9	31.8	**19.7**	24.6	33.4	31.4	27.1	28.4
Sweets	24.2	30.7	16.8	21.4	18.8	25.8	17.9	21.3	27.4	33.3	20.3	27.2	20.7	28.1	17.4	24.0	24.8	28.3	16.4	25.7	23.8	27.9	20.5	27.0
Urge[A]	76.5	25.2	**39.2**	34.8	**54.4**	27.6	**24.9**	25.7	67.2	29.9	**48.8**	31.9	**46.9**	33.3	50.0	31.1	74.7	31.5	**46.2**	29.5	**56.9**	27.8	**38.0**	31.8
DEV																								
Awake			40.9	31.7			45.1	31.3			33.8	29.9			28.1	29.6			36.5	30.6			34.5	27.4
Calm			60.9	36.0			60.7	35.3			47.9	31.9			46.6	29.7			54.4	31.5			43.2	34.5
Concentrate			43.8	30.8			42.0	34.3			24.5	26.3			27.5	26.3			38.5	33.7			27.8	27.1
Dizzy			40.7	33.4			30.1	36.2			33.7	33.5			19.4	27.2			36.4	34.8			26.9	25.8

	Own-Brand Cigarette								JUUL								IQOS							
	Pre-Directed		Post-Directed		Pre-Ad *Lib*		Post-Ad *Lib*		Pre-Directed		Post-Directed		Pre-*Ad Lib*		Post-*Ad Lib*		Pre-Directed		Post-Directed		Pre-*Ad Lib*		Post-*Ad Lib*	
Outcome Variables	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Pleasant[B]			81.4	29.8			81.9	24.9			50.4	31.6			50.6	31.2			58.8	36.0			58.9	34.4
Reduced Hunger			41.9	29.9			33.0	27.7			35.2	27.4			37.1	31.0			29.2	28.8			34.3	26.1
Right Now			62.8	37.7			44.1	37.7			45.4	32.7			35.5	29.1			47.2	39.1			37.5	33.5
Satisfy[B]			84.3	24.4			83.7	24.5			47.0	33.2			46.5	31.5			58.8	30.9			58.8	33.3
Sick			4.1	7.5			2.6	5.2			8.1	14.2			7.8	14.4			9.5	19.0			10.5	16.8
Taste good[B]			77.7	29.5			74.0	32.1			50.5	32.6			51.2	30.7			54.6	36.4			**49.8**	35.7

Means that are significantly different from baseline are presented in bold. Items that are significantly different from own-brand cigarettes at that time point are underlined. Note: CO, expired air carbon monoxide; QSU, Tiffany-Drobes Questionnaire of Smoking Urges-Brief; HH, Hughes-Hatsukami Withdrawal VAS Scale; DEV, Direct Effects of Vaping Questionnaire;

[A] significant interaction,

[B] significant main effect of condition, and

[C] significant main effect of time.