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Effects of electronic cigarette liquid solvents propylene glycol and vegetable glycerin on user nicotine delivery, heart rate, subjective effects, and puff topography

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ABSTRACT

Background: Electronic cigarettes (ECIGs) are a class of tobacco products that produce different effects (e.g., nicotine delivery), depending on the device, liquid, and behavioral factors. However, the influence of the two primary ECIG liquid solvents, propylene glycol (PG) and vegetable glycerin (VG), on ECIG acute effects is unknown.

Methods: Thirty ECIG-experienced, ≥12-h nicotine- abstinent participants completed four conditions consisting of two ECIG-use bouts (10 puffs, 30 s interpuff-interval) differing only by liquid PG:VG ratio (2PG:98VG, 20PG:80VG, 55PG:45VG, 100PG). Device power (7.3 W) and liquid nicotine concentration (18 mg/ml) remained constant. Nicotine delivery, subjective effects, heart rate (HR), and puff topography were assessed.

Results: In the 100PG condition, participants took shorter and smaller puffs but obtained significantly more nicotine relative to the two VG-based conditions. Total nicotine exposure (i.e., area under the curve) was also significantly higher during use of the two PG-based liquids. However, participants reported that the 100 PG liquid was significantly less "pleasant" and "satisfying" relative to the other liquids (all *ps* < .05). Increases in HR and decreases in abstinence symptoms (e.g., "craving") did not differ across conditions.

Conclusions: PG:VG ratio influenced nicotine delivery, some subjective effects, and puff topography. Lower overall product satisfaction associated with the 100PG liquid suggests factors other than nicotine delivery (e.g., aerosol visibility) may play a role in maintaining ECIG use. Regulating ECIG acute effects such as nicotine delivery and subjective effects may require simultaneous attention to liquid PG:VG ratio as well as device, liquid, and behavioral factors known to influence these outcomes.

1. Introduction

The use of electronic cigarettes (ECIGs) has increased exponentially in the U.S. (Jamal et al., 2017; Schoenborn and Gindi, 2015) and globally (Adkison et al., 2013) in recent years. ECIGs share several common features such as an electrical element that heats an often nicotine-containing liquid to produce an inhalable aerosol. However, ECIGs and their associated liquids can vary substantially on factors such as electrical power output (i.e., wattage) and the concentration of nicotine, flavorants, and solvents such as propylene glycol (PG) and vegetable glycerin (VG). A comprehensive understanding of how these various ECIG device/liquid characteristics, in conjunction with user puffing behaviors, influence ECIG users' acute effects (e.g., nicotine delivery, subjective effects) may inform the regulation of these products.

Broadly, ECIG acute effects can be altered by three factors: device features, liquid components, and user puffing behaviors. For example, ECIGs operating at higher wattages deliver nicotine to the user more effectively than lower wattage devices (Wagener et al., 2017). In addition, increasing ECIG liquid nicotine concentration can increase nicotine delivery (Dawkins et al., 2016; Hiler et al., 2017) and alter subjective effect profiles, including greater suppression of nicotine-abstinence symptoms (Dawkins et al., 2013; Hiler et al., 2017) and higher product satisfaction (Hiler et al., 2017). Lastly, longer and larger puffs

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typically observed in experienced ECIG users result in greater nicotine delivery and suppression of abstinence symptoms relative to less intensive puffs typical of inexperienced users (Farsalinos et al., 2015; Hiler et al., 2017). However, the influence of other ECIG components such as the solvents PG and VG which are found, alone or in combination, in most ECIG liquids on the market (Breland et al., 2017) remains uncertain.

PG and VG act as a vehicle to carry nicotine and flavorants to the user's mouth, throat, and/or lungs. ECIG users can purchase liquids containing various combinations of PG and VG (Breland et al., 2017), and anecdotal reports suggest that using different PG:VG ratios can alter aspects of ECIG use (Li et al., 2016). For instance, ECIG users report that liquids containing more PG provide a better "throat hit" and deliver more flavor while liquids containing more VG produce more exhaled aerosol (referred to colloquially as "clouds" or "vapor;" Li et al., 2016). Additionally, limited pre-clinical evidence suggests that when relevant device, liquid, and puff topography factors are held constant, ECIG liquids with higher proportions of PG produce aerosols containing more nicotine relative to liquids containing predominantly VG (Baassiri et al., 2017; Kosmider et al., 2014b). Taken together, anecdotal reports from ECIG users and the available preclinical evidence suggest that ECIG liquid PG:VG ratio may also influence important acute effects in ECIG users such as nicotine delivery and/or suppression of nicotine-abstinence symptoms.

The present study is the first to explore the extent to which ECIG liquid PG:VG ratio influences the acute effects of ECIG use including nicotine delivery, subjective effects, and puff topography. Given the possibility that PG:VG ratio could influence nicotine delivery (based on the available pre-clinical evidence), heart rate (HR) was also included as an outcome measure, as nicotine delivery from ECIGs (Hiler et al., 2017) and other tobacco products (Benowitz et al., 1988) is commonly associated with increases in HR. Similar to prior clinical laboratory examinations of ECIGs (e.g., Hiler et al., 2017) several device, liquid, and puff topography factors were held constant while PG:VG ratio was manipulated systematically, in order to elucidate the individual influence of these liquid solvents on ECIG acute effects.

2. Method

2.1. Participants

This study was approved by Virginia Commonwealth University's (VCU's) institutional review board (IRB). Potential participants were recruited by advertisements (posted online, throughout campus, and at local vape shops) and word-of-mouth (some participants were informed of the study by other individuals and not via advertisement exposure). Eligible participants were healthy (determined via self-reported medical history), over 110 pounds, aged 18–55, used < 5 tobacco cigarettes daily, used ≥1 ml of ECIG liquid daily, used ≥6 mg/ml nicotine concentration, and had used their ECIG ≥3 months. Given reports (e.g., Wagener et al., 2017) that some ECIG users use liquids containing < 6 mg/ml but consume far more than 1 ml of liquid daily (particularly users of more advanced, higher-powered devices), participants were also eligible if they used ≥10 ml of liquid daily of any active liquid nicotine concentration (i.e., excluding non-nicotine containing liquids). Exclusion criteria included: history of chronic disease or psychiatric condition, positive pregnancy test at screening, regular use of a prescription medication, marijuana use > 10 and alcohol use > 25 days in the past 30 (as in Cobb et al., 2010; Hiler et al., 2017), or use of illicit drugs (e.g., cocaine, methamphetamine) in the past 30 days (all according to self-report). Additionally, participants were deemed ineligible at screening if their: resting HR exceeded 110 beats per minute (bpm), systolic blood pressure (BP) exceeded 140 mm Hg or diastolic BP exceeded 100 mm Hg.

Forty-one individuals provided informed consent for the present study. Of these 41 individuals, eleven did not complete the study and were not included in the final analyses: four were determined ineligible at screening (two had been using ECIGs < 3 months, one used < 1 ml of ECIG liquid per day, and one weighed < 110 pounds), and the remaining seven were discontinued before study completion (three failed to attend study sessions, three lacked venous access, and one exhibited an elevated HR). Thus, thirty experienced ECIG users (29 men; 21 White/Caucasian) completed the study (see Supplementary Table 1). An a priori power analysis revealed that 27 participants were required to detect moderate effect sizes and obtain power of at least 0.80, assuming a moderate correlation among repeated measures (i.e., r ≥ 0.50), and an alpha error probability of < .05 (Barcikowski and Robey, 1985). Thus, using these criteria, 30 participants were sufficient to detect within-group differences for all outcome measures in the present study.

2.2. Materials

For all experimental sessions, participants used an "eGo" (3.3 V) battery with a 1.5 ohm (Ω), dual-coil, 510 "cartomizer" (7.3 W; SmokTech; Shenzhen, China). "Cartomizers" were filled with 1 ml of ECIG liquid ("Virginia Pure" tobacco flavor), containing 18 mg/ml of nicotine (AVAIL Vapor, Richmond, VA). Liquid PG:VG ratio differed by session. The PG:VG ratios as labeled by the vendor were: 100:0, 70:30, 30:70, and 0:100. Subsequent independent analysis (see Peace et al., 2016), revealed that the ratios were: 100:0, 55:45, 20:80, and 2:98. Liquid nicotine concentrations were independently verified as ± 1 mg/ml of the labeled concentrations. All "cartomizers" were verified with an Ohmmeter as ± 0.1 Ω of the purported resistance.

2.3. Procedure

Participants completed four sessions lasting ~3.5 h and separated by ≥ 48 h at VCU's Clinical Behavioral Pharmacology Laboratory (CBPL). Session order was determined by Latin square and participants were blinded to the PG:VG ratio during each session. Participants were instructed to abstain from nicotine/tobacco and/or ECIG use for ≥12 h prior to each session. Abstinence from combustible products was verified using participants' expired air carbon monoxide (CO; ≤10 ppm; as in Breland et al., 2002) and abstinence from noncombustible products (e.g., ECIGs) was verified retrospectively by confirming participants' baseline plasma nicotine concentration was ≤5 ng/ml (as in Hiler et al., 2017; Spindle et al., 2017). Additionally, because of prior noncompliance with abstinence requirements by ECIG users (see Hiler et al., 2017), all participants underwent a one-hour observation period prior to each study session during which no nicotine/tobacco product use was permitted. Three study completers were considered to have not abstained prior to at least one session but these participants were ultimately included in all final analyses because the overall study findings were unaffected upon their exclusion and the higher N improved statistical power.

Following the one-hour observation period, an intravenous catheter was inserted into a forearm vein of the participant and monitoring of HR commenced. Thirty minutes after catheter insertion, a baseline blood sample was taken, and participants completed a "directed" ECIG use bout consisting of 10 puffs with 30 s inter-puff-interval (IPI). Participants completed a second ECIG use bout (60 min after the first) to determine the reliability of the results observed after the first bout. Importantly, these "directed" puffing procedures (i.e., two 10-puff bouts with 30 s IPI, separated by 60 min) have been used in examinations of various tobacco products (e.g., little cigars/cigarillos: Blank et al., 2011; ECIGs: Hiler et al., 2017; and tobacco cigarettes: Vansickel et al., 2010), allowing for direct comparisons of acute effects (e.g., nicotine delivery) across products. Additional blood samples were taken at 5, 15, 30, 45, and 55 min after the onset of bout 1 and 5, 15, 30, and 45 min after the onset of bout 2. Subjective questionnaires were administered immediately following each blood sampling. Participants