Drug and Alcohol Dependence 170 (2017) 93–101

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Nicotine levels, withdrawal symptoms, and smoking reduction success in real world use: A comparison of cigarette smokers and dual users of both cigarettes and E-cigarettes

Douglas E. Jorenby*, Stevens S. Smith, Michael C. Fiore, Timothy B. Baker

Division of General Internal Medicine, Department of Medicine, University of Wisconsin School of Medicine and Public Health, Center for Tobacco Research and Intervention, 1930 Monroe St., Suite 200, Madison, WI 53711, United States

ARTICLE INFO

Article history:
Received 7 July 2016
Received in revised form 24 October 2016
Accepted 29 October 2016
Available online 9 November 2016

Keywords:
Cigarette smoking
e-cigarettes
Dual use
Nicotine
Nicotine dependence
Gender differences

ABSTRACT

Introduction: To evaluate how experienced dual users used cigarettes and e-cigarettes in real-world use and under different levels of cigarette availability.
Methods: Dual users (cigarettes + e-cigarettes; n = 74) and a smoke-only group (just cigarettes; n = 74) engaged in a 26-day study with two *ad lib* use intervals, a week of 75% cigarette reduction and three days of 100% cigarette reduction. After a week of *ad lib* use of products, all participants were asked to reduce smoking by 75% (dual users were free to use their e-cigarettes as they wished), followed by another week of *ad lib* use. All participants were then asked to reduce smoking by 100% (cessation) for three days. Primary outcomes were biological samples (carbon monoxide, urinary nicotine and cotinine). Participants also provided real-time reports of product use, craving, and withdrawal symptoms using a smartphone app.
Results: Dual users did not smoke fewer cigarettes than smoke-only participants during *ad lib* periods, but quadrupled their use of e-cigarettes during smoking reduction periods. Dual users were significantly more likely to maintain 100% reduction (97.1% vs. 81.2%). Amongst women, dual use was associated with higher nicotine levels and withdrawal suppression.
Discussion: Among a group of experienced dual users, e-cigarettes helped maintain smoking reduction and reduced some withdrawal symptoms, although both withdrawal symptoms and nicotine levels varied as a function of gender.

1. Introduction

Ever-use of electronic cigarettes (e-cigarettes) in a US probability sample increased from 1.8% in 2010 to 13% in 2013, while current-use (use on some days or every day) climbed from 0.3% to 6.8% over the same time period (McMillen et al., 2015). Current e-cigarette use is highest amongst daily cigarette smokers – one-third reporting use in 2014 (McMillen et al., 2015; Brown et al., 2014; Centers for Disease Control and Prevention, 2013; Dockrell et al., 2013; King et al., 2015).

Tobacco use is a causal factor in about 6 million deaths annually worldwide (World Health Organization, 2011), with the majority attributable to smoking (Prabhat, 2012). E-cigarettes likely have less severe direct health effects than do combustible cigarettes (Farsalinos and Polosa, 2014; Hecht et al., 2015; Polosa, 2015). If e-cigarettes can substitute for cigarettes, they can potentially produce public health benefit.

Whether e-cigarettes will substitute for cigarettes depends, in part, on if they yield effects approximating the cigarette effects thought to cause dependent cigarette use (reduce tobacco withdrawal symptoms, deliver meaningful levels of nicotine; Institute of Medicine, 2012). This study examines whether e-cigarettes appear to produce effects similar to cigarettes (as noted above), and whether e-cigarette use was associated with reduced cigarette use.

This study comprised both "dual users" (*DUs*: users of both e-cigarettes and cigarettes) and those who smoke only (*SOs*). This permitted analysis of the extent to which conjoint e-cigarette use was associated with different patterns of cigarette use and other related outcomes. We were interested in whether DUs 1) smoke fewer cigarettes and have lower carbon monoxide (CO) levels than SOs; 2) show elevated levels of nicotine relative to SOs, espe-

* Corresponding author.
E-mail address: Dej@ctri.wisc.edu (D.E. Jorenby).

http://dx.doi.org/10.1016/j.drugalcdep.2016.10.041
0376-8716/

cially during periods of smoking reduction when they could use e-cigarettes ad libitum; 3) report lower levels of withdrawal symptoms during periods of smoking reduction; and 4) are more able than SOs to reduce and/or stop their cigarette use. We sought to determine whether any observed differences between DUs and SOs were related to gender and nicotine dependence, factors implicated in smoking motivation and cessation success (Perkins et al., 1999; Piper et al., 2008a,b; Wray et al., 2015).

Survey and laboratory research has addressed the effects of e-cigarettes on the outcomes listed above. Survey research (Etter and Bullen, 2011) shows most e-cigarette users report that e-cigarettes are helpful for reducing withdrawal symptoms, craving, and smoking heaviness. Obviously, survey studies provide neither real-time data associated with e-cigarette use, nor data arising from experimental manipulations such as smoking deprivation.

Laboratory research has yielded data on the potential of e-cigarettes to displace or substitute for cigarette use (Bullen et al., 2010; Dawkins and Corcoran, 2014; Dawkins et al., 2012; Nides et al., 2014; Vansickel et al., 2010; Vansickel and Eissenberg, 2013). Such studies suggest that e-cigarettes, especially when used by experienced users, can reduce tobacco withdrawal symptoms, exert appetitive effects, and reduce urges to smoke cigarettes (Farsalinos et al., 2014). Some studies (Bullen et al., 2010; Vansickel et al., 2010) did not use experienced e-cigarette users using their own e-cigarette brands. Evidence shows that experienced users obtain stronger effects from e-cigarettes than do inexperienced users (Farsalinos et al., 2014; Nides et al., 2014; Vansickel and Eissenberg, 2013). Most studies involved only acute use of e-cigarettes and did not observe their effects over extended periods of time in real-world use (Bullen et al., 2010; Dawkins and Corcoran, 2014; Farsalinos et al., 2014; Nides et al., 2014; Vansickel et al., 2010; Vansickel and Eissenberg, 2013).

2. Methods

2.1. Study sample and data collection

This was a 26-day study, conducted March 2013 to May 2014, in the Madison and Milwaukee, WI, metropolitan areas. All participants provided written informed consent and the study received approval from the University of Wisconsin Health Sciences Institutional Review Board.

Eligibility for study participation included: minimum 18 years old; able to read and write English; smoking at least five cigarettes per day for the past six months; not currently using any smoking cessation medication; planning to remain in the area for the study duration; no history of psychosis or bipolar disorder; not planning to quit tobacco use in the next 30 days; willing to follow study procedures; and if female, not be pregnant or nursing and willing to use acceptable methods of birth control during the study. For the Smoke Only group, participants could not have used a single type of alternate tobacco products (e.g., e-cigarettes, *snus*, or chewing tobacco) more than five times in their life *and* not have used alternate tobacco products in the past six months. For the Dual Use group, participants had to have used e-cigarettes at least three times per week for the past three months. Recruitment occurred through point-of-purchase displays at convenience stores in southern Wisconsin and the Milwaukee metropolitan area and through a context-sensitive Facebook ad seeking both smokers and dual users. Interested people completed a brief screening interview and if cleared were invited to attend an in-person initial study visit.

Once informed consent was obtained and eligibility criteria confirmed at Visit 1 (V1, Day 1), participants provided a carbon monoxide (CO) breath sample and a urine sample for nicotine analysis. They also completed a baseline survey including demographics, smoking history, the Fagerstrom Test of Cigarette Dependence (FTCD; Fagerstrom et al., 2012), and the Wisconsin Inventory of Smoking Dependence Motives (WISDM; Piper et al., 2008a,b). Participants were then given a study cellphone with the app preinstalled. They were trained in the use of the app. Participants were asked to use the app to log each time they smoked or vaped throughout the day. DU participants were instructed that a vaping episode meant taking two or more puffs on an e-cigarette close together and isolated in time from other vaping episodes. Four hours after waking, and at two subsequent four hour intervals, the app prompted participants to complete a brief assessment of withdrawal symptoms, the amount of smoking (and/or vaping) in the past four hours, time since last cigarette (or e-cigarette), and environmental factors related to last use. Participants were asked to complete the surveys as soon as possible following the notification.

Participants were instructed to continue smoking and vaping normally over the next week, and to use the smartphone app as directed (see Fig. 1 for study timeline). On Study Day 8 (V2), participants provided CO and urine samples, and completed another survey. Their average daily smoking during the previous week was calculated. All participants were then asked to reduce their smoking to 75% of baseline (rounded to the nearest whole cigarette) for the next week. Participants in the DU group were told they were free to use their e-cigarettes as they wished. Participants made another in-person visit (V3) on Study Day 11 to confirm adherence to reduction by CO level. On Study Day 15 (V4), participants once again provided biological samples and completed a survey. Following that visit, they were instructed to return to their normal cigarette smoking rate over the next week. On Study Day 22 (V5), participants completed regular study visit assessments. Starting the next day, they were instructed to not smoke at all until their visit on Day 26 (100% reduction; DU participants were again told they were free to use their e-cigarettes as they wished). Both 75% and 100% reduction periods were used in order to determine whether hypothesized e-cigarette effects occurred during either partial or full smoking deprivation. Participants returned to assess adherence on Study Days 24 (V6) and 26 (V7).

Participants received financial incentives for attending study visits, completing at least 80% of their smartphone assessments, meeting CO targets during the reduction and cessation intervals, and for returning study smartphones at the end of the study (total possible study compensation = $560).

2.2. Measures

Key outcome measures included biological measures (urinary nicotine, CO), self-reported e-cigarette and cigarette use, and self-reported ratings of craving and negative affect. Biological measures were collected at each of the seven study visits. Daily symptom ratings and cigarette/e-cigarette use were collected via the smartphone app. The craving and negative affect symptom measures were derived from the Wisconsin Smoking Withdrawal Scale (WSWS; Welsch et al., 1999) with items rated on a 0–4 scale from 0 = Strongly Disagree to 4 = Strongly Agree. Craving was measured with a single item: “I have been bothered by the desire to smoke a cigarette.” Negative Affect was measured as the mean of three items: “I have been tense or anxious,Ï have been irritable, easily angered’ and “I have felt sad or depressed."

Urine samples were transferred to storage tubes and frozen immediately following collection. Samples were stored in −20 °C freezers and shipped at two-week intervals to Weck Laboratories (City of Industry, CA). Nicotine levels in each sample were determined using liquid chromatography-mass spectrometry electro-spray positive ionization methods with minimum reporting limits of 20 μg/l.