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Electronic cigarettes for adults with tobacco dependence enrolled in a tobacco treatment program: A pilot study

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Abstract

Introduction: Electronic cigarettes (ECs) have emerged as a potential harm-reducing alternative for tobacco smokers. However, the role ECs might play in treatment settings is unclear. We conducted an exploratory study of treatment-seeking smokers enrolling in a standard tobacco treatment program who were provided with either a nicotine or non-nicotine EC to use as needed to cease tobacco smoking.

Methods: Treatment-seeking smokers received standard tobacco treatment for 8 weeks and were given nicotine transdermal patch therapy, behavioral counseling, and either a nicotine or non-nicotine EC to use as needed. Smoking and EC use patterns were tracked longitudinally to week 24.

Results: 40 subjects were enrolled into the study. At week 24, 6 subjects (15%) were abstinent, and the mean reduction in reported cigarettes smoked per day was 6.8 ± 12. There were no

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Contributors

Dr. Baldassarri and Dr. Toll were involved in the study design, data collection, analysis, manuscript writing, and editing. Dr. Chupp, Dr. Bernstien, and Dr. Fucito were involved in the data collection and editing of the manuscript. Mr. Slade was involved in the data analysis and editing of the manuscript. All authors have contributed to and have approved the final manuscript.

significant differences in smoking outcomes between those who received a nicotine or non-nicotine EC (proportion abstinent at 24 weeks: nicotine EC = 4/20 (20%); non-nicotine EC = 2/20 (10%); p = 0.66). Among subjects assessed at follow-up, 62.5% were EC non-users.

Conclusions: The addition of a 2nd generation EC to outpatient tobacco treatment among tobacco smokers is feasible. Among those who quit smoking, half were still using the EC at 6-month follow-up. Appeal of the EC among smokers was variable, and those who had quit smoking tended to switch to lower strength nicotine solutions. Further research is needed to determine whether ECs can reduce harm and be an effective adjunct to existing tobacco treatment interventions.

Keywords

Electronic cigarette; Tobacco treatment; Smoking cessation

1. Introduction

Electronic cigarettes (EC) have emerged as an alternative for tobacco smokers. ECs may appeal to smokers because in addition to providing nicotine in an aerosolized and non-combustible form, the products allow users to mimic the rewarding behavioral patterns that reinforce smoking. EC use for treatment of tobacco dependence in adults is controversial, and evidence for EC efficacy in promoting cessation from tobacco smoking is limited. The most recent systematic review of the efficacy of ECs for smoking cessation found limited low-quality evidence of a trend toward smoking cessation in adults using nicotine ECs exists compared with other therapies or placebo (Baker, Piper, Stein, et al., 2016). Of note, the review found only 5 suitable studies (4 RCTs and 1 Controlled Pre-Post study) out of 569 total articles. The largest randomized controlled trial of ECs enrolled 657 smokers from a single center (Behar, Hua, & Talbot, 2015). While the investigators found no significant differences in 6-month abstinence rates between groups, significant reductions in average cigarette consumption were observed in the EC group as compared to the nicotine patch.

The use of an EC as part of a structured tobacco treatment program has not been adequately studied, and longitudinal effects of ECs on smoking behavior and pulmonary function have not been well characterized. We conducted a preliminary exploratory study of treatmentseeking smokers enrolling in an outpatient tobacco treatment program who were provided with either a nicotine or non-nicotine EC to use as needed to cease tobacco cigarette use. Our goals were: (Khoudigian, Devji, Lytvyn, et al., 2016) to establish the feasibility of adding an EC to outpatient tobacco treatment as part of a standard care regimen (Bullen, Howe, Laugesen, et al., 2013) to determine if there are differences in smoking behavior and lung function changes between individuals receiving nicotine versus non-nicotine containing ECs; (Miller, Crapo, Hankinson, et al., 2005) to characterize EC use patterns and perceptions in a real-world setting among treatment-seeking smokers; and (Farsalinos, Spyrou, Stefopoulos, et al., 2015), to generate hypotheses regarding potential benefits, risks, and challenges of introducing ECs into tobacco treatment settings.

2. Materials and methods

2.1. Participants

Participants were recruited from the Yale-New Haven Hospital outpatient pulmonary and primary care clinics, Tobacco Treatment Service, and through referrals from medical providers in the Yale-New Haven Health system. Inclusion criteria were (Khoudigian et al., 2016) Age 18 years or older; (Bullen et al., 2013) Smoking 1 or more tobacco cigarettes per day; (Miller et al., 2005) Willing to quit smoking. Exclusion criteria were: (1) Unstable psychiatric or medical conditions requiring hospitalization within the past 4 months; (Bullen et al., 2013) Acute coronary syndromes or stroke within the past 30 days; (Miller et al., 2005) History of allergic reactions to adhesives; (Farsalinos et al., 2015) Women who were pregnant, nursing, or not practicing effective contraception; (Robinson, Hensel, Morabito, et al., 2015) Current use of an EC for the purpose of stopping tobacco cigarette smoking.

2.2. Randomization

Participants were randomized using a random number generator with 1:1 blocked randomization (block size n = 8) to ensure equal numbers in each treatment group. Both groups received standard care (nicotine patch and counseling) and were randomized to: (Khoudigian et al., 2016) *nicotine EC* or (Bullen et al., 2013) *non-nicotine EC*. Treatment assignment was blinded to both the investigators and participants. This research was approved by the Yale University Institutional Review Board.

2.3. Treatment and assessment contacts

Questionnaire assessments and exhaled breath carbon monoxide (exCO) measurements occurred at baseline, bi-weekly at each scheduled treatment visit (week 2, 4, 6, 8), and follow-up (week 24). ExCO levels were measured using a Bedfont Micro + Smokerlyzer Monitor. Spirometry and fraction of exhaled nitric oxide (FeNO) were performed at baseline and 6-month follow-up using a Nspire Koko spirometer and NiOx Mino FeNO detector per American Thoracic Society guidelines (Benowitz, 2010). Subjects received nicotine patches and ECs for the first 8 weeks and were assessed every 2 weeks. This initial intervention was followed by a 16-week period of observation during which subjects were permitted to use any available therapies for tobacco treatment. Subjects were paid $25 at intake and $50 at 24-week follow-up to try to optimize recruitment and maximize study adherence and follow-up. The study had a modest loss to follow-up (20%) at week 24.

2.4. Standard treatment

All participants were asked to set a quit date within a week of their first study visit. Subjects who smoked > 10 cigarettes per day were initially given the 21 mg patch, and subjects who smoked 10 or fewer cigarettes per day were given the 14 mg patch. The dose of the medication was reduced if they were abstinent from tobacco and EC use, or if they reported difficulty tolerating higher doses due to side effects. If they continued smoking, were non-adherent, or were using the EC, the patch dose was not reduced (or was increased to 21 mg if they were started at a lower dose). All participants were given a two-week supply of nicotine patches at each study visit for the first 8 weeks of the study.

The initial study visit and each subsequent study visit consisted of intensive counseling sessions with an Advanced Practice Registered Nurse (APRN) behavioral tobacco treatment specialist or a clinical psychologist trained in motivational interviewing techniques and tobacco dependence pharmacotherapy.

2.5. Experimental conditions

Subjects were given a 2nd generation eGO style EC (650 mAh battery, EVOD clearomizer, 3.7 V, 1.8 Ω single bottom coil), provided with e-liquid purchased from an online vape shop (0 or 24 mg/ml nicotine strength, 70/30 propylene glycol/vegetable glycerin, tobacco flavor), and were instructed to use it as needed as a substitute for tobacco to try to satisfy cravings to smoke. If the patch alone proved adequate to prevent withdrawal and smoking cravings, the subject was advised not to use the EC. Use of the EC as a substitute for cigarette smoking was encouraged but not considered mandatory and was at the discretion of study subjects. Since EC use differs significantly from tobacco smoking (Bullen et al., 2013; Farsalinos et al., 2015; Khoudigian et al., 2016; Kotz, Brown, & West, 2014; PHS Guideline Update Panel La, and Staff, 2008), subjects were advised to take longer and slower puffs (i.e. 3–4 s per puff). Additional EC devices, replacement coils, and liquid were provided as needed for the first 8 weeks of the study.

2.6. Outcome measures

The primary outcome was the change in reported number of cigarettes smoked per day at weeks 8 and 24. Secondary outcomes were smoking status (defined by 7-day point prevalence abstinence and confirmed by exCO ≤ 6 ppm) at weeks 8 and 24, change in percent predicted FEV_1 and FVC from baseline to week 24, and EC use patterns.

2.7. Statistical analysis

SAS v9.4 was utilized for the statistical analyses. Descriptive statistics were calculated by group to determine if statistical differences existed between the nicotine and non-nicotine EC participants. For continuous variables, Student's *t*-test was utilized. For categorical variables, Fisher's exact test was used. Smoking abstinence was assessed by intention-to-treat analysis, assuming those lost to follow-up were smokers.

3. Results

3.1. Overall

Forty subjects were enrolled into the study (Table 1). There were no significant differences in reduction in reported cigarettes smoked per day between those who had received a nicotine or non-nicotine EC at the beginning of the study or in smoking quit rates (Table 2: proportion abstinent at 24 weeks: nicotine EC = 4/20 (20%); non-nicotine EC = 2/20 (10%) p = 0.66). There were no significant differences in the change from baseline to week 24 in the percent predicted FEV_1 (−0.019 ± 0.085), FVC (−0.008 ± 0.09), or FeNO (2.97 ± 8.6 ppb). At week 8, 7 of 40 subjects (17.5%) were biochemically confirmed abstinent from tobacco smoking, and the mean reduction in reported cigarettes smoked per day was 7.9 ± 12. During the observation period between weeks 8 and 24, three individuals had relapsed into smoking, and two spontaneously stopped smoking. At week 24, 6 subjects (15%) were

abstinent, and the mean reduction in reported cigarettes smoked per day was 6.8 ± 12. The most commonly reported side effects among all participants were cough (30%), sore throat (22.5%), increased appetite (17.5%), and vivid dreams (17.5%) (no significant differences by treatment group).

3.2. EC use patterns, perceptions, and trajectories

At 24-week follow-up, 23 subjects (57.5%) reported that ECs helped them reduce or eliminate tobacco smoking. Among the 6 non-smokers at follow-up, 4 (67%) had found the EC helpful in curtailing tobacco smoking during the study period. Half were still using ECs at follow-up (Table 3). The most commonly reported benefits were being able to decrease or quit tobacco smoking (50%), saving money (50%), and clothing smelling less of smoke (43.8%). The most commonly reported problems included the inability of the EC to satisfy the craving to smoke (27.5%), that the EC was too harsh (27.5%), and unpleasant flavor (15%). Among all subjects assessed at follow-up, 12 (37.5%) were EC users.

Among EC users at week 24, 1/3 were using non-tobacco flavored ECs, and (42%) were using low strength or zero nicotine e-liquids.

4. Discussion

We conducted an exploratory study in a real-world treatment setting by providing motivated smokers with a 2nd generation (3.7 V, 1.8 Ω) EC to assist in cessation from tobacco smoking. We noted a 6-month smoking quit rate overall for our study population of 15%. This rate is lower than that typically seen in other tobacco treatment trials (Lee, Gawron, & Goniewicz, 2015; Miller et al., 2005), and more consistent with the low quit rates noted in the largest EC trial to date (Behar et al., 2015). We recruited our population primarily from local medical clinics, where patients tended to be older, had more medical and psychiatric co-morbidities, and were highly nicotine dependent. Real-world abstinence rates among smokers receiving treatment have been observed between 10 and 20% (Robinson et al., 2015). Adherence to treatment was low (30%), which may reflect other demographic features of the population, including low socioeconomic and educational status.

We note that among those who had quit smoking at week 8, three individuals relapsed by week 24 (Table 3). This observation was not surprising given the chronic nature of tobacco dependence, which is characterized by periods of remission and relapse. The relapsing subjects all started in the non-nicotine EC group, and two of them were not using the e-cigarette or nicotine patch at week 24 follow-up. Conversely, there were two individuals who were smoking at week 8 and were able to quit smoking by week 24. Although the late quitters were both initially assigned to the nicotine EC group, one of them did not find the EC useful and used the nicotine patch to quit smoking. The other individual switched to a low strength nicotine EC and used that as an aid to stop smoking. Overall, these findings are consistent with prior studies suggesting that long-term use of nicotine replacement might be beneficial to maintaining smoking abstinence and preventing relapses for up to 24 weeks in some smokers (Schnoll, Goelz, Veluz-Wilkins, et al., 2015). The present preliminary study cannot determine whether long-term EC use would prevent smoking relapses or increase the likelihood of quitting smoking, but these are certainly hypotheses that should be tested in

future studies. Also of note, only one of the six individuals who were abstinent at 24 weeks was using standard therapy (i.e. the nicotine patch) at 24-week follow-up. Perhaps if the nicotine patch were used consistently over the 24 week study period, continuous abstinence rates might have been higher. This raises the question of whether the introduction of ECs makes the use of proven therapies such as NRT less appealing to smokers. This is an important phenomenon to study prospectively in future EC studies.

4.1. EC outcomes and perceptions

Among the 6 subjects who quit smoking at week 24, 2 reported using the nicotine patch exclusively and did not find the EC useful. The remaining 4 subjects found the EC useful in curtailing tobacco use. Interestingly, the non-smokers using ECs were using zero or low strength nicotine solutions with non-tobacco flavors at follow-up. This suggests that the behavioral and environmental cues of the EC rather than nicotine delivery may have been the more important factor in assisting these subjects in quitting smoking.

Among the smokers who followed up at week 24, many reported that the EC helped them cut down on tobacco smoking but could not completely act as a complete cigarette substitute. It was notable that while 35% of persistent smokers who followed up reported using their EC, only 3 (12%) reported frequent EC use. These finding suggests that the vast majority of individuals in this group had abandoned the EC as a smoking cessation tool. There are several possible reasons for why the EC was ineffective in some smokers. There were many factors reported by subjects including that the EC did not satisfy smoking cravings, was too harsh, had a bad taste, or was too inconvenient to use. It is possible that users did not receive sufficient nicotine replacement from the combination of the patch and EC, or that such nicotine delivery did not occur rapidly enough. Furthermore, the EC may fail to deliver other addictive substances found in cigarette smoke such as combustion products of acetaldehydes that can act as MAO-I inhibitors (Spindle, Breland, Karaoghlanian, et al., 2015).

4.2. Study limitations

Our study has several limitations. We note that this is an exploratory study meant primarily to generate hypotheses. We were not powered to detect differences between nicotine and non-nicotine groups, so we cannot determine whether nicotine delivery was a prominent feature of the nicotine ECs provided. We studied a very specific population of smokers that overall tends to have more co-morbidities and lower smoking quit rates. This prevents us from generalizing findings to younger, healthier individuals and to non-treatment seeking smokers. As noted in the Methods, our study had a 20% loss to follow-up at week 24. Participants with Medicaid insurance were more likely to be lost to follow-up as compared with others. There were no significant differences in loss-to-follow-up among other demographic factors including age, race, gender, baseline number of cigarettes smoked per day, or FTND score. It is not clear whether some of those lost to follow-up continued smoking tobacco, became exclusive EC users, or ceased nicotine use completely. We treated all participants lost to follow up as smoking.

We limited our study to a single EC product and nicotine strength, which prevents us from drawing conclusions about EC products in aggregate. We did not have the means to test subjects for nicotine uptake during EC use, so it is unclear whether reported benefits derived primarily from nicotine delivery or behavioral effects. Recent evidence indicates that nicotine delivery might be more effective with higher powered devices (Wagener, Floyd, Stepanov, et al., 2017).

5. Conclusions

In conclusion, the addition of a 2nd generation EC to outpatient tobacco treatment among tobacco smokers was feasible. Fifteen percent of the subjects were abstinent from tobacco at week 24. Among those who quit smoking, half were still using the EC. Appeal of the EC among smokers was variable, and those who had quit smoking tended to switch to lower strength nicotine solutions. Further research is needed to determine whether ECs can reduce harm and be an effective adjunct to existing tobacco treatment interventions.

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Conflict of interest

Dr. Toll received a grant from Pfizer for medicine only for a research study, and he receives funding as an expert witness in litigation filed against the tobacco industry. Dr. Chupp received grants from NIH, Genetech, Glaxo Smith Kline, Astra Zeneca/Medimmune and Boston Scientific. He received consulting/speaking fees from Genetech, Astra Zeneca/Medimmune, Mannkind, and Boston Scientific. There are no other conflicts of interest for the remaining authors.

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HIGHLIGHTS

- Electronic cigarettes can be incorporated into a tobacco treatment program.
- Half of the smokers who quit cigarettes were using e-cigarettes at follow up.
- Low or zero strength nicotine e-liquids were preferred by some smokers.
- Behavioral cues of e-cigarettes were important for modifying smoking behavior.

Table 1

Demographics.

	Overall (n = 40)	Non-Nicotine EC (n = 20)	Nicotine EC (n = 20)
Age, mean (SD), years	53 (10.1)	53.8 (7.8)	52.2 (12.2)
Female, No. (%)	21 (52.5)	13 (65)	8 (40)
Non-white race, No. (%)	14 (35)	8 (20)	6 (15)
Insurance, No. (%)			
Medicaid	18 (45)	10 (50)	8 (40)
Medicare	11 (27.5)	7 (35)	4 (20)
Private	11 (27.5)	3 (15)	8 (40)
Education, No. (%)			
Less than high school	4 (10)	1 (5)	3 (15)
High school	25 (62.5)	13 (65)	12 (60)
College or University	6 (15)	5 (25)	1 (5)
Graduate or Doctoral	5 (12.5)	1 (5)	4 (20)
Employment status, No (%)			
Unemployed	9 (22.5)	5 (25)	4 (20)
Employed	14 (35)	6 (30)	8 (40)
Retired	6 (15)	3 (15)	3 (15)
Disabled	11 (27.5)	6 (30)	5 (25)
Smoking characteristics			
Baseline reported cigarettes smoked per day, mean (SD)	17 (11.5)	17 (12.4)	17 (10.9)
Estimated pack-years, mean (SD)	36 (21.5)	38 (23.1)	35 (20.4)
Fagerstrom Test Score, mean (SD)	5.8 (2.1)	6.0 (2.2)	5.7 (2.0)
Time to first cigarette < 30 min, No. (%)	35 (87.5)	18 (90)	17 (85)
Baseline exhaled carbon monoxide	19 (10.2)	19 (10.8)	19 (9.7)

Table 2

Group comparison of primary outcomes.

	Treatment group assignment				
	Overall (n = 40)	**Non-nicotine EC (n = 20)**	**Nicotine EC (n = 20)**	**95% CI**	**P-value**
Non-smokers at 8 weeks, n (%)	7 (17.5)	5 (25)	2 (10)	0.056–1.971	0.41
Non-smokers at 24 weeks, n (%)	6 (15)	2 (10)	4 (20)	0.362–14.0	0.66
8 week change in reported # cigarettes/day (mean, sd)	−7.85, 12.4	−7.36, 14.7	−8.35, 10.1	−7.1–9.1	0.81
24 week change in reported # cigarettes/day (mean, sd)	−6.78, 11.5	−8.04, 11.6	−5.5, 11.5	−9.9–4.9	0.49
24 week change in % predicted FEV1 (mean, sd)	−0.019, 0.085	−0.037, 0.097	0.0085, 0.057	−0.107–0.015	0.14
24 week change in % predicted FVC (mean, sd)	−0.008, 0.090	−0.0216, 0.103	0.0108, 0.065	−0.098–0.034	0.33
24 week change in FeNO (mean, sd)	2.97, 8.62	3.11, 7.45	2.75, 10.5	−6.33–7.06	0.91

Table 3

Characteristics of participants who quit smoking during the study at week 8 or week 24.

Subject	Initial treatment group assignment (week 0)	Smoking status at week 8	Smoking status at week 24	EC use at 24 weeks?	EC Nicotine strength used at 24 weeks	Nicotine patch use at 24 weeks
1	Non–nicotine EC	Quit	Quit	Yes	1–10 mg/ml	No
2	Non-nicotine EC	Quit	Quit	No	N/A	No
3	Non-nicotine EC	Quit	Relapsed	Yes	Unknown	No
4	Non-nicotine EC	Quit	Relapsed	No	N/A	No
5	Non-nicotine EC	Quit	Relapsed	No	N/A	No
6	Nicotine EC (24 mg/ml)	Quit	Quit	Yes	0 mg/ml	No
7	Nicotine EC (24 mg/ml)	Quit	Quit	No	N/A	No
8	Nicotine EC (24 mg/ml)	Smoking	Quit	Yes	1–10 mg/ml	No
9	Nicotine EC (24 mg/ml)	Smoking	Quit	No	N/A	Yes