Original investigation

An Open Trial of Electronic Cigarettes for Smoking Cessation Among Methadone-Maintained Smokers

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Abstract

Introduction: Smoking cessation pharmacotherapies tested in persons with opioid use disorder have produced low quit rates. Electronic cigarettes (e-cigarettes) have been used by many methadone-maintained (MMT) smokers, but controlled trials evaluating cessation and reduction outcomes have not been performed in this population with deleterious tobacco-related health consequences.

Methods: In this open trial of NJOY e-cigarettes, MMT smokers received 6 weeks of treatment and were instructed to use only e-cigarettes. Outcomes included carbon monoxide confirmed 7-day point smoking cessation prevalence at week 7 (end of treatment) and self-reported change in mean cigarettes per day (CPD) at each 2-week assessment. The final assessment was 2 weeks after treatment ended (week 9).

Results: The 12 participants averaged 46 years old and 50% were male. On average, participants reported smoking 17.8 (± 5.3) CPD. One person had a biochemically confirmed quit at week 7. Participants tended to report marked reductions in mean CPD between quit day (week 1) and the week 3 assessment. Relative to baseline, statistically significant reductions in mean CPD were observed at all follow-up assessments. Mean reductions in CPD were -12.4 (95% confidence interval [CI]: $-15.0, -9.9$; $P < .001$), -14.8 (95% CI: $-17.4, -12.2$; $P < .001$), -13.9 (95% CI: $-16.6, -11.2$), and -10.8 (95% CI: $-13.4, -8.2$; $P < .01$) at the 3-, 5-, 7-, and 9-week assessments, respectively. Adherence to e-cigarettes was 89.1% during the 6 treatment weeks.

Conclusions: E-cigarettes were associated with reductions in cigarette use. Smoking cessation rates in MMT smokers are low and whether long-term smoking reductions can persist and produce health benefits should be studied.

Implications: E-cigarettes were associated with reduced tobacco use in MMT smokers. Adherence to e-cigarettes is high among methadone smokers. Week-7 smoking quit rates are similar to pharmacotherapies tested in this population.

Introduction

Cigarette smoking is the leading preventable cause of morbidity and mortality in the United States and its health consequences remain

particularly high in persons with drug use disorders.¹ With smoking rates far exceeding the general population, methadone-maintained (MMT) smokers with opioid use disorder experience high rates of

tobacco-related health consequences.²⁻⁷ Across studies, at least 80% of methadone treatment participants smoke, despite being aware of the attendant health risks.^{3,8,9}

Over the past decade, researchers have evaluated smoking cessation treatment for persons with opioid use disorder using behavioral treatment in conjunction with pharmacotherapy. All of the randomized trials of smoking cessation pharmacotherapies tested in persons with opioid use disorder, including nicotine replacement therapy (NRT),¹⁰⁻¹⁴ bupropion,¹⁵ and varenicline¹⁶ have produced far lower quit rates than those reported in trials of nondrug users. Novel approaches to reduce the harm from cigarettes in this population that smokes heavily are needed.¹⁷

"Electronic cigarettes" (e-cigarettes) contain liquid nicotine, a battery, and an atomizer, and look and feel like tobacco cigarettes. The liquid nicotine is heated, vaporized, and inhaled, and users exhale odorless "smoke" byproduct. These electronic nicotine delivery systems (ENDS) have gained worldwide attention, with awareness of e-cigarettes, steadily growing in the United States¹⁸⁻²¹ and sales increasing dramatically.²² By 2010, internet searches for e-cigarettes were more popular than for any other smoking cessation product, including NRT and Chantix,²³ despite federal regulations preventing e-cigarettes from being marketed or approved as a smoking cessation aid.

Regardless of how e-cigarettes are being regulated, surveys of current users show a majority of e-cigarette users endorse smoking cessation as the main reason for use.²⁴⁻²⁸ A randomized trial conducted in New Zealand²⁹ found that e-cigarettes were at least as effective as nicotine patch for smoking cessation.³⁰ Surveys have reported that e-cigarettes are effective to varying degrees as cessation aids.³¹⁻³³ In two studies conducted with smokers with no stated desire to quit smoking tobacco cigarettes, findings included carbon monoxide-confirmed tobacco abstinence rates of 8.7% at 52 weeks in one study,³⁴ and 12.5% at 24 months in the other.^{35,36} Additionally, among first time, online e-cigarette purchasers, the 6-month point prevalence abstinence rate was self-reported to be 31%.³⁷ Sustained abstinence was achieved in two of 14 schizophrenic smokers, a notably difficult population to treat, after 52 weeks of follow-up, and 50 percent achieved a self-reported 50% reduction in tobacco cigarette smoking.³⁸

Concerns about e-cigarettes have been raised, including the varying quality of the products, its inefficiency as a nicotine delivery system,³⁹⁻⁴² and the risk of toxicant exposure, although chronic health effects are unclear.^{43,44} However, current users of e-cigarettes perceive them as safer than regular cigarettes,^{20,21,27} report decreased craving and urges to smoke as compared to tobacco cigarettes even when less nicotine is received.^{42,45} Perhaps most important for e-cigarettes potential as a smoking cessation aid, during qualitative interviews about the benefits of NRT versus e-cigarettes, those interviewed believed e-cigarettes were far more effective because they allowed for many of the social and psychological benefits of smoking while avoiding the negative side effects of NRT.⁴⁶ Over 31% of callers to six state smoking quit lines in 2011 and 2012 reported use of e-cigarettes.⁴⁷

We studied whether smokers with opioid use disorder (164 methadone, 151 buprenorphine) had experience with e-cigarettes and reported that 98.7% had heard of e-cigarettes, 73.0% had ever tried them, and 33.8% had used e-cigarettes in the past 30 days.⁴⁸ The most common reasons for use were curiosity (41.4%) and to quit all nicotine (26.0%). The proportion of smokers with opioid use disorder that had ever tried e-cigarettes and used them in the past

month was substantially greater than that found in recent general population surveys.

While e-cigarettes have been used to quit smoking, how to optimize their use remains untested. We conducted a small open pilot trial on the use of e-cigarettes as a smoking cessation aid among methadone maintained smokers.

Methods

We posted a flyer at a large methadone maintenance treatment program in Southeastern New England in April 2015. The poster announced Project ECHO as, "a study about the experiences of individuals in methadone treatment who would like to quit smoking. The purpose of this project is to learn more about the use of e-cigarettes for smoking cessation treatment."

Interested persons approaching research staff on site during regular dosing hours were asked to complete the brief, 10-minute screening questionnaire. Inclusion criteria were: (1) current moderate or heavy cigarette use (10+ cigarettes per day [CPD] for at least 12 months prior to enrollment); (2) current MMT for at least 3 months; (3) ready to make a smoking quit attempt in the next 14 days; (4) plan to remain on MMT for at least 12 weeks. Participants were excluded if they: (1) used e-cigarettes on more than 2 of the past 30 days; (2) currently used medications that may reduce smoking (bupropion, varenicline, NRT); (3) had unstable medical or psychiatric conditions (past-month suicidal ideation or past-year suicide attempt, hospitalization for myocardial infarction or stroke in the prior 3 months); (4) had regular use of marijuana (self-report or positive urine drug test).

Sixteen individuals screened for the study, two were ruled ineligible (in methadone treatment less than 3 months). Prior to informed consent, additional eligibility checks ruled out two additional persons (one person did not appear on the scheduled date, one person smoked fewer than 10 CPD). Research assistants provided informed consent documents to the 12 eligible participants to review and sign, and completed a baseline interview. At the completion of the baseline appointment, participants scheduled a quit day approximately 1 week from baseline.

Research assistants met with participants on their quit day (week 1) to provide a 2-week supply of NJOY e-cigarettes that consisted of three 5-packs of e-cigarettes (15 total), enough for one e-cigarette per day⁴⁹ and instructed in their use. NJOY e-cigarettes provide the nicotine equivalent of 20-30 tobacco cigarettes depending on how they are used (NJOY, Scottsdale, AZ). Although participants were given 5-packs of e-cigarettes at their first distribution, they were not instructed to only use one e-cigarette per day. If participants ran out of e-cigarettes prior to a study visit (other than the week 7 visit), they could request an additional 5-pack (20 total) for the following 2-week study period. NJOY was chosen as it was an independent commercial brand, not owned by a tobacco company, and was easily accessible in the community if participants chose to continue using e-cigarettes after study completion.

Participants were instructed to use the e-cigarettes exclusively for a total of 6 weeks (end of treatment), returning every 2 weeks for assessments (weeks 3, 5, 7) and e-cigarette distribution (weeks 3, 5), and for an additional visit 2 weeks after e-cigarette dispensation halted to learn if they continued to use e-cigarettes that they would buy on their own. No control group was used in this preliminary, pilot, open trial.

All participants were also referred to the state telephone QuitLine for supportive counseling at the quit-day visit (week 1). Research assistants faxed participant contact information to the QuitLine to facilitate cessation support (11/12 agreed to QuitLine referral).

Participants received e-cigarettes free of charge, and were reimbursed \$30 for the week 7 (end of treatment) and week 9 study visits. All procedures were approved by the Butler Hospital Institutional Review Board.

Measures

We used the Time Line Follow Back (TLFB)⁵⁰ to assess daily smoking and use of e-cigarettes throughout the study period. Our primary outcome was defined as carbon monoxide-confirmed abstinence (expired breath scores <8 parts per million) in persons who self-reported abstinence on the 7 days immediately prior to the week-7 assessment. Our secondary outcome was reduction in the average CPD of use in the 7 days prior to each follow-up assessment.

We assessed smoking history and cessation related variables using the Fagerström Test for Nicotine Dependence (FTND),⁵¹ a scale of nicotine withdrawal,⁵² self-efficacy for cessation,⁵³ and Thoughts About Abstinence.⁵⁴ We also asked participants about past experience using e-cigarettes, and their perceptions of their safety and efficacy.

We assessed side effects of e-cigarettes, use of concurrent smoking cessation treatment (eg, nicotine replacement or other pharmacotherapies), and nicotine withdrawal using a modified version of the Minnesota Behavior Rating Scale,⁵² which we have also used to monitor side effects during smoking cessation.¹⁶ Side effects were rated none, slight, mild, moderate and severe at every assessment visit. An adverse effect possibly related to e-cigarette use was defined as positive if the value at baseline was either none or slight AND the value at any of 3, 5, or 7 weeks was mild or more severe.

We assessed other drug use using the Addiction Severity Index substance use module.⁵⁵

Analytical Methods

A priori, we determined our sample size to be able to detect a 50% reduction in mean CPD between baseline and each follow-up with power more than 0.9. We calculated descriptive statistics to summarize the characteristics of the sample and rates of e-cigarette use during follow-up. We plotted mean CPD at each time point and 95% confidence interval (CI) estimates. We include a scatter plot of individual CPDs at each time point to give a picture of variability of the within-subject changes in tobacco CPD over time and the between-subject variation in individual growth trajectories. We estimated fixed-effects panel regression models⁵⁶ to estimate change over time. We used a likelihood-ratio chi-square difference test to compare a linear growth model to an unconstrained growth model in which the effect of time is represented by dummy variables contrasting each follow-up assessment to baseline. The fixed effects estimator uses only within-subject change across panels. Using this estimator, all time invariant between subject differences are controlled. Loss to follow-up was minimal, though given the small *n* we reestimated the model under the assumption that participants had returned to baseline levels of cigarette use (eg, missing values at follow-up were replaced by baseline CPD). Fixed-effects regression was also used to evaluate change in nicotine withdrawal symptoms over time and the association of nicotine withdrawal with CPD.

Results

Participants averaged 45.9 (± 11.5) years of age, six (50.0%) were male, and all were non-Latino white. Mean years of education were 13 (± 2.3), only two (16.7%) participants worked full-time and one (8.3%) worked part time. On average, participants reported smoking 17.8 (± 5.3 , Median = 18.2) CPD. All 12 persons who completed baselines were observed at the 3-week follow-up. One individual dropped out after week 3 and did not return; another completed all follow-up assessments except week 7. One person had a biochemically confirmed quit at week 7; this person smoked two cigarettes in the week prior to the week 9 assessment.

Figure 1 summarizes change in observed mean CPD over the course of observation. Participants reported marked reductions in mean CPD between the quit day (week 1) and the week 3 assessment. Mean CPD and individual trajectories tended to be relatively stable between weeks 3 through 7, and mean CPD increased slightly between weeks 7 and 9 when study e-cigarettes were no longer provided.

The unconstrained (dummy indicators for all follow-ups) growth model for mean CPD fit the data significantly better than a linear growth model ($LR^2 = 74.22$, $df = 3$, $P < .001$). The *F*-test for the model ($F_{4,40} = 43.53$, $P < .001$) indicates significant differences in mean CPD over time. Relative to baseline, statistically significant reductions in mean CPD were observed at all four follow-up assessments. Mean reductions in CPD were -12.4 (95% CI: -15.0, -9.9; $P < .001$), -14.8 (95% CI: -17.4, -12.2; $P < .001$), -13.9 (95% CI: -16.6, -11.2), and -10.8 (95% CI: -13.4, -8.2; $P < .01$) at the 3-, 5-, 7-, and 9-week assessments, respectively.

Mean e-cigarette adherence rates (expressed as % days of reported e-cigarette use) were 82.1 (± 27.3) at week 3, 92.2 (± 13.3) at week 5, 92.9 (± 22.6) at week 7. Adherence at week 9 was 49.3 (± 46.7). Variability in adherence was driven by a small number of participants; 8 (75%), 9 (81.8%), and 9 (90%) of the participants reported using e-cigarettes every day at weeks 3, 5, and 7, respectively.

We also used fixed-effects regression to evaluate change in smoking withdrawal over time. Withdrawal symptoms did not change significantly in either the linear ($F_{1,43} = 1.57$, $P = .216$) or the unconstrained ($F_{4,40} = 0.71$, $P = .590$) growth models. Using fixed-effects regression we also found no statistically significant association ($b = -0.01$; 95% CI: -0.40, 0.38; $P = .970$) between change in mean CPD and change in mean nicotine withdrawal during follow-up.

Figure 1. Change in mean cigarettes/day.

Regarding adverse effects, four of 12 participants reported “headaches,” three reported “coughing” “increased appetite,” “difficulty concentrating,” and “anxious or nervous,” two reported “change in how things taste,” “sore throat,” and “sleep problems,” and one reported “dry mouth,” “dizziness,” and “desire or craving to smoke.”

Discussion

In this first study using e-cigarettes to promote smoking cessation among MMT persons, we found that e-cigarettes were associated with dramatic reductions in self-reported cigarette usage. In this small sample, one in 12 persons quit during the e-cigarette treatment period, a rate comparable to that reported in medication trials in this population known to have extremely low quit rates. Participants reported high rates of e-cigarette use, low adverse effects, and no significant change in smoking withdrawal.

The continued smoking despite reported e-cigarette use demonstrates the difficulty of achieving abstinence in this population, even among those interested in joining a cessation trial. Many factors help to explain the poor abstinence outcomes in MMT persons. Overlapping neurobiological pathways in persons with dual opioid and nicotine dependence may affect withdrawal sensitivities and craving.^{57,58} Methadone itself may produce more intense tobacco craving and withdrawal symptoms and decreases in respiratory symptoms such as cough.^{59–61} Individual factors certainly play a role as well. MMT persons often have psychiatric comorbidities and high levels of stress, and use smoking as an anxiolytic or antidepressant.^{62,63} MMT smokers may have low self-efficacy, and with high community norms for smoking, may have more difficulty refusing nicotine.⁶⁴

We speculate that many study participants viewed smoking reduction, rather than cessation, as an acceptable endpoint. There were significant smoking reductions during the intervention, as seen in other studies.^{20,25,34–36,65} We designed our study such that participants were not “obliged” to be abstinent at any point during the study to continue to receive free e-cigarettes.

The high adherence rate at all time-points suggests many participants did not get discouraged despite an inability to quit, again suggesting that they might have had no true interest in quitting, were satisfied with their progress, and were saving money on tobacco costs. There were no study discontinuations attributed to e-cigarettes, highlighting that the reported side effects were not disruptive. Medication adherence is critical for positive smoking cessation outcomes in studies involving nondrug users.^{66–72} Low medication adherence has been reported in previous medication trials of MMT smokers,^{15,73–76} and the high adherence to e-cigarettes is promising if positive health effects are found over time.⁷⁷ Indeed we found that participants continued to use e-cigarettes when the study stopped providing them after week 7. While participants could have been using study “leftovers” between weeks 7 and 9, such continued use supports the suggestion that participants found e-cigarettes helpful.

Our study had several limitations. First this was a small, open trial, with no control group, testing a single ENDS, and did not include a behavioral intervention. Second, we did not measure use of support line or other counseling services, although acceptance of QuitLine referral was high. Third, we measured adherence and smoking reduction by self-report, although this is research standard. Fourth, we do not know if the e-cigarette brand tested generated adequate blood levels, although the absence of change in withdrawal symptoms over time suggests that e-cigarettes’ nicotine provision

adequately replaced tobacco’s. Finally, we should note that e-cigarettes are not regulated under FDA tobacco regulatory authority and are therefore not approved as smoking cessation treatment.

Cigarette smoking remains the leading preventable cause of disease, disability and death in the United States.⁷⁸ Smoking cessation using existing, approved treatments remains frustratingly difficult in certain populations, including those with opioid use disorder. Our data suggest that ENDS are acceptable among MMT smokers and are associated with dramatic reductions in cigarette use over 6 weeks among persons entering a cessation trial. Whether MMT smokers interested in changing the pattern of their tobacco use would continue to use e-cigarettes over long periods of time, and whether long-term ENDS use would lead to harm reduction remain to be investigated.

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Declaration of Interests

None declared.

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