

E-cigarettes to Promote Smoking Reduction Among Individuals With Schizophrenia

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ABSTRACT

This pilot feasibility project will assess reducing tobacco cigarette smoking among individuals with serious mental illness (SMI) by providing access to an electronic nicotine delivery system (e-cigarette). SMI populations of interest will consist of individuals with schizophrenia, schizoaffective disorder, bipolar disorder, and post-traumatic stress disorder (PTSD). Preliminary data will be used to inform and support a future NIH application to ultimately conduct a full-scale clinical trial to evaluate the efficacy of e-cigarettes as an intervention to treat tobacco addiction in adults with SMI.

Rates of tobacco smoking are 2-4 times higher among individuals with SMI compared to those without mental illness and the rate of smoking decreases has lagged behind that of the general population^{1,2}. Tobacco smokers with SMI are more dependent on nicotine and less likely to quit compared to those without mental illness³⁻⁵. Tobacco-smoking related death and morbidity are high among individuals with SMI, with half the deaths in this population due to tobacco related cancers, respiratory diseases, and cardiovascular conditions^{6,7}. Predominate theories point to a number of potential causal mechanisms including but not limited to: 1) alleviation from negative symptoms and cognitive deficits associated; 2) genetic, environmental, and neural deficits that increase vulnerability to tobacco dependence; and 3) increased susceptibility to withdrawal symptoms^{13,14}. Although tobacco smoking cessation is an ideal goal, many individuals with SMI are not motivated to quit tobacco smoking in the near future. As an alternative strategy, reducing tobacco smoking may result in more viable health gains. For example, smoking reduction has health benefits on its own and also increases the likelihood that smokers may initiate and succeed in quitting smoking in the future^{15,16}. However, reducing tobacco smoking also poses a number of challenges. Simply reducing the number of daily cigarettes smoked may have unintended consequences including compensatory increases in smoking and worsening of psychiatric symptoms. Additionally, two of the first-line medications for nicotine dependence (i.e., varenicline, bupropion) carry black-box warnings for increased risk of psychiatric symptoms and suicidal ideation in patients with a history of psychiatric illness.

E-cigarettes present a potential innovative solution to the challenges of reducing tobacco smoking among adults with SMI. E-cigarettes provide an experience close to tobacco smoking, which may increase their acceptability and use. The long-term health consequences of e-cigarette use are unknown. However, no negative health consequences of short-term use as in the current study have been reported, and most researchers agree that e-cigarettes are likely healthier than tobacco smoking¹⁷. Importantly, two small open-label studies observed decreased tobacco smoking among non-treatment seeking adults with schizophrenia and schizoaffective disorder following one month of access to e-cigarettes^{18,19}. Such results are promising as individuals with schizophrenia exhibit severe tobacco smoking, even when compared to others populations with SMI.

In the current pilot proposal, adults with SMI (N=10/group) interested in reducing their tobacco smoking will be randomized to receive either nicotine replacement therapy (NRT; patch 21 mg) as the standard of care or NRT plus e-cigarettes (36 mg/ml) for one month according to a double-blind, randomized controlled trial design. We will use a previously evaluated e-cigarette including nicotine liquid solutions that have been independently tested.

SPECIFIC AIMS AND HYPOTHESES

Specific Aim 1: Assess feasibility, acceptability, and safety of providing e-cigarettes to adults with SMI to reduce tobacco smoking.

Hypothesis 1.a: *We predict that a high proportion of participants will consent to participate ($\geq 80\%$) and complete ($\geq 70\%$) the study.*

Hypothesis 1.b: *We predict that end of study participant satisfaction ratings will indicate high acceptability of e-cigarettes and likelihood of future use.*

Hypothesis 1.c: *We predict e-cigarettes will be safe as measured by frequency of adverse events (AEs) and side-effects. In addition, we predict e-cigarettes will not be associated with increases in symptom specific measures.*

Specific Aim 2: To compare reductions in tobacco smoking between NRT vs NRT + e-cigarettes (36 mg/ml).

Hypothesis 2: *Significantly greater reductions in smoking (tobacco cigarettes/day, breath CO) will be observed in the NRT + e-cigarette vs. the NRT condition.*

BACKGROUND AND RATIONALE

SMI and Increased Risk of Tobacco Smoking. Rates of tobacco smoking are 2-4 times higher among individuals with SMI compared to those without mental illness and the rate of smoking decreases has lagged behind that of the general population ^{1,2}. Tobacco smokers with SMI are more dependent on nicotine and less likely to quit compared to those without mental illness ³⁻⁵. Tobacco-smoking related death and morbidity are high among individuals with SMI, with half the deaths in this population due to tobacco related cancers, respiratory diseases, and cardiovascular conditions ^{6,7}. Tobacco smoking prevalence among adults with schizophrenia and schizoaffective disorder is 80-90% and Predominate theories point to a number of potential causal mechanisms including but not limited to: 1) alleviation from negative symptoms and cognitive deficits associated; 2) genetic, environmental, and neural deficits that increase vulnerability to tobacco dependence; and 3) increased susceptibility to withdrawal symptoms ^{13,14}.

Benefits of Targeting Tobacco Smoking Reduction. Cessation of tobacco smoking is ideal, but the majority of tobacco smokers with schizophrenia and schizoaffective disorder report no desire to quit in the immediate future ^{28,29}. Therefore, a more viable strategy may be to target reducing tobacco smoking. Epidemiological studies have observed benefits of reduced tobacco smoking on ischemic heart disease, lung cancer, and chronic obstructive pulmonary disease ³⁰, particularly when tobacco smoking reductions occur among heavy smokers ¹⁵. However, results have been mixed with some studies reporting no benefits. Disparate results are likely influenced by compensatory tobacco smoking (longer, deeper, more frequent puffs) to maintain nicotine levels. Compensatory tobacco smoking can be mitigated by providing NRT. A number of randomized controlled trials providing NRT to promote smoking reduction have noted significant decreases in tobacco smoking accompanied by decreases in breath carbon monoxide (CO) and cotinine and other measures of cardiovascular risk ³¹⁻³⁴. Additionally, greater cessation was observed among those receiving NRT vs placebo, suggesting that tobacco smoking reduction with NRT could lead to cessation. This finding is supported in a meta-analysis of 10 randomized-controlled trials comparing pharmacological, behavioral, or combined interventions to promote tobacco smoking reduction among individuals not ready to quit ¹⁶. Results showed that both the pharmacological and combined interventions increased likelihood of long-term abstinence.

Therefore, tobacco smoking reduction can 1) improve tobacco smoking-related health risks, particularly when combined with access to alternative sources of nicotine; and 2) increase the future likelihood of tobacco smoking cessation among those with no desire to quit. However, areas of improvement still exist. For example, some authors in the above studies noted evidence of some compensatory tobacco smoking, albeit at a reduced level with NRT. Additionally, NRT compliance was identified as a target for improvement. E-cigarettes present an innovative solution that may address these two areas and provide an alternative source of nicotine.

E-Cigarettes as a Novel Source of Nicotine. Since their introduction just over a decade ago, awareness and use of e-cigarettes has increased dramatically. E-cigarettes consist of a battery, a heating element, and the ability to store a liquid typically nicotine and flavor. Compared to NRT, e-cigarettes provide an experience closer to tobacco smoking, which may increase their acceptability and use. For example, a secondary post-hoc analysis of 86 individuals identified with mental illness from the ASCEND trial showed greater ratings of acceptability (83% vs 37%), compliance (53% vs. 20%), and significantly greater reductions in tobacco smoking (9.9 ± 7.0 vs. 5.7 ± 6.3) ³⁵ among individuals in the e-cigarette vs. NRT condition. Two open-label trials have examined the effects of providing e-cigarettes to non-treatment seeking tobacco-smokers with schizophrenia and schizoaffective disorder ^{18,19}. Primary outcome measures differed for both studies, but significant reductions in tobacco smoking were observed after one month of e-cigarette access. Additionally, significant reductions in breath CO were observed, suggesting that compensatory tobacco smoking was mitigated. No SAEs were observed and the most common AEs were nausea, throat irritation, dizziness, head ache, and dry cough. Importantly, one study noted no change in positive and negative symptoms of schizophrenia and schizoaffective disorder following smoking reduction, which is in accord with the results from other studies using NRT among those with schizophrenia and schizoaffective disorder ^{36,37}.

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There are a number of potential concerns regarding the use of e-cigarettes as an intervention for tobacco smoking. First, the health consequences of long-term e-cigarette use are currently unknown. However, this is not an issue given the current study's duration. Overall, evidence from chemical, toxicological, and clinical studies designed to evaluate the safety of e-cigarettes suggests they may result in significant reduction in harm compared to continued use of tobacco cigarettes¹⁷. Second, previous studies have not controlled for variability in levels of nicotine delivered via e-cigarettes, an important concern affecting compensatory tobacco smoking. The current proposal addresses this limitation by utilizing e-cigarettes that have been previously studied and by testing the nicotine concentrations in an independent lab³⁸⁻⁴¹, resulting in nicotine delivery that is similar to traditional tobacco cigarettes.

METHODS

Research Team. Dr. Yoon will serve as the PI on the current proposal. Significant collaborators include Drs. Cho, Meyer, Reddy, Eissenberg, Lopez, and Weaver. They have also agreed to serve as collaborators on future grant proposals related to the current project. Dr. Cho is an experienced research psychiatrist and Director of the Integrated Clinical Neuroscience and Treatment Program (ICNTP) for serious mental illness. Dr. Cho will assist in referring participants from the ICNTP. Dr. Meyer is clinical psychologist and expert in the field of bipolar disorder. He is the director of the *Psychological Intervention and Research Laboratory for Mood Spectrum Disorders (PIRL-M)*. The clinic associated with PIRL-M will be helping with recruitment of patients experiencing bipolar disorder. Dry Reddy is a licensed clinical psychologist with expertise in the assessment and treatment of posttraumatic stress disorder. She is the Director of the Clinical and Translational Research Program on Traumatic Stress and the Stress, Trauma, and Recovery Services (STARS) Clinic. The STARS Clinic will recruit patients experiencing PTSD. Drs. Eissenberg and Lopez are experts in e-cigarette research. Many critical aspects of the current study have been informed by their research at the Virginia Commonwealth University Center for the Study of Tobacco Products (VCU CSTP). They have provided recommendations on an effective e-cigarette model and will also provide nicotine solution that has been independently tested. Additionally, they have provided copies of tobacco smoking and e-cigarette related questionnaires used in their studies, which will aid in making cross-study comparisons and also solidify future collaborative efforts. Dr. Weaver is the Medical Director at the Center for Neurobehavioral Research (CNRA) and has previously worked on a number of e-cigarette studies. He will provide medical guidance and ensure participant safety over the course of the study.

Study Design and Overview. We will utilize a double-blind, randomized controlled design to assess the feasibility and acceptability of using e-cigarettes to reduce tobacco smoking among individuals with SMI (schizophrenia and schizoaffective disorder, bipolar disorder, or PTSD). Participants will consist of tobacco smokers with SMI interested in reducing or quitting their tobacco smoking. Note that these two experimental conditions were chosen based on available funds and likelihood of obtaining preliminary data that would be useful in a future NIH grant application. We plan to assess other conditions in the future (e.g., placebo e-cigarette, etc.). Following a one-week baseline lead-in period, participants will be randomized to either the NRT or NRT + e-cigarette condition. Study visits will be scheduled for once a week (5 weeks total).

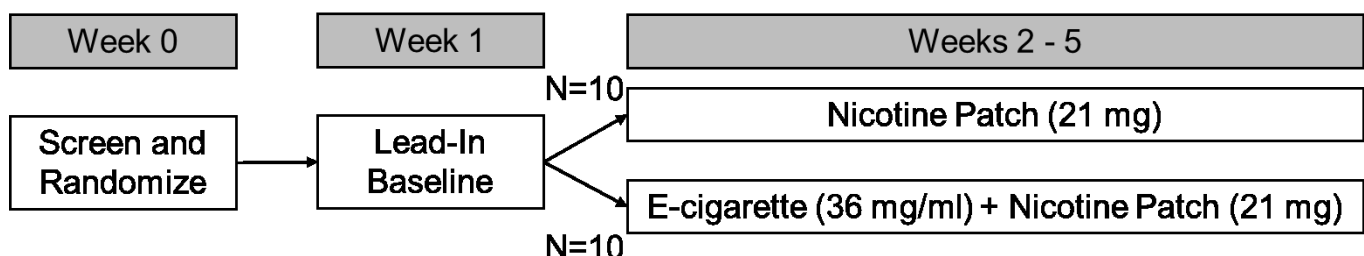


Figure 1. Overview of study design.

Study Procedures and Assessments

Participant Recruitment and Selection. Participants will be recruited from the ICNTP, PIRL-M, and STARS clinic. Eligible participants will meet the following inclusion criteria: 1) be diagnosed with schizophrenia or schizoaffective disorder, bipolar disorder, or PTSD and in stable medical condition (DSM-5); 2) report smoking ≥ 10 tobacco cigarettes/day and present a breath CO ≥ 10 ppm; 3) report wanting to quit or reduce their cigarette smoking; 4) be fluent in English; 5) be between 18 and 65 years of age; and 6) have a stable living situation. Participants will be ineligible if they meet the following exclusion criteria: 1) be currently pregnant or breastfeeding; 2) report wanting to quit smoking in the immediate future; 3) test positive for illicit drugs except THC; and 4) have any illness, medical condition, or use of medications, which in the opinion of the study physicians (Drs. Cho and Weaver) would preclude safe and/or successful completion of the study.

Following informed consent, participants will complete an initial general evaluation protocol (HSC-MS-05-0322; General evaluation of Eligibility for Substance Abuse/Dependence Research) to assess their psychiatric status, medical evaluation, and drug use history.

E-cigarette. The e-cigarette will consist of 1) a 3.3 V, 1000 mAh battery; and 2) a 1.5 Ohm, dual-coil cartomizer (SmokTech; Shenzhen, China). Study staff will load the cartomizer with 1 ml tobacco flavored 70% propylene glycol/30% vegetable glycerin liquid containing nicotine concentrations 36 mg/ml (AVAIL; Richmond, Virginia, USA). Nicotine concentration will be tested at an independent laboratory at VCU (± 2 mg/ml). Virtually every aspect of the e-cigarette (model, voltage, resistance, liquid, and nicotine concentration) has been chosen based on systematically conducted studies by Dr. Eissenberg and his colleagues³⁸⁻⁴¹. With these parameters, e-cigarettes with 36 mg/ml nicotine liquid produce blood plasma nicotine levels similar to that of tobacco cigarettes after 10 puffs. Participants will be provided verbal and written instructions on how to use and maintain the e-cigarettes at Week 1 visit. Risking of spilling nicotine liquid is minimal as the cartomizer contains cotton batting for liquid absorption. However, to mitigate any potential risks, participants will be provided gloves to be used when changing cartomizers. Additionally, they will receive pill bottles to hold spare cartomizers, instructed not to try and open the cartomizer, and told to keep them away from children.

Nicotine Replacement Therapy. Participants will receive nicotine patch (21 mg) starting study Week 1. Participants will be instructed to apply a new patch each morning on a clean, dry, non-hairy area of skin.

E-Cigarette and Tobacco Smoking Related Assessments. Tobacco smoking will be assessed using a combination of breath CO, urinary cotinine, and self-report via time-line follow-back. Standard questionnaires will be used to assess a number of tobacco-smoking related measures. The Fagerstrom Test for Nicotine Dependence (FTND) will be used to assess tobacco cigarette dependence⁴². The Questionnaire of Smoking Urges (QSU) will be used to assess craving for tobacco cigarettes⁴³. The Minnesota Nicotine Withdrawal Questionnaire (MNWQ) will be used to assess withdrawal symptoms from tobacco cigarettes⁴⁴. The Stages of Change Questionnaire will be administered to assess desire to quit from tobacco cigarette smoking⁴⁵. The Clinical COPD Questionnaire (CCQ) will be used to assess changes in COPD-related symptoms⁴⁶. Additional smoking-related assessment will include the Confidence to Quit (CQ) and Hooked on Nicotine Checklist (HONC). E-cigarette related questionnaires developed and provided by Dr. Eissenberg will be used to evaluate e-cigarette dependence, patterns of use, evaluation of using e-cigarettes, and side-effects. These questionnaires will include Confidence to Quit, E-Cigarette Dependence Scale, E-Cigarette Patterns of Use, E-Cig Evaluation, E-Cig Side Effects, and Hooked on Nicotine Checklist.

Assessing Changes in Symptoms Relevant to SMISchizophrenia. The Brief Psychiatric Rating Scale (BPRS)⁴⁷ will assess symptom severity among individuals with SMI. Potential changes in key cognitive domains associated with will be assessed with the MATRICS Consensus Cognitive Battery (MCCB). The Columbia Suicide Severity Rating Scale (CSSRS) will assess suicide ideation. Changes in mood symptomatology including also anhedonia and mania will be assessed with the Beck Depression Inventory (BDI), Snaith-Hamilton Pleasure Scale (SHAPS), and the Altman Self-Rating Mania Scale (ASRM) respectively. Changes in PTSD symptoms will be assessed using the PTSD Checklist for DSM 5.

Safety and Health-Related Measures. Adverse events (AEs) and severe AEs, along with concomitant medications, will be assessed at weekly study visits. Heart Rate (HR) and blood pressure (BP) will also be assessed using standard hospital-grade equipment.

Table 1. Outline of Study Procedures and Assessments.

Study Visits	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5
Procedure and Assessments						
Baseline Screening	X					
Receive E-Cigarettes (36 mg/ml) and NRT Patch (21 mg)			X	X	X	X
Smoking Related Assessments						
Breath CO, QSU, MNWQ, , TLFB, CCQ, CQ, HONC	X	X	X	X	X	X
Urinary Cotinine	X					X
FTND, Stages of Change	X					X
E-Cigarette Questionnaires			X	X	X	X
AEs, Concomitant Meds, HR, BP	X	X	X	X	X	X
BPRS, CSSRS, BDI, SHAPS, ASRM, PTSD	X	X	X	X	X	X
MCCB	X					X

DATA ANALYSIS PLAN

Preliminary data analyses will inspect baseline, group differences as well as correlations between baseline variables and specified outcomes. Baseline or demographic variables demonstrating a correlation with both predictors and outcomes, meet criteria for being potential confounders,^{i,ii} and will result in two sets of analyses: one in which the relevant variable is included as a covariate and one in which it is not. This will determine the degree to which any group differences might confound conclusions regarding treatment. Statistical analyses will use R v. 3.3.0ⁱⁱⁱ and SAS v.9.3.^{iv}

Analyses will primarily use generalized linear modeling. Continuous, count, dichotomous and time-to-event data will utilize linear, Poisson, logistic, and proportional hazards regression respectively (Proc GENMOD and PROC PHREG; SAS v. 9.3, function glm(); R v. 3.3.0). Longitudinal analyses will employ generalized linear mixed models (Proc MIXED, Proc GLIMMIX and Proc MCMC; SAS 9.3). Evaluation of distributional assumptions will use residual plots and, where possible, formal statistical tests. Depending upon statistical technique, transformations, robust estimators, stratification and/or scaling coefficients will address violations of assumptions. Analyses of cross-sectional data with missing values will utilize multiple imputation (Proc MI; SAS v.9.3)^v. Multiple imputation and maximum likelihood are robust to data missing at random. Sensitivity analyses will permit evaluation of the robustness of findings to missing data assumptions.

Specific Aim 1: Assess feasibility, acceptability, and safety of providing e-cigarettes to adults with SMI to reduce tobacco smoking.

Hypothesis 1.a: We predict that a high proportion of participants will consent to participant (80%) and complete the study (70%) completion rate. Descriptive statistics will evaluate consent and completion rates.

Hypothesis 1.b: We predict that end of study participant satisfaction ratings will indicate high acceptability of e-cigarettes and nicotine patch and likelihood of future use. Generalized linear models will evaluate the relationships between participant satisfaction, acceptability of e-cigarettes and nicotine patch, and likelihood of future use.

Hypothesis 1.c: We predict e-cigarettes will be safe as measured by frequency of adverse events (AEs) and side-effects, and not associated with increases in negative symptoms (BPRS) or decreases in cognitive performance (MATRICS). Generalized linear modeling will evaluate relationships between adverse events/side-effects, negative symptoms, and cognitive performance.

Specific Aim 2: To compare reductions in tobacco smoking between NRT vs NRT + e-cigarettes (36 mg/ml).

Hypothesis 2: *Significantly greater reductions in smoking (tobacco cigarettes/day, breath CO) will be observed in the NRT + e-cigarette vs. the NRT condition. Generalized linear modeling will evaluate group differences in smoking reduction between NRT and NRT + e-cigarettes over time as measured by breath CO (using a Gaussian distribution) and tobacco-cigarettes/day (using a Poisson distribution).*

Power/Sample Size Considerations. For the current proposal, power will focus on Aim 2. Effect size is derived using G*Power 3.1.9.2. Assuming $\alpha = 0.05$ and a correlation among repeated measures of 0.5, a sample size of $n = 20$ ($n = 10$ NRT and 10 NRT + e-cigarette) provides 80% power to detect a Cohen's $f = 0.51$ for group differences between NRT and NRT + e-cigarette. The Frequentist findings will be augmented with a Bayesian approach to characterize the probability that effect sizes of varying magnitude exist.

JUSTIFICATION

Results from the current pilot study will be used as preliminary data in support of a future NIH R21 grant submission. The immediate goal of that R21 will be to assess a longer intervention period (3 months), which is the standard in clinical trials, as well as additional experimental conditions (e.g., 0 mg/ml e-cigarette condition) to enhance the experimental rigor of the study. Based on the current results, we will also assess the need for additional intervention components (e.g., contingency management, motivational interviewing, etc.). Finally, we will also assess other indices of reduced tobacco smoking toxicity such as 4-methylnitrosamino-1-3-pyridyl-1-butanol (NNAL) and lung function using spirometry. The R21 will in turn lead to a future R01 application. Additionally, completion of the current proposal will also be beneficial in establishing a history of cooperation with Drs. Cho, Eissenberg, Lopez, and Weaver that will also support the competitiveness of future NIH grant submissions on which they serve as collaborators.

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