Predicting Non-Adherence With Very Low Nicotine Content Cigarettes Among Adults With Serious Mental Illness Who Smoke

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Abstract

Introduction: Reducing the nicotine content of cigarettes is a promising policy intervention to decrease cigarette dependence among people who smoke. Randomized trials support the potential efficacy of a reduced nicotine product standard for cigarettes. However, interpretation of such trials is challenged by incomplete adherence to the randomized treatment assignment, as some participants may continue to use commercial cigarettes not provided by the trial. The current study examined prevalence and predictors of non-adherence among trial participants with serious mental illness (SMI).

Aims and Methods: Adults with SMI who smoke daily and were not trying to quit (*N* = 58) were randomized to receive very low nicotine content (VLNC) or normal nicotine content cigarettes over 6 weeks. We investigated predictors of biologically assessed non-adherence in participants assigned to VLNC cigarettes (*n* = 30). Predictors included subjective responses to VLNC cigarettes, baseline nicotine dependence and dependence motives, and psychiatric symptom severity. We fit a series of linear models regressing non-adherence metrics onto covariates (gender; menthol preference) and focal predictors.

Results: Nearly all participants (96%) were estimated to be less than completely adherent to VLNC cigarettes. Lower enjoyment ratings of respiratory tract sensations of VLNC cigarettes predicted a greater degree of non-adherence (*b* = −.40, SE = .14, 95% CI: −0.71, −0.10).

Conclusions: Less positive subjective response to smoking VLNC cigarettes was the only significant predictor of incomplete adherence among individuals with SMI, consistent with prior research in a general population sample. This suggests the potential for shared strategies to help different smoking populations adjust to a reduced nicotine product standard.

Implications: Results offer preliminary insight into potential barriers to adherence in SMI populations. Adherence might be enhanced by supplementing VLNC cigarettes with alternative sources of non-combusted nicotine, paired with educational campaigns to encourage quitting or switching to less harmful products. Future studies should replicate these analyses in a larger sample of individuals with SMI who smoke.

Introduction

The US Food and Drug Administration is considering a mandatory reduction in the nicotine level of all cigarettes sold nationally, as this may render cigarettes less addictive and help people achieve cessation or reduction.[1] Several randomized clinical trials have shown that when participants who are not trying to quit are assigned to very low nicotine content (VLNC) cigarettes, they reduce the number of cigarettes smoked per day (CPD), and exhibit reductions in nicotine dependence and biomarkers of nicotine exposure.[2] Incomplete adherence is a common limitation across studies investigating VLNC cigarettes, attributable in part to the availability of conventional cigarettes.[3,4] However, because the extent of conventional cigarette use tends to be low in these studies, reductions in nicotine dependence and nicotine and toxicant exposure are observed notwithstanding this incomplete adherence.[2]

Individuals with serious mental illness (SMI) are considerably more likely to smoke than people in the general population,[5]

and tobacco-related diseases cause approximately half of all deaths among people with SMI.[6] Common motives for smoking among people with SMI include reduction of craving, negative affect and negative psychiatric symptoms, and improvement of cognitive functioning; these factors may also contribute to relapse during smoking abstinence and difficulty with achieving cessation.[7] Because this population stands to significantly benefit from a reduced nicotine product standard, it is crucial to evaluate the effects of such a policy among individuals with SMI.

A 6-week randomized controlled trial (RCT) examining the effects of VLNC cigarettes in adults with SMI found that participants assigned to VLNC cigarettes smoked fewer CPD, had lower breath carbon monoxide (CO) levels, and lower craving scores compared to those in the normal nicotine content (NNC) cigarette condition.[8] These results are promising in their similarity to findings in the general smoking population. However, as has been found in prior studies, there was likely a non-trivial degree of incomplete adherence to VLNC

cigarettes in this trial, as suggested by a lack of difference in total nicotine exposure between the VLNC and NNC groups.

Understanding predictors of incomplete adherence with VLNC cigarettes among people with SMI may help regulators and clinicians identify strategies for helping these individuals achieve maximal benefit from a nicotine reduction policy. Predictors have been previously examined in a general adult population.[4] To extend these findings, the current hypothesis-generating study estimated levels of biologically assessed non-adherence in a sample of smokers with SMI, and evaluated predictors of incomplete adherence that may be unique to this population.

Methods

Participants and Parent Study

Data for this study were drawn from the RCT referenced above[8] conducted in Providence, Rhode Island, USA from November 2014 to November 2017. Participants were adults aged 18–70 who met diagnostic criteria for schizophrenia, schizoaffective disorder, or bipolar disorder based on the Structured Clinical Interview for DSM-IV (SCID), were clinically and medically stable, smoked at least 10 cigarettes per day (CPD), and had breath CO levels at least 8 ppm or urinary cotinine levels at least 100 ng/ml. Intention to quit smoking within 30 days and regular use of tobacco products other than machine-made cigarettes (≥9 of the past 30 days) were exclusionary. Participants were randomized to receive VLNC (n = 30; 0.4 mg nicotine/g tobacco) or NNC (n = 28; 15.8 mg/g) cigarettes more than 6 weeks. Participants received brief adherence counseling at weekly sessions, were asked to smoke only the study cigarettes, and were encouraged to honestly report their use of other nicotine and tobacco products.

The study timeline and schedule of assessments are presented in Figure 1. The total number of study and non-study cigarettes participants smoked per day (CPD) was measured through a daily interactive voice response (IVR) phone survey. Nicotine exposure was measured at baseline (when participants continued to smoke their usual brand [UB] cigarettes *ad libitum*) and week 6 (W6) using first-void urine samples for assessment of total nicotine equivalents (TNE),

which is the sum of nicotine, *trans*-3-hydroxycotinine, and their glucuronides.[9]

Calculation of the Outcome Variable

Biologically assessed levels of non-adherence were calculated using the ratio of TNE divided by CPD compared between W6 and baseline (TNE_W6/CPD_W6)/(TNE_BL/CPD_BL).[3,4] Higher ratio values indicated lower adherence, while lower values indicated higher adherence (ie, consistent with more complete switching from UB to VLNC cigarettes). Participants with TNE/CPD ratios greater than 0.1 were classified as non-adherent, while those with ratios less than 0.1 were adherent. This ratio of 0.1 represents a 90% reduction in TNE per cigarette smoked relative to baseline.[3,4]

Predictors of Non-Adherence

Subjective Responses to VLNC Cigarettes.

Subjective responses to VLNC cigarettes at W1 (ie, end of the first week after switching to VLNC cigarettes) were measured using the Cigarette Evaluation Scale (CES)[10] with 5 subscales: satisfaction (satisfying, taste good, enjoy smoking), psychological reward (calm down, more awake, less irritable, help concentrate, reduce hunger), enjoyment of respiratory tract sensations (single item), craving reduction (single item), and aversion (dizziness, nausea). These were previously tested as predictors of non-adherence in a general population of individuals who smoke.[4] Craving for UB and for VLNC cigarettes at W1 was measured using the Questionnaire for Smoking Urges (QSU).[11] Withdrawal symptom severity at W1 was measured with the Minnesota Nicotine Withdrawal Scale (MNWS).[12] We hypothesized that greater craving for UB cigarettes and more severe withdrawal symptoms would predict non-adherence based on prior findings identifying craving and withdrawal as barriers to smoking abstinence in individuals with SMI.[7]

Dependence and Motives for Dependence.

Cigarette dependence at baseline was measured using the Fagerström Test for Cigarette Dependence (FTCD).[13] Dependence motives at baseline were measured using the Brief Wisconsin Inventory of Smoking Dependence Motives
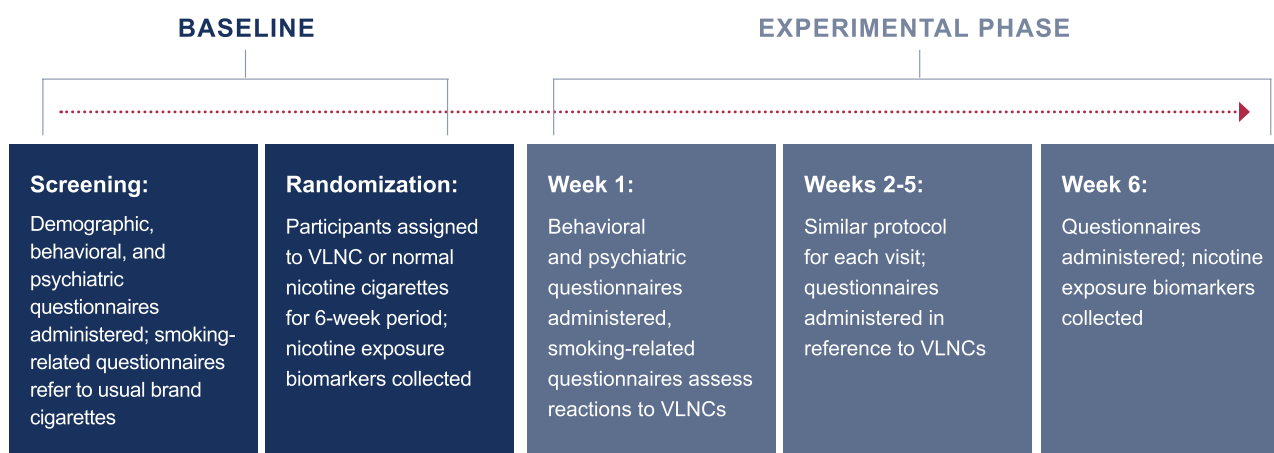
Parent Trial Design and Timeline

BASELINE   **EXPERIMENTAL PHASE**

Screening:	**Randomization:**	**Week 1:**	**Weeks 2-5:**	**Week 6:**
Demographic, behavioral, and psychiatric questionnaires administered; smoking-related questionnaires refer to usual brand cigarettes	Participants assigned to VLNC or normal nicotine cigarettes for 6-week period; nicotine exposure biomarkers collected	Behavioral and psychiatric questionnaires administered, smoking-related questionnaires assess reactions to VLNCs	Similar protocol for each visit; questionnaires administered in reference to VLNCs	Questionnaires administered; nicotine exposure biomarkers collected

Figure 1 Parent trial design and timeline.

(WISDM).[14] The WISDM subscales analyzed as predictors were affective enhancement (smoking to enhance positive feelings or experience), cognitive enhancement (smoking to improve cognitive functioning), and social/environmental influences (potency of social stimuli in increasing smoking motivation), since these factors are common motives for smoking among individuals with SMI.[7]

Psychiatric Symptoms.
Psychiatric symptoms at baseline were measured using the Positive and Negative Syndrome Scale (PANSS)[15] positive, negative, and general subscales. Higher positive scores indicate an increased presence of psychiatric symptoms such as hallucinations, delusions, and confused thoughts, while higher negative scores indicate deficits in normal mental function. Psychiatric symptom severity at W1 was measured using the Brief Psychiatric Rating Scale (BPRS).[16] Depressive symptom severity at W1 was measured using the Calgary Depression Scale for Schizophrenia (CDSS).[17]

Statistical Analyses
Hypotheses were developed a priori and pre-registered using AsPredicted (https://aspredicted.org/s7ir9.pdf, #46192, August 8, 2020). Correlation analysis was used to examine the relationship among the 17 focal predictors (Supplementary Table S1). A series of 17 separate linear models were used to regress the biological non-adherence measure onto baseline characteristic covariates (gender and menthol preference) and each of the focal predictors listed above.

Our initial data analytic plan proposed the investigation of both biologically assessed and self-reported measures of non-adherence, using parallel sets of analyses to compare findings across each measurement approach. However, we determined that biologically assessed and self-reported measures of non-adherence were uncorrelated ($r = .06$, $p = .76$). Because of the lack of correlation between these outcomes and the higher accuracy of biologically assessed measures compared with self-report,[18] we have prioritized the biologically assessed non-adherence findings. Self-reported findings are included in Supplementary Table S2.

Results

Participant Characteristics
Participants were 43.4 ± 9.6 ($M \pm SD$) years old, 60% male, 50% white, and 20% African American; 87% were non-Hispanic. At baseline, participants smoked 20.1 ± 8.8 CPD and had FTCD scores of 6.8 ± 1.5 indicating high levels of nicotine dependence. Most (77%) preferred menthol cigarettes over non-menthol. Psychiatric diagnoses included schizophrenia (43%), schizoaffective disorder (32%), and bipolar disorder (61%). Because of missing data at W1 and W6, analyses for biologically assessed non-adherence included 24 participants for each model, while analyses of self-reported non-adherence included 26 participants.

Estimated Prevalence of Non-Adherence
Nearly all participants were classified as less than completely adherent, with the biologically assessed measure estimating a higher rate of non-adherence (96% of participants) than the self-report measure (85% of participants, who reported smoking one or more non-study cigarettes at W6).

Biologically Assessed Non-Adherence
The results of the linear regression analyses examining predictors of non-adherence are shown in Table 1. The covariate gender (male) was significantly associated with higher levels of biologically assessed non-adherence ($b = -.96$, SE = .42, 95% CI: –1.84, –0.09). Lower CES enjoyment of respiratory tract sensations subscale scores predicted higher levels of biologically assessed non-adherence with VLNC cigarettes ($b = -.40$, SE = .14, 95% CI: –0.71, –0.10). All other predictors were nonsignificant.

Discussion

In trials evaluating the effects of VLNC cigarettes, incomplete adherence is a common observation. Our study identified lower enjoyment ratings of respiratory tract sensations as the only significant predictor of biologically assessed non-adherence with VLNC cigarettes among people with SMI. Although predictors of non-adherence have previously been examined among adults who smoke,[4] our study is the first to examine incomplete adherence among people with SMI, a population that could benefit tremendously from a nicotine product standard, due to their increased risk of heavy smoking and reduced cessation.

The biologically assessed and self-reported non-adherence outcome variables had distinct predictors and were uncorrelated. This was likely because participants overestimated their adherence via self-report. Given this discrepancy, we prioritized predictors of biologically assessed non-adherence in the interpretation of study findings.[3,4,18]

Our finding that lower enjoyment ratings of respiratory tract sensations predicted lower adherence to VLNC cigarettes is similar to prior research in a general smoking population, which identified lower satisfaction with VLNC cigarettes as a significant predictor of non-adherence.[4] This parallel finding (ie, less positive subjective response to smoking VLNC cigarettes driving non-adherence) suggests the potential for shared strategies to improve adherence across different populations. Although one solution might be to change the physical attributes of VLNC cigarettes to improve product appeal, this would increase the likelihood that people will continue to smoke these cigarettes for an extended period. Instead, lack of satisfaction with VLNC cigarettes should be addressed using other strategies, which might include helping people switch to less harmful non-combusted nicotine products and eventually quit smoking completely. One potential approach is to ensure that alternative nicotine delivery systems (ANDS) such as nicotine replacement therapy products, snus, and e-cigarettes, are readily available as a supplement or alternative to VLNC cigarettes if a reduced nicotine policy were implemented.[19] To bolster the success of this strategy, public health education campaigns would be needed to inform people of the harms associated with continued use of cigarettes and the relative health benefit of switching to ANDS or quitting smoking entirely.

The lack of reduction in nicotine level, in conjunction with the finding from the trial that breath CO levels were significantly reduced in the VLNC condition,[8] suggest that participants likely supplemented VLNC cigarettes with alternative non-combusted sources of nicotine during the trial. This suggests that people with SMI, in particular, may benefit from alternative sources of nicotine during a transition period if a reduced nicotine standard for cigarettes were implemented. One study examining the acute effects of VLNC cigarettes paired

Table 1. Prediction of Biologically Assessed Non-Adherence

	Estimate (b)	SE	p	95% CI	n[a]	α[b]
Covariates						
Intercept	.28	.32	.39	(−0.38, 0.95)	30	—
Gender (Ref: male)	−.96	.42	.03*	(−1.82, −0.09)	30	N/A
Menthol (Ref: non-menthol)	.08	.48	.88	(−0.93, 1.08)	30	N/A
Predictor variables—*Subjective responses to VLNC cigarettes*						
QSU: VLNC Cigarettes	.01	.01	.52	(−0.02, 0.04)	22	.97
QSU: Usual Brand	.02	.01	.14	(−0.01, 0.05)	22	.94
CES Psychological Reward	−.02	.03	.66	(−0.08, 0.06)	22	.83
CES Satisfaction	−.09	.06	.14	(−0.21, 0.03)	22	.86
CES enjoyment of respiratory tract sensations	**−.40**	**.14**	**.01***	**(−0.71, −0.10)**	**22**	N/A
CES Craving Reduction	−.17	.12	.17	(−0.41, 0.08)	22	N/A
CES Aversion	.05	.14	.73	(−0.25, 0.35)	22	.15
MNWS Withdrawal	.004	.05	.93	(−0.09, 0.10)	22	.84
Predictor variables—*Dependence and motives for dependence*						
FTCD Dependence	.08	.18	.64	(−0.29, 0.46)	24	.14
WISDM Affective Enhancement	.01	.17	.57	(−0.25, 0.44)	24	.62
WISDM Cognitive Enhancement	.20	.15	.19	(−0.11, 0.51)	24	.75
WISDM Social & Environmental	−.09	.11	.45	(−0.32, 0.14)	24	.88
Predictor variables—*Psychiatric symptoms*						
CDSS	−.02	.09	.86	(−0.19, 0.16)	22	.74
BPRS	−.07	.05	.17	(−0.17, 0.03)	22	.69
PANSS Negative	−.09	.05	.09	(−0.19, 0.02)	24	.77
PANSS Positive	−.06	.08	.44	(−0.22, 0.10)	24	.52
PANSS General	−.07	.05	.21	(−0.18, 0.04)	24	.55

QSU, Questionnaire for Smoking Urges; CES, Cigarette Evaluation Scale; MNWS, Minnesota Nicotine Withdrawal Scale; FTCD, Fagerström Test for Cigarette Dependence; WISDM, Wisconsin Inventory of Smoking Dependence Motives (Brief); CDSS, Calgary Depression Scale for Schizophrenia; BPRS, Brief Psychiatric Rating Scale; PANSS, Positive and Negative Syndrome Scale.
Bold values indicate significant result.
[a]Reduced n's are due to missing participant data at study weeks 1 and 6 in the parent trial.
[b]Cronbach's alpha was computed for each questionnaire measurement scale composed of two or more items; N/A indicates not applicable for single-item scale.

with nicotine patches in smokers with schizophrenia and controls found that this combination preserved cognitive functioning, while a decrease in cognitive performance was observed with placebo patches.[20] Future studies should investigate the long-term effects of VLNC cigarettes combined with nicotine replacement in smokers with SMI in order to determine if this combination improves adherence and outcomes. Such studies are currently underway in other populations.

The results of this study must be considered in light of its limitations. The randomized trial was not powered for this analysis; missing data further reduced analytic power.[8] Additionally, participants were recruited using community-based advertisements, which could have resulted in selection bias. However, as the first study to examine adherence to VLNC cigarettes in an SMI population, these results provide a useful initial contribution to the field. Future studies should replicate these findings in a larger sample of smokers with mental illness. This research may also inform interventions that could increase adherence to VLNC cigarettes in order to address cigarette addiction and ultimately promote smoking reduction and cessation.

Supplementary Material

A Contributorship Form detailing each author's specific involvement with this content, as well as any supplementary data, are available online at https://academic.oup.com/ntr.

Declaration of Interests

The authors have no conflicts of interest to disclose.

Data Availability

The data and code underlying this article will be shared on reasonable request to the corresponding author.

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