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Smoking Topography Characteristics of Very Low Nicotine Content Cigarettes, With and Without Nicotine Replacement, in Smokers With Schizophrenia and Controls

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Abstract

Introduction: Reducing the nicotine content of cigarettes to a minimally addictive level has been proposed as a regulatory strategy for reducing tobacco dependence. However, smokers with schizophrenia (SS) may be prone to changing their smoking topography in efforts to compensate for the reduction in nicotine content. The aims of this study were to compare smoking topography characteristics of usual-brand and very low nicotine content (VLNC) cigarettes in SS and control smokers without psychiatric illness (CS), and to determine whether nicotine replacement reversed any changes in topography produced by VLNC cigarettes.

Methods: Using a within-subjects, counter-balanced design, SS (n = 27) and CS (n = 23) smoked usual brand cigarettes, VLNC cigarettes while wearing placebo patches (VLNC + PLA), or VLNC cigarettes while wearing transdermal nicotine patches totaling 42 mg (VLNC + NIC) during 5-hour *ad libitum* smoking sessions. Cigarettes were smoked through topography measurement devices.

Results: Across conditions, SS smoked more puffs per session and per cigarette, had higher cigarette volumes, and had shorter inter-puff intervals than CS (Ps < .01). During VLNC cigarette sessions, puff duration increased and time between puffs decreased, but participants smoked fewer puffs, resulting in a net decrease in cigarette and total session volume (Ps < .001). There were no significant interactions between group and condition.

Conclusions: These findings indicate that acute use of VLNC cigarettes does not increase intensity of smoking in SS, and support the feasibility of a nicotine reduction policy.

Implications: Reducing the nicotine in cigarettes to a minimally addictive level has been proposed as a means of reducing tobacco dependence. However, smokers, particularly those with schizophrenia (SS) may alter their puffing in an attempt to extract more nicotine from VLNC cigarettes. This study compared smoking topography of usual brand versus VLNC cigarettes, combined with placebo or transdermal nicotine patches, in SS and controls. Although some changes in topography were indicative of compensatory smoking, total puffs and total cigarette volume were reduced with VLNC cigarettes, indicating that acute VLNC cigarette use does not increase smoking in SS.

Introduction

People with schizophrenia are approximately three times more likely to be current cigarette smokers, and have a significantly higher risk of death from cardiovascular and respiratory diseases than the general population.[1–3] Smoking cessation in people with schizophrenia is impeded by numerous factors, including inadequate clinical

attention,[4] poor task persistence,[5] and high levels of craving and withdrawal during abstinence.[6] Pharmacological and behavioral smoking treatments improve cessation rates among people with schizophrenia,[7–9] but cessation rates are very low among those who do not have access to these treatments.[10,11]

A regulated reduction in the nicotine content of cigarettes to a minimally addictive level has been proposed as a means of reducing tobacco dependence,[12,13] and has become possible due to the 2009 Family Smoking Prevention and Tobacco Control Act[14] and the WHO Framework Convention on Tobacco Control.[15] In determining whether to proceed with a nicotine reduction policy, the US Food and Drug Administration (FDA) must weigh the scientific evidence concerning the potential benefits and risks of cigarette nicotine reduction on the health of the US population.[16] One concern is that smokers might try to extract more nicotine per cigarette by altering their smoking behavior, which could expose them to higher levels of tobacco toxins (ie, compensatory smoking). Unlike "light" cigarettes, which yielded low levels of nicotine during machine emissions testing due to product design modifications that were easily overcome by changing smoking behavior,[17] very low nicotine content (VLNC) cigarettes are made with tobacco that is reduced in nicotine content.[18] For VLNC cigarettes with a nicotine content of less than 1 mg, it would be difficult or impossible for smokers to increase their smoking enough to attain nicotine levels comparable to those provided by conventional cigarettes (≥10 mg nicotine).[19] Nevertheless, smokers may, at least transiently, alter their smoking topography characteristics in an attempt to extract higher levels of nicotine from VLNC cigarettes. Smokers with schizophrenia (SS), who smoke more intensely than other smokers according to several topography indices,[20,21] may be particularly vulnerable to compensation.

To date, the evidence that switching to VLNC cigarettes affects smoking topography is mixed. Studies that have found evidence of compensatory smoking include one that compared topography indices collected while participants smoked a single Quest cigarette (a formerly-commercially available cigarette with varying levels of nicotine content, produced by Vector Tobacco) of each type, and found that the cigarette volume (ie, the sum of the volumes for all puffs in each cigarette) smoked of Quest 3 cigarettes (0.6 mg nicotine content, ≤0.05 mg yield) was significantly higher than for Quest 2 (5.1 mg nicotine content, 0.3 mg yield) and marginally higher than for Quest 1 (8.9 mg nicotine content, 0.6 mg nicotine yield) cigarettes.[22] A second study found higher cigarette volumes, higher puff durations, and shorter inter-puff intervals with Quest 3 than Quest 1 cigarettes, although those differences weakened across cigarette trials.[23] Other studies have found no evidence of compensatory smoking of Quest 3 cigarettes relative to Quest 1[24,25]or usual-brand cigarettes.[26] The largest study of VLNC cigarettes to date found that those assigned to Spectrum cigarettes (research cigarettes with varying levels of nicotine content produced for NIDA by 22nd Century Group, Inc) with 0.4 mg/g nicotine content (0.03 mg nicotine yield) had a significantly lower cigarette volumes at week 6 than those assigned to 15.8 mg/g nicotine content (0.8 mg nicotine yield) cigarettes.[27] Notably, all of these studies excluded people with psychosis; to our knowledge, no studies have examined effects of VLNC cigarettes on smoking topography in SS.

Thus, the aims of this study were to compare smoking topography characteristics of usual-brand and VLNC cigarettes in SS and control smokers without psychiatric illness (CS), and to determine whether transdermal nicotine replacement reversed any changes in smoking topography produced by VLNC cigarettes. We hypothesized that SS would take more puffs, have larger cigarette volumes and have shorter inter-puff intervals across cigarette conditions than CS, as has been observed previously,[20,21] that SS would alter their smoking behavior when smoking VLNC cigarettes to a greater degree than CS, and that transdermal nicotine replacement would reverse topography changes seen with VLNC cigarettes in both SS and CS.

Methods

Participants

SS and CS were recruited from the community for a study of the effects of VLNC cigarettes, with and without nicotine replacement, on usual-brand smoking and related subjective and behavioral measures.[28] Participants were required to either have a diagnosis of schizophrenia or schizoaffective disorder (SS) or no Axis I disorder (CS), based on the Structured Clinical Interview for *DSM-IV* (SCID),[29] to be at least 18 years old, to have smoked 20–50 cigarettes per day for at least the past year, and to have a score of at least 6 on the Fagerström Test for Nicotine Dependence (FTND),[30] indicating a high level of dependence. Exclusionary criteria included medical conditions contraindicating use of transdermal nicotine, severe disorientation or uncooperativeness, positive urine drug or pregnancy tests at the study screening or positive breath alcohol level at any session. Procedures were approved by the Brown University Institutional Review Board.

Procedures

This study used a within-subjects design. Sessions took place in 10′ × 8′ observation rooms that were equipped with desks and comfortable chairs and ventilated for smoke exhaustion. Participants were under continuous observation through one-way mirrors. When not smoking, participants were allowed to read magazines and watch videos. In the first session, demographic and smoking history measures were collected and current psychiatric symptom levels in SS were assessed using the Positive and Negative Syndrome Scale (PANSS).[31] In Session 2, participants smoked their usual-brand cigarettes *ad libitum* for 5 hours through Clinical Research Support System desktop topography measurement instruments (Borgwaldt KC, Richmond, VA), so that the rate and timing of their natural smoking behavior could be determined. In Sessions 3–7, participants underwent the following conditions during 5-hour periods, with condition order counterbalanced across participants: VLNC cigarettes + nicotine patches (NIC), VLNC cigarettes + placebo patches (PLA), no smoking + NIC, no smoking + PLA, Usual Brand smoking + no patches. All cigarettes were smoked through the Clinical Research Support System instruments. During sessions in which cigarettes were available, participants were cued to initiate a cigarette according to the timing of their smoking from Session 2, but puffing was not otherwise controlled. Breath carbon monoxide (CO) levels were assessed before and after each 5-hour smoking period. The VLNC cigarettes (Quest 3; Vector Tobacco, Timberlake, NC) had nicotine and tar yields of ≤0.05 mg and 10 mg, respectively. Participants received menthol or non-menthol VLNC cigarettes according to their preference. PLA and NIC patches (GlaxoSmithKline, Parsippany, NJ) were applied, under double-blind conditions, to participants' upper arms (one per arm), for a total of 0 or 42 mg NIC. The current report focuses on topography measures collected during the Usual Brand, VLNC + PLA and VLNC + NIC conditions, as these are most relevant to examining whether a nicotine-reduction policy might affect

smoking topography in SS. Effects of all conditions on craving, withdrawal symptoms and usual-brand smoking behavior have been reported.[28]

Smoking Measures

CO boost was calculated by subtracting CO levels collected at the beginning of the 5-hour smoking periods from CO levels at the end of those periods. Topography measures included total number of puffs smoked in the 5-hour session, total session volume (sum of the volumes of all puffs smoked during the 5-hour session), cigarette volume (sum of the volumes for all puffs smoked per cigarette), number of puffs per cigarette, inter-puff interval (time between puffs), puff volume, puff duration and maximum puff velocity.

Data Analysis

Baseline characteristics of SS and CS were compared using t-tests for continuous variables and chi-square tests for categorical variables. Topography variables and CO boosts were compared using 2 × 3 analysis of variances with the factors Group (SS, CS) and Condition (Usual Brand, VLNC + PLA, VLNC + NIC). Significant effects ($P < .05$) were followed up with post-hoc pairwise comparisons. Effect sizes (partial eta squared, η_p^2) are provided when $P = .05 - .10$, with $\eta_p^2 \leq .05$ indicating small, $\eta_p^2 = .06 - .13$ indicating medium, and $\eta_p^2 \geq .14$ indicating large effect sizes.[32] Analyses were conducted with SPSS version 22 (IBM). CO boost data are missing from one SS due to a technical error.

Results

Demographic, smoking history and other baseline characteristics of SS and CS are shown in Table 1. There were no significant differences between groups on any variable. The usual cigarette brands smoked by 78% of SS and 83% of CS had nicotine yields of ≥1 mg/cigarette (NS). Among SS, 19% reported taking first generation antipsychotic medications and 74% reported taking at least one second generation antipsychotic. No effects of first versus second antipsychotic medication type were observed on usual-brand topography (data not shown). During Session 1 (baseline), SS participants smoked 4.5 ± 3.2 (*M* ± *SD*) cigarettes and CS smoked 3.0 ± 1.4 cigarettes (t (48) = 2.06, $P = .05$).

The effects of group and condition on within-cigarette topography measures are shown in Figure 1 and effects of these variables on total session topography measures are shown in Figure 2. Significant main effects of group were found for total number of puffs and total volume smoked in the session, puffs per cigarette, cigarette volume and inter-puff interval, with means indicating that SS smoked more puffs per session, more puffs per cigarette, had higher cigarette and session volumes, and had shorter inter-puff intervals than CS, across conditions (*P*s < .01). There were no significant differences between groups on puff volume, puff duration, maximum puff velocity or CO boost.

Significant main effects of condition were found for total puffs and total volume smoked during the session, puffs per cigarette, cigarette volume, inter-puff interval (*P*s < .001) and puff duration ($P < .05$). In addition, there was a trend-level effect of condition on puff volume ($P = .08$; $\eta_p^2 = .052$). As shown in Figures 1 and 2, across groups, participants smoked fewer puffs and had lower cigarette and session volumes, shorter inter-puff intervals, longer puff durations and marginally higher puff volumes when VLNC cigarettes were smoked compared to usual brand cigarettes. The VLNC + NIC condition tended to reverse the effects of the VLNC + PLA condition on puff volume, puff duration and inter-puff interval, but not on number of puffs per cigarette or per session, cigarette volume or session volume. There were no effects of condition on maximum puff velocity or CO boost, and there were no significant interactions between group and condition on any measure.

Discussion

The results of this study show that although several puff topography measures were affected by VLNC cigarettes in a manner indicative of compensatory smoking, participants smoked less, overall, during sessions in which VLNC cigarettes were available instead of their usual brand. Specifically, participants took longer puffs, tended to take larger puffs, and had shorter inter-puff intervals (ie, smoked faster) when smoking VLNC cigarettes than when they smoked their usual brand. However, because participants took fewer puffs when smoking VLNC cigarettes, the net effect of these changes was a reduction in cigarette and session volume and no change in CO boost. Thus, overall, the current findings are consistent with studies

Table 1. Baseline Characteristics of Study Participants [*M* (*SD*) or %]

	Schizophrenia (n = 27)	Control (n = 23)	*P*
Age	46.9 (7.9)	45.0 (11.1)	.49
Male	59	48	.42
Race			
White	82	61	.48
African American	11	26	
Hispanic ethnicity	0	4	.27
Employed full- or part-time	7	17	.28
Years of education	11.9 (2.3)	12.0 (1.8)	.85
Cigarettes per day	26.1 (10.0)	23.3 (6.2)	.22
Nicotine dependence severity (FTND score)	7.0 (1.5)	6.5 (1.6)	.32
Baseline CO level (ppm)	32.4 (23.8)	25.5 (15.0)	.23
PANSS total score	51.9 (14.8)		
Antipsychotic drug class	63% atypical 19% typical 11% both		

CO = carbon monoxide; FTND = Fagerström Test of Nicotine Dependence; PANSS = Positive and Negative Syndrome Scale.

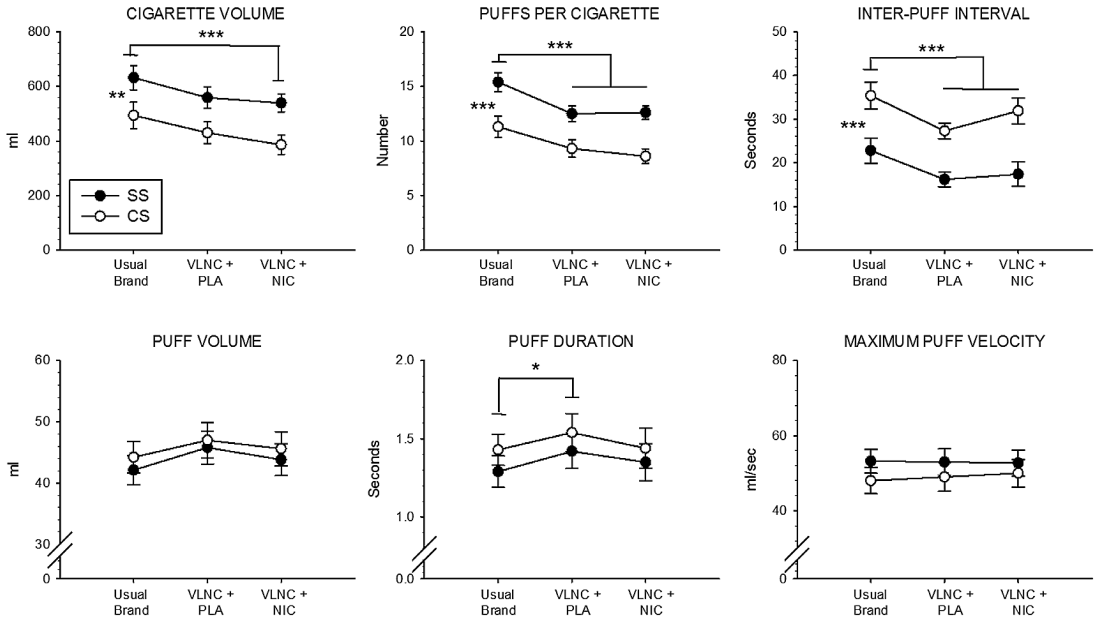

Figure 1. Within-cigarette topography variables collected from smokers with schizophrenia (SS, solid symbols) and control smokers without psychiatric illness (CS, open symbols) during 5-hour *ad libitum* smoking of usual-brand or very low nicotine content (VLNC) cigarettes with placebo or nicotine (42 mg) patches. Symbols represent *M* ± *SEM*. Asterisks represent significant differences between groups or among conditions (**P* < .05, ***P* < .01, ****P* < .001).

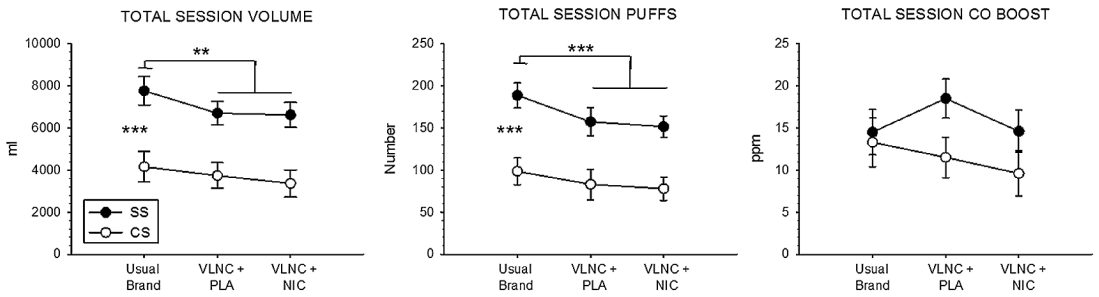

Figure 2. Total session topography variables collected from smokers with schizophrenia (SS, solid symbols) and control smokers without psychiatric illness (CS, open symbols) during 5-hour *ad libitum* smoking of usual-brand or very low nicotine content (VLNC) cigarettes with placebo or nicotine (42 mg) patches. Symbols represent *M* ± *SEM*. Asterisks represent significant differences between groups or among conditions (***P* < .01, ****P* < .001).

that have found that VLNC cigarettes are not associated with compensatory increases in smoking.[24–27]

As hypothesized, SS took more puffs, had shorter inter-puff intervals, and had larger cigarette puff volumes than CS. These results are highly consistent with previous reports from our laboratory[20,33] and another laboratory.[21,34] The shorter inter-puff interval in SS is of particular interest because decreases in this variable are associated with higher nicotine and CO intake.[21,35] Higher nicotine metabolite levels have long been observed in SS relative to CS matched on cigarettes per day,[36] and the shorter inter-puff interval in SS appears to be a key topography variable that explains this difference.[21] Higher nicotine intake in SS has been hypothesized to signal attempts to remediate psychiatric symptoms or cognitive deficits through stimulation of nicotine receptors,[37,38] or may be related to stronger reinforcing efficacy of nicotine in SS.[39] Although in a prior study we observed that first generation antipsychotic use tended to be associated with more intense topography characteristics,[20] as 74% of SS in the current study were using at least one second generation antipsychotic medication, this study was underpowered to detect effects of antipsychotic medication type on topography.

On the other hand, the results of this study did not support the hypothesis that SS would alter their smoking topography to a greater degree than CS when smoking VLNC cigarettes. Both groups responded to VLNC cigarettes with similar changes in puff topography and global indices of smoke intake. We have previously reported that VLNC cigarettes are an effective behavioral replacement for smoking for SS and CS, in that the use of these cigarettes reverses abstinence-induced increases in craving, withdrawal symptoms and usual-brand smoking without affecting psychiatric symptoms.[28] Furthermore, we found that SS rated the sensory effects, craving relief and positive subjective effects of VLNC cigarettes more highly than did CS.[28] Although we found that switching to VLNC cigarettes negatively affects processing speed, inhibitory control, and other cognitive functioning in SS and CS, the co-use of nicotine replacement ameliorates these effects.[40] Thus, studies to date suggest that smoking behavior in SS would not be negatively affected by a nicotine reduction policy to a greater degree than equally-heavy smokers without psychiatric illness, and that any adverse cognitive effects of nicotine reduction that these smokers may experience could be offset with the co-use of nicotine replacement. However, it is important to

note that published reports of VLNC cigarettes in SS to date have examined only their acute effects. Acute use of VLNC cigarettes is likely maintained, at least in part, by conditioned reinforcing effects of sensorimotor smoking cues that have been repeatedly paired with nicotine delivery.[41] Therefore, studies examining the effects of extended use of VLNC cigarettes in SS and other vulnerable populations are vital for informing FDA regulation of tobacco product standards. Research is underway to examine whether extended use of these cigarettes will reduce smoking and increase quit attempts or motivation to quit in SS, as has been found in general population samples of smokers not initially intending to quit.[42,27]

This study has at least two limitations. First, in all conditions, smokers were cued to initiate each cigarette by the researchers based on the natural timing of their usual-brand smoking as measured at baseline. Other topography variables were allowed to vary naturally. The cueing procedure was conducted for the purposes of the primary study in which these data were collected.[28] As VLNC cigarettes were associated with significant reductions in number of puffs smoked and cigarette volume despite the cueing, it is possible that participants might have taken even fewer VLNC puffs without the cueing procedure. Thus, these results may be an underestimate of the effects of VLNC cigarettes on number of puffs smoked and cigarette volume. Conversely, although total puff volume per cigarette is typically considered the most informative measure of compensatory smoking,[22,27] it is possible that smokers could compensate for reductions in nicotine content by smoking more cigarettes rather than more puffs per cigarette, particularly if they are unable to obtain the same number of puffs from VLNC cigarettes as they can from their usual brand. If so, by requiring participants to smoke the same number of cigarettes in the VLNC sessions as they did in the UB session, the cueing procedure may have led to an underestimation of the effects of VLNC cigarettes on compensatory smoking. A recent clinical trial in smokers sampled from the general population found that Spectrum VLNC use reduced, rather than increased, the number of cigarettes smoked per day[27]; nevertheless, whether this will also be true of SS remains to be determined.

A second limitation is that because this study used usual-brand cigarettes rather than normal-nicotine content research cigarettes as the control condition, both pharmacological and expectancy effects may have contributed to the differences observed between these conditions. It is possible that the effects of VLNC cigarettes on topography variables would have been smaller if the cigarettes used during the control condition had been normal-nicotine content research cigarettes. However, we believe that the comparison of usual brand versus VLNC cigarettes is a better model for predicting the potential effects of nicotine reduction regulation on smoking rates in the natural environment. This study also has several strengths, such as the inclusion of a control group of non-psychiatric smokers closely matched to the SS group on smoking history variables, an extensive period of habituation to the topography device, and the inclusion of placebo control for the nicotine replacement.

Despite its limitations, this study contributes to the literature by demonstrating a net decrease in smoking with VLNC cigarettes among smokers who, based on their elevated nicotine intake, would be expected to be at a greater risk of experiencing deleterious effects of nicotine reduction on smoking topography than any other subpopulation of smokers. Given the persistence of smoking among people with serious mental illness,[43] it is likely that multi-modal strategies will be required to reduce the disproportionately high rates of smoking-related disability and death in this population. The current study adds to the evidence that supports the feasibility of reducing the nicotine content of cigarettes as a regulatory approach that may contribute to this effort.

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Declaration of Interests

None declared.

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