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Very-low-nicotine-content cigarettes and dependence among non-daily smokers

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ABSTRACT

Background: The US Food and Drug Administration is considering reductions in the nicotine content of cigarettes to reduce smoking and tobacco dependence. A randomized study showed that even non-daily, intermittent smokers (ITS) reduced their cigarette consumption when switched to very-low-nicotine-content cigarettes (VLNCCs). This paper assesses whether switching ITS to VLNCCs results in decreased dependence and whether subsequent cigarette consumption is mediated by decreased dependence.

Methods: ITS randomized to VLNCCs (n = 118) or normal nicotine content cigarettes (n = 120) completed multiple measures of dependence (Fagerstrom Test of Nicotine Dependence [FTND], Nicotine Dependence Syndrome Scale [NDSS], Wisconsin Inventory of Smoking Dependence Motives [WISDM], and Hooked on Nicotine Checklist [HONC]) at Baseline and 2, 6, and 10 weeks after randomization. A principal component factor score captured common variance among these measures (except FTND). Cigarettes per day (CPD) was assessed by three convergent methods.

Results: Switching ITS to VLNCCs reduced dependence on all measures except the WISDM Secondary Dependence Motives and HONC. Except for the effects on the factor score, these effects of VLNCCs could be accounted for by contemporaneous CPD. Week-2 dependence measures did not prospectively predict weeks 3–4 CPD, once antecedent dependence and CPD were accounted for. "Cheating" among participants who appear to have smoked conventional cigarettes did not affect the findings.

Discussion: Among ITS, switching to VLNCCs results in reduced tobacco dependence. However, the reductions in dependence appear to be secondary to effects on cigarette consumption, and do not appear to be an independent predictor or cause of reduced cigarette consumption.

1. Introduction

Tobacco smoking, the leading cause of preventable mortality (Jacobs et al., 2015), is typically maintained by nicotine dependence (Benowitz, 2010; Stolerman and Jarvis, 1995). Based on this premise, it has been proposed that smoking could be reduced or eliminated if the nicotine levels in tobacco were reduced to a level too low to initiate or maintain dependence (Benowitz and Henningfield, 1994; Henningfield et al., 1998). The US Food and Drug Administration (FDA), which now regulates tobacco (United States Congress, 2009), recently announced that it is considering this approach (Food and Drug Administration (FDA, 2018).

Several studies have examined the effect of switching smokers to very-low-nicotine-content cigarettes (VLNCCs; Benowitz et al., 2007; Donny et al., 2015, 2007). The largest, involving daily smokers of at least 10 cigarettes per day (CPD; Donny et al., 2015), demonstrated that switching to VLNCCs reduced CPD by 23–30% (about 5 CPD). In that study, dependence was also reduced, roughly in proportion to the decrease in CPD, but switching to VLNCCs did not result in more quitting.

More recently, we have completed a similar study (Shiffman et al., 2018), but with non-daily smokers (to whom we refer as intermittent smokers, or ITS), who now comprise 25–33% of all US adult smokers (Jamal et al., 2016; Reyes-Guzman et al., 2017; Substance Abuse and Mental Health Services Administration (SAMHSA, 2014). In this population, switching to VLNCCs resulted in a 51% reduction in smoking, which equated to 1.6 CPD in this very light smoking population. Even while demonstrating greater reductions in smoking, ITS assigned to the VLNCC condition also were more likely to 'cheat' by smoking normal-nicotine commercial cigarettes, and by seeking out e-cigarettes, perhaps as another source of nicotine. Besides paralleling the findings seen

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among daily smokers (Donny et al., 2015), these findings also demonstrated that ITS smoking is motivated by nicotine-seeking.

A further question that arises is whether switching to VLNCCs also reduced dependence among ITS. Donny et al. (2015) also assessed changes in dependence and found that dependence decreased significantly from baseline to the end of their six-week experimental period.

We aimed to assess whether dependence was similarly reduced among ITS assigned to VLNCCs. Perhaps counter-intuitively, dependence is a meaningful construct among ITS. Despite their intermittent smoking, and the fact that ITS go without smoking for days at a time without an increase in craving or withdrawal (Shiffman et al., 2015, 1995), ITS do demonstrate some small degree of dependence, which is also reflected in their smoking behavior (Shiffman et al., 2012b). Thus, we assessed whether ITS who were switched to VLNCCs (vs. being switched to normal-nicotine cigarettes; NNCCs) showed decreases in dependence.

To assess dependence we used multiple scales, all of which have been used previously with ITS samples. The Fagerstrom Test of Nicotine Dependence (FTND; Heatherton et al., 1991) is the most widely used scale for assessing tobacco dependence. It is a good predictor of success at quitting (Baker et al., 2007), and is often referenced as assessing physical dependence, but has in fact been found to be multi-factorial (Haddock et al., 1999; Radzius et al., 2001) and its items do not explicitly assess physical dependence. Uniquely, the FTND includes a measure of cigarette consumption in its score; we scored it without that item, to avoid confounding consumption and dependence as we assessed their relationship. The Nicotine Dependence Syndrome Scale (NDSS; Shiffman et al., 2004) is a multi-factor scale developed to assess dependence using Edwards's syndromal conceptual model of dependence (Edwards, 1986). It contains factors of Drive (impulse to smoke); Tolerance (decreasing efficacy); Continuity (constancy of smoking); Stereotypy (smoking in a fixed pattern); and Priority (favoring smoking over other reinforcers). We analyzed the composite Total score (Shiffman et al., 2004), which draws most heavily from Drive. The Brief Wisconsin Inventory of Smoking Dependence Motives (WISDM; Piper et al., 2004) is a multi-factor scale designed to assess a full range of motives for use. It can be scored into 11 subscales, which themselves factor into the two higher-order factors we analyzed: Primary Dependence Motives (PDM), which cover constructs more typically associated with dependence (craving, tolerance, automaticity, loss of control), and Secondary Dependence Motives (SDM; weight control, social goads, affective enhancement, attachment, cognitive enhancement, affective enhancement, taste-sensory properties, and cue exposure), which are less linked to classical constructs of dependence (Piper et al., 2008a; Smith et al., 2010). The Hooked on Nicotine Checklist (HONC; DiFranza et al., 2002) was developed to assess 'loss of autonomy' over smoking behavior in the very early stages of smoking, and largely assesses craving and loss of control. Each of these scales has been used with both daily and non-daily smokers.

We used multiple scales because the different dependence measures have been shown to correlate only moderately and to capture different aspects of dependence (Baker et al., 2007; Courvoisier and Etter, 2008; Piper et al., 2008b). Moreover, different dependence scales may differ in their sensitivity to dependence at very low levels of dependence, such as those observed among ITS (Carpenter et al., 2010; Etter et al., 1999; MacPherson et al., 2008; Wellman et al., 2006); for example, among ITS, when the four dependence measures were examined, the HONC scale had the lowest correlation with smoking behavior (Shiffman et al., 2012b) and duration of spontaneous abstinence among ITS (Shiffman et al., 2015), while the FTND was unrelated to duration of spontaneous abstinence (Shiffman et al., 2015). The different scales also do not vary in a uniform way across different levels of dependence; for example, ITS scored higher on Secondary than on Primary Dependence Motives scales of the WISDM, whereas the converse was true for daily smokers (Shiffman et al., 2012a).

The intended effect of a policy of switching the population of smokers to VLNCCs is ultimately to decrease dependence in order to increase quitting (Food and Drug Administration (FDA, 2018). Having observed that switching ITS to VLNCCs reduced cigarette consumption but did not significantly increase quitting (Shiffman et al., 2018), we assessed the relationship between cigarette consumption and dependence in two ways. First, we assessed whether any observed decrements in dependence could be accounted for by the decreased cigarette consumption observed when using VLNCCs. Finally, we tested whether subsequent reductions in CPD could be attributed to reductions in dependence, by testing whether dependence measure prospectively predicted subsequent cigarette consumption, over and above cigarette consumption at baseline and at the time of the dependence assessment.

One important confounding factor in studies of VLNCCs is the propensity of participants to 'cheat' by smoking standard commercial cigarettes in place of their assigned cigarettes. This was a predominant phenomenon in Donny et al.'s (2015) study with daily smokers and also was common in our study of ITS (Shiffman et al., 2018). It is possible that cheating might be more common among more dependent participants, who might find it more difficult to tolerate reduction in nicotine. We tested this by assessing the relationship between cheating and dependence. Such cheating might also moderate the relationships between VLNCCs, cigarette consumption, and dependence, both because of measurement issues (cheat cigarettes might not be included in our measures of consumption), and because of substantive effects (cheating with full nicotine cigarettes might mitigate the effect of VLNCCs on dependence). Accordingly, we assessed whether cheating moderated the relationships between cigarette consumption and dependence.

2. Methods

2.1. Participants

Participants were adult ITS (≥18 years old), recruited from the Pittsburgh area via a variety of media, who reported smoking non-daily (4–27 days per month) for at least one year, smoking at any rate for at least three years, and who were not seeking to quit in the next three months. There were no restrictions on the number of cigarettes smoked on smoking days, though those identifying cost as the primary reason for smoking non-daily were excluded. (See Shiffman et al., 2018 for additional inclusion criteria.)

Randomized participants (NNCC: n = 120; VLNCC: n = 118) were an average of 37.9 years of age (SD = 13.8; range 19–80); 54.6% were female; 41.2% college graduates; 63.9% White, 25.6% African American, and 5.1% other ethnicities; 5.5% Hispanic; and reported smoking for an average of 16.8 years (SD = 12.3). Participants smoked an average of 3.7 (SD = 1.4) days per week (16.0 [SD = 6.0] days per month) smoking 3.4 (SD = 2.6) CPD on those days. Almost all participants (97%) reported typically smoking on 5 or fewer days per week. Approximately half (49.6%) had previously smoked daily for at least 6 months, prior to having smoked non-daily for at least the previous year.

2.2. Procedures

The study was a 12-week double-blind randomized clinical trial, approved by the University of Pittsburgh Institutional Review Board, for which participants provided written informed consent. For the initial two-week baseline period, participants smoked their preferred brand of cigarette (provided for free, to parallel conditions in the subsequent experimental period), after which they were randomized (stratified by menthol preference) to receive experimental cigarettes, either VLNCCs or NNCCs, which they were asked to smoke exclusively for the remaining 10 weeks of the study.

VLNCCs and NNCCs were identical in appearance and contained either 0.07 mg of nicotine (VLNCCs; NRC200, NRC201) or 0.8 mg (NNCCs; NRC600, NRC601). The nicotine content was genetically

modified, as opposed to using filtration or ventilation methods to reduce nicotine delivery, as these are more easily circumvented. Cigarettes were approved for use as an Investigational Tobacco Product by the FDA and provided by the National Institute of Drug Abuse.

2.3. Measures

2.3.1. Cigarettes per day

At their initial visit, participants were trained to use an Interactive Voice Response (IVR) system to track their cigarette consumption in real-time and instructed to collect butts from cigarettes smoked each day, which were then returned at each of 10 subsequent visits. In addition, at each visit, participants reported retrospectively via the calendar-based Timeline Follow-Back (TLFB; Sobell et al., 1985) the number of cigarettes smoked each day since the prior visit. These three measures of CPD were highly correlated, as detailed in Shiffman and Scholl (2018). See Shiffman et al., 2018 for detailed study protocol. Daily cigarette consumption was averaged over baseline and over 2-week periods following randomization.

2.3.2. 'Cheating'

We assessed 'cheating' – participants' smoking of conventional cigarettes in lieu of their assigned VLNCCs (or NNCCs) in two ways. Participants were asked to self-report smoking of non-research cigarettes both in TLFB and in IVR; such self-reported cheating was concentrated in 27 participants, who were primarily in the VLNCC group. Separately, we used urinary cotinine assays, and modeling of expected cotinine levels to identify presumed cheaters based on their having higher cotinine levels than could be plausibly explained by their reported smoking or environmental smoke exposure. For these analyses, participants were considered cheaters if they were flagged by either criterion (n = 73, 49 VLNCC, 24 NNCC).

2.3.3. Dependence measures

At baseline and at weeks, 2, 6, and 10 post-randomization, participants completed multiple measures of dependence. The 10-item FTND is scored as a single index, typically producing a value ranging from 0 to 10, with higher values indicating greater dependence. However, as noted above, we removed the item assessing cigarette consumption, resulting in a score ranging from 0-7. The 30-item multidimensional NDSS is scored algorithmically and produces six scores: one for each of the five factors noted above, as well as a Total score reflecting a summary of overall dependence. See Shiffman et al., 2004 for scoring instructions. We scaled the NDSS Total score as a t-score (mean 50, SD 10) and utilized the resulting values in this analysis. The 37-item Brief WISDM results in scores for 11 subscales, which can be further reduced to two summary scores reflecting primary and secondary dependence motives, as previously noted. Finally, the 10-item HONC can produce both a dichotomous score (whereby endorsement of any item is considered to indicate a loss of autonomy) as well as a continuous score (0–10) scale (Wellman et al., 2006). We utilized continuous scoring for this analysis.

2.4. Analysis

We first assessed whether treatment (VLNCC vs. NNCC) affected dependence over time in the study. For most scales, this was assessed using mixed models with random intercepts and slopes and measures running from baseline through end of treatment. As FTND scores were dichotomized (grouped by those whose score either equaled 0 or was ≥ 1), these were analyzed as binary outcomes in GEE. Next, we included contemporaneous CPD measures in the model, to assess whether treatment affected dependence, over and above its effect on cigarette consumption. Finally, to assess whether dependence had any effect in subsequent cigarette consumption, we assessed lagged models, in which assessed dependence two weeks after randomization was used to predict cigarette consumption in the subsequent two weeks (weeks 3–4), while also accounting for CPD in weeks 1–2, as well as baseline (pre-randomization) values of both dependence and CPD. We focused on changes in CPD in Weeks 3–4 for two reasons: (1) changes in CPD flattened out and were non-significant after that time (Shiffman et al., 2018); and (2) because of drop-out, this afforded the largest sample size and this greatest statistical power for analyses. Sensitivity analyses showed that the results were essentially the same at subsequent timepoints.

To assess whether more dependent participants were particularly likely to respond to switching to VLNCCs by cheating using conventional cigarettes, we performed analyses (logistic regression) with cheating as the dependent variable, and evaluated the VLNCC-by-dependence interaction, for each dependence measure. To assess the effects of cheating on the relationship between treatment and dependence, and the role of dependence in subsequent reductions in cigarette consumption, we reran all analyses excluding those deemed cheaters. Additionally, and separately, we included cheating status as a moderator in each model; i.e., testing whether the effects differed between cheaters and non-cheaters.

3. Results

At baseline, there were no differences between groups for any of the dependence measures (see Table 1).

Table 2 shows the correlations among the measures of dependence used in the study. It confirms that the measures are moderately correlated, but some correlations, especially those involving the FTND, are lower than 0.20, and almost all indicate that pairs of measures share less than 50% of their variance. In order to capture the common underlying construct of dependence, we subjected the correlations to a principal component analysis. The FTND was dropped from this analysis, as consistent with the raw correlations, the data showed that FTND did not fit well with the other measures. Among the remaining measures (NDSS, WISDM PDM, WISDM SDM and HONC), a single principal component accounted for 70% of the item variance, with the four scales making approximately equal contributions. This measure (scaled as a T-score, mean 50, *SD* 10) was analyzed in addition to the component measures of dependence. We refer to this measure as the common factor of dependence, or CFOD.

Analyses demonstrated that ITS who were switched to VLNCCs demonstrated greater decreases in dependence over time, compared to those switched to NNCCs. This was true for the NDSS ($p < 0.01$), WISDM PDM ($p < 0.01$), and FTND ($p = 0.03$) measures of dependence, as well as the CFOD ($p < 0.01$; (Figs. 1–4, but not WISDM SDM

Table 1
Baseline dependence measures.

Group	Overall	VLNCC	NNCC	P-value*
Mean (SD)				
NDSS (T-score)	29.75 (5.56)	29.94 (5.41)	29.57 (5.72)	0.61
WISDM PDM	1.74 (0.76)	1.78 (0.84)	1.70 (0.68)	0.42
WISDM SDM	2.45 (0.84)	2.44 (0.81)	2.45 (0.87)	0.94
HONC	3.42 (2.37)	3.52 (2.28)	3.33 (2.47)	0.53
CFOD (T-score)	51.62 (16.59)	52.22 (16.58)	51.03 (16.65)	0.58
%				
FTND = 0	75.11%	71.19%	78.99%	0.16

NNCC normal-nicotine-content cigarettes; *VLNCC* very-low-nicotine-content cigarettes; *NDSS* Nicotine Dependence Syndrome Scale; *WISDM* Wisconsin Inventory of Smoking Dependence Motives; *PDM* Primary Dependence Motives; *SDM* Secondary Dependence Motives; *HONC* Hooked on Nicotine Checklist; *CFOD* Common Factor of Dependence; *FTND* Fagerstrom Test of Nicotine Dependence.

Chi-squared test for FTND and t-tests for the others, as continuous variables.

* Comparing baseline dependence measures between VLNCC and NNCC groups.

Table 2
Correlations among baseline dependence measures.

	NDSS	WISDM PDM	WISDM SDM	HONC
WISDM PDM	0.78			
WISDM SDM	0.61	0.64		
HONC	0.67	0.65	0.56	
FTND	0.39	0.40	0.12	0.22

NDSS Nicotine Dependence Syndrome Scale; *WISDM* Wisconsin Inventory of Smoking Dependence Motives; *PDM* Primary Dependence Motives; *SDM* Secondary Dependence Motives; *HONC* Hooked on Nicotine Checklist; *FTND* Fagerstrom Test of Nicotine Dependence.
*All correlations were significant $p < 0.01$.

($p = 0.12$) or HONC ($p = 0.20$). Sensitivity testing showed that these results held (and were sometimes strengthened) when dependence scores were log-transformed to control skewness (detail not shown).

Analyses that controlled for cigarette consumption (CPD) at the time of dependence assessments suggested that the effect of VLNCCs on each of the individual dependence measures was largely accounted for by their effect on cigarette consumption. When adjusting for CPD, the model coefficients for treatment x time interactions were reduced by about 50%, and none of the effects on individual dependence measures was significant. However, even after controlling for contemporaneous CPD, VLNCC still showed significant effects on the CFOD measure of dependence ($p = 0.045$).

As shown in Table 3, in lagged analyses controlling for prior CPD (and for baseline values of dependence and CPD), none of the Week-2 dependence measures significantly predicted CPD in the subsequent two weeks. In these analyses, prior cigarette consumption (i.e., in the first two weeks of treatment) consistently and uniquely dominated the prediction equation for subsequent smoking.

More dependent participants were not found to be more likely to cheat by supplementing VLNCCs with regular cigarettes (with NNCCs as a control): none of the dependence x treatment effects were significant. We assessed whether cheating may have masked or moderated some of the effects reported above, in two ways: by repeating the analyses while excluding those deemed to have cheated, and by testing cheating status (yes/no) as a moderator in the models. The observed effects were unchanged when cheaters were excluded, and in no case did cheating status demonstrate significant moderating effects (i.e., interactions), regardless of whether CPD was included in the models.

4. Discussion

Previous analyses (Shiffman et al., 2018) demonstrated that switching from commercial own-brand cigarettes to VLNCCs resulted in reduced cigarette consumption and some tendency towards more quitting among ITS. The present analyses show that this reduction in cigarette consumption was also accompanied by reduced dependence, as assessed by multiple validated psychometric scales. Further analyses showed that the reductions in dependence were largely, but not completely coincident with and largely accounted for by the reduced cigarette consumption. Further, lagged analyses showed that dependence did not predict subsequent cigarette consumption, once prior consumption and baseline differences were accounted for.

We considered that some of these effects might be masked or mitigated by 'cheating'; that is, by participants smoking normal cigarettes in lieu of VLNCCs. However, more dependent ITS were not more significantly likely to cheat on VLNCCs (vs NNCCs) than less dependent ITS. Moreover, the observed effects were unchanged when analyses were limited to non-cheaters, and analyses testing whether the effects were different in cheaters vs. non-cheaters showed no such moderating interaction in any model tested.

It was notable that the effect of VLNCCs was evident on diverse measures of dependence, as it has been noted that the different measures do not correlate very highly and appear to be assessing different aspects of dependence (Colby et al., 2000; Courvoisier and Etter, 2008; Piper et al., 2008b; Shiffman et al., 2012b). There were two scales that did not show VLNCC effects. The WISDM SDM scale assesses behavioral or psychological rewards from smoking that are typically not thought of as "dependence" effects, and that have shown more modest differences between ITS and daily smokers (Shiffman et al., 2012a). Thus, it is perhaps not surprising that these motives were not affected by changes in nicotine delivery. The other exception was the HONC scale. Previous analyses have shown that it is relatively insensitive even to differences between ITS and daily smokers (Shiffman et al., 2012b), so it may not be surprising that it did not change in response to switching to VLNCCs.

The fact that the effects of VLNCCs on cigarette consumption and on dependence largely overlap, and that effects on cigarette consumption accounted for most effects on dependence, may not seem surprising. However, it is important to remember that none of the dependence scales directly included any measure of cigarette consumption, so the similarity of effects is not a result of overlapping content in the

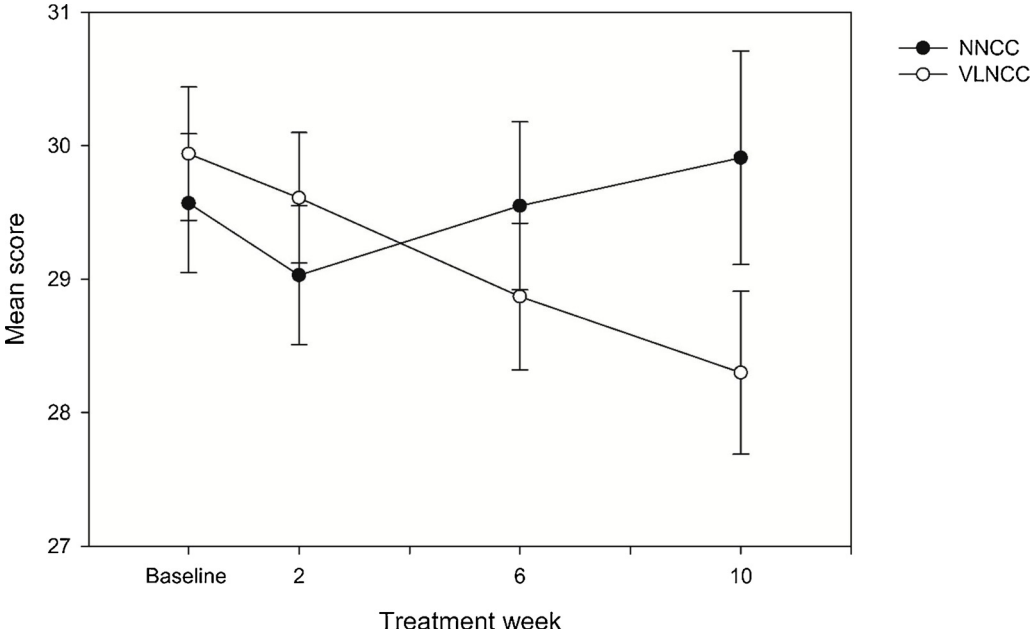

Fig. 1. NDSS t-score, by time and treatment group.
Notes: NNCC normal-nicotine-content cigarettes; *VLNCC* very-low-nicotine-content cigarettes; *NDSS* Nicotine Dependence Syndrome Scale Average NDSS t-scores (observed data, mean ± standard error), at dependence assessment study weeks, among VLNCC and NNCC participant groups. Linear trends in NDSS varied significantly by group (B = -0.11; SE = 0.04; $p < 0.01$). When controlling for contemporaneous CPD, there is no significant difference in trend between the two groups (B = -0.07; SE = 0.04, $p = 0.08$). There were no group differences in quadratic trends

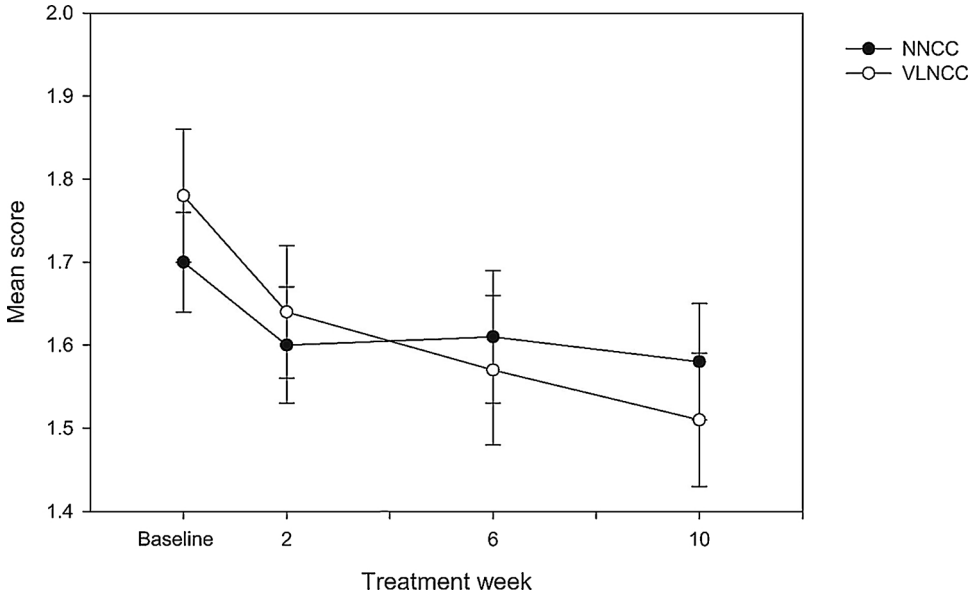

Fig. 2. WISDM Primary Dependence Measure scores, by time and treatment group.
Notes: NNCC normal-nicotine-content cigarettes; *VLNCC* very-low-nicotine-content cigarettes; *WISDM* Wisconsin Inventory of Smoking Dependence Motives Average WISDM PDM scores (observed data, mean ± standard error), at dependence assessment study weeks, among VLNCC and NNCC participant groups. Linear trends in WISDM PDM varied significantly by group (B = -0.010; SE = 0.003; $p < 0.01$). When controlling for contemporaneous CPD, there is no significant difference in trend between the two groups (B = -0.006; SE = 0.004; p = 0.13). There were no group differences in quadratic trends.

measurements, so the result was not pre-ordained. Thus, the findings may suggest that switching to VLNCCs does not have a major effect on dependence, per se, at any given level of smoking, but rather reduced dependence by reducing smoking. The fact that a factor score that aggregated the common variance among multiple measures of dependence did persist in showing effects of switching to VLNCCs, even after accounting for contemporaneous CPD, suggests that some of the difficulty showing independent effects on dependence was due to weaknesses in each of the individual dependence scales. The measures may be particularly challenged to reliably assess changes in dependence among ITS, whose overall dependence is extremely low (Shiffman et al., 2012b).

While the aggregated dependence factor score showed treatment effects even when contemporaneous cigarette consumption was accounted for, lagged prospective analyses showed that no measure of dependence, including the factor score, was independently associated with subsequent smoking, once antecedent dependence and CPD were accounted for. These findings suggest that VLNCC-driven reductions in dependence were incidental to reductions in CPD, and did not drive reductions in CPD as a mediating variable.

It is not clear whether these conclusions would generalize to daily or highly dependent smokers. ITS show only very modest levels of dependence (Shiffman et al., 2012b), and multiple lines of evidence suggest that their smoking is not driven by nicotine dependence, as traditionally conceptualized: they do not show craving and withdrawal when abstaining (Shiffman et al., 2015) and their smoking seems largely driven by situational cues (Shiffman et al., 2014). Their smoking may instead be driven by immediate hedonic reinforcement from smoking (Shiffman et al., 2012a). Since such hedonic effects are reduced by VLNCCs (in daily smokers; Donny et al., 2015), these effects could mediate the effect of VLNCCs on cigarette consumption among ITS.

As the sample means indicate, the ITS in this sample had very, very low levels of dependence, even at baseline. That characteristic is partly what makes these populations interesting. While one might be concerned whether the dependence measures we used would be sensitive to changes, especially reductions, from this low level, the analyses indicate that the measures were not at a 'floor,' in that significant reductions in dependence were observed, prior to adjusting for cigarette consumption as an explanatory variable. Also, previous analyses of ITS

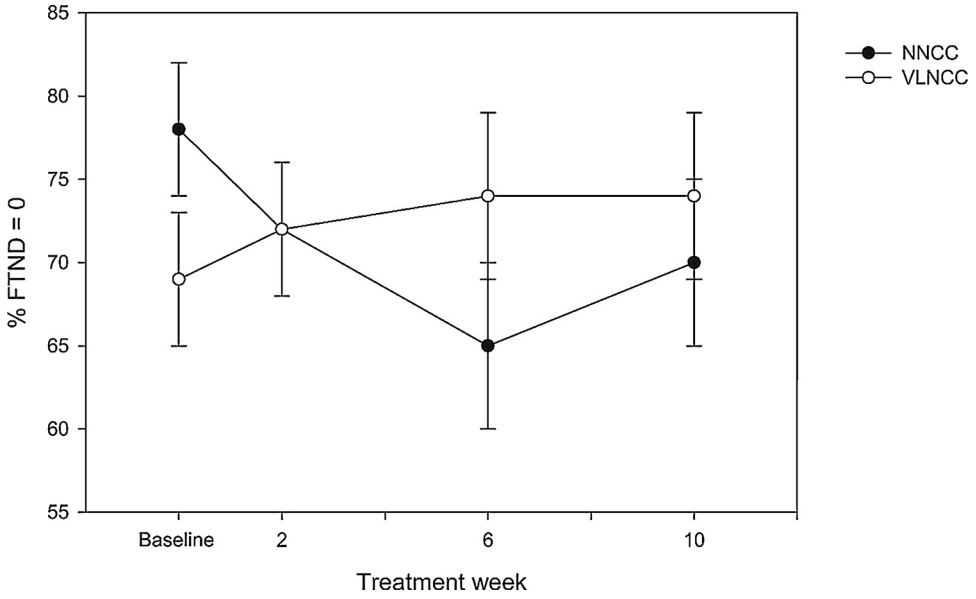

Fig. 3. Percent of subjects with FTND = 0, by time and treatment group.
Notes: NNCC normal-nicotine-content cigarettes; *VLNCC* very-low-nicotine-content cigarettes; *FTND* Fagerstrom Test of Nicotine Dependence. Percent of subjects with FTND score = 0 (observed data, mean ± standard error), at dependence assessment study weeks, among VLNCC and NNCC participant groups. Linear trends in log odds of FTND = 0 varied significantly by group (B = 0.03; SE = 0.01; p = 0.03). When controlling for contemporaneous CPD, there is no significant difference in trend between the two groups (B = 0.02; SE = 0.02; p = 0.35). There were no group differences in quadratic trends.

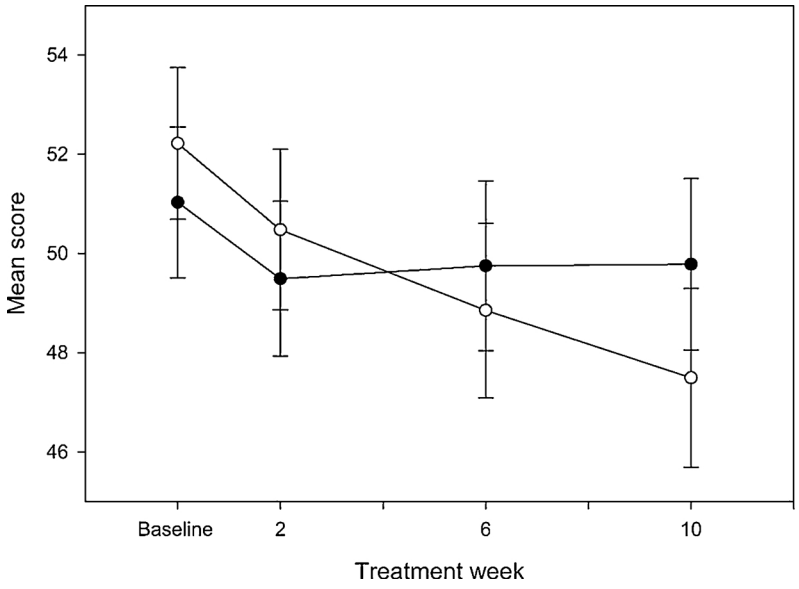

Fig. 4. Common factor of dependence score, by time and treatment group.
Notes: NNCC normal-nicotine-content cigarettes; *VLNCC* very-low-nicotine-content cigarettes; *CFOD* Common Factor of Dependence.
Average CFOD scores (observed data, mean ± standard error), at dependence assessment study weeks, among VLNCC and NNCC participant groups. Linear trends in CFOD varied significantly by group (B = -0.22; SE = 0.07; $p < 0.01$). When controlling for contemporaneous CPD, the difference in linear trends remains significant (B = -0.15; SE = 0.07; p = 0.045). There were no group differences in quadratic trends.

Table 3
Lagged analyses by measure.

	B	SE	t	*p*
NDSS				
Intercept	0.72	0.57		
CPD Baseline	−0.05	0.06	−0.76	0.45
CPD Week 2	0.96	0.05	19.02	< .0001
NDSS Baseline	0.00	0.03	0.09	0.93
NDSS Week 2	−0.03	0.03	−1.05	0.29
WISDM PDM				
Intercept	0.19	0.28		
CPD Baseline	−0.01	0.06	−0.22	0.83
CPD Week 2	0.97	0.05	19.57	< .0001
WISDM PDM Baseline	−0.45	0.25	−1.82	0.07
WISDM PDM Week 2	0.04	0.24	0.17	0.87
WISDM SDM				
Intercept	0.56	0.23		
CPD Baseline	−0.05	0.06	−0.97	0.33
CPD Week 2	0.96	0.05	19.02	< .0001
WISDM SDM Baseline	−0.01	0.22	−0.05	0.96
WISDM SDM Week 2	−0.07	0.22	−0.30	0.77
FTND				
Intercept	−0.01	0.17		
CPD Baseline	−0.05	0.06	−0.90	0.37
CPD Week 2	0.95	0.05	18.81	< .0001
FTND = 0 Baseline	0.002	0.14	0.02	0.99
FTND = 0 Week 2	0.03	0.14	0.23	0.82
HONC				
Intercept	0.19	0.17		
CPD Baseline	−0.05	0.06	−0.82	0.41
CPD Week 2	0.95	0.05	19.24	< .0001
HONC Baseline	−0.12	0.07	−1.68	0.09
HONC Week 2	0.07	0.07	0.97	0.33
CFOD				
Intercept	0.52	0.31		
CPD Baseline	−0.03	0.06	−0.52	0.61
CPD Week 2	0.96	0.05	19.18	< .0001
PC Baseline	−0.01	0.01	−0.86	0.39
PC Week 2	0.00	0.01	−0.08	0.94

NNCC normal-nicotine-content cigarettes; *VLNCC* very-low-nicotine-content cigarettes; *CPD* cigarettes per day; *NDSS* Nicotine Dependence Syndrome Scale; *WISDM* Wisconsin Inventory of Smoking Dependence Motives; *PDM* Primary Dependence Motives; *SDM* Secondary Dependence Motives; *FTND* Fagerstrom Test of Nicotine Dependence; *HONC* Hooked on Nicotine Checklist; *CFOD* Common Factor of Dependence.
Lagged analyses assessing the effect of antecedent CPD and dependence on Week 3–4 cigarette consumption used ANCOVA modelling.

using these measures (Shiffman et al., 2012b) have also shown that these measures make meaningful predictions of smoking and abstinence behavior, even within this limited range.

The proposed policy to mandate that all cigarettes be VLNCCs is justified, in part, by the expectation that VLNCCs would reduce the likelihood novice smokers would develop dependence (Institute of Medicine, 2007). We have previously suggested that, even though they typically have been smoking for a long time (Shiffman et al., 2012c), ITS may resemble smokers early in their developmental trajectory of smoking. Thus, the fact that VLNCCs reduced dependence among ITS supports that policy justification. However, in lagged longitudinal analyses, we did not observe an independent effect of dependence on subsequent smoking, so it is not clear whether dependence, as traditionally construed and assessed, plays a key role in driving cigarette consumption in this population.

The study was subject to several limitations. The sample was drawn from a single geographic region, with limited ethnic diversity, so is not nationally representative. The sample was small and may have lacked power to detect certain effects, such as the residual influence of VLNCCs on dependence after accounting for cigarette consumption. The study also had several strengths. It used multiple measures of dependence, so was not reliant on the idiosyncrasies of any one scale. It used a randomized, double-blind design to assess the effects of VLNCCs, and kept the price of cigarettes (i.e., free) constant between baseline and the experimental period.

In summary, these analyses demonstrated that the reduction in cigarette consumption seen when ITS are switched to VLNCCs is accompanied by a reduction in dependence, but suggest that the reductions in dependence do not mediate the effect of VLNCCs on cigarette consumption, at least in this non-daily smoker sample.

Contributors

Saul Shiffman conceptualized and designed the study and drafted the manuscript. Sarah Scholl oversaw project implementation and data acquisition. Jason Mao conducted the statistical analyses, and Saul Shiffman and Jason Mao interpreted the results. All authors contributed to writing and critically reviewing the manuscript, and read and approved the final content.

Conflict of interest

Saul Shiffman, through Pinney Associates, consults on tobacco

cessation and harm reduction (including nicotine replacement therapy and digital vapor products; by contract, combusted cigarettes are excluded) to Niconovum USA, RJ Reynolds Vapor Company, and RAI Services Company, all subsidiaries of Reynolds American, Inc. and British American Tobacco. Previously, Saul Shiffman consulted to NJOY on e-cigarettes, and to GlaxoSmithKline Consumer Healthcare on smoking cessation medications and treatments. Saul Shiffman holds patents for a novel nicotine smoking-cessation medication that is not under commercial development. Other authors report no competing interests.

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