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A RANDOMIZED TRIAL TO COMPARE SWITCHING TO VERY LOW NICOTINE CONTENT CIGARETTES VERSUS REDUCING CIGARETTES PER DAY

A Dissertation Presented

by

Elias M. Klemperer

to

The Faculty of the Graduate College

of

The University of Vermont

In Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy
Specializing in Psychology

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ABSTRACT

Smoking cigarettes is the most preventable cause of death in the US. Smokers are often unsuccessful at quitting because they are dependent. Reducing nicotine could be one way to reduce dependence. Currently, reducing cigarettes per day (CPD) is the most common strategy to reduce nicotine intake. However, some have proposed switching to very low nicotine content (VLNC) cigarettes to reduce nicotine and dependence. Both reducing CPD and switching to VLNC cigarettes aim to reduce nicotine but do so in different ways. I conducted a randomized trial to compare the degree to which switching to VLNC cigarettes vs reducing CPD 1) is more acceptable and 2) decreases dependence more among smokers not ready to quit.

Sixty-eight adult smokers of ≥ 10 cigarettes/day who were not ready to quit smoked full nicotine study cigarettes ad-lib for 1 week (week 0). I provided all participants with nicotine replacement therapy (NRT) patches and instructions to gradually reduce over the next 4 weeks by either 1) switching to lower nicotine content VLNC cigarettes or 2) reducing the number of full nicotine CPD. I provided VLNC participants with their usual number of cigarettes throughout the study but cigarettes contained only 70% of their usual nicotine at week 1, 35% at week 2, 15% at week 3, and 3% at week 4. I provided CPD participants with full nicotine cigarettes throughout the study but only 70% of their usual number of cigarettes at week 1, 35% at week 2, 15% at week 3, and 3% at week 4. I instructed participants to attempt to smoke only study cigarettes and report use of all (study + non-study) cigarettes via nightly surveys. I used participants’ percent non-study cigarettes/day as a proxy for acceptability and the Nicotine Dependence Syndrome Scale as my primary measure of dependence. Participants completed self-report measures and provided breath and urine samples at weekly visits during the 5-week study period. I tested between-group differences, within-participant change over time, and group by time interactions using multi-level modeling.

Switching to VLNC cigarettes was more acceptable than reducing CPD (F=5.0 p<.05). Acceptability declined over time for CPD participants as they were instructed to reduce more nicotine (F=42.2, p<.001) but this was not true for VLNC participants (F=29.5, p<.001). Dependence declined over time for both VLNC (F=10.5, p<001) and CPD (F=5.0, p<.01) participants but declined more over time for VLNC than CPD participants (F=3.2, p<.05).

This is the first trial to directly compare switching to VLNC cigarettes vs reducing CPD. Large reductions were more acceptable and effective at decreasing dependence among participants who switched to VLNC cigarettes than those who reduced CPD when all were aided by NRT. My findings suggest that regulatory policy that promotes a gradual transition to VLNC cigarettes could be more acceptable and effective at decreasing dependence than the common strategy of reducing CPD. Furthermore, NRT-aided transitions to VLNC cigarettes could be a useful and acceptable component for clinical interventions to reduce nicotine dependence among smokers not ready to quit and thereby make it more likely for smokers to quit and succeed.
ACKNOWLEDGEMENTS

I thank John Hughes for his mentorship both on this study and in my development as a scientist. I thank my dissertation committee for their support and feedback. I thank Joy Benner, Shae Rowlandson, and Nicolas Morley for their work as research assistants, which made this study possible. Finally, I thank Stephen Higgins for his guidance in obtaining funding for this study. This work is supported by research grants 1P50 DA036114 and NCI CA163176 and training grant T32 DA07242 from the National Institutes of Health.
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CHAPTER 1: INTRODUCTION

1.1. Background

Smoking is associated with over 480,000 deaths per year in the United States (US Department of Health and Human Services, 2014). Though the prevalence of smoking has declined dramatically since 1964, it has slowed to less than 1% per year since 1990 (US Department of Health and Human Services, 2014). Currently, only 5% of smokers quit each year (Bondy et al., 2013; Weinberger, Pilver, Mazure, & McKee, 2014) and most are not ready to quit in the near future (PROPEL Centre for Population Health Impact, 2015). Smokers who are more dependent are less likely to quit (US Department of Health and Human Services, 2014). Reducing smokers’ nicotine intakes may be one way to reduce dependence (Benowitz et al., 2009; Benowitz et al., 2007; Donny et al., 2015). Presently, reducing cigarettes per day (CPD) is the most common strategy to reduce nicotine intake (Beard, Fidler, & West, 2011; PROPEL Centre for Population Health Impact, 2015; West & Brown, 2012). Another proposed method to reduce smokers’ nicotine intake and dependence is to switch to very low nicotine content (VLNC) cigarettes (Benowitz & Henningfield, 1994; Hatsukami et al., 2010). In contrast to traditional “light” cigarettes (Benowitz et al., 2005), VLNC cigarettes contain tobacco with reduced nicotine content and result in minimal compensatory smoking (Hatsukami, Donny, Koopmeiners, & Benowitz, 2015).

It is unclear whether switching to VLNC cigarettes or reducing CPD is 1) more acceptable and 2) more effective at decreasing dependence. Though both methods aim to reduce nicotine intake, switching to VLNC cigarettes and reducing CPD may work in
different ways. Individuals smoke cigarettes in response to cues (i.e., Pavlovian conditioning) and to obtain unconditioned (nicotine) and conditioned (smoking sensations) rewards (i.e., operant conditioning; (Conklin & Tiffany, 2002; Russell, 1971)). Both appear to influence cigarette enjoyment (i.e., subjective effects) and dependence (Rose, Behm, Westman, & Johnson, 2000; Rose & Levin, 1991).

Switching to VLNC cigarettes reduces the magnitude of the unconditioned reinforcer (nicotine) without changing conditioned reinforcers (smoking sensations) or restricting smoking behavior in responses to environmental or internal cues to smoke (Figure 1). There are multiple ways in which this could decrease dependence. First, smoking with minimal nicotine as a reinforcer could disrupt associations between smoking behavior and unconditioned reinforcement (path b). Second responding to environmental or internal cues by smoking cigarettes with minimal unconditioned reinforcement (nicotine) could disrupt the association between cues to smoke and smoking behavior (path a). Finally, experiencing smoking sensations with minimal nicotine could disrupt associations between conditioned and unconditioned reinforcers (path d).

![Figure 1: Switching to very low nicotine content (VLNC) cigarettes.](image-url)
Reducing CPD restricts the pattern and frequency of smoking behavior (cigarette/day) without changing unconditioned (nicotine) or conditioned (smoking sensations) reinforcers (Figure 2). This could decrease dependence by providing increased opportunity to practice not smoking in the presence of environmental or internal cues to smoke (path a). Further an overall reduction in the frequency of unconditioned (nicotine; path b) and conditioned (smoking sensation; path c) reinforcers could contribute to decreased dependence.

Figure 2: Reducing cigarettes per day (CPD).

I conducted a randomized trial to compare the extent to which switching to VLNC cigarettes vs reducing CPD 1) is acceptable and 2) decreases dependence among daily smokers who do not want to quit. I had no hypotheses as to whether switching to VLNC cigarettes or reducing CPD would be more acceptable or decrease dependence more because this is an initial test of strategies that both appear effective and I am equally interested in effects in either direction.

Smokers who reduce CPD usually reduce gradually. Though it is unclear how the FDA will introduce nicotine regulation, gradual transitions to VLNC cigarettes has been proposed (Benowitz & Henningfield, 1994; Hatsukami et al., 2015). Therefore I tested gradual transition to VLNC cigarettes vs gradual reductions in CPD.
1.1.1. Switching to Very Low Nicotine Content (VLNC) Cigarettes

I searched PubMed, Medline, Cochrane and my personal library for relevant literature. In addition, I examined articles that referenced or were referenced by relevant studies. Below is a review of the effect of gradual transitions to VLNC cigarettes on compliance (i.e., using only VLNC cigarettes) and dependence in the five published trials that I located. Compliance with VLNC cigarettes has been used as a measure acceptability (Mercincavage et al., 2017). Many of the studies report on the Fagerstrom Test for Cigarette Dependence (FTCD). Importantly, this measure can be administered with or without a measure of cigarettes/day. The studies below report on FTCD with cigarettes/day unless otherwise stated. Participants in all five studies were adult daily smokers who were not ready to quit in the near future. See Table 1 for a summary of studies on gradual transitions to VLNC cigarettes.
Table 1: Trials of gradual transition to very low nicotine content (VLNC) cigarettes.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>N</th>
<th>VLNC cigarettes</th>
<th>Taper duration</th>
<th>Compliance to study cigarettes</th>
<th>Dependence</th>
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<tr>
<td>Benowitz, 2007</td>
<td>21</td>
<td>Weekly taper from UB to 12 mg, 8 mg, 4 mg, 2 mg and 1 mg nicotine content cigarettes.</td>
<td>42 days</td>
<td>Not reported</td>
<td>Significant decrease in FTCD from baseline to the 70-day follow-up.</td>
</tr>
<tr>
<td>Benowitz, 2009</td>
<td>20</td>
<td>Weekly taper from UB to approximately 16.5 mg, 11.3 mg, 6.0 mg, 5.5 mg, and 2.5 mg nicotine content cigarettes.</td>
<td>42 days</td>
<td>Not reported</td>
<td>Significant decrease in FTCD from the end of the taper to the 70-day follow-up.</td>
</tr>
<tr>
<td>Benowitz, 2012</td>
<td>135</td>
<td>Monthly taper from UB to 10.3 mg, 8.5 mg, 3.9 mg, and 1.7 mg nicotine content cigarettes followed by 6 months of a 0.5 mg nicotine content cigarette.</td>
<td>365 days</td>
<td>^40-60% smoked some non-study cigarettes</td>
<td>Significant decrease in FTCD when smoking &lt; 3.9 mg nicotine content cigarettes.</td>
</tr>
<tr>
<td>Hammond, 2014</td>
<td>101</td>
<td>Weekly taper from UB to 8.9 mg, 8.6 mg, and 0.6 mg nicotine content cigarettes.</td>
<td>28 days</td>
<td>^28-44% smoked some non-study cigarettes</td>
<td>Significant decrease in NDSS stereotypy subscale only from baseline to the end of the 28-day taper.</td>
</tr>
<tr>
<td>Mercincavage, 2016</td>
<td>123</td>
<td>Five days of ad-lib UB smoking followed by a taper in three 10-day periods: 8.9 mg, 5.1 mg, and 1.5 mg of nicotine per cigarette.</td>
<td>35 days</td>
<td>^Participants who smoked any non-study cigarettes were removed from the study. There was 25% overall attrition, 8% when smoking 8.9 mg cigarettes, 9% for 5.1 mg cigarettes, and 18% for 1.5 mg nicotine cigarettes.</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

^Biochemical estimation of compliance to 0.5 mg nicotine content cigarettes over a 6-month period in a secondary analysis (Benowitz, Nardone, Hatsukami, & Donny, 2015); ^Participants’ self-report throughout the 4-week taper; ‘Compliance reported in a separate publication (Mercincavage et al., 2017). FTCD=Fagerstrom test for cigarette dependence (Fagerstrom, 2012); mg=Milligram; NDSS=Nicotine dependence syndrome scale (Shiffman, Waters, & Hickcox, 2004); UB=Usual brand; VLNC=Very low nicotine content.
One observational trial instructed 21 participants to smoke their usual brand cigarettes during the first week and then progressively reduce to VLNC research cigarettes containing 12 mg, 8 mg, 4 mg, 2 mg, and 1 mg of nicotine each week over the next 5 weeks (Benowitz et al., 2007). Participants were then followed for 1 month after returning to their usual brand cigarettes or quitting. Five participants quit smoking and mean FTCD scores (1=least and 10=most dependence) (Fagerstrom, 2012) of the remaining smokers decreased from 4.3 at baseline to 3.6 at week 6 (p=.09) to 2.5 at week 10 (p<.001). The FTCD contains an item regarding cigarettes/day and thus is influenced by changes in the number of cigarettes smoked. Cigarettes/day decreased non-significantly from baseline (19 cigarettes/day) to week 6 (18 cigarettes/day) and significantly from week 6 to week 10 (10 cigarettes/day) after participants had returned to their usual brand cigarettes. Though compliance with using only VLNC cigarettes (i.e., not using usual brand cigarettes) was not reported, only one participant withdrew from the study. Cotinine progressively decreased with lower nicotine cigarettes. Cotinine increased at follow-up though remained lower than baseline. Compared to baseline, self-efficacy to quit was higher after the taper and at follow-up and 5 participants quit after the taper. Thus, a relatively short (6-week) taper from full nicotine to 1-mg nicotine content cigarettes appears to affect participants’ dependence, cotinine, and self-efficacy to quit but not their cigarettes/day when smoking VLNC cigarettes.

A similar trial instructed 20 participants to smoke their usual brand cigarettes during the first week and then progressively reduce to commercially available cigarettes with approximately 16.5 mg, 11.3 mg, 6.0 mg, 5.5 mg, and 2.5 mg nicotine content over
the next 5 weeks (Benowitz et al., 2009). Dependence changed from a mean 3.9 FTCD score at baseline to 4.1 at week 6 to 3.3 at week 10. The change from baseline to week 6 was not significant, but baseline to week 10 was significant. Cigarettes/day increased non-significantly from baseline (19 cigarettes/day) to week 6 (22 cigarettes/day) and decreased significantly from week 6 to week 10 (15 cigarettes/day) when participants returned to their usual brand cigarettes. Compliance was not reported but all 20 participants completed the study. Cotinine was stable during weeks 1 to 4 but decreased during weeks 5 and 6. Cotinine increased at follow-up but remained lower than baseline. Compared to baseline, self-efficacy to quit was higher after the taper and at follow-up and 2 participants quit after the taper. Thus, this trial replicates previous findings (Benowitz et al., 2007) that a taper to VLNC cigarettes is associated with reduced dependence and cotinine and increased self-efficacy to quit.

In another observation trial 101 smokers who were not ready to quit in the next month were instructed to gradually transition to VLNC cigarettes over 4 weeks (Hammond & O'Connor, 2014). They initially smoked usual brand cigarettes for 1 week and then progressively reduced to 8.9 mg, 8.6 mg, and 0.6 mg nicotine content cigarettes for 1 week each for the next three weeks. This trial utilized the only VLNC cigarettes that were commercially available at the time of the study and thus had a large and abrupt reduction in nicotine content from week 3 to week 4 (8.6 mg to 0.6 mg). There was a non-significant decrease in dependence from a mean 4.9 FTCD score at week 1 to a mean 4.4 FTCD score at week 4. There was also a significant decrease in the NDSS stereotypy (invariance of smoking) subscale raw scores (-5=least and 5=most dependence) (Shiffman et al., 2004) from a mean of 3.7 at week 1 (when smoking usual brand
cigarettes) to 3.4 at week 4 (when smoking 0.6 mg nicotine content cigarettes), but decreases in the NDSS total and 4 other subscale scores were non-significant. There were no changes in the number of VLNC cigarettes/day across the 4-week study. In contrast to the FTCD, the NDSS is not influenced by changes in cigarettes/day. Twenty eight percent of participants did not complete the taper. In addition the proportion of participants that reported smoking any non-study cigarettes was 28% during week 2 (8.9 mg cigarette), 31% during week 3 (8.6 mg cigarette), and 44% during week 4 (0.6 mg cigarette). Cotinine progressively decreased with lower nicotine cigarettes and there was no change in CO. This brief and relatively abrupt transition to VLNC cigarettes had a decrease in a stereotypy subscale of dependence, decreased cotinine, no effect on cigarettes/day or CO, and low compliance.

A larger and more recent randomized controlled trial (RCT) (Benowitz et al., 2012) used a sample of 135 participants. The VLNC group smoked their usual brand cigarettes for two weeks and then progressively reduced to 10.3 mg, 8.5 mg, 3.9 mg, and 1.7 mg nicotine content cigarettes for 4 weeks each. Participants then smoked 0.5 mg nicotine content cigarettes for the next 6 months and were followed for a year after returning to usual brand cigarettes. The control group smoked usual brand cigarettes as usual for the same amount of time. Change was measured from baseline to weeks 14 and 26 and compared between groups. Two participants in the VLNC and one in the control condition quit smoking by the end of the 26-week taper. Dependence changed from an FTCD score of 5.6 at baseline (when smoking usual brand cigarettes) to an FTCD score of 5.7 at week 14 (when smoking 1.7 mg cigarettes) to an FTCD score of 5.3 at week 26 (when smoking 0.5 mg cigarettes). Change from baseline to week 26 was not significant
but change from week 14 to 26 was. This decrease was significantly greater than the change in FTCD in the control group. In the VLNC group, cigarettes/day did not change during the first 14 weeks but reduced significantly from 24 cigarettes/day at week 14 to 20 cigarettes/day at week 26 when participants switched from cigarettes containing 1.7 to 0.5 mg of nicotine. Ten percent of participants in the control and 11% in the VLNC group withdrew and 21% of participants in the VLNC group reported some non-compliance; i.e., smoking some usual brand cigarettes during the taper to VLNC cigarettes. However, a secondary analysis exploring biochemical verification of compliance concluded that a much higher proportion of participants (40-60%) were non-compliant during the final 6-month period when they were instructed to smoke 0.5 mg nicotine content cigarettes (Benowitz et al., 2015). This is the only study that used biochemical testing to estimate compliance with switching to VLNC cigarettes. Cotinine remained stable until week 14 (1.7 mg cigarettes) and then declined by 44% by week 26 (0.5 mg cigarettes). Carbon monoxide (CO) increased by a mean 4 ppm. There was no change in self-efficacy and 2 participants quit smoking after the taper. Thus, a 26-week taper to VLNC cigarettes appeared to decrease dependence, cotinine, CO, and cigarettes/day but only when participants reduced to the lowest nicotine content cigarettes despite relatively low compliance (Benowitz et al., 2012).

In a recent trial of 123 smokers not ready to quit (Mercincavage et al., 2016), participants were randomized to either smoke their usual brand cigarettes throughout the 35 day study period or progressively switch to VLNC cigarettes. Participants who switched to VLNC cigarettes began with 5 days of ad-lib usual brand cigarettes and then three 10-day periods of cigarettes containing 8.9 mg, 5.1 mg, and 1.5 mg nicotine.
Participants were removed from the study if they reported smoking any non-study cigarettes. In a secondary analysis, the authors examined attrition as a proxy for acceptability (Mercincavage et al., 2017) and found that, there was 25% overall attrition. Attrition was significantly greater in the VLNC vs control conditions and increased as the nicotine content of cigarettes decreased; i.e., 8% when smoking 8.9 mg cigarettes, 9% for 5.1 mg cigarettes, and 18% for 1.5 mg nicotine cigarettes. Cotinine progressively decreased with lower nicotine cigarettes and CO increased when participants switched to 5.1 mg cigarettes. The authors did not report on changes in dependence.

In summary, a gradual transition to VLNC cigarettes appears to vary in acceptability but have positive effects on dependence in smokers who are not ready to quit. Three of five trials measured compliance to study cigarettes and estimated that 25-60% of participants smoked some usual brand cigarettes during their taper to VLNC cigarettes (Benowitz et al., 2015; Hammond & O'Connor, 2014; Mercincavage et al., 2017). All four trials that measured dependence found that switching to VLNC cigarettes is associated with a reduction in dependence. Two trials found decreases in dependence scores from baseline to follow-ups after a taper to VLNC cigarettes (Benowitz et al., 2007; Hammond & O'Connor, 2014). One found a decrease in dependence at lower levels of VLNC cigarettes (Benowitz et al., 2012) and the other found a decrease in dependence from the end of the taper to VLNC cigarettes to a 10 week follow-up (Benowitz et al., 2009). However, it is unclear whether reductions in dependence (5-42%) were clinically significant. Three trials found no change in cigarettes/day while participants were smoking VLNC cigarettes but still showed some reduction in dependence (Benowitz et al., 2009; Benowitz et al., 2007; Hammond & O'Connor, 2014). Thus it appears that,
despite low compliance, gradually switching to VLNC cigarettes decreases dependence but not cigarettes/day in most previous trials.

1.1.2. Reducing Cigarettes per Day (CPD)

Despite a large body of literature on reducing CPD in smokers not trying to quit (Hughes & Carpenter, 2005; Wu, Sun, He, & Zeng, 2015), few studies report on reduction’s effect on dependence or the acceptability of reducing CPD. I reviewed compliance with instructions to reduce CPD as an indication of acceptability. Most reduction trials did not provide a goal to reduce a specific proportion of CPD and thus could not measure compliance. Below I summarize reduction’s effect on dependence as well as the extent to which smokers are able to reduce and the few trials that report compliance with instructions to reduce a specified proportion of CPD (i.e., achieve reduction goals).

I searched PubMed, Medline, Cochrane, and my personal library. In addition, I examined articles that referenced or were referenced by relevant studies. I identified six reviews and meta-analyses on reducing CPD among smokers who are not ready to quit (Asfar, Ebbert, Klesges, & Relyea, 2011; Hughes, 2000; Hughes & Carpenter, 2005, 2006; Moore et al., 2009; Wu et al., 2015) and four studies that reported on the association between reducing CPD and dependence (Etter, Laszlo, Zellweger, Perrot, & Perneger, 2002; Fagerstrom, Hughes, & Callas, 2002; Klemperer, Hughes, & Callas, 2015; Mooney, Johnson, Breslau, Bierut, & Hatsukami, 2011). See Table 2 for a summary of studies that reported on the association between reducing CPD and dependence.
There is a large body of literature regarding reducing CPD. Two of the six identified reviews reported on the extent to which smokers reduced CPD but neither addressed participants’ compliance with assigned reduction goals (Hughes, 2000; Hughes & Carpenter, 2005). The first review identified 5 trials of NRT-aided reduction interventions for smokers who are not ready to quit (Hughes, 2000). The interventions achieved 30-63% reductions in CPD at 1-6 month follow-ups. Another review examined naturalistic and experimental studies of reduction and determined that, while most smokers decrease CPD slightly over time, few achieve substantial reductions (i.e., >50%) on their own (Hughes & Carpenter, 2005). The review identified 19 trials of NRT-aided reduction interventions. The trials provided participants with NRT gum or inhaler or a choice of NRTs. Five trials’ longest follow-ups were at 1 to 5 months and 14 trials’ longest follow-ups were at 6 to 26 months. One trial reported a small mean reduction (6%), nine reported a moderate reduction (18-45%), and 4 reported a large reduction (53-75%) in CPD within the reduction conditions.

A limited number of studies report on smokers’ compliance with instructions to reduce CPD. I examined the 23 trials that were included in the 6 identified meta-analyses and reviews on interventions to reduce CPD (Asfar et al., 2011; Hughes, 2000; Hughes & Carpenter, 2005, 2006; Moore et al., 2009; Wu et al., 2015). Ten trials gave participants explicit goals to reduce their CPD and thus were able to measure compliance. All provided medication to aid reduction and 6 provided counseling. Treatment duration ranged from 4 to 72 weeks (Carpenter, Hughes, & Keely, 2003; Ebbert et al., 2015; Etter et al., 2002; Hatsukami et al., 2004; Hecht et al., 2004; Hurt et al., 2000; Joseph et al., 2008; Rennard et al., 1990; Riley, Jerome, Behar, & Weil, 2002; Stein et al., 2002). Six
trials instructed participants to reduce by ≥50% by the end of treatment. Four of the six
found that 25-39% of participants complied with the goal to reduce 50% of their CPD
over 4 to 26 weeks (Carpenter et al., 2003; Etter et al., 2002; Hatsukami et al., 2004;
Riley et al., 2002). Two of the six trials did not report the proportion of participants that
were compliant but found that participants reduced a mean of 36% of their baseline CPD
over 72 weeks (Joseph et al., 2008) and 63% over 8 weeks (Rennard et al., 1990). Three
trials instructed participants to reduce by 75% by the end of treatment. One reported 26%
compliance over 8 weeks (Ebbert et al., 2015), the second reported 9% compliance over
12 weeks (Hurt et al., 2000), and the third did not report compliance but found that
participants reduced a mean of 40% of their baseline CPD over 12 weeks (Hecht et al.,
2004). One trial instructed participants to reduce 84-92% of their baseline CPD. This trial
did not report compliance or treatment length but found a mean reduction of 75% of
participants’ baseline CPD (Stein et al., 2002). Thus, it appears that large reductions in
CPD are possible but most participants do not comply with the instructed magnitude
(e.g., ≥50%) of reduction in CPD.
Table 2: Studies that reported on the association between reduction in cigarettes per day (CPD) and dependence.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>N</th>
<th>Baseline CPD</th>
<th>Methods</th>
<th>Cigarettes per day</th>
<th>Dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etter, 2002</td>
<td>923</td>
<td>30</td>
<td>Participants randomized to either 6 months of NRT-aided reduction in CPD, placebo control, or no Tx control.</td>
<td>Reduced 33% in the NRT group, 25% in the placebo control, and 8% in the no Tx control.</td>
<td>NRT-aided reduction resulted in significantly lower FTCD scores than the no Tx control.</td>
</tr>
<tr>
<td>Fagerstrom, 2002</td>
<td>38</td>
<td>18-21</td>
<td>Participants from a previous study opted to reduce for 8 weeks with the aid of an Eclipse nicotine inhaler, a standard NRT inhaler, or no Tx.</td>
<td>Reduced 86% with the Eclipse, 68% with the standard inhaler, and no change with no Tx.</td>
<td>*Reduction aided by the standard NRT inhaler significantly decreased FTCD with and without the CPD item.</td>
</tr>
<tr>
<td>Klemperer, 2015</td>
<td>560</td>
<td>20</td>
<td>Participants randomized to receive 4 weeks of brief telephone counseling to reduce CPD, increase motivation, or brief advice to quit. No NRT was provided.</td>
<td>Reduced 19% with reduction counseling, 11% with motivational counseling, and 9% with brief advice to quit.</td>
<td>Reduction in CPD was significantly correlated with reduction in NDSS scores among all participants.</td>
</tr>
<tr>
<td>Mooney, 2014</td>
<td>3,077</td>
<td>28 (lifetime peak)</td>
<td>Participants were asked to recall their peak CPD and peak FTCD in their lifetime.</td>
<td>Reduced 54% from peak CPD.</td>
<td>Reduction in CPD was significantly correlated with reduction in FTCD scores without the CPD item.</td>
</tr>
</tbody>
</table>

*Reduction in FTCD scores were from the beginning of a prior 4-week cross-over trial of NRT inhalers (Fagerstrom, Hughes, Rasmussen, & Callas, 2000) to the end of the 8 week reduction trial (Fagerstrom et al., 2002); CPD=Cigarettes per day; FTCD=Fagerstrom test for cigarette dependence (unless stated otherwise, this measure includes CPD and thus is more sensitive to reduction interventions; (Fagerstrom, 2012)); N= Number of participants in the trial; NDSS=Nicotine dependence syndrome scale (Shiffman et al., 2004); NRT=Nicotine replacement therapy; Tx=Treatment.
Four studies examined the association between reducing CPD and changes in dependence. One RCT of heavy smokers found that a nicotine replacement therapy (NRT) aided intervention to reduce CPD resulted in significantly lower mean FTCD scores (4.3) at a 6-month follow-up than the no treatment comparison condition (5.2) (Etter et al., 2002). However, the FTCD scale included CPD and thus the reduction in “dependence” could be solely due to a reduction in CPD. Another study included 38 participants who had participated in a previous 4-week cross over trial of NRT inhalers (Fagerstrom et al., 2000) and opted to reduce CPD as much as possible with either the standard or Eclipse over 2 months (Fagerstrom et al., 2002). Those who reduced CPD with the standard inhaler had a significant reduction in FTCD scores from 5.6 at the beginning of the initial cross over trial to 3.5 at the end of the reduction study (Fagerstrom et al., 2002). Reduction in FTCD scores among those who used the Eclipse (4.9 to 4.2) was not significant. Reductions in FTCD scores without the CPD item remained significant for the standard inhaler and non-significant for the Eclipse (Fagerstrom et al., 2002). A secondary analysis of 3,077 participants’ retrospective reports of their current vs lifetime peak CPD found that reduction in CPD was highly associated with a reduction in FTCD scores that were modified to exclude CPD (F=30.3) (Mooney et al., 2011). Further, my unpublished secondary analysis of 560 smokers who were not ready to quit and received brief telephone interventions without NRT found a significant correlation between reduction in CPD and NDSS (dependence measure that does not include CPD) scores over 2 months (r=0.31) and 6 months (r=0.35) (Klemperer et al., 2015). In summary, reductions in CPD appear to be associated with decreased
dependence (Etter et al., 2002; Fagerstrom et al., 2002; Klemperer et al., 2015; Mooney et al., 2011).

In terms of biomarkers, medication-aided reduction in CPD decreases carbon monoxide (CO) and cotinine more than placebo and no-treatment controls (Hughes & Carpenter, 2005). However, analyses of changes in CO suggested some compensatory smoking; specifically, CO decreased approximately 1/3 less than CPD among NRT-aided reduction trials (Hughes, 2000; Hughes & Carpenter, 2005).

In terms of quitting, two reviews found that using medication to aid reduction in CPD more than doubled the odds of point-prevalence and prolonged abstinence in comparison to no treatment and placebo controls (Asfar et al., 2011; Moore et al., 2009). One trial found NRT-aided reduction increased the odds of making a quit attempt over a 4.2 fold in comparison to no treatment (Carpenter, Hughes, Solomon, & Callas, 2004) while another found that greater reduction in CPD without NRT also increased the odds of making a QA (OR=1.19 (Klemperer, Hughes, Callas, & Solomon, 2017)). Both trials found that reduction in CPD increased self-efficacy and intention to quit (Carpenter et al., 2004; Klemperer et al., 2017).

In summary, most participants do not achieve interventions’ goals for large reductions in CPD. Nevertheless, reducing some CPD (e.g., 19-68%) appears to have a positive effect on dependence (Table 2). Though the reviewed studies’ methodologies differ substantially, four of four relevant studies found significant associations between reduction in CPD and reduction in dependence, including three trials that had dependence measures not influenced by CPD. Thus it appears that CPD reduction interventions are
associated with decreased dependence even though most participants do not reduce to the magnitude that they are instructed (i.e., they are not fully compliant).

1.2. Aims

Both switching to VLNC cigarettes and reducing CPD appears to decrease dependence. Thus, in this trial I compared smokers who switch to VLNC cigarettes vs reduce the number of full nicotine CPD. It appears that NRT is necessary to achieve substantial reductions in CPD (Hughes, 2000; Hughes & Carpenter, 2005) (Hughes, 2000; Hughes & Carpenter, 2005). NRT also appears to increase the acceptability and effectiveness of switching to VLNC cigarettes (Donny & Jones, 2009; Hatsukami et al., 2013; Rose, Behm, Westman, & Kukovich, 2006; Walker et al., 2012). In both scenarios, NRT could facilitate a net reduction in nicotine (Hurt et al., 1993). Thus I provided all participants with 21-mg NRT patches.

Primary aims

1. Determine whether switching to VLNC cigarettes or reducing CPD is more acceptable for smokers who are not ready to quit.

2. Determine whether switching to VLNC cigarettes or reducing CPD more effectively reduces nicotine dependence.

Secondary aims

Determine whether switching to VLNC cigarettes vs reducing CPD:

3. Reduces cotinine (a nicotine metabolite) levels more.

4. Reduces carbon monoxide (CO) more.

5. Increases self-efficacy and intention to quit smoking more.
6. Increases quit attempts and 7-day point-prevalence abstinence more.
CHAPTER 2: METHODOLOGY

2.1. Design

I conducted a two-arm, randomized trial using a sample of daily smokers not ready to quit (n = 68) between February, 2017 and January, 2018 in Burlington, Vermont. The study was approved by the Committee on the Use of Human Subjects in Research at the University of Vermont and posted on www.clinicaltrials.gov (NCT03060083).

At participants’ initial visit, I randomly assigned participants to 1) switch to VLNC cigarettes or 2) reduce full nicotine CPD (Table 3). During week 0, I provided all participants with enough full nicotine study cigarettes to smoke as much as desired. During weeks 1 through 4, I provided participants with 1) study cigarettes with progressively less nicotine (i.e., switched to VLNC cigarettes) or 2) progressively fewer number of full nicotine study cigarettes (i.e., reduced CPD). See section 2.3 for a full description of nicotine dosage and reduction. I instructed participants to reduce a large amount of nicotine (97%) over a relatively short period of time (4 weeks) because similar reductions appear feasible and decreased dependence with VLNC cigarettes (Benowitz et al., 2009; Benowitz et al., 2007) but has not been tested via reductions in CPD. I instructed participants to do their best to smoke only study cigarettes throughout the study period but to report the use of any non-study (i.e., usual brand) cigarettes on nightly surveys. I informed participants that their compensation was not contingent on smoking study cigarettes. Further, I used a bogus pipeline technique (Aguinis, Pierce, & Quigley, 1993) to increase participants’ self-report of non-study cigarettes that they smoked. Specifically, I (falsely) informed participants that breath and urine tests could detect any
non-study cigarettes that were smoked. I also provided participants with 21-mg NRT patches and instructed them to use one patch per day throughout the study period to help them switch to VLNC cigarettes or reduce CPD. I chose NRT patch primarily because it can provide a consistent amount of nicotine to all participants. Further, NRT appears to be safe, feasible, and effective when used to reduce CPD (Wu et al., 2015) or switch to VLNC cigarettes (Hatsukami et al., 2013).

Participants who were randomized to reduce full nicotine CPD could not be blinded. Thus, I informed participants who were randomized to switch to VLNC cigarettes of the absolute nicotine content of their cigarettes each week as well as the percent relative to the full nicotine cigarettes smoked at week 0.
Table 3: Schedule of reduction and study visits.

<table>
<thead>
<tr>
<th>Study Visit:</th>
<th>Initial</th>
<th>(b_0)</th>
<th>(b_1)</th>
<th>(b_2)</th>
<th>(b_3)</th>
<th>(c_4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Switched to VLNC cigarettes</td>
<td>Cigarettes/day</td>
<td>Ad lib</td>
<td>100% of Week 0</td>
<td>100% of Week 0</td>
<td>100% of Week 0</td>
<td>100% of Week 0</td>
</tr>
<tr>
<td></td>
<td>Nicotine content</td>
<td>100% (16.5 mg)</td>
<td>70% (11.3 mg)</td>
<td>35% (5.5 mg)</td>
<td>15% (2.5 mg)</td>
<td>3% (0.4 mg)</td>
</tr>
<tr>
<td>Reduced number of full nicotine CPD</td>
<td>Cigarettes/day</td>
<td>Ad lib</td>
<td>70% of Week 0</td>
<td>35% of Week 0</td>
<td>15% of Week 0</td>
<td>(d_3)% of Week 0</td>
</tr>
<tr>
<td></td>
<td>Nicotine content</td>
<td>100% (16.5 mg)</td>
<td>100% (16.5 mg)</td>
<td>100% (16.5 mg)</td>
<td>100% (16.5 mg)</td>
<td>100% (16.5 mg)</td>
</tr>
</tbody>
</table>

\(a\)Baseline cigarettes/day established during this time; \(b\)Laboratory visits when participants received 21-mg NRT patches and instructions to use one patch per day; \(c\)Laboratory visit when participants were advised to quit; \(d\)Participants received a minimum of 1 cigarette/day; CPD=Cigarettes per day; mg/g=Milligram nicotine per gram tobacco; NRT=21-mg nicotine replacement therapy patch; VLNC=Very low nicotine content. Participants completed an online follow-up survey 1 month after the end of week 4.
2.2. Participants

2.2.1. Recruitment

I contacted 359 potential participants with Internet advertising on Facebook and Craigslist, flyers posted in the Burlington area, by word of mouth, and from lists of individuals who completed or screened ineligible for other Tobacco Centers of Regulatory Science (TCORS) studies at the University of Vermont and consented to have their contact information shared (see Figure 3). Consenting participants could earn up to $300 compensation for study participation. Compensation was not contingent on compliance with the study reduction strategy or smoking study cigarettes. Seventy-four consenting participants attended the initial study visit (see Table 3) and were randomized. Importantly, differences between conditions did not begin until cigarettes were distributed at the end of study visit 0. Thus, I excluded 6 participants who dropped out after attending the initial study visit, before study visit 0 when nicotine reduction began (Figure 3).
Figure 3: Participant flow diagram.

CPD=Condition that reduced cigarettes/day; DSM-5=Diagnostic and Statistical Manual of Mental Disorders Fifth Edition; NRT=Nicotine replacement therapy; TCORS=Tobacco Center on Regulatory Science; VLNC=Condition that switched to very low nicotine content cigarettes.
2.2.2. Sample Size

In my power analysis I calculated a necessary sample size of 32 per group for a total of 64 participants to obtain a power of 0.8 with a two-sided alpha of 0.05 to detect a 10% within-group difference (0.5 units) in dependence using the Nicotine Dependence Syndrome Scale (NDSS) given a standard deviation of 1. The NDSS is designed to produce z-scores within a standard deviation of approximately 1 (Shiffman et al., 2004). I selected the NDSS as the primary outcome measure because it is widely used, does not rely on cigarettes/day, and has a 5-factor scale with good internal validity, test-retest reliability, convergent validity, and predictive validity (Piper, McCarthy, & Baker, 2006; Shiffman et al., 2004).

2.2.3. Inclusion Criteria

Inclusion criteria were a) ≥ 18 years old, b) smoke ≥10 cigarettes/day seven days per week c) meet DSM-5 criteria for Tobacco Use Disorder, d) have no plans to stop smoking in the next 30 days and is interested in reducing harm from smoking, e) is willing to use NRT and has no contraindications to NRT use, f) have not used non-tobacco nicotine products (e.g., electronic cigarettes) or non-cigarette tobacco products (e.g., smokeless) in the last month, g) has not used nicotine replacement medications, varenicline, bupropion, or received smoking cessation counseling in the last month, h) has not reduced cigarettes/day by ≥ 25% in the last month, i) is currently or has previously been a menthol smoker, j) is not prescribed or currently taking methadone or buprenorphine, k) lives within a 1.5 hour drive of the University of Vermont, l) has been smoking cigarettes daily for ≥ 1 year, m) has access to a telephone on a daily basis, o)
typically goes to sleep between 8:00 PM and 2:00 AM (to maintain a consistent schedule for nightly phone calls) p) is a US citizen or a permanent resident alien with a green card, q) is comfortable reading and writing in English and demonstrates comfort speaking in English, r) is not currently participating in another study that affects the way they smoke cigarettes, and s) is not currently breastfeeding or planning to breastfeed in the next 3 months. Women were excluded if they were pregnant, planning to become pregnant in the next 3 months, or of reproductive potential, sexually active, and not using protection or on birth control. All women of reproductive potential also completed a pregnancy test, whether they reported that they were sexually active or not, to verify that they were not pregnant. I included smokers who tried to reduce cigarettes/day in the past but not in the last month.

I recruited smokers with current or past experience smoking menthol cigarettes because the only available VLNC study cigarettes that have consistent qualities (e.g., filter type and tipping paper perforation) across nicotine contents that allow for a gradual transition to VLNC cigarettes are all mentholated. Therefore I provided all participants with mentholated study cigarettes. A minority of smokers exclusively use menthol cigarettes and most are African Americans (Samet et al., 2011); thus I anticipated a limited number of menthol smokers in the Burlington area and therefore I did not believe recruiting only menthol smokers was feasible. Instead, I recruited participants who have experience smoking menthol cigarettes but usually smoke either menthol or non-menthol cigarettes. I block randomized so that the proportion of usual menthol to non-menthol cigarette smokers was similar between groups. Further, I compared usual menthol vs non-menthol participants’ evaluations of study cigarettes at baseline using the modified
cigarette evaluation questionnaire (Cappelleri et al., 2007) and tested menthol status as a moderator of all outcomes (see section 2.5). Importantly, all participants in this study had to adjust to the novel study cigarettes, regardless of their prior experience with menthol cigarettes.

2.3. Procedure

I screened interested individuals via a 10-minute phone call or online survey to determine eligibility. The initial study visit lasted approximately 1 hour. During this time, I provided potential participants with a consent form and information regarding the study. They were encouraged to ask questions and required to answer a short test to ensure they understood study procedures prior to consenting to participate. Consenting participants were then randomized to 1) the VLNC or 2) the CPD group. Peter Callas, a project statistician, generated a concealed allocation sequence to randomize participant IDs to experimental conditions. Blocked randomization was stratified by whether or not the participant identified as a menthol smoker. All participants answered a series of demographic questions and self-report measures regarding their smoking behavior, and provided a breath sample for CO and urine sample for cotinine analysis. Female participants of reproductive potential also completed a pregnancy test to verify that they were not pregnant.

During week 0, I provided participants in both conditions with 16.5 mg/g nicotine content study cigarettes totaling 150% of their self-reported number of cigarettes/day from the week prior to entering the study. Participants were instructed to smoke ad-lib to establish a baseline cigarettes/day with novel study cigarettes that were provided free of
charge. The 16.5 mg/g nicotine content NIDA study cigarette is estimated to have a nicotine yield (0.8 mg) similar to many commercial cigarettes. Participants were instructed to smoke only study cigarettes, but to smoke as usual during week 0 of the study. Self-reported cigarettes/day from week 0 served as the baseline cigarettes/day from which I calculated the number of study cigarettes to provide participants during weeks 1 through 4 (see Table 3). Although participants were randomized and informed which group they were in during their initial visit, all participants received identical instructions for week 0.

2.3.1. Switching to VLNC Cigarettes

I provided participants who were randomized to switch to VLNC cigarettes with 100% of their number of week 0 cigarettes/day throughout weeks 1 to 4. They received study cigarettes with progressively lower nicotine content (mg/g tobacco) beginning with 11.3 mg/g during week 1; 5.5 mg/g during week 2; 2.5 mg/g during week 3; and 0.4 mg/g during week 4. I selected this schedule based on available VLNC cigarettes and findings that suggest that gradual transitions to cigarettes with a nicotine content of \( \leq 1 \text{mg/g} \) decreases dependence (Benowitz et al., 2012; Benowitz et al., 2007; Hammond & O'Connor, 2014). I also provided participants in this condition with a supply 21-mg NRT patches with instructions to use one patch per day throughout weeks 1 through 4 to help them switch to VLNC cigarettes. I estimated NRT use and compliance with VLNC study cigarettes with daily and weekly self-report.
2.3.2. Reducing CPD

I provided participants randomized to reduce CPD with full nicotine study cigarettes (16.5 mg/g) throughout the 5-week study period and instructed them to only smoke cigarettes provided by the study. After establishing a baseline cigarettes/day during week 0, participants received progressively fewer cigarettes beginning with 70% of their week 0 cigarettes/day for week 1; 35% for week 2; 15% for week 3; and 3% for week 4. Participants received a minimum of 1 cigarette/day during week 4. I also provided participants with a supply of 21-mg NRT patches with instructions to use one patch per day throughout weeks 1 through 4 to help them reduce CPD. This schedule was selected to match the VLNC condition’s percent reduction in nicotine and to encourage participants to reduce as much as possible. I estimated reductions in CPD, compliance with study cigarettes, and NRT use with daily and weekly self-report.

2.3.3. Schedule of Study Visits and Follow-up

All participants completed an initial visit as well as study visits once per week at the end of weeks 0 through 4 (see the first row of Table 3). The initial visit occurred at the beginning of week 0 and consisted of the consent process, randomization, study instructions, an initial questionnaire, distribution of a 1-week supply of full nicotine study cigarettes, and CO and urine samples. Subsequent weekly visits occurred at the end of each week (i.e., visit 0 at the end of week 0, visit 1 at the end of week 1, etc) and consisted of distribution of a weekly supply of study cigarettes and NRT patches as well as completing self-report measures, CO samples, and urine samples (Table 3). See Table 4 for a description of when participants completed each measure throughout the study.
Table 4: Schedule of outcome measures.

<table>
<thead>
<tr>
<th></th>
<th>Assessed Throughout the 5-Week Study Period</th>
<th>Assessed 1 Month After the Study Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nightly</td>
<td>Weekly</td>
</tr>
<tr>
<td><strong>Acceptability Measures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent Non-Study Cigarettes/Day</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Acceptability Questionnaire</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Dependence Measures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine Dependence Syndrome Scales (NDSS)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Fagerstrom Test for Cigarette Dependence (FTCD)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Glover-Nilsson Smoking Behavioral Questionnaire (GN-SBQ)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Addiction Ladder item</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Time to First Cigarette item</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>(TTFC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Biomarkers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cotinine</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Carbon monoxide (CO)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Quit Attempts and Cessation Measures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-Efficacy to Quit (SEQ)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Intention-to-Quit Ladder item</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Plans to Quit Tomorrow item</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Quit Attempts (QA)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>7-Day Point-Prevalence Abstinence (PPA)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>30-Day Prolonged Abstinence (PA)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IVR=Interactive voice response system.
All participants’ completed a short online survey or called a toll free study telephone number nightly throughout the 5 week study period using an Interactive Voice Response (IVR) system. When accompanied by reimbursement that includes bonuses, compliance to daily reporting is very high (e.g., 95%; Hughes et al., 2014). I asked participants who quit during the study to continue to complete nightly questionnaires and attend weekly study visits for the duration of the study.

At the final study visit, I provided all participants with a National Institutes of Health (NIH) brochure regarding the dangers of smoking, information regarding treatment options, and brief advice to quit. I offered an additional 1-month supply of NRT patches to all participants regardless of whether they intended to quit. I did not provide participants with study cigarettes after the 5-week study period. Participants completed a final online survey 1 month after the end of the study period.

2.4. Measures

2.4.1. Acceptability

I calculated participants’ percent non-study (i.e., usual brand) cigarettes/day as my primary measure of the degree to which switching to VLNC cigarettes or reducing the number of CPD was an acceptable nicotine reduction strategy. Compliance with nicotine reduction strategies has been used as a measure of acceptability in prior trials (Mercincavage et al., 2017; Nardone et al., 2016). In the present study, participants reported their number of study and non-study cigarettes/day on nightly questionnaires as well as via timeline follow-back at weekly study visits. I treated missing days among
participants who also missed the prior week’s study visit (and thus did not receive study-cigarettes for the week) as smoking 100% non-study cigarettes/day until they attended their next study visit and received more study cigarettes. I encouraged participants to accurately report non-study cigarettes by 1) falsely telling them I would detect non-study cigarettes and 2) by explaining that smoking non-study cigarettes would not affect their compensation or participation. Specifically, I read the following script to participants prior to distribution of study cigarettes at the end of each study visit:

It’s important that you only smoke study cigarettes during this week. Our breath and urine tests will detect any non-study cigarettes that are smoked. However, if you slip and smoke non-study cigarettes it’s important that you report this as soon as possible on your nightly surveys and weekly questionnaire. You will still be able to participate in the study and will be paid for study activities. Your reimbursement will not depend on how successful you are in using only our cigarettes, however, you should do your best to achieve the goal this week.

I debriefed participants about the use of deception and its rationale at the final study visit or via a mailed letter for those who missed the last study visit. Though prior studies have proposed algorithms to calculate compliance using cotinine (Benowitz et al., 2015; Foulds et al., 2018), these methods are not valid at smaller reductions in nicotine or when using NRT (Benowitz, 2015). Thus, I relied on self-reported non-study cigarettes/day as a measure of acceptability. Finally, I also tested the number of missed study visits as a measure of acceptability because one reason for dropout or missing study visits could be that the reduction strategy was not acceptable to the participant.

I created an acceptability questionnaire comprised of four single-item measures. Specifically I asked all participants to consider the type and number of cigarettes they were provided over the past week and report 1) how willing they are to smoke that type
of cigarette for the next year, 2) how able they are to smoke that type of cigarette for the next year, 3) how willing they are to smoke that number of cigarettes for the next year, and 4) how able they are to smoke that number of cigarettes for the next year. I used mean Likert scale responses (1=least, 5=most) to each item for analysis.

2.4.2. Dependence

My primary measure of dependence is the Nicotine Dependence Syndrome Scale, Overall Score (NDSS-OS; (Shiffman et al., 2004)). Secondary measures of dependence included the five NDSS subscales: 1) the Drive subscale (NDSS-D) assessed craving, withdrawal, and compulsion to smoke, 2) the Priority subscale (NDSS-P) assessed preference for smoking over other reinforcers, 3) the Tolerance subscale (NDSS-T) assessed sensitivity to the effects of smoking, 4) the Continuity subscale (NDSS-C) assessed the regularity of smoking rate, and 5) the Stereotypy subscale (NDSS-S) assessed changes in invariance of smoking. The NDSS scales have good reliability and predictive validity (Piper et al., 2006) and are not influenced by changes in cigarettes/day. The NDSS produces z-scores and the scores are calculated with weighted parameters using subsets of the 19 NDSS items (Shiffman et al., 2004).

I also used a version of the Fagerstrom Test for Cigarette Dependence (FTCD; (Fagerstrom, 2012)) modified to exclude the cigarettes/day item. Responses on the FTCD were summed (0=least and 7=most dependent) for analysis. I excluded cigarettes/day from the FTCD because reducing cigarettes/day was inherent to the strategy used by the CPD reduction condition. The FTCD is the most commonly used measure of dependence.
However, findings are mixed regarding the FTCD’s predictive validity, internal validity, and reliability (Piper et al., 2006).

The Glover-Nilsson Smoking Behavioral Questionnaire (GN-SBQ) is a measure developed specifically to assess the role of behavior in cigarette dependence (Glover et al., 2005). For example, the GN-SBQ includes: “Do you find yourself lighting a cigarette routinely (without craving)?” and “Does part of your enjoyment of smoking come from the steps (ritual) you take when lighting a cigarette?” Participants responded to items using a 0 to 4 Likert scale and I summed responses for analysis (0=least dependent, 44=most dependent). I included the GN-SBQ to assess changes in dependence due to changes in behavioral conditioning that could occur from switching to VLNC cigarettes or reducing CPD (see section 1.1). Though the GN-SBQ has been used in prior reduction studies (O’Brien, Knight-West, Walker, Parag, & Bullen, 2015; Tseng et al., 2016), I could not find a test of the measure’s validity or reliability.

Importantly, the NDSS, FTCD, and GN-SBQ are traditionally used to assess longer-term and stable states of dependence. I was unable to find a measure designed to assess short-term changes in dependence. Thus, I modified instructions for these measures to assess shorter-term changes in dependence within the 5-week study period as well as on the follow-up questionnaire. I instructed participants to respond to all questions only considering their symptoms during the prior 7 days. In addition, I modified the wording of some questions and included a “not applicable” response option. For example, many participants responded “not applicable” to the FTCD question: “In the past 7 days, did you smoke even when you were so ill that you were in bed most of the day?” I recoded all “not applicable” responses as “no” for these dependence measures.
to minimize missing data. A participant who selected “not applicable” likely did so because they did not come into contact with, and thus did not experience, the symptom assessed by the question. Dependence measures at the initial visit asked about pre-study symptoms and thus were not modified. Therefore, dependence measures collected at the initial study visit are not comparable to dependence measures at study visits 0 through 4 or at follow-up.

In addition to the NDSS, FTCD, and GN-SBQ measures, I included two single-item measures of dependence. First, I assessed time to first cigarette (TTFC) after waking. TTFC is an item on the FTCD that correlates well with other measures of dependence (Fu et al., 2011), has good predictive validity for QAs and cessation (Baker et al., 2007; Borland, Yong, O’connor, Hyland, & Thompson, 2010) and is thought to be one of the best single questions to assess dependence (Fagerstrom, 2003). Second, I used an Addiction Ladder to assess changes in how addicted participants felt to cigarettes. This item was adapted from the Intention-to-Quit Ladder (Hughes, Keely, Fagerstrom, & Callas, 2005) and instructed participants to indicate on a Likert scale of 0 (not at all) to 10 (very definitely) how addicted to cigarettes they currently felt. The Addiction Ladder has not been validated in prior studies.

2.4.3. Biomarkers

I collected weekly urine samples to measure changes in cotinine to assess the effectiveness of switching to VLNC cigarettes vs reducing CPD at reducing nicotine exposure. I analyzed urinary cotinine levels using semi-quantitative on-site enzyme immunoassay (Microgenics, Fremont, CA, USA). Cotinine is a nicotine metabolite with a
half-life of approximately 16 hours (Benowitz & Jacob, 1994; West & Hajek, 2011). Smoking within the past 80 hours generally results in elevated urine cotinine levels and thus cotinine is a commonly used measure of nicotine exposure (Benowitz et al., 2002). Changes in cotinine could be influenced by differences in nicotine content, compensatory smoking (e.g., inhaling more vigorously), or number of cigarettes as well as NRT use.

I collected weekly breath samples to measure changes in carbon monoxide (CO) to assess the extent to which participants in each condition reduced their smoke exposure. I analyzed breath samples using a handheld Covita Micro Smokelyzer (http://www.covita.net/). CO is a byproduct of combusted tobacco and has a half-life of approximately 4 hours. Smoking within the past 24 hours generally results in elevated breath CO levels and thus CO is commonly used only as a short-term measure of cigarette smoke exposure (Benowitz et al., 2002). Changes in CO could be influenced by differences in recency, compensatory smoking, or number of cigarettes, but is not directly affected by NRT or the nicotine content of cigarettes. Importantly, I instructed CPD but not VLNC participants to reduce the number of cigarettes/day. Thus I expected CO to change in the CPD condition but not necessarily in the VLNC condition.

2.4.4. Quit Attempts and Cessation Measures

The Self-Efficacy to Quit (SEQ) measure is a commonly used self-efficacy scale in smoking research (Velicer, DiClemente, Rossi, & Prochaska, 1990). Increases in the SEQ has predicted cessation and quit attempts in prior reduction studies (Carpenter et al., 2004; Klemperer et al., 2017). Participants responded to SEQ questions on a 5-point
Likert scale and I calculated the mean response for an overall score (1=least and 5=most self-efficacy to quit).

The Intention-to-Quit Ladder is a single item that instructs smokers to indicate on a 0 (very definitely no) to 10 (very definitely yes) Likert scale how much they intend to quit in the next 30 days (Hughes et al., 2005). Increases in the Intention-to-Quit ladder has predicted cessation and quit attempts in prior reduction studies (Carpenter et al., 2004; Klemperer et al., 2017).

I measured plans to quit tomorrow using a single item on nightly surveys. Specifically, I asked smokers whether they planned to smoke tomorrow rather than if they planned to quit tomorrow because a prior study found that asking about intentions to stop repeatedly (e.g., on 35 occasions) could make participants feel under pressure to try to quit (Hughes et al., 2014). Thus, days when participants reported they did not intend to smoke were considered days when participants planned to quit. In a prior prospective natural history study, plans to quit tomorrow predicted future quit attempts and cessation (Hughes et al., 2014).

I measured quit attempts (QA) that lasted ≥24 hours as well as any QAs (i.e., including very short QAs that lasted < 1 day) using nightly and weekly self-reports. A prior prospective study found QAs (including very short attempts) predicted future longer abstinence (Hughes et al., 2014). Further, making a QA is an inherent pre-requisite to cessation. I did not biochemically verify QAs because many were short and occurred between study visits.

I measured self-reported 7-day point-prevalence abstinence (PPA) weekly and at the online follow-up 1 month after the study period. I measured 30-day prolonged
abstinence (PA) at the 1-month follow-up. Both PPA and PA are commonly used and clinically meaningful outcomes in smoking research (Hughes et al., 2003). I did not biochemically verify abstinence during follow-up because I lacked sufficient funds to collect breath or urine samples during the follow-up period.

2.4.5. Measures Collected But Not Reported in This Dissertation

The following outcomes were collected during this study and will be reported in future publications but not in my dissertation: Questionnaire of Smoking Urges – brief scale (Cox, Tiffany, & Christen, 2001), Minnesota Nicotine Withdrawal Scale (Hughes & Hatsukami, 1986), Perceived Health Risks Rating (Westman, Levin, & Rose, 1992); Cigarette Purchase Task (MacKillop et al., 2008); modified Cigarette Evaluation Questionnaire (Cappelleri et al., 2007).

2.5. Analysis

I conducted all analyses with SPSS (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.) I used multi-level modeling for between-participant comparisons (i.e., VLNC vs CPD groups), within-participant comparisons (i.e., week 0 to week 4), and a condition by time interaction for all continuous and ordinal outcomes. Though some of my outcomes were collected daily, I used week as my time variable for all outcomes because parameter estimates are less accurate in multi-level models with small sample sizes (e.g., N=68) and large number of time-points (e.g., 35 days; (Bijleveld et al., 1998)). Thus, I aggregated nightly data to weekly means in order to have fewer
time-points for this relatively small sample. For binary outcomes, I used logistic regression and Cox regression survival analyses.

2.5.1. Analysis of Continuous and Ordinal Outcomes

The following were continuous or ordinal outcomes: Percent non-study CPD, Acceptability Questionnaire items, NDSS overall scale and subscales, FTCD, GN-SBQ, TTFC, Addiction Ladder, Cotinine, CO, SEQ, and Intention-to-Quit Ladder. In order to test for stability at week 0, I used multi-level modeling to conduct between-participant, within-participant, and day by condition interactions as predictors of changes in measures assessed nightly during week 0: Percent non-study CPD, addiction ladder, TTFC, and total (study + non-study) CPD. None were significant, indicating that participants established stable smoking when they received free study cigarettes to smoke ad-lib during week 0 of the study period.

In my main multi-level models, I entered time and condition as fixed effects and participants as a random effect. I compared Akaike and Bayesian information criteria (AIC and BIC) values between the following covariance structures to choose the best fitting model for each outcome: First order auto-regressive, first order auto-regressive heterogeneous, variance covariance, compound symmetry, and unstructured.

In my between-participant comparisons, I entered condition (VLNC vs CPD) as the predictor and collapsed across weeks 1 through 4. I excluded week 0 in my primary between-participant analyses because reduction did not begin until week 1. Next I collapsed across condition and entered time (i.e., weeks 0 to 4) as the predictor. I also tested time as a predictor of all outcomes separately among VLNC and CPD participants.
Finally, I entered condition, time, and a condition by time interaction as predictors in my full multi-level model.

I tested my full multi-level interaction model (condition, time, and condition by time interaction), when controlling separately for 1) NRT patch compliance and 2) percent non-study cigarettes/day as time-varying covariates. I controlled for NRT patch compliance to examine whether the effectiveness of the nicotine reduction strategies was due to NRT use. I defined NRT compliance as the percent of days during weeks 1 through 4 when participants reported using the patch. I controlled for percent non-study cigarettes/day to examine the extent to which findings could be due to differences in the reduction strategies’ acceptability. Thus, I did not control for percent non-study cigarettes/day for acceptability outcomes. Importantly, I conceptualized percent non-study cigarettes/day as a potential mediator (not a confounder) of the reduction strategies’ influence on dependence, biomarkers, and quitting.

Finally, I tested gender and menthol status (i.e., whether the smoker identified as a menthol or non-menthol smoker at screening) as moderators of all outcomes. However, neither gender nor menthol status moderated any of my outcomes. Therefore I did not report on findings from these analyses in my results.

In a series of post-hoc tests, I compared VLNC vs CPD participants 1) at the end of the study period (week 4) on all continuous and ordinal outcomes and 2) at each week among outcomes where there was a significant condition by time interaction. I also examined within-participant changes in total (study + non-study) cigarettes/day to provide context to interpret changes in percent non-study cigarettes/day (i.e., acceptability) throughout the study period.
2.5.2. Analysis of Binary Outcomes

The following were binary outcomes: Plans to quit tomorrow, any QA, and ≥24 hour QA. I used logistic regression to compare VLNC vs CPD conditions. Using Cox regression survival analyses, I calculated Cox Hazard Ratios and compared time to first event. I also tested all Cox regression survival analyses when controlling separately for 1) percent non-study CPD and 2) NRT patch compliance as time-varying covariates.

2.5.3. Analysis of Follow-Up Outcomes

I analyzed the following continuous or ordinal outcomes at the 1-month follow-up: Total cigarettes/day, NDSS-OS, FTCD, GN-SBQ, Addiction Ladder, SEQ, and Intention-to-Quit Ladder. I used linear regression to compare VLNC vs CPD at follow-up, change from the end of the study period (week 4) to follow-up, change from pre-study to follow-up, and all condition by time interactions. Finally I tested all condition by time interactions after controlling for patch distribution and use during follow-up.

Dichotomous outcomes were whether participants set a quit date at their final study visit and self-reported 7-day PPA and 30-day PA at the 1-month follow-up. I used chi-square tests to compare differences between VLNC vs CPD groups.

2.5.4. Missing Data

There were no significant differences in the number of missed study visits between conditions. Of the 74 consented participants, six did not attend study visit 0 and thus were excluded from my analyses. Of the 68 participants included in my analyses, five participants missed all visits after visit 0, one participant missed visit 1 only, one
participant missed visits 2 through 4, three participants missed visits 3 and 4, one participant missed visit 3 only, and one participant missed visit 4 only. Three hundred and twenty-six (14%) of the 2,380 total nightly IVR surveys (68 participants x 35 day study period) were missing. Participants reported cigarettes/day, TTFC, Addiction Ladder, and QAs on both nightly and weekly surveys (see Table 4). When possible, data from nightly surveys were used for analysis to minimize recall bias. However, in order to minimize missing data, values from weekly surveys were used to impute missing nightly data when participants attended a weekly visit but missed nightly surveys during the subsequent week. After imputing data from weekly surveys, 209 (9%) of the 2,380 total nightly surveys remained missing. Twenty eight (41%) participants missed the online follow-up survey 1 month after the study period. The amount of missing nightly, weekly, and follow-up data did not significantly differ between conditions. Importantly, because I used multi-level modeling for my main analyses of continuous and ordinal data, all missing data were accounted for by the model (Field, 2013). Missing binary data (e.g., QA and cessation) were handled by censoring in my survival analyses and treated as continued smoking in follow-up analyses. Missing continuous data at follow-up (e.g., dependence measures) were treated as missing. I examined the distributions of all outcomes at all time points and none required transformation. I examined all outliers that were beyond two standard deviations from the mean for each outcome at each time point and found no reason to exclude any data.
2.6. Participant Characteristics

Compared with population based samples of current daily smokers (Fagerstrom & Furgerg, 2008; Hughes & Callas, 2010) smokers in this study appear younger, more likely to be male, more likely to be white, non-Hispanic, more educated, more dependent, and smoked more cigarettes/day before the study began (Table 5). There were no significant differences between CPD and VLNC participants.
Table 5: Participant demographics and smoking history. a

<table>
<thead>
<tr>
<th>Demographics</th>
<th>VLNC (n=36)</th>
<th>CPD (n=32)</th>
<th>Total (N=68)</th>
<th>NHIS b and other surveys c, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>38.4 (13.4)</td>
<td>39.3 (13.6)</td>
<td>38.8 (13.4)</td>
<td>42 b</td>
</tr>
<tr>
<td>% Women</td>
<td>38.9</td>
<td>40.6</td>
<td>39.7</td>
<td>46 b</td>
</tr>
<tr>
<td>% White, non-Hispanic</td>
<td>77.8</td>
<td>87.5</td>
<td>82.4</td>
<td>78 b</td>
</tr>
<tr>
<td>% with &gt; 12 years of education</td>
<td>72.2</td>
<td>71.9</td>
<td>72.1</td>
<td>39 b</td>
</tr>
<tr>
<td>% Employed full time</td>
<td>47.2</td>
<td>37.5</td>
<td>42.6</td>
<td>-</td>
</tr>
<tr>
<td>% Married</td>
<td>30.6</td>
<td>25.0</td>
<td>27.9</td>
<td>-</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean cigarettes/day</td>
<td>19.0 (6.1)</td>
<td>19.8 (10.4)</td>
<td>19.4 (8.4)</td>
<td>16 b</td>
</tr>
<tr>
<td>Mean total Fagerstrom Test for Cigarette Dependence (0=lowest, 10=highest)</td>
<td>5.3 (1.9)</td>
<td>5.0 (2.2)</td>
<td>5.1 (2.0)</td>
<td>4.3-4.6 c</td>
</tr>
<tr>
<td>Mean self-efficacy to quit (1=lowest, 5=highest)</td>
<td>2.4 (1.1)</td>
<td>2.3 (0.9)</td>
<td>2.4 (1.0)</td>
<td>-</td>
</tr>
<tr>
<td>Mean Intention to quit in the next month (0=very definitely no, 10=very definitely yes)</td>
<td>3.4 (3.0)</td>
<td>3.5 (3.0)</td>
<td>3.5 (3.0)</td>
<td>-</td>
</tr>
<tr>
<td>Mean carbon monoxide (CO) ppm</td>
<td>22.4 (11.7)</td>
<td>22.3 (11.2)</td>
<td>22.3 (11.4)</td>
<td>-</td>
</tr>
<tr>
<td>Mean cotinine ng/ml</td>
<td>1,364.1 (739.4)</td>
<td>1,464.5 (703.2)</td>
<td>1,412.1 (718.7)</td>
<td>-</td>
</tr>
<tr>
<td>% Menthol smokers</td>
<td>22.2</td>
<td>25.0</td>
<td>23.5</td>
<td>38.8 d</td>
</tr>
<tr>
<td>Mean age at onset of smoking</td>
<td>16.7 (4.7)</td>
<td>15.6 (3.3)</td>
<td>16.2 (4.1)</td>
<td>17 b</td>
</tr>
<tr>
<td></td>
<td>VLNC (n=36)</td>
<td>CPD (n=32)</td>
<td>Total (N=68)</td>
<td>NHIS\textsuperscript{b} and other surveys\textsuperscript{c,d}</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------------</td>
<td>------------</td>
<td>--------------</td>
<td>-------------------------------------------------------------</td>
</tr>
<tr>
<td>Number of times attempted to reduce but not quit in past 12 months</td>
<td>1.0 (1.5)</td>
<td>2.4 (6.3)</td>
<td>1.7 (4.5)</td>
<td>-</td>
</tr>
<tr>
<td>Median number of QAs in life</td>
<td>2.0</td>
<td>3.0</td>
<td>2.0</td>
<td>-</td>
</tr>
<tr>
<td>% Used NRT during a past QA</td>
<td>52.8</td>
<td>40.1</td>
<td>47.1</td>
<td>-</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Standard deviations in parentheses; \textsuperscript{b}(Hughes & Callas, 2010); \textsuperscript{c}(Fagerstrom & Furberg, 2008); \textsuperscript{d}(Villanti et al., 2016); \textsuperscript{e}Assessed at the initial study visit; CPD=Condition that reduced cigarettes per day; NHIS=United States National Health Interview Survey; QA=Quit attempts; VLNC=Condition that switched to very low nicotine content cigarettes.
CHAPTER 3: RESULTS

Due to the large number of outcomes in this study, magnitudes of effects are displayed in tables and figures but not reported in the text for most outcomes. In addition, see Appendix Table 1 for raw means for all outcomes at week 0, week 4, and follow-up.

3.1. Smoking at Week 0

During week 0, all participants received 150% of the number of their pre-study cigarettes/day and were instructed to smoke study cigarettes with 16.5 mg/g nicotine ad-lib. Participants smoked about a pack per day and smoked very few non-study cigarettes (see Table 6). Though prior research indicates that participants smoke more cigarettes when they are free (Shiffman & Scholl, 2017), differences between pre-study commercial cigarettes/day (mean=19.4) and week 0 total cigarettes/day (mean=20.6) were not significant. There were no differences between participants’ evaluation of study cigarettes (mCEQ) based on condition or whether participants identified as a menthol smoker prior to entering the study. Importantly, there were no differences between VLNC and CPD groups during week 0 and smoking characteristics remained stable over time throughout week 0 (see section 2.5).
Table 6: Week 0 smoking characteristics.*

<table>
<thead>
<tr>
<th></th>
<th>VLNC (n=36)</th>
<th>CPD (n=32)</th>
<th>Total (N=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean total cigarettes/day</td>
<td>20.1 (8.8)</td>
<td>21.1 (12.2)</td>
<td>20.6 (10.5)</td>
</tr>
<tr>
<td>Median percent non-study cigarettes/day</td>
<td>1.5</td>
<td>1.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Mean willingness to smoke type of cigarette (1=least, 5=most)</td>
<td>4.3 (1.1)</td>
<td>4.4 (0.9)</td>
<td>4.4 (1.0)</td>
</tr>
<tr>
<td>Mean ability to smoke type of cigarette (1=least, 5=most)</td>
<td>4.1 (1.2)</td>
<td>4.1 (1.1)</td>
<td>4.1 (1.2)</td>
</tr>
<tr>
<td>Mean willingness to smoke number of cigarettes (1=least, 5=most)</td>
<td>4.3 (1.1)</td>
<td>4.2 (1.0)</td>
<td>4.2 (1.1)</td>
</tr>
<tr>
<td>Mean ability to smoke number of cigarettes (1=least, 5=most)</td>
<td>4.1 (1.3)</td>
<td>3.8 (1.1)</td>
<td>3.9 (1.2)</td>
</tr>
<tr>
<td>Mean Nicotine Dependence Syndrome Scale, Overall Score (NDSS-OS; z-scores)</td>
<td>-0.70 (.85)</td>
<td>-0.77 (0.92)</td>
<td>-0.73 (0.88)</td>
</tr>
<tr>
<td>Mean Fagerstrom Test for Cigarette Dependence (FTCD; excluding cigarettes/day; 0=lowest, 7=highest)</td>
<td>3.1 (1.4)</td>
<td>3.0 (1.5)</td>
<td>3.0 (1.5)</td>
</tr>
<tr>
<td>Mean Glover-Nilsson Behavioral Dependence Questionnaire (GN-SBQ; 0=lowest, 44=highest)</td>
<td>15.7 (6.5)</td>
<td>16.1 (6.6)</td>
<td>15.9 (6.5)</td>
</tr>
<tr>
<td>Mean Addiction Ladder (0=lowest, 10=highest)</td>
<td>8.6 (1.9)</td>
<td>8.9 (1.2)</td>
<td>8.7 (1.6)</td>
</tr>
<tr>
<td>Mean Addiction Ladder (0=lowest, 10=highest)</td>
<td>24.8 (20.2)</td>
<td>24.0 (23.0)</td>
<td>24.4 (21.4)</td>
</tr>
<tr>
<td>Mean time to first cigarette (TTFC) in minutes</td>
<td>2.4 (1.1)</td>
<td>2.9 (1.0)</td>
<td>2.7 (1.0)</td>
</tr>
<tr>
<td>Mean Intention-to-Quit Ladder (0=lowest, 10=highest)</td>
<td>4.5 (3.5)</td>
<td>4.0 (3.5)</td>
<td>4.3 (3.5)</td>
</tr>
<tr>
<td>Mean cotinine ng/ml</td>
<td>1,327.1 (665.2)</td>
<td>1,266.7 (567.2)</td>
<td>1,298.3 (616.5)</td>
</tr>
<tr>
<td>Mean carbon monoxide (CO) ppm</td>
<td>24.9 (14.0)</td>
<td>22.5 (12.1)</td>
<td>23.8 (13.1)</td>
</tr>
</tbody>
</table>

*Standard deviations in parentheses; CPD=Condition that reduced cigarettes per day; ng/ml=Nanograms per milliliter; ppm=Parts per million; VLNC=Condition that switched to very low nicotine content cigarettes. Responses are from visit 0.
3.2. Nicotine Replacement Therapy (NRT) Patch Compliance

I provided participants with NRT patches to use daily throughout weeks 1 through 4 to help them reduce. Participants reported NRT use on their nightly and weekly surveys. In the VLNC condition, participants used NRT a median of 82% of days and 44% of participants used NRT > 90% of days. In the CPD condition, participants used NRT a median of 95% of days and 56% of participants used NRT > 90% of days. Differences between VLNC and CPD participants were not significant.

3.3. Acceptability Outcomes

I tested percent non-study cigarettes/day and participants’ willingness and ability to smoke the number and type of study cigarettes to determine whether acceptability differed between VLNC vs CPD or over time. When collapsed across time, CPD participants smoked more non-study cigarettes/day and reported that they were less willing and less able to continue smoking their reduced number of cigarettes/day in comparison to VLNC participants (Table 7).

When collapsed across conditions, percent non-study cigarettes/day increased from week 0 to the end of the study period (week 4). Participants’ willingness and ability to continue smoking the number of study cigarettes provided decreased over time. I also tested within-participant changes separately among VLNC and CPD participants. Among VLNC participants, there were no significant changes over time for percent non-study cigarettes/day, willingness or ability to smoke number of cigarettes, or willingness
or ability to smoke type of cigarettes. Among CPD participants there was an increase over time in percent non-study cigarettes/day (F=42.2, p<.001) and decreases in willingness (F=11.1, p<.001) and ability (F=9.8, p<.001) to smoke the number of cigarettes provided. There was no significant change in willingness or ability to smoke the type of cigarettes provided among CPD participants.

There were condition by time interactions where 1) CPD participants’ percent non-study cigarettes/day increased over time while VLNC participants’ did not (Figure 4 and Figure 5), and CPD participants’ willingness (Figure 6) and ability (Figure 7) to continue smoking their reduced number of cigarettes declined over time while VLNC participants’ did not. These interactions remained significant after controlling for participants’ NRT patch use throughout the study period.

I also examined changes in total (study + non-study) cigarettes/day over time to provide context for changes in percent non-study cigarettes/day. Despite the apparent unacceptability among the CPD reduction group, mean total (study + non-study) cigarettes/day decreased by 60% for CPD participants (F=17.9 p<0.001). Also, despite no instructions to reduce number of cigarettes, total cigarettes/day decreased by 19% for VLNC participants (F=8.1 p<0.001; Figure 8).
Table 7: Acceptability outcomes.\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>VLNC vs CPD (collapsed across weeks 1 to 4)</th>
<th>Week (collapsed across condition)</th>
<th>Condition x Week (interaction)</th>
<th>Condition x Week (controlling for NRT patch use)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Non-Study Cigarettes/Day</td>
<td>5.0*</td>
<td>26.3***</td>
<td>8.0***</td>
<td>29.5***</td>
</tr>
<tr>
<td>Willingness to smoke type of cigarette</td>
<td>0.01</td>
<td>0.2</td>
<td>0.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Ability to smoke type of cigarette</td>
<td>0.5</td>
<td>1.0</td>
<td>0.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Willingness to smoke number of cigarettes</td>
<td>10.4**</td>
<td>5.7***</td>
<td>4.0**</td>
<td>6.0***</td>
</tr>
<tr>
<td>Ability to smoke number of cigarettes</td>
<td>16.0***</td>
<td>4.8**</td>
<td>3.5**</td>
<td>4.1***</td>
</tr>
</tbody>
</table>

\(^a\)F values are reported; *p < 0.05; **p < 0.01; ***p < 0.001; CPD=Condition that reduced cigarettes per day; NRT=Nicotine replacement therapy; VLNC=Condition that switched to very low nicotine content cigarettes.
Figure 4: Condition by week interaction predicts percent non-study cigarettes/day: Weekly means from multi-level model.
CPD=Condition that reduced cigarettes per day; nic=Nicotine; VLNC=Condition that switched to very low nicotine content cigarettes.
Figure 5: Condition by week interaction predicts percent non-study cigarettes/day: Daily raw data.
CPD=Condition that reduced cigarettes per day; nic=Nicotine; VLNC=Condition that switched to very low nicotine content cigarettes.
Figure 6: Condition by week interaction predicts willingness to continue smoking the number of cigarettes/day. CPD=Condition that reduced cigarettes per day; nic=Nicotine; VLNC=Condition that switched to very low nicotine content cigarettes.
Figure 7: Condition by week interaction predicts ability to continue smoking the number of cigarettes/day.
CPD=Condition that reduced cigarettes per day; nic=Nicotine; VLNC=Condition that switched to very low nicotine content cigarettes.
Figure 8: Changes in total (study + non-study) cigarettes/day.
CPD=Condition that reduced cigarettes per day; nic=Nicotine; VLNC=Condition that switched to very low nicotine content cigarettes.
3.3.1. Acceptability Outcomes Post-hoc Tests

The difference in missed study visits between VLNC (missed 3% of visits) vs CPD (missed 4% of visits) participants was not significant. I compared VLNC vs CPD participants 1) at the end of the study period (week 4) for all outcomes and 2) at each week when there was a significant condition by time interaction. Percent non-study cigarettes/day and willingness and ability to smoke the number of cigarettes were the only outcomes that differed at week 4 (Table 8). CPD participants’ percent non-study cigarettes/day became significantly greater than VLNC participants at week 3 and continued for the duration of the study period. CPD participants’ reported willingness and ability to smoke their reduced number of cigarettes became significantly less than VLNC participants at week 2 and continued for the duration of the study period.

Table 8: VLNC vs CPD comparisons at each week: Acceptability.a

<table>
<thead>
<tr>
<th></th>
<th>Week 0 (100% nic)</th>
<th>Week 1 (70% nic)</th>
<th>Week 2 (35% nic)</th>
<th>Week 3 (15% nic)</th>
<th>Week 4 (3% nic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent non-study cigarettes/day</td>
<td>0</td>
<td>1.7</td>
<td>2.9†</td>
<td>15.2***</td>
<td>23.0***</td>
</tr>
<tr>
<td>Willingness to smoke number of cigarettes</td>
<td>0.1</td>
<td>1.2</td>
<td>6.8*</td>
<td>10.9**</td>
<td>17.6**</td>
</tr>
<tr>
<td>Ability to smoke number of cigarettes</td>
<td>0.8</td>
<td>4.6†</td>
<td>11.6**</td>
<td>16.8***</td>
<td>16.8***</td>
</tr>
</tbody>
</table>

aF values are reported; † p < 0.1; *p < 0.05; **p < 0.01; ***p < 0.001; CPD=Condition that reduced cigarettes per day; nic=Nicotine; VLNC=Condition that switched to very low nicotine content cigarettes; Only outcomes that had a significant condition by time interaction were tested at each week.

3.3.2. Acceptability Summary

Overall, reduction was more acceptable in the VLNC than CPD group. There was also a significant decline in acceptability for CPD but not VLNC participants as they reduced over time. Reducing became less acceptable to CPD than VLNC participants at week 2 (35% nicotine) for willingness and ability to smoke the number
of study cigarettes and week 3 (15% nicotine) for percent non-study cigarettes/day. Acceptability of switching to VLNC cigarettes did not decline over time. Thus, even with the aid of NRT, reducing CPD became progressively less acceptable while switching to VLNC cigarettes remained an acceptable strategy to reduce nicotine.

3.4. Dependence Outcomes

I tested dependence measures to determine which reduction strategy was more effective and whether the strategies became more effective over time with greater reductions. When collapsed across time, there were no significant differences between VLNC vs CPD participants on any measure of dependence (Table 9).

When collapsed across conditions, dependence decreased from week 0 to the end of the study period on the NDSS Overall Scale, NDSS Drive subscale, FTCD without cigarettes/day, GN-SBQ, TTFC, and Addiction Ladder. I also tested within-participant changes separately among VLNC and CPD participants. Among VLNC participants, there were significant decreases in NDSS Overall Score (F=10.5, p<.001), NDSS Drive subscale (F=16.3, p<.001), FTCD scores without cigarettes/day (F=3.7, p<.05), GN-SBQ (F=6.1, p<.01), TTFC (F=4.8, p<.001), and Addiction Ladder scores (F=7.2, p<.001) over time but not the NDSS Stereotypy, Priority, Tolerance, or Continuity subscales. Among CPD participants there were significant decreases in NDSS Overall Score (F=5.0, p<.01), NDSS Drive subscale (F=3.4, p<.05), GN-SBQ (F=6.0, p<.01), TTFC (F=3.9, p<.01), and Addiction Ladder scores (F=10.2, p<.001) over time but not FTCD scores without cigarettes/day or the NDSS Stereotypy, Priority, Tolerance, or Continuity subscales.
There were condition by time interactions where VLNC participants’
dependence decreased more over time than CPD participants on the NDSS Overall Score
(Figure 9), NDSS Drive subscale (Figure 10), and the Addiction Ladder (Figure 11). The
NDSS Overall Score remained significant after controlling for NRT patch use but was no
longer significant when controlling for percent non-study cigarettes/day. The NDSS
Drive subscale remained significant after controlling for both covariates. The Addiction
Ladder was not significant after controlling for either covariate.
Table 9: Dependence outcomes.*

<table>
<thead>
<tr>
<th></th>
<th>VLNC vs CPD (collapsed across weeks 1 to 4)</th>
<th>Week (collapsed across condition)</th>
<th>Condition x Week (interaction)</th>
<th>Condition x Week (controlling for NRT patch use)</th>
<th>Condition x Week (controlling for percent non-study cigarette/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDSS Overall Score</td>
<td>0</td>
<td>13.9***</td>
<td>3.2*</td>
<td>3.0*</td>
<td>1.0</td>
</tr>
<tr>
<td>NDSS Stereotypy Subscale</td>
<td>1.0</td>
<td>1.4</td>
<td>0.8</td>
<td>0.9</td>
<td>0.2</td>
</tr>
<tr>
<td>NDSS Priority Subscale</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.3</td>
<td>0.7</td>
</tr>
<tr>
<td>NDSS Tolerance Subscale</td>
<td>1.4</td>
<td>0.9</td>
<td>0.1</td>
<td>0.3</td>
<td>0.7</td>
</tr>
<tr>
<td>NDSS Continuity Subscale</td>
<td>3.4†</td>
<td>0.8</td>
<td>0.7</td>
<td>0.5</td>
<td>1.2</td>
</tr>
<tr>
<td>NDSS Drive Subscale</td>
<td>0.5</td>
<td>14.7***</td>
<td>3.3*</td>
<td>3.5*</td>
<td>5.1**</td>
</tr>
<tr>
<td>FTCD without cigarettes/day</td>
<td>0.1</td>
<td>4.4**</td>
<td>0.5</td>
<td>0.4</td>
<td>1.2</td>
</tr>
<tr>
<td>GN-SBQ</td>
<td>0</td>
<td>12.8***</td>
<td>0.1</td>
<td>0.2</td>
<td>1.2</td>
</tr>
<tr>
<td>TTFC</td>
<td>0.2</td>
<td>7.6***</td>
<td>1.1</td>
<td>0.4</td>
<td>1.9</td>
</tr>
<tr>
<td>Addiction Ladder</td>
<td>0</td>
<td>24.1***</td>
<td>2.4*</td>
<td>1.8</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*F values are reported; †p < 0.1; *p < 0.05; **p < 0.01; ***p < 0.001; CPD=Condition that reduced cigarettes per day; FTCD=Fagerstrom test for cigarette dependence; GN-SBQ=Glover-Nilsson Smoking Behavior Questionnaire; NDSS=Nicotine dependence syndrome scale; NRT=Nicotine replacement therapy; TTFC=Time to first cigarette; VLNC=Condition that switched to very low nicotine content cigarettes.
Figure 9: Condition by week interaction predicts NDSS Overall Score.

CPD=Condition that reduced cigarettes per day; NDSS=Nicotine Dependence Syndrome Scale; nic=Nicotine; VLNC=Condition that switched to very low nicotine content cigarettes.
Figure 10: Condition by week interaction predicts NDSS Drive subscale score.
CPD=Condition that reduced cigarettes per day; NDSS=Nicotine Dependence Syndrome Scale; nic=Nicotine; VLNC=Condition that switched to very low nicotine content cigarettes.
Figure 11: Condition by week interaction predicts Addiction Ladder.
CPD=Condition that reduced cigarettes per day; nic=Nicotine; VLNC=Condition that switched to very low nicotine content cigarettes.
3.4.1. Dependence Outcomes Post-hoc Tests

The NDSS Drive subscale was the only measure where participants differed significantly at week 4: VLNC participants had significantly less dependence than CPD participants. Differences between VLNC and CPD participants were not significant at any single week in my post-hoc comparisons of dependence on the NDSS Overall Scale and Addiction Ladder (Table 10).

<table>
<thead>
<tr>
<th>Week</th>
<th>NDSS Overall Score</th>
<th>NDSS Drive</th>
<th>Addiction Ladder</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0.2</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0.1</td>
<td>0.3</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>1.2</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>2.9†</td>
<td>7.3*</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Table 10: VLNC vs CPD comparisons at each week: Dependence.a

F values are reported; †p < 0.1; *p < 0.05; **p < 0.01; ***p < 0.001; CPD=Condition that reduced cigarettes per day; NDSS=Nicotine dependence syndrome scale; nic=Nicotine; VLNC=Condition that switched to very low nicotine content cigarettes. Only outcomes that had a significant condition by time interaction were tested at each week.

3.4.2. Dependence Summary

There were no overall differences in dependence between switching to VLNC cigarettes vs reducing CPD. However, dependence significantly declined over time for both groups on most measures. On my primary and two secondary measures of dependence, there were interactions in which dependence decreased more over time for VLNC than CPD participants. This effect appeared largest on the NDSS Drive subscale which measured craving, withdrawal, and compulsion to smoke. Thus, with the aid of NRT, both VLNC and CPD conditions decreased dependence. However, switching to VLNC cigarettes appears more effective at decreasing dependence at greater magnitudes of reduction.
3.5. Biomarker Outcomes

I tested cotinine to determine which reduction strategy was more effective at decreasing nicotine exposure and whether nicotine exposure decreased more over time. Nicotine was supplemented via NRT patch during weeks 1 through 4 but this did not differ by week or condition. I tested CO to determine which reduction strategy decreased smoke exposure more and whether this changed over time. Importantly, CPD participants were, but VLNC participants were not instructed to reduce smoking. When collapsed across time, cotinine values were significantly less for VLNC than CPD participants (Table 11). In contrast, CO values were significantly less for CPD than VLNC participants.

When collapsed across conditions, both cotinine and CO decreased over time. I also tested within-participant changes separately among VLNC and CPD participants. Among VLNC participants, both cotinine (F=9.9, p<.001) and CO (F=2.7, p<.05) declined over time. Among CPD participants, cotinine increased, not decreased, over time (F=2.5, p<.05) and CO decreased over time (F=5.8, p<.001).

There were condition by time interactions where 1) cotinine decreased for VLNC participants but increased for CPD participants over time (Figure 12) and 2) CPD participants’ CO values decreased more at weeks 1 to 3 than VLNC participants (Figure 13). The condition by time interactions for both cotinine and CO remained significant after controlling for NRT patch use but were no longer significant when controlling for percent non-study cigarettes/day.
Table 11: Biomarker outcomes.a

<table>
<thead>
<tr>
<th></th>
<th>VLNC vs CPD (collapsed across weeks 1 to 4)</th>
<th>Week (collapsed across condition)</th>
<th>Condition x Week (interaction)</th>
<th>Condition x Week (controlling for NRT patch use)</th>
<th>Condition x Week (controlling for percent non-study cigarette/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cotinine</td>
<td>8.3**</td>
<td>5.3***</td>
<td>7.7***</td>
<td>9.3**</td>
<td>2.3†</td>
</tr>
<tr>
<td>CO</td>
<td>4.9*</td>
<td>4.3**</td>
<td>3.3*</td>
<td>3.0*</td>
<td>1.6</td>
</tr>
</tbody>
</table>

F values are reported; †p < 0.1; *p < 0.05; **p < 0.01; ***p < 0.001; CO=Carbon monoxide; CPD=Condition that reduced cigarettes per day; NRT=Nicotine replacement therapy; VLNC=Condition that switched to very low nicotine content cigarettes.
Figure 12: Condition by week interaction predicts cotinine.
CPD=Condition that reduced cigarettes per day; ng/ml=Nanograms per milliliter; nic=Nicotine; VLNC=Condition that switched to very low nicotine content cigarettes.
Figure 13: Condition by week interaction predicts carbon monoxide (CO).
CPD=Condition that reduced cigarettes per day; nic=Nicotine; ppm=Parts per million; VLNC=Condition that switched to very low nicotine content cigarettes.
3.5.1. Biomarker Outcomes Post-hoc Tests

Cotinine values for VLNC participants became significantly lower than CPD participants at week 2 and remained lower for the rest of the study period (Table 12). In contrast, CO was significantly lower for CPD than VLNC participants between weeks 1 through 3 only.

Table 12: VLNC vs CPD comparisons at each week: Biomarkers.a

<table>
<thead>
<tr>
<th></th>
<th>Week 0</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(100% nic)</td>
<td>(70% nic)</td>
<td>(35% nic)</td>
<td>(15% nic)</td>
<td>(3% nic)</td>
</tr>
<tr>
<td>Cotinine</td>
<td>0.2</td>
<td>0.3</td>
<td>4.8*</td>
<td>12.3**</td>
<td>20.3***</td>
</tr>
<tr>
<td>CO</td>
<td>0.5</td>
<td>4.8*</td>
<td>6.3*</td>
<td>4.4*</td>
<td>0.6</td>
</tr>
</tbody>
</table>

*F values are reported; *p < 0.05; **p < 0.01; ***p < 0.001; CO=Carbon monoxide; CPD=Condition that reduced cigarettes per day; nic=Nicotine; VLNC=Condition that switched to very low nicotine content cigarettes; Only outcomes that had a significant condition by time interaction were tested at each week.

3.5.2. Biomarker Summary

Switching to VLNC cigarettes effectively reduced nicotine exposure (as measured by cotinine). In contrast reducing CPD increased, not decreased, nicotine exposure. Differences between VLNC and CPD participants’ cotinine became apparent at week 2 when participants were instructed to reduce to 35% of their nicotine intake.

Smoke exposure (as measured by CO) decreased more for CPD than VLNC participants. This difference was expected because the CPD reduction strategy required a decrease in smoking while switching to VLNC cigarettes did not. Smoke exposure decreased over time for both groups but decreased more for CPD participants. Post-hoc comparisons indicate CPD participants had lower CO than VLNC participants only during weeks 1 through 3.
3.6. Quit Attempts and Cessation Measures

3.6.1. Self-Efficacy and Intention to Quit

I tested which reduction strategy increased self-efficacy (SEQ) and intention to quit more and whether this increased over time. When collapsed across time, neither SEQ nor intention to quit significantly differed between VLNC vs CPD conditions (Table 13).

When collapsed across conditions, intention to quit increased over time but there was no significant change in self-efficacy. I also tested within-participant changes separately among VLNC and CPD participants. Among VLNC participants, both self-efficacy (F=5.3, p<.01) and intention to quit (F=10.8, p<.001) increased over time. Among CPD participants intention to quit increased over time (F=3.2, p<.05) but self-efficacy did not.

There was a significant condition by time interaction where self-efficacy to quit increased over time for VLNC but not CPD participants (Figure 14). This effect remained significant after controlling for NRT patch use but not when controlling for percent non-study cigarettes/day.
<table>
<thead>
<tr>
<th></th>
<th>VLNC vs CPD (collapsed across weeks 1 to 4)</th>
<th>Week (collapsed across condition)</th>
<th>Condition x Week (interaction)</th>
<th>Condition x Week (controlling for NRT patch use)</th>
<th>Condition x Week (controlling for percent non-study cigarette/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Self-Efficacy to Quit (SEQ)</strong></td>
<td>1</td>
<td>1.6</td>
<td>3.7**</td>
<td>4.0**</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Intention-to-Quit Ladder</strong></td>
<td>3.2†</td>
<td>12.3***</td>
<td>1.3</td>
<td>1.1</td>
<td>2.3†</td>
</tr>
</tbody>
</table>

*aF values are reported; †p < 0.1; *p < 0.05; **p < 0.01; ***p < 0.001; CPD=Condition that reduced cigarettes per day; NRT=Nicotine replacement therapy; VLNC=Condition that switched to very low nicotine content cigarettes.*
Figure 14: Condition by week interaction predicts self-efficacy to quit.
CPD=Condition that reduced cigarettes per day; nic=Nicotine; VLNC=Condition that switched to very low nicotine content cigarettes.
3.6.2. Self-Efficacy and Intention to Quit Post-hoc Tests

Self-efficacy to quit became significantly greater for VLNC than CPD participants at week 4 (Table 14). Though the condition by week interaction was not significant, intention to quit was also greater for VLNC than CPD participants at week 4 (F=6.2, p<.05).

Table 14: VLNC vs CPD comparisons at each week: Self-efficacy and intention to quit.a

<table>
<thead>
<tr>
<th></th>
<th>Week 0 (100% nic)</th>
<th>Week 1 (70% nic)</th>
<th>Week 2 (35% nic)</th>
<th>Week 3 (15% nic)</th>
<th>Week 4 (3% nic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-Efficacy</td>
<td>2.3</td>
<td>0</td>
<td>0</td>
<td>1.7</td>
<td>9.6**</td>
</tr>
<tr>
<td>to Quit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aF values are reported; *p < 0.05; **p < 0.01; ***p < 0.001; CPD=Condition that reduced cigarettes per day; nic=Nicotine; VLNC=Condition that switched to very low nicotine content cigarettes; Only outcomes that had a significant condition by time interaction were tested at each week.

3.6.3. Plan to Quit, Quit Attempts, and Abstinence

In a series of logistic regressions I tested whether more VLNC vs CPD participants made a plan to quit tomorrow, any QA (including very short attempts), and ≥ 24 hour QA. More participants in the CPD condition (41%) than VLNC condition (17%) made any QA between weeks 1 through 4 (OR=3.3, 95% CI=1.04, 10.13). Differences between the number of VLNC vs CPD participants who made a plan to quit tomorrow (VLNC=56%, CPD=59%) or made a ≥ 24 hour QA (VLNC=19%, CPD=16%) were not significant. One CPD participant and no VLNC participants were 7-day point-prevalence abstinent at the end of the study period.

In a series of survival analyses, I tested whether time to first plan to quit, any QA (including very short attempts), and ≥ 24 hour QA differed between conditions.
from week 1 to 4. Time to first any QA was significantly shorter for the CPD than the VLNC condition (Figure 15). This effect remained after controlling for NRT patch use and percent non-study cigarettes/day throughout the study period (Table 15).

Table 15: Time to first plan to quit and quit attempt.*

<table>
<thead>
<tr>
<th></th>
<th>Cox Hazard Ratio (95% CI)</th>
<th>Cox Hazard Ratio Adjusted for NRT Patch Use (95% CI)</th>
<th>Cox Hazard Ratio Adjusted for Percent Non-Study Cigarettes/Day (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plan to Quit</td>
<td>1.6 (0.8, 3.1)</td>
<td>1.7 (0.9, 3.2)</td>
<td>1.6 (0.8, 3.3)</td>
</tr>
<tr>
<td>Any QA</td>
<td>3.2 (1.2, 8.2)</td>
<td>3.1 (1.2, 8.1)</td>
<td>5.1 (1.5 17.7)</td>
</tr>
<tr>
<td>≥ 24 hour QA</td>
<td>1.9 (0.4, 3.7)</td>
<td>1.8 (0.4, 8.2)</td>
<td>1.9 (0.4, 8.3)</td>
</tr>
</tbody>
</table>

*VLNC condition is the reference group; CI=Confidence interval; QA=Quit attempt.

I excluded QAs made during week 0 from my primary analyses because reduction did not begin until week 1. Two CPD participants and no VLNC participants made any QA and no participants made a ≥ 24 hour QA during week 0. Findings from sensitivity analyses that included the two participants who made a QA during week 0 were similar to my primary findings reported above.
Figure 15: Condition predicts time to first any quit attempt.
CPD=Condition that reduced cigarettes per day; QA=Quit attempt; VLNC=Condition that switched to very low nicotine content cigarettes.
3.6.4. Quit Attempts and Cessation Measures Summary

Overall, more CPD than VLNC participants made a QA that lasted any length of time and there was a shorter time to first any QA among CPD than VLNC participants. There were no significant differences between conditions in number of participants who made a plan to quit tomorrow, number of participants who made a QA that lasted ≥ 24 hours, number of participants who were 7-day point prevalence abstinent, self-efficacy to quit, or intention to quit. Intention to quit increased over time for both groups and self-efficacy increased for VLNC but not CPD participants.

3.7. One-Month Follow-Up Outcomes

3.7.1. Dependence, Self-Efficacy to Quit, and Intention to Quit at Follow-Up

See Appendix Table 1 for participants’ smoking characteristics at follow-up. Forty (59%) participants responded to the follow-up survey. Missing data did not significantly differ by condition. None of the dependence, self-efficacy, or intention to quit measures significantly differed between VLNC vs CPD conditions at follow-up (Table 16).

When collapsed across conditions, intention to quit decreased from week 4 to the follow-up. I also tested within-participant changes separately among VLNC and CPD participants. Among VLNC participants, intention to quit decreased from week 4 to follow-up (F=4.4, p<.05) but there were no changes in dependence, cigarettes/day, or self-efficacy. Among CPD participants, cigarettes/day increased from week 4 to follow-
up (F=5.9, p<.05) but there were no changes in the dependence, self-efficacy, or intention to quit measures.

There was a condition by time interaction where mean total cigarettes/day increased in the CPD group but did not change significantly for the VLNC group from week 4 to the follow-up (Figure 16). This effect remained significant after controlling for NRT patch distribution and use during the follow-up period (Table 16).
<table>
<thead>
<tr>
<th></th>
<th>VLNC vs CPD at Follow-Up</th>
<th>Time (Week 4 to Follow-Up)</th>
<th>Condition x Time (interaction)</th>
<th>Condition x Time (controlling for NRT patch use)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cigarettes/Day</td>
<td>2.0</td>
<td>0.2</td>
<td>7.3**</td>
<td>6.7*</td>
</tr>
<tr>
<td>NDSS Overall Score</td>
<td>0.1</td>
<td>1.1</td>
<td>0.3</td>
<td>0.1</td>
</tr>
<tr>
<td>FTCD without cigarettes/day</td>
<td>1.7</td>
<td>2.2</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>GN-SBQ</td>
<td>0.1</td>
<td>0</td>
<td>0.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Addiction Ladder</td>
<td>0.9</td>
<td>3.4†</td>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>Self-Efficacy to Quit</td>
<td>0.1</td>
<td>3.5†</td>
<td>1.1</td>
<td>1.2</td>
</tr>
<tr>
<td>Intention-to-Quit Ladder</td>
<td>0.1</td>
<td>4.2*</td>
<td>0.7</td>
<td>0.6</td>
</tr>
</tbody>
</table>

*F* values are reported; †p < 0.1; *p < 0.05; **p < 0.01; ***p < 0.001; CPD = Condition that reduced cigarettes per day; FTCD = Fagerstrom test for cigarette dependence; GN-SBQ = Glover-Nilsson Smoking Behavior Questionnaire; NDSS = Nicotine dependence syndrome scale; NRT = Nicotine replacement therapy; VLNC = Condition that switched to very low nicotine content cigarettes.
Figure 16: Condition by time interaction predicts change in total cigarettes/day from week 4 to follow up. CPD=Condition that reduced cigarettes per day; VLNC=Condition that switched to very low nicotine content cigarettes.
3.7.2. Quit Attempts and Cessation at Follow-Up

Most participants set a quit date and requested NRT patches at their final study visit (visit 4). There were no differences between VLNC vs CPD conditions in prolonged abstinence, point-prevalence abstinence, or QAs at follow-up (Table 17).

Table 17: Quit attempts and cessation at follow-up.*

<table>
<thead>
<tr>
<th></th>
<th>VLNC</th>
<th>CPD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=36)</td>
<td>(n=32)</td>
<td>(N=68)</td>
</tr>
<tr>
<td>Number completed follow-up survey</td>
<td>23 (64%)</td>
<td>17 (53%)</td>
<td>40 (59%)</td>
</tr>
<tr>
<td>Number who set a quit date at final study visit (visit 4)</td>
<td>18 (50%)</td>
<td>13 (41%)</td>
<td>31 (46%)</td>
</tr>
<tr>
<td>Number 30-day prolonged abstinent (PA)</td>
<td>5 (14%)</td>
<td>2 (6%)</td>
<td>7 (10%)</td>
</tr>
<tr>
<td>Number 7-days point-prevalence abstinent (PPA)</td>
<td>6 (17%)</td>
<td>4 (13%)</td>
<td>10 (15%)</td>
</tr>
<tr>
<td>Number made a QA ≥ 24 hours</td>
<td>10 (28%)</td>
<td>4 (13%)</td>
<td>14 (21%)</td>
</tr>
<tr>
<td>Number made any QA</td>
<td>16 (44%)</td>
<td>10 (31%)</td>
<td>26 (38%)</td>
</tr>
</tbody>
</table>

*Percents are calculated from total sample of participants; CPD=Condition that reduced cigarettes per day; QA=Quit attempt; VLNC=Condition that switched to very low nicotine content cigarettes.

3.7.3. Change from Pre-Study to Follow-Up

Among participants who responded to the follow-up survey (N=40), mean total cigarettes/day decreased from 19.3 (SD=9.4) during the week prior to entering the study (i.e., pre-study) to 13.9 (SD=9.0) at follow-up (F=6.0, p<.05). Mean self-efficacy to quit (1=lowest, 5=highest) increased from 2.2 (SD=0.8) to 2.8 (SD=0.8; F=6.5, p<.05) and mean intention to quit in the next 30 days (0=least, 10=most) increased from 3.6 (SD=3.1) to 5.2 (SD=3.3; F=4.6, p<.05). The degree to which participants smoked menthol cigarettes (i.e., percent of cigarettes/day that are mentholated) did not change over time or differ by condition. There were no significant condition by time interactions.
3.8. Adverse Events

There were 70 moderate or mild adverse events (e.g., trouble sleeping) reported on 38 of the 408 study visits. There were no serious adverse events (SAE) reported during the study period or follow-up that could have plausibly been related to study participation.
CHAPTER 4: DISCUSSION

4.1. Summary of Findings

I encourage readers to refer to Table 18 for a full summary of my findings. Briefly, switching to VLNC cigarettes was more acceptable than reducing CPD when both were aided by NRT. Acceptability declined for CPD participants over time as they were instructed to reduce down to 3% of their baseline nicotine. The equivalent reduction remained acceptable for VLNC participants throughout the study period. Dependence declined throughout the study period for both groups and appeared to decline more for VLNC participants as they were instructed to reduce more nicotine. Biomarker findings indicate that VLNC participants had less nicotine exposure (i.e., less cotinine) while CPD participants had less smoke exposure (i.e., less CO). Intention to quit increased over time for both groups while self-efficacy increased over time for VLNC but not CPD participants. More participants in the CPD condition made any QA and they had a shorter time to their first QA than VLNC participants.
Table 18: Summary of findings.

<table>
<thead>
<tr>
<th></th>
<th>Between-Participant VLNC vs CPD</th>
<th>Within-Participant VLNC</th>
<th>CPD</th>
<th>Condition x Time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Findings</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Acceptability:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Which strategy was more acceptable and did this change over time?</td>
<td>VLNC &gt; CPD on 3 of 5 measures</td>
<td>↓ over time on 3 of 5 measures</td>
<td></td>
<td>CPD ↓ over time and VLNC did not on 3 of 5 measures</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>↓ over time on 5 of 5 measures</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ over time on 4 of 5 measures</td>
<td>+ 1 subscale</td>
<td>VLNC ↓ more than CPD over time on 2 of 5 measures + 1 subscale</td>
</tr>
<tr>
<td><strong>Dependence:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Which strategy decreased dependence more and did this change over time?</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>↑ over time on 5 of 5 measures</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ over time on 4 of 5 measures</td>
<td>+ 1 subscale</td>
<td>CPD ↓ more than VLNC at weeks 1, 2, and 3 only</td>
</tr>
<tr>
<td><strong>Secondary Findings</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Biomarkers:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Which strategy reduced biomarkers more and did this change over time?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cotinine</td>
<td>CPD &gt; VLNC</td>
<td>-</td>
<td>↑ over time</td>
<td>VLNC ↓ and CPD ↑ over time</td>
</tr>
<tr>
<td>Carbon monoxide (CO)</td>
<td>VLNC &gt; CPD</td>
<td>-</td>
<td>↓ over time</td>
<td>CPD ↓ more than VLNC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
<td>↓ over time</td>
<td>at weeks 1, 2, and 3 only</td>
</tr>
<tr>
<td><strong>Quitting:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Which strategy increased measures of quitting more and did this change over time?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-efficacy to quit</td>
<td>-</td>
<td>↑ over time</td>
<td>-</td>
<td>VLNC ↑ over time and CPD did not</td>
</tr>
<tr>
<td>Intention to quit</td>
<td>-</td>
<td>↑ over time</td>
<td>↑ over time</td>
<td>-</td>
</tr>
<tr>
<td>Participants with a plan to quit tomorrow</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Participants with any QA</td>
<td>CPD &gt; VLNC</td>
<td>CPD participants had a shorter time to first any QA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants with ≥ 24 hour QA</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

CPD=Condition instructed to reduce cigarettes/day; QA=Quit attempt; VLNC=Condition instructed to switch to very low nicotine content cigarettes.
4.2. Interpretation

Instructions to make large reductions in nicotine (i.e., 97%) were more acceptable via switching to VLNC cigarettes than reducing CPD when both were aided by NRT. Reducing CPD emerged as a less acceptable strategy than switching to VLNC cigarettes only after instructions to reduce down to ≤ 35% of baseline nicotine. One interpretation is that it was less acceptable for smokers to inhibit responses to cues to smoke (i.e., reduce CPD) than to reduce the magnitude of the unconditioned reinforcer (nicotine) without restricting their smoking behavior (i.e., switching to VLNC cigarettes). Further, reducing the magnitude of the unconditioned reinforcer (i.e., nicotine) without restricting responses to cues to smoke (i.e., switching to VLNC cigarettes) remained acceptable throughout the study period. For example, VLNC participants’ non-study cigarettes/day and willingness and ability to smoke study cigarettes did not significantly change from ad-lib smoking at week 0 to smoking cigarettes with 3% nicotine content at week 4.

Dependence declined over time for both groups despite the finding that cotinine decreased for VLNC but not CPD participants. Thus, decreases in dependence do not necessarily appear to be due to changes in the total amount of nicotine intake per se. Instead, decreases in dependence could be due to changes in conditioning or smoking behavior. VLNC participants could have decreased dependence by engaging in smoking behavior with diminished unconditioned reward (i.e., less nicotine) and thus disrupting operant and Pavlovian conditioning. CPD participants could have decreased dependence by increasing practice not responding to cues to smoke (i.e., fewer cigarettes/day) and
thus decreasing their frequency of exposure to conditioned and unconditioned reinforcers from smoking. Though there is no prior research that suggests NRT per se decreases dependence, NRT patch use could have contributed to a decrease in dependence in both conditions. NRT could have helped to decrease dependence by providing a steady state of nicotine independent of smoking and thus disrupting associations between cigarettes and nicotine. The finding that decreases in dependence appeared greater for VLNC than CPD participants could have been because reducing CPD became less acceptable and thus less effective over time. This interpretation is supported by the finding that the time by condition interaction was no longer significant on two of three measures of dependence after controlling for percent non-study cigarettes/day (i.e., acceptability).

With regard to dependence, the condition by time interaction was most pronounced on the NDSS Drive subscale (which assessed craving, withdrawal, and compulsion to smoke) and remained significant after controlling for percent non-study cigarettes/day. This finding appears consistent with animal research that suggests extinction occurs when an organism responds to stimulus cues in the absence of a reinforcer (i.e., smoking without nicotine) but not when prevented from responding to cues (i.e., not smoking) (Bouton, Trask, & Carranza-Jasso, 2016). In other words, by smoking cigarettes with low nicotine, VLNC participants could have learned that smoking in response to stimulus cues was associated with less pharmacological reward (nicotine) and thus experienced a decrease in the drive to smoke. In contrast, CPD participants could have learned to resist the drive to smoke in response to stimulus cues with less actual change in the drive to smoke per se. However, differences between VLNC and CPD participants were not significant on multiple secondary measures of
dependence. It is particularly surprising that there were no between group differences on the dependence scales that focus on behavioral aspects of dependence (e.g., the GN-SBQ, or the NDSS Continuity and Stereotypy subscales) because the CPD reduction strategy targeted change in smoking behavior while the VLNC strategy did not.

Cotinine decreased for VLNC participants but unexpectedly increased for CPD participants over time. Thus, when both were aided by NRT, switching to VLNC cigarettes was effective at reducing overall nicotine exposure, but reducing CPD was not. Importantly, the increase in cotinine among CPD participants conflicts with prior findings (Hughes & Carpenter, 2005) and thus requires replication and should be interpreted with caution. One potential explanation for this finding could be that a combination of NRT use and compensatory smoking (i.e., smoking remaining cigarettes more vigorously) could have contributed to an increase in nicotine exposure despite CPD participants’ reduction (mean 60%) in total cigarettes/day. A prior study estimated that daily NRT patch use provides approximately 50% of the nicotine that would be obtained from heavy smoking (Hurt et al., 1993). In this trial, NRT’s influence on cotinine levels is supported by the observation that cotinine appears to have increased from week 0 to week 1 for both groups (see Figure 12) when participants began using NRT patches. However, differences between VLNC vs CPD participants’ cotinine over weeks 0 to 4 remained after controlling for NRT, and NRT use did not differ between groups. Thus differences between VLNC and CPD participants’ nicotine exposure appear to be due to more than NRT use per se. With regard to compensatory smoking, a prior review (Hughes & Carpenter, 2005) estimated that 33% compensation occurs when reducing CPD with the aid of NRT, but found compensation as high as 64% in some cases (Rennard et al., 1994).
In my trial, CO (another biomarker used to assess compensatory smoking) decreased for CPD participants over time which suggests that, while some compensation likely occurred, it was not enough to offset all biomarkers. Thus, though changes in cotinine were likely influenced by a combination of NRT use plus some compensatory smoking, it is unclear why cotinine decreased for VLNC but increased for CPD participants over time.

Both VLNC and CPD participants reduced CO over time. However, CPD participants had greater reductions in CO. This is not surprising given that CPD participants were instructed to reduce their smoking while VLNC participants were not. The reduction in CO reflects CPD participants’ mean 60% reduction in total cigarettes/day. VLNC participants’ reduction in CO reflects their mean 19% reduction in total cigarettes/day and suggests that NRT-aided transitions to VLNC cigarettes also prompts a reduction in smoke exposure despite no instructions to reduce cigarettes/day. Further, VLNC participants’ reductions in CO supports a prior review on compensatory smoking (Hatsukami et al., 2015) and suggests gradual transitions to VLNC cigarettes do not result in compensation when aided by NRT. Differences in CO between CPD and VLNC participants diminished at week 4. This could be due to an increase in CPD participants’ non-study cigarettes, a decrease in VLNC participants’ total cigarettes/day, or both.

Importantly, neither condition by time interaction for cotinine or CO was significant after controlling for percent non-study cigarettes/day (i.e., acceptability).
Thus, differences in nicotine and smoke exposure were likely influenced by differences in acceptability.

Another unexpected finding was that self-efficacy to quit increased in the VLNC and not CPD group, but more CPD than VLNC participants attempted to quit. One explanation for the self-efficacy finding is that, despite substantial reductions in cigarettes/day (i.e., 60%), most CPD participants’ did not achieve the trial’s large reduction goals (i.e., 97%). Thus, the failure to achieve study goals may have served as a barrier to building self-efficacy to quit. Quitting requires not smoking in response to environmental or internal cues. Thus, the fact that CPD participants had more practice not smoking in the presence of cues to smoke could have prompted them to make more QAs than VLNC participants. Condition’s effect on making any QA remained after controlling for percent non-study cigarettes/day, which suggests findings were not due to differences in acceptability. It is unclear why the CPD intervention increased QAs but not self-efficacy to quit. Further, there were no between-group differences in ≥ 24 hour QAs or longer periods of abstinence. This could be because factors that influence quit attempts differ from those that influence ability to remain abstinent (Vangeli, Stapleton, Smit, Borland, & West, 2011).

At follow-up, there was a time by condition interaction in which total cigarettes/day did not significantly change for VLNC participants but increased for CPD participants from week 4 to follow-up. One interpretation is that VLNC participants reverted to comfortable levels of nicotine intake while CPD participants reverted to comfortable frequencies of smoking behavior. VLNC participants who continued to
smoke after the study period had to switch from study cigarettes with 3% nicotine to full nicotine commercial cigarettes because VLNC cigarettes are not commercially available. Thus, it is likely that VLNC participants increased their nicotine intake to levels more similar to baseline despite a non-significant decrease in number of cigarettes/day from week 4 to follow-up. CPD participants significantly increased their smoking from a mean 8.5 cigarettes/day (40% of baseline) to 16.5 cigarettes/day (78% of baseline). Thus CPD participants appeared to have reverted to smoking behavior more similar to baseline.

4.3. Comparison to Prior Reduction Studies

This is the first trial to directly compare switching to VLNC cigarettes vs reducing CPD. Thus, comparison to prior studies is limited to my within-participant findings in the VLNC and CPD conditions. In terms of VLNC cigarettes’ acceptability, one prior trial of gradual transitions reported participants smoked a mean 20% non-study cigarettes/day when they were instructed to switch to VLNC cigarettes with 0.6 mg/g nicotine (Hammond & O'Connor, 2014). Similarly, in the present study participants smoked a mean 21% non-study cigarettes/day when they were instructed to smoke study cigarettes containing 0.4 mg/g nicotine. My finding that dependence decreased over time among participants who switch to VLNC cigarettes is consistent with the four prior trials of progressive transitions to VLNC cigarettes that measured dependence (Benowitz et al., 2009, 2012; Benowitz et al., 2007; Hammond & O'Connor, 2014). In terms of biomarkers, my findings replicated results from the five prior VLNC trials that measured change in cotinine: all found significant declines as participants transitioned to progressively lower nicotine content cigarettes (Benowitz et al., 2009, 2012; Benowitz et
In contrast to my finding that CO declined for VLNC participants, two prior trials found small increases in CO (Benowitz et al., 2012; Mercincavage et al., 2016) and one found no change (Hammond & O'Connor, 2014) over time. Differences may have been due to the fact that I provided NRT, which likely decreased compensatory smoking, but the prior trials did not. In terms of self-efficacy to quit, my results were consistent with two trials’ findings that switching to VLNC cigarettes increased self-efficacy (Benowitz et al., 2009; Benowitz et al., 2007). However a third trial of switching to progressively lower nicotine VLNC cigarettes did not find changes in self-efficacy (Benowitz et al., 2012). No prior trials of gradual transitions to VLNC cigarettes reported on intention to quit or QAs. Two studies found that 24% (Benowitz et al., 2007) and 10% (Benowitz et al., 2009) of participants achieved point-prevalence abstinence at a 30-day follow-up. In my trial 17% of VLNC participants achieved 7-day point-prevalence abstinence and 14% achieved 30-day prolonged abstinence at the 1-month follow-up.

Comparison between the CPD condition in my trial and prior trials of reduction in CPD are limited due to multiple methodological differences. For example, I set a large reduction goal for CPD participants to be comparable to equivalent reductions in nicotine using VLNC cigarettes. In contrast, prior trials either set smaller (e.g., 50% reduction) or no reduction goals. Acceptability was not directly measured in prior reduction trials. CPD participants in my trial reduced more total cigarettes/day (60%) than most (Hughes, 2000; Hughes & Carpenter, 2005) but not all (Stein et al., 2002) prior NRT-aided reduction trials for smokers not ready to quit. My finding that CPD participants decreased dependence over time is consistent with all four of the prior reduction studies that
measured dependence (Etter et al., 2002; Fagerstrom et al., 2002; Klemperer et al., 2015; Mooney et al., 2011). In terms of biomarkers, my finding that cotinine increased over time conflicts with findings from a prior review (Hughes & Carpenter, 2005) and thus requires replication. In contrast, my finding that CO decreased over time is consistent with conclusions from the same review (Hughes & Carpenter, 2005). In terms of self-efficacy and intention to quit, two prior trials found that interventions to reduce CPD resulted in increases in both (Carpenter et al., 2004; Klemperer et al., 2017). In this trial, I used the same measures and found that intention to quit increased among CPD participants but self-efficacy did not. One explanation for differences in self-efficacy is that prior trials instructed participants to set achievable goals to reduce CPD with the rationale that this could enhance self-efficacy to quit (Carpenter et al., 2004; Klemperer et al., 2017). As previously discussed, I set a very ambitious reduction goal for participants, which the majority of participants did not achieve.

Two prior trials tested CPD reduction interventions and found 47% and 54% made any QA and 31% and 43% made a QA that lasted ≥ 24 hours over the course of 6 months (Carpenter et al., 2004; Klemperer, Hughes, Solomon, Callas, & Fingar, 2016). In contrast, I assessed quitting over a 1-month period and found fewer made any QA (41%) or a QA that lasted ≥ 24 hours (16%). Differences are likely due to the fact that my trial measured quitting over a shorter duration than prior trials. Trials included in prior reviews on NRT-aided reduction for smokers not ready to quit varied in treatment length and duration of follow-up and found a range of abstinence from 1% to 35% (Asfar et al., 2011; Hughes & Carpenter, 2006; Moore et al., 2009; Wu et al., 2015). The trial that was most similar to mine in duration (1 month) found 5% of participants quit at some point.
during the study period and 2% were abstinent at a 1-month follow-up (Fagerstrom, Tejding, Ake, & Lunell, 1997). In my study 13% of CPD participants were 7-day point-prevalence abstinent and 6% achieved 30-day prolonged abstinence at the 1-month follow-up.

4.4. Implications

4.4.1. Policy Implications

My findings suggest that a policy to reduce cigarettes’ nicotine content could provide smokers not ready to quit with a more acceptable and effective strategy to reduce nicotine intake than the commonly used strategy of reducing CPD. Moreover such a policy could also provide smokers with a more effective strategy to reduce dependence. Importantly, it is unclear whether future tobacco regulation will require abrupt switching to the lowest level VLNC cigarettes or allow for a gradual transition to VLNC cigarettes with progressively less nicotine. My within-participant findings for the VLNC condition suggest that policies that allow for or require gradual transitions to VLNC cigarettes could provide an acceptable strategy for smokers not ready to quit to decrease dependence, cotinine, and CO and increase self-efficacy and intention to quit. However, my findings and others’ (Donny et al., 2015) demonstrate that the greatest reductions in dependence and biomarkers are achieved at the lowest level nicotine cigarettes. Thus, if feasible, a policy requiring abrupt transitions to the lowest level VLNC cigarettes is likely to result in the most rapid benefit to smokers.
Policies that promote reduction in CPD could also provide benefits to smokers not ready to quit. For example, reducing CPD decreased CO and increased QAs more than switching to VLNC cigarettes in my study. Future research is needed to test the degree to which policy that promotes the combination of switching to VLNC cigarettes plus reducing CPD would provide benefit beyond a policy that promotes one or the other. Importantly, I provided NRT and instructed participants to follow a weekly schedule and make large reductions over a relatively short period of time. Thus, my findings are limited in the extent to which they apply to the likely slower reduction that would occur in response to tobacco regulation policies.

4.4.2. Clinical Implications

Within-participant changes from switching to VLNC cigarettes and reducing CPD appear clinically meaningful when both strategies are aided by NRT. With regard to dependence, mean NDSS Overall Scores decreased by 0.94 units for VLNC and 0.47 for CPD participants. A one unit decrease in NDSS Overall Score in my prior 1-month reduction trial among smokers not ready to quit predicted a 62% increase in the odds of attempting to quit and a 54% increase in the odds of 7-day point prevalence abstinence 6 months later (Klemperer et al., 2017). With regard to biomarkers, VLNC participants in this trial decreased cotinine by a mean 42% and CO by 20%. CPD participants increased cotinine by a mean 20% and decreased CO by a mean 27%. Prior reduction trials found greater decreases in cotinine predicted cessation at a 6-week follow-up (Dermody, Donny, Hertsgaard, & Hatsukami, 2014) and greater decreases in CO predicted cessation at a 13-week follow-up (Rose, Behm, & Westman, 1998), though the magnitudes of these
effects were not clear. In this trial, self-efficacy to quit increased by a mean one unit for
VLNC participants but did not significantly change for CPD participants. A one unit
increase in the same self-efficacy scale predicted a 54% increase in the odds of making a
QA over the next 6 months but did not predict cessation in my prior reduction trial
(Klemperer et al., 2017). In this trial, mean intention to quit increased by 3.2 units for
VLNC participants and 1.5 for CPD participants. A one unit increase in the same
intention to quit scale predicted a 35% increase in the odds of making a QA and a 35%
increase in the odds of 7-day point prevalence abstinence 6 months later in my prior trial
(Klemperer et al., 2017).

Clinical interventions for smokers not ready to quit will likely need to be
adapted when the FDA regulates cigarettes’ nicotine content. In my trial, a structured 4-
week NRT-aided transition to VLNC cigarettes was an acceptable strategy that produced
clinically meaningful decreases in dependence and biomarkers and increases in self-
efficacy and intention to quit. Thus, progressively reducing to lower nicotine content
cigarettes with the aid of NRT could be an important component of future interventions
for smokers not ready to quit. However, my secondary findings demonstrate that reducing
CPD increased initial attempts to quit and decreased CO more than switching to VLNC
cigarettes. Thus, future research should examine whether the benefits of switching to
VLNC cigarettes and reducing CPD can be achieved with the same intervention. Further,
though widely available, NRT is used infrequently (Shiffman, Brockwell, Pillitteri, &
Gitchell, 2008). In contrast, alternative nicotine delivery systems such as e-cigarettes may
be a more acceptable way to supplement nicotine intake in future interventions to
facilitate reduction in nicotine from combustible cigarettes.
My findings also demonstrate that, with the aid of NRT, large reductions in nicotine, cigarettes/day, and dependence are possible among smokers not ready to quit. I instructed participants to reduce most of their nicotine over a short period of time because this appeared effective in prior VLNC studies (Benowitz et al., 2009; Benowitz et al., 2007) and it was unclear whether the equivalent reduction in CPD was feasible. VLNC participants achieved substantial nicotine reductions and CPD participants achieved substantial reductions in cigarettes/day over a 4 week period with the aid of NRT. Thus ambitious reduction goals appear feasible among smokers not ready to quit. I also found convergent validity demonstrating that reductions in dependence are feasible over a relatively short period of time. Nicotine dependence is often measured as a participant characteristic at baseline. However, my findings support prior prospective trials that found within participant change in dependence (Benowitz et al., 2012; Fagerstrom et al., 2002) and suggest that reducing dependence is a feasible short-term goal for interventions targeting smokers not ready to quit.

4.4.3. Behavioral Implications

Broadly, my findings indicate that reducing the magnitude of an unconditioned reinforcer (e.g., switching to VLNC cigarettes) could be a more acceptable strategy to promote behavior change than restricting responses to stimulus cues (e.g., reducing CPD). Differences between the strategies’ influence on behavior change could be due to differences in learning. As previously discussed (see Figure 1 and Figure 2 in section 1.1), reducing the magnitude of an unconditioned reinforcer could promote extinction by disrupting associations between 1) a response behavior and unconditioned reinforcer, 2)
stimulus cues and a response behavior, and 3) conditioned and unconditioned reinforcers. In contrast, restricting behavior in response to stimulus cues provides increased practice with response inhibition and decreased exposure to unconditioned and conditioned reinforcers but may not promote extinction per se. My finding that switching to VLNC cigarettes appeared to decrease dependence more than reducing CPD supports the theory that reducing the magnitude of an unconditioned reinforcer promotes extinction more than restricting behavioral responses to stimulus cues. Nonetheless, the fact that more CPD participants made a QA suggests that increased practice restricting behavior in response to stimulus cues may promote initial, but not necessarily sustained, behavior change. Future research is needed to examine the extent to which findings from this study can be applied to behavior change in humans beyond cigarette smoking.

4.5. Limitations and Assets

4.5.1. Limitations

As previously mentioned, one limitation is that all study cigarettes were mentholated because of the limited cigarettes available to us from NIDA. Thus we block randomized so that the proportion of menthol to non-menthol smokers was similar between groups. This may have been less of a problem because all study cigarettes were novel. In addition subjective evaluation of cigarettes did not differ between groups or between participants that identified as menthol vs non-menthol smokers before entering the study. Whether participants identified as menthol smokers or not before entering the study did not moderate any outcomes. Finally, there was no difference in the amount of menthol cigarettes smoked before entering the study vs during the follow-up period.
Due to limited funding, this study did not include a control condition (i.e., a group that smoked as usual for the entire study period). Thus I used within-participant comparisons to examine the effectiveness of reduction strategies compared to participants’ ad-lib smoking during week 0. Secondary findings measured at follow-up were also limited because 41% of participants were missing at the 1-month follow-up. Further, after the study period, participants in the CPD condition could continue smoking fewer cigarettes but those in the VLNC condition could not continue smoking VLNC cigarettes because they are not commercially available in the US.

Another limitation is that I was unable to biochemically verify compliance with instructions to only use study cigarettes and not usual brand cigarettes. Biochemical estimation of compliance was not possible because participants used NRT and most study cigarettes contained too much nicotine to detect non-compliance (Benowitz, 2015). In order to increase the validity of participants’ self-report, I 1) informed participants that self-reported noncompliance does not influence their payment or future participation and 2) employed a bogus pipeline technique that has been used in multiple prior studies (Aguinis et al., 1993). Prior studies have found discrepancies between self-report and biochemical estimations of compliance (Nardone et al., 2016). Thus the percent non-study cigarettes/day was likely higher in both groups, though I have no reason to believe that discrepancies between actual and self-reported non-study cigarettes/day differed between groups.

I instructed participants to reduce most of their nicotine over a short period of time to compare transitions to VLNC cigarettes to equivalent reductions in CPD.
Importantly, clinical interventions to reduce CPD often provide smaller goals or no goals at all. My prior studies found dose response relationships where greater magnitudes of reduction were associated with greater decreases in dependence (Klemperer et al., 2015) and increases in QAs (Klemperer, Hughes, & Naud, 2018) and cessation (Klemperer & Hughes, 2016). Thus, the overall effects of reduction on dependence and quitting would likely be smaller among smokers who reduced less. Prior studies suggest that switching to VLNC cigarettes may be most impactful at the lowest level of nicotine (i.e., 3%) (Donny et al., 2015). Thus, while it was more internally valid to compare equivalent reductions between VLNC and CPD conditions, VLNC participants may have experienced more clinically meaningful changes had they smoked the lowest level cigarettes for more than 1 week.

I conducted analyses to examine 22 outcomes which increased the probability of false positives. However I did not include p value corrections because, like many statisticians, I am concerned that these adjustments are based on arbitrary cutoffs and increase the probability of type II errors (Feise, 2002). I limited my moderator analyses to gender and menthol status. However, this study was underpowered to detect moderator effects which could be one reason why my moderator analyses were not significant.

I used a convenience sample and inclusion criteria that may have limited the generalizability of my findings. Participants in my study were less diverse and had more years of education than a nationally representative sample of smokers (Hughes & Callas, 2010). Further, because blinding participants to the number of cigarettes they smoke was not possible, neither participants nor researchers in my study were blind to condition.
Awareness of switching to VLNC cigarettes or reducing CPD may have influenced outcomes. Finally, participants’ nightly responses to surveys about their smoking may have influenced their smoking (McCarthy, Minami, Yeh, & Bold, 2015).

4.5.2. Assets

This randomized trial is the first to directly compare the FDA proposed strategy to switch to VLNC cigarettes vs the commonly used strategy of reducing CPD. Participants in both groups were instructed to use different strategies to attempt to reduce a similar amount of nicotine. This comparison also provided an opportunity to examine the influence of reducing the magnitude of an unconditioned reinforcer (VLNC condition) vs restricting behavior in response to stimulus cues (CPD condition) in humans. Most smokers are not ready to quit in the near future but few interventions are designed for this population (PROPEL Centre for Population Health Impact, 2015).

Importantly, this trial compared two reduction strategies that can be used to design or improve clinical interventions for smokers not ready to quit. In addition to between-group comparisons, this trial made within-participant comparisons, which is a more valid test of behavior change (Sidman, 1960). I collected data weekly and nightly to minimize recall bias (Shiffman, 2009). There was a relatively low rate of missing data (9%) and dropouts (7%). In addition, I used an adequate sample size to detect changes in nicotine dependence and included multiple measures to assess convergent validity for both of my primary outcomes. Finally, findings from this study contribute to the science of nicotine addiction on a theoretical, clinical, and policy level.
4.6. Future Research

Future research is needed to replicate and expand on findings from my dissertation as they relate to behavioral, clinical, and regulatory sciences. A laboratory study to test the degree to which reducing the magnitude of unconditioned reward from drug use vs restricting response to stimulus cues disrupts behavioral conditioning could inform basic understanding of drug dependence in humans. My finding that dependence decreased despite an increase in nicotine exposure among CPD participants was unexpected and thus future research is needed to replicate this effect and examine the influence of behavior change vs nicotine intake on dependence. Further, research testing the reduction strategies in this trial in combination with existing interventions could inform clinicians on how to treat smokers not ready to quit when VLNC cigarettes are commercially available in the US. Finally, a pragmatic trial to compare switching to VLNC cigarettes vs reducing CPD in a less structured “real world” context could be useful to inform future tobacco regulation policy.

4.7. Conclusions

This is the first trial to compare the FDA proposed strategy of switching to VLNC cigarettes vs the commonly used strategy of reducing CPD. Both reduction strategies were aided by NRT. Broadly, there are two main conclusions from my dissertation. First, reducing was more acceptable when switching to cigarettes with progressively less nicotine (VLNC cigarettes) than when progressively reducing the number of CPD. Second, though both reduction strategies decreased dependence over time, switching to VLNC cigarettes appeared to decrease dependence more than reducing
CPD. Thus, when both are aided by NRT, switching to VLNC cigarettes appears to be a more superior reduction strategy than reducing CPD for smokers not ready to quit.
REFERENCES


Fagerstrom, K. O. (2012). Determinants of tobacco use and renaming the FTND to the Fagerstrom Test for Cigarette Dependence. *Nicotine & Tobacco Research, 14*(1), 75-78. doi:10.1093/ntr/ntr137


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West, R., & Brown, J. (2012). Smoking and smoking cessation in England 2011: Findings from the smoking toolkit study. *Age (years), 1*, 1.01-01.02.


## 5. APPENDIX

Appendix Table 1: Week 0, week 4, and follow-up smoking characteristics.\

<table>
<thead>
<tr>
<th></th>
<th>Week 0</th>
<th>Week 4</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VLNC (n=36)</td>
<td>CPD (n=32)</td>
<td>Total (N=68)</td>
</tr>
<tr>
<td>Mean total cigarettes/day</td>
<td>20.1 (8.8)</td>
<td>21.1 (12.2)</td>
<td>20.6 (10.5)</td>
</tr>
<tr>
<td></td>
<td>16.2 (9.8)</td>
<td>8.5 (6.9)</td>
<td>12.6 (9.3)</td>
</tr>
<tr>
<td></td>
<td>11.9 (7.7)</td>
<td>16.5 (10.2)</td>
<td>13.9 (9.0)</td>
</tr>
<tr>
<td>Mean percent non-study cigarettes/day</td>
<td>7.1 (16.9)</td>
<td>7.4 (11.5)</td>
<td>7.2 (14.5)</td>
</tr>
<tr>
<td></td>
<td>21.4 (36.5)</td>
<td>72.1 (33.9)</td>
<td>44.5 (43.4)</td>
</tr>
<tr>
<td>Median percent non-study cigarettes/day</td>
<td>1.5</td>
<td>0.1</td>
<td>1.2</td>
</tr>
<tr>
<td>Mean willingness to smoke type of cigarette</td>
<td>4.3 (1.1)</td>
<td>4.4 (1.0)</td>
<td>4.4 (1.0)</td>
</tr>
<tr>
<td></td>
<td>4.1 (1.5)</td>
<td>4.3 (0.9)</td>
<td>4.2 (1.2)</td>
</tr>
<tr>
<td>Mean ability to smoke type of cigarette</td>
<td>4.1 (1.2)</td>
<td>4.1 (1.1)</td>
<td>4.1 (1.2)</td>
</tr>
<tr>
<td></td>
<td>4.2 (1.3)</td>
<td>4.0 (1.0)</td>
<td>4.1 (1.2)</td>
</tr>
<tr>
<td>Mean willingness to smoke number of cigarettes</td>
<td>4.3 (1.1)</td>
<td>4.2 (1.0)</td>
<td>4.2 (1.1)</td>
</tr>
<tr>
<td></td>
<td>4.4 (1.2)</td>
<td>2.9 (1.4)</td>
<td>3.7 (1.5)</td>
</tr>
<tr>
<td>Mean ability to smoke number of cigarettes</td>
<td>4.1 (1.3)</td>
<td>3.8 (1.1)</td>
<td>3.9 (1.2)</td>
</tr>
<tr>
<td></td>
<td>4.1 (1.3)</td>
<td>2.7 (1.3)</td>
<td>3.5 (1.5)</td>
</tr>
<tr>
<td>Mean Nicotine Dependence Syndrome Scale, Overall Score (NDSS-OS)</td>
<td>-0.70 (-.85)m</td>
<td>-0.77 (0.92)</td>
<td>-0.73 (0.88)</td>
</tr>
<tr>
<td></td>
<td>-1.64 (0.83)</td>
<td>-1.24 (0.88)</td>
<td>-1.45 (0.9)</td>
</tr>
<tr>
<td>Mean Fagerstrom Test for Cigarette Dependence (FTCD; excluding cigarettes/day; 0=lowest, 7=highest)</td>
<td>3.1 (1.4)</td>
<td>3.0 (1.5)</td>
<td>3.0 (1.5)</td>
</tr>
<tr>
<td></td>
<td>2.3 (1.7)</td>
<td>2.6 (1.7)</td>
<td>2.4 (1.7)</td>
</tr>
<tr>
<td>Mean Glover-Nilsson Behavioral Dependence Questionnaire (GN-SBQ; 0=lowest, 44=highest)</td>
<td>15.7 (6.5)</td>
<td>16.1 (6.6)</td>
<td>15.9 (6.5)</td>
</tr>
<tr>
<td></td>
<td>10.5 (8.2)</td>
<td>11.1 (6.8)</td>
<td>10.8 (7.5)</td>
</tr>
<tr>
<td></td>
<td>9.8 (8.2)</td>
<td>10.4 (4.8)</td>
<td>10.1 (6.9)</td>
</tr>
<tr>
<td></td>
<td>Week 0</td>
<td>Week 4</td>
<td>Follow-Up</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td></td>
<td>VLNC (n=36)</td>
<td>CPD (n=32)</td>
<td>Total (N=68)</td>
</tr>
<tr>
<td>Mean Addiction Ladder (0=lowest, 10=highest)</td>
<td>8.6 (1.9)</td>
<td>8.9 (1.2)</td>
<td>8.7 (1.6)</td>
</tr>
<tr>
<td>Mean time to first cigarette (TTFC) in minutes</td>
<td>24.8 (20.2)</td>
<td>24.0 (23.0)</td>
<td>24.4 (21.4)</td>
</tr>
<tr>
<td>Mean self-efficacy to quit (SEQ; 1=lowest, 5=highest)</td>
<td>2.4 (1.1)</td>
<td>2.9 (1.0)</td>
<td>2.7 (1.0)</td>
</tr>
<tr>
<td>Mean Intention-to-Quit Ladder (0=lowest, 10=highest)</td>
<td>4.5 (3.5)</td>
<td>4.0 (3.5)</td>
<td>4.3 (3.5)</td>
</tr>
<tr>
<td>Mean cotinine ng/ml</td>
<td>1,327.1 (665.2)</td>
<td>1,266.7 (567.2)</td>
<td>1,298.3 (616.5)</td>
</tr>
<tr>
<td>Mean carbon monoxide (CO) ppm</td>
<td>24.9 (14.0)</td>
<td>22.5 (12.1)</td>
<td>23.8 (13.1)</td>
</tr>
</tbody>
</table>

*Standard deviations in parentheses; CPD=Condition that reduced cigarettes per day; ng/ml=Nano grams per milliliter; ppm=Parts per million; VLNC=Condition that switched to very low nicotine content cigarettes.