



## Supplement Article

# Reducing the Nicotine Content of Cigarettes: Effects in Smokers With Mental Health Conditions and Socioeconomic Disadvantages

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## Abstract

In this commentary, we review results from laboratory studies and randomized clinical trials that have examined the effects of very low–nicotine-content cigarette use in smokers with mental health conditions and socioeconomic disadvantages. On the basis of scientific evidence to date, we conclude that a reduced-nicotine standard for cigarettes would likely reduce cigarette smoking in these populations, without increasing psychiatric symptoms or compensatory smoking.

As the Food and Drug Administration weighs the adoption of a reduced-nicotine standard for cigarettes, it is important to consider how this action might affect smokers who have heightened vulnerability to tobacco use and tobacco-related disease. Most laboratory studies and randomized clinical trials (RCTs) of very-low-nicotine-content (VLNC) cigarettes have focused on two vulnerable populations: smokers with mental health conditions (MHCs) and those with socioeconomic disadvantages. Both populations have elevated rates of tobacco use compared to the general US population.<sup>1,2</sup> In this commentary, we describe results from studies of VLNC cigarettes in smokers with MHCs and socioeconomic disadvantages and use this information to infer how a reduced-nicotine standard for cigarettes might affect these smokers.

## What Are the Effects of VLNC Cigarettes on Cigarette Abuse Liability Measures in These Smokers?

Two laboratory studies have examined effects of VLNC cigarettes in smokers with MHCs. A single-site study compared responses of smokers with schizophrenia and controls to usual-brand and Quest 3 VLNC cigarettes (1.0 mg nicotine/g tobacco) plus placebo or 42 mg

nicotine patches,<sup>3</sup> and a multisite study compared responses to Spectrum cigarettes with normal-nicotine content (NNC; 15.8 mg/g) and reduced-nicotine content (RNC; 5.2, 2.4 and 0.4 mg/g) in smokers with past-year depression and/or anxiety disorders, those with opioid use disorders, and women with less than 12 years of education.<sup>4</sup> Both studies found that smokers rated the positive subjective effects of VLNC cigarettes lower than those of usual-brand or NNC cigarettes, and the multisite study found that cigarettes with less than or equal to 5.2 mg/g nicotine were less likely to be chosen than NNC cigarettes when the effort required to obtain puffs from these cigarettes was the same.<sup>4</sup> Both studies collected smoking topography and breath carbon monoxide (CO) levels and found no indication of compensatory smoking of VLNC cigarettes.<sup>3–5</sup>

Results are also emerging from RCTs that have investigated the effects of extended VLNC cigarette use in smokers with MHCs. In a secondary analysis of a multisite RCT,<sup>6</sup> smokers with elevated depressive symptoms who were randomized to Spectrum cigarettes with 2.4 mg/g nicotine or less smoked fewer cigarettes per day (CPD) at week 6 than those who were randomized to NNC cigarettes.<sup>7</sup> An RCT in smokers with schizophrenia or bipolar disorder found that those randomized to Spectrum cigarettes with 0.4 mg/g nicotine

smoked fewer CPD and had lower breath CO levels at week 6 than those who were randomized to NNC cigarettes.<sup>8</sup> Preliminary topography results also indicate that total puff volume was decreased in both conditions.<sup>9</sup> Finally, preliminary results from a two-arm, double-blind, parallel-group RCT that compared the effects of progressively reduced-nicotine condition (from 11.6 mg/cigarette to 0.2 mg/cigarette in 3-week steps) versus an NNC condition (11.6 mg/cigarette for 18 weeks) in 188 smokers with current or past mood and/or anxiety disorders indicate that those in the RNC condition smoked fewer CPD and had lower CO, nicotine metabolite and cigarette dependence levels at the end of the randomization phase than the NNC group.<sup>10</sup> At the end of the randomization phase, all participants were encouraged to quit, and those interested in quitting were provided with nicotine replacement and brief counseling. At a follow-up session 12 weeks later, there was a higher rate of quitting (biochemically confirmed) in the reduced-nicotine condition than in the NNC condition.<sup>11</sup>

Two studies have investigated the effects of VLNC cigarettes on abuse liability measures in socioeconomically disadvantaged smokers. As noted earlier, a multisite laboratory study that included socioeconomically disadvantaged women found that Spectrum cigarettes with 2.4 mg/g nicotine or less were less satisfying, rewarding, and chosen less often than NNC cigarettes.<sup>4</sup> Preliminary results from a two-arm, double-blind, parallel-group RCT that evaluated the effects of progressively reduced-nicotine condition (from 11.6 mg/cigarette to 0.2 mg/cigarette in 3-week steps) versus an NNC condition (11.6 mg/cigarette for 18 weeks) in 245 socioeconomically disadvantaged smokers indicate that participants in the reduced-nicotine condition smoked fewer CPD and had lower CO, nicotine metabolite, and cigarette dependence levels at the end of the randomization phase compared to the NNC group.<sup>12</sup> Overall, these studies consistently support the idea that a reduced-nicotine standard for cigarettes would reduce smoking in smokers with MHCs or socioeconomic disadvantages. Importantly, all of the studies reviewed above included measures of smoking topography and/or breath CO levels and found no evidence of compensatory smoking of VLNC cigarettes. The preliminary finding of increased quitting among smokers with MHCs who underwent nicotine reduction is particularly noteworthy because none of these study participants were trying to quit when they enrolled.<sup>10,11</sup>

### **Is There Any Reason to Think That These Vulnerable Populations Differ From Other Smokers With Regard to Their Sensitivity to Cigarette Nicotine Content?**

As most RCTs with VLNC cigarettes have been conducted in smokers sampled from the general population, it is important to know how a reduced-nicotine standard based on results from those studies would affect vulnerable populations. In a laboratory study in smokers with schizophrenia and controls, the MHC group rated positive subjective effects of Quest 3 VLNC cigarettes higher than did controls,<sup>3</sup> but the VLNC cigarettes had similar effects on smoke intake in both groups.<sup>5</sup> A secondary analysis of a multisite laboratory study<sup>4</sup> that examined whether affective disorder diagnosis or severity moderated subjective responses or choices for Spectrum cigarettes (15.8, 5.2, 2.4, and 0.4 mg/g) found no moderation.<sup>13</sup> Similarly, a secondary analysis of a multisite RCT<sup>6</sup> found similar effects of Spectrum cigarettes with 2.4 mg/g nicotine or less on cigarette use in smokers with higher versus lower depressive symptoms.<sup>7</sup>

All of the earlier studies were conducted in smokers who were not trying to quit. In a pragmatic smoking cessation effectiveness trial conducted in New Zealand, treatment-seeking smokers were randomized to a cessation intervention involving usual Quitline care (nicotine replacement plus behavioral support) versus usual Quitline care plus access to Quest 3 VLNC cigarettes. The effect of the active intervention on abstinence was similar in those with and without socioeconomic disadvantage (<12 years of education).<sup>14</sup> Overall, these studies suggest that sensitivity to nicotine dose is similar in smokers with MHCs and socioeconomic disadvantages compared to smokers without these vulnerabilities, although, as noted earlier, one study found stronger positive subjective responses to Quest 3 VLNC cigarettes in smokers with schizophrenia compared to controls.<sup>3</sup>

### **Does VLNC Cigarette Use Exacerbate Psychiatric or Other Symptoms in Smokers With MHCs?**

To date, no studies have reported that VLNC cigarette use exacerbates psychiatric symptoms in smokers with MHCs. Preliminary results from a two-arm, double-blind, parallel-group RCT that evaluated the effects of progressively reduced-nicotine content versus NNC cigarettes in 188 smokers with current or past mood and/or anxiety disorders indicate that the groups did not differ on measures of depression, anxiety, or mental distress throughout the trial.<sup>10</sup> A secondary analysis from a multisite RCT<sup>6</sup> found that smokers with elevated depressive symptoms who were randomized to use Spectrum cigarettes with less than or equal to 2.4 mg/g nicotine actually had significantly lower depressive symptoms at week 6 than those randomized to NNC cigarettes.<sup>7</sup> However, cognitive performance is one area of functioning that may be negatively affected by nicotine reduction. A laboratory study that investigated the effects of Quest 3 (1.0 mg/g nicotine) and usual-brand cigarettes in smokers with schizophrenia and controls found no effects on psychiatric symptoms,<sup>3</sup> but decrements in cognitive task performance were observed in both the patient and control groups, which were attenuated with concurrent nicotine replacement.<sup>15</sup> In summary, studies to date do not suggest that a reduced-nicotine standard for cigarettes would exacerbate psychiatric symptoms in smokers with MHCs. However, there is some indication that heavy smokers (with or without schizophrenia) might experience cognitive performance decrements, which could be mitigated with nicotine replacement.

### **Should the Scope of the Proposed Reduced-Nicotine Standard for Cigarettes be Expanded to Include Other Combusted Products That Are Smoked Like Cigarettes?**

There is a high rate of other combusted tobacco product (ie, cigars, little cigars, cigarillos, roll-your-own cigarettes) use among smokers with MHCs and socioeconomic disadvantage compared to smokers in general.<sup>1</sup> In Pennsylvania, use of roll-your-own tobacco is higher among socioeconomically disadvantaged smokers because of the lower tax rate on roll-your-own tobacco.<sup>16</sup> Preliminary results from a laboratory study that modeled the effects of increasing cigarette price on cigarette purchasing and substitution with non-premium cigars found a greater substitution among socioeconomically disadvantaged smokers (ie,  $\leq 12$  years of education) than among non-disadvantaged smokers.<sup>17</sup> These studies indicate that smokers with MHCs and socioeconomic disadvantage, who are already more prone than other

smokers to use alternative combusted tobacco products, might increase their use of alternative tobacco products if the proposed reduced-nicotine standard does not also extend to these products.

## Conclusions

The evidence to date from laboratory studies and RCTs indicates that reducing the nicotine content of cigarettes to a minimally addictive level is likely to reduce cigarette smoking in smokers with MHCs and socioeconomic disadvantages, without leading to increases in psychiatric symptoms or smoke intake indicative of compensatory smoking. Preliminary findings from one study suggest that this regulation could even increase quitting among smokers with MHCs.<sup>11</sup> However, smokers with MHCs might benefit from adjunctive non-combusted sources of nicotine, based on results from one study.<sup>15</sup> Furthermore, because substitution of alternative tobacco products is observed in socioeconomically disadvantaged smokers when access to cigarettes is restricted through price increases, a reduced-nicotine standard might lead to increased use of alternative combusted tobacco products if the standard does not also extend to these products.

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## Declaration of Interests

None declared.

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