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Modeling nicotine regulation: A review of studies in smokers with mental health conditions

Jennifer W. Tidey[a,*], Danielle R. Davis[b], Mollie E. Miller[a], Irene Pericot-Valverde[b], Rachel L. Denlinger-Apte[a], Diann E. Gaalema[b]

[a] Department of Behavioral and Social Sciences, Brown University, USA
[b] Department of Psychiatry, University of Vermont, USA

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ABSTRACT

Smokers with mental health conditions (MHCs) lose approximately 15 years of life relative to non-smokers without MHCs, of which two-thirds are attributable to smoking. The Food and Drug Administration (FDA) recently announced a new regulatory strategy for tobacco that includes a reduction in the nicotine content of cigarettes sold in the US to a minimally-addictive level. This action could improve cessation rates in smokers with MHCs by reducing their dependence on nicotine. However, nicotine reduction also could have unintended negative consequences in smokers with MHCs. Thus, it is important to conduct randomized controlled trials to investigate the potential effects of nicotine reduction in smokers with MHCs. Several studies of the acute or extended effects of nicotine reduction in smokers with emotional disorders or serious mental illness have been recently completed or are underway. Studies to date indicate that when smokers with MHCs are switched, under randomized, double-blind conditions, to cigarettes with very low nicotine content, they reduce their cigarette intake, with minimal or no effects on withdrawal, psychiatric symptoms, or compensatory smoking. However, some deleterious effects of nicotine reduction on cognitive performance measures in smokers with schizophrenia have been observed, which are offset by providing concurrent nicotine replacement. We review these studies and provide suggestions for potentially increasing the effectiveness of a nicotine reduction strategy for reducing smoking in people with MHCs. The research described was conducted in the United States in 2010–2018.

1. Introduction

Approximately 40% of cigarettes consumed by adults in the US are smoked by those with mental health conditions (MHCs) (Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality, 2013a). Smokers with mental health conditions (MHCs) lose approximately 15 years of life relative to non-smokers without MHCs, of which two-thirds are attributable to smoking (Tam et al., 2016). Although rates of smoking cessation attempts among smokers with MHCs are comparable to those without MHCs (McClave et al., 2010), smokers with MHCs relapse at higher rates, due to factors that may include increased sensitivity to nicotine reinforcement, limited access or sensitivity to alternative reinforcers, reduced access to effective cessation treatments, and use of cigarettes to ameliorate stress, negative mood, psychiatric symptoms, cognitive deficits, or side effects of psychiatric medications (Audrain-McGovern et al., 2015; Kalman et al., 2005; Tidey and Miller, 2015; Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality, 2013b; Ziedonis et al., 2008). Pharmacological smoking cessation treatments such as varenicline, bupropion and nicotine replacement are effective in smokers with MHCs (Anthenelli et al., 2016), but many smokers with MHCs do not have access to these treatments, and more broadly-available, less-intensive treatments such as state quit lines have limited efficacy in these smokers (Vickerman et al., 2015).

The Food and Drug Administration (FDA) recently announced a new regulatory strategy for tobacco, of which a key component is the consideration of a mandated reduction in the nicotine content of cigarettes sold in the US to a minimally-addictive level (Gottlieb and Zeller, 2017). Clinical studies have consistently found that switching smokers to very low nicotine content cigarettes results in reduced daily cigarette use, nicotine exposure, and cigarette dependence severity (Benowitz et al., 2007; Hatsukami et al., 2010; Donny et al., 2015). A reduced-nicotine standard for cigarettes has the potential to improve cessation rates in smokers with MHCs by reducing their dependence on nicotine, which may increase their responsiveness to cessation treatments and

* Corresponding author at: Center for Alcohol & Addiction Studies, 121 South Main Street, Box G-S121-5, Providence, RI 02912, USA.
E-mail address: Jennifer_Tidey@brown.edu (J.W. Tidey).

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other tobacco control strategies. However, smokers with MHCs could also respond to a reduced-nicotine standard for cigarettes with protracted elevations in withdrawal symptoms, increases in psychiatric symptoms, decreases in cognitive function, and increases in smoking topography in efforts to overcome these effects. Given that nearly a third of nicotine-dependent individuals have an MHC (Grant et al., 2004), it is important to consider how these smokers might respond to reductions in the nicotine content of cigarettes.

A previous narrative review discussed the potential effects of a reduced-nicotine standard for cigarettes in smokers with MHCs, based on the responses of these smokers to smoking cessation treatments and to very low nicotine content (VLNC) cigarettes (also referred to as "denicotinized" cigarettes, i.e., cigarettes with < 2 mg nicotine/g tobacco) in a small number of acute laboratory studies (Gaalema et al., 2015). That review discussed 4 laboratory studies that compared the acute effects of normal-nicotine and VLNC cigarettes on mood or other psychiatric symptoms in smokers with depression or post-traumatic stress disorder (PTSD), 8 laboratory studies that compared the effects of experimentally-induced smoking abstinence on nicotine withdrawal and psychiatric symptoms in smokers with mood or anxiety disorders, and 29 treatment studies that compared the effects of smoking cessation on withdrawal and psychiatric symptoms in smokers with and without mood or anxiety disorders. The review concluded that smokers with MHCs appear to be more sensitive than other smokers to the effects of smoking abstinence on withdrawal symptoms, at least initially, but that use of VLNC cigarettes reduces the effects of nicotine abstinence on craving and withdrawal, presumably due to their sensorimotor effects. However, the studies covered in the previous review were not designed to model the effects of a reduced-nicotine standard for cigarettes, and thus did not include the wide range of subjective, behavioral and physiological measures necessary for assessing the potential effects of this policy – both positive and negative – in smokers with MHCs.

Since that review, several studies have been published or are underway that attempt to model how smokers with MHCs might respond to a reduced-nicotine standard for cigarettes. The current narrative review examines this research, specifically in smokers with emotional disorders (mood and anxiety disorders (Barlow et al., 2016; Brown et al., 1998)) and those with serious mental illness (schizophrenia and bipolar disorder). Responses to nicotine reduction in smokers with emotional disorders are important to consider because these disorders are the most prevalent MHCs among smokers in the US (Grant et al., 2004). Responses in smokers with serious mental illness are important to consider because these smokers tend to be highly nicotine dependent (de Leon et al., 2002; Estrada et al., 2016) and thus may be more vulnerable than other smokers to any negative consequences of nicotine reduction.

2. Emotional disorder

Recently, a large multi-site trial was conducted by the Center for the Evaluation of Nicotine in Cigarettes (CENIC) Tobacco Center on Regulatory Science (TCORS), to investigate the effects of cigarettes varying in nicotine content on smoking behavior and biomarkers of nicotine and tobacco toxin exposure among smokers sampled from the general population (Donny et al., 2015). Adult, medically-stable smokers (N = 839), who smoked ≥5 cigarettes per day (CPD) and were not trying to quit smoking, were randomized to receive either their usual cigarette brand or research cigarettes varying in nicotine content from 0.4–15.8 mg nicotine/g tobacco. They were provided with these cigarettes free of charge for six weeks, and were asked to use only these cigarettes. Participants used an interactive voice response system each day to report the number of study cigarettes, non-study cigarettes and other tobacco and nicotine products they had consumed since the previous day, and completed other subjective, behavioral and physiological assessments during weekly laboratory visits. Results of this study by Donny et al. (2015) indicated that, at the end of the study (Week 6), those who had been randomized to the 0.4 mg/g cigarettes smoked significantly fewer CPD, had lower biomarker levels of nicotine exposure and were less nicotine dependent than those who had been assigned to smoke either usual-brand or 15.8 mg/g nicotine research cigarettes, with no indication of compensatory smoking (i.e., increased smoking intensity at lower nicotine doses) (Donny et al., 2015). Furthermore, although no participants were actively trying to quit smoking when they enrolled in the study, those who had been randomized to the 0.4 mg nicotine/g tobacco cigarettes were significantly more to attempt to quit smoking after the study than those who had been randomized to the 15.8 mg nicotine/g tobacco cigarettes (Donny et al., 2015).

Given the importance of understanding how reduced-nicotine cigarettes would impact smokers with MHCs, a secondary analysis of the Donny et al. study was conducted (Tidey et al., 2017) to determine whether the effects of reduced-nicotine cigarettes differed among the subset of participants (n = 109) who had reported scores ≥16 on the Center for Epidemiologic Studies–Depression (CES-D) scale (Radloff, 1977) at baseline, indicating possible clinical depression. To increase statistical power for this analysis, the research cigarettes with 0.4–2.4 mg/g nicotine were combined into a reduced-nicotine content cigarette condition, and the usual brand and 15.8 mg/g nicotine research cigarettes were combined into a normal-nicotine content condition. Linear regression analyses were conducted to compare the effects of normal nicotine and reduced nicotine cigarettes among those with baseline CES-D scores < 16 vs. ≥16 on the following outcomes at Week 6: CPD, urinary total nicotine equivalents, breath carbon monoxide (CO) levels, total puff volume, nicotine dependence, cigarette craving, withdrawal symptoms, self-reported alcohol and cannabis use, self-reported quit attempts after the 6-week cigarette intervention period ended, positive and negative affect, and depressive symptom severity as assessed by the CES-D.

Results at Week 6 indicated that participants in the reduced-nicotine condition reported smoking fewer CPD and had lower urinary nicotine levels, nicotine dependence scores, and cigarette craving scores than those in the normal-nicotine condition, and that baseline depressive symptom severity did not moderate these effects. There were no significant effects of cigarette condition on CO level, alcohol use, cannabis use, nicotine withdrawal symptoms or positive affect in either group. Among participants with lower depressive symptoms at baseline, those assigned to reduced-nicotine cigarettes were significantly more likely to have made a quit attempt during the follow-up period than those in the normal-nicotine condition, as had been reported in the overall sample (Donny et al., 2015); results were similar in participants with higher depressive symptoms at baseline but this effect was not significant. Total puff volume, a measure of smoke inhalation, was lower in the reduced-nicotine condition among participants with lower depressive symptoms at baseline and did not change among those with higher depressive symptoms. The only significant interaction between cigarette condition and baseline CES-D score was on Week 6 CES-D score: among those with lower baseline depressive symptoms, there was no effect of cigarette condition on Week 6 CES-D scores, while among those with higher baseline depressive symptoms, those in the reduced-nicotine condition had lower Week 6 CES-D scores than those in the normal-nicotine condition (Fig. 1).

The results of this secondary analysis by Tidey et al. (2017) suggest that the effects of a reduced-nicotine product standard for cigarettes in smokers with elevated depressive symptoms would be similar to the effects observed in smokers without elevated depressive symptoms. However, several limitations were noted. First, as only 109 participants (15.2%) in the Donny et al. study had elevated depressive symptoms at baseline, the secondary analysis by Tidey et al. was underpowered to detect significant effects of nicotine content on all outcomes in this group. However, the pattern of effects of reduced-nicotine cigarettes in smokers with elevated depressive symptoms was similar to the pattern of effects in those with lower depressive symptoms. That is, no increases were observed in measures that would indicate that reduced-nicotine

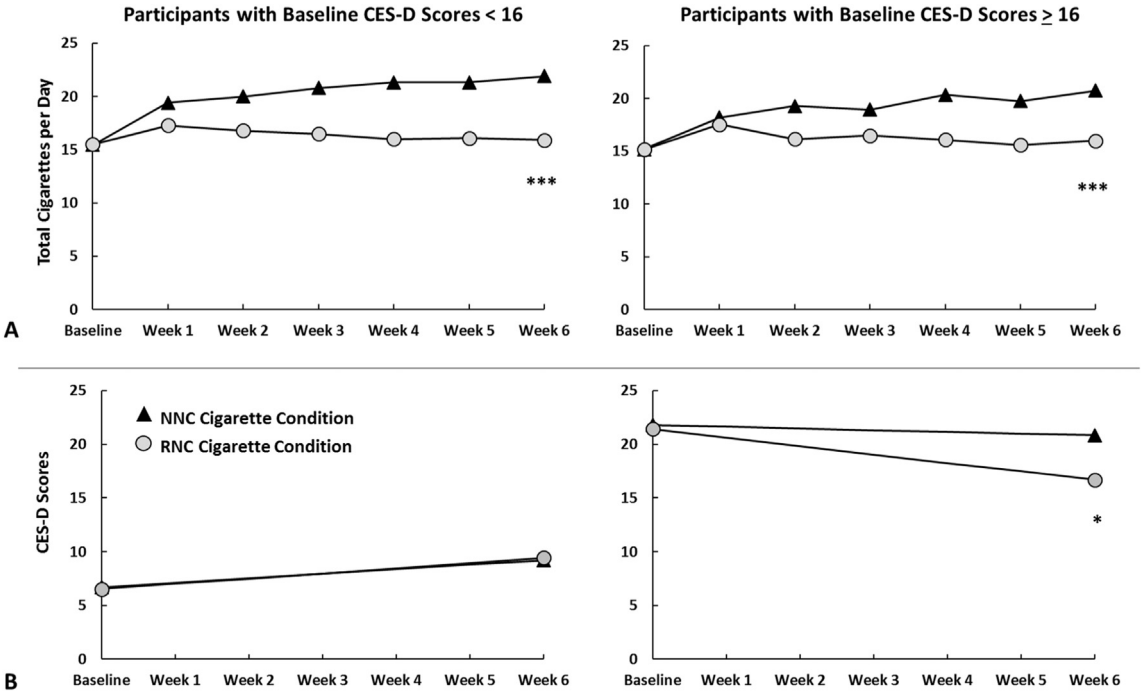

Fig. 1. Panel A – Mean number of cigarettes smoked per day in participants assigned to normal-nicotine content (NNC) cigarettes (triangles) and reduced-nicotine content (RNC) cigarettes (circles). Panel B – Mean CES-D scores at Baseline and Week 6 by nicotine content. * indicates significant difference between groups at the $p < .05$ level; *** indicates significant difference between groups at the $p < .001$ level. Note that in the graph at lower left, the lines for the NNC and RNC conditions overlap. This research (Tidey et al., 2017) was conducted in the United States in 2011–2016.

cigarettes increased cigarette intake, nicotine dependence, depressive symptoms or negative mood among smokers with elevated depressive symptoms at baseline. Second, although scores of ≥16 on the CES-D scale are considered indicative of possible clinical depression, participants in this study had not been clinically diagnosed with depression using a clinical interview, and it is unclear to what extent these results may generalize to smokers who have been clinically diagnosed with depression.

The University of Vermont (UVM), in collaboration with Brown and Johns Hopkins Universities, formed a TCORS with the specific intent of investigating the effects of reduced-nicotine cigarettes in vulnerable populations. This TCORS recently completed a comprehensive study of the acute addiction potential of research cigarettes varying in nicotine content in three vulnerable subpopulations of smokers: socioeconomically disadvantaged women, men and women with opioid dependence, and men and women with emotional disorders (Higgins et al., 2017). Results from all three samples were published by Higgins et al. (2017) and only results in smokers with emotional disorders will be discussed here. Participants were adults who smoked at least 5 CPD, were clinically stable, and did not intend to quit smoking within the next 30 days. The diagnostic inclusion criterion was a past-year diagnosis of major depressive disorder, dysthymia, generalized anxiety disorder, obsessive-compulsive disorder, specific phobia, or panic disorder with or without agoraphobia, or a lifetime diagnosis of one of these disorders along with current treatment for their condition. Diagnoses were based on the Mini International Neuropsychiatric Interview (Sheehan et al., 1998) (MINI 6.0), a structured diagnostic interview to evaluate psychiatric disorders based on DSM-IV criteria.

Participants completed 14 experimental sessions across three experimental phases and were abstinent for approximately 6–8 h (confirmed with CO < 50% of their baseline CO level) before every session. In the first session, participants smoked their own brand of cigarette through a smoking topography device to familiarize themselves with session procedures and tasks. In Phase 1 (Sessions 2–5), participants used the smoking topography device to smoke a single cigarette from one of the four research cigarette conditions (0.4, 2.4, 5.2, or 15.8 mg/g nicotine) under double-blind conditions, with condition order counterbalanced across participants. They rated the subjective effects of that cigarette and their craving and nicotine withdrawal levels, which were repeated every 15 min for an hour. In Phase 2 (Sessions 6–11), participants completed a behavioral assessment of the relative reinforcing efficacies of the cigarette doses. In each session, two doses (0.4, 2.4, 5.2, or 15.8 mg/g nicotine) were presented under double-blind conditions. Each time that participants wished to smoke, they responded 10 times to receive 2 cigarette puffs of either cigarette. Participants had 3 h in which they could smoke as much of either cigarette as they wanted. In Phase 3 (Sessions 12–14), participants completed a concurrent choice task in which they could make 10 responses for two puffs of the 0.4 mg/g cigarette or a progressively-increasing number of responses for two puffs of the 15.8 mg/g cigarette.

Participants with emotional disorders (n = 56) were approximately 35 years old, 55% female, 71% non-Hispanic White, smoked 16.3 CPD, and had mean scores above the clinical thresholds on depression and anxiety symptom measures. Results from the Phase 1 comparison of the cigarette conditions on measures of cigarette subjective effects, craving, withdrawal symptoms and smoking topography indicated that decreasing the nicotine content of the research cigarettes led to decreases in the positive subjective effects of the cigarettes (e.g., effects on satisfaction; Fig. 2). All of the cigarette doses attenuated craving and withdrawal symptoms, although the higher doses were more efficacious. Finally, no effects of nicotine content on breath CO level or smoking topography were observed, suggesting that compensatory smoking did not occur at lower doses. Phase 2 results indicated that participants preferred the higher dose cigarette in each pair comparison when the puffs from each cigarette were available at equal response cost (Fig. 2). Phase 3 results (not shown) indicated that increasing the response cost for the higher nicotine content cigarette switched preference to the lower-nicotine cigarette. In sum, results from this study indicate that reducing the nicotine content of cigarettes reduces their addiction potential, as assessed by well-validated behavioral and

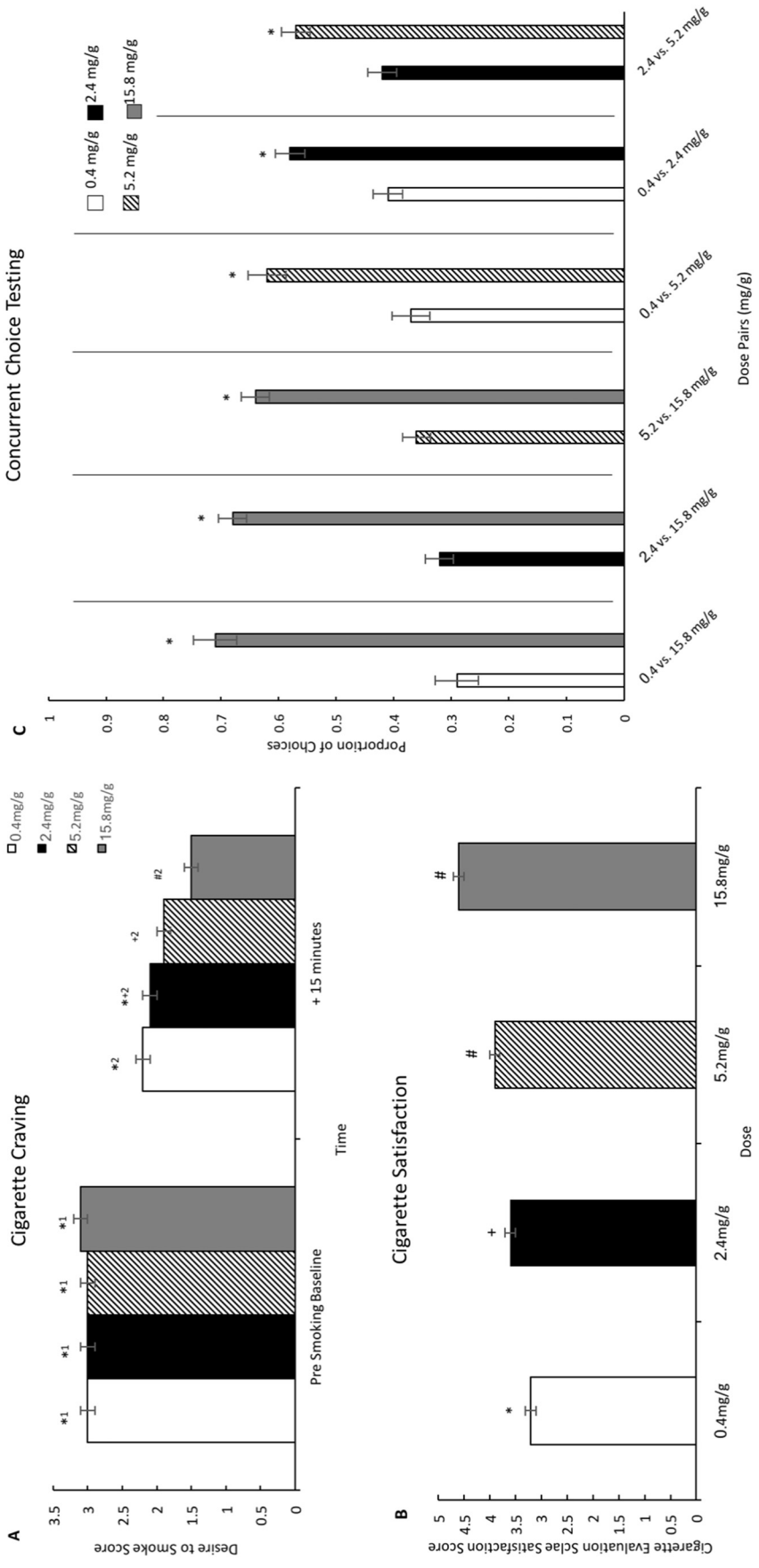

Fig. 2. Effects of cigarette nicotine content in smokers with emotional disorders on cigarette craving (Panel A), satisfaction (Panel B) and preference during concurrent choice testing sessions (Panel C). Bars represent Mean ± SEM. In Panels A and B, data points with different symbols within a testing time-point differ significantly ($p < .05$). In Panel C, * indicates significant difference at the $p < .05$ level in proportion of choices within each dose pair. This research (Higgins et al., 2017) was conducted in the United States in 2013–2017.

subjective measures, without increasing craving, withdrawal, or topography measures indicative of compensatory smoking.

The Higgins et al. (2017) study set the stage for an investigation of the effects of extended use of reduced-nicotine cigarettes in smokers with emotional disorders. Two such trials are currently underway. The UVM TCORS, again in collaboration with Brown University, is currently conducting a double-blind randomized clinical trial of the effects of research cigarettes varying in nicotine content on CPD, cigarette subjective effects, psychiatric symptoms, neurocognitive function, and biological markers of tobacco exposure over a 12-week period in over 200 smokers with emotional disorders, using the same diagnostic inclusion criteria as the Higgins et al. (2017) study. After a one-week baseline period during which participants smoke their usual brand of cigarettes, they are randomized to either 15.8, 2.4, or 0.4 mg/g nicotine research cigarettes. They are provided with these cigarettes free of charge for 12 weeks and instructed to smoke only these cigarettes. Participants use an interactive voice response system to report the number of study cigarettes, non-study cigarettes, and other tobacco and nicotine products that they use every day, and complete assessments of cigarette craving, withdrawal symptoms, psychiatric symptoms, and cigarette subjective effects at weekly laboratory visits. Cognitive performance, puff topography and physiological measures of nicotine exposure, tobacco toxin exposure, pulmonary function and cardiovascular function are assessed at baseline, Week 6 (mid-way through the intervention period) and Week 12 (end of intervention period). At Week 12, participants are provided with a financial incentive ($100) to abstain from smoking for one day (based on CO $<$ 50% of CO level at the Week 12 visit), and those with CO-verified abstinence complete questionnaires, cognitive tasks, and a smoking vs. money choice task aimed at assessing whether 12-week use of reduced-nicotine cigarettes has reduced the relative reinforcing value of smoking. Participants are recontacted 30 days later to evaluate their current smoking status and to assess whether use of the 0.4 mg/g cigarettes increased quit attempts, as was observed in the Donny et al. (2015) study.

A second trial of the effects of nicotine reduction in smokers with emotional disorders is currently underway by a TCORS at the Pennsylvania State University (Penn State) in collaboration with Massachusetts General Hospital (Allen et al., 2017). Unlike the study by the UVM TCORS described above, which is examining the effects of an immediate reduction in the nicotine content of cigarettes, the Penn State TCORS is evaluating the effects of a gradual reduction in the nicotine content of cigarettes over a 34-week period on CPD, toxicant exposure and psychiatric symptoms in 200 smokers with emotional disorders. Adults who smoke at least 5 CPD, are not trying to quit smoking, and meet criteria for a current or lifetime unipolar mood and/or anxiety disorder complete a baseline period consisting of a week of their usual brand of cigarettes followed by 2 weeks of using research cigarettes with 11.6 mg nicotine/cigarette. Next, participants are randomly assigned under double-blind conditions to either continue smoking research cigarettes with 11.6 mg nicotine/cigarette throughout the trial or to a condition in which the nicotine content of their research cigarettes is progressively reduced to 0.2 mg nicotine/cigarette in five steps over 18 weeks. At the end of the randomization phase, participants are offered the choice between (1) quitting smoking with assistance, (2) continuing to receive free research cigarettes, or (3) purchasing their own usual-brand cigarettes to use during the final 12 weeks of the study. Outcome measures include nicotine exposure, breath CO level, tobacco toxin exposure, psychiatric symptom levels, nicotine dependence severity, CPD and quit attempts (Allen et al., 2017).

Together, the studies by the UVM and Penn State TCORS will not only thoroughly investigate the subjective, behavioral and physiological effects of a reduced-nicotine standard for cigarettes in smokers with emotional disorders, but will also address the important question of which approach to nicotine reduction – immediate or gradual – will be more effective and better tolerated by smokers with these disorders. An immediate reduction in nicotine presumably would reduce CPD and improve smoking-related health measures more quickly than a gradual reduction, but a gradual reduction might be less likely to lead to increases in nicotine withdrawal, increases in psychiatric symptoms, decreases in cognitive function, and increases in smoke intake in efforts to overcome these effects.

3. Smokers with schizophrenia

Smokers with schizophrenia have higher nicotine intake when smoking, and experience more severe craving, withdrawal, and cognitive impairment than non-psychiatric smokers when abstinent (Tidey and Miller, 2015). Based on their responses to abstinence, a reduced-nicotine standard for cigarettes could lead to affective and cognitive disruption in these smokers, and could result in compensatory increases in cigarette use in attempts to ameliorate these effects.

Tidey et al. (2013) investigated the separate and combined acute effects of VLNC cigarettes (Quest 3 cigarettes, Vector Tobacco, with 0.6 mg nicotine content) and 42 mg transdermal nicotine replacement therapy (NRT) on smoking, cigarette subjective effects, craving, and withdrawal symptoms in 30 smokers with schizophrenia compared to 26 equally-heavy smokers without psychiatric disorders (Tidey et al., 2013). As in the studies by Tidey et al. (2017), Higgins et al. (2017), and the UVM and Penn State TCORS studies currently underway, this study was conducted in smokers who were not actively trying to quit smoking. This work evolved from a prior study in which it was observed that smokers with schizophrenia were less sensitive to the effects of 42 mg NRT on smoking reinstatement after 5-h abstinence than were control smokers (Tidey et al., 2008). Based on a large body of work conducted in smokers without psychiatric disorders (Rose, 2006), we hypothesized that VLNC cigarettes would provide sensorimotor replacement for usual-brand cigarettes and therefore reduce the effects of abstinence on craving, withdrawal, and smoking reinstatement compared to when participants did not use any cigarettes. Although two studies by Smith et al. (2001, 2002) had compared the effects of VLNC and higher nicotine cigarettes on psychiatric symptoms and cognitive performance in smokers with schizophrenia, neither had investigated the effects of VLNC cigarettes on smoking. We further hypothesized that combining VLNC cigarettes with NRT would be most effective at reducing craving, withdrawal symptoms and smoking.

The Tidey et al. (2013) study used a within-subjects design in which the participants completed 5 study conditions in counter-balanced order: 42 mg NRT plus VLNC cigarettes, placebo patches plus VLNC cigarettes, 42 mg NRT without VLNC cigarettes, placebo patches without VLNC cigarettes, and usual brand cigarettes. Each session consisted of a 5-h pre-treatment period in which participants underwent one of the above conditions, followed by assessments of craving, withdrawal, and cognitive function, followed by a 90-min period in which participants could smoke their usual-brand cigarettes ad libitum. Results, shown in Fig. 3, below, indicate that: (1) the smokers with schizophrenia had higher nicotine withdrawal symptom scores than the controls; (2) use of VLNC cigarettes during the 5-h periods significantly reduced craving, nicotine withdrawal symptoms, and usual-brand smoking in both groups compared to sessions in which participants did not smoke; (3) NRT significantly reduced craving and tended to reduce nicotine withdrawal, but did not reduce usual-brand smoking in either group; and (4) NRT did not augment the effects of VLNC cigarettes on these measures. Psychiatric symptom severity scores in the smokers with schizophrenia were not affected by either NRT or VLNC cigarette use (Tidey et al., 2013).

A comparison of the effects of usual brand cigarettes, VLNC cigarettes with placebo patches, and VLNC cigarettes with NRT on several measures of cognitive performance collected in the Tidey et al. (2013) study was published separately (Ahnallen et al., 2015). Across conditions, the smokers with schizophrenia were slower than the controls on motor and visual working memory tasks, and had poorer target

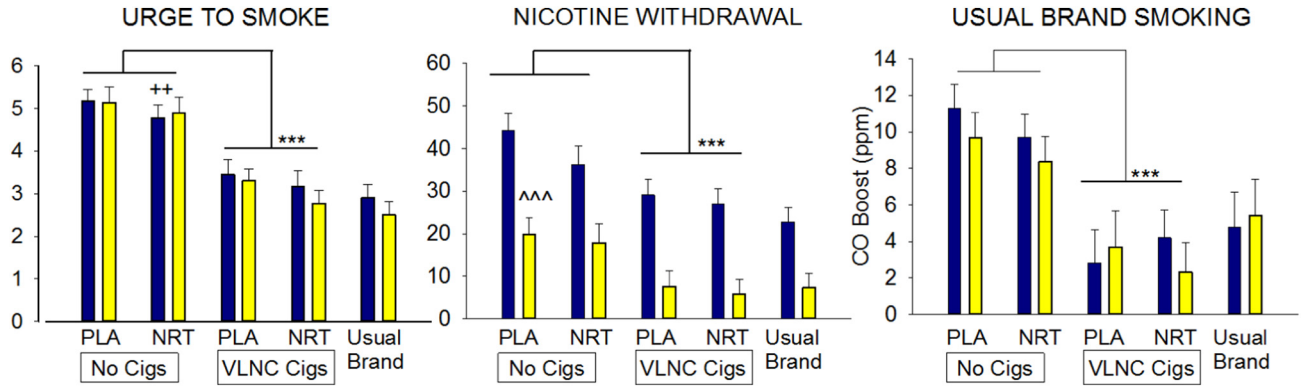

Fig. 3. Separate and combined effects of very low nicotine content (VLNC) cigarettes and 42 mg transdermal nicotine replacement therapy (NRT) on smoking urge, nicotine withdrawal symptoms and usual-brand smoking in smokers with schizophrenia (dark bars) and controls (light bars). *** indicates significant difference between cigarette conditions at the $p < .001$ level. ++ indicates significant effect of NRT at the $p < .01$ level. ^^^ indicates significant difference between groups at the $p < .001$ level. This research (Tidey et al., 2013) was conducted in the United States in 2006–2011.

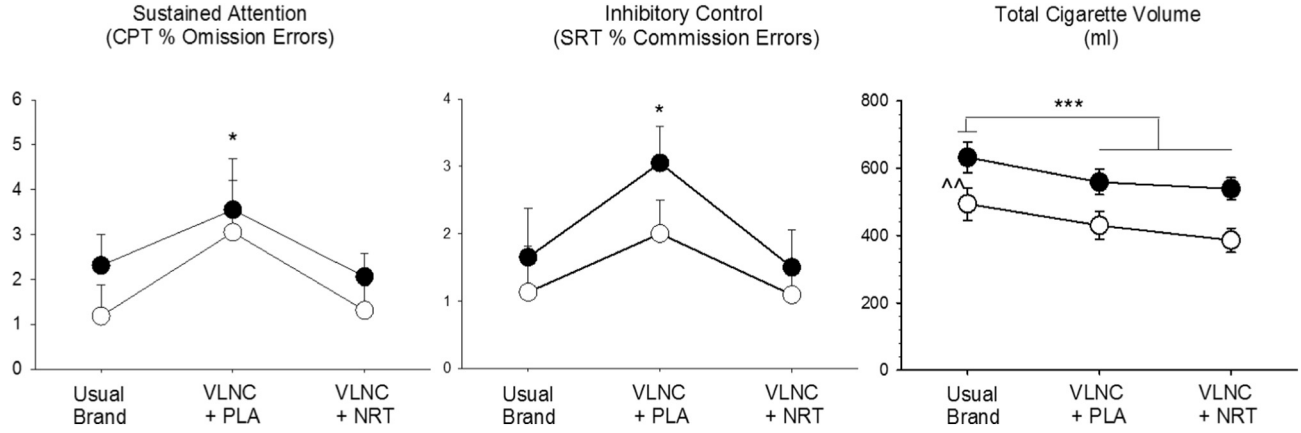

Fig. 4. Effects of very low nicotine content (VLNC) cigarettes with placebo (PLA) or 42 mg transdermal nicotine replacement therapy (NRT) on cognitive performance and total cigarette smoke volume in smokers with schizophrenia (filled symbols) and controls (unfilled symbols). Asterisks indicate differences between cigarette conditions (*$p < .05$, ***$p < .001$). ^^ indicates differences between groups ($p < .01$). This research (Ahnallen et al., 2015) was conducted in the United States in 2006–2011.

detectability on a visual sustained attention task. When participants used VLNC cigarettes with placebo patches, performance in domains of visual sustained attention, inhibitory control, processing speed, and response variability was impaired in both groups, and restored in both groups when VLNCs were combined with NRT (Ahnallen et al., 2015) (Fig. 4, left and middle). In addition, a comparison of usual brand cigarettes and VLNC cigarettes on smoking topography indices from the Tidey et al. (2013) study was conducted (Tidey et al., 2016). The smokers with schizophrenia had more intense puff topography indices (i.e., more puffs per cigarette, more puffs per session, and shorter inter-puff intervals) than the controls, as has been reported previously (Tidey et al., 2005; Williams et al., 2011). When smoking VLNC cigarettes, participants in both groups took longer puffs and had shorter inter-puff intervals, but smoked fewer puffs, resulting in an overall decrease in cigarette puff volume that did not differ by group (Fig. 4, right). The co-use of NRT tended to reverse the effects of VLNC cigarettes on puff volume, duration, and inter-puff interval, but not on number of puffs or total volume smoked (Tidey et al., 2016).

Overall, results from this series of studies indicate that the acute effects of VLNC cigarettes are more effective than NRT in reducing craving, withdrawal, and smoking reinstatement in smokers with schizophrenia, apparently because the sensorimotor effects of these cigarettes provide conditioned reinforcing effects that reduce craving and withdrawal even in the absence of nicotine. Furthermore, use of VLNC cigarettes did not appear to cause increases in total smoke intake under these acute laboratory conditions. However, the use of VLNC cigarettes without nicotine led to impairments in cognitive performance in both smokers with schizophrenia and controls, which were reversed by the co-administration of NRT. Thus, if a reduced-nicotine standard for cigarettes were implemented, heavy smokers with and without schizophrenia may benefit from co-use of NRT or another source of non-combusted nicotine.

4. Effects of extended VLNC use in smokers with serious mental illness

A study was recently completed at Brown University, as part of the CENIC TCORS, that investigated the effects of VLNC cigarette use over a 6-week period on a comprehensive battery of tobacco use, mood, and health outcomes in smokers with schizophrenia and bipolar disorder. Adult smokers with one of these disorders, who smoked ≥10 CPD, were psychiatrically-stable, and not trying to quit smoking, were randomized to receive research cigarettes containing either 0.4 mg/g or 15.8 mg/g nicotine. Participants were provided with these cigarettes free of charge for six weeks and were asked to smoke only these cigarettes. They used an interactive voice response system each day to report the number of study cigarettes, non-study cigarettes, and other tobacco and nicotine products they had consumed since the previous day, and completed other subjective, behavioral, and physiological assessments during weekly laboratory visits. At the end of the 6-week intervention period, participants underwent an abstinence assessment to determine if use of the 0.4 mg/g cigarettes facilitated abstinence and reduced craving and

withdrawal symptoms during abstinence. Participants received a follow-up phone call one month after the end of this period to assess their smoking patterns and to assess whether use of the 0.4 mg/g cigarettes increased quit attempts, as was observed by Donny et al. (2015) in smokers without MHCs.

This study recently completed enrollment and data analysis is underway. Based on results from Donny et al. (2015), it is hypothesized that, at Week 6, those who were randomized to the 0.4 mg/g cigarettes will report smoking fewer CPD, have lower levels of nicotine exposure and will report lower cigarette dependence severity than those who had been assigned to the 15.8 mg/g nicotine research cigarettes. The effects of these cigarettes on psychiatric symptoms, cigarette acceptability, craving, withdrawal symptoms, cognitive functioning, smoking topography, and biomarkers of nicotine exposure and tobacco carcinogen exposure will also be compared. Because the measures in this study were selected to substantially overlap those used in the Donny et al. (2015) study in non-psychiatric smokers and the UVM and Penn State TCORS studies of smokers with emotional disorders, researchers will have the opportunity to compare how these groups of smokers respond to nicotine reduction.

5. Summary and future directions

An FDA-mandated reduction in the nicotine content of cigarettes sold in the US to a minimally-addictive level has the potential to reduce tobacco dependence and increase smoking cessation rates among vulnerable subpopulations of smokers, such as people with MHCs, who have difficulty quitting despite making as many quit attempts as those without MHCs (McClave et al., 2010). To date, acute studies of the effects of cigarettes varying in nicotine content among smokers with emotional disorders (Higgins et al., 2017), smokers with schizophrenia (Tidey et al., 2013), and smokers sampled from the general population (Rose, 2006; Johnson et al., 2004) indicate that VLNC cigarettes have significantly less abuse liability than normal-nicotine cigarettes, as indicated by well-validated subjective and behavioral laboratory measures. Furthermore, the use of VLNC cigarettes acutely reduces craving and withdrawal symptoms compared to cigarette abstinence (e.g., see Figs. 2 and 3, above), presumably because the sensorimotor stimuli provided by these cigarettes buffer the effects of nicotine abstinence on these symptoms. Although the effects of extended VLNC use on psychiatric symptoms in smokers with MHCs have not yet been reported, such studies are currently underway. To date, one study of the acute effects of VLNC cigarettes in smokers with schizophrenia (Tidey et al., 2013) and one of the extended effects of VLNC cigarettes in smokers with elevated depressive symptoms (Tidey et al., 2017) did not find deleterious effects on psychiatric symptoms; in fact, depressive symptoms improved among those randomized to VLNC cigarettes compared to those assigned to normal-nicotine cigarettes (Tidey et al., 2017).

However, one area of functioning where deleterious effects of nicotine reduction have been observed is cognitive performance (Ahnallen et al., 2015) as shown in Fig. 4, above. Whether these effects would persist past the acute nicotine withdrawal phase is unknown. These cognitive performance decrements were reversed by the concurrent use of NRT, and presumably also would be offset by the co-use of other nicotine products such as alternative nicotine delivery systems (ANDS), although this is currently unknown. Limiting the nicotine content of combustible tobacco products, while supporting switching to non-combusted nicotine products such as ANDS and NRT, are potentially complementary tobacco regulatory approaches that together may have a greater impact on public health than either alone (Benowitz et al., 2017).

Another concern is that if a reduced-nicotine standard were applied only to cigarettes, smokers with MHCs may switch to other combusted tobacco products, such as filtered little cigars and cigarillos (LCCs), rather than reduce their tobacco use. LCCs are often used as lower-cost substitutes for cigarettes (Delnevo et al., 2017; Corey et al., 2017) and deliver nicotine and toxins at levels that are similar to, or higher than, those of cigarettes (Goel et al., 2017; Pickworth et al., 2018). Therefore, to maximize the potential public health benefits of a nicotine-reduction standard, this standard should be applied to combusted tobacco products more broadly, rather than to cigarettes exclusively.

Given the persistence of tobacco dependence among people with MHCs, multi-pronged strategies may be necessary to decrease cigarette smoking, dependence, and tobacco-related morbidity and mortality among these smokers. Reducing the nicotine content of cigarettes to a minimally-addictive level may increase quit attempts among smokers with MHCs, as has been seen in those without MHCs (Donny et al., 2015), and has the potential to increase the effectiveness of other tobacco control approaches and smoking cessation treatments. Results from studies to date are promising, and results from studies underway will further evaluate the safety and feasibility of a nicotine reduction standard as a policy-based approach to reducing health inequalities in people with MHCs and other vulnerable populations.

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Conflicts of interest

None.

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