Reduced Nicotine Content Cigarettes and Cannabis Use in Vulnerable Populations

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Objective: We estimated whether recent cannabis use moderates response to cigarettes varying in nicotine content (0.4, 2.4, 5.2, 15.8 mg/g) among smokers with concurrent affective disorders, opioid dependence, or socioeconomic disadvantage. **Methods:** We conducted a secondary analysis of a multi-site, double-blind, laboratory study examining acute response to reduced nicotine content cigarettes (RNCC) in 169 adult smokers with co-morbid conditions. Participants positive for recent cannabis use or self-reported past 30-day cannabis use at baseline were categorized as current cannabis users (N = 63). Repeated measures analysis of variance tests assessed whether baseline cannabis use moderated cigarette reinforcement, tobacco withdrawal, craving, smoking topography, or carbon monoxide boost. **Results:** Cannabis users were younger, less educated, and had more depression and anxiety than non-users ($p < .05$). Cannabis use status did not moderate the effects of nicotine dose on concurrent choice testing, subjective effects of RNCCs, or smoking topography. After adjusting for sociodemographic characteristics, cannabis users had higher ratings on Smoking Satisfaction, Enjoyment of Respiratory Tract Sensations, and Craving Reduction across all nicotine doses. Cannabis users reported longer withdrawal symptom duration and more rapid decline of carbon monoxide boost than non-users. **Conclusions:** Findings suggest RNCCs decrease the addiction potential of cigarettes in vulnerable populations independent of cannabis use status.

Key words: cannabis; marijuana; nicotine reduction; smoking; tobacco regulation; vulnerable populations
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The 2009 Family Smoking Prevention and Tobacco Control Act gave the Food and Drug Administration (FDA) regulatory authority to reduce the nicotine content in cigarettes.[1] A growing body of research indicates that reducing the nicotine content in cigarettes to minimally addictive levels has the potential for tremendous beneficial impact on public health.[2] Indeed, lowering the nicotine content of cigarettes significantly decreases smoking rate, dependence severity, and toxicant exposure when used over extended periods of time.[3-7] Until recently, however, research with reduced nicotine content cigarettes (RNCC) generally has been limited to healthy smokers.[8-10]

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There have been efforts to examine effects of cigarettes varying in nicotine content among cigarette smokers with co-morbid psychiatric conditions or socioeconomic disadvantage.[8-12] Because these populations have higher prevalence of smoking and nicotine dependence, they are important populations to consider when examining the potential impact of a national nicotine reduction policy.[13-15] So far, evidence from acute- and extended-exposure studies suggest that RNCCs have lower abuse potential, lower toxicant exposure, and do not produce compensatory smoking or untoward craving or withdrawal among these vulnerable populations.[8-11,16]

Given the shifting legal landscape and growing prevalence of cannabis use,[17] individuals who co-use tobacco and cannabis are of interest when examining the effects of nicotine reduction on smoking. In the general population, cigarette smokers are more likely to use cannabis and use it daily.[18] A number of genetic, environmental, and pharmacological factors also suggest potential interactions between these 2 drugs.[19] Additionally, rates and severity of cannabis use are often greater among populations with psychiatric disorders or socioeconomic disadvantage.[20-22] Given the unique risks associated with tobacco and cannabis use among vulnerable populations, it is important to examine whether cannabis use status may moderate response to RNCCs in these smokers.

We know of only one prior study examining the influence of cannabis use on response to RNCCs, in which there was no association between cannabis use status and RNCC effects among healthy smokers over a 6-week period.[11] Whereas these results are promising, further research is needed to assess effects of cannabis use status among smokers who have concurrent vulnerabilities to smoking, and thus, may be uniquely influenced by co-use of cannabis. In this secondary analysis we compared acute response to RNCCs among vulnerable smokers who do versus do not use cannabis.

METHODS

Participants and Procedures

Participants in this double-blind, multi-site study included 169 adult daily smokers (56 with affective disorders as an exemplar of smokers with mental illness, 60 with opioid dependence as an exemplar of smokers with co-morbid substance use disorders, 53 women of reproductive age with less than an associate's degree as an exemplar of smokers with socioeconomic disadvantage) who provided written informed consent. Additional details on participant selection and other study methods can be found in the previously published report of the parent study.[8]

Cannabis use was measured at study intake via self-report ("How many days did you use marijuana in the past 30 days?") and urine toxicology (ie, tetrahydrocannabinol [THC] positive). Those who tested positive for THC or self-reported past 30-day cannabis use were classified as current cannabis users (N = 63). Non-users did not test positive for THC or self-report past 30-day cannabis use (N = 106).

Briefly, participants completed 14 experimental sessions organized into 3 phases. All sessions were conducted following brief smoking abstinence (≤50% baseline breath carbon monoxide (CO) level); participants were also instructed to refrain from cannabis use as this could affect breath CO ratings. During Phase 1 (Sessions 2-5), participants sampled one of 4 research cigarettes varying in nicotine content (15.8, 5.2, 2.4, 0.4mg/g) in separate sessions. Participants smoked the research cigarettes *ad lib* through a Clinical Research Support System (CReSS) desktop smoking topography device.[23] Breath CO samples were collected immediately before smoking and every 15 minutes for 60 minutes after smoking the assigned cigarette. CO boost was calculated by subtracting pre-smoking from post-smoking CO values.[24] Participants also completed a behavioral economic simulation task, the Cigarette Purchase Task (CPT), and the modified Cigarette Evaluation Questionnaire (mCEQ) immediately after smoking as well as the Minnesota Tobacco Withdrawal Scale (MTWS)[25] and Questionnaire of Smoking Urges-Brief (QSU-Brief)[26] prior to and every 15 minutes for 60 minutes after smoking. The QSU-Brief has 2 factors. Factor 1 measures craving for positive reinforcing effects of smoking and Factor 2 measures craving to reduce abstinence-related negative affect.[26]

In Phase 2 (Sessions 6-11), the relative reinforcing effects of each nicotine dose cigarette were evaluated by allowing participants to choose which cigarette they preferred to smoke when each dose-pair combination was available at an equal response cost of 10 mouse clicks. One dose pair was tested per session.[27,28] Phase 3 (Sessions 12-14) compared

only the lowest and highest dose cigarettes using a similar arrangement to Phase 2 but placing access to the high dose on a progressive ratio schedule; secondary analyses on Phase 3 results will be reported elsewhere.

Data Analysis

Repeated-measures analysis of variance, using a general linear mixed model adapted for use in a crossover study, examined the effects of baseline cannabis use on study outcomes. From Phase 1, overall effects on the CPT, mCEQ, MTWS, QSU-Brief, and CO boost were assessed using nicotine dose and time (when appropriate) as within-participant factors. All analyses included random effects adjusting for study site and research-cigarette sequence. Population differences were not examined because there were minimal differences between those with concurrent affective disorders, opioid dependence, or socioeconomic disadvantage in the parent study. Additional details on the data analysis plan are provided in that report.[8] Dose-by-cannabis use interactions examined whether effects differed by dose and cannabis use, and dose-by-time-by-cannabis interactions tested whether effects differed by dose and cannabis use status over time. First, unadjusted models were run, followed by models controlling for covariates that differed at baseline (ie, age (continuous), education, Beck Depression Inventory (BDI) and Overall Anxiety and Severity Impairment Scale (OASIS) scores, and sex). Interaction terms that were not statistically significant were deleted and the analyses were repeated. For the CPT, all demand indices were empirically quantified from observed values. Maximal expenditure, maximal price, breakpoint, and alpha values were $\log_{10}$ transformed to correct for skewness. For Phase 2, differences in dose-pair preferences were estimated using repeated-measures analysis of variance in a similar manner, with each dose-pair combination as the within-participant factor. All p-values < .05 were considered statistically significant. Significant effects were followed by *post hoc* testing using the Bonferroni correction. Analyses were conducted using SAS software version 9.4.[29]

RESULTS

Baseline Characteristics

At baseline, 37.3% of participants were characterized as cannabis users (N = 63). Of these, 58.7% (N = 37) reported cannabis use and provided a THC-positive urine specimen at study intake, 36.5% (N = 23) reported recent cannabis use but tested negative for THC, and 4.8% (N = 3) tested positive for THC but did not report use. Current cannabis users reported using cannabis an average of 12.5 (SD = 12.4) days during the past month. Relative to non-users, cannabis users were more likely to be younger ($t(167) = 3.45$; $p < .001$), less educated (χ^2 (3, N = 169) = 7.94; p = .047), and have higher BDI ($t(167) = -3.47$; $p < .001$) and OASIS scores ($t(166) = -2.98$; $p = .003$) (Table 1).

Relative Reinforcing Effects

There were no statistically significant effects of cannabis use status on concurrent choice between cigarette pairs ($F(1,113) = 0.37$; $p = .55$). Overall significant effects were seen among the dose pairs ($F(5,831) = 6.58$; $p < .001$), with participants preferring higher over lower nicotine doses across all dose pairs (*t*s > 3.45; p < .02). Cannabis use status did not interact with that relationship ($F(5,826) = 0.82$; $p = .53$). On the behavioral economic simulation task, there were statistically significant dose differences across each CPT index (all F*s* (3, 446) > 5.07; $p \leq .01$), with more intense/persistent demand at higher doses. However, dose did not interact with cannabis use status (all F*s* < 2.38; p*s* > .05).

mCEQ Subscales

Cannabis users reported higher ratings than non-users on 3 of the 5 mCEQ subscales (Figure 1): Smoking Satisfaction ($F(1,159) = 9.62$; $p = .002$), Enjoyment of Respiratory Tract Sensations ($F(1,159) = 4.68$; $p = .03$), and Craving Reduction ($F(1,157) = 6.63$; $p = .01$). Mean mCEQ subscale scores changed as an orderly function of dose ($p < .001$), but those effects did not interact with cannabis use status (F*s* < 0.89, p*s* > .05).

Withdrawal and Craving

The time-course of MTWS Total Scores differed significantly between cannabis users and non-users, with scores returning to baseline sooner (by 60 minutes) among non-cannabis compared to cannabis users (cannabis-by-time-interaction; $F(4,665) = 5.83$; $p < .001$). There was also a dose-by-time interaction, with effects of higher doses having

Table 1
Participant Characteristics

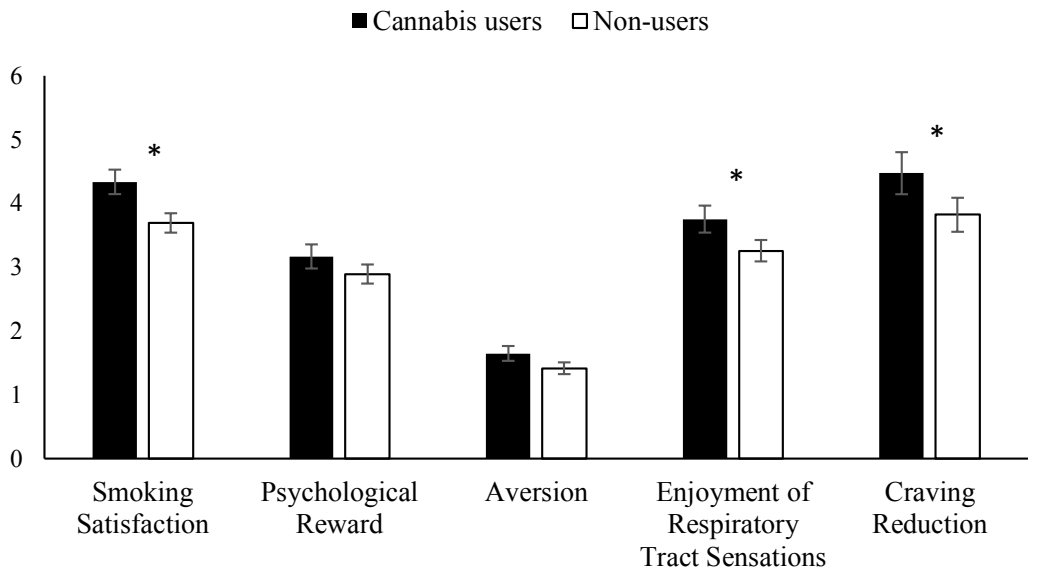
	All participants (N = 169)	Cannabis users (N = 63)	Non-users (N = 106)	p-value
Age, Mean (SD), Years	35.6 (11.4)	31.8 (9.5)	37.8 (11.8)	< .001
Female	120 (71.0%)	44 (69.8%)	76 (71.7%)	.797
Race/Ethnicity				.113
Non-Hispanic White	127 (75.2%)	52 (82.5%)	75 (70.8%)	
Non-Hispanic Black	23 (13.6%)	3 (4.8%)	20 (18.9%)	
Other	19 (11.2%)	8 (12.7%)	11 (10.4%)	
Education				.047
College Graduate	10 (5.9%)	5 (7.9%)	5 (4.7%)	
Some College	74 (43.8%)	28 (44.4%)	46 (43.4%)	
High-School Graduate	58 (34.3%)	26 (41.3%)	32 (30.2%)	
Some High-School	27 (16.0%)	4 (6.3%)	23 (21.7%)	
Marital Status				.384
Never Married	103 (60.9%)	42 (66.7%)	61 (57.5%)	
Married for the First Time	27 (16.0%)	10 (15.9%)	17 (16.0%)	
Divorced	39 (23.1%)	11 (17.5%)	28 (26.4%)	
Age Started Smoking Regularly, Mean (SD), Years	16.3 (4.3)	15.7 (2.9)	16.6 (4.9)	.135
Primary Menthol Smoker	61 (36.1%)	17 (27.0%)	44 (41.5%)	.069
Cigarettes per Day, Mean (SD)	15.8 (7.5)	16.3 (8.6)	15.5 (6.7)	.549
Nicotine Dependence, FTND Total, Mean (SD)	5.0 (2.2)	4.8 (2.1)	5.2 (2.2)	.289
Baseline Carbon Monoxide (CO), Mean (SD)	22.7 (11.8)	24.7 (13.3)	21.5 (10.8)	.090
Beck Depression Inventory (BDI) Score	12.6 (11.6)	16.4 (12.6)	10.3 (10.3)	< .001
Overall Anxiety Severity and Impairment Scale (OASIS) Score	5.7 (5.3)	7.2 (5.4)	4.8 (5.0)	.003
Opioid Dependent	60 (35.5%)	19 (30.2%)	41 (38.7%)	.263

Note.
Unless otherwise indicated, data are expressed as number (%) of participants. Cannabis users were defined as either positive urine or reporting use in the past 30 days at screening.
FTND = Fagerström Test for Nicotine Dependence

longer duration ($F(12,2002) = 2.77$; $p < .001$); no cannabis-by-dose-by-time interaction was noted ($F(12,1991) = 0.80$; $p = .65$).

Regarding the single MTWS 'Desire to Smoke' item, cannabis users reported greater tobacco craving than non-users across all doses and times ($F(1,159) = 5.20$; $p = .024$). Whereas each of the doses reduced ratings post-smoking, the dura-

Figure 1
Modified Cigarette Evaluation Questionnaire (mCEQ) Subscale Scores by Cannabis Use Status



Note.
Mean mCEQ scores (±95% Confidence Intervals) are shown across all research cigarette doses. Asterisks denote statistical significance at p < .05. Range of y-axis scale limited to permit improved visual inspection.

tion of effects was greater for the 15.8 mg/g dose ($t(2237) = 4.66$; $p = <0.001$). That relation did not interact with cannabis use status ($F(12,1990) = 0.74$; $p = .71$).

No statistically significant effects of cannabis use status were noted on the QSU-Brief Factor 1 or 2 scales ($p = .06$ and .40 for Factors 1 and 2, respectively) nor interactions of cannabis use status, dose, and time ($Fs > 1.74$; $ps > .05$). All cigarette doses reduced pre- to post-smoking ratings on the QSU-Brief Factors 1 and 2 ($ts > 2.96$ and 3.71, respectively; $p < .001$).

Smoking Topography and CO Boost

There were no statistically significant effects of cannabis use status on smoking topography ($Fs < 3.51$; $ps > .05$). However, there were effects of dose on 3 of the 6 measures (total puff volume, mean maximum flow rate, puff number; $Fs > 3.46$; $p < .02$), with participants taking larger, more intense, and a greater number of puffs with the highest nicotine dose.

CO boost among cannabis users declined more rapidly compared to non-users even after adjusting for baseline CO levels during the 60-minute observation period (cannabis-by-time interaction; $F(3,498) = 3.41$; $p = .02$; Supplemental Figure 1). There were no statistically significant effects of dose or interactions of dose and cannabis use status.

DISCUSSION

In this secondary analysis, we compared acute response to cigarettes varying in nicotine content among smokers with psychiatric comorbidity (ie, opioid dependence, affective disorders) or low socioeconomic status who were versus were not current cannabis users. This study provides evidence that reducing the nicotine content of cigarettes decreases the addiction potential of smoking in these vulnerable smokers independent of whether they are current cannabis users consistent with results reported previously on this question in healthier smokers.[11] Whereas cannabis users reported significantly greater positive subjective effects from

smoking than non-users on several mCEQ subscales, those differences did not interact with the effect of dose reduction on those subscales or any of the other measures of addiction potential, withdrawal, craving, or smoking topography. This is an important observation as prevalence of cannabis is elevated among smokers and vulnerable populations[20,22] and one might anticipate an increase in cannabis use as laws governing cannabis are further liberalized.[30] Knowing that cannabis users are not adversely or differentially impacted by nicotine reductions in cigarettes is important for tobacco regulatory policy as decriminalization of cannabis will likely continue to expand.

That cannabis users might differ on some subjective effects of cigarette smoking is not surprising as these are self-selecting cannabis users who may use substances because of enhanced subjective effects.[31] Despite this, there was no evidence that RNCC use in these smokers was associated with increased withdrawal or craving.[5] Furthermore, findings indicate cannabis users are not engaging in compensatory smoking, as cannabis co-users did not differ from non-users on the smoking topography measures examined.

Study strengths include double-blind research cigarette testing, the highly controlled laboratory model, extensive battery of dependent measures, direct testing of relative reinforcing effects that are central to an assessment of addiction potential,[32,33] and the multi-site design with a diverse population of vulnerable smokers. Cannabis user status was determined with both self-report and biochemical verification. Limitations include the fact that self-reported past-month cannabis use or positive toxicology screen may not indicate typical cannabis use or cannabis use disorders. In addition, our socioeconomically disadvantaged group only included women of reproductive age leaving older women and men unexamined.

IMPLICATIONS FOR TOBACCO REGULATION

In summary, these data suggest that reducing the nicotine content of cigarettes reduces the addiction potential of smoking among vulnerable smokers with concurrent cannabis use. A national regulatory policy that reduces nicotine product standards has the potential to benefit smokers from vulnerable populations independent of their use of cannabis.

Human Subjects Statement

The Institutional Review Boards at the University of Vermont, Brown University, and Johns Hopkins University School of Medicine approved the study. Clinical Trials Identifier: NCT02250534.

Conflicts of Interest Statement

None declared.

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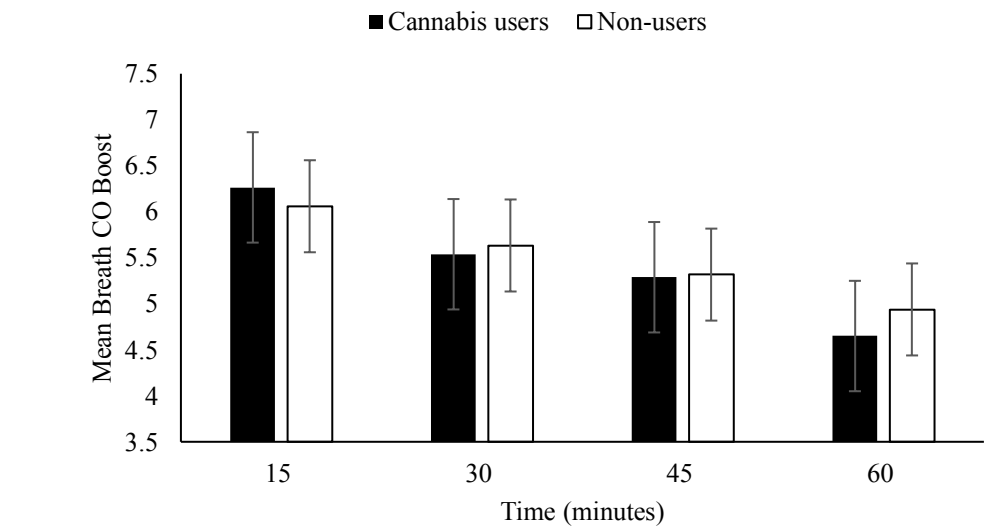
Supplemental Figure 1
Carbon monoxide (CO) Boost by Cannabis Use Status



Note.
Mean CO Boost scores (±95% Confidence Intervals) are shown across all research cigarette doses.