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Does Menthol Cigarette Use Moderate the Effect of Nicotine Metabolism on Short-term Smoking Cessation?

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Ms. Jao and Drs. Hitsman and Schnoll contributed to the study concept and design. All authors contributed to the acquisition, statistical analysis, or interpretation of data. Ms. Jao wrote the draft of the manuscript with input from Drs. Hitsman and Smith. All authors contributed to and approved the final manuscript.

This study was conducted by Ms. Jao as a part of her master's thesis under the supervision of Dr. Hitsman. She is currently a graduate student in the Clinical Psychology PhD program at Northwestern University Feinberg School of Medicine in Chicago, IL. A preliminary version of this study was presented at the 2016 meeting of the Society for Research on Nicotine and Tobacco held in Chicago, IL.

Drs. Hitsman and Schnoll receive varenicline and placebo free of charge from Pfizer for use in ongoing National Institutes of Health supported clinical trials. Dr. Hitsman has served on a scientific advisory board for Pfizer. Dr. Schnoll has provided consultation to Pfizer and GlaxoSmithKline. Dr. Tyndale has consulted for Apotex, on unrelated topics. All other authors declare that they have no potential conflicts of interest.

Abstract

The nicotine metabolite ratio (NMR) has been shown to predict response to the transdermal nicotine patch, such that faster nicotine metabolism is associated with a lower abstinence rate. Menthol cigarette use, vs. non-menthol cigarette use, slows nicotine metabolism and therefore may attenuate the effect of NMR on smoking abstinence. In this study, we evaluated whether cigarette type (menthol vs. non-menthol) modified the association between NMR and short-term abstinence. This was a secondary analysis examining treatment in the first 8 weeks of 21 mg/day nicotine patch therapy in a completed clinical trial (n=474). Menthol cigarette use was based on self-report. NMR was defined dichotomously (0=fast, 1=slow) to distinguish between fast (0.47) versus slow NMR. Using logistic regression analysis, we tested whether cigarette type moderated the association between NMR and bioverified 7-day point prevalence abstinence at week 8. Covariates include nicotine dependence, age, race, and sex. 302 participants reported smoking menthol cigarettes, of which 234 (77%) were classified as slow NMR. Among the 172 non-menthol smokers, 136 were classified as slow NMR (79%). Contrary to our expectations, the NMR by cigarette type interaction effect on abstinence was not significant (Odds Ratio [OR]=0.91, $p=.86$). Excluding the interaction variable, fast NMR was associated with decreased likelihood of abstinence (OR=0.55, $p=.03$), but menthol cigarette use was not (OR=1.15, $p=.56$). Further exploration of risk factors among menthol cigarette smokers, especially among racially diverse and light smokers, could clarify the association between menthol cigarette use and poorer smoking outcomes.

Keywords

nicotine metabolism; menthol; cigarette smoking; smoking abstinence

Although the smoking prevalence in the U.S. has reached a record low of 15.1% (Jamal et al., 2016), menthol cigarette use continues to increase in the United States, with rates among smokers increasing significantly from 35% in 2010 to 39% by 2014 (Villanti et al., 2016). Menthol, which is extracted from the peppermint plant and creates a minty or cooling sensation, is a common cigarette additive used to relieve the harshness of cigarette smoke (Strasser et al., 2013; Willis, Liu, Ha, Jordt, & Morris, 2011). However, menthol may influence much more than just the taste of cigarette smoke by directly affecting the biological processing of nicotine.

Nicotine, the primary addictive component in cigarettes, is metabolized to cotinine by CYP2A6 enzymes, which are responsible for up to 90% of nicotine clearance (Messina, Tyndale, & Sellers, 1997). The metabolic process can be measured by the nicotine metabolite ratio (NMR) (Benowitz, Pomerleau, Pomerleau, & Jacob, 2003; Strasser et al., 2011; Tyndale & Sellers, 2002; Xu, Goodz, Sellers, & Tyndale, 2002). Having a higher NMR, and therefore faster nicotine clearance, is often associated with greater risk for poor treatment outcomes (Chenoweth et al., 2016; Hendricks, Delucchi, Benowitz, & Hall, 2014; Strasser, Malaiyandi, Hoffmann, Tyndale, & Lerman, 2007). For instance, we previously observed that smokers with fast NMR were less likely to quit smoking than smokers with slow NMR after 8 weeks of treatment with 21 mg nicotine patch and behavioral counseling (Kaufmann et al., 2015). While NMR appears to be determined mainly by genetic

influences, there are other individual factors in smoking behavior, such as menthol cigarette use, which may influence nicotine clearance.

Basic animal and human studies provide compelling evidence indicating that menthol cigarette use may inhibit NMR by regulating nicotinic acetylcholine receptor functioning and metabolic pathways involved in up to 80–90% of nicotine breakdown (Ashoor et al., 2013; Benowitz, Herrera, & Jacob, 2004; Farco & Grundmann, 2013; Kabbani, 2013; Wickham, 2015). By slowing the rate of nicotine metabolism, menthol cigarette use may attenuate the effect of fast nicotine metabolism on treatment outcome. While menthol cigarette use, as opposed to non-menthol cigarette use, has been found to be associated with a greater degree of nicotine dependence and with smoking persistence (Delnevo, Gundersen, Hrywna, Echeverria, & Steinberg, 2011; Fu et al., 2008; Smith, Fiore, & Baker, 2014), especially for Black smokers (Foulds, Hooper, Pletcher, & Okuyemi, 2010), it is unclear how menthol cigarette use may interact with nicotine metabolism to affect smoking abstinence, especially during smoking cessation treatment. For instance, previous studies have focused on examining the relationship between menthol cigarette use and nicotine metabolism without cessation (Fagan et al., 2015; Perez-Stable, Herrera, Jacob, & Benowitz, 1998), the relationships between menthol cigarette use and smoking abstinence without treatment (Fagan et al., 2010; Hyland, Garten, Giovino, & Cummings, 2002; Muscat, Richie, & Stellman, 2002; Pletcher et al., 2006), or nicotine metabolism's influence only on smoking cessation treatment outcomes (Chenoweth et al., 2016; Lerman et al., 2010). Also, there are sex-differences in nicotine metabolism and menthol cigarette use that may be important to our understanding of smoking cessation treatment response (Benowitz, Lessov-Schlaggar, Swan, & Jacob, 2006; Curtin et al., 2014). For example, research suggests that menthol cigarette use was associated with faster initial rates of brain nicotine accumulation after smoking among men but not among women (Zuo et al., 2015). However, the relationship between nicotine metabolism and cigarette type on smoking cessation treatment outcomes remains under-explored. As improving the efficacy of smoking cessation treatment will require a better understanding of the biological mechanisms to treat nicotine dependence, it is important to examine whether individual factors that influence nicotine metabolism, such as menthol cigarette use, may be associated with smoking cessation treatment response.

The purpose of this study was to examine the impact of menthol cigarette use on the association between nicotine metabolism, measured using NMR, and short-term abstinence among smokers who completed 8 weeks of treatment involving 21 mg/day nicotine patch plus behavior counseling. We hypothesized that menthol cigarette use would moderate the relationship between NMR and abstinence at 8 weeks by attenuating the increased risk for continued smoking among smokers with fast NMR. Therefore, we expected that menthol cigarette use would increase the likelihood of achieving short-term abstinence, however, only among individuals with fast NMR. Due to potential sex-differences, we also examined the impact of cigarette type on NMR and smoking abstinence by sex.

Method

Participants

The current study was a secondary data analysis of a randomized controlled trial of 21 mg/day transdermal nicotine patch for smoking cessation (Kaufmann et al., 2015; Schnoll et al., 2015). The study was conducted at the University of Pennsylvania and Northwestern University, which provided Institutional Review Board oversight and approval (ClinicalTrials.gov Identifier: NCT01047527). Key eligibility criteria included: 18 years old, current smoking rate of ≥ 10 cigarettes/day, and the ability to use nicotine patch safely. Exclusion criteria included: lifetime DSM-IV diagnosis of mania, psychosis, or current suicidality; pregnant, lactating, or planning a pregnancy; or current or planned enrollment in another smoking cessation program.

Procedures

Participants were recruited through advertisements for a free smoking cessation treatment study at universities in Chicago, IL and Philadelphia, PA. After an initial telephone screen, eligible participants were enrolled at an in-person baseline session, where they completed measures and were randomized to receive either 8, 24, or 52 weeks of 21 mg/day nicotine patch. For the present study, we used data through the first 8 weeks of treatment, where all participants received 8 weeks of treatment with nicotine patch and behavioral counseling (Nicoderm CQ; GlaxoSmithKline, Research Triangle Park, NC). During this treatment period, participants completed measures and received brief counseling at Pre-Quit (week -2), Target Quit Day (week 0), week 4, and week 8 (Clinical Practice Guideline Treating Tobacco, Dependence Update Panel, & Staff, 2008). Participants completed an in-person follow-up visit at week 8. For full details, refer to Schnoll et al (2015).

Measures

Sociodemographic variables—Participants completed a self-report survey at baseline with demographic variables, including gender, age, and race.

Nicotine metabolite ratio (NMR)—NMR is the ratio of 3'-hydroxycotinine to cotinine analyzed from saliva samples (5 ml) collected at the baseline visit (Benowitz & Jacob, 2000; Dempsey et al., 2004). Participants were coded as fast or slow nicotine metabolizers, with fast NMR established as ≥ 0.47 (range: 0.01 – 1.29) as done in prior studies (Kaufmann et al., 2015; Schnoll et al., 2009). For full details on the NMR analysis, refer to Kaufmann et al (2015).

Cigarette type—Prior to enrolling in treatment, participants were asked whether they smoke menthol or non-menthol cigarettes (or both).

Nicotine dependence—The Heaviness Smoking Index (HSI) (Heatherton, Kozlowski, Frecker, Rickert, & Robinson, 1989) is a measure of nicotine dependence computed from two items (time to first cigarette and total number of cigarettes smoked per day) from the Fagerström Test for Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991). Scores range from 0 to 6, with higher scores reflecting greater dependence.

Smoking abstinence—Smoking abstinence was assessed by self-report at week 8 using a timeline follow-back measure (Shiffman, 2009). Participants' self-report was bioverified using a breath carbon monoxide (CO) reading (Vitalograph Breath CO) to determine 7-day bioverified point prevalence abstinence. As in the parent trial, participants were classified as abstinent if: 1) they reported not smoking for 7 days prior to the assessment, and 2) had a CO $\leq$ 10 parts per million (ppm). Participants who reported current smoking, had a CO $>$ 10 ppm, withdrew from the study, or did not provide a breath sample were classified as smoking (SRNT Subcommittee on Biochemical Verification, 2002).

Statistical analysis plan

All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, N.Y., USA). First, we examined differences in NMR, cigarette type, and NMR $\times$ cigarette type by demographic and smoking characteristics using chi-square analysis and analysis of variance (ANOVA). Using logistic regression analysis, we examined the relationship between NMR (0 = fast, 1 = slow) and cigarette type (0 = menthol, 1 = non-menthol) on smoking abstinence outcomes at week 8 (0 = smoking, 1 = abstinent). Covariates included variables known to be associated with cigarette type and NMR, including HSI, age, race, and sex (Benowitz et al., 2006; Schnoll et al., 2014; Stahre, Okuyemi, Joseph, & Fu, 2010; Zuo et al., 2015). Using an interaction term (cigarette type $\times$ NMR), we tested whether the association between NMR and smoking abstinence was moderated by cigarette type. We also examined the association of each primary variable of interest (cigarette type and NMR) and covariate individually with smoking abstinence. Additionally, we tested whether there were any sex differences in the association between NMR and cigarette type on abstinence status (sex $\times$ cigarette type $\times$ NMR). Although there are differences in menthol use (Jones, Apelberg, Tellez-Plaza, Samet, & Navas-Acien, 2013; Lawrence et al., 2010) and NMR (Rubinstein, Shiffman, Rait, & Benowitz, 2013; Schnoll et al., 2014) between Black and White participants, we did not have sufficient data to examine the three way interaction of NMR $\times$ cigarette type $\times$ race.

Results

Demographic and Smoking Characteristics

Of the 525 participants recruited into the parent trial, participants missing NMR data ($n = 26$) were excluded from analyses. Participants who reported their racial group as something other than White or Black ($n=18$) or reported smoking both menthol and non-menthol cigarettes ($n = 7$) were also excluded in order to simplify the race and cigarette type variables. Therefore, the current sample included 474 participants, with 104 (23%) participants classified with fast NMR and 302 (64%) participants reported smoking menthol cigarettes.

Participant characteristics by NMR and menthol cigarette use are presented in Table 1. We did not observe significant differences between menthol and non-menthol groups by sex, age, HSI, number of cigarettes smoked per day, years smoked, or NMR in both continuous and categorical measures (all $p > .10$). The menthol group was more likely than the non-menthol group to identify as Black (85% vs. 43% White; $\chi^2(1,474) = 90.94, p < .001$), but 8 week abstinence did not differ by race (32% Black vs. 29% White; $p > .05$) or sex (32%

male vs. 29% female; $p > .05$). There was no significant difference in abstinence by cigarette type at week 8 (31% menthol vs. 29% non-menthol; $\chi^2(1,474) = 22, p = .64$). However, we observed a significant association between NMR and 8-week abstinence status (33% slow NMR vs. 22% fast NMR; $\chi^2(1,474) = 4.30, p = .04$).

NMR, Cigarette Type, and Smoking Abstinence at Week 8

Of the 474 participants, 15 (3.2%) fast NMR, menthol smokers compared to 79 (16.7%) slow NMR, menthol smokers were abstinent at Week 8; 8 (1.7%) fast NMR, non-menthol smokers compared to 42 (8.9%) slow NMR, non-menthol smokers were abstinent at Week 8. After adjusting for covariates, the interaction between NMR and cigarette type was not significantly associated with abstinence (Odds ratio [OR] = 0.91, 95% Confidence Interval [CI] = 0.31 – 2.69, $p = .86$), indicating that the association between NMR and abstinence was not moderated by menthol cigarette use (see Table 2). Excluding the interaction variable, there was no main effect of cigarette type on abstinence (OR = 1.15, 95% CI = 0.72 – 1.84, $p = .61$), although there was a main effect of NMR (fast) on abstinence (OR = 0.55, 95% CI = 0.32 – 0.93, $p = .03$). Of the covariates, only HSI score was associated with abstinence (OR = 0.74, 95% CI = 0.63 – 0.88, $p < .001$). The results were unchanged when defining NMR by the continuous measure or median split. Also, there were no sex differences found in the association between NMR and cigarette type on abstinence status.

Discussion

Based on basic animal and human studies providing compelling evidence that menthol may slow nicotine metabolism, relative to non-menthol cigarettes, we examined the influence of cigarette type on the association between NMR and short-term smoking abstinence after 8-week treatment with 21 mg/day nicotine patch and behavior counseling. This study was the first to explore the interactive effects of NMR and cigarette type on smoking cessation treatment outcomes. Our findings indicate that cigarette type does not moderate the association between NMR and abstinence, even after examining the potential for sex-differences. Rather our results are consistent with previous studies demonstrating that abstinence outcomes are independent of menthol cigarette use (Murray, Connett, Skeans, & Tashkin, 2007; Muscat et al., 2002), even after long follow-up periods (D'Silva, Boyle, Lien, Rode, & Okuyemi, 2012; Hyland et al., 2002). Inconsistent findings may be due to variations in menthol concentration due to different brand, cigarette design, how menthol is added, and a variety of environmental factors (i.e., storage time, temperature) (Ahijevych & Garrett, 2004; Celebucki, Wayne, Connolly, Pankow, & Chang, 2005; Ferris Wayne & Connolly, 2004; Yerger & McCandless, 2011), which future human laboratory studies may examine. With the inconsistent association between menthol cigarette use and smoking cessation, our results may be a preliminary indication that the influence of menthol on NMR and smoking abstinence necessitates further examination, especially in specific subgroups.

As most treatment studies, including this study, have involved adults who report smoking at least 10 cigarettes per day, it may be possible that we were limited by our inclusion criteria. Rather, the impact of menthol cigarette use on NMR may be represented among non-daily or light (i.e., <10 cigarettes/day) smokers, particularly as individuals with slow NMR

(Chenoweth et al., 2014) or who smoke menthol cigarettes (Frost-Pineda, Muhammad-Kah, Rimmer, & Liang, 2014; Lawrence et al., 2010; Muscat et al., 2002) are more likely to have lower rates of cigarette use. Menthol's cooling sensation in cigarettes may allow smokers to inhale more deeply or take more puffs to obtain more nicotine per cigarette and result in lower cigarette count (Jarvik, Tashkin, Caskey, McCarthy, & Rosenblatt, 1994; Lawrence, Cadman, & Hoffman, 2011). Future studies including non-daily or light smokers could generate a more generalizable sample to better inform smoking cessation treatment, especially as the prevalence of non-daily adult smokers is increasing in the general population (King, Dube, & Tynan, 2012).

Additionally, as our study did not have a sufficient sample to examine the three way interaction of NMR by cigarette type by race, racial differences may be masking the expected effect of cigarette type on NMR, especially as there is a disproportionately high rate of menthol cigarette use among Black/African American smokers (Alexander et al., 2016; Kulak, Cornelius, Fong, & Giovino, 2016; Rolle, Beasley, Kennedy, Rock, & Neff, 2016). Although our study had a greater number of Black, menthol cigarette smokers in the fast NMR group, we did not find any differences in abstinence rates in our examination of race. As previous studies have found that menthol cigarette use is associated with poorer smoking cessation success, especially among African American females (Smith et al., 2014), future studies need to be specifically designed to evaluate the interaction between biological factors and menthol cigarette use among Blacks versus White smokers while accounting for possible sex-differences.

Despite these limitations, our study had notable strengths. First, the large sample of White menthol smokers in our study (43% of Whites smoked menthol cigarettes) contributes to the literature that is often limited by difficulty in recruiting this group (Cropsey et al., 2009; Fagan et al., 2015; Hoffman & Miceli, 2011). As the proportion of menthol cigarette users continues to increase, especially among White smokers (Villanti et al., 2016), our sample may become increasingly generalizable to the overall population. Second, despite the established metabolic interactions between menthol and NMR, studies rarely report smoking cessation outcomes by cigarette type. Therefore, while existing studies indicate that menthol cigarette use is associated with increased nicotine dependence and poor smoking cessation outcomes, our findings question this pattern by raising the question of whether menthol cigarette use should remain as a commonly viewed risk factor in smoking persistence. Third, we also examined response after a standard 8 week regiment of a consistently high dose of 21 mg of the nicotine patch, which is both effective and highly utilized by treatment providers (Leyro et al., 2013; Tonnesen et al., 1999). In a large scale, time-limited nicotine replacement therapy giveaway program, menthol cigarette smokers reported greater use of any nicotine replacement therapy, but had lower quit rates (Thihalolipavan, Jung, Jasek, & Chamany, 2014). As previous studies have suggested that fast nicotine metabolizers may require higher doses of nicotine replacement therapy in order to compensate for their metabolism rates (Chen et al., 2014; Lerman et al., 2006), we were able to examine a steady maximized dose of nicotine patch rather than the standard slow increase of medication dose over time (i.e. 8 mg to 21 mg).

CONCLUSIONS

This study was the first to examine whether cigarette type moderates the relationship between nicotine metabolite ratio and smoking abstinence among a community-based sample of smokers treated with 8 weeks of 21 mg/day nicotine patch. Contrary to our expectations, we found no indication that menthol cigarette use was a moderator or an independent risk factor for continued smoking after 8 weeks of treatment with a 21 mg/day nicotine patch. However, given the increasing rates of menthol cigarette use (Villanti et al., 2016) and evidence for flavorings enhancing nicotine's reinforcing and rewarding value (Audrain-McGovern, Strasser, & Wileyto, 2016), further study of smoking cessation among these smokers may help to better characterize their smoking cessation efforts, especially among racially diverse and light smokers, to reconcile the divergent biological and clinical findings regarding menthol cigarette use and smoking cessation treatment outcomes.

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Public Significance Statement

Although faster nicotine metabolism has been associated with lower smoking cessation rates, menthol cigarette use may slow metabolism and attenuate risk for poor outcome. However, this study did not find an indication that the nicotine metabolism–abstinence association was moderated by cigarette type. Our findings suggest future research needs to consider the potential influence of individual differences for smoking cessation among menthol cigarette smokers.

Table 1

Baseline Characteristics by Cigarette Type and Nicotine Metabolite Ratio

	Menthol smoker		Non-Menthol smoker		Total sample <i>n</i> = 474
	Slower NMR <i>n</i> = 234	Faster NMR <i>n</i> = 68	Slower NMR <i>n</i> = 136	Faster NMR <i>n</i> = 36	
Sex, % Female	49.1	60.3	45.6	55.6	50.2
Race, % White	32.1	41.2	77.2	88.9	50.6
Age, in years (Mean, SD)	46.5 (12.2)	50.3 (9.1)	45.1 (12.7)	47.5 (11.6)	46.7 (12.0)
Heaviness Smoking Index score (Mean, SD)	3.2 (1.1)	3.2 (1.4)	3.1 (1.3)	2.9 (1.4)	3.1 (1.2)
Cigarettes per day (Mean, SD)	16.4 (7.6)	18.1 (8.9)	18.0 (7.6)	17.7 (6.7)	17.2 (7.8)
Years smoked (Mean, SD)	29.5 (12.4)	32.2 (11.0)	27.7 (13.7)	28.5 (12.0)	29.3 (12.6)
Nicotine metabolite ratio (Mean, SD)	0.25 (0.11)	0.65 (0.19)	0.27 (0.10)	0.67 (0.17)	0.35 (0.21)
Week 8 abstinence, % abstinent	33.8	22.1	30.9	22.2	30.4

Note. The Heaviness Smoking Index score is a measure of nicotine dependence ranging from 0–6. The nicotine metabolite ratio is the ratio of 3'-hydroxycotinine to cotinine analyzed from saliva samples (5 ml) collected during the baseline visit. Based on an intent-to-treat model, abstinence was defined as self-reported 7 days abstinence and bioverified with a carbon monoxide sample of 10 parts per million (ppm).

Table 2

Logistic Regression Analysis Examining Moderation by Cigarette Type on Association between NMR and 8 Week Smoking Abstinence (n = 474), Controlling for Covariates

<i>Predictor (reference)</i>	<i>OR</i>	<i>95% C.I. for OR</i>	<i>p</i>
Race (White)	1.06	0.66 – 1.71	.80
Sex (Male)	1.22	0.81 – 1.82	.35
Age, years	1.01	1.00 – 1.03	.12
Nicotine dependence, HSI score	0.74	0.63 – 0.88	.001
Cigarette Type (Menthol)	1.17	0.71 – 1.93	.55
NMR (Faster NMR)	0.59	0.24 – 1.41	.23
Cigarette Type x NMR	0.91	0.31 – 2.69	.86

Notes: Abbreviations: HSI = heaviness smoking index, NMR = nicotine metabolite ratio, OR = odds ratio, C.I. = confidence intervals. Covariates are race, sex, age, and HSI.