Drug and Alcohol Dependence 133 (2013) 845–851

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

A tale of two stimulants: Mentholated cigarettes may play a role in cocaine, but not methamphetamine, dependence☆

Theresa M. Winhusen[a,*], Bryon Adinoff[b,c], Daniel F. Lewis[a], Gregory S. Brigham[a,d], John G. Gardin II[e], Susan C. Sonne[f], Jeff Theobald[a], Udi Ghitza[g]

[a] Cincinnati Addiction Research Treatment and Education Center (CinARTEC), Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, 3210 Jefferson Avenue, Cincinnati, OH 45220, USA
[b] Department of Psychiatry, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390, USA
[c] VA North Texas Health Care System, Dallas VAMC, 4500 South Lancaster Road, Dallas, TX 75216, USA
[d] Maryhaven, 1791 Alum Creek Drive, Columbus, OH 43207, USA
[e] ADAPT, Inc., 548 SE Jackson Street, Roseburg, OR 97470, USA
[f] Medical University of South Carolina, 171 Ashley Avenue, Charleston, SC 29425, USA
[g] National Institute on Drug Abuse, Center for the Clinical Trials Network, 6001 Executive Boulevard, Room 3118, Bethesda, MD 20892, USA

ARTICLE INFO

Article history:
Received 3 June 2013
Received in revised form 2 September 2013
Accepted 3 September 2013
Available online 11 September 2013

Keywords:
Menthol
Cigarettes
Cocaine dependence
Methamphetamine dependence

ABSTRACT

Background: Research suggests that mentholated cigarettes may play a role in cocaine dependence. The purpose of the present study was to expand upon the research on mentholated cigarettes and cocaine dependence and to evaluate the role of mentholated cigarettes in methamphetamine dependence.
Methods: Secondary analysis of a multisite, randomized trial evaluating the impact of smoking-cessation treatment in stimulant-dependent outpatients ($N = 538$). Participants' reasons for concurrent use of cigarettes and illicit stimulants were assessed via self-report. Stimulant-abstinence was measured by self-report and urine drug screens. Smoking cessation was assessed via self-report and carbon monoxide levels.
Results: Of the 301 cocaine-dependent participants, 201 (67%) were menthol and 100 (33%) were non-menthol cigarette smokers. Cocaine-dependent participants who smoked menthol, compared to non-menthol, cigarettes were significantly more likely to report that cigarettes prolong their cocaine high ($X^2(1) = 16.3$, $p < .0001$, OR = 3.58 [95% CI: 1.88–6.79]) and were less likely to be stimulant abstinent during active treatment ($W = 3.6$, $p < 0.001$, $d = .39$ [95% CI: 0.16–0.62]), at 3-month follow-up ($X^2(1) = 14.4$, $p < 0.001$, OR = .32 [95% CI: 0.17–0.58]), and at 6-month follow-up ($X^2(1) = 4.6$, $p = 0.03$, OR = .53 [95% CI: 0.29–0.95]). No parallel differences were found between menthol and non-menthol methamphetamine-dependent smokers. The prevalence of Caucasian menthol smokers was significantly greater in the cocaine-dependent participants (37.2%) than in the methamphetamine-dependent participants (17.61%), ($X^2(1) = 14.4$, $p < .001$, OR = 2.77 [95% CI:1.62–4.73]). Smoking cessation was not significantly associated with cigarette type for either cocaine- or methamphetamine-dependent participants.
Conclusions: The present results suggest that mentholated cigarettes play a role in cocaine, but not methamphetamine, dependence.

1. Introduction

In 2009, the Family Smoking Prevention and Tobacco Control Act granted the Food and Drug Administration (FDA) regulatory power over particular aspects of tobacco products, including flavor additives (Family Smoking Prevention and Tobacco Control Act, 2009). Since that time, the FDA has banned flavored cigarettes, with the exception of mentholated cigarettes, and commissioned an advisory committee to report on the impact that mentholated cigarettes have on public health (Benowitz and Samet, 2011). The report from the advisory committee noted that, while there is not conclusive evidence to suggest that menthol, relative to non-menthol, cigarette smokers have worse disease outcomes, there is evidence that mentholated cigarettes lead to more smoking initiation and greater difficulty with smoking cessation and, thus, public health would benefit from the elimination of mentholated cigarettes (Benowitz and Samet, 2011). However, there has been

☆ *Trial registration*: Clinical Trials.gov http://www.clinicaltrials.gov; Identifier: NCT01077024.

* Corresponding author. Tel.: +1 513 487 7802; fax: +1 513 487 7819; mobile: +1 513 310 0442.
E-mail address: winhusen@carc.uc.edu (T.M. Winhusen).

0376-8716/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.drugalcdep.2013.09.002

reluctance to ban menthol cigarettes based on concern that such a ban would lead to a black market for menthol cigarettes (Carter, 2013). Additional data on the potential impact of mentholated cigarettes on public health would be helpful in weighing the potential costs and benefits of banning them.

A potential negative impact of mentholated cigarettes that has received minimal attention is their potential role in cocaine dependence. Cocaine dependence represents a significant problem as evidenced by the sheer number of lives affected, its associated medical and legal consequences, and the difficulty finding effective treatments (Winhusen et al., 2007). The scope of the cocaine problem is largely attributed to the advent of crack, an inexpensive, smokable and, thus, particularly addictive form of cocaine, in the mid-1980s. In 2010, over one million people in the United States were abusing or dependent on cocaine (Substance Abuse and Mental Health Services Administration (SAMHSA), 2011). Because psychosocial interventions are associated with high relapse rates, an impressive amount of resources have been devoted to finding pharmacological treatments that could be used in conjunction with psychosocial treatments; yet there still is no widely used, safe and effective treatment for cocaine dependence (Kuehn, 2009). A link between cigarette smoking and cocaine abuse has been established in both clinical and laboratory studies. The rate of smoking in cocaine abusers is 75–80% (Budney et al., 1993; Sees and Clark, 1993; Gorelick et al., 1997) and smoking cigarettes is associated with more severe cocaine dependence, including more frequent cocaine use, a greater likelihood of injecting or smoking cocaine, and more severe employment and legal difficulties (Budney et al., 1993; Roll et al., 1997). Human laboratory studies have found that cocaine administration increases the rate of cigarette smoking (Nemeth-Coslett et al., 1986; Roll et al., 1996), and that mecamylamine, a nicotine antagonist, reduces cue-induced cocaine craving (Reid et al., 1999) while nicotine increases it (Reid et al., 1998).

Menthol has been shown to enhance transdermal and transbuccal absorption of other drugs (Ahijevych and Garrett, 2004). It has been posited that, when inhaled, menthol may increase the permeability of drugs in the lungs as well, thereby increasing the pulmonary absorption of constituents found in smoke (Ahijevych and Garrett, 2004; Clark et al., 1996). If used together with other substances of abuse, menthol may enhance the reinforcing effects of other substances by affecting the calcium conductance of cells involved in drug reinforcement (Clark et al., 1996). Research suggests that the association between cigarette and cocaine use may be more pronounced for patients who smoke mentholated cigarettes. Specifically, Sees and Clark interviewed cocaine-dependent patients about their cigarette and cocaine use to better understand why these behaviors co-occur at such high rates (1993). In the course of these interviews, participants noted that mentholated cigarettes prolong the cocaine high, allow them to smoke crack for longer periods due to the cooling effects of menthol, and even produce feelings similar to the effects of cocaine in the absence of cocaine use (Sees and Clark, 1993). Consistent with this report, a small study by Wiseman and McMillan found that cocaine-dependent participants preferring mentholated cigarettes cited the ability of menthol to make the cocaine high last longer and as a substitute for cocaine among the reasons for their preference (1998). Wiseman and McMillan (1998) hypothesized that irritants in menthol cigarettes may increase lung permeability increasing exposure to smoked cocaine. If menthol increases the subjective effects of cocaine then one might expect greater dependence severity, as indicated by more difficulty abstaining from cocaine, in cocaine-dependent patients using menthol, relative to non-menthol, cigarettes.

A recent multi-site trial conducted by the National Institute on Drug Abuse (NIDA) National Drug Abuse Treatment Clinical Trials Network (CTN) evaluated the impact of concurrent substance use disorder (SUD) and nicotine dependence treatment for cocaine and/or methamphetamine-dependent patients who were also nicotine dependent. The present study utilized this dataset to explore the potential role of mentholated cigarettes in cocaine dependence. Specific aims included evaluating participants' reasons for using cocaine and cigarettes together, the relative level of cocaine dependence severity, and success in achieving smoking cessation, all as a function of cigarette type (i.e., menthol vs. non-menthol). It was predicted that menthol, relative to non-menthol, cocaine-dependent cigarette smokers would be more likely to report that cigarettes prolong the cocaine high, and would be less likely to be illicit-stimulant abstinent and to achieve smoking cessation. Finally, while smoking rates are estimated to be 87% or higher in methamphetamine abusers (Grant et al., 2008; Weinberger and Sofuoglu, 2009), past research has not evaluated the potential role of mentholated cigarettes in methamphetamine; completing an initial evaluation of a potential relationship was an aim of the present study.

2. Methods

2.1. Study design

Details of the clinical trial are provided elsewhere (Winhusen et al., 2012a, in press). Briefly, the study was a 10-week, two-group, randomized trial to evaluate the impact of providing smoking cessation treatment (SCT) with SUD treatment as usual (TAU), compared to TAU alone, in smokers who are in outpatient treatment for cocaine or methamphetamine dependence. Eligible participants were randomized to TAU or TAU + SCT in a 1:1 ratio. Follow-up visits were completed at 3 and 6 months following study day 20, which was the target smoking-quit date for the TAU + SCT participants. The trial was completed at 12 SUD outpatient treatment programs that did not provide smoking-cessation treatment as part of their standard treatment. During the 10-week treatment phase, participants were scheduled to attend two research visits per week for efficacy and safety assessments. Participants randomized to TAU participated in treatment as typically provided by the study site, which consisted of at least one non-nicotine SUD treatment session per week during the 10-week treatment phase. Participants randomized to the TAU + SCT arm received TAU and SCT consisting of extended-release (XL) bupropion 300 mg/day, nicotine inhaler, individual 10 min smoking-cessation counseling weekly for 10 weeks, and prize-based contingency management for smoking abstinence (Carbon Monoxide (CO) < 4 ppm) during the post-quit phase. The CO cut-off of <4 ppm was based on research findings that the use of 2–3 ppm produces the most accurate identification of smoking abstinence whereas 8–10 ppm, which has been traditionally used to verify abstinence, may occasionally result in smokers falsely being classified as abstinent (Javors et al., 2005; Cropsey et al., 2006).

2.2. Participants

The main inclusion criteria were: being at least 18 years old, meeting DSM-IV-TR criteria for cocaine- and/or methamphetamine-dependence, smoking at least 7 cigarettes daily and a CO level $\geq$8 ppm, being enrolled in outpatient SUD treatment, interested in quitting smoking, and being in good physical health as determined by medical history, vital signs, and electrocardiogram. Exclusion criteria included a medical or psychiatric condition potentially making study participation unsafe, current treatment for nicotine dependence; for women, pregnancy, breastfeeding, or unwillingness to use adequate birth control.

The present study sought to replicate and expand upon prior reports of a connection between menthol cigarette and cocaine use while doing an initial evaluation of a potential relationship between menthol cigarettes and methamphetamine use. Thus the participants included in the present analyses met criteria for either cocaine-dependence (n = 301) or methamphetamine-dependence (n = 209) while the participants meeting criteria for both cocaine and methamphetamine-dependence (n = 27) were excluded.

2.3. Measures

Participants were coded as menthol or non-menthol cigarette smokers based on the Smoking History Survey, which is a modified version of the Mayo Nicotine Dependence Center Patient Questionnaire, administered by a research assistant at baseline. Reasons for using cigarettes with cocaine/methamphetamine were assessed via a self-report questionnaire created for the trial in which participants selected all of their reasons for using the substances together. The choices included: "Cigarette smoking helps the high from crack/cocaine or methamphetamine to last longer," "cigarette smoking is just a habit – no particular reason for using cigarettes with crack/cocaine or methamphetamine," "cigarette smoking helps to feel more relaxed/calm," "smoking cigarettes slows down crack/cocaine/methamphetamine