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The present study investigated the effects of two herbal components (BACCOFF™ and DIPSTOP™) of a commercially available smokeless tobacco treatment program for reducing subjective withdrawal symptoms during deprivation. One component, BACCOFF™, is a non-nicotinic chew. The second component, DIPSTOP™, is a liquid containing the alkaloid lobeline, which to some extent mimics peripheral nicotinic effects. All participants (*N* = 22 males) were placed in four conditions: BACCOFF™ + DIPSTOP™, BACCOFF™ + placebo control, DIPSTOP™ only, and placebo control only. The conditions involved 48 h of deprivation, and subjects were exposed to one condition per week for 4 weeks. Withdrawal measures were taken at baseline, 24 h, and 48 h of deprivation. Individuals were randomly assigned, and conditions were counterbalanced. Results showed that BACCOFF™, as compared with DIPSTOP™, significantly reduced withdrawal symptoms but not craving. These data suggest that behavioral/sensory substitutes' influence on withdrawal might be routed through the product's ability to approximate the preferred moist snuff.

Introduction

Smokeless tobacco consumption in the USA, particularly among moist snuff users, has been on the rise over the past three decades, while the consumption of other nicotine products has progressively decreased (USDA, 1993; USDHHS, 1996). Although white males between the ages of 18 and 35 tend to report the highest rates of daily smokeless tobacco use (USDHHS, 1996), other epidemiological evidence suggests that greater numbers of male adolescents and children, often under the age of 12, are experimenting with and progressing toward using smokeless tobacco on a regular basis (Hill, Harrell, & McCormick, 1992; Simon, Sussman, Dent, Burton, & Flay, 1993). The extent to which smokeless tobacco use produces physical dependence via frequent and prolonged nicotine exposure (West, 1988) may increase the likelihood that these young smokeless tobacco users will become highly dependent on nicotine much earlier and that they may have more difficulty initiating and maintaining abstinence. Moreover, greater health risks associated with regular smokeless tobacco use, which include periodontal problems, soft tissue alterations/leukoplakia, and cancers of the oral cavity and pharynx (see Hatsukami & Severson, 1999), highlight the importance of examining factors that aid our understanding of smokeless tobacco use, maintenance, and eventual cessation.

One plausible mechanism that may contribute to the entrenched consumption patterns of young, dependent smokeless tobacco users is the level of nicotine withdrawal such people experience when they attempt to abstain from use. Insofar as aversive withdrawal symptoms promote relapse and the anticipation of aversive symptoms reduces the motivation to attempt to quit, elevated nicotine withdrawal symptoms, especially during the first 48 h of abstinence, may hinder smokeless tobacco users' efforts to maintain abstinence. Nicotine

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withdrawal severity as it pertains to implications for future smokeless tobacco treatment is an area that is not well understood. Cigarette smokers and smokeless users show similar signs and symptoms of nicotine withdrawal (Hatsukami, Gust, & Keenan, 1987; McChargue & Collins, 1998) and report comparable withdrawal severity ratings within the first 48 h of nicotine abstinence (McChargue & Collins, 1998). As such, it may be reasonable to suggest that severe nicotine withdrawal symptoms may also place smokeless tobacco users at a heightened risk for relapse. Moreover, our ability to abate unpleasant nicotine withdrawal symptoms may substantially help a person to resist the urge to return to using smokeless tobacco following abstinence.

To our knowledge, no study has tested the hypothesis that elevated nicotine withdrawal symptoms predict smokeless tobacco relapse. At best, previous research has shown that nicotine replacement treatments (NRT) alleviate withdrawal symptoms in most studies (Hatsukami, Anton, Keenan, & Callies, 1992; Hatsukami *et al.*, 2000) but not all (Hatsukami, Jensen, Allen, Grillo, & Bliss, 1996). Although Hatsukami and colleagues showed that NRT significantly enhanced rates of abstinence at 6 months (point-prevalence abstinence) and up to 15 weeks (continuous abstinence), it remains unclear whether NRT effectiveness was a result of the lowering of withdrawal symptoms.

There is some evidence to suggest that non-nicotinic products reduce nicotine withdrawal symptoms. In particular, citric and ascorbic acid devices (Levin *et al.*, 1993), and de-nicotinized cigarettes (Butschky, Bailey, Henningfield, & Pickworth, 1995) have been used as sensory substitutes. Previous studies have shown that smokers report comparable satisfaction ratings for sensory substitutes as compared with cigarettes (Rose & Hickman, 1987), as well as report lower nicotine withdrawal symptoms, including craving, during abstinence (Behm *et al.*, 1993; Butschky *et al.*, 1995; Levin *et al.*, 1993). Although there are some data to suggest sensory substitutes may aid in smoking cessation (e.g., Levin *et al.*, 1993), such evidence is very preliminary and in need for further research.

Less is known about the effects of non-nicotinic replacements that approximate behaviors and sensations of smokeless tobacco. Three studies currently report the use of behavioral/sensory replacements (e.g., mint-leaf snuff) in smokeless tobacco treatment. For example, when a quit kit of oral substitutes such as chewing gum, toothpicks, and a tin of ground mint-leaf non-tobacco snuff was given as a part of a smokeless tobacco intervention, Stevens, Severson, Lichtenstein, Little, and Leben (1995) found that the use of oral replacements were significant predictors of quitting at 3- and 12-month follow-up. Zavala, Harrison, Smith, Smith, and Manske (1995) also reported that use of mint snuff was highly associated with more days tobacco-free. Despite the promise that mint snuff may help prolong abstinence, it has been difficult to determine whether the increased abstinence rates were a direct result of the use of behavioral/sensory replacements. More recently, Hatsukami *et al.* (2000) conducted a study that examined the effectiveness of mint snuff and transdermal nicotine patch to aid in smokeless tobacco abstinence. Participants were only blinded to the patch condition (active vs. placebo), whereas they either received or did not receive the mint snuff. Although mint snuff users reported lower levels of withdrawal symptoms (i.e., craving, irritability/frustration/anger, anxiety, and depressed mood) during nicotine abstinence, the use of mint snuff did not affect abstinence rates.

If non-nicotinic replacement treatments encourage nicotine abstinence through potential withdrawal-alleviating effects, despite some initial evidence to the contrary (Hatsukami *et al.*, 2000), a better understanding of factors that may influence the magnitude of withdrawal reduction while prolonging abstinence rates would help resolve some inconsistent findings reported in previous research. The present study attempted to further evaluate the effects of non-nicotine replacements on nicotine withdrawal symptoms of moist snuff users. We aimed to test the hypothesis that two commercially produced non-nicotine replacements (herbal snuff and liquid lobeline by Ralston, Inc.) would substantially reduce withdrawal symptoms during 48 h of nicotine deprivation. Insofar as such non-nicotinic replacements represent alternative reinforcers that approximate the properties and effects of moist snuff, the more effective they might be at reducing negative consequences associated with nicotine abstinence. In other words, we expected the replacement products that were reported to produce the closest behavioral, sensory, and physiological responses to moist snuff during 48-h deprivation would also greatly mitigate signs and symptoms of nicotine withdrawal.

Method

Participants

Male moist snuff users (N = 22) were recruited from undergraduate introductory psychology courses at Oklahoma State University and were given extra credit for their participation. Three participants did not complete the protocol. There were no significant demographic differences for people who did not complete the study. A lottery for $100 was also conducted at the end of each semester. Participants completing the entire protocol were eligible for the lottery as an extra incentive.

Participants had a mean (±SD) age of 19.81±1.87 years and a Smokeless Tobacco Dependence Questionnaire (SMTDQ, described more fully later) score of 7.94±3.0. Smokeless tobacco users consumed more than two tins per week (11 participants consumed more than four tins per week) and had at least 2 years of continuous moist snuff usage without currently using any other form of nicotine product or attempting to quit or cut down on smokeless tobacco consumption.

Materials

Compliance measures. The primary compliance measures were self-reported nicotine abstinence and self-reported product usage at 24- and 48-h nicotine deprivation. Previous research has shown that the expectation of biochemical verification of tobacco use produces more accurate self-reports than without the threat of biochemical verification (Hansen, Malotte, & Fielding, 1985; Murray, O'Connell, Schmid, & Perry, 1987). Thus, saliva samples were collected and individuals were informed that the saliva samples would be used to assess systemic nicotine levels from smokeless tobacco use. No physiological or pharmacological indices were derived from the samples. Furthermore, the Vitalograph Breath-COa monitor (Model 29.700) assessed for alveolar carbon monoxide (COa) levels during deprivation conditions. To assess for compensatory cigarette smoking during smokeless tobacco deprivation, a COa less than 8 ppm was defined as not using cigarettes.

Non-nicotinic replacement products. Two commercial non-nicotinic products were used in this study: BACCOFF™ and DIPSTOP™ (Ralston Inc., Selma, AL). Research has shown that BACCOFF™ produces sensory cues similar to common brands of moist snuff (Coffey & Lombardo, 1998). BACCOFF™ consists of a variety of tea leaves, USP glycerine, sugar, salt, natural and artificial flavors, and sodium benzoate. The primary ingredient of the DIPSTOP™ liquid drops was lobeline, an alkaloid shown to mimic peripheral nicotinic effects in human and animal studies (Stolerman, 1990). As a control for the DIPSTOP™ condition, water was placed in empty DIPSTOP™ liquid drop containers.

Nicotine dependence. The SMTDQ (Boyle, Jensen, Hatsukami, & Severson, 1995) is a 10-item self-report measure designed to assess aspects of smokeless tobacco use, which correspond with dependence. Scores range from 4 to 19, with higher scores indicating greater levels of smokeless tobacco dependence. Boyle *et al.* (1995) showed a strong correlation between SMTDQ scores and salivary cotinine ($r = 0.47$, $p<0.0001$).

Nicotine withdrawal. The Minnesota Nicotine Withdrawal Scale (MNWS) assesses nicotine withdrawal symptoms from cigarettes (e.g., Hughes & Hatsukami, 1986) and smokeless tobacco (Hatsukami *et al.*, 1987; 1992). The MNWS has good construct validity and high reliability (Patten & Martin, 1996). Individual items include craving, irritability–anger, insomnia, anxiety–tension, concentration problems, restlessness, drowsiness, impatience, increased appetite, and depressed mood. Smokeless tobacco craving was derived from the 'craving' item on the MNWS. Total withdrawal represented the aggregate score of all items on the MNWS, minus craving.

Smokeless tobacco approximation scale (SMTAS). This scale was developed specifically for the present study and assesses participants' reports of how closely the non-nicotine substitutes approximated their original moist snuff product. The smokeless tobacco approximation scale consists of 11 Likert-format items that range from 1 (not at all similar) to 10 (extremely similar). Specific items inquire whether the participant perceives the non-nicotine substitute to taste, feel, produce saliva, smell, pack within mouth, arouse, produce a buzz, affect his performance on tasks or exercise, relax, curb appetite, or affect his concentration similar to his preferred moist snuff. Within the present study, a coefficient alpha of 0.86 was produced by the data.

Procedure

Baseline assessment. Informed consent was obtained from participants, and the SMTDQ was administered during the initial baseline assessment period. Participants were instructed to use their preferred moist snuff for 10 min. Following the using period, individuals were instructed to expectorate into a test tube. Carbon monoxide measures were obtained, and the MNWS was administered. Individuals were then instructed to abstain from any form of nicotine use for 2 days and to return the following day. Participants were given the products predetermined for that week and were instructed to use those products *ad lib* for the 2-day abstinence period. Graduate research assistants also informed participants 'the products may or may not help during abstinence.'

Twenty-four-hour assessment. A graduate research assistant recorded the number of times individuals used the product and inquired on the participant's ability to abstain. Saliva and COa measures were collected. The MNWS self-report measure was also administered. Participants were instructed to continue abstinence and use the supplied products for another 24 h.

Forty-eight-hour assessment. Participants followed the same procedure as the 24-h assessment period. After the last self-report measures (MNWS and SMTAS) were taken, any remaining products were given to the graduate researcher. Participants were asked to return to their regular nicotine use until the beginning of the next assessment week.

Results

Design and statistical approach

A within-subject 2×2×3 factorial design reflects three independent within-subject variables: BACCOFF™ (BACCOFF™ vs. No BACCOFF™), DIPSTOP™ (DIPSTOP™ vs. water), and time (0, 24 or 48 h). One-tailed repeated-measure analyses of variances (ANOVAs) were conducted on each of the dependent variables. The ANOVAs analyzed main effects for the independent variables of BACCOFF™, DIPSTOP™, and time. Interaction effects were also tested across the three independent variables, which produced four different

Table 1. The relationship between use patterns of non-nicotinic replacements with smokeless tobacco craving and nicotine withdrawal symptoms

Product use	24-h Craving	48-h Craving	24-h Withdrawal	48-h Withdrawal
BACCOFF	−0.55*	−0.49	−0.07	−0.08
DIPSTOP	0.08	0.05	0.00	−0.27
WATER	0.21	0.05	−0.43	−0.48

* $p<0.05$.

comparisons. The interaction comparisons included BACCOFF™ vs. DIPSTOP™, BACCOFF™ vs. time, DIPSTOP™ vs. time, and BACCOFF™ vs. DIPSTOP™ vs. time. Post-hoc simple effect tests were used to differentiate significant interactions. Significant differences within the simple effects were followed up with Tukey Honestly Significant Differences tests at the 0.05 alpha level. Order effects were also tested using 3 (time)×4 (order) ANOVAs. Order of product administration was not shown to influence dependent measures.

Descriptive carbon monoxide levels and product frequency data

All participants indicated full compliance. COa measures demonstrated that participants were within the cut-off of 8 ppm during deprivation periods. Participants also reported adequate BACCOFF™, DIPSTOP™, and placebo self-administration during deprivation. The mean number and standard deviations of product self-administration at 24- and 48-h deprivation were as follows: BACCOFF™ averaged 4.4±2.5 and 5.4±2.3, DIPSTOP™ averages were 3.0±0.7 and 3.5±1.0, and means for water drops were 2.9±1.0 and 3.6±1.0, respectively. Participants who reported self-administrating greater amounts of BACCOFF™ at 24 h of nicotine deprivation had significantly lower ratings of craving for smokeless tobacco at the same time-point (see Table 1). There were no other significant relationships found comparing product use with changes in craving and withdrawal across time.

Non-nicotinic product influence on withdrawal and craving scores

Significant time-main effects were observed for the total withdrawal ($F[2,30] = 4.40$, $p<0.01$), craving ($F[2,30] = 7.17$, $p<0.001$), and irritability scores ($F[2,30] = 6.19$, $p<0.006$). A BACCOFF™ main effect ($F[1,15] = 4.94$, $p<0.05$) was shown for the drowsiness score, and a DIPSTOP™ main effect ($F[1,15] = 4.75$, $p<0.05$) was shown for the difficulty-concentrating score. Post-hoc tests (Tukey's HSD) indicated that total withdrawal, craving, and irritability were significantly greater at 24 and 48 h, compared to baseline, for each measure. In addition, participants reported significantly lower problems with concentration when DIPSTOP™ was present and lower drowsiness when BACCOFF™ was present.

Significant interactions were observed for BACCOFF™ × time as a function of changes in total withdrawal ($F[2,30] = 2.54$, $p<0.05$), restlessness ($F[2,30] = 4.49$, $p<0.05$), and appetite scores ($F[2,30] = 6.00$, $p<0.01$). To illustrate the interaction effects, Figure 1 presents the overall interaction of total withdrawal. Simple effects tests indicated that total withdrawal, appetite, and restlessness scores were not substantially different at the three time periods when BACCOFF™ was present ($F[2,30] = 1.55$, 0.06, and 0.92, NS). However, there were significant increases in total withdrawal and appetite when BACCOFF™ was not present ($F[2,30] = 10.93$ and 10.48, $p<0.01$), with a similar trend for restlessness ($F[2,30] = 2.23$, $p<0.06$). Post-hoc comparisons indicated that total withdrawal and appetite scores were significantly higher at 24- and 48-h deprivation, compared to baseline, when BACCOFF™ was not present. However, the interaction for restlessness scores was seen only when comparing such scores at 48 h between BACCOFF™ and no BACCOFF™ conditions. Restlessness scores were significantly higher when BACCOFF™ was not present compared with when it was present ($t[15] = 2.6$, $p<0.02$).

Non-nicotinic replacement approximation to moist snuff

Scores on the SMT approximation questionnaire were tabulated at the end of each 48-h assessment period in order to evaluate which products participants reported as most similar to their preferred most snuff. Two-tailed *t*-tests were conducted on SMT approximation scores among BACCOFF™, DIPSTOP™, and water condi-

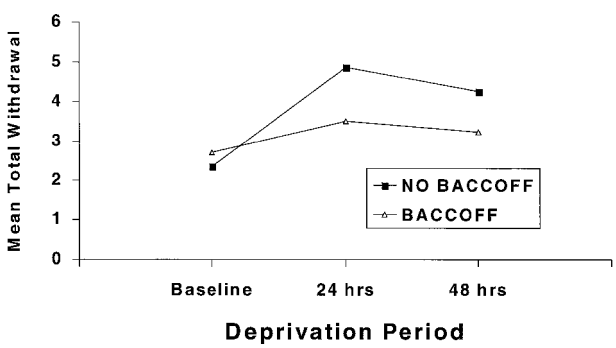

Figure 1. Mean total withdrawal ratings for BACCOFF™ vs. No BACCOFF™ differences across time. Significantly elevated total withdrawal was noted in the No BACCOFF™ treatment.

tions. Results showed that BACCOFF™ (mean±SD = 46.38±14.76) approximated participants' preferred moist snuff product more closely than DIPSTOP™ (32.91±8.8) and water (17.84±6.93) conditions, $t(15) = 4.08$ and 8.21, $p<0.001$. Likewise, DIPSTOP™ was substantially more similar to moist snuff than water, $t(15) = 2.46$, $p<0.05$.

Discussion

The results of the study showed that a non-nicotinic herbal product effectively reduced withdrawal symptoms among individuals dependent on smokeless tobacco. These observed herbal effects support the concept that psychological factors (e.g., conditioned stimuli) influence signs and symptoms elicited during nicotine deprivation. Researchers have historically posited that the primary determinant of withdrawal symptoms was the physiological removal of nicotine from the system (Hatsukami, Hughes, & Pickens, 1985; Shiffman, 1979). Our data, however, demonstrate that approximating similar sensory features of smokeless tobacco behavior substantially buffers certain aversive effects believed to derive from nicotine's removal.

Of particular interest was the finding that BACCOFF™ administration was reported to be the closest approximation to participants' preferred moist snuff. The extent to which BACCOFF™ also produced a withdrawal-specific buffering effect across time implicates the importance of using behavioral/sensory substitutes within smokeless tobacco treatment that are of a similar taste, feeling, packing-consistency, and smell (to name a few) as moist snuff. Although previous treatment studies have employed similar mint snuff products and produced conflicting results (Hatsukami *et al*., 2000; Stevens *et al*., 1995; Zavala *et al*., 1995), an assessment of the substitute's approximation effect may help clarify the mixed results.

Our findings also support recent studies conducted in our laboratory examining the potential usefulness of alternative sensory substitutes. For example, recent studies have investigated the influence of chewing gum on smoking behavior as well as on nicotine withdrawal and craving (Cohen, Britt, Collins, al'Absi, & McChargue, 2001; Cohen, Britt, Collins, Stott, & Carter, 1999; Cohen, Collins, & Britt, 1997). Overall, studies conducting in our laboratory show that chewing gum helps with withdrawal when cigarette smokers could not smoke. The present data show comparable withdrawal effects during short-term smokeless tobacco deprivation. However, nicotine-free substitutes in the present study did not affect craving with smokeless tobacco users, whereas, in previous studies, craving was reduced when smokers were given chewing gum in some cases (Cohen *et al*., 1997), but not all (Cohen *et al*., 2001). One explanation for this inconsistent finding is that craving is multidimensional, comprised of appetitive and withdrawal components (Rohsenow, Niaura, Childress, Abrams, & Monti, 1990–1991). It is possible that the BACCOFF™ acted as a conditioned stimulus eliciting an appetitive craving response, while deprivation without the BACCOFF™ elicited withdrawal-based craving of a similar intensity level. This would have negated any possible differences in craving during BACCOFF™ administration. It is not apparent that chewing gum would have produced analogous effects because of its dissimilarity to cigarettes.

The DIPSTOP™ (liquid lobeline) component neither influenced craving nor nicotine withdrawal across 48 h of deprivation. There are a couple of feasible interpretations of the ineffectiveness of lobeline to influence craving and withdrawal symptoms. First, similar to cigarette withdrawal, lobeline may not be effective in assuaging the aversive qualities associated with smokeless tobacco deprivation. In fact, many researchers believe that agents that approximate nicotinic effects on the central nervous system (CNS) may be more important in the reduction of nicotine withdrawal and craving during abstinence (e.g., Picciotto, 1998). Because lobeline produces, to some extent, peripheral stimulant effects similar to nicotine, the lack of CNS activation may contribute to lobeline's inability to buffer smokeless tobacco withdrawal. Second, our study allowed smokeless tobacco users to self-administer the lobeline product *ad lib* during deprivation. Although such a procedure is consistent with smokeless tobacco cessation programs, *ad lib* usage prevented the present study from standardizing the administered dose. Thus, it remains unclear whether a controlled dose-specific administration might have produced the desired effects in our laboratory study.

Elevated withdrawal during the placebo condition appeared to be comparable to 48-h smokeless tobacco deprivation effects in a previous study (McChargue & Collins, 1998). These findings suggest that smokeless tobacco withdrawal produces reliable effects within our deprivation challenge protocol. Although the present study reports withdrawal severity that are lower than the Hatsukami *et al*. study (1987), they were analogous to the McChargue and Collins study examining smokeless tobacco withdrawal using a similar methodology and dependent undergraduate population. It is suggested that the generalization of our findings to the population of smokeless tobacco users may be limited. Our sample consisted of young adults who reported low dependence ratings (mean = 7.8) on the smokeless tobacco dependence questionnaire. It remains unclear whether more dependent smokeless tobacco users may respond as favorably to the sensory substitute provided in the present study.

A final limitation of this study reflects the lack of biochemically verified abstinence. Although a biochemical assessment would have increased our confidence in the data, we employed a bogus pipeline to increase the probability of more accurate self-reported abstinence. As with other studies exploring cessation or deprivation effects of tobacco users that also employed a bogus pipeline (Hansen *et al*., 1985; Murray *et al*., 1987), post-study debriefing questions suggested that our

participants did not misrepresent their abstinence reports. Additionally, carbon monoxide levels suggested that participants did not substitute smokeless tobacco with cigarettes during the forced deprivation.

In conclusion, research examining smokeless tobacco cessation appears to be sound but has not been well evaluated. The few studies that have implemented behavioral/sensory adjunctive components within smokeless tobacco treatment protocols have reported minimal effects. The present study documented effective reductions in withdrawal as a function of an herbal behavioral/sensory substitute within a laboratory setting, with such reductions possibly tied to how similar the substitute approximated moist snuff. These results exemplify the need for further work investigating behavioral/sensory components that may contribute to the treatment of smokeless tobacco users.

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