ALTERNATIVE TO SMOKELESS TOBACCO: DOCUMENTED REDUCTIONS IN WITHDRAWAL PATTERNS

By

DENNIS E. MCCHARGUE

Bachelor of Science
State University of New York College at Oswego
Oswego, New York
1993

Master of Science
Oklahoma State University
Stillwater, Oklahoma
1994

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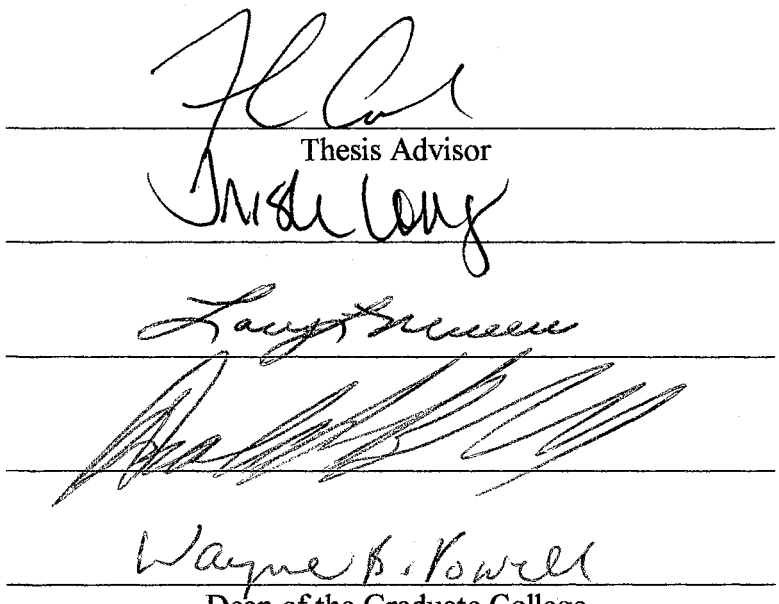

Thesis Advisor

Dean of the Graduate College

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Figure Page

Alternative to Smokeless Tobacco: Documented Reductions in Withdrawal Patterns

Dennis E. McChargue

Oklahoma State University

Abstract

The present study investigates two commercially produced over-the-counter smokeless herbal mixtures (FDA approved), DIPSTOP™ and BACCOFF™, influence on subjective withdrawal symptoms during smokeless tobacco deprivation. Participants (n = 19) were studied under BACCOFF™ X Water, BACCOFF™ X DIPSTOP™, DIPSTOP™ only, and Water only conditions, one condition per week. The order of the conditions was assigned using a Latin square methodology and participants were randomly assigned to each order. The Nicotine Abstinence Scale, Beck Depression Inventory, and State-Trait Anxiety Inventory were administered at baseline, 24-hour, and 48-hour deprivation for each condition. Within subject analysis of variances were conducted across all dependent measures. Results showed that BACCOFF™ significantly reduced symptoms that reflect DSM-IV criteria for nicotine withdrawal compared with other symptoms of withdrawal, including craving. Future research should explore the effectiveness of these substitutes in smokeless tobacco cessation.

Alternatives to Smokeless Tobacco: Documented Reductions in Withdrawal Patterns

Over the past decade, smokeless tobacco use has increased by 38.4% in the United States, while use of other nicotine products have progressively decreased (USDA, 1993). Among the estimated 10 million American smokeless users, over one third of them are below the age of 21 (Consensus Conference, 1986). Moreover, the number of adolescent and younger smokeless users appears to be increasing (Hill, Harrell & McCormick, 1992, Simon, Sussman, Dent, Burton & Flay, 1993). Concerns about these estimates involve the known risks of developing of nicotine dependence at younger ages (Jaffe, 1990; West, 1988), including the significant health problems associated with chronic smokeless tobacco use (Hoffmann, Adams, Lisk, Fisenne & Brunnemann, 1987; Hoffmann, Djordjevic, Fan, Glynn & Connolly, 1995). This increasing number of young individuals using smokeless tobacco necessitates further systematic exploration examining variables that facilitates smokeless tobacco cessation, such as possible substitutable reinforcers of this behavior.

Within the framework of a reinforcement paradigm, the psychological and physiological cues associated with smokeless tobacco consumption strengthen the behaviors related to repeated smokeless tobacco use. Upon removal of these cues, a distinct cluster of reactive symptoms, known as nicotine withdrawal, is elicited (Hatsukami, Gust & Keenan, 1987). Withdrawal symptoms are viewed as the primary variable that prompts relapse (Hughes, 1993). However, the differentiation between psychological versus physiological (pharmacological) factors that influence the exacerbation of withdrawal symptoms is not well understood. Given that nicotine administration has a distinct pharmacological effect, most researchers have concentrated

on examining the effectiveness of pharmacological adjuncts to isolate (Benowitz, 1988; Cooper & Clayton, 1994), mimic (Bradshaw, 1973; London, 1963), or block (Clarke, 1991; Hughes, 1993) nicotinic effects and reduce withdrawal. Combined with cognitive-behavioral therapy, these attempts have met with minimal success.

Behavioral economics theory posits that reduction of a targeted behavior may be accomplished with the simultaneous presentation of substitutable reinforcers, such as pharmacological adjuncts (Bickel, Hughes, Degrandpre, Higgins & Rizzuto, 1992). However, an adequate reduction of the original behavior constitutes the substitutable reinforcer to approximate the original behavior as close as possible (Hursh & Bauman, 1987). For example, smokeless tobacco use have both behavioral (including smokeless tobacco topography) and pharmacological components. Thus, a suitable reinforced substitution should approximate both components before one might witness a reduction in the targeted behaviors. Theoretically, the lack of a behavioral substitute within smokeless tobacco cessation studies may have contributed to the reduced treatment efficacy documented in most studies.

The present study was designed to provide evidence that is consistent with this behavioral economic model of nicotine use by testing the primary components of a commercial smokeless tobacco cessation package. This package contains two possible herbal alternative adjuncts to smokeless tobacco. One herbal mixture, BACCOFF™, approximates the behavioral, including topographical, components associated with smokeless tobacco use without the pharmacological effects of nicotine. The other herbal mixture, DIPSTOP™, produces peripheral nicotinic pharmacological properties. It is

suggested that the administration of these herbal preparations will substantially reduce the effects of withdrawal during deprivation.

It is noteworthy to mention that this study does not directly evaluate the behavioral economic model of substitutable reinforcers because smokeless tobacco use is artificially stopped for the purpose of examining withdrawal symptoms. A direct evaluation of this model would document naturalistic reductions in smokeless tobacco use as a function of herbal administration. Nevertheless, an indirect evaluation of the behavioral economic model of nicotine administration focusing on etiological factors, such as withdrawal symptoms, supplies valuable information. The documentation of withdrawal suppression with herbal administration provides two important contributions. First, the suppression of withdrawal symptoms would implicate use of these herbal preparations as potential substitutable reinforcers within the framework of a smokeless tobacco cessation program, subsequently increasing treatment efficacy. Second, substituting herbal preparations for smokeless tobacco would significantly reduce the health risks involved with smokeless tobacco use.

Health Risks

Epidemiological studies have consistently shown a relationship between smokeless use and oral cancer (Council on Scientific Affairs, 1986; Hoffman et al., 1987; 1995). The substance of nicotine is not, in itself carcinogenic, but this tobacco alkaloid is a precursor to a group of carcinogens called the tobacco-specific nitrosamines (Hoffman & Hecht, 1985). It is speculated that high concentrations of nitrosamine found in smokeless tobacco increase the rate of oral cancer among smokeless tobacco users. More specifically, two of these nitrosamines, N-nitrosamine 4-(methylnitrosamine)-1-(3-

pyridyl)-1-butanone (NNK) and N`-nitrosonornicotine (NNN) have been shown to produce cancer of the nose, trachea, esophagus, and liver in animals (Consensus Conference, 1986; Hecht et al., 1986). Moist snuff contains 1.6 to 135 mg/kg of NNN and .1 to 14 mg/kg of NNK while US foods and beverages are allowed to contain no more than .01 mg/kg of nitrosamine (Hoffmann et al., 1995). Furthermore, a recent study has demonstrated significantly higher concentrations of these nitrosamine in the three leading brands of moist snuff (i.e., Copenhagen, Skoal, Kodiak) sold in the United States compared to other brands, such as Hawkins and Skoal Bandits (Hoffmann et al., 1995). To date, no evidence has documented decreases of these deleterious concentrations in smokeless tobacco (Hoffmann et al., 1995).

Models of Nicotine Dependence

Learning Paradigm

Pavlovian Conditioning. Pavlovian conditioning has been used to explain one component of nicotine dependence. Rose and Levin (1991) and Iwamoto, Fudala, Mundy, and Williamson (1987) contend that Pavlovian conditioning contributes to the repeated use of nicotine. Nicotine administration (UCS) produces psychological and physiological states (UCR) which are paired with neutral environmental stimuli (CS). Iwamoto et al. suggest that these conditioned neutral stimuli pervade environmentally (e.g., sitting in front of a computer) and/or psychologically (e.g., anxiety, anger) specific contexts. Rose and Levin purport that cues from nicotine or the nicotine apparatus, such as the texture of the nicotine in smokeless tobacco or the smokeless tobacco tin, may represent conditioned stimuli. Over time, repeated pairings between a neutral

environmental stimuli and nicotine administration produce a conditioned response (e.g., craving) that initiates and maintains drug-seeking behavior.

Reinforcement. Classical reinforcement theory postulates that an individual forms associations between stimuli and their response to the stimuli. These associations strengthen or weaken the behaviors related to the response. In general, nicotine use, including smokeless tobacco use, appears to fit within this paradigm. The administration of nicotine is associated with an individual's response to the drug. This association strengthens the behaviors related to nicotine use (e.g., drug-seeking behaviors).

Rachlin, Battalio, Kagel, and Green (1981) suggest that classical reinforcement theory should consider the context of the reinforcing event and the choice of the individual to partake in nicotine related behaviors, as well. Theoretically, an individual chooses situations that will maximize reinforcement properties in an environment (Rachlin et al., 1981). Nicotine possesses a multitude of positive and negative reinforcement properties (Jarvik, 1991). For example, abstinence during sleep resensitizes tolerance and elicits withdrawal symptoms in the morning (Benowitz, 1990). This phenomenon produces a euphoric (aroused) response from the first cigarette (chew) of the day (Benowitz, 1990). In this situation, nicotine use is strengthened from both positive (e.g., euphoria) and negative (e.g., withdrawal) reinforcement. Similarly, sedation effects reinforce usage after a meal, and improvement on working memory and/or attention reinforces nicotine use during activities such as studying or working. Although there have been inconsistent findings in research examining the reinforcing properties of nicotine use (Dunne, MacDonald & Hartley, 1986), a majority of studies have provided evidence to warrant

consideration (Golding, & Mangan, 1982a, 1982b; Peeke & Peeke, 1984; Rusted & Eaton-Williams, 1991).

It appears that nicotine use is strengthened by multiple situations. Classical reinforcement theory would conclude that this strengthened nicotine related behaviors demonstrate reinforcement. However, the complexity of this reinforcement is not as clear when conceptualizing nicotine dependence solely within this model. Rachlin et al. (1981) postulated that nicotine users are not influenced by all of the possible situations that strengthen nicotine-related behavior. Thus, an element of choice must be involved in the reinforcement of these behaviors. Nicotine users may, in fact, maximize the overall reinforcement property of nicotine by choosing a combination of situations that provide the optimal strengthening of behaviors associated with an individual's pattern of nicotine consumption.

Behavioral Economics

Behavioral economic theory explains the relationship between nicotine use and the effort (cost) to obtain the substance. This theory applies reinforcement and conditioning principles to the process of nicotine dependence. Behavioral economics can equally interpret increases in nicotine usage in terms of the reinforcing qualities of the drug-effects. Nicotine use is also strengthened from the interaction between desired drug-effects and the efforts to obtain the substance. Moreover, behavioral economics delineates the importance of mimicking both conditioned and reinforced properties of nicotine during cessation protocols.

This theory consists of four basic components: (1) demand law, (2) elasticity, (3) unit price, and (4) alternative reinforcing stimuli. The demand law states that drug

consumption (demand or drug effect) decreases as the effort or cost to obtain the substance (response requirement) increases (Allison, 1979). For example, if new laws (response requirement) prohibited nicotine use (demand), nicotine consumption would decrease as the penalty for using the substance increases.

Elasticity refers to the degree of demand and response requirement (cost) fluctuations (DeGrandpre et al., 1992). A substance is considered elastic when drug use significantly changes in relationship to an increase in response requirement. For example, exacerbated health risks may reduce or eliminate nicotine use. However, when drug use changes only slightly with an increase in response requirement, the substance is considered inelastic. Individuals who continue using nicotine after they are diagnosed with cancer exemplify inelasticity.

Unit price refers to the interaction between the magnitude of the reinforcing property of a substance and the magnitude of the response requirement (Hursh, Raslear, Shurtleff, Bauman & Simmons, 1988). The unit price illustrates second-order properties of drug reinforcement. For example, as drug effects decrease with a stable response requirement, drug usage increases to stabilize the demand-response requirement relationship. This effect demonstrates the acquisition of tolerance. Conversely, as the response requirement increases (e.g., withdrawal symptoms elicited from conditioned stimuli) with a stable drug-effect, usage increases to counteract the withdrawal patterns.

Alternative reinforcing stimuli refers to the ability of other stimuli (e.g., nicotine gum) to act as a substitute or compliment of the original reinforcing agent (e.g., smokeless tobacco). A substitutable relationship increases behaviors associated with other stimuli as the behavior associated with the original stimulus decreases (Bickel, Hughes, Degrandpre,

Higgins & Rizzuto, 1992). The more similar an alternative reinforcer is to the original substance, the more effective the behavioral change. In other words, an alternative reinforcer that approximates the properties and effects of the original substance will be more effective at reduced the behaviors associated with the original substance (Hursh & Bauman, 1987). Conversely, complimentary relationships mimic the fluctuations of the original stimulus (Bickel et al., 1992). As the behaviors related to the original substance increases, the behaviors associated with the complimentary reinforcer increases as well. For example, coffee consumption (a compliment) will increase as nicotine use increases.

Theoretically, substitutes for nicotine use should possess similar properties associated with nicotine dependence. An adequate substitute elicits comparable responses from conditioned stimuli and strengthens behaviors associated with positive and negative reinforcing properties of nicotine. All else being equal, a substitutable reinforcer stabilizes the relationship between drug use and response requirement without administering the original drug. This stabilization suppresses negative reinforcing properties elicited from abstinence.

Smokeless Tobacco Cessation

Smokeless tobacco cessation studies have focused on self-directed intervention in a variety of settings (Glover, Wang & Glover, 1994; Stevens, Severson, Lichtenstein, Little & Leben, 1995; Williams, Arheart & Klesges, 1995). Self-directed interventions have also examined replacement treatments (Sinusas & Coroso, 1993; Stevens et al., 1995) and multiple baseline treatment protocols (Dilorenzo, Kern & Pieper, 1991). This research has demonstrated minimal abstinent rates (approximately 20%), which are less than the typical 30% abstinent rate from smoking cessation programs (Carmody, 1990). Low abstinent

rates inherently implies the entrenched behavioral patterns associated with smokeless tobacco use and higher level of dependency.

Prior to 1993, researchers had not studied replacement treatments within smokeless tobacco cessation programs (Sinusas & Coroso, 1993). Sinusas and Coroso were the first to study the effectiveness of nicotine gum with smokeless tobacco users. A 12-month follow-up study showed minimal abstinence maintenance. Stevens et al. (1995) employed mint leaf non-tobacco products, chewing gum, and toothpicks as substitutes for smokeless tobacco related behaviors within their cessation protocol. Although the substitutes were not directly evaluated, this study demonstrated a 33%, 12-month abstinence rate.

It is evident that smokeless tobacco cessation and possible components to treatment have not thoroughly been investigated. Recently, studies have suggested that replacement treatments may be possible avenues to control smokeless tobacco withdrawal during cessation (Sinusas & Coroso, 1993; Stevens et al., 1995). Nevertheless, abstinent rates have been marginal and inconclusive at best. More systematic exploration of the effectiveness of smokeless tobacco substitutes to reduce withdrawal symptoms is necessary prior to planning new innovative treatment protocols that implement such substitutes.

Nicotine Withdrawal

The Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV; American Psychiatric Association, 1994) delineates withdrawal symptoms that consistently produce effects from nicotine abstinence. Individuals who meet DSM-IV criteria for nicotine withdrawal must experience four or more of the following symptoms or groups of symptoms during abstinence: (1) dysphoric or depressed mood; (2) insomnia; (3)

irritability, frustration, or anger; (4) anxiety; (5) difficulty concentrating; (6) restlessness; (7) decreased heart rate; and (8) increased appetite or weight gain (American Psychiatric Association, 1994). They must also report daily use for at least several weeks, exhibit withdrawal symptoms that cause clinically significant distress or impairment in daily functioning, and experience symptoms that are not better accounted for by a medical condition or other mental disorders.

Craving, a withdrawal symptom excluded from DSM-IV, represents a motivational state that perpetuates drug-using behavior and precipitates relapse during abstinence (Kozlowski & Wilkinson, 1987; Marlatt, 1985; West & Schneider, 1987). It has been posited that this motivational (central) state subsumes both "physical" and "psychological" determinants (Ludwig, Wilkers & Stark, 1974; Kozlowski & Wilkinson, 1987; Tiffany & Drobes, 1991). Researchers have found it difficult to separate craving elicited from physical determinants, such as withdrawal symptoms (Shiffman, 1987), and psychological determinants, such as an intense desire for drug-seeking behavior (Rankin, Hodgson & Stockwell, 1979; Tiffany & Drobes, 1991). Craving was removed from the DSM-IV nicotine withdrawal criteria partially due to the difficulties in differentiating between psychological and physiological determinants (Hughes, 1996).

There is ample evidence, however, to warrant the study of this concept with nicotine dependent individuals during abstinence. For instance, craving remains a prominent feature of nicotine abstinence (Glassman et al., 1984; Hughes & Hatsukami, 1986), and consistently predicts relapse (Killen et al., 1992; Marlatt, 1985). Moreover, research examining how craving interacts with withdrawal patterns is also needed.

Nicotine withdrawal research has historically focused on the abstinence effects of smokers (Hughes & Hatsukami, 1986; Hughes, Higgins & Hatsukami, 1990). In particular, deprivation studies have identified a host of withdrawal symptoms (e.g., anxiety, depression, irritability) related to smokers, usually beginning within 24-hours and peaking within 48-hours of deprivation (Hughes, Higgins & Hatsukami, 1990). Researchers typically have compared both the 24-hour and 48-hour deprivation periods to a baseline (pre-quit) period using self-report and physiological measurements (Hughes et al., 1990; Hughes & Hatsukami, 1986).

There have been few studies addressing deprivation effects related to smokeless tobacco users. The overall results from these studies have demonstrated a similar response pattern to smokers, only qualitatively less intense (Hatsukami, Gust & Keenan, 1987; Keenan, Hatsukami & Anton, 1989). A recent study comparing young college student smokeless tobacco user and smoker's withdrawal patterns exemplifies the consistency in withdrawal patterns between smokers and smokeless users (McChargue & Collins, 1998). Contrary to Hatsukami et al. and Keenan et al., however, McChargue and Collins found that smokeless users' withdrawal severity were proportional to smokers.

Less intense smokeless tobacco withdrawal severity and comparable withdrawal patterns between smokers and smokeless users have led researchers to minimize the importance of smokeless tobacco withdrawal. The premise that both forms of nicotine administration elicit equivalent withdrawal patterns appeared to negate the importance of psychological (e.g., conditioning) compared with physiological components of nicotine withdrawal. In essence, it was suggested that withdrawal symptoms are a function of the substance regardless of the mode of administration. Consequently, DSM-IV nicotine

withdrawal criteria (American Psychiatric Association, 1994) delineate symptoms that support this hypothesis. It does not differentiate among different forms of nicotine use.

Recent literature on reinforcement properties of nicotine and Pavlovian conditioning effects provide evidence that supports the idea that withdrawal patterns may be a function of the nicotine administration method (e.g., chewing, smoking) and the environment. Conditioned stimuli (e.g., texture of tobacco, smokeless tobacco tin) are paired with both drug-effects and withdrawal symptoms. Furthermore, the multitude of situations that produce positive and negative reinforcement influence individuals to maximize the optimal reinforcement properties of nicotine. It is clear that smokeless users are able to use the substance in many settings that smokers are restricted from use due to the form of administration. For example, smokeless tobacco is easily used in sports and work areas that restrict smoking because of second-hand smoke issues. Thus, topographically conditioned cues (e.g., tin, texture, taste) unique to smokeless tobacco use may elicit differential withdrawal symptoms compared with smoking cues (e.g. taste of cigarette, cigarette package).

Smokeless Tobacco Topography

Pavlovian conditioning and behavioral economics theories illustrate the importance of topographical specificity when investigating nicotine dependence and possible treatment issues. Theoretically, conditioned topography elicits biphasic responses. It either cues behaviors associated with nicotine use or activates withdrawal symptoms.

Unlike a cocaine user's well defined and elaborate topographical routine, a smokeless tobacco user's routine appears more subtle and less involved, but equally as important to the smokeless user. Hatsukami, Keanan, and Anton (1988) outlined some topographical

features associated with smokeless tobacco users, such as mean number of tins per week, duration of smokeless tobacco use, and dips per day. It is suggested that other behavioral features (e.g., packing moist snuff with tongue), not yet empirically documented, may also contribute to the overall topographical conditioned effect.

Hatsukami, Keenan, and Anton's (1988) produced the only empirical evidence detailing topographical features of smokeless tobacco. They reported that the results demonstrated a potential contribution to dependence, but they did not speculate how these topographic features related to classical conditioning. For example, Hatsukami et al. documented that the mean number of dips/day was 6.3 (SD = 2.2). The average male user was 20.7 years (SD = 1.9); the mean age of onset was 16.2 (SD = 2.3); and the average duration of smokeless tobacco use was 5.2 years (SD = 2.4). Over 5.2 years, a male smokeless user will have taken 11,924.64 dips of tobacco (6.3 dips/day X 7 day/wk X 52 wk/yr. X 5.2 years of usage). Moreover, a male smokeless tobacco user will spend approximately 39.9 (SD = 16.5) minutes per dip of tobacco (Hatsukami et al. 1988). Adding the amount of time performing this behavior into the equation, an average dipper will spend approximately 765,538.95 hours using smokeless tobacco within 5.2 years. Considering the magnitude of these estimates, the behaviors associated with smokeless tobacco use should be well conditioned after 5.2 years and should play an important role in cessation.

Researchers have not yet documented topographical behaviors associated with smokeless use. It is suggested that after many years of use, the behaviors associate with this administration become well-ingrained conditioned stimuli. For example, the proverbial ring formed on the back pocket of jeans from years of placing tins in the

pocket, carrying a tin of tobacco at all times, snapping the tin to pack the tobacco before use, and placing the dip in a specific location along the gums appear to be conditioned pairings. This speculation is consistent with research examining placed-conditioning of nicotine (Fudala & Iwamoto, 1986; Fudala, Teoh & Iwamoto, 1985). Placed-conditioning research has demonstrated the importance of context-specific stimuli (Fudala et al., 1985). Although researchers commonly purport environmental stimuli, such as a specific location in a maze with animals and a specific situation or activity (e.g., at a computer, studying) with humans, conditioned contextual stimuli may be reduced to the specific behaviors associated with the use of smokeless tobacco.

Similarly, the behaviors associated with dipping duration also may become conditioned stimuli, especially after the average user's 765,538.95 hours of use over 5.2 years. For example, the location of the dip placement may become conditioned during use. Research has shown that older dippers absorb nicotine at a quicker rate than novice dippers (Russell, Jarvis, Devitt & Feyerabend, 1981; Russell, Jarvis & Feyerabend, 1980). This provides some evidence that the mouth adapts to the placement of the tobacco, thus conditioning a specific location. Furthermore, the packing behavior of the tobacco during dipping may be similarly conditioned. Anecdotally, this is evinced by the ritualistic placing of the tongue in that specific location during abstinence or without smokeless tobacco in the mouth. Additionally, the amount of saliva produced during smokeless use is also conditioned. Although no research has quantified the amount of saliva produced during use or elicited from cues, its function is speculated to be similar to findings in other classical Pavlovian conditioning studies (Russell et al., 1981). Other possible conditioned stimuli during dipping are the taste and texture of the tobacco. Similar to the other

conditioned stimuli, tactile and taste stimuli are significantly paired after numerous learning trials.

This evidence supports the idea that smokeless tobacco use consists of well ingrained behavioral and sensory conditioned responses. The large amount of conditioned pairings from numerous topographical features exemplify the importance of developing techniques that control for conditioning effects during cessation.

One possible alternative for extinguishing these behaviors is through viable substitutes that address these issues. A behavioral economic paradigm provides the theoretical foundation for such a substitute. According to behavioral economics, individuals should increase the use of a substitute as the target behavior (e.g., smokeless tobacco use) decreases. Furthermore, potential behavioral substitutes should closely approximate the target behaviors before it is effective (Hursh & Bauman, 1987). Therefore, a substitute that looks, feels, and tastes like smokeless tobacco and is packaged in a similar container void of nicotine, theoretically, would be a viable substitute for the topographical features of smokeless tobacco.

Pharmacological Therapies

Behavioral economics theory provides a theoretical basis for pharmacological therapies. Alternative drug substitutes and/or alternative forms of nicotine administration have played a substantial role in the reduction or elimination of withdrawal patterns during abstinence. Jarvik and Henninfield (1988) have discussed multiple pharmacological approaches to facilitate cessation or deprivation. Traditionally, there have been four specific avenues applied to nicotine dependence: (1) nicotine replacement, (2) withdrawal relief, (3) aversive nicotine intake, (4) and nicotine receptor blockage. Current literature

has focused on replacement approaches using nicotine polacrilex (gum), transdermal systems (patch), and nasal sprays (to a lesser degree). However, over-the-counter commercial products have manufactured other supplements (e.g., Nikoban) which contain substances that attempt to alleviate withdrawal symptoms. Although previous research has found mixed results concerning effectiveness of supplement substances, such as lobeline (the primary ingredient in Nikoban), they still appear to play a part in smoking cessation. Other pharmacotherapies will be further discussed later in this section.

Nicotine Replacement Therapies

Nicotine polacrilex (Nicotine Gum). Nicotine gum is typically administered to smokers with 2 to 4 mg of nicotine per piece of gum (Leischow, Sachs, Hensen & Bostrom, 1995) and individuals chew 10-15 pieces of gum per day (Benowitz, 1988). Although some research has demonstrated a decrease in cigarette smoker's withdrawal symptoms with individuals averaging 8.6 pieces per day (West, Hajek & Belcher, 1989), Benowitz suggests that fewer than 10 pieces may not ensure an adequate amount of nicotine for noticeable dose effects, resulting in therapeutic failure.

It is suggested that treatment should last no more than three months with the gradual reduction of nicotine (Benowitz, 1988). Once placed on nicotine gum, triturating the dosage does not exacerbate withdrawal symptoms. Research has shown a decrease in cigarette smoker's withdrawal symptoms while progressively reducing the dosage over a four week period (West et al., 1989). Furthermore, prolonged treatment may create dependence to the nicotine gum. Studies have shown substantial increases in withdrawal symptoms with treatments lasting more than three months (West and Russell, 1985;

Hughes, Hatsukami & Skoog, 1986). Whereas, Hatsukami, Huber, Callies, and Skoog (1993) demonstrated minimal withdrawal symptoms after 1 and 3 months of usage.

Other factors to consider when administering nicotine gum are properly instructing clients on how to use the gum, combining treatment with psychotherapy, and potential side effects. First, research has demonstrated the importance of proper instructions. Instructions have been shown to influence craving reduction (Hughes, Gulliver, Amori, Mireault & Fenwick, 1989) and improper usage has been shown to decrease the effectiveness of the gum (Lee & D'Alonzo, 1993). For example, drinking coffee and carbonated beverages while using the gum significantly diminishes the amount of nicotine absorbed (Lee & D'Alonzo, 1993). Furthermore, the gum is not chewed like bubble gum, it is gently chewed periodically to elicit an effect (similar to puffing a cigarette) and then parked between the teeth to ensure maximum absorption (Miller & Cocores, 1991). Moreover, swallowed nicotine in saliva is altered before entering the blood stream, minimizing the amount of nicotine absorbed in the system (Cooper & Clayton, 1994; Miller & Cocores, 1991). Second, research has shown that combining behavior therapy with nicotine gum is more effective than behavior therapy alone or nicotine gum treatment alone (Hughes, 1991). Lastly, common side effects include a sore throat or mouth, hiccups, tired jaws, nausea or other gastrointestinal symptoms, palpitations, and occasionally, mouth ulcers (Benowitz, 1988).

Transdermal Systems Therapy (Nicotine Patch). There are 16-hour and 24-hour transdermal patches available, usually consisting of 15 to 24 mg of nicotine per patch (Cooper & Clayton, 1994). Commercially manufactured transdermal systems (i.e., Nicoderm, Habitrol, Nicotrol, and Prostep) suggest an average of 14 weeks of transdermal

treatment for smokers including gradual reduction of dosage (Cooper & Clayton, 1994). A meta-analysis conducted by Fiore, Stevens, Smith, Jorenby, and Baker (1994), however, demonstrated that treatment of smokers beyond 8 weeks including dose reduction did not appear to increase efficacy. Furthermore, developing drug dependence from the patch has not been thoroughly investigated. Therefore, it is recommended that treatment duration should be planned and monitored carefully.

The patch has certain advantages over nicotine polacrilex. First, there is no risk of minimizing the administration of nicotine because nicotine is absorbed directly through the skin into the blood (Glover & Glover, 1994). Second, individuals using the patch experience fewer adverse physiological effects than cigarettes (Muller et al., 1990) and fewer side effects than nicotine gum (Rose, Herskovic, Trilling & Jarvik, 1985). The only noticeable side effect is skin irritation. However, rotating the application site will minimize the skin irritation (Cooper & Clayton, 1994). Other systemic effects, such as nausea, vomiting, sweating, dizziness, abdominal pain, chills, and headaches were seen as frequently with placebo groups (Cooper & Clayton, 1994). Third, the patch has been shown to be significantly more effective than a placebo regardless of adjunctive approaches, such as combining the patch with counseling (Fiore et al., 1994). In addition, research has demonstrated significant decreases in spontaneous smoking (Pickworth, Bunker & Henningfield, 1994), reduced withdrawal and depressive symptoms (Levin et al., 1994), and a doubled rate of continuous abstinence up to one year (Stapleton et al., 1995).

Nicotine Nasal Sprays and Aerosols. Nicotine nasal sprays and aerosols were originated in hopes to increase dose accuracy and absorption rates. Absorption rates with

nicotine polacrilex and transdermal nicotine systems are clearly more gradual with a correspondingly slower uptake to the brain (McDonald & Olson, 1994). However, nicotine aerosol effects have been shown to be similar to cigarette effects, eliciting a sharp rise in plasma nicotine followed by a slower decline (Pomerleau, Flessland, Pomerleau & Hariharan, 1992). Furthermore, as a supplement for smoking cessation, nasal sprays have been shown to decrease nicotine concentrations after 4 weeks (Sutherland, Russell, Stapleton, Feyerabend & Ferno, 1992). The side effects experienced from nasal sprays, such as lightheadedness and slight dizziness (Sutherland et al., 1992), combined with reports of nasal aerosols being somewhat aversive (Pomerleau et al., 1992), warrant further research. There are few studies investigating the effectiveness of nicotine nasal delivery devices, dependence issues, and safety issues. Therefore, more research is needed before implemented into cessation programs.

Withdrawal Relief Therapy

Lobeline Therapy. Lobeline is a derivative of the lobelia, or Indian Tobacco, plant which mimics peripheral effects of nicotine (Dorsey, 1963). Although studies have shown aversive side effects, such as dizziness, nausea, and vomiting; appearing 15-30 minutes after administration (Ejrup, 1960), London (1963) demonstrated that .5 mg of lobeline sulfate in a cherry flavored pastille reduced the side effects of lobeline and suppressed craving for nicotine. Typically, lobeline is administered in .5 mg capulates mixed with an antacid (Bradshaw, 1973) or flavored pastilles (London, 1963). Individuals taking lobeline derivatives are instructed to take 3 to 4 capulates a day (Davison & Rosen, 1972). The length of administration ranges from one week to eight weeks. However, the length

of administration has not been shown to be an important variable in the improvement treatment efficacy (Davison & Rosen, 1972).

Research demonstrating the effectiveness of lobeline to reduce smoking behavior has been mixed (Berstein, 1969; Bradshaw, 1973; Schuster, Lucchesi & Emley, 1979); there are no studies that have examined lobeline with smokeless tobacco users. Although reviews of lobeline have stated that the few controlled studies have not consistently shown lobeline to be more effective than a placebo, recent evidence has shown that sublingual lobeline sulfate significantly reduced cigarette smoker's withdrawal symptoms (Schneider et al., 1996). Despite the lack of consistent findings showing lobeline as effective nicotine deterrent, over-the-counter lobeline products are still available. Bantron is sold as a mixture of 2 mg of lobeline sulfate and 1200 mg of antacid, and Nikoban is presented in .5 mg capsules of lobeline and a flavored inactive base (Davison & Rosen, 1972). It is suggested that lobeline has not been thoroughly researched. Future studies examining the effectiveness for reducing withdrawal symptoms in conjunction with behavior therapy is warranted.

Other Therapies. Clonidine, an antihypertensive medication, and Scopolamine, a medication for motion sickness, have been suggested as potential supplements (Miller & Cocores, 1991). In both cases, these drugs have been shown to reduce withdrawal symptoms (Corores, Sinaikin & Gold, 1989; Glassman, Jackson & Walsh, 1984). Furthermore, both substances are administered through transcutaneous patches for 3 to 4 weeks, gradually triturating the doses (Miller & Cocores, 1991). It is important to note that the research concerning both clonidine and scopolamine is scanty. Therefore, the effectiveness of these drugs are unclear.

Several antidepressant and antianxiety medications have also been studied for their effectiveness as a smoking deterrent (Robbins, 1993). This line of research is relatively new and the results of a few studies have not elicited conclusive evidence supporting the use of antidepressants or antianxiety medications (Glassman, Jackson, Walsh & Roose, 1984; Robbins, 1993).

Aversive Nicotine Intake

Silver Acetate. Silver acetate is available without prescription. Individuals are instructed to take 2.5 mg flavored lozenges every 4 hours for 3 weeks (Miller & Cocores, 1991). The flavored lozenges produce an aversive taste in the mouth after the first puff of a cigarette (Miller & Cocores, 1991). To date, few controlled studies have been conducted (Malcolm, 1986; Rosenberg, 1977). Therefore, the effectiveness of this product is not clear.

Nicotine Receptor Blockage

Mecamylamine. The purpose of mecamylamine is to facilitate the pharmacological extinction of smoking behavior (Clarke, 1991). This substance increases smoking behavior while decreasing the reinforcing effects of nicotine (Hughes, 1993). Withdrawal symptoms have not been noted after the removal of mecamylamine. Hughes hypothesizes that the diminished withdrawal results because mecamylamine does not occupy nicotinic receptor sites. It simply blocks these receptor sites, preventing nicotine from affecting the organism. Prohibitive side effects (e.g., signs of ganglion blockade have caused participants to prematurely leave studies), however, warrant further research in this area (Clarke, 1991; Hughes, 1993).

BACCOFF™ and DIPSTOP™

BACCOFF™ AND DIPSTOP™ are two commercially produced over-the-counter (FDA approved) herbal mixtures made specifically to combat smokeless tobacco dependence. The products were designed to alleviate the aversive effects of withdrawal during cessation. Theoretically, BACCOFF™ and DIPSTOP™ should produce similar topographical and pharmacological nicotinic responses to smokeless tobacco use. The lack of empirical evidence showing that both products effectively change smokeless tobacco behaviors warrants systematic exploration of components that may mediate this response (e.g., withdrawal).

The DIPSTOP™ product has not been empirically studied. Its primary herb, lobeline, reliably mimics nicotinic effects in human and animal studies (Stolerman, 1990) and has helped prevent significant withdrawal symptoms during tobacco deprivation (Schneider et al., 1996). Research has primarily found lobeline to be ineffective at reducing smoking behavior (Berstein, 1969; Bradshaw, 1973; Schuster, Lucchesi & Emley, 1979). It was speculated that the ineffective results were possibly influenced by the disparate absorption rates between lobeline and cigarettes (Schuster et al., 1979). The absorption of lobeline is a gradual process which plateaus with continuous use (Stolerman, 1990). This pattern appears to be closer to smokeless tobacco absorption rates than cigarette absorption rates. According to behavioral economics, effective substitutes should closely approximate the original substance. Therefore, studies demonstrating similar nicotinic effects and absorption rates provide evidence that lobeline may be more appropriately employed with smokeless users rather than cigarette smokers.

Typically, research has not provided empirical evidence documenting lobeline effects on withdrawal patterns with cigarette smokers or smokeless users. However, recent research, emphasizing withdrawal reduction, has found that sublingual lobeline sulfate significantly reduces cigarette smoker's withdrawal symptoms (Schneider et al., 1996). These promising findings need to be replicated and extended to a smokeless tobacco population.

BACCOFF™ is a commercially produced herbal mixture that has no nicotinic properties. It is administered ad lib similar to moist snuff products. There has been only one empirical study examining the similarities between BACCOFF™ and smokeless tobacco. Researchers found that BACCOFF™ produced similar olfactory, tactile, and taste responses to smokeless tobacco (Coffey & Lombardo, 1996). These findings suggest that BACCOFF™ may help control for topographical components (e.g., conditioned stimuli) of nicotine dependence.

Goals of the Current Study

Purpose

The present study will investigate 24-hour and 48-hour deprivation effects during the administration of two alternative smokeless tobacco reinforcers (DIPSTOP™ and BACCOFF™). Four groups were constructed for the purpose of this study: BACCOFF™ + Water, BACCOFF™ + DIPSTOP™, DIPSTOP™ only, and Water only. Water was used as a placebo to reduce potential expectancy effects from DIPSTOP™ administration. However, it was not feasible to employ a placebo for the BACCOFF™ condition. The groups will help differentiate deprivation effects associated with topographical features

(BACCOFF™) compared with physiological features (DIPSTOP™) of the alternative reinforcers.

In general, the elimination or minimization of nicotine withdrawal during abstinence has been viewed as an important component in the treatment of nicotine dependence. Previous research has shown that withdrawal latency and magnitude (severity) qualitatively contribute to our understanding of the differences among withdrawal symptoms (McChargue & Collins, 1998). For example, McChargue and Collins showed the smokeless tobacco users withdrawal symptoms consistent with DSM-IV criteria showed significant elevations during 24-hour deprivation (short latency) compared with craving and other withdrawal symptoms, but did not show this difference in 48-hour deprivation. Their findings suggest that withdrawal symptoms consistent with DSM-IV criteria may be more amenable to deprivation effects compared with other signs and symptoms of withdrawal. Therefore, it was deemed necessary to evaluate 24-hour and 48-hour deprivation compared with a baseline period. These data points will help elucidate differential latency and magnitude deprivation effects during product administration.

These substitutable reinforcers theoretically possess entrenched topographical stimuli and physiological responses similar to smokeless tobacco. The purpose of BACCOFF™ is to approximate topographically conditioned stimuli as DIPSTOP™ elicits similar systemic effects to smokeless tobacco. Overall, the administration of the products diminishes negatively reinforcing withdrawal symptoms while simultaneously controlling conditioned stimuli and positively reinforcing physiological effects. The purpose of the study exemplifies how conditioned stimuli, positive reinforcement, and negative reinforcement

influence nicotine dependence. This complex interaction between conditioning and reinforcing variables associated with nicotine dependence demonstrates the need for comprehensive treatments.

Hypotheses

It is predicted that BACCOFF™ administration during 24 hour and 48 hour deprivation will significantly reduce craving, DSM-IV withdrawal, total withdrawal, state anxiety, and depression scores compared to 24 and 48 hour deprivation without BACCOFF™ or DIPSTOP™ administration. The suppression of withdrawal symptoms associated with the administration of topographical variables will provide evidence to suggest that variables other than physiological responses (e.g., nicotine patch) may play a significant role in the development and maintenance of nicotine dependence.

DIPSTOP™ administration during 24 and 48 hour deprivation is also expected to reduce craving, DSM-IV withdrawal, total withdrawal, state anxiety, and depression scores compared to 24 and 48 hour deprivation without DIPSTOP™ or BACCOFF™ administration. Documented reductions will reflect the effectiveness of an agonist to control withdrawal symptoms and will provide support for the utilization of non-nicotine treatments for smokeless tobacco cessation. Little is know about the pharmacological treatment of smokeless tobacco. This evidence may help validate and foster further research.

Furthermore, the administration of BACCOFF™ and DIPSTOP™ is predicted to significantly reduce craving, DSM-IV withdrawal, total withdrawal, state anxiety, and depression scores during 24 hour and 48 hours deprivation compared to 24 and 48 hour BACCOFF™ x water, DIPSTOP™ only, and water only conditions. This evidence will

strongly reflect the importance of controlling conditioned stimuli, positive reinforcement, and negative reinforcement properties of smokeless tobacco. Moreover, this data will help us to differentiate between psychological and physiological components to smokeless tobacco consumption and direct our effort toward refining current treatment protocols.

Method

Participants

Male undergraduate students (n=18) were recruited from undergraduate introductory psychology courses (PSYCH 1113) at Oklahoma State University and were given extra credit in their psychology classes as compensation for their participation. A research questionnaire (See Appendix A) was administered during their respective classes to assess for potential participants. A lottery for $100.00 was also conducted at the end of each semester. Participants completing the protocol were eligible for the lottery as an extra incentive. Although the lottery was an added incentive, participants received some incentive for their participation; All participants received extra credit.

Participants who reported at least two consecutive years of smokeless tobacco use without the use of any other nicotine product, was currently using 1 ½ tins/week, were over the age of 18, and scored above a 6.5 on the Smokeless Tobacco Dependence Scale were included in the project. Two participants were excluded from the study for repeated failure to abstain from nicotine products during the deprivation days. Participants had a mean age of 19.81 (SD = 1.87) years. The Smokeless Tobacco Dependence Questionnaire scores (M = 7.94, SD = 3.0) were higher than the cutoff mean score of 6.5 found in previous research (Boyle, Jensen, Hatsukami & Severson, 1995). Participants reported more than 2 years of continuous smokeless tobacco usage without currently

using any other form of nicotine products or attempting to quit or cut down on smokeless tobacco. These data suggest that the participants' dependency to smokeless tobacco was equivalent to participants in other withdrawal studies (Boyle et al., 1995; McChargue & Collins, 1998). See Table 1 for more detail demographics from the Smokeless Tobacco Dependence Questionnaire.

Materials

Saliva Samples. Saliva was collected to facilitate abstinence compliance. Individuals were informed that cotinine levels were collected and analyzed to assess systemic nicotine levels. No physiological or pharmacological indices, however, were derived from the samples. Saliva was stored in 16 X 100mm Pyrex cultured screw cap test tubes. All samples were placed in a freezer and discarded at the end of the study. Latex gloves were worn during all phases involving the handling of saliva samples.

Alveolar Carbon Monoxide Monitor. Alveolar carbon monoxide (COa) was taken to facilitate deprivation compliance and to assess for other forms of tobacco use. Carbon monoxide levels are an effective measure of smoking behavior, but cannot identify smokeless tobacco use. Participant COa samples were obtained using a Vitalograph BreathCOa monitor (Model 29.700). COa levels of 8 ppm indicate significant carbon monoxide ratings, which may be caused by smoking. Individuals possessing COa levels of 8 or higher were considered using nicotine products.

Herbal Products. Two commercial herbal products were used in this study; BACCOFF™ and DIPSTOP™ (Ralston Inc., Selma, AL). BACCOFF™ is an herbal tea leaf product that has been shown to approximate salivary, olfactory, tactile, and taste responses elicited from a variety of commercial smokeless tobacco products (Coffey &

Lombardo, 1996). The ingredients contained in this product include tea leaves, natural and artificial flavors, glycerin, and sodium benzoate. The BACCOFF™ product was administered in a tin similar to smokeless tobacco moist snuff products. This method of administration approximates moist snuff usage, which allowed participants to use the product at the same frequency and amount as his original moist snuff product. For the purpose of this study, wintergreen and straight flavored BACCOFF™ were given to Skoal and Copenhagen moist snuff users, respectively.

DIPSTOP™ was developed to produce systemic effects that approximate peripheral physiological nicotinic responses. Systemic effects were activated by the products primary ingredient lobeline, a nicotinic agonist (Stolerman, 1990). Other active ingredients within the DIPSTOP™ liquid drops are valerian root, wild lettuce, dandelion root, scullcap, borage, yerba mansa root, red clover blossom, chamomile flower, African cayenne, distilled water, and 35% natural glycerine by volume. Participants were instructed to ingest the substance four times per day through liquid drops regularly placed in a drink.

Placebo. Water was placed in DIPSTOP™ containers to act as a placebo for the liquid drops. Participants and experimenters were blind to the substance in the liquid drop containers. No placebo was used for the BACCOFF™ product.

Beck Depression Inventory (BDI). The BDI was designed to assess the severity of depression symptomatology (Beck & Steer, 1987). This scale consists of 21 items in a Likert-scale format ranging from 0 to 4. Scoring categories are 0-9 (normal range), 10-15 (mild depression), 15-20 (mild-moderate depression), 20-29 (moderate-severe depression), and 30-63 (severe depression). The BDI is also indicative of adjustment difficulties among college student (Gotlib, 1984; Tanaka-Matsumi & Kemeoka, 1986).

Researchers found that changes in BDI scores paralleled changes in the clinical levels of depression, indicating a consistent relationship between BDI scores and the patients clinical state (Stehouwer, 1985). The reliability figures were consistently above $r = .90$ ($p < .001$). Bumberry, Oliver, and McClure also found concurrent validity between the inventory and psychiatric ratings using university students, $r = .77$ ($p < .01$).

State-Trait Anxiety Inventory, Form Y (STAI). The STAI (Speilberger, Gorsuch, Lushene, Vagg & Jacobs, 1983) contains one scale measuring state anxiety and another scale assessing trait anxiety. The STAI-State consists of 20 items designed to assess acute (state) anxiety levels. The STAI-Trait consists of 20 items designed to evaluate chronic (trait) anxiety levels. Items are rated on a 4 point Likert-type scale (1-4), and total scores range from 20 to 80, with higher scores indicative of more anxiety. STAI-Trait scores were not used for this study. Internal consistency of the state-anxiety scale, as indexed by coefficient alpha, ranges from .86 to .95 (Chaplin, 1984). In addition, validity correlation coefficients tend to be .70 and higher (Speilberger et al., 1983).

Smokeless Tobacco Dependence Questionnaire (SMTDQ). The SMTDQ (Boyle, Jensen, Hatsukami & Severson, 1995) is a 10 item self-report measure designed to measure aspects of smokeless tobacco use which correspond with dependence. This scale is a modified version of the Fagerstrom Tolerance Questionnaire (FTQ; Fagerstrom & Schneider, 1989) with added questions that reflect the unique characteristics of smokeless tobacco behavior and consumption. No cutoff scores were reported for this measure. However, Boyle, Jensen, Hatsukami, and Severson documented that the mean total score of 6.75 ($SD = 1.76$) was significantly correlated with cotinine levels ($r = .47$).

Nicotine Abstinence Scale (NAS). The NAS is a modified version of the Withdrawal Symptom Checklist (Hughes & Hatsukami, 1986) that was designed specifically for this study (See Appendix B). It consists of 30 items in a Likert-scale format (0-none; 1-mild; 2-moderate; 3-severe) assessing both state and general withdrawal patterns. This study only utilized the state scale to assess across 48-hour deprivation conditions. The NAS is designed to produce Craving, DSM-IV withdrawal, and total withdrawal scores. To date, this scale has no reliability or validity data.

The DSM-IV score is obtained by taking the sum of participants' responses to items 3, 4, 5, 11, 12, and 15. The highest score among DSM-IV grouped criteria, represented in items 2, 13, or 14, is also added to the DSM-IV score. Item 1 is evaluated separately to compare craving effects on overall withdrawal. The total withdrawal score is the sum of all of the items on the NAS. This score accounts for the overall withdrawal severity of the nicotine user.

Procedure

Latin square counterbalancing approach. Participants were placed in four conditions, BACCOFF™ X Water, DIPSTOP™ only, BACCOFF™ X DIPSTOP™, and Water only. These conditions were systematically ordered to reduce the probability of order and sequence effects. A Latin square design was used to ensure that the presentation of the orders was represented equally among all participants during each week of the protocol. The problem with a completely balanced Latin square design is that the number of groups and participants required may be prohibitive (Kazdin, 1992). Thus, the approach taken has inherent limitations. For example, conducting a completely balanced Latin square design was not feasible.

Given that BACCOFF™ is administered with a liquid drop (DIPSTOP™ or Water) twice for each participant, the first order of the conditions (represented at the beginning of this section) was organized to minimize potential sequence effects by the potential consecutive presentation of BACCOFF™. In this initial order, the first and third weeks were slotted for BACCOFF™ administration with liquid drops and the liquid drop only administration were placed in the second and fourth weeks. The exact placement of each BACCOFF™ + liquid drop and liquid drop only conditions were randomly chosen. Consecutive orders were organized so that each condition would be represented an equal number of times during each week. The Latin square design used in this study is illustrated in Appendix C.

Random assignment and procedure overview. The conditions were ordered using a Latin square design described above and assigned a number from 1 to 16. Numbers were drawn from a box and undergraduate assistants who were not involved in the protocol randomly assigned orders associated with the numbers to participants. Graduate researchers were blind to the DIPSTOP™ and Water components. All conditions entailed participants to attend three assessment periods (0 hours, 24 hours, and 48 hours) starting Monday and ending Wednesday for four consecutive weeks, one condition per week. Participants experienced all four conditions across the four weeks. Assessments were conducted the same time each day for all conditions. A summary of the experimental procedure is illustrated in Appendix D.

0 hour assessment. Informed consent was obtained from all participants and the SMTDQ was administered during the initial 0-hour assessment period. Participants were given a disposable cup and a paper towel, and instructed to use their preferred moist snuff

for ten minutes. Following the using period, individuals were instructed to expectorate into a test tube. Carbon monoxide measures were then obtained using the COa monitor. A graduate researcher administered the BDI, STAI, and NAS to establish a baseline score for each scale. After the baseline assessment, individuals were instructed to abstain from any form of nicotine use for two days and to return the following day. Furthermore, participants were instructed to use a products assigned to that condition ad lib for the two-day abstinence period. Graduate researchers also informed participants that "the products may or may not help during abstinence."

24 hour assessment. Graduate researchers recorded the number of times individuals used the product (See Appendix E) and inquired on the participant's ability to abstain. Saliva and COa measures were collected. BDI, STAI, and NAS self-report measures were also administered. Participants were instructed to continue abstinence and using the supplied products for another twenty-four hours.

48 hour assessment. During the third assessment day, participants followed the same procedure as the 24-hour assessment period. After the last self-report measure was taken, any remaining products were given to the graduate researcher. Participants were encouraged to return to their regular nicotine use until the beginning of the next assessment week. This recidivism re-established baseline levels of nicotine use for each assessment week.

At the end of the last assessment week, all participants were debriefed (See Appendix F) and given further information about the BACCOFF™ and DIPSTOP™ products. Each completed participant's name and phone number was then placed into a jar for the $100.00 lottery at the end of the semester.

Design and Statistical Approach

A 2 X 2 X 3 factorial design reflects three independent within subject variables, BACCOFF™ (BACCOFF™ vs. No BACCOFF™), DIPSTOP™ (DIPSTOP™ vs. Water) and Time (0 hr., 24 hr., 48 hr.). One-tailed repeated measure analysis of variances (ANOVAs) were conducted on each of the dependent variables. The dependent variables included NAS DSM-IV withdrawal scores, NAS Total withdrawal scores, NAS Craving scores, BDI scores, and STAI-State scores. A total of five ANOVAs were conducted, one for each dependent variable. 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 comparisons. The interaction comparisons included BACCOFF™ x DIPSTOP™, BACCOFF™ x Time, DIPSTOP x Time, and BACCOFF™ x DIPSTOP™ x Time. Post-hoc simple effect tests were used to differentiate significant interactions. Significant differences within the simple effects were followed up with Tukey's Honestly Significant Differences tests, at the .05 alpha level.

Results

Power Analysis

Power was calculated prior to the data collection phase of this study using the effect size from a previous research examining a similar population (McChargue & Collins, 1998). An estimate sample size of 16 participants was equivalent to a beta of .95 at the .05 alpha level. This estimate dictated the sample sized used for this study. Post analysis of the actual power for this study showed a beta of .90 at the .05 alpha level. This post

analysis confirmed that the sample size for this study significantly reduces the probability of making a Type 1 error (rejecting the null hypothesis when it is true).

Descriptive COa Levels and Product Frequency Data

Deprivation compliance and product administration are vital to the outcome of the study. Compliance alveolar measures demonstrated that smokeless tobacco users were within the COa cutoff of 8 ppm during deprivation periods. Table 2 illustrates mean COa levels. Participants also reported adequate BACCOFF™, DIPSTOP™, and water self-administration during deprivation as evidenced by endorsed frequency records. These findings suggest that the independent variables were effectively manipulated. This data is represented in Tables 3, 4, and 5, respectively.

Order Effects

A 2 (Time) by 4 (Order) ANOVA was conducted on the dependent variables (i.e., craving, total withdrawal, and DSM-IV withdrawal scores) that showed significant effects. The within subject independent variable was the repeated measure of time (0 hr., 24-hr., and 48-hr.). The order that the conditions (BACCOFF™ + DIPSTOP™, BACCOFF™ + Water, DIPSTOP™, and Water) were administered served as a between subject independent variable for this analysis. Craving, total withdrawal, and DSM-IV withdrawal scores showed no significant order effects as a function of time, $F(3, 12) = 3.27$, .99, and .65, ns, respectively. These findings suggest that order effects had no influenced on the data.

NAS DSM-IV Withdrawal Scores

A 2 BACCOFF™ (BACCOFF™ vs. no BACCOFF™) X 2 DIPSTOP™ (DIPSTOP™ vs. water) X 3 TIME (0-hr., 24-hr., and 48-hr.) repeated measures ANOVA

was conducted on the NAS DSM-IV withdrawal scores. A significant time main effect was observed for withdrawal symptoms consistent with DSM-IV criteria, $F(2, 30) = 4.40$, $p < .01$. As seen in Figure 1, post hoc tests indicated that participants significantly increased in withdrawal from 0 hour ($M = 2.53$, $SD = 2.89$) deprivation compared to 24 hour ($M = 3.96$, $SD = 2.61$) and 48 hour ($M = 3.74$, $SD = 2.70$) deprivation. BACCOFF™ and DIPSTOP™ main effects were not significant, $Fs(1, 15) = .91$ and 1.31, ns, respectively.

Analyses testing the interaction among BACCOFF™, DIPSTOP™, and Time conditions showed a significant interaction between BACCOFF™ X Time, $F(2, 30) = 2.54$, $p < .05$. Simple effects tests indicated that NAS DSM-IV withdrawal scores were not substantially elevated from 0 hour ($M = 2.72$, $SD = 2.86$) deprivation to 24 hour ($M = 3.5$, $SD = 2.42$) and 48 hour ($M = 3.22$, $SD = 2.26$) during BACCOFF™ administration, $F(2\ 30) = 1.55$, ns. Significant withdrawal elevations were observed in conditions without BACCOFF™, $F(2, 30) = 10.93$, $p < .001$ as a function of time. As illustrated in Figure 2, follow-up analyses showed that withdrawal scores during 24 hour ($M = 4.86$, $SD = 4.33$) and 48 hour ($M = 4.25$, $SD = 3.13$) deprivation were significantly higher than 0 hour ($M = 2.34$, $SD = 2.91$) deprivation. Comparisons of BACCOFF™ X DIPSTOP™, $F(1,15) = 1.49$, ns, DIPSTOP™ X Time, $F(2, 30) = .25$, ns, and BACCOFF™ X DIPSTOP™ X Time, $F(2, 30) = .37$, ns, were not significant.

NAS Craving Scores

A 2 BACCOFF™ (BACCOFF™ vs. no BACCOFF™) X 2 DIPSTOP™ (DIPSTOP™ vs. water) X 3 TIME (0-hr., 24-hr., and 48-hr.) repeated measures ANOVA was conducted on NAS Craving scores. The main effect for time showed significant increases

in craving symptoms, F (2, 30) = 7.17, p < .001. Tukey post-hoc tests exhibited lower craving scores during 0 hour (M = 1.00, SD = 1.22) deprivation compared to 24 hour (M = 1.61, SD = .94) and 48 hour deprivation (M = 1.86, SD = .95), as shown in Figure 3. BACCOFF™ and DIPSTOP™ main effects were not significant, Fs (1, 15) = 1.33 and 1.85, ns, respectively.

There were no substantial interaction differences among BACCOFF™, DIPSTOP™, and Time comparisons. Interactions between BACCOFF™ X DIPSTOP™, F (1, 15) = 1.48, ns, BACCOFF™ X Time, F (2, 30) = 1.65, ns, and DIPSTOP™ X Time, F (2, 30) = 1.16, ns, were all nonsignificant. The three way interaction of BACCOFF™ X DIPSTOP™ X Time, F (2, 30) = 1.30, ns, demonstrated no significant differences, as well.

NAS Total Withdrawal Scores

A 2 BACCOFF™ (BACCOFF™ vs. no BACCOFF™) X 2 DIPSTOP™ (DIPSTOP™ vs. water) X 3 TIME (0-hr., 24-hr., and 48-hr.) repeated measures ANOVA was conducted on the NAS total withdrawal scores. No significant main effect differences for BACCOFF™ and DIPSTOP™ were found, Fs(1, 15) = 1.86 and 1.12, ns, respectively. Similar to Craving scores, Total withdrawal scores appear to significantly increase across time, F (2, 30) = 6.92, p < .001. Post-hoc tests showed that 0 hour (M = 5.49, SD = 4.85) deprivation evinced significantly lower withdrawal scores compared to 24 hour (M = 8.10, SD = 4.97) and 48 hour (M = 8.14, SD = 5.46) deprivation withdrawal scores. Time main effect results are shown in Figure 4.

Significant interaction differences were not observed with total withdrawal scores. Consistent with Craving and DSM-IV scores, no significant results were observed with

BACCOFF™ X DIPSTOP™, F (1, 15) = .53, ns, BACCOFF™ X Time, F (2, 30) = 1.49, ns, and DIPSTOP™ X Time, F (2, 30) = .05, ns, interactions. The BACCOFF™ X DIPSTOP™ X Time interaction also demonstrated no substantial differences, F (2, 30) = .16, ns.

BDI Scores

A 2 BACCOFF™ (BACCOFF™ vs. no BACCOFF™) X 2 DIPSTOP™ (DIPSTOP™ vs. water) X 3 TIME (0-hr., 24-hr., and 48-hr.) repeated measures ANOVA was conducted on the Beck depression scores. There were no significant BDI score findings. BACCOFF™, DIPSTOP™, and Time main effects were not significantly different, Fs(1, 15) = .88, .54, and 1.35, ns. Furthermore, BACCOFF™ X DIPSTOP™, F (1, 15) = .87, ns, BACCOFF™ X Time, F (2, 30) = 1.19, ns, and DIPSTOP™ X Time, F (2, 30) = .17, ns, comparisons showed no significant results. Moreover, no substantial differences were observed among the BACCOFF™, DIPSTOP™, and Time interaction, F (2, 30) = .04, ns.

STAI-State Scores

A 2 BACCOFF™ (BACCOFF™ vs. no BACCOFF™) X 2 DIPSTOP™ (DIPSTOP™ vs. water) X 3 TIME (0-hr., 24-hr., and 48-hr.) repeated measures ANOVA was conducted on the STAI-State scores. Main effects for BACCOFF™, F (1, 15) = .04, ns, DIPSTOP™, F (1, 15) = .10, ns, and Time, F (2, 30) = 1.95, ns, did not significantly produce differences. Equally negligible were the BACCOFF™ X DIPSTOP™, F (1, 15) = .60, ns, BACCOFF™ X Time, F (2, 30) = .55, ns, and DIPSTOP™ X Time, F (2, 30) = .02, ns. The BACCOFF™ X DIPSTOP™ X Time interaction demonstrated no significant effects as well, F (2, 30) = .27, ns.

Discussion

BACCOFF™ Administration

The results partially supported the hypothesis that a variety of symptoms associated with smokeless tobacco 48-hour withdrawal would substantial reduce during BACCOFF™ administration. This study demonstrated that the withdrawal symptoms delineated in DSM-IV nicotine withdrawal criteria were suppressed across 48-hour deprivation as participants used the herbal substitute, BACCOFF™. This effect was not observed in conditions without BACCOFF™. When smokeless tobacco users were not given BACCOFF™, they endorsed significant more DSM-IV criteria withdrawal symptoms during 24 hour and 48-hour deprivation compared with a pre-quit baseline.

Smokeless tobacco user's total withdrawal symptoms, craving, depression levels, and/or state anxiety levels showed no effects during BACCOFF™ administration. These results may reflect inherent differences between diagnosable symptoms versus general withdrawal patterns. Research has consistently documented nicotine withdrawal effects encompassing the dependent variables used in this study (Hughes & Hatsukami, 1986). It has also been suggested that DSM-IV withdrawal criteria may have stronger effects on smokeless tobacco users compared with other signs and symptoms of nicotine withdrawal (McChargue & Collins, 1998). Our data may help us better understand the relationship between DSM-IV nicotine withdrawal criteria and smokeless tobacco dependence. One possible explanation is that psychological components (e.g., topographical conditioning) may significantly contribute to the development of withdrawal symptoms associated with DSM-IV criteria while other withdrawal symptoms may be more pharmacologically based.

Dose-response limitations associated with the administration of the liquid drops may have also confounded these results.

DIPSTOP™ Administration

The hypothesis that smokeless tobacco 48-hour withdrawal would reduce during DIPSTOP™ administration was not supported by the results. Smokeless tobacco users' DSM-IV criteria withdrawal, craving, total withdrawal, depression levels, and anxiety levels were not influenced by DIPSTOP™ administration. Previous research examining lobeline (the primary ingredient in DIPSTOP™) effects on cigarette smokers' withdrawal symptoms has documented substantial reduction in withdrawal symptoms as the cumulative dosage of lobeline increased (Schneider et al., 1996). Given that lobeline appears to be more effective with increasing amounts, our data may reflect the lack of adequate dosing. Although dosing rates were found to be comparable with pre-established dosing rates, participants controlled the amount of lobeline administered during each dose. Thus, the lack of standardized dosing may have influenced our results.

Expectancy Effects

The water condition was used to control expectancy effects related to DIPSTOP™ administration. There was no indication of a placebo response resulting from water administration. A placebo response would have been implicated if withdrawal symptoms reduced during the administration of water. These results would have suggested that participants were influenced by the possible expectancy that they were receiving an active substance that controls withdrawal symptoms. Our results did not show such an effect. Withdrawal symptoms substantially increased during water administration.

Instructions given during the administration of each product further contributed to the control of expectancy effects. Participants were told that they might or may not receive a substance that would help during deprivation. Anecdotally, participants consistently reported their uncertainty about the water condition containing an active substance during the debriefing.

Although though participants reported an expectation that the DIPSTOP™ condition contain an active substance that may have helped with withdrawal, effects caused by these expectation could not be determined due to the lack of adequate dosing and significant results. The present study's methodology would have been strengthened with lobeline administration by tablets and a placebo sugar pill.

BACCOFF™ administration was more susceptible to expectancy effects. The product characteristics (e.g., similar tin, taste, and form of administration) and lack of a placebo allows for potential expectancy effects. Although it is possible that the significant findings associated with BACCOFF™ administration may have been influenced by expectancies, the probability is low. If expectancy effects influenced BACCOFF™ administration, it is feasible to think that the results would not have been circumscribed to DSM-IV withdrawal symptoms. Other withdrawal patterns would have been equally affected. Therefore, disparate withdrawal findings during BACCOFF™ administration reduce the probability of expectancy effects.

Effects of Time

As smokeless users were deprived of nicotine use for 48 hours, their reported withdrawal symptoms appeared to increase over time. Previous withdrawal research has demonstrated that signs and symptoms of withdrawal are elevated in smokeless tobacco

users during deprivation (Hatsukami et al., 1987; Keenan et al., 1989, McChargue & Collins, 1998). Consistent with this research, participant's DSM-IV criteria withdrawal, craving, and total withdrawal substantially increased during 24 hour and 48 hour deprivation compared to baseline. This evidence suggests that 48-hour deprivation was an adequate amount of time to evidence withdrawal patterns.

The depression and anxiety measures, however, were not affected by deprivation. These negligible results may reflect differences in severity and/or response patterns of smokeless tobacco users compared with smokers. It is well established that severe depression and anxiety problems are associated with cigarette smokers (Breslau, Kilbey & Andreski, 1991; Kendler et al., 1993). These symptoms are exacerbated during deprivation, especially with nicotine dependent individuals who have a history of major depression and/or anxiety disorders (Hall, Munoz & Reus, 1996; Hall et al., 1996). Current research examining smokeless tobacco users' withdrawal patterns has not thoroughly examined the relationship among depression, anxiety, and smokeless tobacco dependence. It is feasible to postulate that our nonsignificant findings may reflect affective constructs that do not influence smokeless tobacco withdrawal symptoms or may play a minimal role in the elicited withdrawal patterns.

Conclusions

Behavioral economics theory suggests that a substance's reinforcing properties control drug related behaviors as the individual interacts with the environment through their efforts to obtain the substance. This study sought to suspend smokeless tobacco behavior to elicit negative reinforcing properties (e.g., withdrawal) by prohibiting its use. The simultaneous introduction of two substitutable positive reinforcers that would mimic

reinforcing and conditioned properties of smokeless tobacco were employed to evaluate the effects of deprivation. More specifically, smokeless tobacco withdrawal signs and symptoms were used to index these effects. If smokeless tobacco withdrawal did not significantly elevate from deprivation during product administration, substitutable reinforcers successfully influenced the course of negative reinforcing properties that typically prompt drug-seeking behaviors.

Overall, this study provided some promising effects of substitutable reinforcers and extended our understanding of smokeless tobacco dependence related to withdrawal. Supporting evidence found that withdrawal symptoms consistent with DSM-IV criteria were suppressed during the administration of BACCOFF™, a nicotine-free herbal mixture. This effect was consistent with the concept that conditioned topographical features play an important role in maintaining smokeless tobacco behavior.

Despite the promising effects found during BACCOFF™ administration, reduced smokeless tobacco withdrawal symptoms were not evidenced during DIPSTOP™ administration, a nicotinic agonist. This substance's ineffectiveness further illustrates the importance of conditioned topographical features. Historically, researchers have posited that the primary determinant of withdrawal symptoms was the physiological removal of nicotine from the system (Hatsukami, Hughes & Pickens, 1985; Shiffman, 1979). Withdrawal reduction without pharmacological adjuncts suggests that the physiological determinant of withdrawal may not be primary variable to consider during smokeless tobacco cessation. These findings implicate the possibility that conditioned reinforcers may override the physiological effects of withdrawal as nicotine dissipates from the system.

DSM-IV withdrawal symptoms' differential reduction observed during BACCOFF™ administration also suggests that these withdrawal symptoms are more amenable to smokeless tobacco reinforcing properties than craving and other symptoms not associated with DSM-IV. This study provided evidence that DSM-IV withdrawal, craving, and total withdrawal increased over time as a function of deprivation. BACCOFF™ administration's inability to control craving and total withdrawal symptoms experienced by smokeless tobacco users may suggest that these symptoms are more prone to physiologically based determinants. Furthermore, the lack of depressive and anxiety symptoms may suggest that smokeless tobacco users do not respond similarly to these symptoms compared to cigarette smokers. An alternative explanation is that the depression and anxiety measures did not accurately capture smokeless tobacco users expression of anxiety and depressive symptoms.

Limitations

The lack of a placebo for BACCOFF™ is the most significant limitation of this study. Although participants were instructed that the administered products might not help with withdrawal, a BACCOFF™ placebo would have further decreased the potential of expectancy effects. It cannot be definitely stated that the BACCOFF™ effects found in this study were caused by product administration only. It is feasible that the reduced withdrawal symptoms may be a function of an expectation that BACCOFF™ would help alleviate withdrawal symptoms.

The duration and frequency of DIPSTOP™ administration may have been limited as well. A previous lobeline study found significant results as a function of the increased cumulative frequency, duration, and amount of the substance (Schneider et al., 1996).

Thus, there may be a critical period of adaptation to an individuals system before lobeline becomes an effective substitute. Furthermore, participants reported that the DIPSTOP™ product contained an unpleasant smell and taste. This potentially aversive component may have negatively affected the products potential. Moreover, the participant and not the researcher controlled the quantity of administered DIPSTOP™. Controlling the dose amount enhances the ability to quantify the substance's effect.

The sole modality of measurement was collected through verbal report. This represents another limitation to the study. Multimodal assessment may have been more sensitive to smokeless tobacco withdrawal. Lang (1968) postulated that individuals express affective states through three systems: behavioral, cognitive, and physiological. This affective expression varies across individuals. For example, a smokeless user may experience the affective component of withdrawal (e.g., irritability) more physiologically compared with cognition and behavioral indices. This disparate response style may reflect minimized self-reported items with elevated muscle tension and increase heart rate. Although irritability may not have been identified through self-report measures in this example, a physiological assessment may have suggested an irritable state. Lang's theory is known as the bioinformational model of emotions. Theoretically, this approach may have evidenced physiological effects of DIPSTOP™ that could not be detected by verbal report measures.

The NAS measure lacked reliability and validity data, which represented another limit to this study. Although the NAS has been shown to been sensitive enough to detect withdrawal differences in other studies (McChargue & Collins, 1998), it is unclear whether this measure reliably tests the construct of withdrawal. For instance, there may

be floor effects as a result of the measure's 4-point rating system. The standardization of this scale is needed to reduce the possibility of introducing error as an artifact from the assessment measures.

Order effects must be considered as a possible limitation as well. The Latin square design directly manipulates the order of the conditions, which reduces randomization. This approach reduces the probability of order effects, but does not eradicate it. In addition, the statistical analyses testing for order effects significantly reduced the probability that the results were influenced by the order of presentation.

The sample size of 16 participants may be too small to detect significant differences. Pre- and post-power analyses were conducted to assess the change in power from the use of previous effect sizes compared with the actual effect size. Possible reduction in power from pre- to post-analysis may limit our ability to draw conclusions from this study. The results of the power analyses indicated that power did not change from pre- to post-analysis. These findings suggest that the sample size was adequate to identify significant differences.

Finally, participants could have used smokeless tobacco during deprivation without the researcher's knowledge. COa levels are not produced by smokeless tobacco usage and budget limitations prevented the saliva samples from being analyzed. Therefore, these measures were employed to increase compliance and not used to detect smokeless tobacco consumption during deprivation. Although a deprivation compliance check at the end of the study identified that participants accurately documented their compliance during the protocol, retrospective reporting is inherently limited. Thus, cotinine analyses from the collected saliva samples would have been more exact.

Clinical Implications and Future Directions

Smokeless tobacco treatment research has utilized pharmacological adjuncts, including nicotine-free adjuncts, as a component of treatment (Sinusas & Coroso, 1993; Stevens et al., 1995). However, these studies have only documented abstinent rates following treatment. This study illustrated the role nicotine-free adjuncts may play in treatment protocols. Our results showed that pharmacological substitutes that mimic reinforcing and conditioned properties are important in reducing withdrawal symptoms during abstinence. Treatment programs should emphasize components that will influence multiple reinforcing and conditioned properties, while controlling for a variety of withdrawal symptoms that may be elicited from different systems (psychological vs. physiological).

The components of this study are relatively new in smokeless tobacco withdrawal research and have not been thoroughly examined. Future research should attempt to replicate the BACCOFF™ findings and explore a different duration of lobeline administration. It is also suggested that future research should utilize a less aversive and more controlled lobeline product, such as a tablet. Furthermore, a placebo for the BACCOFF™ product would strengthen our ability to draw definitive conclusions about the observed withdrawal effects. Moreover, the implementation of BACCOFF™ and lobeline in a formal treatment protocol is needed to further elucidate the effectiveness of these substances.

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Appendix A

RESEARCH QUESTIONNAIRE

Please Print Clearly (All information will remain confidential)

Name _____ Address_____

Age____ Phone: ( ) _____

Best Time to Call _____ Sex M / F Psychology Instructor: _____

Section #: _____

1. Do you have any medical conditions (for example, heart problems)? Yes No If yes, what type _____

2. Do you currently use tobacco products? (Circle one):

   Smoker Smokeless Tobacco User Both Don't use

(IF YOU DO NOT USE TOBACCO, DO NOT COMPLETE THE REST OF THIS FORM)

3. Approximately how many times do you use smokeless tobacco or smoke a cigarette per day? (Circle One)

Smokers: Less than 10 11-15 16-20 21-25 more than 25

Smokeless: 1 2 3 4 5 more than 5

4. How long have you smoked or used smokeless tobacco?

   Smokers _____ mnths / yrs Smokeless _____ mnths / yrs

5. Have you ever tried to quit before? (Circle One)

   Smoking: Yes No Smokeless: Yes No Both: Yes No

6. If yes for #5, when was the last time you tried? Mo/Yr _____

7. Have you substituted one form of tobacco use for another? Yes No

8. Are you currently trying to quit smoking/smokeless tobacco or cut down?

   Smoking: Yes No Smokeless: Yes No

Appendix B

NAS (Page 1)

CO ___/___ Subject #: SMT _____ Week 1 2 3 4 Day 1 2 3 Date: ____

Directions: Please rate (circle) the degree to which each of the following descriptive words applies to you **AT THIS MOMENT.**

At this Moment, I ...	None	Mild	Moderate	Severe
1. Craving to smoke and/or chew/dip	0	1	2	3
2. Feeling irritable	0	1	2	3
3. Feeling anxious	0	1	2	3
4. Having difficulty concentrating	0	1	2	3
5. Feeling restless	0	1	2	3
6. Experiencing a headache	0	1	2	3
7. Feeling drowsy	0	1	2	3
8. Experiencing stomach pains and/or nausea	0	1	2	3
9. Feeling tired/fatigued	0	1	2	3
10. Feeling impatient	0	1	2	3
11. Feeling hungry	0	1	2	3
12. Feeling down/depressed	0	1	2	3
13. Feeling angry	0	1	2	3
14. Feeling frustrated	0	1	2	3

15. Did you have trouble sleeping last night? Yes No

Heart Rate: _____(beats per 60secs)

Appendix B(Continued)

NAS (Page 2)

Subject #: SMT _____ Study: SMT-03 Week: 1 2 3 4 Day: 1 2 3

Directions: Please rate (circle) the degree to which each of the following descriptive words applies to you **IN GENERAL.**

In General, I have been...	None	Mild	Moderate	Severe
1. Craving to smoke and/or chew/dip	0	1	2	3
2. Feeling irritable	0	1	2	3
3. Feeling anxious	0	1	2	3
4. Having difficulty concentrating	0	1	2	3
5. Feeling restless	0	1	2	3
6. Experiencing a headache	0	1	2	3
7. Feeling drowsy	0	1	2	3
8. Experiencing stomach pains and/or nausea	0	1	2	3
9. Feeling tired/fatigued	0	1	2	3
10. Feeling impatient	0	1	2	3
11. Feeling hungry	0	1	2	3
12. Feeling down/depressed	0	1	2	3
13. Feeling angry	0	1	2	3
14. Feeling frustrated	0	1	2	3
15. Did you have trouble sleeping last night?			Yes	No

Appendix C

LATIN SQUARE OF CONDITIONS

Subject #	1st Week	2nd Week	3rd Week	4th Week
01	B X W	DIPSTOP ONLY	B X D	WATER ONLY
02	DIPSTOP ONLY	B X D	WATER ONLY	B X W
03	B X D	WATER ONLY	B X W	DIPSTOP ONLY
04	WATER ONLY	B X W	DIPSTOP ONLY	B X D
05	B X W	DIPSTOP ONLY	B X D	WATER ONLY
06	DIPSTOP ONLY	B X D	WATER ONLY	B X W
07	B X D	WATER ONLY	B X W	DIPSTOP ONLY
08	WATER ONLY	B X W	DIPSTOP ONLY	B X D
09	B X W	DIPSTOP ONLY	B X D	WATER ONLY
10	DIPSTOP ONLY	B X D	WATER ONLY	B X W
11	B X D	WATER ONLY	B X W	DIPSTOP ONLY
12	WATER ONLY	B X W	DIPSTOP ONLY	B X D
13	B X W	DIPSTOP ONLY	B X D	WATER ONLY
14	DIPSTOP ONLY	B X D	WATER ONLY	B X W
15	B X D	WATER ONLY	B X W	DIPSTOP ONLY
16	WATER ONLY	B X W	DIPSTOP ONLY	B X D

Note. B X W = BACCOFF x Water, B X D = BACCOFF x DIPSTOP

Appendix D

Experimental Procedure

0 Hour Assessment	Informed Consent	(Initial Assessment Only)
	Smokeless Tobacco Questionnaire	(Initial Assessment Only)
	10 Minute Smokeless Use	
	Salivary Samples and Carbon Monoxide Levels	
	Questionnaires: BDI, STAI, NAS	
	Product Administration	
24 Hour Assessment	Frequency of Product Use Recorded	
	Salivary Sample and Carbon Monoxide Levels	
	Questionnaires: BDI, STAI, NAS	
48 Hour Assessment	Frequency of Product Use Recorded	
	Salivary Sample and Carbon Monoxide Levels	
	Questionnaires: BDI, STAI, NAS	
	Debriefing	(Final Assessment Only)
	Enter into lottery	(Final Assessment Only)

Appendix E

Frequency of Product Use]

Subject # _____ Week # _____

Day #_____

BACCOFF (Yes or No) # of times used _____

Drops # of times used _____

Day #_____

BACCOFF (Yes or No) # of times used _____

Drops # of times used _____

Day #_____

BACCOFF (Yes or No) # of times used _____

Drops # of times used _____

Appendix F

PARTICIPANT DEBRIEFING SHEET

Purpose of the study

The present study was designed to document the effects of Dipstop™ (herbal nicotine agonist) and BACCOFF™ (herbal mixture) on withdrawal symptoms during smokeless tobacco deprivation. In recent years, smokeless tobacco sales and consumption have increased, especially adolescent and young adult consumption, compared to other tobacco products. There have been few studies, however, examining components of smokeless tobacco dependence, such as withdrawal patterns, and the effectiveness of psychopharmacological adjuncts with this population. This paucity of research necessitates systematic exploration in this area.

Lobeline (main ingredient in Dipstop™) reliably mimics nicotinic effects in human and animal studies. Theoretically, lobeline administration should help prevent significant withdrawal symptoms during tobacco deprivation. Previous research, however, has been unable to demonstrate significant reductions in smoking behavior as a result of lobeline. To date, research has not provided empirical evidence documenting lobeline effects on withdrawal patterns with cigarette smokers or smokeless users. Furthermore, it has been speculated that the ineffective results in smoking behavior are a function of disparate absorption rates between lobeline and cigarettes. Research has shown that the absorption of lobeline is a gradual process which plateaus with continuous use. This pattern appears to be closer to smokeless tobacco rates. Thus, lobeline may be more appropriately employed with smokeless users rather than cigarette smokers.

BACCOFF™ research has primarily been anecdotal. This evidence suggests that BACCOFF™ may be an effective substitute for smokeless tobacco. There has only been one empirical study using BACCOFF™. This study examined cue reactivity related to smokeless tobacco. Researchers found that BACCOFF™ produced similar olfactory, tactile, and taste responses to smokeless tobacco. These findings suggest that BACCOFF™ may help control behavioral components (e.g., reinforcement stimuli) of nicotine dependence.

Deception

Participants were told that carbon monoxide levels would detect nicotine in the system. However, research has shown that COa levels are good indicators for smokers only. The CO monitor measures the level of carbon monoxide in the lungs. Smokeless tobacco does not produce carbon monoxide in the lungs. Thus, this measure was used to facilitate abstinence compliance.

Saliva samples were not used to analyze cotinine levels. The samples were stored in a freezer until the participant completed the study. After completion, samples were discarded. This measure was used to increase abstinence compliance as well.

The purpose of these measures were to create an environment that appeared easy to detect nicotine use during abstinent days. Remaining nicotine-free for two consecutive days each week for four weeks was vital to the experiments success. Using nicotine during the abstinent days (Tues. and Weds.) may influence the participants level of

reported withdrawal and skew our results. Therefore, it was important to facilitate compliance.

APPENDIX G

OKLAHOMA STATE UNIVERSITY
INSTITUTIONAL REVIEW BOARD
HUMAN SUBJECTS REVIEW

Date: 09-17-96 **IRB#:** AS-97-010

Proposal Title: ALTERNATIVES TO SMOKELESS TOBACCO: DOCUMENTED REDUCTIONS IN WITHDRAWAL PATTERNS

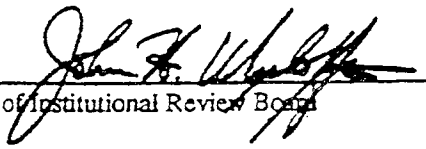
Principal Investigator(s): Frank Collins, Dennis McChargue

Reviewed and Processed as: Expedited

Approval Status Recommended by Reviewer(s): Approved

ALL APPROVALS MAY BE SUBJECT TO REVIEW BY FULL INSTITUTIONAL REVIEW BOARD AT NEXT MEETING, AS WELL AS ARE SUBJECT TO MONITORING AT ANY TIME DURING THE APPROVAL PERIOD.
APPROVAL STATUS PERIOD VALID FOR ONE CALENDAR YEAR AFTER WHICH A CONTINUATION OR RENEWAL REQUEST IS REQUIRED TO BE SUBMITTED FOR BOARD APPROVAL.
ANY MODIFICATIONS TO APPROVED PROJECT MUST ALSO BE SUBMITTED FOR APPROVAL.

Comments, Modifications/Conditions for Approval or Reasons for Deferral or Disapproval are as follows:

Signature:  Date: October 23, 1996

Chair of Institutional Review Board

Table 1
Frequency of Demographic Information from Smokeless Tobacco Dependence Questionnaire Items among Smokeless Tobacco Participants

SMDTQ Item	Responses	Smokeless Tobacco Participant
Preferred Smokeless Tobacco	Skoal	9
	Copenhagen	7
Tins per Week	< 2	0
	> 2 and < 4	5
	> 4	11
Hours Dipping per Day	< 14.5	4
	> 14.5 and < 15.5	7
	> 15.5	5
Difficulty Refraining from Use	Yes	9
	No	7

Table 2

Mean Alveolar Carbon Monoxide Levels Arcoss Time and Condition

Condition	Baseline	24 Hour	48 Hour
BACCOFF™ X Water	1.6 (1.3)	1.9 (1.3)	1.4 (1.2)
BACCOFF™ X DIPSTOP	1.3 (1.0)	1.8 (1.1)	1.9 (1.2)
DIPSTOP™ Only	1.4 (1.1)	1.1 (0.8)	1.3 (0.9)
Water Only	1.6 (0.7)	1.0 (.73)	1.4 (1.0)

Table 3

Deprived Smokeless Tobacco Users' Mean BACCOFF™ Administration Across Condition

Condition	24 hours	48 hours
BACCOFF™ X DIPSTOP™	4.4 (2.5)	5.4 (3.7)
BACCOFF™ X Water	4.6 (3.7)	5.2 (2.3)
DIPSTOP™ Only	--	--
Water Only	--	--

Table 4

Deprived Smokeless Tobacco Users' Mean Liquid Drop Administration Across Condition

Condition	24 hours	48 hours
BACCOFF™ X DIPSTOP™	3.1 (1.1)	3.2 (1.2)
BACCOFF™ X Water	2.9 (1.0)	3.6 (1.0)
DIPSTOP™ Only	3.0 (0.7)	3.5 (1.0)
Water Only	2.9 (0.9)	3.6 (1.2)

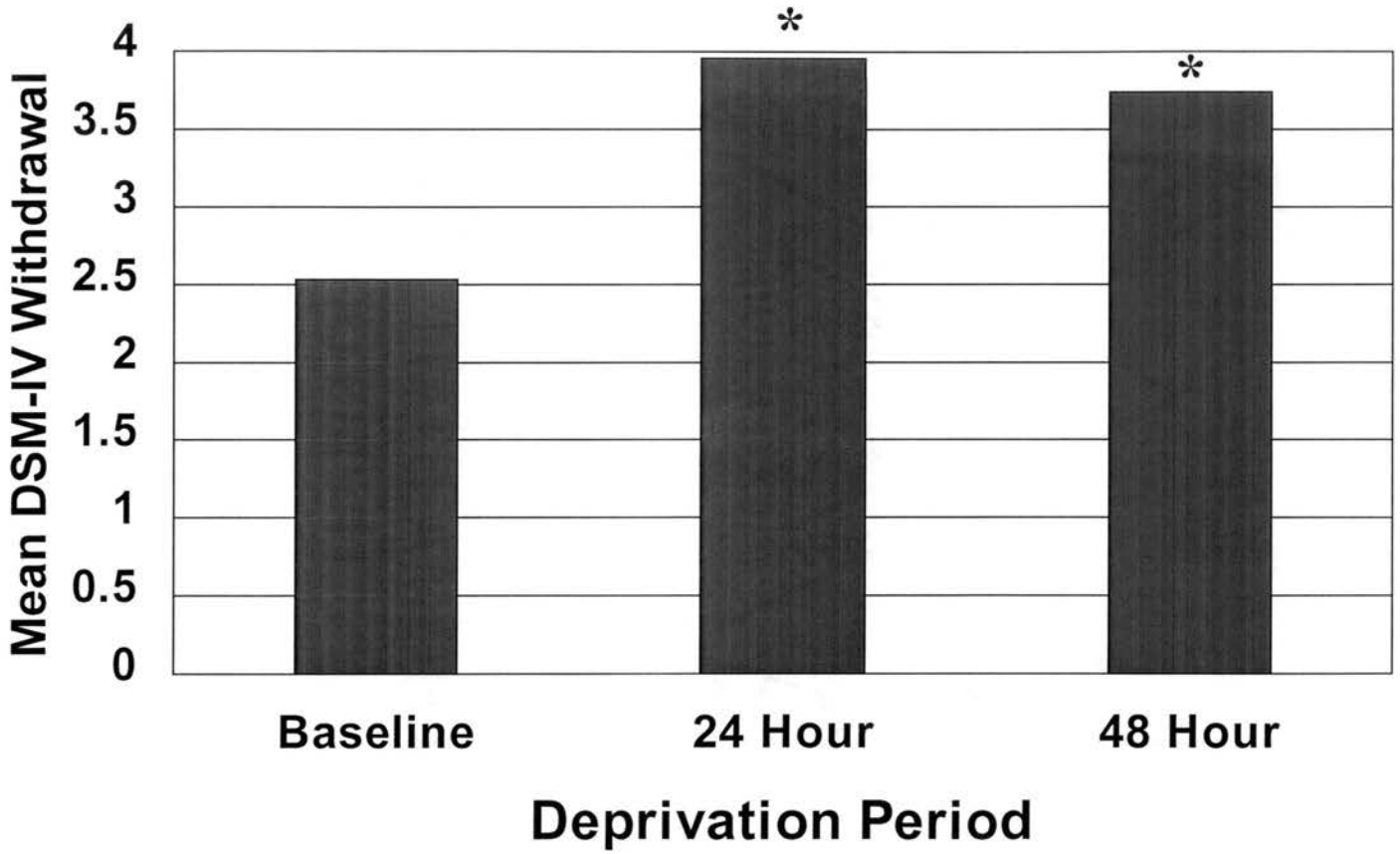
Figure Captions

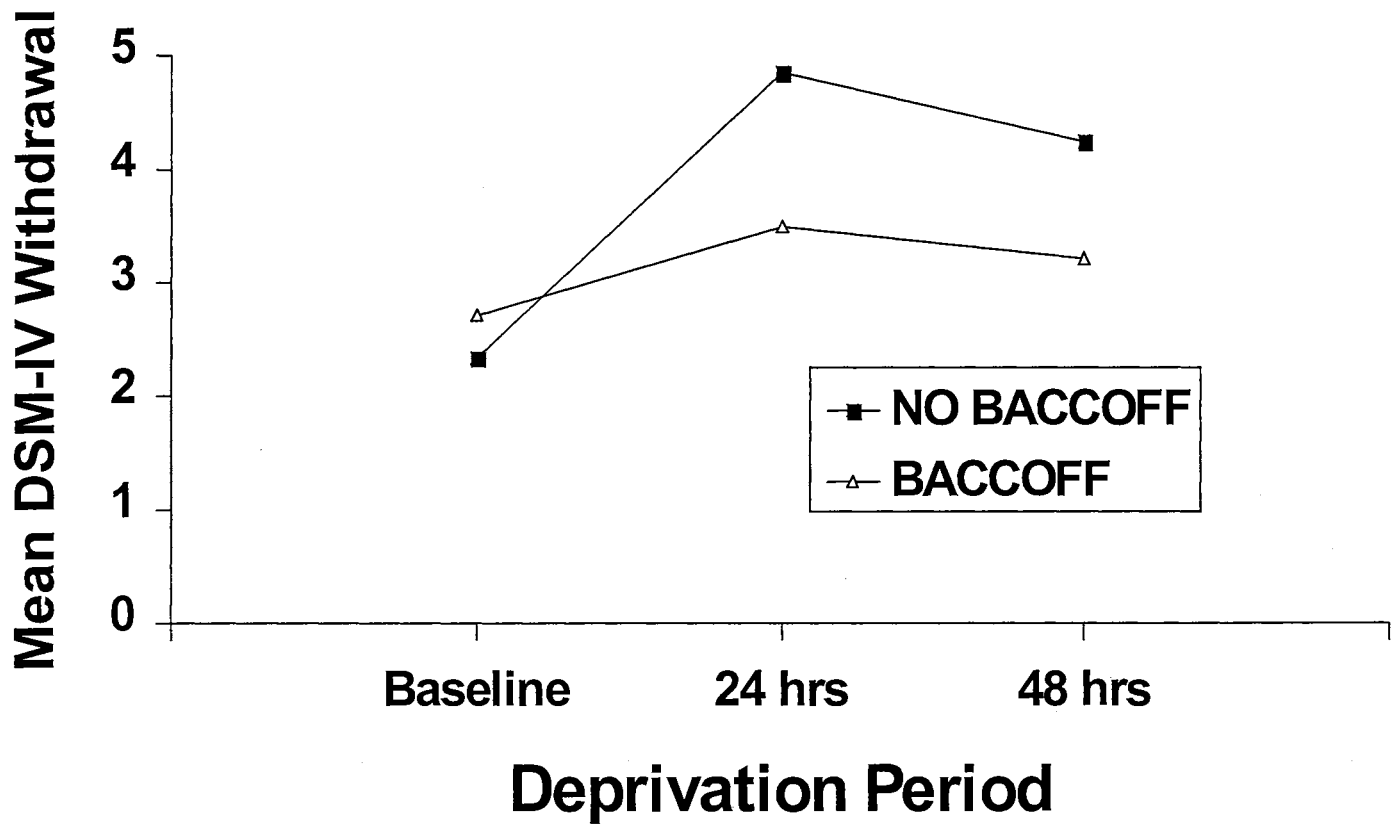
Figure 1. Mean NAS DSM-IV withdrawal rating across time for smokeless tobacco users (N = 16). Significant withdrawal differences as a function of time are denoted with an asterisk.

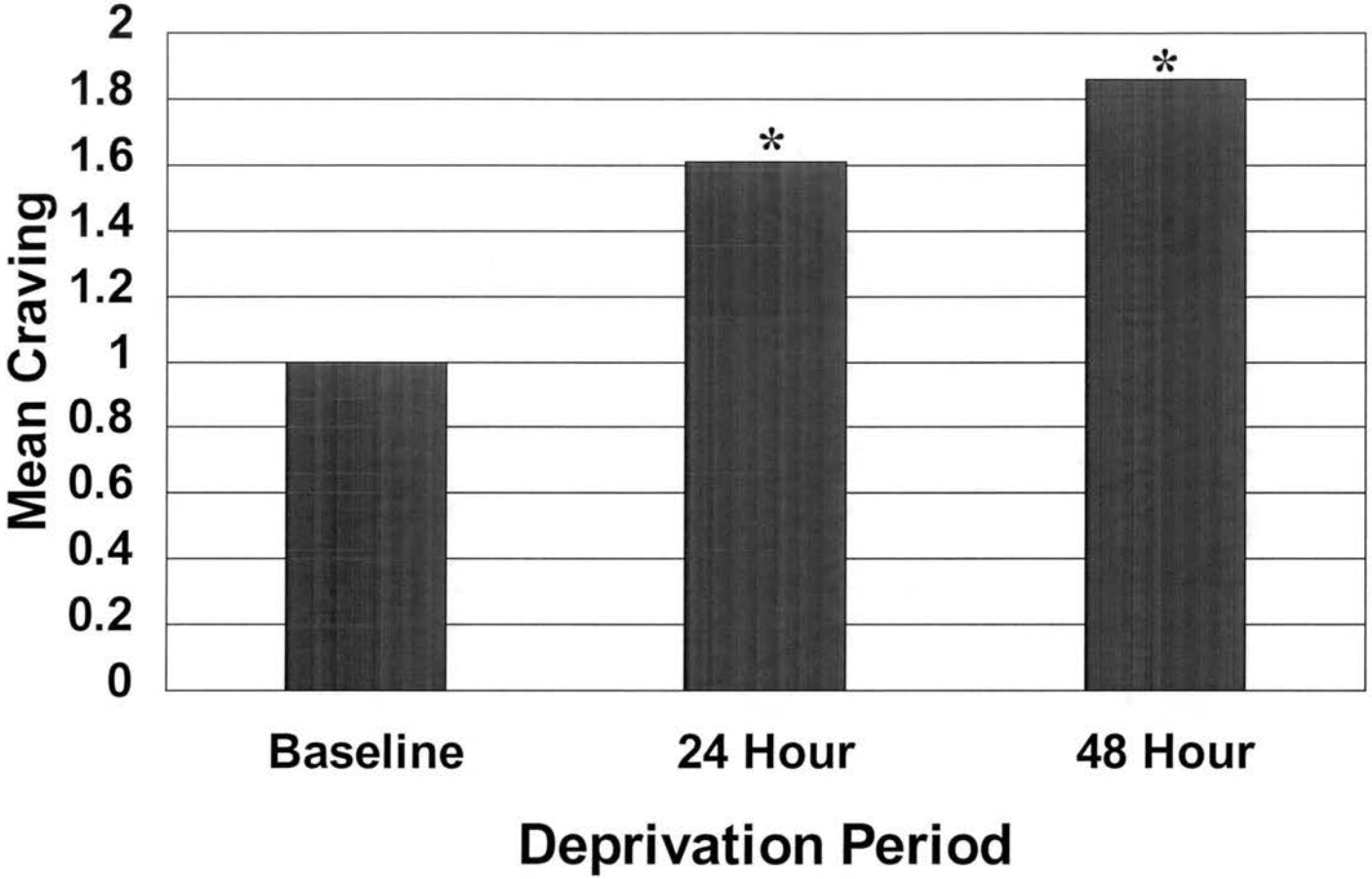
Figure 2. Mean DSM-IV withdrawal ratings for BACCOFF™ vs. No BACCOFF™ differences across time. Differences were noted in the No BACCOFF™ treatment.

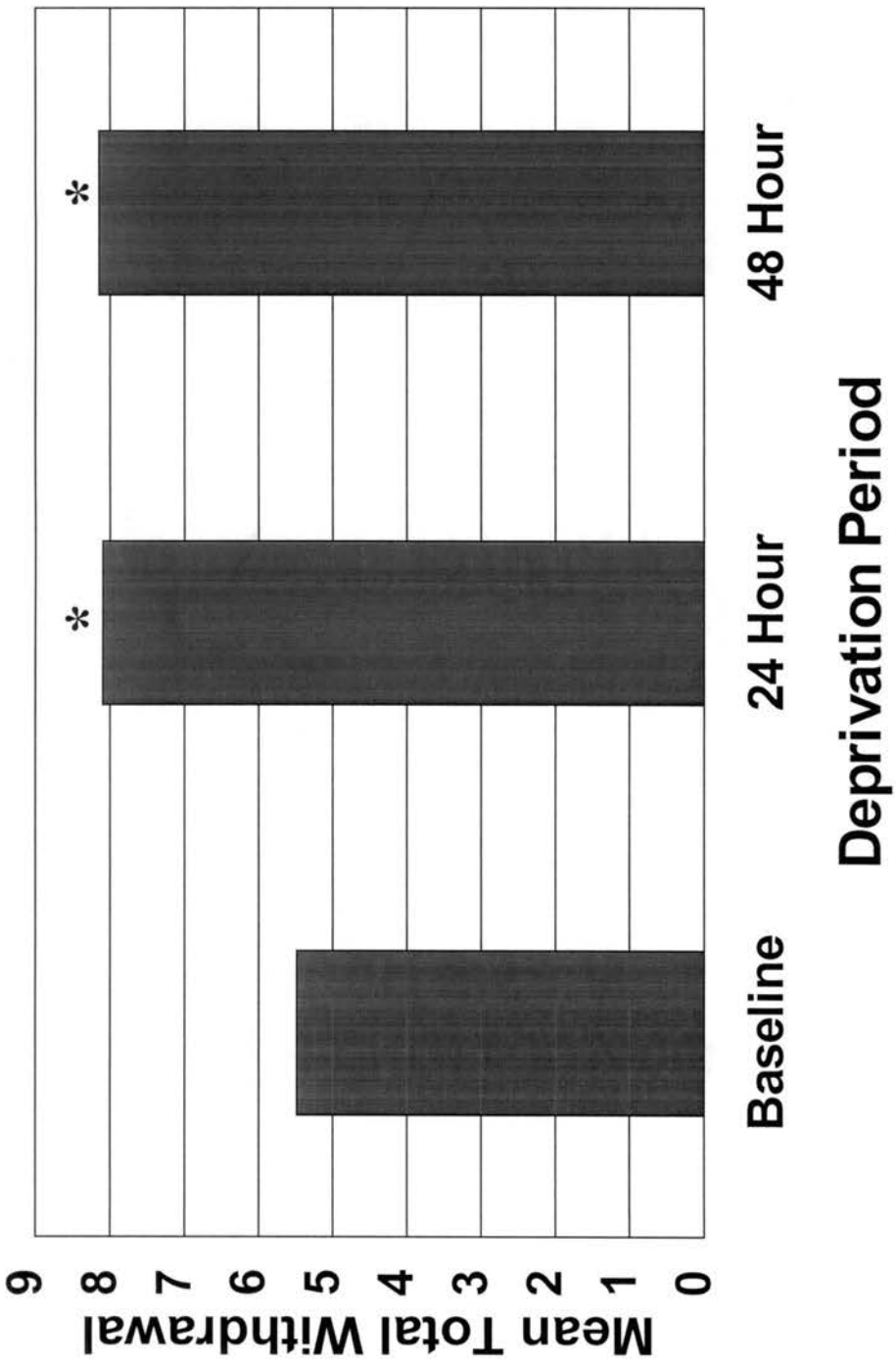
Figure 3. Mean NAS Craving ratings across time for smokeless tobacco users (N = 16). Significant craving differences as a function of time are denoted with an asterisk.

Figure 4. Mean NAS Total withdrawal ratings across time for smokeless tobacco users (N = 16). Significant withdrawal differences as a function of time are denoted with an asterisk.


Mean DSM-IV Withdrawal
4
3.5
3
2.5
2
1.5
1
0.5
0
*
*
Baseline
24 Hour
48 Hour
Deprivation Period


Mean DSM-IV Withdrawal
5
4
3
2
1
0
NO BACCOFF
BACCOFF
Baseline
24 hrs
48 hrs
Deprivation Period


Mean Craving
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
*
*
Baseline
24 Hour
48 Hour
Deprivation Period


Mean Total Withdrawal
0
1
2
3
4
5
6
7
8
9
*
*
Baseline
24 Hour
48 Hour
Deprivation Period

VITA

Dennis E. McChargue

Candidate for the Degree of

Doctor of Philosophy

Thesis: ALTERNATIVES TO SMOKELESS TOBACCO: DOCUMENTED REDUCTIONS IN WITHDRAWAL PATTERNS

Major Field: Psychology

Biography:

Personal Data: Born in Angeles City, Philippines, December 27, 1967, the son of David and Diane McChargue.

Education: Graduated from Rome Free Academy, Rome, New York, in May 1986; received a Bachelor of Arts Degree in Psychology from the State University of New York, College at Oswego, Oswego, New York in May 1993; received a Master of Science Degree in Psychology from Oklahoma State University, Stillwater, Oklahoma, in July 1994; completed the requirements for the Doctor of Philosophy Degree in Clinical Psychology at Oklahoma State University, Stillwater, Oklahoma, in December 1998.

Professional Experience: Clinical Psychology Intern, Boston DVAMC/Tufts Medical Center Consortium, Boston, Massachusetts, September 1997 – September 1998; Research Associate, Behavioral Psychopharmacology Laboratory, Department of Psychology, Oklahoma State University, Stillwater, Oklahoma, September 1994 – August 1997; Inpatient Psychiatric Counselor, Griffin Memorial Hospital, Norman, Oklahoma, July 1996 – June 1997; Behavioral Medicine Specialist, HealthSouth Rehabilitation Hospital, Behavioral Medicine Department, Oklahoma City, Oklahoma, August 1995 – July 1996; Substance Abuse Summer Trainee, VA Medical Center, Oklahoma City, Oklahoma, June 1995 – September 1995; Psychological Associate, Psychological Services Center, Oklahoma State University, Stillwater, Oklahoma, September 1994 – May, 1995; Graduate Assistantship, Psychology Diversified Student Program, Department of Psychology, Oklahoma State University, Stillwater, Oklahoma, August 1993 – August 1994.

Professional Memberships: Association for the Advancement of Behavior Therapy, American Psychological Association, Society for Research in Nicotine and Tobacco