THE EFFECT OF CONFECTIONARY CHEWING GUM ON PARASYMPATHETIC NERVOUS SYSTEM ACTIVITY

By

CAMERON C. WEAVER
MASTER OF ARTS IN CLINICAL PSYCHOLOGY
MINNESOTA STATE UNIVERSITY, MANKATO
MANKATO, MN
2005

BACHELOR OF ARTS IN PSYCHOLOGY
LUTHER COLLEGE
DECORAH, IA
2003

Submitted to the Faculty of the
Graduate College of the
Oklahoma State University
in partial fulfillment of
the requirements for
the Degree of
MASTER OF SCIENCE
December, 2007

THE EFFECT OF CONFECTIONARY CHEWING GUM ON PARASYMPATHETIC NERVOUS SYSTEM ACTIVITY

Thesis Approved:

Dr. Frank L. Collins Jr.

Thesis Adviser

Dr. Jennifer L. Callahan

Dr. Thad R. Leffingwell

Dr. A. Gordon Emslie

Dean of the Graduate College

TABLE OF CONTENTS

Chapter Page

LIST OF TABLES

Table Page

LIST OF FIGURES

Figure Page

CHAPTER I

INTRODUCTION

The negative effects of smoking have been well documented over the last 40 years (Hymowitz, 2005). In 2004, The Surgeon General and the Centers for Disease Control and Prevention (CDC) reported that smoking causes most cases of lung cancer (U.S. Department of Health and Human Services, 2004). In addition to lung cancer, cigarette smoke can cause cancer of the oral cavity, pharynx, larynx, and esophagus. Smoking also contributes to other pulmonary diseases including Chronic Obtrusive Pulmonary Disease (COPD). Recently, the CDC (2005) stated that smoking causes 440,000 deaths in the United States alone. From a financial standpoint, cigarette smoke causes the United States 150 billion dollars each year.

Despite the clear health risks related to smoking, approximately 45.1 million adults in the United States are current smokers (CDC, 2005). However, adults are not the only individuals in the U.S. who are smoking cigarettes. The CDC (2003) report from the National Youth Tobacco Survey 13.3% of middle school and 28.4% of high school students use tobacco products. Despite these troubling findings and related health problems, cigarette smoking continues to be a problem in the United States. The goal of this paper is to review the relevant research on Nicotine Dependence including symptoms and treatment. In addition, new strategies for reducing cravings and withdrawal will be

discussed with special attention given to a biological indicator for determining a reduction in stress.

Avoiding or eliminating withdrawal symptoms is a key focus in the treatment of Nicotine Dependence (Kornitzer, Boutsen, Dramaix, & Gustavsson, 1995; Sweeney et al., 2001; Goldstein, 2003). Many strategies have been employed in the treatment of Nicotine Dependence. The most prevalent therapies include pharmacotherapy (e.g., Nicotine Replacement Therapy) brief behavior therapy and intensive behavior therapy.

In addition, to these therapies, some research has focused on the use of regular, confectionary, chewing gum as a means to reduce cravings and withdrawal (Britt, Cohen, Collins, & Cohen, 2001; Cohen, Collins, & Britt, 1997; Cohen, Britt, Collins, Stott, & Carter, 1999; Cohen et al., 2001). Cohen et al. (1997) found that smokers who were given the gum reported significantly less global withdrawal. Furthermore, Cohen et al. (2001) found that chewing gum while nicotine deprived was associated with lower withdrawal symptoms than when not given confectionary gum. While these studies and others like them have found support for the use of confectionary gum at decreasing withdrawal symptoms, research in this area has relied on self report data. Nothing is known regarding the mechanism for this reduction in self-reported withdrawal symptoms.

One explanation may be that nicotine deprived smokers actually experience an increase in parasympathetic nervous system activity. This would indicate that the smokers are physiologically more relaxed when chewing gum while in deprivation than when not chewing gum while in deprivation. Another explanation may be that individuals self report fewer withdrawal symptoms because they expect gum to help. This

expectancy may not include a physiological change because participants may simply be responding in a socially desirable manner.

One method of measuring parasympathetic tone is utilizing heart rate variability (HRV; Porges, 1992). HRV is the measurement of R-R intervals of the heart and is measured in both high frequency (HF) and low frequency (LF; Berston et al., 1997). Increased HF HRV is associated with greater variability in heart rate (Berston et al.). Greater variability in heart rate is indicative of vagal control of the heart.

Research on addiction has supported differences among users and non-using controls. Ingjaldsson, Laberg, and Thayer (2003) found that alcohol dependent individuals have lower HF HRV than non-dependent controls. In addition, research on alcohol dependent individuals has also shown a decrease in HF HRV when these individuals are confronted with alcohol cues (Rajan, Naga Venkatesha Murthy, Ramakrishnan, Gangadhar, & Janakiramaiah, 1998). Finally, research suggests that fetuses exposed to cigarette smoking have lower vagal tone (Zeskind & Gingras, 2006).

While studies exist that have examined HRV as it relates to addiction, there exists a dearth of literature examining HRV during withdrawal. In addition, no research exists examining the mechanisms that underlie confectionary gum's role in reducing withdrawal symptoms and severity. The aim of the current study is to examine PNS activity as a mechanism for understanding how confectionary gum helps reduce withdrawal symptoms. It is hypothesized that smokers will experience greater parasympathetic tone when given confectionary gum during 24 and 48 hours of nicotine deprivation, as indicated by higher HF HRV, compared to 24 and 48 hour deprivation when given no chewing gum.

CHAPTER II

REVIEW OF THE LITERATURE

The American Psychiatric Association (APA) groups dependence to all tobacco products into one broad category. According to the Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition, Text Revised (DSM-IV-TR) Nicotine Dependence is defined as a maladaptive pattern of nicotine use that leads to clinically significant impairment or distress. Individuals who meet the criteria for nicotine dependence also may develop a tolerance to nicotine evidenced by increased consumption of nicotine (e.g., increasing the number of cigarettes smoked per day). Nicotine dependent individuals will also experience withdrawal symptoms as the time since the last dose of nicotine increases (APA, 2000). In addition to withdrawal and tolerance, the DSM-IV-TR states that it is also necessary for the individual to exhibit a desire or unsuccessful efforts to reduce or eliminate smoking behavior. Also individuals with Nicotine Dependence continue to use despite obvious health risks (Abrams & Niaura, 2003).

While it is necessary to exhibit three or more of the above symptoms to warrant a diagnosis (APA, 2000), research suggests that withdrawal may be primary reason for the continued use of nicotine (Cohen, Britt, Collins, al'Absi, & McChargue, 2001). Symptoms of nicotine withdrawal include: irritability or frustration, anxiety, difficulty concentrating, restlessness, decreased heart rate, depressed mood, insomnia, and increased appetite or weight gain (Hughes, 1992).

Hughes (1992) examined the withdrawal symptoms reported by 178 self-quitters. Participants were rated on a number of withdrawal dimensions that are listed above. Hughes found that nicotine withdrawal symptoms are time-limited. This suggests most withdrawal symptoms peak around 48 hours of deprivation from nicotine. Furthermore, many symptom scores returned to precessation levels between 7 and 30 days. In addition, this research suggests that withdrawal from nicotine is expected to last for two to four weeks.

Despite the relatively short duration of withdrawal symptom severity, many smokers avoid withdrawal as quickly as two hours following a cigarette (Abrams & Niaura, 2003). Research suggests that the primary reason that many smokers avoid withdrawal is due to the negatively reinforcing nature of nicotine dependence. Essentially, nicotine dependent individuals are able to "self-medicate" by administering nicotine to control withdrawal symptoms (Abrams & Niaura). Therefore, individuals are able to escape or avoid the aversive effects of nicotine withdrawal by self-administering more nicotine. While this is an effective strategy for eliminating withdrawal symptoms, it increases the probability that the individual will engage in smoking behavior in the future in order to eliminate or avoid withdrawal symptoms.

In addition to withdrawal, smokers often report cravings for cigarettes (APA, 2000). While these cravings are common, there are no current diagnostic criteria for cravings within the DSM-IV-TR (Sweeney, Fant, Fagerstrom, McGovern, & Henningfield, 2001). While it is not a separate entity from withdrawal, Sweeney et al. state that craving can be an indirect, but persistent, measure of nicotine withdrawal.

Avoiding or eliminating withdrawal symptoms is a key focus in the treatment of Nicotine Dependence (Kornitzer, Boutsen, Dramaix, & Gustavsson, 1995; Sweeney et al., 2001; Goldstein, 2003). Many strategies have been employed in the treatment of Nicotine Dependence. The most prevalent therapies include pharmacotherapy (e.g., Nicotine Replacement Therapy) brief behavior therapy and intensive behavior therapy. In addition, to these therapies, some research has focused on the use of regular chewing gum as a means to reduce cravings and withdrawal (Britt, Cohen, Collins, & Cohen, 2001; Cohen, Collins, & Britt, 1997; Cohen, Britt, Collins, Stott, & Carter, 1999; Cohen et al., 2001). These interventions targeting withdrawal will be discussed in turn.

Treatments for Nicotine Dependence and Withdrawal

Behavioral Interventions. Behavioral interventions for nicotine dependence are typically broken down into brief and intensive behavior therapy (Abrams, Niaura, Brown, Emmons, Goldstein, & Monti, 2003). Brief behavior therapy is delivered in a very short amount of time, typically 10 to 15 minutes (Shadel & Niaura, 2003). Intensive behavior therapy consists of multiple sessions, often lasting the course of seven weeks (Brown, 2003).

Brief behavior therapy is essentially composed of five key points originally developed by the National Cancer Institute (Fiore et al., 2000). These five components are better known as the "5 A's." Clinicians begin by *asking* about smoking behavior and *advise* the smoker to quit. Clinicians then *assess* the smoker's willingness to quit. If they are ready to quit clinicians moves on to step four, if the smoker is not ready to quit clinicians utilize motivational interviewing techniques to increase change talk regarding willingness to quit (Miller & Rollnick, 2002). Stage four consists of clinicians *assisting*

the smoker in a quit attempt. This consists of setting a quit date and establishing goals to be met as the smoker moves toward his or her quit date. During the final stage clinicians focus on *arranging* follow-up appointments in order to track progress and identify problem areas as the smoker moves closer to his or her quit date. This whole process can take as few as 10 to 15 minutes of contact and can easily be provided by health care professionals who are not clinical psychologists (Shadel & Niaura, 2003). While brief interventions have found support, they do little to address nicotine withdrawal. Thus, many clinicians may suggest the use of Nicotine Replacement Therapy as a part of a comprehensive nicotine cessation program (NRT; Bock, Niaura, Neighbors, Carmona-Barros, & Azam, 2005).

While brief interventions have proven effective, more traditional intensive behavior therapies have an advantage over pure brief interventions in that they more directly address withdrawal symptoms. This is achieved through nicotine fading. Nicotine fading consists of reducing nicotine consumption by switching to brands with lower nicotine content and/or gradually reducing the number of cigarettes smoked daily as the smoker moves toward the pre-arranged quit date (Becoña & García, 1993; Brown, 2003).

Pharmacotherpy Treatments. Pharmacotherapy treatments for nicotine dependence consist of Nicotine Replacement Therapy (NRT). Current NRT's approved by the Food and Drug Administration (FDA) include nicotine gum, transdermal patch, nasal spray, and the nicotine inhaler (Sweeney, Fant, Fagerstrom, McGovern, & Henningfield, 2001).

The most common first-line pharmacotherapies for Nicotine Dependence are of the over-the-counter variety. NRT's have been established as an effective treatment for

Nicotine Dependence. NRT's work to reduce the withdrawal and craving symptoms associated with nicotine deprivation. Sweeney et al. (2001) found that utilizing NRT's can double the chance of long-term smoking cessation.

Research has supported oral NRT's for reducing urge to smoke (Demazieres et al., 2006). In addition, gum NRT has been shown to reduce cued-induced cravings (Shiffman, et al., 2003). Also, Shiffman, Ferguson, Gwaltney, Balabanis, and Shadel (2006) found that high-dose NRT (via the nicotine patch) can significantly reduce withdrawal and cravings produced by 24 and 48 hour abstinence.

Sweeney et al. (2001) suggest that the best way to utilize the benefits of NRT's may be to combine both the fast and slow administration of nicotine. This suggests that is effective to administer slow release NRT's (i.e., nicotine patch) to provide a stable rate of nicotine in the system and to administer fast acting NRT's (i.e., nicotine gum or lozenge) to help control "breakthrough cravings" (Fagerstrom, Schneider, & Lunell, 1993).

Kornitzer, Bousten, Dramaix, Thijs, & Gustavsson (1995) compared groups of participants all of whom smoked 10 or more cigarettes in a day. Kornitzer et al. grouped participants into one of three groups: active patch plus active gum, active patch plus placebo gum, and placebo patch plus placebo gum. Their results support the use of combination treatments; finding significantly higher abstinence rates in the combined active group compared to the other two groups at 12 week and 24 week follow-up.

Another interesting finding from this study was that the active patch/placebo gum group only achieved significantly greater abstinence rates at 12 weeks when compared to the placebo patch/placebo gum group. This derives two possible implications. One, the nicotine patch is as effective as placebo in achieving abstinence in participants (which is

clearly not supported in the literature). Two, that the process of chewing gum (nicotine or confectionary) has a benefit for the smoker in promoting abstinence to such a degree that it makes observing the difference in abstinence rates between placebo patch and nicotine patch at 24 and 36 weeks difficult. It is the later implication that is of interest to the present study.

Similarly, Shiffman et al. (2003) included a placebo confectionary gum condition in their study of the acute administration of nicotine gum during cue-provoked craving. The results suggested that individuals in the confectionary gum condition received some craving reduction when chewing the placebo gum. This finding is consistent with a body of literature that supports the use of confectionary gum to reduce withdrawal and craving symptoms.

Confectionary Gum. The use of confectionary gum in the treatment of Nicotine Dependence has received some support in recent years. Although it does not provide nicotine to the abstinent smoker, it has been shown to reduce the withdrawal and cravings that are considered to be important reasons for relapse. The research in this area has found support for the use of confectionary gum in the reduction of affective stress to more specific withdrawal symptoms and craving (Britt et al., 2001; Cohen et al., 1997; Cohen et al.,1999; Cohen et al., 2001).

Cohen et al. (1997) investigated the effect of confectionary gum on self reported craving and global withdrawal symptoms in smokers who had been abstinent from nicotine while watching a movie. Participants were then given ratings of cravings and withdrawal following the movie (Time 1) and again 30 minutes after the time 1 measures (Time 2). The results indicated that smokers who were given the gum reported

significantly less global withdrawal at time 1 and time 2. In addition, these participants also reported significantly less cravings at time 2, but not time 1. A similar study found that when smokers are given the choice to choose between gum plus a reward or a cigarette they take fewer puffs and wait longer to have their first cigarette (Cohen et al., 1999).

Cohen et al. (2001) continued this line of research by examining withdrawal symptoms of participants as they completed two separate conditions: a confectionary gum condition and a no gum condition. Participants were asked watch a two hour movie to establish enough latency between cigarettes for them to experience withdrawal. Self-report withdrawal symptoms were monitored directly following the movie, 30 minutes after the movie, and again 60 minutes after the movie. The results indicated that chewing gum while nicotine deprived was associated with lower withdrawal symptoms at 150 minutes of deprivation and again at 180 minutes of deprivation. These findings support the use of confectionary gum as a means to decrease the withdrawal symptoms associated with nicotine deprivation.

Britt et al. (2001) attempted to add support to the above findings. The researchers recruited participants to engage in a contrived public speaking stressor task. During the task participants were assigned to either a smoke group, a gum group, or a control group. Participants were then asked to self-report their urge to smoke, their withdrawal symptoms, and their anxiety symptoms at five distinct time intervals through-out the task. The results indicated that although being able to smoke was the best for decreasing urge to smoke, chewing confectionary gum was as effective as smoking at time 5 in reducing withdrawal symptoms. There were no significant effects on anxiety symptoms.

While these studies support the efficacy of confectionary gum as a tool to decrease withdrawal symptoms, there still remains one key problem. Participants in all of these studies were self-reporting withdrawal and craving symptoms. It is unclear if these results are do to actual physiological changes in the symptoms of withdrawal or simply reactivity that may be experienced by participants who are filling out questionnaires that may be face valid. Thus it is necessary to examine the reduction of withdrawal in nicotine deprived participants using measures that indicate a physiological reduction in symptoms that may be related to the stress response that is related to the clinical significant distress experienced by withdrawal (see Hughes, 2006).

Autonomic Nervous System and the Stress Response

The autonomic nervous system (ANS) is responsible for maintaining homeostasis in the body. The ANS is essentially made-up of two systems; the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). The SNS is responsible for preparing the body for action. This system is regulated by the hypothalamus and brain stem, specifically the medulla oblongata (al'Absi, 2006). Conversely, the PNS is responsible for returning the body to homeostasis following the activation of the SNS.

More specifically, the hypothalamus sends messages, via the pituitary gland, to send the hormone cortisol to areas of the body to aid in the glucose metabolism necessary for sympathetic activity (Collins, Sorocco, Haala, Miller, & Lovallo, 2003). This system is better known as the hypothalamic-pituitary-adernalcortical (HPA; al'Absi, 2006) axis. Once a stressor dissipates the PNS works to return the body to homeostasis by helping to reduce the amount of cortisol in the blood, thus reducing heart rate, slowing respiration, and stimulating digestion.

The autonomic response is not only activated by life threatening stimuli. It is also activated by stress. This is evidenced by increased levels of cortisol in the body when individuals are under stress (Lovallo, 2005; al'Absi, 2006). In addition, this cortisol response is positively correlated with negative mood states (Ice, 2005). Negative mood states associated with the stress response are found among individuals with nicotine dependence while under deprivation (Cohen et al., 2001).

The fight or flight response stimulated by the SNS is related to increases in heart rate associated with the presence of a stressor. Therefore, it is possible to monitor PNS activity by examining reductions in heart rate. Researchers have discovered that chemically blocking the vagus nerve (e.g., the use of atropine) leads to dramatic increase in heart rate (Kawachi, 1997). This highlights the role of vagal control over the heart rate and alludes to the connection between the PNS and heart rate.

Porges (1992) elaborates on the above assertion. Porges stated that the SNS responds to external stimuli and the PNS works to return the body to homeostasis by responding to the changes in the viscera created by SNS activity. Therefore, in the absence of stressors (e.g., withdrawal symptoms) increased PNS activity may represent homeostasis.

Respiratory Sinus Arrhythmia and Heart Rate Variability

Possibly the best index of PNS tone, or vagal control, is obtained through heart rate patterns (Porges, 1992). Analyzing heart rate rhythms is a non-invasive process of measuring autonomic control (Kobayashi, Ishibashi, & Noguchi, 1999). Although the use of an electrocardiogram (ECG) was essential for this purpose, recent advances in exercise

technology have made it possible to analyze heart rate with a portable monitor worn around the torso.

Respiratory Sinus Arrhythmia. Essential to the study of parasympathetic activity of the heart is the respiratory sinus arrhythmia (RSA). The relationship between RSA and parasympathetic activity has been noted for over 30 years (Katona & Jih, 1975). The RSA is primarily controlled by respiratory gating of parasympathetic signals to the heart via the vagus nerve (Grossman, 1992). Specifically, parasympathetic signals to the heart that work to reduce heart rate are blocked during inspirations and are enabled during expiration.

RSA has proven to be beneficial in the study of the stress response. Lane, Adcock, and Burnett (1992) noted that differences in RSA may play a role in how individuals respond to stressors and how quickly they recover. Lane et al. found that individuals with greater variability between heartbeats while at rest experienced less sympathetic arousal and greater parasympathetic activity during the sympathetic response.

Heart Rate Variability. The above mentioned variability in beat to beat interval of the RSA is most commonly referred to as heart rate variability (HRV; Grossman, 1990; Kobayashi et al., 1999). Kobayashi et al. elaborate on this assertion stating that HRV is comprised of the RSA and variability in blood pressure. For the purposes of this paper, focus will be given to the former because it is representative of parasympathetic tone (Pomeranz et al., 1985).

HRV is the measurement of R-R intervals of the heart. HRV refers to the frequency of these intervals. These intervals have both a low frequency (LF; .04-.15 Hz)

and high frequency (HF; .18-.40 Hz) component. The LF band is associated with sympathetic activity while the HF band is associated with parasympathetic activity (Berston et al., 1997; Kobayashi et al., 1999). For the purposes of this paper focus will be given to the HF component of HRV.

Berston et al. (1997) discuss the role of HF HRV as it relates to parasympathetic activity. Increased HF HRV is associated with greater variability in heart rate. Greater variability in heart rate is indicative of vagal control of the heart. Lower HF HRV indicates a decrease in HRV and thus less PNS control. Spectral analysis (the analysis of heart rate within a discrete period of time) of HRV has been widely discussed as an effective method of analyzing HRV (Crawford et al., 1999; Berston et al., 1997; Kobayashi et al., 1999; Berston, Cacioppo, & Grossman, 2007).

Several factors have been shown to affect HRV. Elsenbruch, Harnish, and Orr (1999) found that fluctuations with HRV during wake and sleep cycles. Their results indicated a decrease in HF HRV during REM sleep as compared to non-REM sleep. Thus, suggesting increased SNS activity and decreased PNS control over heart rate during REM sleep. In addition, they discovered that males exhibited significantly lower HF HRV during wake cycles, indicating less vagal control compared to females.

In addition to sex and sleep studies, some researchers have examined psychosocial factors that affect HRV. Horsten et al. (1999) studied the influence of psychosocial factors on HRV in women. The results indicated that isolation, low social support, and internalizing anger were associated with decreased vagal control. These results are similar to those discussed by Lane et al. (1992) that suggest that type B personalities have increased HF HRV.

Studies focusing on general medical conditions have produced evidence that individuals with coronary problems also experience a decrease in vagal tone. Gianaros et al. (2005) found that postmenapausal women experiencing a calcification of blood vessels had less parasympathetic tone as evidenced by a decrease in HF HRV. Other studies have found that decreased vagal tone significantly predicts death due to heart attack (e.g., Kleiger, Miller, Bigger, & Moss, 1987).

Research on HRV has also focused on psychological disorders. Thayer, Freidman, and Borkovec (1996) found that individuals with GAD had lower HF HRV than non-anxious controls. In addition, participants instructed to worry had significantly lower HF HRV than when instructed to relax. This research suggests that individuals experience less vagal control and more SNS activity during worry. Similar finding have been discussed for Panic Disorder (Friedman & Thayer, 1998).

Research on addiction has supported differences among users and non-using controls. Ingjaldsson, Laberg, and Thayer (2003) found that alcohol dependent individuals have lower HF HRV than non-dependent controls. In addition, research on alcohol dependent individuals has also shown a decrease in HF HRV when these individuals are confronted with alcohol cues (Rajan, Naga Venkatesha Murthy, Ramakrishnan, Gangadhar, & Janakiramaiah, 1998). Finally, research suggests that fetuses exposed to cigarette smoking have lower vagal tone (Zeskind & Gingras, 2006).

In addition to the spectral analysis of HRV, statistical analysis has also been utilized. Essentially, this consists of examining the overall variability of beat to beat intervals (Kleiger, Stein, Bosner, & Rottman, 1992). While the specific HF and LF components are not specifically examined, the differences observed are similar; such that

Several studies have utilized the RMSSD statistic to examine vagal control. For example, researchers have demonstrated that compared to normal controls individuals with paranoid schizophrenia have significantly less variability in heart rate, suggesting less vagal control of the heart (Boettger et al., 2006). Similar findings have been observed for women with premenstrual dysphoric disorder (Landén et al., 2004). In addition, individuals with depression experienced an increase HRV, as indicated by increased RMSSD following cognitive-behavioral therapy (Carney et al., 2000).

RMSSD has also been utilized outside the clinical setting. Wang, Huang, and Wang (2001) found that enlisted men in the Chinese military exhibiting decreased RMSSD during artillery training. This suggests a decrease in parasympathetic, or vagal, control during a stressful event. Furthermore this data provides additional support for the use of RMSSD as an indicator for examining the presences or absence of parasympathetic control and infers that decreases in HRV are associated with the sympathetic response.

While some research has focused on addiction and cigarette use, there is a substantial lack of literature examining HRV in individuals going through withdrawal. Research on withdrawal from nicotine has indicated that both nicotine gum and

confectionary gum can aid in decreasing self-reported withdrawal symptoms. However, none of the aforementioned studies utilized a physiological measure of withdrawal. Due to the similarities between withdrawal symptoms and the stress response it stands to reason that HRV could be utilized as a physiological marker for stress.

The aim of the current study is to examine if PNS activity is a mechanism for understanding how confectionary gum helps reduce withdrawal symptoms. It was hypothesized that smokers will display greater variability in RR intervals (indicating greater parasympathetic tone) when given confectionary gum during 24 and 48 hours of nicotine deprivation than when given no gum. More specifically, participants will exhibit a greater RMSSD HRV during the gum conditions and a smaller RMSSD during the no gum condition. With respect to the spectral analysis component of HRV it was hypothesized that participants would experience greater HF HRV during the gum conditions than during the no gum condition.

CHAPTER III

METHODOLOGY

Participants

Participant data was analyzed from a previous study of 49 participants who were solicited from Texas Tech University and Oklahoma State University and the surrounding communities of the two universities (Cohen, VanderVeen, Weaver, & Collins, 2007). At Texas Tech University, 63 individuals were scheduled to participate in the current study. Of these sixty-three individuals, 28 completed the experimental protocol (22 men, 6 women), 19 never presented for their initial interview after agreeing to participate (11 men, 8 women) and 16 individuals began the protocol but dropped out before completion (11 men, 5 women). At Oklahoma State University, 57 individuals were scheduled to participate in the current study. Of these 57 individuals, 21 completed the experimental protocol (11 men, 10 women), 21 never presented for their initial interview (7 men, 14 women), and 15 individuals began the protocol but dropped out before completion (5 men, 10 women).

These participants did not differ in number of pieces chewed by condition, $F(1, 47) = .219$, $p = .64$, or gender, $F(1, 47) = .70$, $p = .41$. Of these participants, 41 provided heart rate data. The participants ranged in age from 18 to 39. All participants met the DSM-IV-TR criteria for nicotine dependence and scored at or above a 5 on the Fagerstrom Test of Nicotine Dependence (Fagerstrom, 1978). In addition, all participants smoked 16 cigarettes or more per day and were willing to chew gum upon request. All

participants were reimbursed 50 dollars per week for four weeks with an additional 100 dollar bonus for completing the study. Thus, participants were reimbursed 300 dollars for completing the study. Funding for reimbursement came from a research grant provided by the Wrigley Company.

Materials and Apparatus

Fagerström Test of Nicotine Dependence (FTND). The FTND is a 6-item self-report measure of nicotine dependence. Scores range from 0 to 10, with higher scores indicating more severe nicotine dependence (Fagerström, 1978).

DSM IV Screening. The DSM IV screening consisted of a structured interview of the DSM criteria for Nicotine Dependence (APA, 2000). Participants were asked questions such as "over time did you smoke a lot more to the same effect as before?" Participants had to meet at least three of the seven criteria list in the DSM.

Gum Use Monitoring Form. A gum use monitoring form was given to participants for each day of every trial. The form was used as a log of gum chewing activity and recorded the time, number of pieces chewed, and behavior engaged while chewing the gum. In addition to the self-monitoring, the form acted as a prompt to remind participants that gum could be chewed during cravings for nicotine.

Carbon Monoxide Monitoring. The carbon monoxide (CO) monitor was utilized as a means to ensure that our participants were in deprivation throughout each trial. CO readings, via a Vitalograph CO breathalyzer, were utilized to ensure that all participants had smoked frequently enough prior to the study in order to qualify. This required participants to have at least 10 ppm of CO in their blood. In addition to screening, the CO monitor ensured that the smokers had maintained abstinence during each trial to ensure

that they were experiencing deprivation. Thus participants had to have less than 10 ppm CO in their blood or have a 50% reduction in CO reading during the deprivation periods. The above parameters were set by the Society for Research on Nicotine and Tobacco's (SRNT) Subcommittee on Biochemical Verification (Benowitz et al., 2002).

Heart Rate Monitor. Participants' parasympathetic tone was analyzed using a Polar 810s Exercise Heart Rate Monitor. The monitor is a thin band that was worn around the torso across the Xiphoid Process. In addition to the band, a watch was worn on the wrist that monitors and records the heart rate data gathered from the heart rate band. Upon completion of the heart rate recording the data from the wrist unit was synced to a computer where the data was entered and saved. Use of this particular exercise heart rate monitor has been shown to be in strong agreement with the more commonly used ECG recording device. Kingsley, Lewis, and Marson (2005) found a strong linear relationship between the Polar 810s and a digital ambulatory ECG ($r(6436) = .93$, $p < .001$ to $r(1746) = .99$, $p < .001$). Finally, all data was then cleaned for imperfections in the recording procedure.

HRV software. Additional software was needed in order to conduct the spectral and statistical analysis of the heart rate data. Kubios HRV Analysis version 2.0 beta (Tarvainen & Niskanen, 2005) was utilized in order to determine the variability between RR intervals. This software allowed researchers to analyze specific time domains and extract statistical analyses such as RMSSD and HF HRV data (Chellakumar, Brumfield, Kunderu, & Schopper, 2005; Niskanen, Tarvainen, Ranta-aho, & Karjalainen, 2002).

Confectionary Gum. The confectionary, non-nicotine, gum was provided by the Wrigley Company. Three different flavors of gum were utilized for the three different

gum trials. Flavors were labeled by number, not flavor in order to keep participants blind to gum ingredients as the flavors used were not for sale by the manufacturer. While the participants were blind to gum flavor, the flavors were mint, vanilla, and apple-cardamom. Gum was disbursed in silver zip-sealed packets of 20 pieces.

Procedure

Participants were recruited via newspaper advertisements and referral from former participants. After the initial contact a phone interview was conducted in order to determine eligibility. If the potential participant had a FTND score of 5 or more, met DSM criteria for nicotine dependence, fit the age range, smoked 16 or more cigarettes daily, and was willing to chew gum he or she was given further information regarding the study.

These participants were then informed that the study would be conducted over a four week period during which they would be asked to quit smoking in four, 48 hour increments (one period of deprivation per week for four weeks). Willing participants were then scheduled for an initial session that began by checking CO levels to determine if the participant smoked regularly prior to participation in order to be able to experience deprivation during the 48 hour periods of abstinence. Participants with 10 ppm or more CO were allowed to continue in the study.

At the initial session participants were randomly assigned to one of four conditions: no gum, vanilla gum, apple-cardamom gum, and peppermint gum. Individuals would participate in all four conditions over a four week period. Each participant would receive a new condition that would consist of one of the gum flavors (one flavor per week for three weeks) and one no gum (control) week. Participants were then informed that the

gum that they would be receiving was non-nicotine gum, but was not a flavor that they could necessarily find in a store and that substituting a store bought gum was unacceptable.

Participants then completed a demographic survey and were administered the FTND and DSM screener. Participants were then instructed to put on the heart rate monitor and watch. Once the heart rate monitor was in place the participants were asked to remain seated for 20 minutes during which time they completed other questionnaires not essential to this particular investigation. After 20 minutes had expired the participants were asked to engage in an orthostatic challenge for 5 minutes (participants instructed to stand for 5 minutes) designed to create sympathetic arousal. The purpose of the orthostatic challenge was to provide a control comparison of HRV. Standing from a rest state eliminates parasympathetic tone and serves as a control comparison of HRV analysis across the conditions.

Following this period participants were asked to refrain from smoking cigarettes or using other nicotine products for 48 hours. The participants were then given the flavor of gum assigned for that week or no gum if that was the conditioned assigned. Participants were then instructed to refrain from using other confectionary products including other gums, candies, or breath strips.

Participants returned to the lab at the same time the next day. This allowed researchers to assess for adherence and obtain 24 hour deprivation measures. Participants began by taking a CO reading. If participants had experienced a 50% reduction in CO levels or had a CO level below 10 ppm, they were invited to stay to provide 24 hour deprivation heart rate data. Heart rate data collection followed the same protocol listed

above. Those who did not meet this criterion were assumed to have not abstained from smoking and were asked to come back the following week to restart the condition. Participants who completed the heart rate recording were given more gum if needed and scheduled to come in at the same time the following day.

On day three participants returned to the lab to provide heart rate data for 48 hour deprivation. Again participants were asked to provide a CO measurement to check for abstinence and continued deprivation. Following the heart rate protocol participants were instructed to return to normal smoking behavior until the following week when they were to return to the lab to begin the next assigned condition.

Weeks two through four followed week 1 protocol. Participants stayed in the experiment until they had completed all four conditions. Each week participants received a new condition (gum or no gum control). Participants completed each condition only once.

Once heart rate data was collected using the Polar exercise software, the heart rate data was cleaned of errors that occurred during recording and saved as a new file for separate analysis. Heart rate analysis was conducted using only the final 5 minutes of the 20 minute rest period. This allowed 15 minutes time for the participant to acclimate to the heart rate monitor and setting, thus giving the researchers 5 minutes of resting heart rate data for analysis. In addition, the orthostatic challenge heart rate data was analyzed for comparison to the rest data.

This data was then converted into a text format as required by the Kubios HRV software. Once all data was converted to text files the data was then opened using the HRV software. The HRV software provided the RMSSD and HF HRV data that was

needed by simply opening a desired text file through the software. Data rendered was then entered into SPSS for analyses.

CHAPTER IV

FINDINGS

Due to insufficient heart rate data, only 26 of the original 41 participants were included in the final analyses. All participants for whom no errors occurred in the HRV recording process were included in the sample. Of the remaining 26 participants, 6 participants were missing data only for baseline data collection. Since no intervention had been administered during the baseline phase of each condition, it was decided to average the baseline heart rate data from the baselines of each participant's other baseline conditions. This data was entered in the missing data fields for both the HF HRV and RMSSD HRV variables. Therefore, all other participants from the original study (Cohen et al., 2007) were not included in the analyses of the current study. The hypotheses of the current study were tested using only the 26 participants with complete heart rate data.

All data was analyzed using within subjects planned contrasts. Due to the small sample size contrasts provided a reasonable solution to power difficulties (Venter & Maxwell, 1999). Consistent with our stated hypotheses, the planned contrasts made it possible to analyze the data by comparing the no gum condition to the three gum conditions. Therefore, analysis was conducted by statistically collapsing the three gum conditions in order to analyze the difference in HRV between confectionary gum and no gum. Finally, separate analyses were conducted for each of the phases (baseline, 24 hour deprivation, and 48 hour deprivation).

Participant demographics of this sample were consistent with those observed in similar research examining nicotine withdrawal in smokers (Cohen et al., 2001). The average number of cigarettes smoked per day by the sample was almost 19 cigarettes (M = 18.85, SD = 5.10). The participants had an average score of 6 (SD = 1.44) on the FTND, indicating an adequate level of nicotine dependence. In addition participants did not differ in total number of pieces of gum chewed between gum 1 and gum 2 ($t(25) = 1.14$, $p = .266$), gum 1 and gum 3 ($t(25) = .028$, $p = .978$), and gum 2 and gum3 ($t(25) = -.942$, $p = .355$).

Within subjects planned contrasts revealed no significant differences between the gum and no gum conditions for the HF HRV variable at baseline ($F(1, 25) = .741$, $p = .398$, partial eta squared = .03, observed power = .16). Similar results were observed at 24 of deprivation, $F(1, 25) = .084$, $p = .775$, partial eta squared = .00, observed power = .05. However, there was a significant difference between the gum and no gum conditions at 48 hours deprivation ($F(1, 25) = 4.48$, $p = .04$, partial eta squared = .15, observed power = .52) such that there was significantly larger HF HRV during the no gum condition and the gum conditions (see Table 1 for means and standard deviations). In addition, the orthostatic challenge displayed no differences across recording phases, indicating that the challenge provided an attenuation of the HF HRV spectrum (see Figure 1).

With respect to the time domain (RMSSD) data, no significant differences were observed between the gum and no gum conditions at baseline, $F(1, 25) = .121$, $p = .730$, partial eta squared = .00, observed power = .05. In addition, no differences were observed at 24 and 48 hour of deprivation, $F(1, 25) = .696$, $p = .412$, partial eta squared = .03,

observed power = .16, and $F(1, 25) = .163$, $p = .690$, partial eta squared = .01, observed power = .06, respectively. However, visual analysis of the means (see Figure 2) suggests that participants had greater HRV, as indicated by larger RMSSD, during the gum conditions than the no gum condition (see Table 2 for means and standard deviations). However, Figure 2 demonstrates that the orthostatic challenge did not attenuate the RMSSD of HRV at 24 and 48 hours deprivation. This is likely due to the nature of obtaining an overall, "big picture," statistical analysis of variability within the heart rate.

CHAPTER V

CONCLUSION

The purpose of this study was to determine if parasympathetic nervous system activity is an effective mechanism by which confectionary chewing gum has its effect on self-reported withdrawal symptom attenuation. It was hypothesized that nicotine dependent participants would display higher HF HRV during the confectionary gum conditions than during the no gum condition during 24 and 48 hours of deprivation. It was also hypothesized that these participants would demonstrate greater variability in RR intervals (greater RMSSD) during the confectionary gum conditions than during the no gum condition. Results of this study suggest that the participants did not experience significantly greater parasympathetic activation (greater vagal control of the heart) when given confectionary gum compared to when they were given no gum.

Although these results are non-significant, it is interesting that the means represented for each dependent variable suggests a trend toward a different outcome. While the significant HF HRV data would suggest that the no gum conditioned produced greater parasympathetic control, the effect size was quite small. Conversely, the RMSSD data would suggest greater parasympathetic control during the confectionary gum conditions; however, the differences were not significant.

While this appears to suggest that the results are contradictory, there is some evidence to suggest that these results are encouraging. Malik and colleagues (1996) stated that spectral analysis (HF analysis) of HRV can be difficult to determine if the individual

is not stationary. Although our participants were sitting down, they were chewing gum. Therefore chewing gum during the trial may have actually created artifact in the data by disrupting the spectral components of the heart rate. In addition, participants were asked to fill out forms related to another study regarding withdrawal symptoms and mood during the heart rate recording procedure. This may have also affected the participants' autonomic response by forcing the participants to reflect on their emotional states at the time of recording.

Conversely, the statistical methods used during the data recording period do not focus solely on one spectral component of HRV. The RMSSD data views the sampled HRV data and computes the general variation in the total HRV regardless of the LF and HF spectrum. This statistical method of analyzing short-term periods of HRV may be more representative of the participant's vagal tone during the recording. Although this provides an explanation for the observed results, it is still largely speculative at this point and further research is needed.

Regardless, the RMSSD data remains promising. While the data was non-significant, the displayed means suggest that confectionary chewing gum may play a role in activating the parasympathetic nervous system. In addition, the non-significant findings may reflect the limitations of the study such as small sample size and experimenter error as opposed to the absence of parasympathetic control.

There is, however, an alternative explanation of the findings that warrants some discussion. It is possible that these data are non-significant because confectionary chewing gum does not produced activation of the parasympathetic nervous system. This is to say that chewing confectionary gum does not reduce physiological signs of

withdrawal, such as sympathetic nervous activity, or the attenuation of sympathetic arousal via activation of the parasympathetic branch. This conclusion is inconsistent with the findings in previous studies examining the effect of confectionary gum on withdrawal and cravings that suggest that chewing gum does ameliorate withdrawal and cravings (Britt et al., 2001; Cohen et al., 1997; Cohen et al.,1999; Cohen et al., 2001). If this conclusion is true, it would suggest that previous research in this area has demonstrated that confectionary gum provides relief to the extent that participants expect confectionary gum to help, so they report that it was efficacious relative to the no gum condition. Again, this conclusion is speculative and, given the limitations of the study, further research is clearly necessary.

Limitations

Despite the non-significant findings, this study had some important limitations. The limitations most crucial to this discussion are those of experimenter error and small sample size. Each of these limitations will be discussed in turn.

The first limitation is the possible role of experimenter error. There is no doubt that experimenter error and apparatus malfunction led to the loss of necessary heart rate data prior to analyses, but it is possible that additional errors were made. Specifically, the protocol called for the participants to chew gum during the heart rate recording phase; however, only a small number of adherence checks were conducted during the data collection phase and it is possible that not all participants were chewing gum during the recording phase. While this would eliminate the artifact hypothesis regarding the HF HRV data, it may have led to a decrease in HF HRV during the recording if the actual

behavior of chewing gum does not attenuate the parasympathetic response (as inferred from the artifact hypothesis).

The second, and most salient, limitation is that of sample size. From the original 41 participants, only 26 were able to be utilized in the final analyses due to insufficient heart rate data. This limits the power of the study substantially even for a within subject design. A separate power analysis was conducted to determine how many participants would have been necessary to reach significance even at a small effect size. This analysis suggested that a study of this type would require 36 participants to achieve significant findings ($p < .05$) with a small effect size ($d = .25$). As indicated by the results, our existing sample of 26 participants had very little power and very small effect sizes. Furthermore, the current study ran separate analyses at each time period. Even with the inflated alpha that results from multiple tests, the results are non-significant. Although it is inappropriate to infer a direction or trend from the observed means, more participants would clearly be helpful in determining whether or not these observed means are toward or further away from significance. Therefore additional research is needed.

It is necessary that additional research address many of these limitations. For example, further researchers should address the faults in the experimental design. Due to the possible confound created by chewing gum and completing self report measures of withdrawal and mood states during the recording phase, researchers should eliminate the demands placed on participants during the protocol. This would optimize the degree to which researchers could conclude that the participants were truly relaxed during the recording procedure.

In addition, it may be helpful to use more than one measure of physiological arousal. While heart rate may be affected by chewing gum, it is possible that changes at the neurological level may occur. The use of neuroimaging techniques may provide an excellent method for discriminating physiological changes in emotion across the conditions. Also, more behavioral measures could be helpful. Ekman and Friesen (1976) suggested a code for identifying facial movements, this may be an additional marker of the emotional response of stress and it may relate to withdrawal induced stress (Ekman, Levenson, & Friesen, 1983).

Finally, it should be noted that reducing human emotion (e.g., withdrawal-induced stress states) to physiology discounts the complexity of human emotion. While past research supports the use of confectionary gum to reduce self-reported withdrawal, it is unclear as to whether PNS activity is a mechanism for understanding this phenomenon. It is stands to reason that the withdrawal response has both a physiological and a psychological component that cannot, and should not, be observed independently from the other.

Conclusion

The purpose of this study was to determine if autonomic activity, specifically parasympathetic control of the heart, is a mechanism by which confectionary chewing gum decreases withdrawal symptoms in nicotine deprived smokers. Results suggest that confectionary gum did not have a significant effect on the vagal control of the heart as indicated by non-significant differences in the variability of the RR intervals. Significant differences were found at 48 hour deprivation for HF HRV, suggesting that no gum may lead to greater parasympathetic nervous system activity than actually chewing gum.

While this result appears troublesome because it is in the opposite direction as expected, it is likely due to the effect of a motor behavior (i.e., chewing gum) may have on spectral analysis of heart rate. Therefore, we suggest that the RMSSD data is more representative of the parasympathetic activity (vagal control) observed within the sample.

The RMSSD data did not yield significant differences between gum and no gum conditions; however, the means suggest that there is greater variability in heart rate during the gum conditions than during the no gum condition. Further research is necessary to determine the extent to which chewing confectionary gum affects autonomic responses. This line of research should include larger samples, more frequent adherence checks to ensure accurate data collection, fewer demands placed on participants during the heart rate recording procedure, and additional physiological or behavioral measures of withdrawal.

REFERENCES

Abrams, D. B. & Niaura, R. (2003). Planning evidence-based treatment of tobacco dependence. In D. B. Abrams, R. Niaura, R. A. Brown, K. M. Emmons, M. G. Goldstein, & P. M. Monti (Eds.), *The tobacco dependence treatment handbook: A guide to best practices* (pp. 1-26). New York: Guilford.

Abrams, D. B., Niaura, R., Brown, R. A., Emmons,K. M., Goldstein, M. G., & Monti, P. M. (Eds.). (2003). *The tobacco dependence treatment handbook: A guide to best practices*. New York: Guilford.

al' Absi, M. (2006). *Hypothalamic-pituitary-adrenocortical responses to psychological stress and risk for smoking relapse*. International Journal of Psyhcophysiology, 59, 218-227.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text revision). Washington, DC: Author

Becoña, E. & García, M. P. (1993). Nicotine fading and smokeholding methods in smoking cessation. *Psychological Reports, 73,* 779-786.

Benowirz, N. L., Jacob, P., III, Ahijevych, K., Jarvis, M. J., Hall, S., LeHouezec, J., et al. (2002). Biochemical verification of tobacco use and cessation. *Nicotine and Tobacco Research, 4,* 149-159.

Berston, G. G., Bigger, T., Jr., Eckberg, D. L., Grossman, P., Kaufman, P.G., Malik, M.,

et al. (1997). Heart rate variability: Origins, methods, and interpretive caveats. *Psychophysiology, 34,* 623-648.

Berston, G. G., Cacioppo, J. T., & Grossman, P. (2007). Whither vagal tone. *Biological Psychology, 74,* 295-300.

Bock, B. C., Niaura, R. S., Neighbors, C. J., Carmona-Barros, R., & Azam, M. (2005). Differences between Latino and non-Latino White smokers in cognitive-behavioral characteristics relevant to smoking cessation. *Addictive Behaviors, 30,* 711-724.

Boettger, S., Hoyer, D., Falkenhahn, K., Kaatz, M., Yeragani, V., & Bär, K. (2006). Altered diurnal autonomic variation and reduced vagal information flow in acute schizophrenia. *Clinical Neurophysiology, 117,* 2715-2722.

Britt, D. M., Cohen, L. M., Collins, F. L., Jr., Cohen, M. L. (2001). Cigarette smoking and chewing gum: Response to a laboratory-induced stressor. *Health Psychology, 20,* 361-368.

Brown, R. A. (2003). Intensive behavioral therapy. In D. B. Abrams, R. Niaura, R. A. Brown, K. M. Emmons, M. G. Goldstein, & P. M. Monti (Eds.), *The tobacco dependence treatment handbook: A guide to best practices* (pp. 118-177). New York: Guilford.

Carney, R. M., Freedland, K. E., Stein, P. K., Skala, J. A., Hoffman, P., & Jaffe, A. S., (2000). Change in heart rate variability during treatment for depression in patients with coronary heart disease. *Psychosomatic Medicine, 62,* 639-647.

Centers for Disease Control and Prevention. (2003). Tobacco use among middle school

and high school students: United States 2002. *MMWR Morbidity and Mortality Weekly Reports, 52,* 1096-1098.

Centers for Disease Control and Prevention. (2005). Annual smoking-attributable mortality, years of potential life lost, and productivity losses: United States, 1997-2001. *MMWR Morbidity and Mortality Weekly Reports, 54,* 625-628.

Centers for Disease Control and Prevention. (2005). Cigarettes use among adults. *MMWR Morbidity and Mortality Weekly Reports, 55,* 1145-1148.

Cohen, L. M., Britt, D. M., Collins, F. L., Jr., al'Absi, M., McChargue, D. E. (2001). Multimodal assessment of the effect of chewing gum on nicotine withdrawal. *Addictive Behaviors, 26,* 289-295.

Cohen, L. M., Britt, D. M., Collins, F. L., Jr., Stott, H. D., Carter, L. C. (1999). Chewing gum affects smoking topography. *Experimental and Clinical Psychopharmacology, 7,* 444-447.

Cohen, L. M., Collins, F. L., Jr., Britt, D. M. (1997). The effect of chewing gum on tobacco withdrawal. *Addictive Behaviors, 22,* 769-773.

Cohen, L. M., Collins, F. L., Jr., Weaver, C. C., & VanderVeen, J. (2007). *The effect of chewing gum on withdrawal symptoms and mood in nicotine-deprived smokers*. Manuscript in preparation.

Collins, F. L., Jr., Sorocco, K. H., Haala, K. R., Miller, B. I., & Lovallo, W. R. (2003). Stress and health. In L. M. Cohen, D. E. McChargue, & F. L. Collins, Jr. (Eds.), *The health psychology handbook: Practical issues for the behavioral medicine specialist* (pp. 169-186). Thousand Oaks, CA: Sage.

Crawford, M. H., Bernstein, S. J., Deedwania, P. C., DiMarco, J. P., Ferrick, K. J.,

Garson, A., Jr., et al. (1999). ACC/AHA guidelines of ambulatory electrocardiography: A report of the American College of Cardiology / American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology, 34,* 912-948.

Demazieres, A., Luthringer, R., Coppel, E., Gilles, C., Fleury, C., Roegel, J. C. et al. (2006). Ability of a new oral nicotine substitute to reduce smoking urge in moderate smokers. *Addictive Behaviors, 31,* 537-543.

Ekman, P., & Friesen, W. V. (1976). Measuring facial movement. *Environmental Psychology and Non-verbal Behavior, 1,* 56-75.

Ekman, P., Levenson, R. W., & Friesen, W. V. (1983). Autonomic nervous system activity distinguishes among emotions. *Science, 221,* 1208-1210.

Elsenbruch, S., Harnish, M. J., & Orr, W. C. (1999). Heart rate variability during waking and sleeping cycles in healthy males and females. *Journal of Sleep Research and Sleep Medicine, 22,* 1067-1071.

Fagerstrom, K. O. (1978). Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. *Addictive Behaviors, 3,* 235-241.

Fagerstrom, K. O., Schneider, N. G., & Lunell, E. (1993). Effectiveness of nicotine patch and nicotine gum as individual versus combined treatments for tobacco withdrawal symptoms. *Psychopharmacology, 111,* 271-277.

Fiore, M. C., Bailey, W. C., Cohen, S. J., Dorfman, S. F., Goldstein, M.G., Gritz, E. R., et al. (2000). *Treating Tobacco Use and Dependence.* Clinical Practice Guideline. Rockville, MD: U.S. Department of Health andHuman Services. Public Health Service.

Friedman, B. H. & Thayer, J. F. (1998). Autonomic balance revisited: Panic anxiety and heart rate variability. *Journal of Psychosomatic Research, 44,* 133-151.

Gianaros, P. J., Salomon, K., Zhou, F., Owens, J. F., Edmundowicz, D., Kuller, L. H., et al. (2005). A greater reduction in heart rate variability to a psychological stressor is associated with subclinical coronary and aortic calcification in post-menopausal women. *Psychosomatic Medicine, 67,* 553-560.

Goldstein, M. G. (2003). Pharmacotherapy for smoking cessation. In D. B. Abrams, R. Niaura, R. A. Brown, K. M. Emmons, M. G. Goldstein, & P. M. Monti (Eds.), *The tobacco dependence treatment handbook: A guide to best practices* (pp. 230-248). New York: Guilford.

Grossman, P. (1992). Respiratory and cardiac rhythms as windows to central and autonomic biobehavioral regulation: Selection of window frames, keeping the panes clean and viewing the neural topography. *Biological Psychology, 34,* 131-161.

Grossman, P., Stemmler, G., & Meinhardt, E. (1990). Paced respiratory sinus arrhythmia as an index of cardiac parasympathetic tone during varying behavioral tasks. *Psychophysiology, 27,* 404-416.

Hughes, J. R. (2006). Clinical significance of tobacco withdrawal. *Nicotine and Tobacco Research, 8,* 153-156.

Hughes, J. R. (1992). Tobacco withdrawal in self-quitters. *Journal of Counseling and Clinical Psychology, 60,* 689-697.

Hymowitz, N. (2005). Tobacco. In R. J. Frances, S. I. Miller, & A. H. Mack (Eds.), *Clinical Textbook of Addictive Disorders* (3rd ed.). New York: Guilford.

Ingjaldsson, J. T., Laberg, J. C., & Thayer, J. F. (2003). Reduced heart rate variability in chronic alcohol abuse: Relationship with negative mood, chronic thought suppression, and compulsive drinking. *Biological Psychiatry, 54,* 1427-1436.

Kleiger, R. E., Stein, P. K., Bosner, M. S., & Rottman, J. N. (1992). Time domain measurements of heart rate variability. *Cardiology Clinics, 10,* 487-498.

Katona, P. G. & Jih, F. (1975). Respitory sinus arrhythmia: Noninvasive measure of parasympathetic cardiac control. *Journal of Applied Physiology, 39,* 801-805.

Kawachi, I. (1997). Heart rate variability. Retrieved June 6, 2007, from the Research Network on Socioeconomic Status and Health. Web site: http://www.macses.ucsf.edu/Research/Allostatic/notebook/heart.rate.html.

Kleiger, R. E., Miller, J. P., Bigger, J. T., Jr., & Moss, A. J. (1987). Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *American Journal of Cardiology, 59,* 256-262.

Kobayashi, H, Ishibashi, I., & Noguchi, H. (1999). Heart rate variability: An index for monitoring and analyzing human autonomic activities. *Applied Human Science, 18,* 53-59.

Kornitzer, M., Bousten, M., Dramaix, M., Thijs, J., & Gustavsson, G. (1995). Combined use of the nicotine patch and gum in smoking cessation: A placebo controlled clinical trial. *Preventive Medicine, 24,* 41-47.

Landén, M., Wennerblom, B., Tygesen, H., Modigh, K., Sorvik, K., Ysander, C., et al. (2004). Heart rate variability in premenstrual dysphoric disorder. *Psychoneuroendocrinology, 29,* 733-740.

Lane, J. D., Adcock, A., & Burnett, R. E. (1992). Respiratory sinus arrhythmia and

cardiovascular responses to stress. *Psychophysiology*, *29*, 461-470.

Lovallo, W. R. (2005). *Stress and health: Biological and psychological interactions*. Thousand Oaks, CA: Sage.

Malik, M., Bigger, J. T., Camm, A. J., Kleiger, R. E., Malliani, A., Moss, J., et al. (1996). Heart rate variability: Standards of measurement, physiological, interpretation, and clinical use. *European Heart Journal, 17*, 354-381.

Miller, W. R., & Rollnick, S. (2002). *Motivational interviewing: Preparing people for change*. New York: Guilford.

Niskanen, J. P., Tarvainen, M. P., Ranta-aho, P. O., & Karjalainen, P. A. (2002). Software for advanced HRV analysis. *Computer Methods and Programs in Biomedicine, 76*(1), 73-81.

Pomeranz, B., MacCaulay, R. J. B., Caudill, M. A., Kutz, I., Adam, D., Gordon, D., et al. (1985). Assessment of autonomic function in humans by heart rate spectral analysis. *American Journal of Physiology, 17*, 151-153.

Porges, S. W. (1992). Vagal tone: A physiologic marker of stress vulnerability. *Pediatrics*, *90*, 498-504.

Ragan, I., Naga Venkatesha Murty, P. J., Ramakrishnan, A. G., Gangadhar, B. N., & Janakiramaiah, N. (1998). Heart rate variability as an index of cue reactivity in alcoholics. *Biological Psychiatry, 43*, 544-546.

Shadel, W. G. & Niaura, R. (2003). Brief behavioral treatment. In D. B. Abrams, R. Niaura, R. A. Brown, K. M. Emmons, M. G. Goldstein, & P. M. Monti (Eds.), *The tobacco dependence treatment handbook: A guide to best practices* (pp. 101-117). New York: Guilford.

Shiffman, S., Ferguson, S. G., Gwaltney, C. J., Balabanis, M. H., & Shadel, W. G. (2006). Reduction of abstinence-induced withdrawal and craving using high-dose nicotine replacement therapy. *Psychopharmacology, 184,* 637-644.

Shiffman, S., Shadel, W. G., Niaura, R. S., Khayrallah, M. A., Jorenby, D. E., Ryan, C. F., et al. (2003). Efficacy of acute administration of nicotine gum in relief of cue-provoked cigarette craving. *Psychopharmacology, 166,* 343-350.

Sweeney, C. T., Fant, R. V., Fagerstrom, K. O., McGovern, J. F., & Henningfield, J. E. (2001). Combination nicotine replacement therapy for smoking cessation: Rationale, efficacy, tolerability. *CNS Drugs, 15*, 453-467.

Tarvainen, M. P. & Niskanen, J. P. (2005). Kubios HRV analysis version 2.0 beta: User's guide. Retrieved October 12, 2005, from University of Kuopio, Biosignal Analysis and Medical Imaging Group Web site: http://venda.uku.fi/research/biosignal

Thayer, J. F., Friedman, B. H., & Borkovec, T. D. (1996). Autonomic characteristics of generalized anxiety disorder and worry. *Biological Psychiatry, 39,* 255-266.

Venter, A. & Maxwell, S. E. (1999). Maximizing power in randomized designs when N is small. In R. H. Hoyle (Ed.), *Statistical strategies for small sample research* (pp. 33-57). Thousand Oaks, CA: Sage.

Wang, L., Huang, P., & Wang, Q. (2001). The effect of stress on function of cardiac autonomic nerve in artillery testing personnel. *Chinese Mental Health Journal, 15*, 297-298.

Zeskind, P. S. & Gingras, J. L. (2006). Maternal cigarette-smoking during pregnancy disrupts rhythms in fetal heart rate. *Journal of Pediatric Psychology, 31*(1), 5-14.

APPENDIX A

Table 1

HF HRV Means and Standard Deviations

	Baseline		24 hour		48 hour	
Condition	*M*	*SD*	*M*	*SD*	*M*	*SD*
No Gum	.275	.056	.264	.043	.277	.057
Gum 1	.264	.065	.273	.061	.261	.064
Gum 2	.261	.068	.282	.058	.258	.062
Gum 3	.270	.067	.247	.062	.245	.045
Combined Gum	.265	.067	.267	.060	.255	.057

Note. HF HRV data are presented in Hz.

Table 2

RMSSD Means and Standard Deviations

	Baseline		24 hour		48 Hour	
Condition	*M*	*SD*	*M*	*SD*	*M*	*SD*
No Gum	27.05	16.865	46.01	23.58	44.94	27.13
Gum 1	25.30	17.432	57.69	32.48	47.85	24.89
Gum 2	29.04	21.397	45.05	22.82	42.52	23.40
Gum 3	29.88	24.65	44.34	30.37	50.76	31.86
Combined Gum	28.07	21.15	49.03	28.56	47.03	26.72

Note. RMSSD data is presented in ms.

APPENDIX B

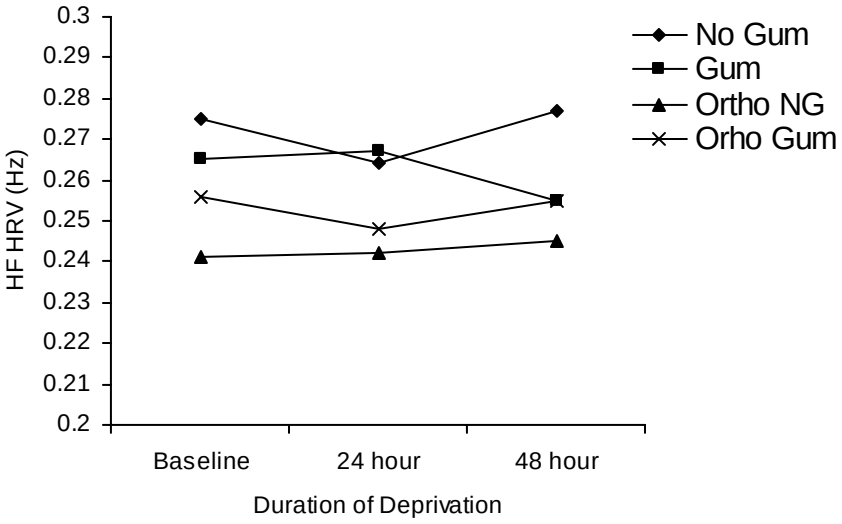

Figure 1. HF HRV observed means for the resting heart rate phase and orthostatic challenge. Gum conditions have been collapsed to more accurately represent the conducted analysis.

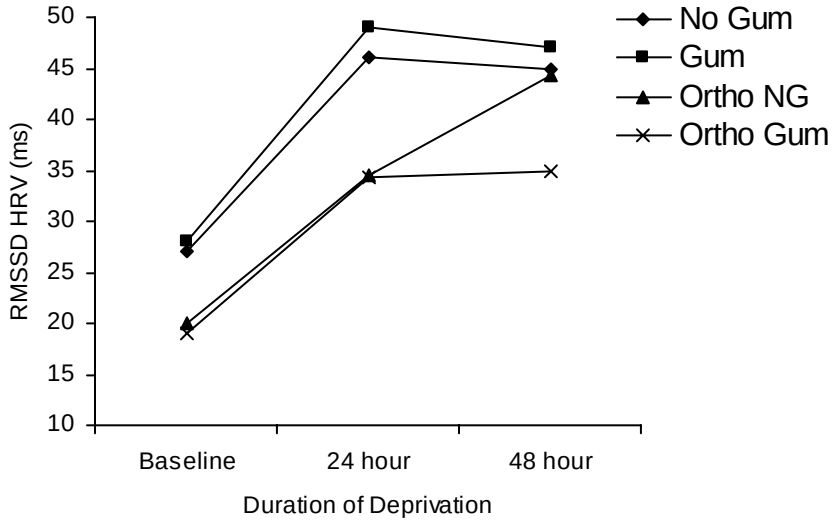

Figure 2. RMSSD HRV observed means for the resting heart rate phase and orthostatic challenge. Gum conditions have been collapsed to more accurately represent the conducted analysis.

APPENDIX C

Oklahoma State University Institutional Review Board

Date:	Wednesday, March 29, 2006
IRB Application No	AS0681
Proposal Title:	The Effects of Chewing Gum Flavor on Nicotine Withdrawal
Reviewed and Processed as:	Expedited

Status Recommended by Reviewer(s): Approved Protocol Expires: 3/28/2007

Principal Investigator(s

Frank L Collins
215 N Murray
Stillwater, OK 74078

The IRB application referenced above has been approved. It is the judgment of the reviewers that the rights and welfare of individuals who may be asked to participate in this study will be respected, and that the research will be conducted in a manner consistent with the IRB requirements as outlined in section 45 CFR 46.

☒ The final versions of any printed recruitment, consent and assent documents bearing the IRB approval stamp are attached to this letter. These are the versions that must be used during the study.

As Principal Investigator, it is your responsibility to do the following:

1. Conduct this study exactly as it has been approved. Any modifications to the research protocol must be submitted with the appropriate signatures for IRB approval.
2. Submit a request for continuation if the study extends beyond the approval period of one calendar year. This continuation must receive IRB review and approval before the research can continue.
3. Report any adverse events to the IRB Chair promptly. Adverse events are those which are unanticipated and impact the subjects during the course of this research; and
4. Notify the IRB office in writing when your research project is complete.

Please note that approved protocols are subject to monitoring by the IRB and that the IRB office has the authority to inspect research records associated with this protocol at any time. If you have questions about the IRB procedures or need any assistance from the Board, please contact Beth McTernan in 415 Whitehurst (phone: 405-744-5700, beth.mcternan@okstate.edu).

Sincerely,

Sue C. Jacobs, Chair
Institutional Review Board

VITA

Cameron C. Weaver, M.A.

Candidate for the Degree of

Master of Science

Thesis: THE EFFECT OF CONFECTIONARY CHEWING GUM ON PARASYMPATHEITC NERVOUS SYSTEM ACTIVITY

Major Field: Clinical Psychology

Biographical:

Education: Completed a Bachelor of the Arts in Psychology from Luther College in Decorah, IA in May, 2003. Completed a Master of the Arts in Clinical Psychology from Minnesota State University, Mankato in Mankato, MN in July, 2005.Completed the requirements for the Master of Science or Arts in Clinical Psychology at Oklahoma State University, Stillwater, Oklahoma in December, 2007.

Experience: Worked as a Behavioral Specialist at Mercy Medical Center in Cedar Rapids, IA from 2001 to 2003. Worked as a Clinical Psychology practicum student in the Anxiety Disorders Clinic at Mayo Clinic in Rochester, MN during the summer of 2004. Currently work as a Psychological Associate in the Psychological Services Center at Oklahoma State University and as a Behavioral Health Intern at the Indian Health Care Resource Center in Tulsa, OK.

Professional Memberships: Student member of the Association for Behavioral and Cognitive Therapy (ABCT) 2004 to present. Student member of the American Psychological Association (APA) 2007 to present.

Name: Cameron C. Weaver, M.A. Date of Degree: December, 2007

Institution: Oklahoma State University Location: Stillwater, Oklahoma

Title of Study: THE EFFECT OF CONFECTIONARY CHEWING GUM ON PARASYMPATHETIC NERVOUS SYSTEM ACTIVITY

Pages in Study: 44 Candidate for the Degree of Master of Science

Major Field: Clinical Psychology

Scope and Method of Study: Recent research has suggested that confectionary chewing gum is effective in reducing withdrawal symptoms in nicotine deprived smokers. However, no research has examined the mechanism by which chewing gum has an effect. It is possible that increased parasympathetic activity may be associated with chewing gum during deprivation. One method of measuring parasympathetic control is through heart rate variability (HRV). The aim of the present study is to determine if chewing gum during deprivation leads to increased HRV. Forty-one smokers were assessed at 24 and 48 hours deprivation over four weeks during which time they received four distinct conditions: 3 gum conditions and 1 no gum condition. It was hypothesized that participants would experience greater HRV during the gum conditions than the no gum condition.

Findings and Conclusions: There were no significant differences in the variability of HRV between the no gum and gum conditions. However, the average variability in HRV is larger during the gum conditions. This suggests that, although non-significant, chewing confectionary gum may produce greater parasympathetic control as indicated by more variability with RR intervals. Although there were no significant findings, the results are encouraging; however, further research with more participants is needed.

ADVISER'S APPROVAL: Frank L. Collins, Jr.