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ORIGINAL INVESTIGATION

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Efficacy of acute administration of nicotine gum in relief of cue-provoked cigarette craving

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Abstract *Rationale:* Acute cravings, often provoked by exposure to smoking cues, appear to be important triggers for smoking relapse. Relief of acute craving may therefore be an important step in preventing relapse. *Objectives:* This study was undertaken to assess the effectiveness of nicotine gum in relieving acute craving. *Methods:* A multi-center, randomized, placebo-controlled study was conducted with smokers (n=296) who quit by using either active or inactive gum for 3 days. On their third day of abstinence, smokers participated in a laboratory session in which they were exposed to a provocative smoking cue, chewed active or inactive gum, and then rated their craving at 5-min intervals for 35 min. *Results:* Craving initially decreased in both groups. After 15 min, however, the smokers using active nicotine gum experienced significantly greater craving reductions. *Conclusions:* These results suggest that nicotine gum can effectively reduce acute craving following exposure to smoking cues.

Keywords Nicotine replacement · Smoking cessation · Craving · Cue reactivity · Nicotine gum

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Introduction

Craving is an important clinical challenge for those attempting to quit smoking (American Psychiatric Association 1995; Pickens and Johanson 1992). Following a quit attempt, (ex-) smokers report moderate levels of craving throughout the day (Shiffman et al. 1997), and those with more intense cravings are more likely to relapse (Killen and Fortman 1997; Shiffman et al. 1997). Superimposed against this background of more-or-less steady craving, smokers also experience episodic increases in craving (Shiffman et al. 1996, 1997), which can result in relapse (Curry and Marlatt 1985; Marlatt and Gordon 1985; Shiffman et al. 1996). These acute craving episodes, 'temptations' (Shiffman 1982a, Shiffman et al. 1996), or 'high-risk situations' (Marlatt and Gordon 1985) can be provoked by exposure to smoking-related cues, such as smoking paraphernalia, smoking itself, or affective disturbances (Shiffman 1982a; Baker et al. 1987; Bliss et al. 1989; Shiffman et al. 1996). Evidence suggests that temptation episodes can result in relapse unless coping is implemented to deal with those episodes (Shiffman 1982a; Shiffman et al. 1996; O'Connell et al.

1998). Clearly, then, it is important to identify effective interventions that help smokers to manage provoked cravings.

Nicotine replacement therapy (NRT), a well-validated treatment for smoking cessation, typically doubles quit rates relative to placebo (Fiore et al. 2000). NRT is designed to temporarily replace some of the nicotine that is lost and craved after smokers quit smoking (Jarvik and Henningfield 1993). Indeed, NRT has demonstrated consistent efficacy in reducing average craving levels (Transdermal Nicotine Study Group 1991; Hughes et al. 1991; though see West and Shiffman 2001). However, the effect of NRT on craving has typically been studied by examining average craving, and NRT's ability to reduce tonic, background, craving levels is well established. However, the effect of NRT on acute craving episodes is not well documented.

Conceptually, different forms of NRT are expected to have different effects on craving. Transdermal nicotine patches reach peak plasma nicotine concentrations slowly over 4–6 h (Jarvik and Schneider 1992; Fant et al. 1999), providing the user with a relatively continuous infusion of nicotine while the patch is worn (Srivastava et al. 1991). This pharmacokinetic profile is theoretically suited to address background levels of craving and has in fact been shown to do so (Transdermal Nicotine Study Group 1991; Shiffman et al. 2000). However, a recent study (Tiffany et al. 2000) found that active patch was no better than placebo at blunting stimulus-provoked craving.

While nicotine patches provide steady-state nicotine infusion, other forms of NRT can provide acute doses of nicotine. When used at regular intervals, nicotine gum, like nicotine patch, can maintain relatively steady blood nicotine concentrations (Goldstein et al. 1989; Jarvik and Henningfield 1993; Fant et al. 1999). However, the ability to administer gum acutely also allows the user to achieve an acute increase in nicotine levels following voluntary self-administration (i.e., ad lib use; Goldstein et al. 1989). After a piece of gum is used, blood nicotine levels begin to rise, reaching levels of approximately 6 ng/ml after 10 min (for 4 mg gum), and peak levels within 30 min (Benowitz et al. 1988). Nicotine nasal spray yields faster rises in blood nicotine levels, yielding peak blood levels within 5–10 min (Fagerström 2000). Thus, these products may be useful as "rescue medication" to relieve acute, provoked craving (Fagerström et al. 1993).

Hurt and colleagues (1998) tested the effects of nicotine gum and nasal spray on rapid relief of craving and reported that spray produced acute effects, while gum did not. However, this study may have lacked adequate power to detect the effects of gum. More importantly, the study did not specifically test craving relief under conditions of acute exacerbations of craving or temptation, but rather tested smokers as they rested on a research ward devoid of cues for smoking and craving. Laboratory paradigms have been developed to model the effect of naturally occurring temptations and craving episodes (Abrams et al. 1988; Niaura et al. 1992, 1998; Sayette and Hufford 1994; Carter and Tiffany 1999), and these may allow testing of the effect of acute NRT on craving episodes.

The purpose of this study was to assess the effect of nicotine gum on relief of craving following exposure to a provocative craving cue. We used a cue exposure procedure to provoke craving among smokers (Sayette and Hufford 1994; Carter and Tiffany 1999) who were randomized to use either active nicotine gum or an inert control gum following the craving provocation. We hypothesized that use of nicotine gum would reduce craving after approximately 15 min, with the effect following the time course of the product's pharmacokinetics.

Materials and methods

Participants

A total of 296 participants from four study sites (two academic sites and two commercial clinical research organization sites) were recruited through advertisements in local media to participate in a smoking cessation program. Participants were recruited into one of two groups based on their reported number of cigarettes smoked per day: light smokers smoking 11–24 cigarettes per day (n=178) and heavy smokers smoking more than 24 cigarettes per day (n=118)[1]. These correspond to the U.S. indications for use of 2 mg and 4 mg Nicorette gum. To qualify for the study, participants had to be 18–65 years of age, be motivated to quit smoking [i.e., score above 70 on a 100-point scale that ranged from 0 (not at all motivated) to 100 (extremely motivated)], and weigh at least 100 pounds. Participants were excluded if they had a history of or current allergy to adhesives, severe skin disease, or frequent skin rashes[2]; had abused drugs or alcohol within the last 3 months; had a history of severe mental illness; had lung cancer or unstable cardiovascular disease (e.g., unstable angina, severe congestive heart failure, or uncontrolled hypertension); or had used supplemental oxygen. Participants who completed the study were compensated with a free course of nicotine gum treatment (i.e., a 3-month supply) and US $100. This research was approved by appropriate ethics committees, and all subjects gave informed consent prior to participating in the study.

Procedures

Pre-treatment

Study participants first completed an assessment of their smoking history, quitting history, and craving for cigarettes (described below), and provided an expired air carbon monoxide (CO) sample. Participants were then stratified into two groups by their smoking rate. Within each of these two strata, participants were randomly assigned to receive either Nicorette gum (4 mg for heavy smokers; 2 mg for light smokers; in the original flavor), or inactive (i.e., control) gum. The inactive gum was not an identical placebo preparation of nicotine gum, but a sugarless confectionery gum that resembled the nicotine gum in size and shape and was unlikely to be familiar to participants. The inactive gum had a very strong taste and long-lasting tingle, which corresponded closely to the taste characteristics and sensations of nicotine gum. All medications were removed from their packaging and placed in sealed

[1] Light smokers were over-sampled on the expectation that the 2 mg gum would show weaker effects and require a larger sample

[2] The full study design also involved other subjects who were randomized to nicotine patches; these comparisons are not reported here

plastic bags along with re-written package insert instructions. Both the nicotine and inactive gums were re-packaged into identical opaque containers prior to being placed in the sealed plastic bags. Participants were instructed to use their assigned gum following Food and Drug Administration (FDA) guidelines for use of Nicorette (i.e., every 1–2 h, with a maximum of 24 pieces per day) and provided with enough medication for 2 days. They were advised to stop smoking on day 1 and were given written self-help cessation materials [based on *Freedom from Smoking* (National Cancer Institute, 1993; Agency for Health Care Policy and Research, 2000), but with reference to NRT removed]. No other pharmacological or behavioral treatment was provided, and subjects stayed on their assigned treatment (active or inactive gum) for the entire study, including both the quitting phase (days 1–3) and the laboratory craving test phase (day 3). Following enrollment, baseline assessment, and randomization, the procedures were as follows.

Day 1. Participants were instructed to stop smoking on this day and to begin using their assigned study medication. They did not visit the study center on this day.

Day 2. Participants returned to the study center for a treatment adherence check (i.e., number of cigarettes smoked, expired air CO measure), to answer questions about their assigned study medication, and to complete practice assessments of their craving for cigarettes. Any participant who reported smoking five cigarettes per day or more, had a CO value >15 ppm, or withdrew consent was discontinued from the study at this time. Participants who continued in the study were provided with their assigned study medication for day 3.

Day 3. On day 3 post-quit, subjects participated in the cue exposure manipulation.[3] Within each treatment, participants were randomly assigned to be tested in the morning or in the evening. Prior to their day-3 visit, participants were instructed to abstain from alcohol for the entire day and to abstain from caffeine or food for 60 min prior to their visit. Participants were also directed to avoid chewing their assigned gum within 90 min of the day-3 session (to conform to U.S. labeling for Nicorette, which suggests chewing one piece every 1–2 h). Individuals who reported smoking any cigarettes and/or had CO levels >10 ppm on day 3 were discontinued from further participation.

Cue exposure manipulation

Participants were seated in a comfortable chair in a well-lit, temperature-controlled, sound-attenuated room. Participants began the session by completing a baseline craving questionnaire, described below. After 5 min of adaptation, the cue-exposure manipulation was begun (Abrams et al. 1988; Sayette and Hufford 1994; Niaura et al. 1998). Subjects were instructed to lift up an opaque bowl, under which had been placed an unopened pack of their favored brand of cigarette, two lighters (one as back-up), and an ashtray. They were then instructed to: (1) unwrap and open their pack of cigarettes; (2) remove one cigarette; (3) hold the cigarette in their hand and light it without placing it in their mouth; and (4) hold the lit cigarette directly in front of them without smoking it. These procedures were standardized and designed to take 30 s. Participants were instructed to look at the lit cigarette for 60 s and then extinguish it in the ashtray. Immediately after extinguishing the cigarette (i.e., approximately 2 min after the start of the provocation), participants completed a craving assessment (i.e., the 2-min post-cue assessment).

One minute after completing the post-cue craving assessment, which fell 2 min after the beginning of the cue exposure manipulation, participants were instructed to start chewing a piece of gum for 30 min. (Prior to the actual start of the testing session, participants rinsed their mouths with tap water in order to retain approximately equivalent oral pH levels). Subsequently, participants provided craving ratings at 5-min intervals for 35 min (5, 10, 15, 20, 25, 30, and 35 min later). To standardize procedures, all instructions were delivered via audiotape, and performance across all sites was monitored for quality control by two experienced investigators (W.G.S. and R.N.). Participants were unobtrusively monitored via closed-circuit video and audio equipment located outside of the laboratory room.

Craving assessment

On each assessment occasion, participants completed a craving scale consisting of five items (Tiffany and Drobes 1991; Kozlowski et al. 1996; Shiffman et al. 1996): "I have a desire for a cigarette right now"; "If it were possible I would smoke right now"; "All I want right now is a cigarette"; "I have an urge for a cigarette"; "I crave a cigarette right now". Responses to each item were rated using a scale that ranged from 0 (not at all) to 100 (the strongest feeling possible), and responses were averaged over the five items to produce a total craving score at each time point. Reliability (Cronbach's alpha) for the craving rating scale was ≥0.95 at all assessment time points. An additional assessment of craving was collected at some time points using a magnitude estimation procedure (Acri and Grunberg 1992). These data are not reported here, but the results mirror those obtained using the craving scale rating.

Data reduction and analytic plan

Baseline craving ratings at the beginning of the test session were compared between treatment groups. The effect of provocation was assessed as the difference in craving between baseline craving at the beginning of the test session (5 min before the provocation) and ratings at the end of the provocation (the post-cue assessment), adjusted for site and time of testing. The primary efficacy outcome was the change between the post-cue craving ratings and ratings made between minutes 15 and 30; this interval was specified a priori because pharmacokinetic data suggested that this is when nicotine gum reaches peak plasma nicotine levels (Benowitz et al. 1988). The four craving ratings during this period (taken at 5-min intervals) were averaged and contrasted with the ratings obtained immediately following the provocative cue, using repeated-measures ANCOVA. Additionally, we examined trends in craving across the assessment interval, using repeated-measures ANCOVA to compare the two groups, while controlling for baseline craving (linear and quadratic effects).

Study center and time of testing had no effect on the outcomes, and they are not discussed further, but they were retained in analyses as covariates. Analyses were virtually identical for light and heavy smokers, so the analyses reported collapse across these groups, and smoking rate group was entered as a covariate in all analyses; heavy and light smokers were weighted to be equally represented in the analyses.

Results

Subject attrition

Most (82.9%) participants completed the study. Attrition rates did not differ by condition (control 80.4%; active 85.5%; χ^2=1.65; p=0.20) or by study center (χ^2=0.75; p=0.86). Subjects who did not complete the study appeared to be more nicotine dependent than completers:

[3] This timing was selected because nicotine patches achieve steady state after 3 days of use; however, the results for the separate nicotine patch groups are not reported here

Table 1 Demographic and baseline characteristics of participants by treatment and smoking groups

Item	Heavy smoking group		Light smoking group		All participants (*n*=296)
	Active gum (*n*=60)	Control gum (*n*=58)	Active gum (*n*=88)	Control gum (*n*=90)	
Demographics					
Female (%)	66.7	56.9	50.0	62.2	58.4
Minority (%)	30.0	32.8	31.8	32.2	31.8
Age (years)	40.2 (9.4)	42.9 (10.9)	37.6 (11.2)	38.1 (12.5)	39.3 (11.3)
Weight (kg)	75.8 (15.6)	77.2 (17.7)	74.3 (15.6)	74.2 (15.9)	75.1 (16.1)
Smoking measures					
Cigarettes per day[a]	30.8 (5.4)	31.0 (5.3)	18.1 (2.9)	17.7 (3.6)	23.1 (7.6)
Baseline CO (ppm)[a]	30.1 (12.8)	27.7 (11.4)	23.5 (10.3)	23.6 (10.4)	25.7 (11.4)
Years of smoking	25.1 (10.3)	27.8 (11.6)	22.3 (11.3)	22.4 (11.4)	24.0 (11.3)
Fagerström score[a]	7.9 (1.6)	8.2 (1.7)	6.1 (2.0)	6.1 (1.9)	6.9 (2.1)

Entries are percentages or means with associated standard deviation
Comparative analyses adjusted for site
[a] Light and heavy smokers differed significantly, per group assignment

non-completers smoked more cigarettes per day at baseline ($F_{1,352}$=6.48, P=0.01), had higher baseline CO values ($F_{1,350}$=6.41, P=0.01), and higher Fagerström Tolerance Questionnaire (FTQ) scores ($F_{1,352}$=16.72, P<0.001). Additionally, all 11 participants who dropped out between visits 2 and 3 did so because they did not maintain abstinence. In other words, some of the more dependent smokers were non-completers because they could not maintain abstinence until day 3.

Demographics

Table 1 presents the demographic and smoking data by treatment and smoking groups for participants completing the study. Pairwise comparisons by treatment group and by smoking group were conducted. No notable differences were found among the treatment groups in demographics. As expected, light smokers reported fewer cigarettes per day, had lower CO concentrations, and lower FTQ scores (all P values <0.01).

Use of gum

Use of the assigned gum was assessed by self-report on day 2 and day 3, and by an inventory of returned medication. Subjects in the active condition reported using fewer pieces of gum than those in the control condition on day 1 and day 2 [active 9.0±4.8 (mean±SD); control 10.9±6.2; t_{294}=2.87, P=0.004 and active 9.3±5.3; control 10.8±6.4; t_{293}=2.11, P=0.04], respectively. Gum use on day 3 prior to the test session varied by testing time: for morning sessions, participants had reportedly used an average of 1.7±1.3 and 2.0±2.1 pieces of active and control gum, respectively (t_{157}=1.25, P=0.22). For evening sessions, use averaged 5.7±3.4 and 7.7±4.5 pieces, respectively (t_{134}=2.85, P=0.01).

Baseline and cue exposure effects

The two gum groups began the test session with similar levels of baseline craving [active 33.11±2.57 (mean±SE); control =36.95±2.59; $F_{1,290}$=1.15, P=0.28]. Craving rating change scores were calculated as the increase in craving from baseline to the first post-cue assessment. In both groups, craving increased significantly as a result of the provocation (P values <0.0001, adjusting for study center and time of testing). The cue-provoked increase in craving was similar between the treatment groups (mean±SE increase: active 9.04±1.59; control 7.53±1.60; $F_{1,290}$=0.46, P=0.50). Time of testing had no effect and did not interact with treatment.

Although there was an overall response to the provocative cue, not all participants reacted to the cue with increased craving. A little more than half of the participants (67 heavy smokers; 100 light smokers) showed increased cravings (defined as an increase of more than 1 point in average craving) and were classified as "reactors"[4]. As in the entire sample, both treatment groups (restricted to reactors) showed similar increases in craving [active 21.15±1.80 (mean±SE); control 18.88±1.85; $F_{1,161}$=0.81, P=0.37]. The percentage of reactors was similar across treatment groups (active 56.8%; control 56.1%; χ^2=0.01; P=0.91) and among light and heavy smokers (light 56.2%; heavy 56.8%; χ^2=0.01; P=0.92). Reactors and non-reactors had similar baseline (pre-cue) craving levels [reactors 35.1±2.4 (mean±SE); non-reactors 34.9±2.7; $F_{1,289}$<0.01, P=0.94, controlling for treatment group].

In subsequent analyses, we separated reactors and non-reactors in the analysis. The primary focus was on the 167 reactors whose craving was increased by cue

[4] The reactors differed from the non-reactors (after adjustment for study center) in that they were younger ($F_{1,291}$=15.68, P<0.001; reactors 37.15±0.85; non-reactors 42.14±0.96), had smoked fewer years ($F_{1,291}$=7.66, P=0.01; reactors 22.52±0.87; non-reactors 26.09±0.98), and had lower baseline CO measures ($F_{1,289}$=5.68, P=0.02; reactors 24.83±0.84; non-reactors 27.79±0.94)

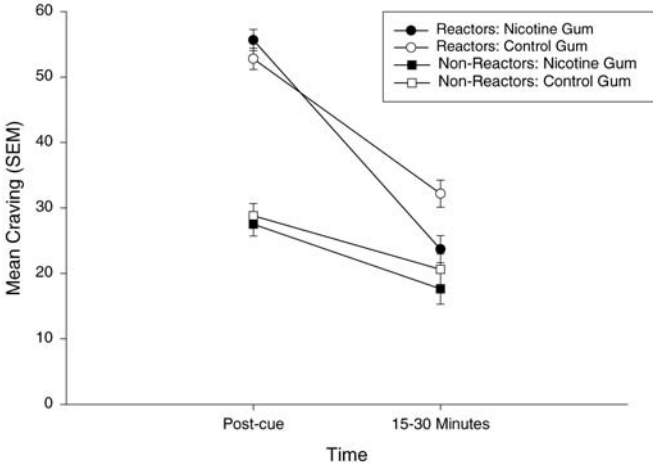

Fig. 1 Baseline-adjusted craving after cue exposure and during the subsequent designated treatment period (15–30 min after the provocation), by treatment condition, for subjects whose craving increased after cue exposure (reactors) and those who did not (non-reactors)

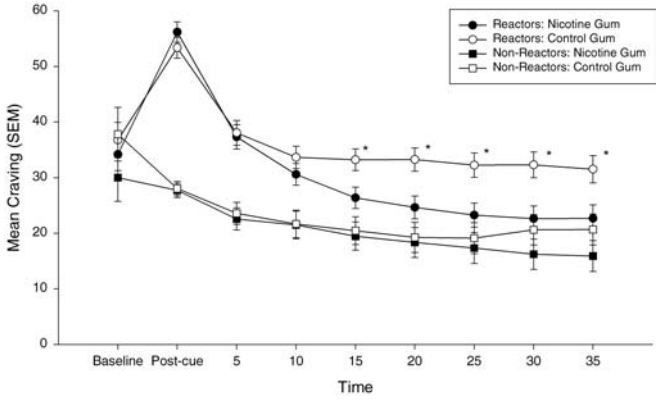

Fig. 2 Mean craving ratings for all post-cue craving assessments. Statistically significant differences between treatments at $P \leq 0.05$ are denoted with *. Shown for subjects whose craving increased after cue exposure (reactors) and those who did not (non-reactors). Unadjusted baseline craving values are presented; values thereafter are adjusted for baseline values. The analysis was based on baseline-adjusted values

exposure. The study aimed to assess the effect of interventions on cue-provoked craving; this can only be assessed (and is only clinically relevant) in those who indeed experienced provoked craving in the first place. However, we also present analyses contrasting reactors and non-reactors, as it is useful in interpreting the results observed among the reactors who did demonstrate cue-provoked craving.

Treatment effects

The effects of treatment were first evaluated by examining the change in craving from the post-cue assessment and the average craving reported between 15 min and 30 min after the provocation, as specified a priori based on pharmacokinetic considerations. A repeated-measures 2 (treatment condition) × 2 (reactors vs non-reactors) × 2 (time) ANCOVA, controlling for study center, smoking group, baseline craving (linear and quadratic), and testing time, evaluated the change in craving over time. Figure 1 presents the mean ratings of immediate post-cue craving and the average craving 15–30 min later, for reactor and non-reactor subsets. The analysis shows a three-way interaction between reactivity, treatment, and change ($F_{1,285}$=4.36, P=0.04). Analysis of the stratified effects indicates that, among the non-reactors, active and control gum result in equivalent change over time ($F_{1,285}$=0.23, P=0.63). In contrast, among the reactors, there is a significant treatment effect, such that use of active gum results in significantly greater reductions in craving ($F_{1,285}$=13.81, P<0.001), as hypothesized.

Figure 2 presents a more detailed picture of the craving data, showing reported craving through 35 min following the provocative cue exposure. We analyzed the time trends following cue exposure through a repeated-measures ANOVA with between-subject terms for treatment (active versus inactive) and reactivity (reactive versus not) and a within-subject term for time. An analysis of all subjects combined showed a treatment by time (linear and quadratic effects) interaction ($F_{2,287}$=5.65, P=0.004), indicating that, across all subjects, subjects on active gum showed more change over time. There was also a near-significant interaction of treatment × reactivity × time (linear+ quadratic effects; $F_{2,285}$=2.97, P=0.053). Given these trends, and the interaction observed above between reactivity and treatment effects, we further analyzed the effect of treatment on craving, focusing on linear trends in craving for reactive and non-reactive subjects. Among non-reactors, there were no treatment effects ($F_{1,120}$=2.02, P=0.16): craving dropped at the same rate for subjects using active and inactive gum. For reactive subjects, there was a significant treatment effect, such that craving dropped significantly faster among subjects using active gum ($F_{1,158}$=10.65, P=0.001). (Similar effects were observed for quadratic effects.)

To localize the effect of treatment with active gum, we examined the change in craving across time intervals. Across the first two 5-min intervals (0–5 min and 5–10 min), active and inactive gum yielded similar decreases: i.e., there were no treatment effects (0–5 min: $F_{1,158}$=1.75, P=0.19; and 5–10 min: $F_{1,158}$=1.18, P=0.28). However, between minute 10 and minute 15, subjects using active gum showed substantially and significantly steeper drops in craving ($F_{1,158}$=7.35, P=0.008). Thereafter, the two groups follow similar trajectories (i.e., no treatment by time interaction over minutes 15–35: linear effects: $F_{1,158}$=0.75, P=0.39; and linear and quadratic effects: $F_{2,158}$=1.11, P=0.33). Put another way: by 15 min, and at every time point thereafter, participants on active gum demonstrated significantly lower craving than those on control gum (15 min: $F_{1,158}$=6.66, P=0.011; 20 min: $F_{1,158}$=8.94, P=0.003; 25 min: $F_{1,158}$=8.80, P=0.004;

30 min: $F_{1,158}$=9.29, P=0.003; 35 min: $F_{1,158}$=6.88, P=0.010). Thus, among subjects who experienced provoked craving, at about the time that nicotine gum begins delivering substantial nicotine doses, active nicotine gum results in reductions in craving that are not accounted for by the act of chewing gum per se.

Gender effects

We tested gender differences in cue reactivity (change in craving following the cue exposure); there were none ($F_{1,288}$=1.96, P=0.16); nor were there differences in the proportion of males and females who were defined as "reactive" (i.e., showed any change: males 55.3%, females 57.2%, $\chi^2(1)$=0.11, P=0.74). We also tested whether gender interacted with the effect of active gum in reducing craving (post-exposure to the pre-defined treatment interval); there was no interaction ($F_{1,287}$=0.91, P=0.34).

Discussion

When trying to quit smoking, smokers frequently experience acute craving in response to smoking-related stimuli and triggers (Shiffman 1982a; Niaura et al. 1992, 1998; Shiffman et al. 1996), and these acute craving or temptation episodes are important antecedents and likely causes of relapse (Shiffman 1982b; Marlatt and Gordon 1985; O'Connell and Martin 1987; Shiffman et al. 1996). Thus, treatments that can be used as "rescue medication" to help alleviate acute craving may be an important tool in promoting successful smoking cessation.

The purpose of this study was to evaluate the efficacy of acute nicotine administration, via nicotine gum (Nicorette), on acute craving among smokers engaged in quitting. The study demonstrated that acute use of nicotine gum can relieve craving following provocation by smoking cues. Comparison of the effects seen with use of active nicotine-containing gum to those seen with inactive gum allowed the study to discriminate the behaviorally mediated effects of chewing gum, per se, versus the pharmacological effect of nicotine delivered by the active gum. Among smokers who reacted to the cue exposure with increased craving, even those using inactive gum showed a sharp drop in craving equal to that seen with nicotine gum over the first 5–10 min of chewing. This is consistent with research by Britt et al. (2001), which showed that confectionary gum can produce some craving reduction[5]. However, whereas the craving of smokers chewing inactive gum then leveled off, smokers using active nicotine gum showed continued decreases in craving, diverging significantly from the control gum after 15 min, just when nicotine gum begins to yield significant blood levels of nicotine (Jarvik and Schneider 1992). This demonstrates that nicotine gum can relieve craving and that the effect is pharmacological rather than purely behavioral. This in turn suggests that nicotine gum can be used to help smokers to reduce acute cravings and, by extension, to help smokers avert a slip or relapse. As suggested by Hurt and colleagues (1998), other acute forms of NRT, such as nicotine nasal spray, may also find use in this way.

The data establish that active gum relieved craving in these subjects following a provocative cue exposure. A question is whether one could say that the treatment relieved the craving that was provoked by the cue exposure. One challenge is that the observed effect of active gum occurred after subjects' craving had returned to "baseline" pre-cue values, which were reached after 5 min of chewing either gum. It could be argued that any subsequent reduction in craving should not be attributed to reduction in provoked craving. However, this argument assumes that a subject's baseline state is completely free from provoked craving. Even before the formal experimental cue exposure, subjects were placed in a cue-inducing environment: they were likely to be anxious, focused on thoughts about smoking, and experiencing considerable anticipation of the impending cue exposure. Thus, the measured "baseline" state is unlikely to represent a true "clean" state. Indeed, even before being exposed to the experimental cue, the reported craving intensity (34.5) of the subjects was already at more than one-third the span of the 0–100 point scale. Thus, the observed reduction in craving may still be attributed to reduction in induced craving.

The inclusion of a control group that was exposed to a non-provocative neutral cue would have been one way to address differential effects on provoked craving as opposed to craving in general, but our design did not include this control. However, contrasting subjects in this study who did and did not respond to the provocative cue provided a context for interpreting the effects observed among those who did react. Notably, a significant benefit for craving relief of chewing nicotine-containing gum was only seen among the subjects whose craving had initially increased with cue exposure. No reliable effect was seen among smokers who showed no cue-induced craving. Although the non-experimental comparison precludes the strongest inferences, this suggests that the active gum was reducing cue-induced craving. In any case, whatever the mechanism, the ability to reduce craving following a provocative cue exposure should have considerable clinical utility in preventing relapse.

The positive effect seen for nicotine gum in this study is at odds with the conclusions of Hurt and colleagues (1998), who reported that nicotine gum had no effect on craving. The present study differs from that of Hurt and colleagues in several key respects: both the use of a

[5] Contrast of these data to data from smokers in this study who had been randomized to nicotine patch (not reported in detail) provided additional evidence that this initial reduction in craving was due to the effect of chewing gum, and not just to the passage of time and decay of the provocation effect. Specifically, smokers who chewed the inactive gum experienced a steeper drop in craving during this time, relative to smokers wearing an active nicotine patch, suggesting a behavioral effect of chewing gum

larger sample and the use of a highly reliable multi-item craving assessment lent the current study greater sensitivity and statistical power. Our study examined smokers who were actually quitting and had quit and, thus, may have better modeled the clinical situation. Perhaps most importantly, whereas Hurt and colleagues studied the effects of gum in the context of steady-state craving observed without provocation in a relatively benign environment devoid of smoking cues, we studied the effects of gum after provoking craving with validated procedures meant to model real-world temptations. Indeed, when we examined data from subjects who were not effectively provoked, the effect of gum was blunted.

Two incidental findings are worth mentioning. First, although Perkins (1999) has suggested that women may be more responsive to smoking cues, we found no gender differences in cue reactivity in this experimental test. Perkins has also suggested that men are more sensitive to nicotine effects, but we found no evidence that gender moderated nicotine's acute effects on craving. Second, we observed that response to a smoking cue was weakest among heavy, long-time smokers. This is consistent with Herman's (1974) findings many years ago and suggests that, over time, conditioned cue effects come to be overridden by endogenous cues for long-time smokers.

Methodological limitations of this study should be noted. The study did not use an exactly matched placebo gum, though the confectionery gum used as a control did resemble active nicotine gum. About 17% of the subjects originally enrolled were lost before their craving could be assessed. These were heavier, more dependent smokers, and they dropped out primarily because they were unable to maintain abstinence. The study examined response to an analogue provocation in a laboratory setting. However, we drew upon long-standing work on laboratory cue-reactivity (Abrams et al. 1988; Niaura et al. 1992, 1998; Sayette and Hufford 1994) and used a standard provocation stimulus that has been validated in prior studies (Sayette and Hufford 1994). Our comparison of reactive and non-reactive subjects was based on observed individual differences in reactivity and is not a substitute for a no-cue control. Reactive and non-reactive subjects differed and may have differed further in unobserved ways. However, it was reassuring that reactive and non-reactive subjects had similar baseline craving levels, and that both had room to demonstrate subsequent reduction in craving, as evident in Fig. 2.

The study also featured several important strengths. This is the first study we know of that assessed cue reactivity in a clinical sample of smokers trying to quit. We used a well-validated controlled laboratory paradigm, which was carefully standardized across sites. The sample was large, and the craving assessments highly reliable, affording statistical power for group comparisons. The gum was used according to FDA directions.

The finding that nicotine gum is effective following provoked craving has implications for its clinical use. As smokers proceed through abstinence, the intensity of overall background cravings fades rather quickly (Shiffman et al. 1997). However, episodic cravings particularly those provoked by situational stimuli continue much longer (Shiffman 1982a; Shiffman et al. 1997). This suggests that nicotine gum could be used as rescue medication to deal with emergent acute cravings, even when background cravings have faded. Currently, approved instructions for nicotine gum in the U.S. call for use of the gum to stop after 3 months (most European jurisdictions allow for 6 months of use). Given that relapse risk and episodic cravings continue after 3 months time, it may be clinically useful for patients quitting smoking to occasionally use nicotine gum in an ad lib fashion after this time to combat episodic cravings. While the data demonstrated the efficacy of gum in relieving craving once it had been provoked, it is also possible that nicotine gum could be used effectively to prevent the onset of severe craving, by using it just before a predictable craving provocation (e.g., attending a party or a tense meeting). This application of nicotine gum should be tested. Finally, the data suggest the utility of a medication strategy that supplements steady-state medications such as nicotine patch or bupropion (Jorenby et al. 1995) with nicotine gum for acute dosing and relief of episodic craving. Indeed, combinations of patch and gum (Fagerström et al. 1993) and patch and spray (Blondal et al. 1999) have demonstrated incremental efficacy, in contrast to treatments that simply increased doses of nicotine, administered transdermally (Jorenby et al. 1995; Dale et al. 1995; Hughes et al. 1999). The specific effect of these combinations may be due to synergy between different strengths of each form: patch for steady-state nicotine delivery and reduction of background craving, and nicotine gum/spray for acute dosing and relief of episodic craving.

In summary, this study was the first to assess the effectiveness of nicotine gum for relief of craving following experimental induction of craving by smoking cues. The findings demonstrate that acute dosing with nicotine gum was more effective than inactive nicotine gum for relieving acute craving elicited by smoking cues. These findings suggest that reactive use of nicotine gum as a "rescue medication" may be effective to help smokers who have quit to manage acute craving, which may in turn prevent relapse.

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