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Pharmacology, Biochemistry and Behavior 72 (2002) 559–568

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

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Flavor improvement does not increase abuse liability of nicotine chewing gum

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Received 25 September 2001; received in revised form 3 December 2001; accepted 21 December 2001

Abstract

Because the taste of nicotine gum has impeded compliance with dosing recommendations, nicotine gum with improved taste (mint, orange) was developed and marketed. Prior to marketing, the Food and Drug Administration (FDA) required a rigorous abuse liability assessment to examine whether enhanced palatability of nicotine gum would increase its abuse liability. Subjective, physiological, and psychomotor effects of mint flavor and original nicotine gum were tested in adult smokers (22–55 years old); a group of younger subjects (18–21 years old) was also included to allow for assessment of abuse liability in young adults specifically. Amphetamine and confectionery gum served as positive controls for abuse liability and palatability. Subjects rated palatability of mint gum higher than original nicotine gum, but substantially lower than confectionery gum. Palatability decreased with increasing dose of nicotine. Neither original nor mint gum increased ratings of traditional abuse liability predictors [Good Effect, Like Effect, Morphine–Benzedrine Group (MBG) scales of Addiction Research Center Inventory (ARCI)], while amphetamine increased ratings of all these measures. Both flavors of nicotine gum decreased craving during 2 h of abstinence. These effects were more pronounced in the adult group and mint gum was more effective than original gum. Younger subjects reported fewer withdrawal symptoms and lower ratings for drug effects and flavor. Improved flavor of nicotine gum does not increase abuse liability, but may be associated with enhanced craving reduction.

Keywords: Nicotine gum; Abuse liability; Flavor; Craving; Nicotine

1. Introduction

Sixty-eight percent of the 47 million smokers in the United States indicate they are interested in quitting (Centers for Disease Control and Prevention, 1997). Nicotine replacement therapy (NRT) products (e.g., gum, patch, inhaler, and nasal spray) are marketed as smoking cessation aids and deliver nicotine through various routes of administration other than cigarette smoke inhalation, thereby reducing withdrawal symptoms in abstinent smokers. NRT products have proven efficacious; they approximately double long-term (6–12 months) quit rates when compared to placebo (e.g., Law and Tang, 1995; USDHHS, 2000).

When nicotine gum was developed in the 1970s, providing nicotine in a safe and effective manner while minimizing risk to children who might have inadvertent access to the gum was a key challenge (Ferno, 1977; Ferno et al., 1973; Jarvik and Henningfield, 1993). A peppery flavoring was added to reduce nicotine's unpleasant taste and burning sensation, thereby providing an acceptable formulation for persons motivated to quit smoking, yet not so pleasant as to be attractive to children and nonsmokers (Ferno, 1977; Ferno et al., 1973). That is, flavoring was chosen with the objective of providing a satisfactory medicine without fostering abuse of the product; the choice of flavor was effective in this regard (Nemeth-Coslett and Henningfield, 1986; West et al., 2000).

The gum's aversive taste is an important clinical issue; among smokers trying to quit who use nicotine gum as a smoking cessation aid, the major clinical problem is undermedication resulting from failure to use adequate levels per day (Rose, 1996; Henningfield and Stitzer, 1991; Fortmann

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0091-3057/02/$ – see front matter
PII: S0091-3057(02)00723-2

et al., 1988), and the taste of nicotine gum is an important impediment to compliance with recommended dosing regimens (Rose, 1996; Jarvik and Henningfield, 1993). The reputation of bad taste may also keep some smokers from trying the gum. Improved taste of nicotine gum therefore may increase both its efficacy and the number of smokers using it, and in response to consumer feedback the pharmaceutical industry has developed and marketed nicotine gums with more appealing flavors (e.g., mint, orange). Prior to the marketing of a nicotine-containing gum with enhanced palatability, concerns were raised about a potential increase in abuse potential. That is, with enhanced palatability, the product may appeal to gum-chewers in general, especially of a younger age, and thus lead to nicotine abuse/dependence in nonsmokers. In addition, the enhanced palatability may increase perception of positive nicotine effects, a potentially important interaction in light of the growing availability of nicotine replacement products and the current efforts of the pharmaceutical industry to develop oral nicotine replacement products in addition to the gum already marketed (e.g., sublingual tablet, Molander and Lunell, 2001). For these reasons, the U.S. Food and Drug Administration (FDA) required an abuse liability study of flavored nicotine gum as part of the approval process. Thus, the present study was designed to determine the abuse liability, subjective effect, and physiological response profile of a mint-flavored nicotine gum as compared to the original nicotine gum in adults (22–55 years old) and young adults (18–21 years old). Several doses of mint-flavored and original nicotine gum (0, 2, 4, and 8 mg) were compared to each other and amphetamine, a drug with known abuse liability. A commercial non-nicotine-containing mint gum was included to serve as a comparison for flavor ratings. In a broader perspective, the abuse liability study described here is a unique application of abuse liability testing, addressing the potential interaction between increased palatability of an oral drug vehicle and a drug's effects. This application is especially relevant in the context of the continuing efforts of the pharmaceutical industry to develop new nicotine delivery systems with improved appeal and palatability.

2. Methods

2.1. Subjects

Twenty-four subjects between 18 and 50 years old (12 in the 18–21-year-old group and 12 in the 22–50-year-old group) completed the study. Table 1 shows demographic information and smoking variables for both groups. The groups did not differ in any of the demographic characteristics displayed, with the exception of age. All subjects were non-treatment-seeking smokers; all smoked 15 or more cigarettes per day and had a baseline afternoon expired carbon monoxide level of 15 ppm or higher. All subjects were screened medically before participation in the study; exclusion criteria included significant medical or psychiatric illness, abnormal ECG, pregnancy, and drug abuse as assessed by self-report and urine analysis (enzyme-multiplied immunoassay technique, Quest Diagnostics, Baltimore, MD). This study was approved by the local Institutional Review Board and all subjects provided written informed consent prior to participation.

Table 1
Demographic characteristics (mean ± S.E.M.)

	Adults	Young adults	*P* value[a]
n	12	12	
Age	37.3 ± 2.5	18.9 ± 0.3	< .01
Female (%)	25	50	ns
Black (%)	58	25	ns
Cigarettes per day	22.6 ± 1.9	20.6 ± 1.2	ns
CO	26.6 ± 3.2	23.6 ± 2.9	ns
FTQ[b] score	7.5 ± 0.4	6.8 ± 0.6	ns

[a] Comparison between age groups.
[b] Fagerstrom Tolerance Questionnaire (Fagerstrom, 1978).

2.2. Study design

This was a randomized, double-blind, double-dummy, placebo-controlled, outpatient laboratory study using 12 conditions and a cross-over design. During 12 experimental sessions, subjects were exposed to each of the 12 different experimental conditions once (see under Experimental Conditions). Session order was determined by Latin-square. A practice session was scheduled before the experimental sessions and served to familiarize subjects with the study procedures. During the practice session, subjects received placebo capsules (lactose-loose filled) and a nonnicotine fruit-flavored chewing gum (Juicy Fruit, Wrigley). Data from this session were not included in the data analysis.

2.3. Experimental conditions

Table 2 shows the 12 different experimental conditions. Subjects received only one drug (nicotine or amphetamine or placebo) and one flavor gum in each session. The original flavor gum was included to enable us to compare the abuse liability of the mint flavor gum with that of the standard nicotine gum used for smoking cessation. The different doses of nicotine for both flavors of gum were included to allow for assessment of potential Dose×Flavor interactions. The selected dose range of nicotine gum (0–8 mg) has been shown to produce clear dose-related effects on subsequent smoking and subjective responses, without producing any unexpected adverse events (Nemeth-Coslett et al., 1987). The amphetamine conditions were included as a positive control condition, that is, to demonstrate sensitivity of the measures and design to indices of abuse liability. The dose of D-amphetamine (20 mg/70 kg) has been shown previously to significantly increase responses on measures of abuse liability, including subjective visual analog scale

Table 2
Experimental conditions

Session number[a]	Nicotine dose[b]	Amphetamine dose	Gum flavor	Smoking
Practice	na	placebo	confectionery fruit[c]	none
1	placebo	placebo	original	none
2	2 mg	placebo	original	none
3	4 mg	placebo	original	none
4	8 mg	placebo	original	none
5	placebo	placebo	mint	none
6	2 mg	placebo	mint	none
7	4 mg	placebo	mint	none
8	8 mg	placebo	mint	none
9	placebo	20 mg/70 kg	original	none
10	placebo	20 mg/70 kg	mint	none
11	na	placebo	confectionery mint[c]	none
12[d]	na	placebo	na	two cigarettes

[a] Order of sessions 1–12 was determined by Latin-square.
[b] In each session, two pieces of gum were chewed; combinations were 0/0, 0/2, 2/2, and 4/4 mg of nicotine for the two pieces of gum.
[c] Marketed gums were included for practice with the chewing procedure (Session 1) or palatability comparison (Session 11).
[d] Data from the cigarettes session will not be presented in this article; these data were excluded from the analysis.

(VAS) scores of drug liking, as well as the Morphine–Benzedrine Group (MBG) scale of the Addiction Research Center Inventory (ARCI), which measures drug-induced "euphoria" (e.g., Henningfield and Griffiths, 1981), and thus serves as an appropriate positive control condition. Active amphetamine was tested in combination with both flavors of gum to control for potential Drug Effect×Flavor interactions. The confectionery gum was included to allow for a comparison of the mint-flavored nicotine gum with that of a mint-flavored gum marketed and sold primarily for its taste. Finally, the cigarette smoking condition was included to allow for a comparison of abuse liability of mint gum and regular smoking. However, several subjects appeared to have interpreted questions about drug effects as pertaining to effects of the gum and capsules they consumed only, not of the cigarettes; data from this condition appeared inconsistent as a result and were therefore not used in any of the analyses.

2.4. Experimental sessions

Sessions lasted 3.5 h. Session starting times were separated by at least 24 h and were scheduled at approximately the same time each day for each subject. During each session, following a baseline period, subjects received two capsules containing D-amphetamine (0 or 20 mg/70 kg); time of capsule administration was determined to be time-point 0. Thirty minutes later, subjects smoked one cigarette to ensure standardization of time since last cigarette during the session. At 105 min, subjects chewed two pieces of gum (original flavor nicotine: placebo, 2, 4, and 8 mg; mint flavor nicotine: placebo, 2, 4, and 8 mg; or confectionery gum [Ice Breakers, Nabisco]) for 15 min or smoked two cigarettes for 15 min. Amphetamine and nicotine were administered double-blind; for obvious reasons, gum flavor was not.

The timing of the end of gum administration was chosen to coincide with the peak pharmacological effect of D-amphetamine (2 h after oral administration, Physician's Desk Reference, 1997).

Physiological data and subjective and performance measures were collected throughout the session. Subjective questionnaires and performance tasks were selected to assess abuse liability, gum palatability, drug effects, and tobacco withdrawal and craving.

2.5. Gum chewing procedure

The gum chewing procedure was standardized and identical to those used previously (e.g., Nemeth-Coslett et al., 1987) with one exception; duration of chewing was 15 min rather than 20. This time frame was chosen because previous research has shown 15 min of chewing to be optimal for compliance and nicotine delivery (Henningfield et al., 1990).

Subjects were instructed to chew every 3 s and they were prompted to do so by a computer-generated tone. The procedure was closely supervised by a research assistant to ensure compliance.

2.6. Dependent measures

2.6.1. Physiological measures

Physiological measures, including systolic and diastolic blood pressure and heart rate were monitored throughout the session starting at 70 min after capsule administration. These measures were collected every 3 min by an automatic physiologic monitoring device (Noninvasive Patient Monitor model 506, Criticare Systems, Waukesha, WI) that was interfaced with a Macintosh computer (Cupertino, CA).

2.6.2. Subjective questionnaires

Several subject-rated and performance measures were collected before and after drug administration. Subject-rated measures included VAS, a smoking withdrawal scale adapted from Shiffman and Jarvik (1976), the Tiffany–Drobes Questionnaire on Smoking Urges (QSU, Tiffany and Drobes, 1991), the short form of the ARCI (Martin et al., 1971), and a recently developed Behavioral Economics Interview (Bickel, personal communication). The Shiffman–Jarvik Withdrawal Scale, the QSU, and all VAS, except the Drug Effect Analog Scale and the Gum Scale, were administered at baseline (−15 min) and 90, 120, 150, and 180 min after capsule administration. The Gum Scale was administered only during gum chewing, at 110, 115, and 120 min. The Drug Effect Analog Scale was administered at 110, 115, 120, 150, and 180 min. The short form of the ARCI was administered at baseline and at 90, 120, and

180 min. The Behavioral Economics Interview was administered at 120 min only.

Four VAS items assessing cigarette craving were derived from Schuh and Stitzer (1995): "How pleasant would a cigarette be right now?," "How much of an urge or desire do you have to smoke right now?," "How much do you need to smoke right now, just for relief?," "How much do you want to smoke right now?" Seven VAS items representing nicotine effects ("heart racing," "nausea," "clammy skin," "dizzy," "lightheaded," "burning throat," and "tingling sensations") were presented. Six VAS items assessing drug effects were presented: "Do you feel any drug effect?," "How strong is the drug effect?," "Does the drug have any good effects?," "Does the drug have any bad effects?," "Do you like the drug effect?," "Do you dislike the drug effect?" Eleven items evaluating the gum were presented: "Do you like the gum's taste?," "Is the gum easy to chew?," "Does the gum taste good?," "Does the gum taste bad?," "Would you chew this gum just for its taste?," "Would you chew this gum just to get the drug effect?," "Does the gum have a strong taste?," "How sweet is the gum?," "How bitter is the gum?," "How much do you like the gum overall (taste plus drug effect)?," and "How much do you dislike the gum overall (taste plus drug effect)?" Ten VAS items assessing nicotine withdrawal were derived from Hughes and Hatsukami (1986): "urges to smoke," "irritable," "anxious," "difficulty concentrating," "restless," "hunger," "impatient," "craving a cigarette," "drowsiness," and "depression/feeling blue." VAS were presented on a computer screen as a 100-point horizontal line, anchored on the left side with *not at all* and on the right side with *extremely*. Subjects moved the 1-mm cursor along the line with a mouse and pressed the button when the cursor was at the appropriate point to indicate their response to the item presented.

Twenty-five items pertaining to smoking withdrawal were derived from Shiffman and Jarvik (1976) and presented as a seven-point scale with labels ranging from *very definitely* to *very definitely not*. The wording of the items was such that *very definitely* indicated a high level of dysphoria for half the items and a low level of dysphoria for the other half. The items were divided into five subscales: Craving, Psychological Discomfort, Physical Symptoms, Stimulation/Sedation, and Appetite. The QSU (Tiffany and Drobes, 1991) was presented as a seven-point Likert scale labeled at the extreme ends with *strongly agree* and *strongly disagree*. The items were divided into two subscales, one representing craving for the positive effects of the cigarette (Factor 1) and one representing anticipation of relief from withdrawal (Factor 2).

The short form of the ARCI consists of 49 true–false items that yield five subscales: MBG (sensitive to euphoric effects); Pentobarbital, Chlorpromazine, Alcohol Group (PCAG, sensitive to sedative effects); Lysergic Acid Diethylamide (LSD, sensitive to somatic and dysphoric changes); Benzedrine Group (BG), and Amphetamine (Amph) scales (sensitive to amphetamine effects) (Martin et al., 1971). The Behavioral Economics Interview was included in this study for initial validation. Both the instrument and the results will be described elsewhere.

2.6.3. Psychomotor performance assessment

The Digit Symbol Substitution Task (DSST) is used routinely in studies assessing drug effects to provide a measure of drug effects on psychomotor performance. The DSST was administered at baseline (−15 min) and 90, 120, 150, and 180 min after capsule administration. However, no significant drug effects were observed and data will not be reported.

2.6.4. Data analysis

Data were analyzed using ANOVA. Mint nicotine gum was first compared to the original nicotine gum, in these analyses only the nicotine gum conditions were included (total of eight). Thus, comparisons of palatability and abuse liability between the two flavors of gum included flavor (two levels: original and mint), dose (four levels: 0, 2, 4, and 8 mg), and time (number of levels dependent on number of timepoints) as within-subjects factors and age (two levels) as a between-subjects factor. Second, for comparison of palatability of the nicotine gums and confectionery gum, the confectionery gum condition was added and the factors flavor and dose were replaced with one factor: gum (nine levels: eight nicotine gum and one confectionery gum). Finally, for comparisons between the different nicotine gum conditions with a standard of abuse liability, the two amphetamine conditions were included in the analyses. In these analyses, factors were: age, flavor, time, and drug, which included all eight nicotine gum conditions and the two amphetamine conditions. For analysis of drug effects in each age group separately, factors flavor, time, and dose were included. When appropriate, follow-up analyses were performed using Tukey's post hoc comparisons.

3. Results

3.1. Subjective effects

3.1.1. Palatability

Fig. 1 shows ratings of "Do you like the gum's taste?" at timepoint 110, after 5 min of chewing. In the interest of clarity, only one timepoint is shown. Ratings decreased with time during the 15 min of chewing ($P<.001$) and the 110 timepoint was chosen because the differences between mint and original gum were most clear at this timepoint. Overall, subjects rated the mint gum higher on "Do you like the gum's taste?" than the original nicotine gum and they rated confectionery gum substantially higher than all nicotine gums. Responses to several other questions pertaining to gum palatability followed a similar pattern. Subjects scored higher on "Do you like the gum's taste?," "Does

Fig. 1. Mean (±S.E.M.) VAS ratings of "Do you like the gum's taste?" as a function of gum flavor and nicotine content, for subjects age 18–21 years ($n=12$) and 22–50 years ($n=12$). A mint-flavored confectionery gum (Ice Breakers, Nabisco) was included as a positive control condition for gum palatability.

the gum taste good?," and "How sweet is the gum?" and lower on "Does the gum taste bad?" for mint gum than original gum for all doses of nicotine [$F(1,22)>6.22$, $P<.03$]. Confectionery gum was rated higher than both mint and original gum across all doses of nicotine on ratings of "Do you like the gum's taste?," "Does the gum taste good?," "How sweet is the gum?," "Is the gum easy to chew?," "Would you chew this gum just for its taste?," "How much do you like the gum overall (taste plus drug effect)?" and lower on "Does the gum taste bad?," "How bitter is the gum?," and "How much do you dislike the gum overall (taste plus drug effect)?" [$F(8,176)>7.76$, $P<.01$, for main effect of gum, all Tukey's tests comparing confectionery gum to all others $P<.05$].

Nicotine decreased ratings of gum palatability across flavors. Scores on Like Taste, Taste Good, Chew for Taste, and How Sweet decreased significantly with increasing dose for both original and mint-flavored gum [$F(3,66)>15.15$, $P<.001$]. Ratings of Taste Bad, Strong Taste, How Bitter, and Dislike (taste plus drug effect) on the other hand increased with nicotine dose [Dose×Flavor: $F(3,66)>15.33$, $P<.001$].

Younger subjects showed overall lower ratings of palatability of nicotine gum regardless of flavor; they responded with significantly lower ratings of "Would you chew this gum just to get the drug effect?" and "Like overall (taste plus drug effect)?" and with significantly higher ratings of "Bad taste" and "Dislike overall (taste plus drug effect)?" than older subjects [$F(1,22)>4.28$, $P<.05$]. In contrast, young adults rated confectionery gum higher than adults on the items "Would you chew this gum just to get the drug effect?," "Like overall (taste plus drug effect)," and "Strong taste" (Tukey, $P<.05$).

3.2. Drug effects

Fig. 2 shows effects of mint-flavored and original nicotine gum and amphetamine for several subjective variables at timepoint 120, 2 h after amphetamine administration and at the end of the 15-min gum-chewing procedure. Amphetamine produced typical responses on the MBG scale of the ARCI, and on the Like Effect and Good Effects scales of the Drug Effects Questionnaire. On these measures, ratings by both younger and older subjects were increased significantly as compared to placebo and active nicotine gum conditions at all timepoints [$F(4,84)>6.85$, $P<.01$, for main effect of drug, all Tukey's tests comparing amphetamine to nicotine gum conditions $P<.05$]. In addition to these traditional abuse liability predictors, amphetamine increased scores on the Amph and the LSD scales of the ARCI as compared to all nicotine gum conditions at all timepoints (Tukey, $P<.05$), with the exception of the LSD scale at the 90-min timepoint. Amphetamine did not produce changes on ratings of Bad Effects or Dislike Effect.

Nicotine gum did not produce dose-related increases in any of the subjective effects associated with abuse liability; scores on the Good Effects and Like Effect scales of the Drug Effect Questionnaire, and on the MBG scale of the ARCI were not significantly altered by increasing doses of nicotine as compared to placebo. In contrast to the variables associated with increased abuse liability, scores on Bad Effects, Strong Effect, and Dislike Drug Effect did increase significantly with increasing dose of nicotine in both flavor conditions [$F(3,66)>3.89$, $P<.02$]. All active nicotine doses increased ratings of "burning throat" immediately after chewing as compared to placebo [$F(3,66)=$

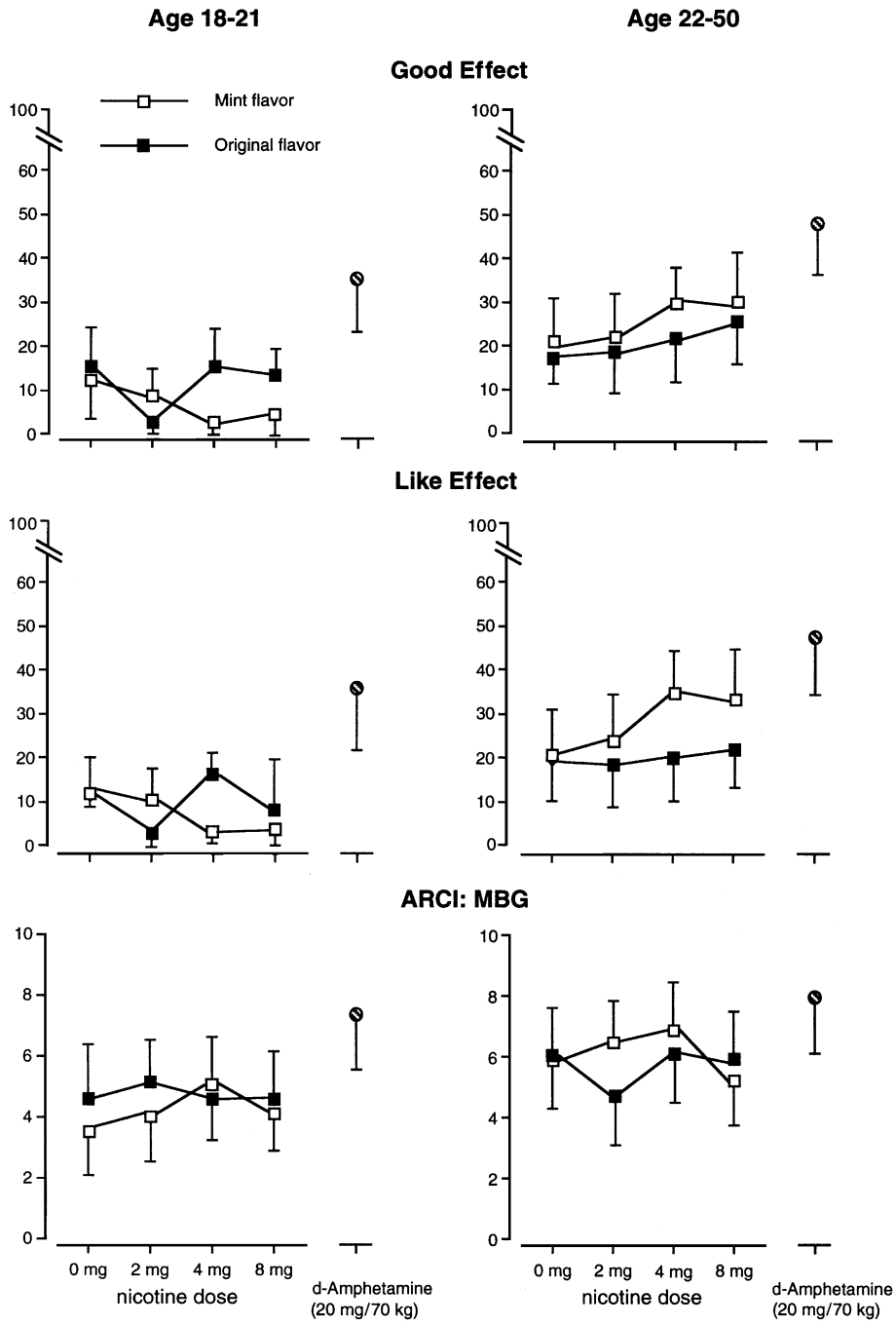

Fig. 2. Mean (±S.E.M.) VAS ratings of "Does the drug have any good effects?," "Do you like the drug effect?," and the MBG scale of the ARCI as a function of gum flavor and nicotine content for subjects age 18–21 years ($n=12$) and 22–50 years ($n=12$). A D-amphetamine condition was included as a positive control condition for abuse liability; this score reflects the average for the two amphetamine conditions (with original placebo gum and with mint placebo gum).

7.55, $P=.001$, Tukey, $P<.05$]. There was an interaction effect of Flavor × Dose [$F(3,66)=3.93, P=.030$] for "burning throat" as well, and post hoc comparisons showed that original gum increased scores on this variable more than mint gum in the 4-mg condition and less in the 8-mg condition (Tukey, $P<.05$). Flavor did not exert other independent or interaction effects on any of the drug effect measures.

Younger subjects showed lower ratings of Like Drug Effect than older subjects across doses and gum flavors [$F(1,21)=4.66$, $P=.043$], while scores for Good Effects showed a trend in that direction [$F(1,21)=3.99$, $P=.059$]. Post hoc analyses showed this pattern for ratings of nicotine gum as well as for amphetamine; younger subjects rated Good Effects and Like Effect of amphetamine lower than older subjects (Tukey, $P<.05$).

3.3. Withdrawal symptoms

Withdrawal symptoms as measured by the Hughes–Hatsukami Scale and the Shiffman–Jarvik Questionnaire subscales increased with time during the session across conditions [$F(4,88) > 3.42$, $P < .03$], with the exception of the Psychological Discomfort Scale of the Shiffman–Jarvik Questionnaire. Nicotine decreased Total Withdrawal Score of the Hughes Hatsukami Scale [$F(3,66) = 3.41$, $P = .031$]. Post hoc comparisons showed that 4- and 8-mg nicotine gum significantly decreased the total Hughes–Hatsukami withdrawal score immediately after subjects had chewed the gum (timepoint 120). Total withdrawal scores did not differ significantly from placebo or from other active nicotine doses for any of the other timepoints in the session. Nicotine did not affect any of the subscales of the Shiffman–Jarvik Scale other than the Craving subscale (see under Craving).

Younger subjects tended to endorse fewer withdrawal symptoms than older subjects; younger subjects had lower scores on the Physical Symptoms subscale of the Shiffman–Jarvik Scale [$F(1,22) = 9.48$, $P = .005$] and there was a trend in this direction for the Total Withdrawal Score of the Hughes–Hatsukami Scale [$F(1,22) = 3.82$, $P = .063$]. Further examination showed that older subjects scored higher than younger subjects on the individual items "restlessness" and "impatient" of the Withdrawal Scale and on "Is your heart beating faster than usual?" and "Do you have fluttery feelings in your chest right now?" of the Physical Symptoms subscale of the Shiffman–Jarvik Scale [$F(1,22) > 4.6$, $P < .05$].

Mint gum appeared more effective than original flavor at reducing withdrawal symptoms. Scores for the individual items "craving cigarettes" and "anxious" were significantly lower for the mint condition than the original flavor condition [$F(1,22) > 4.6$, $P < .05$] and there was a trend for scores to be lower for the mint condition for the total Withdrawal Scale [$F(1,22) = 3.5$, $P = .075$]. Finally, post hoc tests showed that there was a significant effect of flavor on withdrawal items in the adult group only (items "anxious" and "restlessness" of the Hughes–Hatsukami Scale and the Physical Symptoms subscale of the Shiffman–Jarvik Scale, Tukey, $P < .05$, for craving-related withdrawal symptoms, see under Craving).

3.4. Craving

Fig. 3 shows ratings of the individual item "craving a cigarette" after administration of nicotine gum. Nicotine dose-dependently reduced craving for cigarettes. Scores on responses to various questions and scales related to craving were significantly reduced with increasing doses of nicotine in both the mint gum and the original flavor gum condition. Specifically, scores on the "How much do you need to smoke right now, just for relief?" item, the Craving subscale of the Shiffman–Jarvik Questionnaire, Factor 1 of the QSU, and the item "craving cigarettes" from the Hughes–Hatsukami Scale showed significant decreases with dose [$F(3,66) > 3.8$, $P = .05$] in all cases. Post hoc analyses of the Craving subscale of the Shiffman–Jarvik Questionnaire showed that both the 4- and 8-mg gum suppressed scores immediately after chewing (timepoint 120); ratings were significantly lower than placebo for both doses, and significantly lower than the

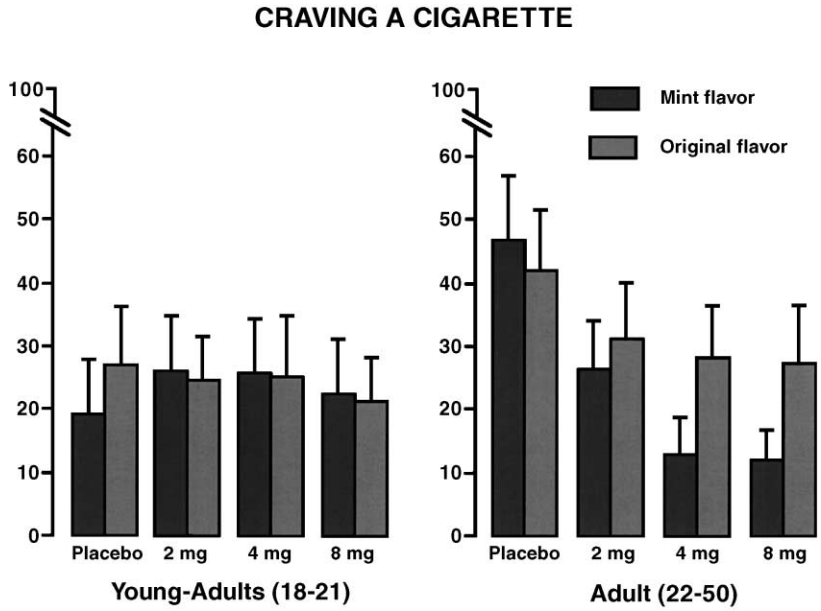

Fig. 3. Mean (±S.E.M.) VAS ratings of the "craving a cigarette" item (derived from Hughes and Hatsukami, 1986) as a function of gum flavor and nicotine content for subjects age 18–21 years ($n = 12$) and 22–50 years ($n = 12$).

2-mg condition for the 8-mg condition. Scores on this scale remained lower for the 8-mg condition than the placebo condition until 30 min after chewing (timepoint 150). Scores on the other craving-related questionnaires followed a similar pattern: scores for Factor 1 of the QSU were significantly lower for 8 mg than placebo and than 2 mg immediately after chewing, scores on the "craving cigarettes" item of the Hughes–Hatsukami Scale were lower for 8 mg than placebo immediately after chewing and 30 min later, and scores for Factor 2 of the QSU were lower for all active doses of nicotine than placebo immediately after chewing, and 30 min later for nicotine 2 and 8 mg. Craving was not significantly affected by amphetamine.

In addition to the independent effect of nicotine, a significant interaction between age and nicotine dose was observed for several of the craving-related variables [the "craving cigarettes" item of the Hughes–Hatsukami Scale, $F(3,66)=3.45$, $P=.021$, Fig 3], the VAS "How much of an urge or desire do you have to smoke right now?," "How pleasant would a cigarette be right now," and "How much do you want to smoke right now" [$F(3,63)>3.00$, $P<.05$]. Follow-up analyses showed that the nicotine effects on craving were significant in the adult group ($P<.05$ for all items), but not in the young adult group.

Finally, there was a significant difference between mint and original gum with regard to craving reduction. Specifically, mint gum reduced craving scores ("craving for cigarettes," "Rate your need to smoke for relief") more than original gum [$F(1,21)=4.6$, $P=.044$, for "need to smoke" item; $F(1,22)=4.68$, $P=.042$, for "craving cigarettes" item, see Fig. 3]. Although there was no significant interaction between flavor and age with regard to craving scores, post hoc tests showed that there was a significant effect of flavor on craving items in the adult group only (item "craving a cigarette" of the Hughes–Hatsukami Scale and the item "rate your need to smoke, just for relief", $P<.05$).

3.5. Physiological measures

Heart rate and systolic and diastolic blood pressure decreased during the sessions [$F(6,132)>7.34$, $P<.001$]. Older subjects had higher diastolic blood pressure than younger subjects [$F(1,22)=7.35$, $P=.013$] across conditions, and marginally significantly higher systolic blood pressure and heart rate [$F(1,22)>3.8$, $P<.065$]. Nicotine increased heart rate and systolic blood pressure [Nicotine×Time: $F(18,396)>1.6$, $P<.05$]; follow-up analyses showed that the 8-mg nicotine gum increased heart rate as compared to placebo and both other doses of nicotine (2 and 4 mg) during and after chewing gum of both flavors, but none of the post hoc comparisons for systolic blood pressure were significant. In the 8-mg condition, original flavor gum increased heart rate and systolic blood pressure more than mint gum ($P<.05$). Amphetamine increased heart rate and systolic and diastolic blood pressure as compared to all other conditions in both older and younger subjects ($P<.05$).

4. Discussion

This study was designed to assess the abuse liability of mint-flavored nicotine gum, as required by the FDA. Results suggest that mint flavoring increases the palatability of nicotine gum but does not increase its abuse liability in adults (22–50 years) or young adults (18–21 years). Mint flavor gum was given higher subjective ratings (e.g., mean Like Taste rating after 5 min of chewing was 34 for placebo on a scale from 0 to 100) as compared to the original flavor gum (mean rating 20), but substantially lower than confectionery gum (mean rating 78), which is marketed for its palatability. Thus, although ratings of palatability for the mint flavor nicotine gum were higher than for the original nicotine gum, they were still relatively low. Ratings of Like Taste decreased substantially with nicotine dose, which in combination with the high price of nicotine gum reduces the likelihood that the gum will be chewed just for taste. Thus, in part because of the results of this study, mint-flavored nicotine gum was approved for marketing in 1998, and orange-flavored gum in 2000. The study design may therefore serve as an example for abuse liability testing of future oral nicotine replacement products by other investigators.

Nicotine gum did not increase ratings of variables associated with abuse liability, such as Like Drug Effect, Good Effects, and the MBG scale of the ARCI (Jasinski et al., 1984; Fischman and Foltin, 1991). These data support previous studies showing that original flavor nicotine gum has little abuse liability (Nemeth-Coslett and Henningfield, 1986; West et al., 2000). At first glance, these results may appear counterintuitive, since the abuse liability of nicotine per se has been firmly established (see Stitzer and de Wit, 1998). However, abuse liability of a compound depends on several factors, one of which is the rate of absorption, with a higher rate associated with increased abuse liability (e.g., Henningfield and Keenen, 1993). Nicotine when inhaled in cigarette smoke is rapidly absorbed by lung tissue and transported to the brain, while absorption through the skin, as occurs with the nicotine patch, or the mucous membrane, as occurs with nicotine gum, is much slower (Benowitz et al., 1988). Accordingly, nicotine replacement products such as nicotine gum and patch show little abuse liability. It is possible that individuals who try the gum outside the laboratory would chew at a faster rate than the procedures in this study allowed. Since abuse potential increases with speed of drug delivery (Stitzer and de Wit, 1998), faster chewing may increase abuse potential. However, the absorption rate would still be significantly lower than that which occurs with smoke inhalation.

In addition to confirming the low abuse liability of nicotine gum, results of the present study show that improved flavor of the gum does not increase abuse liability. Although palatability of the mint-flavored gum is higher than of original gum, no effects of flavor or interactions between flavor and nicotine were observed on any of the parameters typically used to predict abuse liability. That is,

ratings of Good Effects, Like Effect, and the MBG scale of the ARCI did not differ as a function of flavor. Importantly, the study showed that improved flavor did not increase abuse liability either in adults or young adults, who may have a higher vulnerability to abuse. These findings suggest that the potential clinical benefits of improved palatability, including better acceptability and compliance, can be achieved without enhancing abuse liability.

Mint flavor gum may have some benefits not previously documented. Specifically, mint flavor gum was associated with enhanced withdrawal-reducing effects as compared to original flavor gum; subjects in the adult group reported fewer withdrawal effects, specifically craving-related effects, after chewing mint gum than after chewing original gum. The individual items ''restlessness,'' ''craving for cigarettes,'' ''need to smoke for relief,'' and ''anxious'' specifically were reduced more by mint gum than original gum. The differences may be due to greater absorption of nicotine from the better-tasting mint flavor gum. That is, although the standardized chewing procedure wherein subjects were required to chew every 3 s at a computer-generated tone was monitored and strictly enforced by a research assistant, subtle differences in chewing patterns, for example in intensity of chewing, may have occurred as a result of the differences in palatability. However, there were no differences in any of the direct drug effect ratings of the two gums, and original gum actually increased heart rate and systolic blood pressure more than mint gum in the 8-mg condition. Although it is unclear what this difference can be attributed to, it argues against the likelihood of a higher nicotine intake from the mint gum. Moreover, the increasing doses of nicotine (2, 4, and 8 mg) did produce increasing effects on drug effect ratings and some physiological measures, showing the measures' sensitivity to nicotine. If differences in nicotine absorption due to different chewing patterns for the two gums would be large enough to affect withdrawal symptoms, they would be expected to produce some differences on these variables as well. Nevertheless, blood nicotine levels would have been a useful addition to the study. Alternatively, the mint taste itself may reduce some withdrawal symptoms. Sensory factors, such as taste, heat, odor, and pharyngeal stimulation, have been shown to be important in the subjective effects of cigarette smoking behavior (Stolerman et al., 1987; Lazev et al., 1999). In this respect, it is possible that the mint taste contributed to the reduction of some withdrawal symptoms. An effect of the mint taste might be explained also by the fact that a substantial subgroup (11 subjects) of our sample smoked menthol cigarettes. However, inspection of the individual data did not suggest the differences in craving reduction existed in the menthol smokers only.

While measures of abuse liability did not differ between age groups, the adult group (22–50 years old) reported stronger withdrawal symptoms, including craving, than the young adult group (18–21 years old), suggesting a difference in nicotine/cigarette dependence between the groups. Nicotine reduced craving symptoms in the adult group but not the young adult group, confirming this hypothesis. Younger subjects also rated fewer positive and more negative aspects of both flavor and drug effects of nicotine gum. However, self-reported number of cigarettes per day and scores on the Fagerstrom Tolerance Questionnaire were not significantly different between the two age groups. In addition, there were no apparent differences between the groups in physiological responses to nicotine. However, the possibility that more subtle differences in dependence may account for the differences between the groups cannot be excluded. Alternatively, differences in response tendencies or expectancies may explain the differences between the groups as well. The demographic make-up of the groups was somewhat different. Males and Blacks were more highly represented in the adult group than in the young adult group, which precludes any direct examination of nicotine effects as a function of age. However, the study was not intended to examine nicotine effects as a function of age; the younger group was included to address concerns about mint nicotine gum in this age group specifically, and the design was appropriate for this purpose.

The finding that young adults (18–21 years old) reported more negative and fewer positive effects of nicotine gum than adults suggests this smoking cessation aid may not be the most appropriate treatment for the young adults age group. Since smoking cessation treatments are typically tested in adult smokers (age 21 and up), and since there is growing concern regarding younger smokers, a more elaborate evaluation of acceptability and efficacy of smoking cessation aids in adolescents/young adults is warranted (see also Henningfield et al., 2000).

Although palatability ratings were higher for mint gum than for the original gum, they decreased over the 15-min chewing period and were still substantially lower than for the confectionery gum. Special care was taken in the development of this gum to ensure the gum's palatability would not be so high as to appeal to children and nonsmokers. As a result, our findings are limited to moderate flavor enhancements, and development of oral nicotine replacement products with greater palatability may need additional testing.

Improved flavor nicotine gum has been approved and is currently being marketed. The data presented in this article were critical in the approval process and the method that we used continues to be relevant. Indeed, the FDA routinely relies on abuse liability testing to establish scheduling of new medications and delivery systems.

In conclusion, mint-flavored nicotine gum was rated as more palatable than the original nicotine gum, but the improvement in flavor did not increase abuse liability in adults (22–50 years old) or young adults (18–21 years old). Since the aversive taste of the original nicotine gum was an important impediment to compliance (Rose, 1996) and treatment initiation, the availability of nicotine gum in different flavors and the development of alternative oral nicotine replacement products with appealing flavors may

improve compliance and expand the range of options for those attempting to quit smoking, without posing an increased risk of abuse. Younger subjects (18–21 years old) reported fewer positive and more negative effects of nicotine gum, suggesting nicotine gum may not be an appropriate smoking cessation aid for this age group. Finally, the potentially enhanced reduction of withdrawal symptoms, including craving, by mint-flavored nicotine gum observed in the present study may prove an added benefit of this particular gum.

Acknowledgments

The authors thank John Yingling, Erin Moffett, Tim Mudric, and Michael di Marino for technical assistance and statistical analyses. This study was supported by SmithKline Beecham Consumer Healthcare.

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