Long-term Use of Nicotine vs Placebo Gum

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• Medical patients (n = 315) who wished to quit smoking were randomly assigned in a double-blind manner to receive either nicotine or placebo gum. Subjects were advised to stop gum use by 4 months. Among abstinent smokers, 46% of those receiving nicotine gum and 17% of those receiving placebo gum used the gum beyond the recommended 4-month period. By 10 months after cessation 17% of quitters receiving nicotine gum and 6% receiving placebo gum were still using gum. Gradual reduction of nicotine gum did not result in withdrawal and cessation of nicotine gum did not increase the probability of relapse to smoking or weight gain. We conclude that use of nicotine gum is due, in part, to the effects of nicotine; however, long-term use is uncommon.

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Long-term use of nicotine gum does occur[1,2] and has been inferred to be due to dependence on the nicotine in the gum.[2] We believe such a conclusion is warranted only when four facts have been demonstrated[2]: (1) persistent use of nicotine gum despite a clear recommendation to stop, (2) nicotine gum is continuously self-administered on a regular basis for a substantial period of time, (3) greater use of nicotine than placebo gum, and (4) greater self-administration of nicotine gum is not simply due to mere cessation with the nicotine gum.

Persistent use in the face of clear recommendations to stop gum use is required because often physicians do not clearly recommend cessation of nicotine gum. Continuous use is required because about 25% of nicotine gum users start and stop the gum on multiple occasions.[2] Greater use of nicotine than placebo is required because dependence typically refers to use due to the drug within a substance.[3]

Dependence typically refers to use of a drug for its nontherapeutic effects.[3] As an example of how increased use of nicotine gum could be due to therapeutic effects, assume 100 smokers receive nicotine gum and 100 receive placebo gum. Then assume nicotine has a therapeutic effect and 30 in the nicotine group and 20 in the placebo group stop smoking for 1 year. Next, assume 15 in the nicotine group and 10 in the placebo group are still using gum at 1 year. Finally, assume that continuous long-term use of gum is restricted to abstinent smokers. All of these assumptions are consistent with existing data.[2]

With this scenario, most prior studies would have calculated the incidence of long-term use based on all subjects prescribed the gum and concluded the incidence of long-term use was 15% (15/100) for nicotine and 10% (10/100) for placebo gum. However, in this example, the increased long-term use in the nicotine group would be due solely to the effect of nicotine gum to increased quit rates. The therapeutic effect can be eliminated by examining long-term use *only among abstinent smokers*. In this group, the incidence of long-term use is 50% (15/30) for the nicotine group and 50% (10/20) for the placebo group.

We were unable to locate a study that fulfilled the four criteria described above; however, a placebo-controlled trial we conducted[4] provided data that fulfilled these criteria.

SUBJECTS AND METHODS

Subjects

Three hundred fifteen smokers who wished to stop smoking were recruited from two family practice clinics. Inclusion criteria were daily smoking and ability to chew gum. Exclusion criteria were prior use of nicotine gum, use of tobacco other than cigarettes, and contraindication to nicotine gum.[5]

Subjects were middle-aged (X = 37.0 ± 9.9 years), mostly married (71%), high school graduates (96%), white collar professionals (53%) of fairly high income (65% earned more than $30 000/y). They were moderate smokers (X = 29.6 ± 11.3 cigarettes per day) of middle-to-low nicotine cigarettes (X = 0.71 ± 0.29 mg/cigarette) who had been smoking about 20 years (X = 19.4 ± 9.4 years) and who had tried to quit several times before (X = 4.1 ± 2.6 times). These characteristics were similar to those of the average US adult smoker.[4] Subject's mean Fagerstrom score[6] was 5.8 ± 1.5, which is below the cutoff for dependent smokers[6] and is lower than that in withdrawal clinic samples.[7] The nicotine group had a higher proportion of married and high-income subjects than the placebo group but these two characteristics were not associated with different durations or rates of gum use (see below). Otherwise the two groups were comparable.

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Procedures

Subjects completed informed consent and were counseled by the study nurse and their physician for 10 minutes each, were given a smoking cessation booklet, shown a 13-minute slide/tape about nicotine gum, and were given a prescription for free gum. One to 2 weeks after their quit date subjects attended a follow-up session in which they were counseled briefly by the nurse and physician (10 minutes each).[8]

Subjects were randomly assigned to nicotine or placebo gum in a double-blind manner in a 2:1 ratio. The nicotine gum was the 2-mg dose (Nicorette; Marion-Merrell-Dow, Cincinnati, Ohio). The placebo was gum flavored to match the taste and irritancy of nicotine gum.

Subjects were instructed in gum use according to the Food and Drug Administration-approved guidelines[9] except subjects were not given set guidelines about how much gum to chew per day. We told subjects to use the gum until they felt confident they had conquered the withdrawal from tobacco. Subjects were told that use of the gum beyond 3 months was not recommended, were sent a letter 3 months after their quit date reminding them to stop gum use, and were given three specific strategies to taper gum; however, gum was available for 12 months.

Subjects could obtain gum only at the pharmacy located in each clinic. With each refill the pharmacist collected the old box of gum, recorded the date, counted the number of empty gum blisters, and issued another box of gum. All gum was free. To encourage subjects to return all blisters (empty and filled), they had to pay $3 if they failed to return all blisters. To encourage subjects to return prior to running out of gum, they were also charged $3 if they returned with all their gum blisters empty.

Follow-up forms were mailed to the subject when they had not returned for gum within 6 weeks. These forms asked whether subjects were still taking the gum. If not, subjects were asked how many pieces of gum they had left. If they had stopped the gum, subjects were asked when and why they had stopped the gum and about withdrawal symptoms (using a validated scale[10]), side-effects, and if they believed they had received nicotine or placebo gum.

Smoking status was recorded at 1 week and at 1, 6, and 12 months using self-report and observer (ie, spouse, friend) follow-ups.

Data Analysis

Analyses of gum use in the first month was calculated using those who quit at 1 month. Analyses on gum use in months 2 to 6 were calculated using those who had quit at both 1 and 6 months. Analyses for months 6 to 10 were calculated using those who had quit at 1, 6, and 12 months. Data for gum use in the 11th and 12th month were not used because some subjects who obtained gum in the 10th month may not have required gum until after the 12th month when the study ended. For statistical analyses, we used survival analysis curves.[11] For clinical outcomes, prevalence was calculated by first determining when the subjects last refill occurred. Then the subjects' self-reported duration of the last box was added. (Results using only prescription data and using prescription and self-report data were similar.) A one-tailed P value was used in the analyses due to our a priori hypothesis of greater use of nicotine than placebo gum based on results of prior studies.[2]

RESULTS

Initial Compliance

Almost all subjects obtained and used some gum (85% of the nicotine group and 88% of the placebo group). Among the 157 subjects abstinent at 1-month follow-up, 74% of the nicotine group and 77% of the placebo group returned for a second box of gum and 80% of the nicotine group and 70% of the placebo group returned for a box of gum after the first month (P = not significant).

Table 1.—Number and Percent of Abstinent Smokers Who Used Gum Beyond Certain Follow-up Periods*

	Months No. (%, 95% CI)		
	>4†	>6†	>10‡
Nicotine	24 (46, 33-60)	14 (25, 14-36)	7 (17, 6-35)
Placebo	3 (17, 3-43)	2 (11, 0-30)	1 (6, 0-31)

*CI indicates confidence interval.

†Among 6-month abstainers (n = 56 for nicotine group, n = 18 for placebo group).

‡Among 1-year abstainers (n = 36 for nicotine group, n = 16 for placebo group).

Dependence

Almost half of the abstinent smokers in the nicotine group used nicotine gum beyond the recommended period compared with less than 20% of the placebo group (Table 1). By 10 months, less than 20% of the nicotine group and one person (6%) in the placebo group were still using the gum daily. A higher proportion of abstinent smokers in the nicotine group than in the placebo group used gum beyond 4 months (P = .02) and beyond 6 months (P = .04). A similar trend occurred for use beyond 10 months (P = .07).

Survival Analyses

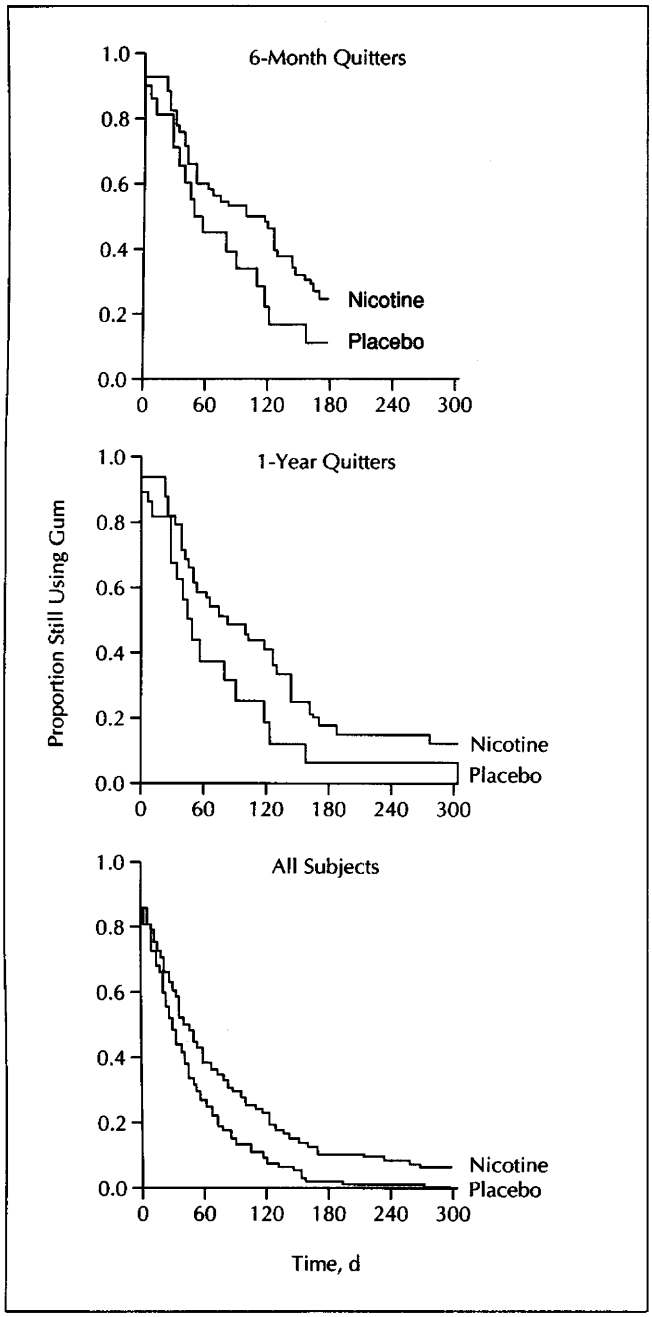
Among subjects who were abstinent at 1-month follow-up, the duration of use of nicotine and placebo gums in the first month did not differ. Among 6-month abstainers there was a greater incidence of continuous use of nicotine than placebo gum (Mantel-Cox, P = .06, Figure). The median duration of nicotine gum use among 6-month abstainers was 101 days (interquartile range, 36 to 168 days) vs 46 days for placebo gum (interquartile range, 27 to 117 days). A similar effect occurred among 1-year abstainers (Mantel Cox, P = .04). The median duration of nicotine gum use among 1-year abstainers during the first 10 months was 80 days (interquartile range, 36 to 105 days) and 43 days for placebo gum (interquartile range, 27 to 90 days, P = .04).

Daily Rate of Gum Use

Daily rate (pieces per day) was calculated by taking the number of missing gums in a box and dividing it by the number of days between the date of obtaining and returning the box. The mean number of pieces of gum per day among abstainers for nicotine vs placebo gums were 8.1 ± 3.5 (n = 121) vs 9.1 ± 7.5 (n = 59) for the first box, 7.1 ± 4.1 (n = 75) vs 5.1 ± 3.6 (n = 25) at 1 month, 5.2 ± 3.0 (n = 27) vs 6.7 ± 7.1 (n = 4) at 6 months, and 7.0 ± 6.1 (n = 7) and 3.0 ± 4.8 (n = 2) at 9 months. When these rates were entered into a 2 × 3 repeated-measures analysis of variance with gum content (nicotine vs placebo) as the grouping factor and follow-up as a within factor, neither a main effect for gum content nor an interaction with time was statistically significant.

Self-Report About Gum Use

Forty-three subjects (27%) in the nicotine group and 34 subjects (41%) in the placebo reported chewing gum and smoking concurrently on 2 or more days (P = .04). Among all subjects, the major reasons cited for stopping gum were relapse to smoking (39% in the nicotine group and



Percent of subjects using nicotine or placebo gum among 6-month abstainers (n=74, upper panel), 1-year abstainers (n=55, middle panel), and all subjects (n=315, lower panel).

43% in the placebo group), the subject believed he/she no longer needed the gum (21% and 24%) and bad taste/side-effects (22% and 17%). Few cited our recommendations to stop gum use by 4 months (9% and 3%). The distribution of these reasons did not differ between nicotine and placebo groups.

Among 6-month quitters who stopped gum use by 6 months, 14% of those in the nicotine group and 14% of those in the placebo group reported that it was moderately or very difficult to stop using the gum. If we assume that the 14 nicotine and two placebo subjects who continued to use gum at 6 months did so because it was moderately or very difficult to stop and assign them to the moderately or very difficult to stop group, then the prevalence of such a rating would increase to 38% of those receiving nicotine gum and 25% of those receiving placebo gum.

Table 2.—Rates of Relapse and Weight Gain by Gum Use Among Subjects Abstinent at 1-Month Follow-up

Gum Use	No. (%) Relapsed Between 1 and 6 mo	No. (%) Relapsed Between 1 mo and 1 y	Mean (SD), Weight Gain (kg) Between 1 and 6 mo
Chewed nicotine gum at 1 mo and stopped by 6 mo	47/71 (58)	49/71 (61)	5.0 (3.8)
Chewed placebo gum at 1 mo and stopped by 6 mo	17/28 (61)	18/28 (64)	5.2 (3.5)
Not chewing nicotine gum at 1 or 6 mo	11/23 (43)	16/23 (70)	4.5 (3.8)
Not chewing placebo gum at 1 or 6 mo	8/13 (62)	8/13 (62)	5.4 (4.9)

The ratings of withdrawal during tapering of the gum and the ratings of the same symptoms before cessation were entered into a 2 × 2 analysis of variance with time (before cessation vs after cessation) as a repeated factor and drug (nicotine vs placebo) as a grouping factor. Among 6-month abstainers, symptoms during the taper were not greater than before cessation and did not differ between nicotine and placebo gums.

Predictors of Gum Use

Possible predictor variables were entered along with content of gum and duration of abstinence (<1 month, 1 to 6 months, 6 to 11 months, and 12 months) into a series of regression equations predicting duration of gum use. We were interested not only in whether a variable predicted duration of gum use but also whether it predicted differential use of nicotine and placebo gums (ie, interacted with the drug group available in the equation). The predictor variables entered were age, sex, number of cigarettes per day, duration of smoking, age of onset of smoking, nicotine yield of cigarette, number of prior unsuccessful quit attempts, Fagerstrom Tolerance Score[6] and its component items, Tomkins scores for addiction and smoking to relieve negative affect,[12] history of alcohol or drug abuse problems, daily rate of gum use during the first box, side-effects from the gum, and self-rated certainty that one received nicotine gum. Among the 21 variables, only smoking more in the morning (an item on the Fagerstrom scale) predicted duration. Those who smoked more in the morning used gum longer ($P=.05$) and this was especially true for long-term (1 year) cigarette abstainers ($P=.005$). This prediction occurred for both nicotine and placebo gum. Neither smoking more in the morning nor any of the 21 variables predicted differential use of nicotine and placebo gums.

Cessation of Gum, Relapse to Smoking, and Weight Gain

The rate of relapse to smoking between 1 month and 6 months was examined among several groups differing in

Table 3.—Long-term Use of Nicotine Gum Among Abstinent Smokers*

Source, y	Setting	n	Continuous Use Required	% Using (Dose) 6 mo	% Using (Dose) 10-12 mo
Instructed cessation of gum at 3 mo					
Harackiewicz et al,[15] 1988	Cessation program	197	?	50 (2)	17 (2)
Instructions unclear					
Barrett and Connor,[50] 1989	Cessation program	70	?	29 (2, 4)†	0 (2. 4)†
Hajek et al,[1] 1988	Cessation program	538	?	. . .	25 (2, 4)†‡
Hjalmarson,[16] 1984	Cessation program	205	?	54 (2) 0 (0)	. . . . . .
Jarvis, et al,[17] 1982	Cessation program	106	Yes	. . .	22 (2) 17 (0)
Llivina et al,[18] 1988	Cessation program	216	?	35 (2) 7 (0)	8 (2) 4 (0)
Tonneson et al,[34] 1988	Medical practice	173	?	. . .	15 (2, 4)†
Toomes and Paul,[28] 1983	Unclear	54	?	12 (2)	. . .
Combined results§	. . .	. . .	. . .	37 (2, 4)§ 4 (0)§	18 (2, 4)§ 8 (0)§
Present study	Medical practice	315	Yes	25 (2) 11 (0)	17 (2) 6 (0)

*Blondal[27] and Hall et al[51] reported no difference in the prevalence of nicotine and placebo gum use among long-term abstainers but did not report actual prevalence rates. Hughes et al[13,14] were not included as the sample sizes for long-term abstainers were small in both studies (<12/dose).
†Subjects used both 2- and 4-mg doses.
‡All studies used free gum except in Hajek et al.[1] Subjects paid a third of the price for first 10 boxes and full price thereafter.
§Using Mantel-Haenszel procedures and combining 2-mg and 2- and 4-mg doses.

their gum use (Table 2). There was no evidence that subjects who had stopped nicotine or placebo gum between 1 and 6 months had a higher rate of relapse to smoking compared with those who had previously stopped gum use. In addition, the rate of relapse to smoking (23%) among the 13 nicotine subjects who stated they stopped using gum due to our recommendations was not elevated. Finally, the rate of relapse to smoking was not higher among those who stopped nicotine than those who stopped placebo gum. Analyses of relapse between 6 months and 1 year showed similar results. Cessation of nicotine or placebo gum also did not induce greater weight gain by 6 months compared with those who continued gum use or those who did not use gum after 1 month.

COMMENT

Our major findings were (1) 46% of abstinent smokers used nicotine gum longer than recommended, (2) this rate of use was greater than that for placebo (17%), but (3) by 10 months only 17% of abstinent smokers were still using nicotine gum vs 6% using placebo gum.

In the introduction we argued that studies of long-term use of nicotine gum should demonstrate (1) persistent use of nicotine gum in the face of a clear recommendation to stop, (2) continuous self-administration of nicotine gum for a substantial period, (3) a longer duration of use of nicotine gum than placebo gum, and (4) a greater self-administration of nicotine gum when only abstinent smokers are examined. To our knowledge, our study is the first to fulfill all four of these criteria. In addition, almost all of the prior studies used retrospective self-reports of gum. Our study used prescription dates and gum counts. Finally, most previous studies used patients attending a cessation program. Our study used patients attending a medical practice.

Eight studies have reported long-term gum use among abstinent smokers (Table 3; our own two prior studies[13,14] were deleted due to small sample sizes). Among these eight studies, only one presented clear instructions about duration of use,[15] three had placebo control groups,[16-18] and one reported requiring continuous use.[17] When the data from these studies are combined using a Mantel-Haenszel analysis, the 6-month prevalence rates are similar and the 10- to 12-month rates are almost identical to those of this study (Table 3).

We have labeled our long-term use "dependence" for two reasons: (1) long-term use persisted despite clear recommendations to stop the substance, and (2) long-term use was due, in part, to the psychoactive effects of nicotine. Similar long-term use of benzodiazepines among anxious patients[19] and of opioids among patients with chronic pain[20] have often been labeled dependence.

On the other hand, there are arguments against labeling such long-term use a dependence: (1) long-term use has not been shown to be harmful (in fact, nicotine gum may be safer than cigarettes due to the lower levels of nicotine and the absence of carbon monoxide and carcinogens,[21]) (2) withdrawal symptoms were not seen on cessation, and (3) in other studies, by 2- to 3-year follow-ups almost all subjects have stopped gum use.[16,18,22-25] On the other hand, (1) nicotine via nicotine gum may increase cardiovascular disease and ulcers[21] and the risks of long-term use of nicotine gum have not been studied,[21] (2) gradual tapers (as in our study) abate drug withdrawal symptoms, and (3) continuous use of a drug for 1 year is not usually required to show dependence; eg, many users of benzodiazepines, cocaine, and other drugs have difficulty stopping the drug but eventually do so.

The term *dependence* has many connotations and these connotations can have important consequences (eg, de-

creasing the likelihood patients will request and use adequate amounts of nicotine gum or decreasing the likelihood that physicians will prescribe nicotine gum to help smokers stop). Discussion of these consequences is beyond the limits of this article and is similar to prior discussions about long-term use of benzodiazepines and narcotic analgesics.[1,2] Thus, physicians may wish to educate patients about nicotine gum in a manner similar to the way they educate patients about these drugs; ie, inform them that dependence is a risk and requires some monitoring, but is uncommon and should not deter adequate use.

In most prior studies and in this study, long-term users of nicotine gum used less than 6 mg/d[1,15,17,26-30]; thus, their blood levels of nicotine should be modest. Although this appears to contradict our conclusion that many of these users are dependent on nicotine, a recent study[13] suggests the daily dosage of nicotine necessary to prevent withdrawal may be small.

We failed to replicate prior positive results relating nicotine gum use to gender and age,[30-32] smoking habit,[1,17,23,29,30,33-35] dependence,[1,23,31,34] or psychologic factors.[1,11,30,32] In addition, a history of alcohol-drug abuse often predicts long-term use of psychoactive prescription medications,[36-38] but this did not occur in this study. Our failure to replicate prior studies may be due to sample (medical outpatients rather than program attendees) or methodologic differences (examining short-term vs long-term use, rate vs duration of use, absence vs presence of a placebo group). As in other studies,[2] side-effects were not strongly related to gum use. Three factors that have been shown to influence gum use but that we did not test were price of the gum,[2,14] dose,[1,13,34,39,40] and instructions.[41-45]

Cessation of nicotine gum did not induce withdrawal. The gradual taper of gum used in this study may have prevented withdrawal seen in prior studies of abrupt cessation of nicotine gum.[46,47]

Cessation of nicotine gum did not increase relapse to smoking. Many, but not all, studies have described a retrospective association between length of gum use and relapse to smoking[2] and interpreted this to mean that longer gum use prevents relapse. Longitudinal[2] and experimental[48] tests have yet to support this belief. One alternate interpretation is that a third variable, eg, compliance or motivation, increases both gum use and the probability of cessation (however, see Jackson et al[31]). In any case, our scientific data are not sufficient to suggest physicians should encourage long-term use of nicotine gum.

Cessation of gum did not lead to weight gain. Several studies have associated greater use of nicotine gum with smaller weight gain, or found less weight gain between nicotine gum and control groups (see Hajek et al[1] for a review plus two more recent studies[10,49]). We are unaware of prior studies that have prospectively tested if cessation of nicotine gum would lead to weight gain.

In summary, our results have several implications for use of nicotine gum. First, use beyond the recommended period was prevalent but rarely persisted. Thus, physicians can probably defer treatment for long-term use unless subjects are continuing to use gum for 1 year after cessation. Second, in contrast to abrupt cessation, with a gradual taper most subjects had little difficulty in stopping the gum and did not have withdrawal symptoms. Thus, physicians should continue to advise tapering of nicotine gum. Third, despite the beliefs of patients and investigators, cessation of nicotine gum after an appropriate time period did not increase the probability of relapse to smoking. Thus, physicians should continue to advise subjects to taper gum use.

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