Smoking Cessation in Primary Care

A Randomized Controlled Trial of Nicotine-Bearing Chewing Gum

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The results are reported from a multicentered, randomized clinical trial of a physician-delivered smoking cessation intervention package. All physicians attended a four-hour training session during which the rationales for the different aspects of the intervention were discussed, including a detailed description of the proper use of nicotine-bearing chewing gum. Patients were randomized to receive an offer of a prescription of 2 mg of nicotine chewing gum in addition to the basic intervention (n = 111) or the basic intervention alone (n = 112). The basic intervention included advice, setting a date for quitting, self-help materials, and the offer of supportive follow-up visits. Receptionists were instructed to recruit the first two smokers attending the practice each day.

One-year smoking cessation was validated by cotinine saliva analysis. The validated three-month sustained abstinence rates at one year were 8.1 percent and 9.8 percent in the gum and no-gum groups, respectively. The 95 percent confidence interval about this difference was −9.3 percent to 6.4 percent.

There is no evidence from this study that the offer of 2 mg of nicotine-bearing gum enhances smoking cessation rates when added to a comprehensive intervention offered to all smokers in primary care. Until larger trials are completed, however, the possibility that this dose of nicotine gum may produce small beneficial effects cannot be excluded.

In 1983 the Food and Drug Administration (FDA) in the United States approved nicotine chewing gum. The drug was made available for clinical use in March 1984. Blum[1] reported that the FDA approved this drug on the basis of one American study[2] and one foreign study.[3] The original purpose of the controlled American trial was to investigate the influence of the gum on oral soft tissues. The success rate on smoking at six weeks was a secondary outcome of the study.

Both Jamrozik et al[4] and Lam et al[5] have reviewed studies of nicotine-bearing chewing gum. Their reviews cover studies both in clinic and in primary care settings and examine placebo-controlled and no-gum-controlled trials. Although a number of studies have shown a treatment effect of gum,[3,6,7] the essence of the reviews indicates that nicotine gum is effective in a clinic setting but may be ineffective in a general practice setting. The potential value of gum would be severely limited if its effectiveness were restricted to special smoking clinics. Whereas 70 percent of the population is seen by primary care physicians within a year,[8] relatively few patients frequent smoking clinics. Trials selecting patients from primary care have now been reported in the United Kingdom, Europe, and North America.[4,9,10–13] More recent evidence[14] suggests that a higher dose of the gum (4 mg) may be particularly effective. The 4-mg gum was given in the context of a fairly intensive program, six free group-counseling sessions of 1.5 hours each, in a single practice in Denmark. Thus, the generalizability and applicability of this finding to the North American setting is still questionable.

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A randomized controlled trial, done concurrently with the one reported here, has evaluated an intervention involving formal training of physicians on how to advise about smoking cessation.[15] Physicians in this intervention group were to follow a protocol that included advice, encouraging the patient to set a quit date, giving self-help materials to take home, offering a prescription for nicotine gum (2 mg), and offering follow-up supportive visits. This intervention was found to produce higher quit rates at one year than two other less-intensive maneuvers, one of which simply involved usual care, and the second of which involved instruction to the physicians to advise all smokers to quit and to recommend nicotine gum. The second group, however, was not told how to advise patients or how the gum was best used. The intensive intervention differed in many ways from the other two in the same study. Thus, many components of the intervention may have been responsible for producing the effect. In the results being presented in this paper, one component of the main intervention, namely, nicotine gum, has been separated out in an attempt to determine whether this component is an essential part of the intervention. Following the example of Russell et al,[9] the offer of gum was not restricted to any particular group of smokers, although there is some evidence that patients who are more heavily addicted may benefit more from nicotine gum.[16] This trial of nicotine gum compared with no-gum control differed in a number of aspects from previous trials. First, physicians were given a formal training session involving considerable instruction on how to educate patients on the proper use of the nicotine gum. In addition, several different criteria for successful outcome were employed.

METHODS

This randomized trial compared the effect of (1) advice to quit, setting of a quit date, self-help materials, and supportive follow-up visits of one group (support group) with (2) the same maneuver plus the offer of a prescription of nicotine-bearing gum (support plus gum).

Inclusion and Exclusion Criteria for Patients

Patients who presented as smokers to nine participating primary care physicians over four months were considered for the trial. Physicians were drawn from both solo and group practices, were predominantly in urban areas, and cared for an average of 2,000 patients. Patients were eligible if they were aged between 16 and 65 years, and smoked at least one cigarette every day or most days. Patients were excluded if they were pregnant or breast feeding. Recruitment began at the start of each day, and receptionists were to ask each smoker who attended the practice for a regular office visit to read a study consent letter until a maximum of two each day agreed to join the study. The restriction to the entry of no more than two patients per practice per day was done to prevent physicians from falling behind in their daily schedule and from having too many follow-up visits within a short span of time. Although this recruitment strategy could have been abused in the sense that receptionists might approach only more motivated patients, the treatment comparison would still not be biased, since patients were randomized only after they agreed to participate. The consent letter asking patients to participate in the study indicated that all patients would be offered smoking-cessation treatment and that some patients would also be offered a prescription. There was no indication that the prescription would be for nicotine gum.

Baseline Assessment

Each patient completed a standardized initial assessment form, which outlined the inclusion-exclusion criteria and included questions on demographic information, medical and smoking history, and attitudes toward smoking cessation.

Allocation to Treatment

After obtaining informed consent from patients, physicians were presented with a sealed envelope indicating treatment allocation by the receptionist. Each physician's patients were randomized to either the support group or the support-plus-gum group, with the restriction that allocation was balanced within each block of four patients for each physician.

Regimens

All physicians participating in the study attended a four-hour continuing education session. The maneuver has been described in detail and reported elsewhere.[17] In brief, all patients were to be given advice by the physician to quit smoking. The patient was then to be advised to select a quit date within the next 30 days in conjunction with the physician.

Patients randomized to the support-plus-gum group were to receive brief advice about the use of nicotine gum at the initial visit, but actual prescription of the gum was to be delayed until the patient returned for the quit-date visit. Patients in both groups were to receive self-help literature in the form of quit tips at the initial visit. The support-plus-gum group received ten quit-tips sheets including two covering the use of gum, whereas the support

group received only the eight sheets that did not pertain to gum use. The prescription was for 2-mg gum, and patients were required to pay for it personally.

At the quit date those patients who had been randomized to the support-plus-gum group were to be given more elaborate instructions on the use of the gum. The instructions about gum were to include a warning to stop smoking before starting to chew the gum, a discussion of the daily dose and how to chew the gum, an explanation of how the gum works, and advice to stay on gum for two to three months. No physician was taught to assess nicotine dependence. All patients were to be offered four follow-up supportive visits, the first to occur within a few days of the quit date, followed by a visit one week, one month, and two months after the quit date. At each of these visits the physician was to individualize advice and support. Physicians were guided through the follow-up visits by reminder sheets that highlighted issues such as weight gain, stress, and social pressures to smoke as possible problems to discuss.

The patients in the support group were not to be offered nicotine-bearing gum, but if they insisted on receiving it, the physicians were to use their judgment about whether to comply with the patient's request.

Patient Follow-up

Patient progress was determined by follow-up visits to the physician, self-administered questionnaires at two months and at one year, telephone interviews, and, among patients who reported quitting, by a scheduled home visit to collect saliva for a cotinine test at one year.[18] Using a standard questionnaire at two months, all patients were asked to report on their current smoking habits, on any advice regarding smoking given to them by the physician, and on the quantity and usefulness of the nicotine gum. Patients who did not return their questionnaire by mail were telephoned for their answers.

At one year all patients received a mailed questionnaire that inquired about their current smoking habits, the use of nicotine gum, and contacts with their family physicians. Patients who reported quitting were not made aware that the purpose of the subsequently arranged home visit was for biochemical validation.

Compliance

On the two-month follow-up questionnaire, patients in the support-plus-gum group who had stopped smoking were asked about their use of nicotine gum. At one year all patients were asked to best describe their experience in the past year with nicotine gum.

Sample Size

In designing the trial, the number of smokers who quit at one year was identified as the main outcome measure. At the time this study was beginning, it was felt that the best estimates of treatment effect could be derived from the studies of Russell et al[9] and Fagerstrom.[10] Russell et al observed self-reported one-year quit rates of about 16 percent and 12 percent, respectively, among patients who did and did not receive the offer of nicotine gum. This study included all smokers attending practices. Averaging over long and short follow-up conditions, Fagerstrom found one-year validated quit rates of about 25 percent and 9 percent among gum and no-gum groups, respectively. Based on this information, cessation rates of 12.5 percent in the support group and 25 percent in the support-plus-gum group were forecast. To provide a power of 80 percent, using a one-tailed alpha of 0.05, a sample size of 120 patients per cell (total equal 240) was required.

Chart Audit

All study participant flow-sheets for eight of the nine physicians in the trial were reviewed. (One physician had inadvertently thrown out his project flow-sheets.) This chart review allowed the number of patients who showed up for quit dates and for each of the four follow-up visits to be determined.

Definition of Outcome

Three definitions of successful outcome were used. In the primary definition of outcome, patients were considered to be successful quitters if on the one-year questionnaire (1) they reported not having smoked even a puff of a cigarette in the past week, and (2) they reported not smoking a pipe, or cigar, or chewing tobacco, and (3) the biochemical validation indicated that the patient had not smoked (cotinine value of $\leq$10 ng/mL), and (4) they reported not having smoked for at least three months prior to one-year follow-up. Patients who reported that they were nonsmokers but still chewing nicotine gum were validated by determining a saliva thiocyanate level. A patient was classified as a nonsmoker if the saliva thiocyanate level was less than 1,724 μmol/L (100 ng/mL).

The second definition of success was similar to the first with the exception that patients needed only to have reported not smoking for at least one week prior to the one-year follow-up. The final definition of success was similar to the second but also required that patients report not smoking at the two-month follow-up.

Statistical Methods

The primary method of analysis employed logistic regression, which allowed for evaluation of the effect of treatment while adjusting for important baseline predictors of smoking cessation. Variables included in the model were those found to be related with any of the three outcomes (one-year success, two-point success, three-month abstinence) at a $P < .05$ level.

RESULTS

Adherence to Protocol

Of 279 patients logged by the receptionists, a total of 223 (80 percent) consented to participate and were entered into the trial. Follow-up data were obtained for 92.3 percent of patients on the two-month questionnaire. At the one-year validation, 11 patients in the support group and eight patients in the support-plus-gum group were not located, giving a follow-up rate of 91.5 percent. Patients not located were considered to be smokers for the purpose of analysis.

Chart Audit

There was a 71.4 percent attendance rate for the quit date visit in the support group compared with 69.4 percent in the support-plus-gum group. These figures exclude the 23 patients of the one physician who inadvertently discarded the project flow-sheets before they could be collected. Since these patients constituted only 10 percent of the entire sample, it is unlikely that their inclusion would have altered results. In addition, assuming a maximum of four follow-up (post-quit date) visits per patient, the rate of attendance for such visits was 41.7 percent in the support group compared with 44.7 percent in the support-plus-gum group. These differences were not statistically significant.

Baseline Data

The two treatment groups were well balanced on 14 key baseline variables, including number of cigarettes smoked per day in the week prior to study entry, the number of years the patient had smoked cigarettes, history and success of past quit attempts, desire to quit, willingness to make a quit attempt within the next month, confidence in becoming a nonsmoker, reasons for quitting, smoking prevalence among friends, co-workers, and housemates, and education, age, and sex. There were no statistically significant differences between the groups.

Clinical Outcome Measures

Self-report of smoking cessation at two months showed a 15.2 percent abstinence in the support group and 12.6 percent abstinence in the support-plus-gum group.

Nineteen patients who had moved or left their physician's practice were considered to be smokers in all analyses of outcome. Three outcomes were assessed: (1) biochemically validated one-year cessation, (2) three-month sustained quitting at one year assessed by biochemical validation at one year and self-reported length of abstinence, and (3) two-point prevalence assessed by biochemical validation at one year and self-report of quitting at the two-month follow-up. Twenty-eight patients reported being abstinent for at least one week at the one-year follow-up, but seven of these patients were found on biochemical validation testing to be smokers.

The analysis proceeded in two steps. First, logistic regression was performed for each of the outcomes on all the baseline variables outlined above. Any baseline variable that predicted any of the three outcomes with a univariate $P < .05$ was included in addition to the treatment variable in the final model for all of the outcomes. The only variable that had statistically significant predictive value was the longest time off cigarettes on a past quit attempt. This variable was dichotomized using a minimum of three months off as the criterion for a good attempt. The regression analyses were then performed using longest time off and treatment as predictors of outcome. The β coefficients and P values for each analysis are shown in Table 1. In all analyses the treatment effect does not approach statistical significance. The actual unadjusted rates of cessation using the different outcome criteria are presented in Table 2. The rates of cessation for the support group were marginally higher than that of the support-plus-gum group for both one-year prevalence (10.7 percent vs 8.1 percent) and three-month abstinence (9.8 percent vs 8.1 percent). Restricting the analyses to patients who smoked at least 25 cigarettes per day and who smoked their first cigarette within 15 minutes of arising had no effect on the results.

Models including variables usually associated with cessation, such as desire to quit, cigarettes smoked per day, and confidence in quitting, were also assessed. The inclusion of these variables had virtually no impact on the estimate of the treatment effect. Results of the model including only significant variables are presented, since multivariate models exclude all cases with even a single missing variable.

Table 3 displays the validated success rate by gum use. Patients who could not be located were excluded from this table, since there were no data on either gum use or smoking status. In those patients who did not use gum, the rate was 13.7 percent compared with a 5.5 percent

TABLE 1. RESULTS OF LOGISTIC MODELING

Outcome	β Weights	P	Relative Risk of Quitting*	95% Confidence Interval
Three-month sustained abstinence				
Predictors				
Treatment	−.096	.845	.91	.35, 2.34
Longest time off	1.31	.008	3.71	1.45, 9.50
One-year prevalence				
Predictors				
Treatment**	−.206	.666	.81	.32, 2.05
Longest time off***	1.188	.013	3.28	1.33, 10.76
Two-point prevalence				
Predictors				
Treatment	.240	.660	1.27	.44, 3.66
Longest time off	.940	.087	2.56	.88, 7.44

** Technically, this estimate is an odds ratio. In the case where the probabilities of interest are low, as in the case of probability of quitting, the relative risk and odds ratio are approximately equal*

*** For treatment, the relative risk of quitting reflects the probability of quitting in the support-plus-gum group compared with the probability of quitting in the support-only group*

**** For longest time off, the relative risk of quitting reflects the probability of quitting in patients who had previously quit for at least 3 months compared with those who had not*

TABLE 2. RATES OF CESSATION

Outcome	Support-plus-Gum (n = 112)	Support (n = 111)	95% Confidence Interval (Support-plus-Gum)
One-year prevalence	10.7	8.1	−10.3, 5.8
Abstinent for the last 3 months	9.8	8.1	−9.3, 6.4
Two-point prevalence (two months and one year)	6.3	7.2	−6.0, 7.6

TABLE 3. SUCCESS RATE (one-year prevalence) BY GUM USE*

Group	None No. (%)	Gum Less Than 1 Month No. (%)	Gum At Least 1 Month No. (%)
Support	85 (14.1)	15 (0.0)	1 (0.0)
Support-plus-gum	32 (12.5)	58 (6.9)	12 (8.3)
Total	117 (13.7)	73 (5.5)	13 (7.6)

** On one-year follow-up, 11 patients in the support group and 8 patients in the support-plus-gum group could not be located.*

rate in patients who used gum for less than one month. Patients who used the gum for at least one month had a success rate of 7.6 percent. The comparison between the extreme groups, those who did not use gum and those who used gum for at least one month, was not statistically significant ($\chi^2 = .37$, P = .54).

DISCUSSION

No beneficial effects on smoking cessation were observed for patients who were offered nicotine-bearing chewing gum in addition to the full intervention without gum. The 95 percent confidence interval on the difference between support vs support-plus-gum, in terms of sustained abstinence at one year, was −9.3 percent to 6.4 percent. The spread of this confidence limit is such that the difference between the groups is likely to lie anywhere between a 9.3 percent advantage in cessation for support over support-plus-gum, and a 6.4 percent advantage of support-plus-gum over support. Thus, although the results do not allow the hypothesis of no difference between groups to be rejected, the true difference is possibly substantial and may lie within the realm of clinical significance. Nevertheless, the results are consistent with other studies of gum in primary care settings.

It is important to remember as well that this study was an effectiveness trial. Approximately 30 percent of the

patients in the support-plus-gum group did not attend the quit date visit and did not have the opportunity to obtain their gum prescription, although they did receive quit tip sheets discussing gum. It is known, however, from previous studies[15] that the success rate among noncompliant patients tends to be low, and presumably few of these patients would have quit even if they had received their prescription on the entry visit. Another possible concern is that relatively light smokers who might not derive much benefit from nicotine gum were included in the study. In fact, only 9.4 percent of the sample smoked fewer than ten cigarettes per day prior to entry, so it is unlikely that inclusion of light smokers was an important factor contributing to the absence of a gum effect. A final factor that might have mitigated against finding an effect of gum is that the effect of gum may have been swamped by the effect of the comprehensive intervention, which included the offer of follow-up. Considering the relatively low cessation rates, it seems unlikely that the comprehensive intervention masked effects of the nicotine gum.

While it would be interesting to compare the overall rates of cessation with other primary care trials of nicotine gum, differences between trials prohibits valid comparison. Fagerstrom recruited only motivated patients, while Jamrozik et al recruited failures from an earlier study. The most similar study was carried out by Russell et al, who produced comparable estimates of two-point prevalence, although biochemical validation at a comparably early follow-up was not done.

This trial was not designed to assess the efficacy of nicotine-bearing gum but to test whether the addition of gum to a maneuver made up of advice, quit date, self-help material, and the offer of follow-up would have any clinical effect when offered to all smokers attending a family practice. There was no consideration of nicotine dependence, so that smokers for whom nicotine replacement might be judged less appropriate were offered this treatment. It should be pointed out, however, that Russell et al did find a significant advantage for gum in a similar patient population. As reported, it was found that patients who had no gum use had a marginally higher rate of cessation than patients who took at least one month of gum, although this result was not statistically significant.

Previous trials have been criticized on the grounds that the physicians were not properly trained in gum rationale and use.[19] Given the study training program and that the physicians were volunteers who were interested in smoking cessation, inadequate training does not appear to be a reasonable explanation for the lack of treatment difference in this trial. Some patients in the support group did obtain a prescription and some of the support-plus-gum group did not use gum. There is no information as to whether support patients using gum obtained the gum during this trial or from previous encounters with the same or other physicians. In any case, these 16 patients had a zero success rate, so contamination is not an important factor.

There is no evidence from this study that 2-mg nicotine-bearing gum offered to all smokers enhances cessation rates when added to a comprehensive intervention in a primary care setting. Until further trials are completed, however, the possibility that the gum produces small beneficial effects cannot be excluded. In contrast to other studies, a positive relationship between gum use and quit rates was not found.

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