

Nicotine Gum Treatment Before Smoking Cessation

A Randomized Trial

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Background: New ways of improving the efficacy of nicotine therapy need to be explored. We tested whether starting nicotine polacrilex gum treatment 4 weeks before the quit date improved smoking abstinence rates compared with starting treatment on the quit date.

Methods: An open randomized trial of 314 daily smokers (mean, 23.7 cigarettes/d) enrolled through the Internet and by physicians in Switzerland from November 2005 to January 2007. In the precessation treatment group, participants received nicotine polacrilex gum (4 mg, unflavored) by mail for 4 weeks before and 8 weeks after their target quit date, and they were instructed to decrease their cigarette consumption by half before quitting. In the usual care group, participants received the same nicotine gum for 8 weeks after their quit date and were instructed to quit abruptly. Instructions were limited to a booklet sent by mail and access to a smoking cessation Web site. Results are expressed as self-reported abstinence rates at the

end of treatment and as biochemically verified smoking abstinence (cotinine plus carbon monoxide) after 12 months.

Results: Eight weeks after the target quit date, self-reported 4-week abstinence rates were 41.6% in the precessation treatment group and 44.4% in the usual care group ($P = .61$). One year after the target quit date, biochemically verified 4-week smoking abstinence rates were 20.8% in the precessation treatment group and 19.4% in the usual care group ($P = .76$).

Conclusion: Starting nicotine gum treatment 4 weeks before the target quit date was no more effective than starting treatment on the quit date.

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TOBACCO SMOKING IS A LEADING cause of mortality in high- and low-income countries.¹ Nicotine therapy (NT) is a widely used and effective treatment of tobacco dependence, but a meta-analysis² of more than 100 NT trials shows that the absolute difference in quit rates between NT

is to start NT a few days or weeks before the quit date.^{4,5} Some evidence suggests that precessation treatment with the nicotine patch improves abstinence rates compared with treatment initiation on the quit date in smokers who are motivated to quit smoking.^{4,6} Whether this effect extends to the faster-acting NT products is unclear. Only 2 precessation treatment trials of the nicotine polacrilex gum have been conducted, and these trials showed no significant effect.^{7,8} More trials are necessary to establish whether precessation treatment with nicotine gum is effective. Except for 1 study,⁷ all precessation NT investigations were conducted in clinical settings in which patients received counseling from a health professional. It is unclear whether precessation NT is also effective outside of clinical settings in over-the-counter settings where smokers use NT without receiving counseling from a health professional. It is important to test the efficacy of

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and control conditions is only 7% (17% quit rate for NT vs 10% quit rate for control conditions). Furthermore, long-term findings show that this already modest effect is attenuated by one-third after 5 years.³ In addition to researching new and more effective medications and treatments of tobacco dependence, it is important to find new ways of improving the reach and efficacy of NT. One possibility

NT in over-the-counter settings because about twice as many NT users obtain these products over the counter rather than on a medical prescription.⁹

In several countries, nicotine products, particularly the chewing gums, are licensed for precessation treatment in smokers willing to quit ("cut down to quit").¹⁰ However, the evidence for this new indication was derived largely from smoking reduction studies^{10,11} conducted in smokers who did not want to quit. In these studies, smoking reduction was a goal in itself, not a preparation strategy before a quit attempt. In fact, the cut-down-to-quit approach is largely undocumented for the fast-acting products like the nicotine gum in smokers willing to quit.

Therefore, the objective of this study was to test whether starting the nicotine gum treatment 4 weeks before the target quit date was more effective than starting treatment on the quit date. Nicotine gum was sent by mail, and participants did not receive face-to-face counseling.

METHODS

SETTING AND PARTICIPANTS

Participants were recruited in Switzerland from November 2005 to January 2007 through advertisements on a smoking cessation Web site (<http://www.stop-tabac.ch>), via newspaper advertisements, and by physicians in private practice. Inclusion criteria comprised smoking of at least 15 cigarettes per day, age 18 years or older, commitment to quit smoking at a target quit date set in the next 2 months, commitment to use at least 10 pieces per day of nicotine gum during the prescribed duration, and residence in the Swiss cantons of Geneva or Vaud. Exclusion criteria comprised lactation, current or planned pregnancy, unstable angina pectoris, and myocardial infarction or stroke in the past 3 months. Patients with substance use disorder or a psychiatric condition and those with a dental or mouth problem were excluded if a physician indicated that these conditions might interfere with participation in the trial. All participants provided a health status questionnaire signed by a physician covering the exclusion criteria.

RANDOMIZATION

After eligibility assessment, participants were randomly assigned to the precessation treatment group or the usual care group. Randomization was based on a list of random numbers generated by a computer.

INTERVENTIONS

In the precessation treatment group, participants received nicotine polacrilex gum (Nicorette [4 mg, unflavored]; Pfizer, Helsingborg, Sweden) by mail for 4 weeks before and 8 weeks after their target quit date, and they received the recommendation to decrease their cigarette consumption by half before quitting. No particular reduction schedule was specified. In the usual care group, participants received the same nicotine gum for 8 weeks after their target quit date, and they were instructed to quit abruptly. In both groups, participants were instructed to use at least 10 pieces of gum per day before and after cessation. Instructions were limited to a booklet sent by mail and access to the smoking cessation Web site at <http://www.stop-tabac.ch>.^{12,13} We had no in-person contact with participants except for the carbon monoxide test after the 12-month

survey. Telephone contact was limited to administrative purposes, and no smoking cessation counseling was given over the telephone. All participants were required to set a target quit date 2 months after answering the baseline questionnaire and to commit to quit on this date precisely.

HYPOTHESES

We hypothesized that precessation treatment would be more effective than postcessation treatment for 3 reasons. First, precessation treatment would enable smokers to gradually reduce their daily cigarette consumption before the target quit date, which would make it easier for them to quit. Second, we thought that precessation treatment would give participants time to get used to the harsh and spicy taste of the nicotine gum and that this familiarization process would enable them to use more gum during the first crucial days after cessation and to have less severe withdrawal symptoms. Third, we thought that precessation treatment would break the conditioned behavioral pairing between smoking and nicotine reward and make cigarettes less rewarding. In other words, we thought that obtaining nicotine from gum instead of cigarettes would weaken cigarette reinforcement.

OUTCOMES AND FOLLOW-UP

Participants answered a baseline survey and 3 follow-up surveys. Baseline questionnaires, consent forms, and health status forms were collected on paper by mail. The first follow-up survey (3-day survey) took place 3 days after the target quit date (when withdrawal symptoms usually peak), the second follow-up survey (8-week survey) took place at the end of treatment (8 weeks after the target quit date), and the third follow-up survey (12-month survey) took place 12 months after the target quit date. Participants who provided an e-mail address answered the follow-up surveys on the Internet, and those who had no e-mail address returned the follow-up surveys by mail.

On the 3-day survey, smoking status was assessed with the question "Do you currently smoke tobacco?" Those responding "No, I have quit smoking" were considered abstinent. On the 8-week survey, participants were considered abstinent if they reported not having smoked even a puff of tobacco in the previous 7 days, 4 weeks, or 2 months. These 2 surveys also included the following: confidence in ability to quit, number of days using NT, number of nicotine gum pieces currently used per day, whether participants quit smoking abruptly or gradually, preference for study group (precessation treatment or usual care), number of cigarettes per day during the week before the quit date, body weight (height and weight had been self-reported at baseline), withdrawal symptoms (Minnesota Withdrawal Form¹⁴ and Cigarette Withdrawal Scale¹⁵), Fagerström Test for Nicotine Dependence¹⁶ and Cigarette Dependence Scale scores,¹⁷ and selected items from the Attitudes Toward Smoking Scale¹⁸ reflecting the rewarding effect of cigarettes. The 12-month survey included self-reported smoking abstinence during the previous 7 days, 4 weeks, 6 months, and 12 months.

BIOCHEMICAL VERIFICATION

The main outcome was biochemically verified (cotinine plus carbon monoxide levels) smoking abstinence (no puff of tobacco in the previous 4 weeks) after 12 months. Biochemical verification was conducted at the 12-month follow-up only. Participants who declared that they had not smoked even a single puff of tobacco during 4 weeks before the 12-month survey received a plastic vial (Salivette; Sarstedt, Nümbrecht, Ger-

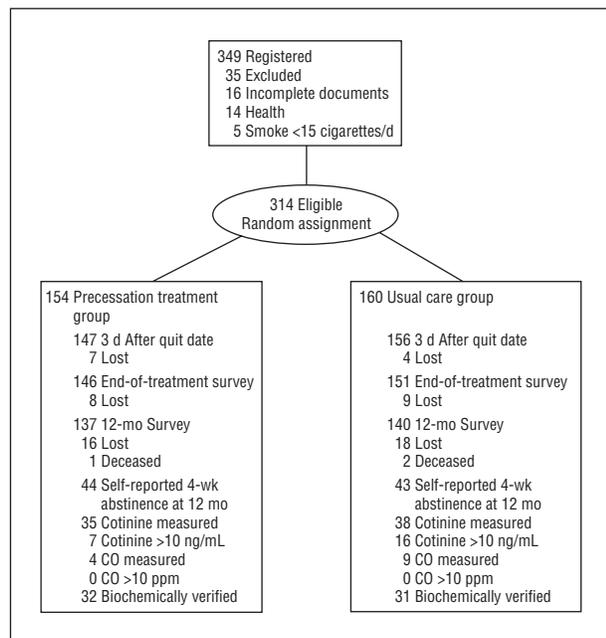


Figure. Flowchart of study participants. CO indicates carbon monoxide; lost, unavailable for follow-up.

many) for analysis of saliva cotinine levels. Cotinine analysis was conducted using gas-liquid chromatography (ABS Laboratories, London, England).¹⁹ Participants whose saliva cotinine levels exceeded 10 ng/mL were considered smokers²⁰ and were invited to visit our center to perform a test of expired carbon monoxide levels (Micro Smokerlyzer; Bedfont, Rochester, England). Those whose carbon monoxide level exceeded 10 ppm were considered smokers. Participants who did not return the saliva sample or did not come for the carbon monoxide test were considered smokers.

ETHICS AND REGISTRATION

The trial was approved by the ethics committees of the Association of Physicians of Geneva and of the Faculty of Biology and Medicine of the University of Lausanne and by the Swiss medications authority (Swissmedic), as required by Swiss law. The trial was registered (controlled-trials.com Identifier ISRCTN60585119).

STATISTICAL ANALYSIS

We used χ^2 tests and odds ratios to compare proportions. We computed change scores for withdrawal symptoms (follow-up minus baseline) and compared groups on these change scores using *t* tests. We used change scores because withdrawal is defined as change in symptom intensity between smoking and abstinence. We used paired-samples *t* tests to assess change in withdrawal ratings within groups.

RESULTS

PARTICIPATION

We received 349 applications but excluded 35 ineligible respondents (16 with incomplete documents, 14 because of health status, and 5 who smoked <15 cigarettes/d), leaving 314 participants (mean, 23.7 cigarettes/d) eligible for randomization. The participation rate was 96.5%

Table 1. Baseline Characteristics of Study Participants

Characteristic	Precessation Treatment Group (n=154)	Usual Care Group (n=160)	P Value
Age, y	42.0	44.1	.10
Men, %	64.9	52.5	.03
School, y	14.5	14.7	.62
Body weight, kg	73.7	71.0	.09
Body mass index ^a	24.0	24.0	.90
Often feels sad or depressed, %	24.7	19.4	.21
Cigarettes per day	24.0	23.4	.54
Minutes to first cigarette of the day	30.6	34.4	.52
Cigarette Dependence Scale (0-60 scale)	48.4	48.3	.83
Fagerström Test for Nicotine Dependence (0-10 scale)	5.5	5.4	.66
Confidence in ability to quit smoking (0-100 scale)	65.6	69.1	.18
Made a 24-h quit attempt in past 12 mo, %	42.9	41.9	.86
Used nicotine therapy in past, %	51.9	49.4	.65
Prefers to be in, %			
Precessation treatment	61.0	64.4	.32
Usual care	21.4	16.9	.32

^aCalculated as weight in kilograms divided by height in meters squared.

(303 of 314) for the 3-day survey, 94.6% (297 of 314) for the 8-week survey, and 88.2% (277 of 314) for the 12-month survey (**Figure**). Participation rates were similar in both groups. Among self-reported quitters at the 12-month follow-up, participation in the saliva cotinine test was 83.9% (73 of 87) and was similar in both groups ($P=.26$). Among those with positive cotinine test results, participation in the carbon monoxide test was 56.5% (13 of 23) and was similar in both groups ($P=.97$). Slightly more men were in the precessation treatment group than in the usual care group (**Table 1**), but because sex was not associated with smoking cessation at any follow-up, we did not adjust for sex in subsequent analyses. No serious adverse event was reported during the treatment phase.

SMOKING CESSATION RATES

Smoking cessation rates were high in both groups, and they were similar in both groups on all follow-up surveys (**Table 2**). Half of those who were abstinent at the 8-week survey had relapsed at the 12-month follow-up.

HYPOTHESES TESTING

The first hypothesis was verified (**Table 3**) because daily cigarette consumption during the week before the quit date, as reported on the 3-day survey, was lower in the precessation treatment group than in the usual care group (12.4 vs 21.3 cigarettes/d; $P<.001$). The second hypothesis was not verified because, at the 3-day survey, the proportions of nicotine gum users were similar in the precessation treatment and usual care groups (92.5% vs 86.9%; $P=.21$) and because among gum users the daily number of gum pieces used was similar in both groups (9.2 pieces/d; $P=.90$). In both groups, levels of craving

among quitters decreased significantly and levels of appetite and hunger increased significantly between baseline and the 3-day survey. In the usual care group only, a statistically significant increase was noted between baseline and the 3-day survey in ratings on the Minnesota Withdrawal Form and in anxiety and depression. However, the differences between groups in change of withdrawal symptoms over time were not statistically significant. The third hypothesis (precessation treatment would make cigarettes less rewarding) was tested in 92 participants who continued to smoke after the quit date. This hypothesis was partially verified because only the endorsement of "I love smoking" was significantly lower in the precessation treatment group than in the usual care group.

POST HOC ANALYSIS OF ABRUPT VS GRADUAL CESSATION

On the 3-day survey, we asked participants if they had quit smoking abruptly or if they had first reduced their cigarette consumption before quitting. Overall, 54.5% (84 of 154) of those who had quit abruptly were abstinent on the 8-week survey (criterion of no puff of tobacco in the previous 4 weeks) compared with 36.7% (40 of 109) of those who had first reduced consumption and then quit (odds ratio, 1.49; 95% confidence interval, 1.12-1.98; $P = .004$). This trend was found in both study groups when analyzed separately (data not shown). This effect was no longer statistically significant on the 12-month survey (24.0% [37 of 154] for biochemically validated 4-week quit rate for abrupt and 16.5% [18 of 109] for gradual, $P = .14$).

WEIGHT GAIN

Participants who had quit smoking at the 12-month survey (biochemically verified) gained 3.8 kg from baseline (from 70.9 to 74.7 kg; $P < .001$, paired-samples t test), whereas those who continued to smoke gained 0.9 kg (from 72.2 to 73.1 kg; $P = .001$). The change difference between quitters and smokers in body weight over time was statistically significant (2.8 kg; $P < .001$, independent-samples t test).

USE OF BEHAVIORAL SUPPORT AND BUPROPION

At the 8-week survey, similar proportions of participants in both groups declared that after enrollment in the study, they had visited a physician to quit smoking (11.6% precessation treatment vs 12.5% usual care, $P = .12$), visited a smoking cessation Web site (26.2% precessation treatment vs 35.1% usual care; $P = .12$), or called a telephone quit line (0.9% vs 2.5%; $P = .33$). At each follow-up, 3 to 5 respondents in each group reported using bupropion hydrochloride. Varenicline tartrate had not yet been introduced in Switzerland at the time of the study.

NICOTINE GUM USE AFTER 12 MONTHS

After 12 months, 9.2% of participants were still using NT daily. Gum users chewed on average 5 pieces per day (Table 4). These values were similar in both groups.

Table 2. Smoking Status at the 3 Follow-up Surveys With Nonrespondents Counted as Smokers

Variable	No. (%)		P Value
	Precessation Treatment Group (n=154)	Usual Care Group (n=160)	
3-d Survey			
Self-reported quitting	96 (62.3)	113 (70.6)	.12
8-wk Survey, Self-report			
Made a serious quit attempt in past 3 mo	128 (83.1)	122 (76.3)	.21
No puff of tobacco in past			
7 d	70 (45.5)	75 (46.9)	.80
4 wk	64 (41.6)	71 (44.4)	.61
2 mo	61 (39.6)	65 (40.6)	.86
12-mo Survey			
Self-report of no puff of tobacco in past			
7 d	47 (30.5)	46 (28.8)	.73
4 wk	44 (28.6)	43 (26.9)	.74
6 mo	37 (24.0)	36 (22.5)	.75
12 mo	33 (21.4)	34 (21.3)	.97
Cotinine and carbon monoxide-verified no puff of tobacco in past			
7 d	34 (22.1)	33 (20.6)	.75
4 wk	32 (20.8)	31 (19.4)	.76

COMMENT

We tested whether starting nicotine gum treatment 4 weeks before the target quit date was more effective than starting treatment on the quit date and found that both courses of treatment were similarly effective. Precessation treatment decreased by half the number of cigarettes smoked per day during the week before the quit date, but no statistically significant effect was noted of precessation treatment on withdrawal symptoms just after the quit date, on gum use just after the quit date, or on smoking cessation rates. These results contrast with those of previous studies^{4,6,21-24} showing that precessation treatment with the nicotine patch for 2 to 4 weeks was more effective than standard NT. However, our results agree with previous studies^{7,8} showing that precessation treatment with nicotine gum did not significantly improve cessation rates.

There are several possible explanations why precessation treatment did not affect quit rates. First, this approach may be effective with the nicotine patch but not with the nicotine gum. When smokers use a nicotine patch, they have a steady level of nicotine in the bloodstream, which may make cigarettes less rewarding. In contrast, because of the short half-life of nicotine, quitters may smoke to reduce craving between gum pieces, and cigarettes may continue to be rewarding. In our study, cigarettes were slightly less rewarding in the precessation treatment group among those who failed to quit smoking, a result that would contradict this interpretation. Nevertheless, a direct comparison of precessation treatment with patch vs gum is needed to test whether

Table 3. Smoking Behavior and Withdrawal Symptoms at the 3-Day Survey

Variable	Precessation Treatment Group	Usual Care Group	P Value
All Participants			
	(n=154)	(n=160)	
Cigarettes per day during the week before target quit date, mean	12.4	21.3	<.001
Confidence in ability to quit smoking (0-100 score), mean	72.5	72.9	.88
Prefers to be in, %			
Precessation treatment	88.7	45.3	<.001
Usual care	11.3	54.7	<.001
Quitters at the 3-d Survey			
	(n=96)	(n=113)	
Quit, %			
Abruptly	34.1	98.1	<.001
Gradually	65.9	1.9	<.001
Change in			
Cigarette Withdrawal Scale, total SD U	0.04	0.04	.93
Anxiety and depression	-0.08	0.16 ^a	.06
Irritability and impatience	0.04	0.09	.73
Craving	-0.48 ^b	-0.50 ^c	.89
Difficulty concentrating	0.13	-0.10	.10
Appetite and hunger	0.61 ^c	0.65 ^c	.85
Insomnia	0.19	0.17	.91
Minnesota Withdrawal Form, total SD U	0.10	0.17 ^b	.55
Smokers at the 3-d Survey			
	(n=50)	(n=42)	
Cigarettes per day			
Mean	10.3	10.8	.79
Median	10	10	.82
Minutes to first cigarette of the day, median	30	15	.17
Agree, %			
I love smoking	28.6	32.5	.05
It feels so good to smoke	22.0	28.2	.63
Smoking calms me down when I am upset	44.9	50.0	.78
A cigarette calms me down when I am stressed	48.0	45.0	.82
After a cigarette, I am able to concentrate better	26.0	25.7	.79

^a $P \leq .05$ for change over time in withdrawal scores.

^b $P \leq .01$ for change over time in withdrawal scores.

^c $P \leq .001$ for change over time in withdrawal scores.

Table 4. Nicotine Gum Use at the 3 Follow-up Surveys

Characteristic	Precessation Treatment Group	Usual Care Group	P Value
	(n=154)	(n=160)	
3-d Survey			
Gum pieces per day in week before target quit date, mean	7.9	2.1	<.001
Days using nicotine therapy in past 30 d, median	30	4	<.001
Use nicotine therapy daily now, %	82.9	80.4	.21
Gum pieces per day now among daily gum users, mean	9.2	9.2	.90
Use nicotine therapy occasionally (not daily)	9.6	6.5	.21
8-wk Survey			
Days using nicotine therapy in past 60 d, mean	46.2	45.6	.80
Gum pieces per day, mean			
In first month after quitting	9.5	9.4	.84
In second month after quitting	7.4	7.2	.71
Use nicotine therapy daily, %	40.9	40.3	.45
Gum pieces per day now among daily gum users, mean	7.6	7.5	.92
12-mo Survey			
Use nicotine therapy daily, %	7.8	10.6	.22
Days using nicotine in past 30 d among daily nicotine therapy users	18.7	17.8	.72
Gum pieces per day now among daily gum users, mean	5.2	5.1	.62

there is a difference in the rewarding effects of cigarettes after precessation treatment with these products.

Second, all precessation patch investigations were conducted in clinical settings in which smokers received

in-person counseling. In our study and in the study by Bullen et al,⁷ both of which showed no effect of precessation treatment with nicotine gum, smokers did not receive face-to-face counseling. Therefore, it is possible that

precessation treatment works only in clinical settings with face-to-face counseling. Again, this hypothesis should be tested directly by comparing precessation patch investigations in clinical vs over-the-counter settings.

Third, in the present study, both groups had to delay their target quit date by 2 months, which is a procedure that few smokers will use spontaneously.²⁵ Therefore, a preparation phase, an important ingredient of precessation treatment, was present in both study conditions, which may have attenuated the difference between conditions.

Confirming our first hypothesis, smokers in the precessation treatment group reduced their cigarette consumption before the quit date, probably because they titrated their overall nicotine intake and they received the instruction to reduce consumption.²⁶ Contrary to our expectation that gradual reduction before the quit date would improve quit rates, we observed that quit rates at the end of treatment were in fact substantially higher among those who quit abruptly than among those who reduced gradually, and this effect was observed in both study groups. This undermines the cut-down-to-quit strategy and may imply that abrupt quitting is more effective than gradual quitting, as suggested by other investigators.^{27,28}

Although the main outcome did not differ between the 2 treatment groups, abstinence rates were high in both groups (19.4%-20.8% at 12 months) considering that there was no face-to-face counseling. However, these quit rates were not unusual: quit rates after 6 to 12 months were at least 20% in 4 of 15 studies included in a meta-analysis² of the effect of nicotine gum with low-intensity behavioral support. Compliance was also remarkably good because participants used on average 9 pieces of gum per day during the first month and 7 pieces per day during the second month after the quit date. The participation rates at follow-up were also high. This is probably explained by the fact that participants were motivated to quit (all committed to quit in the next 2 months, and 42.4% had made a quit attempt in the year before the study) and were highly educated, but it may also indicate effectiveness of the procedures used in this study (nicotine gum sent by mail, access to a Web site, written commitment to quit at a target quit date, and written commitment to use ≥ 10 pieces of gum per day). Studies^{29,30} show that combining NT with Web-based behavioral support is an effective strategy. However, few participants in this study sought support or information from the smoking cessation Web site, from a physician, or from a telephone quit line. Strategies to increase the reach of these sources of support should be explored. One-third of participants in the precessation treatment group quit abruptly, and a few participants in the usual care group quit gradually. This may have attenuated the difference in outcomes between groups. Finally, because the between-group differences in quit rates were small, it is unlikely that these are false-negative results.

CONCLUSIONS

Starting nicotine gum treatment 4 weeks before the quit date did not improve abstinence rates, nor did this ap-

proach have any deleterious effect. Therefore, in smokers willing to quit, the cut-down-to-quit approach with the nicotine gum is not supported by data. Nevertheless, precessation NT is easily implemented and has the potential to increase the reach of NT by appealing to smokers who do not want to quit abruptly. Nicotine therapy is used by 1 in 4 smokers trying to quit.³¹ Therefore, there is a need to explore strategies to increase the reach and efficacy of NT.

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