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Smoking cessation with smokeless tobacco and group therapy: An open, randomized, controlled trial

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Smokeless tobacco might be effective as an adjunct for smoking cessation. We evaluated the efficacy of smokeless tobacco and group support for smoking cessation in an open, randomized study that compared smokeless tobacco plus group support versus group support only. The study enrolled 263 healthy smokers (M_{age}=49 years) who smoked a mean of 24 cigarettes/day, with a mean of 31 pack-years. Smokeless tobacco was provided for 7 weeks (or up to 12), combined with eight group support visits provided by nurses. The control group received group support only. Smoking cessation rates were statistically significantly better in the smokeless tobacco group than in the control group during the first 7 weeks. Point-prevalence abstinence rates at 7 weeks were 36.4% versus 20.8% (*OR*=2.52, *p*=.001), respectively; and continuous abstinence rates from weeks 4 to 7 were 31.5% versus 19.2% (*OR*=1.94, *p*=.023), respectively. The primary outcomes (i.e., 6-month point prevalence) were 23.1% versus 20.8%, respectively (*OR*=1.31, *ns*). Smokeless tobacco was relatively well tolerated, although 15 subjects (11.2%) stopped use due to adverse events. A total of 25 subjects (17.5 %) were still using smokeless tobacco after 6 months. This trial demonstrated short-term efficacy of smokeless tobacco in combination with group support for smoking cessation but no long-term efficacy.

Introduction

The most important reason for continued smoking is nicotine addiction (American Psychiatric Association, 1994; U.S. Department of Health and Human Services, 1998). Nicotine replacement products are the drug of choice for smoking cessation, with well-documented efficacy. In more than 100 trials, nicotine replacement almost doubled the quit rate compared with placebo (Silagy, Lancaster, Stead, Mant, & Fowler, 2006); however, 1-year quit rates are in the range of 10%–30%. Room for improvement clearly exists. Plasma nicotine concentrations attained with nicotine replacement therapy (NRT) are around one-third to two-thirds of those obtained during smoking, and quit rates increase in parallel with increasing nicotine substitution (McNabb, Ebert, & McCusker, 1982; Nørregaard, Tønnesen, Simonsen, & Sæwe, 1992). Plasma nicotine levels in some users of smokeless tobacco (ST) are comparable with those found in cigarette smokers (Benowitz, Porchet, Sheiner, & Jacob, 1988; Gritz, Baer-Weiss, Benowitz, Van Vunakis, & Jarvik, 1981). Thus ST might be a more effective agent than NRT for smoking cessation, considering that smokers might be habituated to components in tobacco other than nicotine (Fowler, Logan, Wang, & Volkow, 2003; Sutton, Russell, Iyer, Feyerabend, & Saloojee, 1982).

Many physicians might consider the substitution of one form of tobacco (smokeless) for another form (cigarettes) to be odd and rather controversial. Within the tobacco control community, heated debate continues over this topic. Opponents have asked whether marketing of ST as an aid to quitting might backfire, leading to increased use of tobacco by children (including experimentation with ST and initiation of cigarette smoking) and increased recidivism among former smokers to ST. However, an argument for the legitimacy of ST use in cessation

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has been that it could get people to quit using a far more dangerous form of tobacco—cigarette smoking (National Institutes of Health, 2006). Clinical studies of ST as a cessation agent have been called for (National Institutes of Health, 2006).

The present trial examined the feasibility, efficacy, and safety of ST for smoking cessation used for 7 weeks (or up to 12) combined with group counseling, compared with group counseling alone. The primary outcome was the 6-month quit rate.

Method

Subjects and study design

This was an investigator-initiated, single-site, open, randomized trial with two treatment groups: ST plus group counseling and group counseling alone (Figure 1).

Smokers were recruited using newspaper advertisements, and then screened by telephone. At the first screening visit in the clinic subjects were randomized to the ST and control groups using a randomization list. Enrollment lasted from February to October 2005. Eligible subjects were aged 25–70 years, smoked more than 13 cigarettes daily (to exclude lighter smokers), had smoked for more than 5 years, were motivated to stop smoking, and were willing to follow the study protocol. Excluded from the study were smokers who had used either NRT or bupropion during the previous 3 months, or who had any serious disease or psychiatric disorder, consumed more than six alcoholic drinks per day, or were unable to adhere to the protocol. All participants provided informed consent, and the regional ethics committee approved the study protocol.

Clinic visits

The individual screening visit was followed by eight group meetings, involving 15–20 participants. The eight group visits occurred on the target quit day, after 1, 2, 3, 4, 7, and 12 weeks, and at the 6-month follow-up.

Each group session lasted 1.5 hr and was conducted by two nurses and a medical student. At each visit, assessments were performed during the first 20 min (body weight, expired carbon monoxide [CO] levels, usage of ST, and possible adverse events), followed by a 5-min presentation of the day's program, and a 20-min round-table discussion during which each participant told how he or she had handled not smoking since the last visit. A 15-min nurse-led counseling session on smoking cessation followed, with another round-table discussion during which each participant was advised how to handle "not smoking" in the next study period. Subjects also were given take-home material with tips on smoking cessation. One of six different PowerPoint presentations (14–27 slides per presentation) was shown at each session, with information on how to use ST and advice about smoking cessation.

At the 4-week visit, subjects were advised to try to gradually reduce their use of ST over the next 3 weeks. At the 7-week visit, this advice was repeated, with the goal of tapering daily use of ST to zero by the 12-week visit, modified depending on the magnitude of withdrawal symptoms. After 12 weeks, subjects had to buy ST themselves if they needed to extend the treatment. The tapering followed essentially the same principles as for nicotine replacement products. The PowerPoint series focused on how to handle withdrawal symptoms, relaxation techniques, relapse prevention, and, for the group that did not use ST, the advantages of no longer being exposed to nicotine.

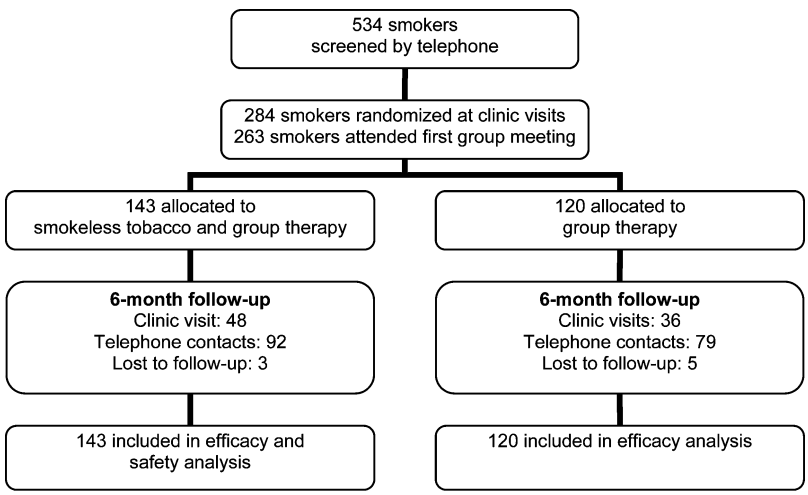

Figure 1. Study flow diagram.

All nurses had experience with smoking cessation. Three training sessions for the nurses covered how to use the study treatment, adequate dosing, and how to standardize the group counseling. Standardized counseling guidelines were followed.

Smokeless tobacco

For subjects in the ST group, use of the study medication for 7 weeks was recommended, with the possibility of continuing for up to 12 weeks if the subject felt it appropriate. The ST product used was a tobacco pellet produced by Oliver Twist (Odense, Denmark). Three flavors of the product were used (Royal, Eucalyptus, and Tropical). Each pellet consists of small pieces of rolled tobacco flavored with licorice and comes in a pocket-sized plastic box containing about 30–35 pellets. Each tobacco pellet measures 1cm × 0.5cm and contains 5.9 mg nicotine (95% *CI*=5.5–6.3), water (about 27%), sweeteners (30, 50, and 60 mg sugar), flavorings (licorice, anise, eucalyptus), thickeners, moisture retainers, and acidity regulators to a pH of about 5.1. The tobacco-specific nitrosamine (TSNA) content is 560 ng per pellet (95% *CI*=510–610), or 2.6 μg/g.

According to the manufacturer's instructions, the pellet should be placed in the mouth between the cheek and jaw and left there but can be chewed for 30 sec for more rapid nicotine release whenever needed. After 1–1.5 hr the used pellet should be replaced by a new pellet. The total release of nicotine is around 2 mg per pellet. The recommended dose was 5–6 pellets per day (maximum 10–15/day). The week before the target quit day, the use of one pellet daily was recommended to smokers to get used to the pellets. Study treatment was free of charge.

Assessments

CO was measured at each visit (Bedfont Smokerlyzer, Sittingbourne, U.K.). Any subject with an expired CO level of more than 8 ppm was categorized as a smoker (Jarvis, Russell, & Saloojee, 1980). Nicotine dependence was assessed using the Fagerström Test for Nicotine Dependence (FTND), which ranks dependence from 0 (none) to 10 (maximum) (Fagerström, Heatherton, & Kozlowski, 1991). Plasma samples were taken at entry and after 4 weeks and analyzed for nicotine using a validated method (Feyerabend & Russell, 1990; Jarvis, Primatesta, Erens, Feyerabend & Bryant, 2003). Body weight was measured at each visit, with shoes and coat removed.

Motivation to quit smoking and to reduce the number of cigarettes smoked was assessed on a 10-cm numerical visual analog scale using the following questions: "How motivated are you to quit smoking completely?" and "How motivated are you to cut down your number of cigarettes now?" (0=lowest motivation, 10=highest). Also asked were the questions "How important is it for you to quit smoking?" (0 =not important, 4=most important) and "How difficult do you believe it will be to quit?" (0=easy, 5=impossible). Motivation to quit and motivation to reduce smoking were measured and used in the analysis as two independent variables. We did not construct a norm-referenced motivation scale because motivation to reduce smoking can be quite strong without any motivation to stop smoking, and vice versa. The two items simply assess different kinds of motivations.

Subjects rated their withdrawal symptoms at each visit with five-point scales for "craving" and "total withdrawal symptoms" (0=none, 1=mild, 2=moderate, 3=severe, 4=very severe). Adverse events with ST were recorded throughout the study by asking subjects in the ST group an open-ended question at each visit. Adverse events were evaluated by the principal investigator as minor, moderate, or severe. Subjects who did not attend the 6-month visit were contacted by phone to assess smoking status and possible adverse events.

Definition of success

Point-prevalence abstinence was defined as self-reported abstinence during the previous week, verified by an exhaled CO level of less than 8ppm. Continuous abstinence was defined as self-reported abstinence, combined with a CO level of less than 8ppm, at all visits from weeks 4 to 7 and at month 6.

Point-prevalence smoking reduction included only those subjects who were still smoking daily at the endpoints and who had reduced their smoking to less than 7 cigarettes/day. Subjects not attending a visit were counted as smokers.

Data analyses

Based on the assumption of success rates of 30% in the ST arm and 15% in the control arm, a total of 120 patients were needed in each arm for a power of 80% and a two-tailed significance level of .05. The analyses of treatment effect were calculated on an intention-to-treat basis, with subjects who withdrew regarded as failures and included in the outcome analyses. The main outcome was analyzed using logistic regression. All analyses were performed using Stata release 9.

Results

Baseline characteristics and study completion

A total of 263 smokers were enrolled in the study. Baseline characteristic are shown in Table 1. The two

Table 1. Baseline characteristics of study subjects at randomization.

Characteristic	Group therapy only	Smokeless tobacco plus group therapy
Number of smokers	120	143
Sex (females/males)	57/63	71/72
Age (years)[a]	48.6 (10.2)	49.2 (10.7)
Number of daily cigarettes	24.5 (8.0)	25.1 (8.1)
Pack-years	30.9 (13.5)	30.9 (15.4)
Carbon monoxide (ppm)	21.1 (9.3)	21.3 (9.5)
FTND score (0–10)	5.9 (2.0)	6.0 (2.0)
Previous number of quit attempts	3.4 (2.7)	3.4 (2.5)
Duration of longest quit attempt (days)	299 (576)	433 (999)[b]
Previous use of nicotine replacement therapy (percent)	47.5 (50.1)	50.0 (50.2)
Motivation to quit smoking: 0 (low) – 10 (high)	8.4 (2.3)	8.5 (2.2)
Motivation to reduce smoking: 0 (low) – 10 (high)	8.1 (3.0)	8.4 (2.6)
How important is it to quit smoking? 0 (low) – 4 (high)	3.5 (0.6)	3.5 (0.6)
How difficult do you believe it will be to quit? 0 (low) – 5 (high)	3.6 (0.7)	3.4 (0.8)

Note. FTND = Fagerström Test for Nicotine Dependence. [a]All values from this point on are means with standard deviations. [b]The seemingly high difference in mean duration is due to one person in the "smokeless tobacco plus group therapy" group having a quit period of more than 20 years.

treatment groups were well balanced. At the 6-month visit, 8 subjects (3.0%) were lost to follow-up. Telephone follow-up was used for 171 subjects (65%; see Figure 1).

Smoking cessation

Abstinence rates were higher in the ST group than in the control group during the first 7 weeks, assessed as point prevalence for 4 of 5 comparisons and for continuous abstinence (Table 2). Continuous abstinence rates from weeks 4 to 7 were 31.5% for the ST group and 19.2% for the control group (OR=1.94, 95% CI=1.05–3.62, p=.023). No statistically significant difference in abstinence was found from week 7 up to 6 months, and the continuous abstinence rates were low: 11.9% for ST versus 8.3% for the control group (OR=1.48, *ns*).

Smoking reduction

The reduction rate (<7 cigarettes/day) was very low, and the difference between the ST and control groups was not statistically significant: 9.0% versus 13.3% at 4 weeks, 6.0% versus 5.3% at 7 weeks, and 4.5% versus 2.7% at 6 months, respectively.

Use of smokeless tobacco and nicotine levels

Compliance with the ST pellets was moderate. A total of 62% of subjects used ST pellets at week 1, and the percentage declined gradually to 20% at week 12 (Figure 2). The number of ST pellets used by compliant subjects was high (>8 pellets daily) until week 3 and declined to 3.6 pellets daily at week 12. After 6 months, 17.5% of subjects were still using a mean of 4.8 ST pellets per day. The figures cited here do not consider smoking status (abstinent, reduced smoking, or unchanged smoking status).

At 4 weeks, plasma nicotine levels showed the degree of nicotine substitution from ST to be 53% of baseline (smoking) values (Table 3).

Withdrawal symptoms

Withdrawal symptoms (craving and total withdrawal symptoms) were relatively low, and we found no difference between the two treatment groups, whether assessed for all subjects (independent of

Table 2. Point-prevalence and continuous abstinence rates for smokeless tobacco plus group therapy versus group therapy only.

	Group therapy only (n = 120)		Smokeless tobacco plus group therapy (n = 143)			
	Number of subjects	Percent	Number of subjects	Percent	Odds ratio	p value
Point-prevalence abstinence						
Week 1	40	33.3	75	52.4	2.67	.001
Week 2	35	29.2	61	42.7	2.14	.003
Week 3	36	30.0	51	35.7	1.52	.115
Week 4	41	34.2	68	47.6	2.1	.004
Week 7	25	20.8	52	36.4	2.52	.001
Week 12	26	21.7	39	27.3	1.56	.123
Month 6	25	20.8	33	23.1	1.31	.371
Continuous abstinence						
Week 4 to week 7 (inclusive)	23	19.2	45	31.5	1.94	.023
Week 7 to month 6 (inclusive)	10	8.3	17	11.9	1.48	.344

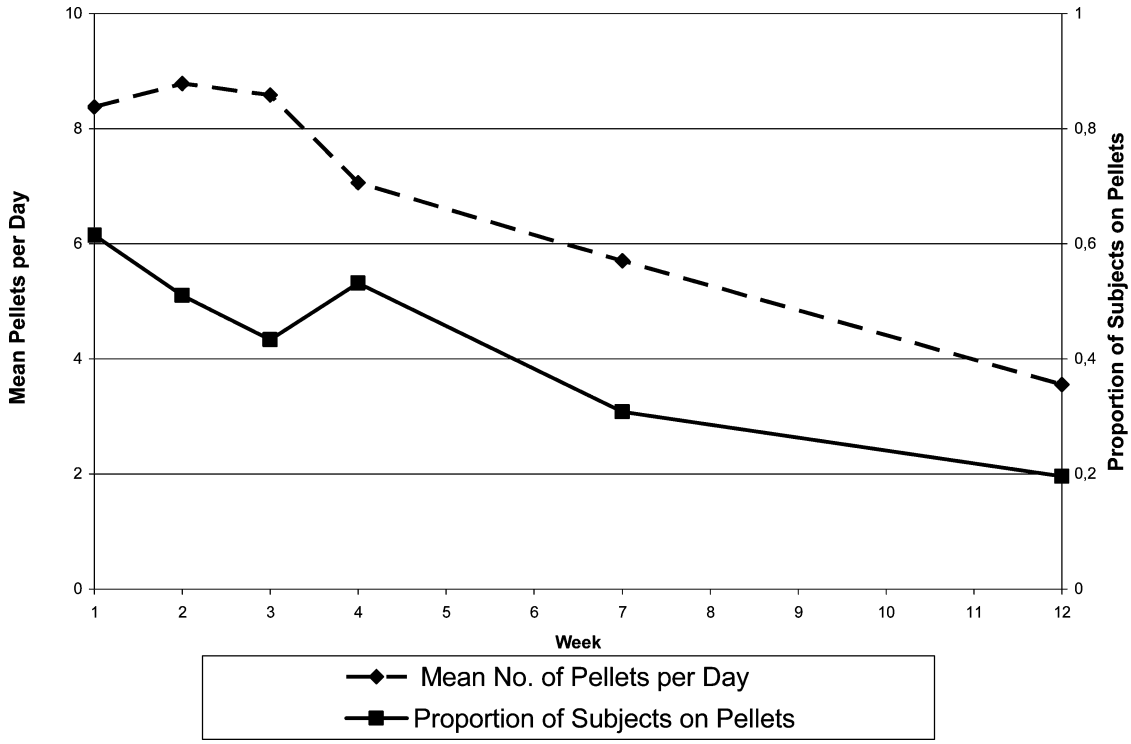

Figure 2. Mean number of smokeless tobacco pellets per day and proportion of subjects using smokeless tobacco pellets by treatment week.

smoking status) or for abstainers only. The mean craving score declined relatively rapidly during the first 3 weeks and then leveled off, with a more gradual decline up to the 6-month visit (Table 4).

Weight changes

For all subjects who attended the 6-month follow-up visit, mean body weight had increased significantly both in absolute weight (by 3.8 kg in the non-ST group and by 2.4 kg in the ST group) and in relative weight (5.2% and 3.3%, for the two groups, respectively). The difference in weight change between the two groups was statistically insignificant. When we subdivided the ST group into those who had stopped using ST and those still using it at 6 months, the mean weight gain in the subgroup that had stopped using ST was 2.9 kg (3.9%; $p \leq 001$), compared with 0.3 kg (1.1%; $p > .6$) in the subgroup still on ST pellets. That is, the mean weight gain in the ST group still on pellets was minimal. Due to small numbers, the difference in weight change between the two subgroups was statistically insignificant.

Adverse events

Adverse events were assessed only in the ST group. A total of 344 adverse events were reported during the study and coded into 63 different groups. The 10 most common adverse events, which comprised 65% of all events, were "air in stomach" (9.3%), pyrosis (8.4%), dry mouth or throat (7.3%), tiredness (5.8%), colic-like pain (4.9%), cough (4.4%), flushing (3.8%), mouth irritation (3.2%), and hiccups (1.9%). Adverse events were scored as moderate in 12 subjects, and severe in 3 subjects. A total of 15 subjects (11.2%) stopped using ST due to adverse events (8 subjects in week 1, 4 in week 2, and 3 in week 3). Reasons for

Table 3. Plasma nicotine concentration (ng/ml) at entry and after 4 weeks for the smokeless tobacco group versus group therapy only in abstainers.

	Group therapy only			Smokeless tobacco plus group therapy				
Abstainers (abstinent week 4)	Mean	*SD*	*n*	Mean	*SD*	*n*	Difference	*p* value
Plasma nicotine, week 0 (ng/ml)	15.8	1.4	34	16.0	1.0	64	0.3	.874
Plasma nicotine, week 4 (ng/ml)	1.2	1.4	34	8.5	1.0	64	7.3	.000
Difference week 0 – week 4 (ng/ml)	14.6*			7.5*				

Note. *n*= number of subjects; *SD*= standard devation; *$p < .000$.

Table 4. Craving in abstainers, according to treatment group (group therapy only and smokeless tobacco plus group therapy).

	Group therapy only			Smokeless tobacco plus group therapy				
Time point	Mean	*SD*	*n*	Mean	*SD*	*n*	Difference	*p* value
Week 1	2.2	0.2	40	1.8	0.1	73	−0.3	.19
Week 2	1.6	0.2	35	1.7	0.1	60	0.1	.58
Week 3	1.6	0.2	36	1.6	0.2	50	0.0	.95
Week 4	1.3	0.2	40	1.3	0.1	68	0.0	.87
Week 7	1.1	0.2	25	1.2	0.1	52	0.1	.67
Week 12	0.6	0.2	25	0.9	0.2	38	0.4	.18
Month 6	0.4	0.2	22	0.4	0.1	31	0.0	.90

Note. *n*= number of subjects; *SD*= standard deviation.

stopping were adverse taste (n=5), colic pain (n=4), sore throat (n=2), bad mood (n=1) and "other" (n=3).

Discussion

For the primary outcome of 6-month quit rate, we found no statistically significant effect between the two arms. However, we observed that it was feasible to use ST pellets for smoking cessation. ST users achieved acceptable nicotine substitution levels, and had an increased abstinence rate compared with the control group in the short term, but ST did not have any significant long-term treatment effect. The odds ratio for abstinence with ST, compared with the control group, was around 2 up to week 7, which is similar to that of NRT and bupropion SR versus placebo (Fiore et al., 2000; Hjalmarson, Franzon, Westin, & Wiklund, 1994; Hjalmarson, Nilsson, Sjostrom, & Wiklund, 1997; Silagy et al., 2006).

Several limitations of the present study might have contributed to lack of long-term efficacy. The overall success rate in both arms was lower than expected, and repeating the power calculations showed that approximately 281 subjects would have been needed in each group to avoid under-powering.

Several studies that used group therapy to examine the effect of NRT versus placebo have found a doubling of the success rate with NRT up to 1 year (Fiore et al., 2000; Hjalmarson et al., 1994; Hjalmarson et al., 1997; Silagy et al., 2006). However, the success rate in our study was very low. One contributing factor may have been that therapy was delivered by nurses (Rice & Stead, 2004). Another potential bias may have been the large early dropout of failures from the study. The subjects who dropped out were not exposed to the effect of more support and ST. We reduced the potential bias of early dropout by contacting 90% of subjects at the 6-month follow-up. Most participants who stopped attending the scheduled visits either did not quit smoking or relapsed, although at enrollment all were committed to quitting. A high dropout rate is common in many smoking cessation studies, although recent trials of new smoking cessation drugs initiated by the pharmaceutical industry reported much higher adherence, perhaps because subjects were receiving a new investigational product combined with more frequent visits, such as weekly visits for the first 7–12 weeks (Bohadana, Nilsson, Rasmussen, & Martinet, 2000; Gonzales et al., 2006; Hays et al., 2001; Jorenby et al., 2006). In addition, the inclusion criteria for smokers in these studies were narrower so that only highly motivated smokers were enrolled. However, the smokers enrolled in the present study scored high on motivation to quit and importance of quitting, although they believed it might be difficult to quit (see Table 1).

Other limitations of the present study should be noted. A placebo-controlled trial would have been preferable, but we would not work with the tobacco industry, and funding for the study came from our own limited budget. Moreover, the nurses involved in this study were involved in other smoking cessation trials during the study period so they did not have much time to speculate on the overall study outcome. In addition, we do not believe that the therapists induced a positive expectation in the ST group. Our impression is that the nurses were not convinced that ST would help or would be accepted by the smokers. In the control group we tried to focus on the beneficial aspects of quitting without using nicotine medication, and on being "nicotine-free" from the quit day. During recruitment the local newspapers ran a campaign about the disadvantages of using NRT to quit smoking, which helped to convince our study participants to quit without using NRT. Analysis of the degree of nicotine substitution from ST among abstainers at week 4, compared with their nicotine levels during smoking (at study entry), showed the nicotine substitution level to be 53%. This degree of nicotine substitution is in the same range that occurs with NRT, particularly the higher substitution levels attained by concomitant usage of two different formulations of NRT (McNabb, 1984; McNabb et al., 1982; Nørregaard et al., 1992; Tønnesen, Nørregaard, Simonsen, & Sæwe, 1991).

However, although the abstainers who were using ST attained a relatively high degree of nicotine substitution, no effect on withdrawal symptoms was observed compared with the "cold turkey" quitters. Only 62% used the ST after 1 week, declining to approximately 50% during weeks 2–4. This low compliance with ST might have affected the quit rate negatively. Future studies should focus more on adequate use of ST, as abstinence during the first few weeks after the quit day correlates with long-term abstinence (Tønnesen et al., 1999).

Dependence on ST was a potential concern when planning the trial. Almost 20% of subjects were still using ST after 6 months, which is in the same range or a little higher than reported long-term use rates with nicotine chewing gum or nasal spray (Fiore et al., 2000; Silagy et al., 2006; Sutherland et al., 1992; Tønnesen, Nørregaard, Mikkelsen, Jørgensen, & Nilsson, 1993). However, prolonged used of ST among subjects who continued to smoke was not reported.

The ST product used in this study was well tolerated, and most adverse events did not influence use. The 11% discontinuation rate with ST is in the same range as that reported for smoking cessation medications such as bupropion SR (Hurt et al., 1997; Tønnesen et al., 2003), and varenicline (Gonzales et al., 2006; Jorenby et al., 2006) but is higher than the 1%–5% discontinuation rates reported with NRT (Sutherland et al., 1992; Tønnesen et al., 1993). The harm from ST is estimated to be much lower than that from cigarette smoking; thus harm from long-term ST use is of minor importance compared with the harm from continued smoking per se (Bask & Melkersson, 2003; Hatsukami, Lemmonds, & Tomar, 2004; Hatsukami, Lemmonds, Zhang et al., 2004; Siegel, Benowitz, Ernster, Grady, & Hauck, 1992). However, given that almost 20% of subjects used ST for more than half a year, the potential harmful effects from ST have to be compared with those associated with other smoking cessation drugs such as nicotine replacement products, varenicline, and bupropion. The TSNA levels in the ST product used in the present study were similar to those found in Swedish snuff; that is, they were in the low range as compared with other ST products (Hatsukami, Lemmonds, Zhang et al., 2004; Rodu & Jansson, 2004). Of the 11 brands of ST available in the United Kingdom, 10 had detectable levels of TSNA that varied 130-fold (McNeil, Bedi, Islam, Alkhatib, & West, 2006; Stepanov, Jensen, Hatsukami, & Hecht, 2006). Thus our choice of a ST product with low TSNA levels seems an adequate one for smoking cessation.

The present study found that, compared with group support only, ST used for 7 (up to 12) weeks in combination with group sessions increased short-term but not long-term abstinence. ST use for smoking cessation was feasible, and ST was well tolerated. Further trials of ST as a potential smoking cessation aid, compared with NRT in combination with individual sessions, are ongoing.

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