Nicotine & Tobacco Research, Volume 14, Number 8 (August 2012) 902–909

Original Investigation

Comparing an Immediate Cessation Versus Reduction Approach to Smokeless Tobacco Cessation

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Received September 20, 2011; accepted November 18, 2011

Abstract

Introduction: Relatively few studies have investigated pharmacological or behavioral treatment of smokeless tobacco (ST) users who do not have immediate quit plans. In this study, we compared a reduction treatment approach with an immediate cessation approach in a population of ST users who reported no immediate plans to quit.

Methods: Subjects randomly assigned to the immediate cessation condition set a quit date soon after enrollment and were offered 2 weeks of nicotine patch therapy to help in their cessation efforts. Subjects assigned to the ST reduction group were provided with their choice of either 4 mg nicotine lozenge or ST brand switching to help them reduce their ST use or levels of nicotine exposure, respectively. Quit date was 6 weeks after the onset of treatment. Follow-up was at 12 weeks and 26 weeks postenrollment and 26 weeks postquit.

Results: Both 7-day point prevalence abstinence and prolonged abstinence rates following the quit date were significantly higher in the immediate cessation group versus the reduction group at 12 and 26 weeks (all p values $\leq .04$) and for prolonged abstinence at 6 months postquit ($p = .002$). Significant reductions in ST use among nonquitters were observed for both groups ($p < .0001$) with no differences between groups.

Conclusion: Our study demonstrated that immediate cessation with an established quit date resulted in greater cessation success than a gradual reduction approach among ST users who do not have an immediate quit plan but are motivated to quit.

Introduction

In recent years, there has been an increase in smokeless tobacco (ST) use in the United States among adolescents (Johnston, O'Malley, Bachman, & Schulenberg, 2011) and young adult males (Centers for Disease Control and Prevention, 2010). Concerns about the increasing prevalence of ST use are associated with the addiction potential of ST (Hatsukami & Severson, 1999; U.S. Department of Health and Human Services, 1986), and once addicted, the negative health consequences experienced by the ST users including oral pathologies, such as oral cancer (Bile, Shaikh, Afridi, & Khan, 2010; Boffetta, Hecht, Gray, Gupta, & Straif, 2008; Weitkunat, Sanders, & Lee, 2007), increased risk of pancreatic cancer (International Agency for Research on Cancer, 2007), both acute and fatal myocardial infarction (Bolinder, Alfredsson, Englund, & de Faire, 1994; Henley, Thun, Connell, & Calle, 2005; Piano et al., 2010; Teo et al., 2006), possibly Type 2 diabetes (Norberg, Stenlund, Lindahl, Boman, & Weinehall, 2006; Persson et al., 2000), and fetal toxicity (Rogers, 2009). Despite these concerns, relatively few studies have been conducted investigating the pharmacological and/or behavioral treatment of ST users. Results from prior well-controlled pharmacological treatment studies have produced outcomes with 3- to 12-month abstinence rates ranging from 10% to 45% (Dale et al., 2002, 2007; Ebbert et al., 2007; Fagerström, Gilljam, Metcalfe, Tonstad, & Messig, 2010; Hatsukami et al., 2000; Howard-Pitney, Killen, & Fortmann, 1999; Stotts, Roberson, Hanna, Jones, & Smith, 2003) and behavioral treatments have produced outcomes ranging from 10% to 55% (Boyle, Pronk, & Enstad, 2004; Boyle et al., 2008; Cigrang, Severson, & Peterson, 2002; Severson, Andrews, Lichtenstein, Gordon, & Barckley, 1998; Severson, Gordon, Danaher, & Akers, 2008; Severson et al., 2009; Walsh et al., 2003).

To date, most studies have targeted smokeless tobacco users who are planning to quit immediately. Previous studies have shown that among cigarette smokers, less than 20% are prepared to take action in quitting, that is, intending to quit within the next 30 days and having made a quit attempt in the past year (Etter, Perneger, & Ronchi, 1997; Fu et al., 2011; Wewers, Stillman, Hartman, & Shopland, 2003). Although no data are available among ST users, we can presume similar rates. These results suggest that the majority of the ST population is likely

doi:10.1093/ntr/ntr302
Advance Access Published on January 4, 2012

not ready to quit, yet no intermediary or alternative treatment approach has been developed.

Three preliminary studies have been conducted that were aimed at ST users who did not have immediate quit plans and which examined different approaches to reducing smokeless tobacco consumption rather than quitting. These approaches included (a) switching to ST products with lower levels of nicotine (Hatsukami et al., 2007), (b) substitution of ST use with tobacco-free snuff (Hatsukami et al., 2008), and (c) substitution of ST use with nicotine lozenge (Ebbert, Edmonds, Luo, Jensen, & Hatsukami, 2010). All these methods demonstrated a significant reduction in usual brand ST use, reduction in toxicant exposure (e.g., urinary 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and its glucuronides or total NNAL, a biomarker for a tobacco specific nitrosamine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone or NNK), and approximately 14%–26% of the population achieved 7-day point prevalence abstinence at 12 weeks in the active intervention groups (Ebbert et al., 2010; Hatsukami et al., 2007, 2008).

The present study compared ST reduction treatment with an immediate cessation approach in a population of ST users who reported no immediate plans to quit. In the reduction treatment condition, methods (brand switching and nicotine lozenge) found to be effective in reducing tobacco exposure in the prior studies were offered to the ST users. The primary outcome variables included appeal of treatment after randomization, the duration in treatment, point prevalence abstinence, the prevalence of prolonged abstinence (abstinence since quit date), and the extent of reduction of ST use. We hypothesized that offering tobacco exposure reduction methods would enhance retention in the study, would not reduce attempts at abstinence, and may in fact facilitate abstinence. Furthermore, we hypothesized that individuals unable to quit would sustain reduction from ST with no difference between groups.

Methods

Subjects

ST users more than 18 years old and who were interested in reducing ST use but not quitting (having an established quit date) within the next 90 days were recruited from advertisements on television and radio or in metropolitan and campus newspapers. ST users who were interested in the study telephoned our research clinic and were informed of the general overall goals of the study. They were initially screened over the phone to determine whether they met specific inclusion criteria. These criteria included daily use of ST for the past 6 months, good physical and mental health, and not regularly using other nicotine containing products. Eligible physical and mental health were confirmed by obtaining standardized medical and psychological history and approval by the study physician prior to enrollment. Female subjects could not be pregnant or nursing. Interested and eligible subjects were assigned a randomization number at this first phone contact, and the appropriate study description (reduction or immediate cessation) was given to the subject. Subjects were asked to come into the research clinic for an orientation visit to obtain informed consent and engage in more thorough screening. The orientation for those assigned to the immediate cessation condition was held separately from the orientation for those assigned to the reduced use condition. This approach was taken to minimize contamination across groups.

Subjects assigned to the immediate cessation condition were provided with a current standard treatment approach, where they were advised to set a quit date for the next clinic visit in 2 weeks. The harms associated with ST were discussed along with discussions of personal risks for continued use, benefits for quitting, and concerns or perceived obstacles for quitting. Subjects were then scheduled for their next (Week 0) visit on the quit date and given one patch for their first day. On the Week 0 quit day visit, a 2-week supply of pharmacological treatments (nicotine patch) was offered to this group. For the immediate cessation group, the nicotine patch was used because we believed that this treatment would lead to greater ease of use and compliance as well as a steady amount of nicotine. Additionally, we did not want to contaminate the immediate cessation group with the use of an oral nicotine product that may serve as a substitute for ST as intended in the gradual reduction group. Subjects were advised to use the patch per product insert instructions. If a subject experienced adverse effects from the 21 mg nicotine patch, they were downtitrated to the 14 mg patch. The subjects were told that they could purchase product if they decided to continue nicotine replacement therapy (NRT) use after the 2-week supply was used. Only a 2-week supply was provided because although nicotine replacement products have been observed to reduce withdrawal symptoms, they have not been found to improve cessation compared with placebo in ST users (Hatsukami, Jensen, Allen, Grillo, & Bliss, 1996; Hatsukami et al., 2000).

The treatment content outlined by the Agency of Research and Quality (Fiore et al., 2000) was followed for the behavioral counseling sessions. During the course of treatment, methods for sustaining cessation were discussed (e.g., identification of triggers and how to deal with these triggers). A self-help manual developed for ST users was given to the subject.

For those unable to quit after the quit date, subjects were asked whether they would like to set another quit date and were provided counseling on ways to deal with situations that led to a slip and relapse. They were not supplied with additional NRT. If subjects did not want to set another quit date, then a positive message reinforcing their attempt at quitting was given, they were encouraged to continue to attend clinic visits, and their ST use was tracked through the remainder of the study.

Subjects who were assigned to the ST reduction group were also given information on the harms associated with tobacco use; the reduction in exposure to toxic substances with reduction in use (as confirmed by prior studies); the uncertainty of whether reduction in level of use will result in significant reduction in harm, although some harms are presumed to be dose-related; and the importance of making cessation the ultimate goal to achieve true reduction in harm. On the Week 0 visit, subjects were provided with their choice of either 4 mg nicotine lozenge (Commit(r)) or brand switching to help them reduce their ST consumption.

Nicotine lozenge was offered because in our pilot ST reduction study, there was a trend toward more subjects achieving a $\geq$75% reduction in dips per day and a higher 7-day self-reported tobacco abstinence rate (14% vs. 6.7%) compared with the no nicotine lozenge group (Ebbert et al., 2010). The lozenge was also offered because lozenge use sustains some of the sensory aspects of ST

use. Subjects choosing the lozenge were instructed on appropriate use of the lozenge as described in the product insert. Subjects were advised to substitute a lozenge for every other dip at the 50% reduction for the first 2 weeks and use lozenges in a 3:1 ratio to meet the 75% reduction goal. If subjects assigned to the 4 mg lozenge experienced symptoms of nicotine toxicity, they were downtitrated to the 2 mg product.

Subjects choosing brand switching switched to Skoal Long Cut Straight or Long Cut Wintergreen to meet the ~25% to 50% nicotine reduction for the first 2 weeks. These ST products have a free nicotine content of 4.99 and 4.41 mg/g, respectively. The usual brand products popular among subjects in our study included Kodiak Wintergreen, Grizzly Long Cut Wintergreen, and Copenhagen Long Cut Regular, which have free nicotine content that ranges from 5.67 mg/g to 7.14 mg/g (Richter, Hodge, Stanfill, Zhang, & Watson, 2008). Subjects then switched to Skoal Bandits Wintergreen or Skoal Bandits Straight for the 4 weeks of ≥75% nicotine reduction (free nicotine content 0.39 and 0.03 mg/g, respectively; Centers for Disease Control and Prevention, 1999; Richter et al., 2008). ST users who already used Skoal as their usual brand were encouraged to be in the nicotine lozenge reduction arm. A targeted quit date after the 4 weeks of ≥75% reduction was established. Subjects, however, could spontaneously express an interest in quitting prior to Week 6.

Strategies for reduction were discussed and concerns or obstacles about reduction were elicited from the subject. A structured treatment plan for reduction was provided, including ways to monitor use. At 6 weeks, on their quit date, subjects received a phone call for behavioral counseling. For quitting, the same treatment and treatment materials provided to the immediate cessation group were utilized. The number of contacts and duration of contact (10–15 min per session) in this group were similar to the immediate cessation condition. If they were unable to quit, they were encouraged to maintain reduction or further reduce but were given the message that quitting remains the ultimate and only safe goal.

Figure 1 provides a schema of the design. All subjects were followed with a clinic visit at Weeks 0 (quit date or assignment to reduction product), 2, 4, 8, 12, and 26 after enrollment in the study. Additionally, at Week 6, subjects were followed with a phone call. The reduction group was seen for an additional visit at 32 weeks for the 6-month postquit follow-up visit. Tobacco use diaries were completed during the day, and subjects were asked to record the time and amount of ST, medicinal nicotine, or other tobacco product use for a period of 8 weeks. They also indicated when they opened a new tin. At each of the clinic visits, subjects were assessed for tobacco and nicotine product use, carbon monoxide, and vitals (heart rate and blood pressure).

Biochemical Measures

The level of carbon monoxide (CO) was measured in subjects' expired breath to assess whether they were smoking. Urinary cotinine, a major nicotine metabolite, was assessed to measure the level of nicotine intake during treatment and for abstinence confirmation at follow-up (Society for Research on Nicotine and Tobacco Subcommittee on Biochemical Verification, 2002). Urinary anatabine, a minor tobacco alkaloid not present in nicotine replacement products, was used as a tobacco exposure marker and to verify abstinence in subjects receiving NRT (Jacob et al., 2002). Urinary samples were obtained at baseline, Weeks 4, 8, 12, and 26 to assess for cotinine or anatabine (if subject was using a medicinal nicotine product) and analyzed as previously described (Hecht et al., 1999; Murphy et al., 2004). Biochemical confirmation of abstinence was considered for subjects with CO <6 ppm, urinary cotinine <20 ng/ml, and anatabine <2 ng/ml (among those using medicinal nicotine products).

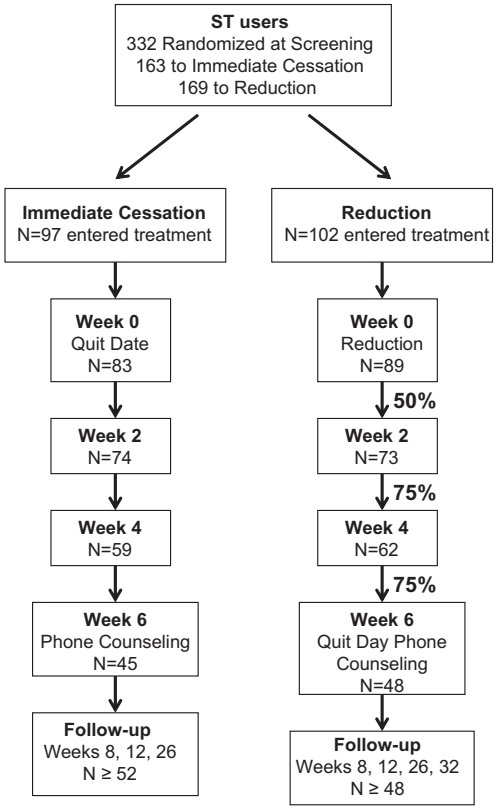

Figure 1. Study design. The number of subjects enrolled at each time point and the treatment schema are shown. The percent reduction is shown for Weeks 0 through 4 in the reduction arm.

Compensation

Subjects were paid $25.00 for each visit for a total of $150 for the immediate cessation group and $175 for the ST reduction group (extra $25 was due to additional follow-up).

Statistics

Summary statistics, mean (*M*) ± standard deviation (*SD*) for continuous variables and frequency (%) for discrete variables, were calculated for baseline and follow-up data. To compare different treatment groups, *t* test and Wilcoxon rank-sum test were, respectively, used for normally and nonnormally distributed continuous variables, and chi-square test or Fisher's exact test was used for discrete variables, as appropriate. Comparisons between different time points within a group were conducted with paired *t* test or Wilcoxon's sign-rank test. Linear mixed models were used for analyzing the amount of ST use at different time points adjusting for the background level reported at the orientation visit, for each treatment group. For all analyses, *p* values of .05 or less were considered statistically significant.

Results

Subject Characteristics

There were 332 subjects who were randomized at the phone screening (163 in the immediate cessation group and 169 in the reduction group). Of the 332 subjects, 206 subjects attended an orientation meeting with 101 in the immediate cessation and 105 in the reduction group, indicating that one approach was not favored over another ($OR = 1.01$, $p = .98$). Of the 206 enrolled, 7 were found to be ineligible, leading to a total of 199 subjects who continued with the study (97 in the immediate cessation group and 102 in the ST reduction group).

Among the randomized subjects, 99.7% were male, the $M \pm SD$ age was 34.8 ± 8.5, the number of tins per week was 3.6 ± 2.4, and the duration of the use of at least 6 dips per day was 11.8 ± 8.2 years. Almost all subjects used one brand of ST, but the brands varied from subject to subject. The most popular brands, which together were used by 81% of subjects at baseline, were Grizzly, Copenhagen, Skoal, and Kodiak. Subjects who entered treatment compared with those who chose not to enter treatment after randomization were significantly older (35.9 ± 9.0 vs. 33.2 ± 7.5, $p = .005$), but no other demographic and ST use history were significantly different. Among those who entered treatment, no significant differences were observed between the groups.

Subject Dispositions

A substantial dropout rate was observed (see Figure 1). Among the 199 subjects who were eligible and attended orientation, no significant differences were observed in retention rates for immediate cessation and ST reduction groups at Week 2 (76% vs. 72%, respectively), Week 4 (61% vs. 61%, respectively), and at Week 6 (46% vs. 47%, respectively).

Product Use and ST Use During Treatment

Among subjects assigned to the immediate cessation group, three were unable to tolerate the patch and switched to nicotine lozenge and two subjects were reduced to the 14 mg patch. During the 2-week medication assignment, 77.3% reported use of NRT (40.2% for all 14 days). Analysis of ST reduction across all subjects in the immediate cessation group revealed significant reductions for ST use from Week 0 to Week 2 of ~7 dips per day and ~3 tins per week ($p < .0001$), whereas the reduction from Week 2 to Week 6 was not statistically significant (see Table 1).

Among subjects assigned to the ST reduction group, 14 subjects used Skoal products at baseline and were assigned to the nicotine lozenge, 24 chose brand switching, 53 chose nicotine lozenge for ST reduction, and 11 were assigned reduction but dropped before choosing a reduction method. Of the 24 subjects who chose brand switching, 96% used Skoal Long Cut Straight or Long Cut Wintergreen and 83% substituted this product for their usual brand >80% of the time over the first 2 weeks. About 79% used Skoal Bandits Wintergreen or Skoal Bandits Straight and 50% substituted this product for their usual brand >80% of the time over the subsequent 4 weeks. Of those who chose nicotine lozenge for ST reduction, 52% used nicotine lozenge most of the time during the first 6 weeks (80% of the days or more) and 10% did not use at all. Significant reductions were observed for ST use in the nicotine lozenge group from Week 0 to Week 2 of ~4 dips per day and ~2 tins per week ($p < .0001$) and from Week 2 to Week 4 of ~1 dip per day and ~0.5 tins per week ($p < .001$ dips/day; $p < .01$ tins/week); whereas the reduction from Week 4 to Week 6 was not statistically significant (see Table 1).

Abstinence Rates at Follow-up

Biochemically confirmed abstinence rates were calculated as intent-to-treat (dropouts or missing values were considered using ST). Seven-day point prevalence abstinence was higher among those in the immediate cessation versus reduction group at Week 12 ($p = .04$), Week 26 ($p = .03$), and near significance when comparing Weeks 26 versus 32 to equilibrate time since quit between the two groups ($p = .06$). Prolonged abstinence, defined as cessation from quit date, was significantly higher in the immediate cessation group versus reduction group at Week 12 ($p = .02$), Week 26 ($p = .002$), and when comparing Weeks 26

Table 1. *M* (*SD*) Product Use

Group	Baseline	Week 2	Week 4	Week 6
Immediate cessation (*N*)	97	74	59	45
Percent using ST		26	22	33
ST use (dips/day)	7.5 (6.9)	0.5 (1.6)	0.8 (2.2)	0.6 (1.5)
Tins per week	3.5 (3.1)	0.3 (0.9)	0.7 (2.8)	0.4 (1.0)
Cotinine, ng/ml	2,522 (2,319)		646 (1,252)	
Brand switching (*N*)	24	23	17	15
Dips/day	8.2 (3.0)	7.6 (2.8)	5.9 (3.4)	4.7 (2.9)
Tins per week	3.9 (1.7)	3.7 (2.5)	2.7 (1.0)	2.0 (1.2)
Cotinine, ng/ml	2,420 (1,848)		1,977 (1,697)	
Nicotine lozenge (*N*)	68	50	45	33
Percent using lozenge		94	82	70
Lozenge/day		2.6 (1.5)	3.4 (1.6)	3.7 (2.4)
Dips/day	6.9 (2.5)	2.9 (1.6)	1.8 (1.6)	1.3 (1.9)
Tins/week	3.4 (3.4)	1.5 (1.3)	1.0 (1.1)	0.8 (1.1)
Cotinine, ng/ml	2,354 (1,861)		1,462 (1,197)	

Note. ST = smokeless tobacco.

Table 2. Point Prevalence and Prolonged Abstinence Rates by Treatment

Group	Week 12	Week 26	Week 32
7-day point prevalence abstinence			
Immediate cessation (%)	31	21	NA
Reduction (%)	17	10	11
p Value	.04	.03	.06[a]
Prolonged abstinence			
Immediate cessation (%)	13	11	NA
Reduction (%)	4	1	1
p Value	.02	.002	.002[a]

Note. [a]26 weeks for immediate cessation versus 32 weeks for reduction (6-month postquit date).

versus 32 ($p = .002$) (see Table 2). At follow-up, among those who used ST in the past 7 days, significant decreases were observed for dips per day and tins per week of >4.6 and ~2, respectively, for the immediate cessation group and >2.8 and ~2 for the reduction group (all $p < .0001$), but no significant differences were observed across the two groups at each time point.

Discussion

The results of this study were contrary to the hypothesis: ST users who do not have an immediate plan for quitting are more likely to be successful using an immediate cessation approach rather than a reduce-to-quit approach. Several trials have assessed the effect of smoking reduction on cessation among smokers who do not have a plan to quit. Some of these trials have found that treatments that reduce cigarette smoking also increase cessation rates (Carpenter, Hughes, Solomon, & Callas, 2004; Rennard et al., 2006; Wennike, Danielsson, Landfeldt, Westin, & Tonnesen, 2003). In other studies, smokers who reduced by at least 50% had a greater probability of future cessation (Falba, Jofre-Bonet, Busch, Duchovny, & Sindelar, 2004; Farkas, 1999; Hyland et al., 2005). However, studies have also found that reducing smoking has no significant effect on cessation rates (Carpenter, Hughes, & Keely, 2003; Etter, Laszlo, & Perneger, 2004; Hughes, Lindgren, Connett, & Nides, 2004; Joseph et al., 2008). Overall, the impact of reduction on future smoking cessation and how this may relate to ST users is unclear. The results of our study with ST users point to the importance of establishing an immediate quit date to maximize success. However, it is possible that among those who are not interested in quitting at all, the gradual reduction approach may be used as a method to engage them in an intervention.

In this study, the 7-day point prevalence abstinence rates at 12 and 26 weeks for the immediate cessation group were similar or superior to the rates found in other studies that utilized behavioral treatments, including motivational cessation counseling (Boyle et al., 2008; Severson et al., 1998, 2009). For the reduction group, the 7-day point prevalence was also similar to that observed in our other reduction studies at the 12-week follow-up period (14%–26% in active interventions; Ebbert et al., 2010; Hatsukami et al., 2007, 2008). However, the abstinence rates in our study were not as high as other studies that utilized bupropion sustained-release (Dale et al., 2002), varenicline (Fagerström et al., 2010), behavioral web (Severson et al., 2008) and telephone-based interventions (Cigrang et al., 2002) or a combination of pharmacologic and behavioral interventions (Dale et al., 2007; Hatsukami et al., 2000).

Although reduction did not lead to higher cessation success, significant reductions in use occurred both during and following treatment. At follow-up, the extent of reduction was significant among both treatment groups with reductions in ST of more than 4 dips per day and almost 2 tins per week. These results are consistent with prior studies that we conducted which showed significant reductions in the amount of ST use, cotinine, and total NNAL during treatment as well as follow-up (Ebbert et al., 2010; Hatsukami et al., 2008).

Given a choice, more subjects preferred using nicotine lozenge to reduce their use of ST rather than brand switching. Anecdotal reports indicate that smokeless tobacco users motivated to eventually quit ST use were not interested in switching to another tobacco product but rather preferred a medicinal product as a means toward cessation.

In this study, we observed a substantial dropout rate. Following the phone screen, 38% of the subjects dropped before they came for the first clinic visit. Similar high dropout rates between telephone screening and the first clinic visit of 27%–40% have been observed in other ST studies that we have conducted (Ebbert et al., 2010; Hatsukami et al., 2007, 2008) as well as ST studies conducted by others (Ebbert, Croghan, Severson, Schroeder, & Hays, 2011; Ebbert et al., 2007). The rationale for randomizing subjects during the phone screen was to determine if there was a difference in appeal between the two quitting approaches as measured by attendance on the first clinic visit. We found no difference in dropout rate between the immediate cessation group and reduction group, indicating that there was no difference in appeal between these two approaches. Among those who did attend the first clinic visit, our dropout rates prior to completion tended to be higher than other ST trials (Dale et al., 2007; Ebbert et al., 2007, 2011; Ebbert, Severson, Croghan, Danaher, & Schroeder, 2009; Fagerström et al., 2010; Wallstrom, Bolinder, Hasseus, & Hirsch, 2010). The difference may be due to some of these trials having more frequent clinic visits (Ebbert et al., 2007), which may increase retention, or increased retention due to more subjects having successfully quit (i.e., higher abstinence rates; Ebbert et al., 2009, 2011; Wallstrom et al., 2010) or both (Dale et al., 2007; Fagerström et al., 2010). Nonetheless, these results show that once in the study, one approach is not superior over another approach in retaining ST users in the treatment program.

In summary, among ST users, immediate cessation with an established quit date showed greater cessation success than a gradual reduction approach among those who do not have a quit plan but are motivated to quit. Nevertheless, future studies should consider ST users who are unmotivated to quit to determine if recommendations to reduce would engage them in treatment.

Funding

This work was supported by the National Institute on Drug Abuse of the National Institutes of Health (R01DA14404) and the National Heart, Lung and Blood Institute of the National Institutes of Health (T32HL007741).

Declaration of Interests

Dorothy Hatsukami had received a grant from Nabi Biopharmaceutical to conduct a clinical trial on the nicotine vaccine for smoking cessation.

Acknowledgments

The authors would like to thank Herb Severson for his valuable input on the design of the study.

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