Nicotine & Tobacco Research Volume 9, Number 1 (January 2007) 43–52

Effect of high-dose nicotine patch therapy on tobacco withdrawal symptoms among smokeless tobacco users

Jon O. Ebbert, Lowell C. Dale, Christi A. Patten, Ivana T. Croghan, Darrell R. Schroeder, Thomas P. Moyer, Richard D. Hurt

Received 26 August 2005; accepted 9 January 2006

No pharmacotherapies have been shown to increase long-term (⩾6-month) abstinence rates among smokeless tobacco (ST) users. Available evidence suggests that underdosing may occur with standard-dose nicotine replacement therapy (NRT) in ST users. We investigated the effect of high-dose nicotine therapy on tobacco withdrawal symptoms among ST users in a randomized, controlled clinical pilot study. A total of 42 ST users using at least 3 cans or pouches per week were randomized to nicotine patch doses of 63, 42, or 21 mg/day or placebo for 8 weeks. Multiple daily assessments of tobacco withdrawal and nicotine toxicity were obtained with an electronic diary. During the first week of nicotine patch therapy, we observed a dose-response relationship such that higher nicotine patch doses were associated with less decreased arousal ($\chi^2=6.87$, $p=.009$), less negative affect ($\chi^2=3.85$, $p=.05$), and less restlessness ($\chi^2=3.90$, $p=.048$). During the second week, higher nicotine patch doses were associated with less decreased arousal ($\chi^2=6.77$, $p=.009$). Overall, the frequency of nicotine toxicity symptoms did not differ by dose group. Of specific symptoms, nausea was observed to be more frequent in the 63 mg/day dose group compared with placebo ($p=.035$). In conclusion, high-dose nicotine patch therapy resulted in a greater reduction of tobacco withdrawal symptoms among ST users using at least 3 cans per week. High-dose nicotine patch therapy is safe and well tolerated in this population of tobacco users.

Introduction

Approximately 7.7 million individuals aged 12 years or older in the United States report current (past month) use of smokeless tobacco (ST), which includes moist snuff and chewing tobacco (Substance Abuse and Mental Health Services Administration, 2004). ST is estimated to be the greatest exogenous source of human exposure to carcinogenic nitrosamines (U.S. Department of Health and Human Services, 2002), and long-term ST use is known to increase the risk for periodontal disease (Offenbacher & Weathers, 1985), precancerous oral lesions (Mattson & Winn, 1989; Silverman, Gorsky, & Lozada, 1984; Sinusas, Coroso, Sopher, & Crabtree, 1992) and oropharyngeal cancer (Stockwell & Lyman, 1986; Winn, 1992; Winn, Blot, Shy, Pickle, Toledo, & Fraumeni, 1981). ST use also may increase the risk of cancers of the esophagus, larynx, stomach, and pancreas (Alguacil & Silverman, 2004; Connolly, Winn, Hecht, Henningfield, Walker, & Hoffmann, 1986; Mattson & Winn, 1989). Effective interventions are needed because long-term ST use leads to tobacco dependence (National Institutes of Health, 1986) and 64% of ST users report the desire to stop ST use (Severson, 1992).

Results from clinical trials assessing the efficacy of interventions for ST users have been promising but mixed. A systematic review of behavioral interventions for the treatment of ST use (Severson, 2003) observed that treatments provided in the setting of a dental office visit (Severson, Andrews, Lichtenstein, Gordon, & Barckley, 1998; Stevens, Severson, Lichtenstein, Little, & Leben, 1995) or athletic team (Walsh, Hilton, Masouredis, Gee, Chesney, &

Jon O. Ebbert, M.D., M.Sc., Lowell C. Dale, M.D., Christi A. Patten, Ph.D., Ivana T. Croghan, Ph.D., Darrell R. Schroeder, M.S., Thomas P. Moyer, Ph.D., Richard D. Hurt, M.D., Mayo Clinic College of Medicine, Rochester, MN.

Correspondence: Jon O. Ebbert, M.D., M.Sc., Mayo Clinic College of Medicine, 200 1st Street SW, Rochester, MN 55905, USA. Tel: +1 (507) 266-1944; Fax: +1 (507) 266-7900; E-mail: ebbert.jon@mayo.edu

ISSN 1462-2203 print/ISSN 1469-994X online
DOI: 10.1080/14622200601078285

Ernster, 1999) were the most efficacious. However, pharmacologic interventions for increasing tobacco abstinence rates among ST users have been disappointing (Ebbert, Rowland et al., 2004).

Pharmacotherapy is an essential element of a multicomponent approach to the treatment of tobacco use and dependence (Fiore et al., 2000). Tobacco withdrawal symptoms and craving experienced during tobacco abstinence promote relapse to tobacco use (Killen & Fortmann, 1997; West, Hajek, & Belcher, 1989), and NRT effectively moderates these symptoms in both cigarette smokers (Fant, Owen, & Henningfield, 1999; Hughes, 1993; Shiffman, Khayrallah, & Nowak, 2000) and ST users (Hatsukami et al., 2000; Hatsukami, Jensen, Allen, Grillo, & Bliss, 1996). However, although NRT has been shown to increase tobacco abstinence rates at 6 months or longer among cigarette smokers (Silagy, Lancaster, Stead, Mant, & Fowler, 2004), NRT has not been shown to increase long-term abstinence rates in ST users (Ebbert, Rowland et al., 2004).

Among the randomized controlled trials of pharmacologic interventions for adult ST users conducted to date, two have investigated the efficacy of the nicotine patch (Hatsukami et al., 2000; Howard-Pitney, Killen, & Fortmann, 1999). In these studies, nicotine patch was delivered in "standard" doses of 15 mg/day (Howard-Pitney et al., 1999) and 21 mg/day (Hatsukami et al., 2000). Despite improvements in short-term tobacco abstinence, reductions in craving and withdrawal symptoms (Hatsukami et al., 2000) and decreased relapse rates (Howard-Pitney et al., 1999), nicotine patch therapy was not effective for increasing long-term (>6-month) tobacco abstinence rates.

Experiments quantifying daily nicotine exposure during cigarette and ST use have shown that although maximal serum concentrations of nicotine are similar between cigarettes and ST, overall nicotine exposure has been observed to be twice as high after single doses in ST users as it is in cigarette smokers (Benowitz, Porchet, Sheiner, & Jacob, 1988). Higher doses of nicotine patch therapy may, therefore, be needed in ST users to increase the long-term efficacy of NRT. However, the clinical recommendation for use of higher than "standard" doses of nicotine patches (14 or 21 mg/day) for ST users may be hampered by clinician discomfort and concerns about safety despite extant literature demonstrating that higher doses are safe in cigarette smokers (Benowitz, Zevin, & Jacob, 1998; Dale, Hurt, Offord, Lawson, Croghan, & Schroeder, 1995; Fredrickson et al., 1995; Hughes et al., 1999).

To assess the effect of high-dose nicotine patch therapy on tobacco withdrawal symptoms and obtain preliminary efficacy estimates, we conducted a prospective, randomized Phase II clinical pilot study of ST users randomized to nicotine patch doses of 21, 42, or 63 mg/day or placebo.

Method

Subjects

The Mayo Foundation Institutional Review Board and the U.S. Food and Drug Administration reviewed and approved the study protocol prior to recruitment and enrollment. Subjects were recruited from the community of Rochester, Minnesota, between November 2003 and October 2004 through press releases and local advertisements.

Eligible subjects were required to be at least 18 years of age, be in good general health, have used ST daily for the past year, be interested in stopping ST use, and be using at least 3 cans or pouches of ST per week at the time of enrollment. We selected subjects who used at least 3 cans or pouches per week to minimize the risk of patients experiencing nicotine toxicity symptoms with the higher doses. Subjects were excluded if they had unstable angina, myocardial infarction, or coronary angioplasty in the past 3 months; had clinically significant depression; had a history of active alcoholism or drug abuse in the past year; had hypersensitivity to nicotine patches; had serious skin allergies or dermatoses; used another form of tobacco (cigarettes, pipes, or cigars) in the past 10 days; used an investigational drug, an antipsychotic or antidepressant medication, or another tobacco treatment intervention within 30 days of enrollment; were pregnant or lactating or likely to become pregnant during the medication phase; or were unable or unwilling to use a personal digital assistant (PDA) electronic diary; or if another member of their household participated in the study.

Procedures

After initial telephone prescreening, eligible ST users attended an information meeting at which time the study was explained, inclusion and exclusion criteria were discussed, informed consent was obtained, and questionnaires were completed. Subjects underwent a screening history and physical exam by a physician prior to randomization.

The study was divided into 3 stages: an out-patient preadmission phase (stage 1), an in-patient General Clinical Research Center (GCRC) phase (stage 2), and an out-patient treatment and follow-up phase (stage 3). During each stage, an electronic diary (Stone & Shiffman, 2002) was used to assess symptoms of tobacco withdrawal and nicotine toxicity.

The electronic diary system was designed by Invivodata (Pittsburgh, Pennsylvania) and implemented on Palm (Milpitas, California) m500 PDA

palm-top computers. The electronic diary system was password-protected and provided alarm and delay functions for subject convenience and safety. A simple consistent user-interface was used to present questions and record answers. The software has been used extensively in previous research (Shiffman et al., 1997; Shiffman, Hickcox, Paty, Gnys, Kassel, & Richards, 1996; Shiffman, Paty, Gnys, Kassel, & Elash, 1995). Information was collected with audible PDA-prompted morning reports, 5 random daily assessments, and evening reports. We used the electronic diary to obtain tobacco withdrawal data from the start of stage 1 through the end of stage 3. Nicotine toxicity symptoms were collected on the electronic diary during stages 2 and 3 of the study.

Tobacco withdrawal data were drawn from affect assessments and sleep disturbance factors. The 5 random daily prompts collected affect assessments on the following specific parameters (Shiffman, Paty, Gnys, Kassel, & Hickcox, 1996): negative affect (irritable, miserable, sad, and/or tense); decreased arousal factor (tired, energetic, and/or overall arousal level); attention disturbance factor (difficulty concentrating); and restlessness. Participants rated mood adjectives derived from the circumplex model of affect (Russell, 1980). The circumplex model specifies that affect consists of bipolar dimensions: positive-negative affect and arousal. These items were scored on a 4-point scale (''NO!!, no??, yes??, YES!!''; Meddis, 1972). We included bipolar items to directly tap these key circumplex dimensions as well as items based on affect dimensions drawn from the *Diagnostic and Statistical Manual of Mental Disorders* (4th edition) criteria for tobacco withdrawal (American Psychiatric Association, 1994). Sleep disturbance factors (i.e., trouble falling asleep, numbers of awakenings, and sleep quality) were collected from morning reports. A 4-point scale was used to assess trouble falling asleep and number of awakenings. A 5-point scale was used to rate the quality of sleep.

The electronic diary collected adverse events potentially related to nicotine toxicity based on a questionnaire used in previous trials (Dale et al., 1995; Ellenhorn & Barceloux, 1995) modified for ST users. Toxicity symptoms were rated on a 4-point scale (none, mild, moderate, or severe). Symptoms were collected during the evening reports. Subjects were asked to rate the greatest severity of symptoms experienced over the course of the day for the following symptoms: nausea, vomiting, excessive saliva production, abdominal pain, diarrhea, perspiration, headache, dizziness, hearing and visual disturbances, confusion, weakness, exhaustion, shortness of breath, and fainting spells (Ellenhorn & Barceloux, 1995).

Stage 1 (out-patient preadmission) was a 1-week period prior to the in-patient stay to obtain baseline measures. During this period, subjects were trained on the use of the electronic diary in two individual sessions conducted on consecutive days. The first session lasted for 1 h and reviewed the study protocol and rationale for use of the electronic diary. The second session lasted 90 min and was devoted to the electronic diary performance task training and rehearsal. Sessions were conducted by clinical research assistants who were trained and supervised by one of the investigators. Baseline tobacco withdrawal data were collected for 1 week prior to entering the GCRC.

Stage 2 (in-patient GCRC) consisted of a 3-day in-patient stay at the Mayo GCRC. Patients were admitted for observation to ensure subject safety with the high doses of nicotine used in the study. On day 1, subjects were allowed to use ST ad libitum during the day and asked to quit ST at 2400 hours. Day 2 was the target quit date.

On GCRC day 2, subjects were randomly assigned in a double-blind fashion to nicotine patch doses of 21, 42, or 63 mg/day or placebo. Placebo patches were designed to be identical in appearance to active nicotine patches, which were developed by and purchased from 1-800 patches (www.1800PATCHES.com). Patches were labeled (A, B, and C), and all subjects received an equal number of patches. The A patch was active for the 21 mg/day group, the A and B patches were active for the 42 mg/day group, and all 3 patches were active for the 63 mg/day group. Study personnel who did not have subject contact used the randomization schedule to dispense the appropriate study patches into containers labeled according to subject identification number. Group assignment with allocation concealment was determined by a randomization schedule, and subjects were assigned the next sequential subject identification number upon arrival at the GCRC. Patches were distributed from a central pharmacy. Instructions for patch use and a body map demonstrating appropriate placement and rotation were reviewed with the subjects.

Each subject wore three patches simultaneously. Such a scheme allowed for blinded removal of active nicotine patches if nicotine toxicity developed because patches were added and removed in the same order. Daily patch application was staggered: Patches A and B were applied at 0800 hours, and patch C was applied at 0900 hours. This approach was based on our previous research (Ebbert, Dale, Vickers, Gauvin, Bunge, & Hurt, 2004) and on reports suggesting that subjects receiving nicotine patch doses of 63 mg/day may experience nicotine toxicity when all patches are applied simultaneously (Benowitz et al., 1998). Patches were worn on

different anatomical sites each day. If a subject experienced insomnia or vivid dreams, nocturnal removal of the patches was allowed.

Subjects experiencing symptoms of nicotine toxicity removed patches in the following order: A then B then C. One patch was removed at a time, and subjects were monitored. Patients were rechallenged with the same dose if the symptoms resolved. If the subject did not tolerate patch rechallenge, the subject completed the study on the maximum tolerated number of patches. Subjects participated in group and individual behavioral therapy conducted by the investigators. The electronic diary was used to collect tobacco withdrawal symptoms and, after the nicotine patches were started, nicotine toxicity symptoms.

Stage 3 (out-patient treatment and follow-up) consisted of 8 weeks of nicotine patch therapy with a taper. Subjects wore 3 patches during weeks 0–4, two during weeks 5 and 6, and one during weeks 7 and 8. Subjects used the electronic diary to collect tobacco withdrawal and toxicity symptoms during this phase. Subjects had weekly visits in each of the 4 weeks following discharge from the GCRC. During these visits, subjects' electronic diary information was encrypted and uploaded to the Invivodata database, and subjects obtained new patches and received a brief behavioral intervention counseling session with a clinical research assistant. Subjects received enough nicotine patches to last until their next appointment.

Data analyses

Tobacco withdrawal was the primary outcome for the present study. The sample size was established to provide statistical power of approximately 80% to detect an association between tobacco withdrawal symptoms and nicotine patch dose consistent in magnitude with that observed previously in cigarette smokers (Dale et al., 1995). To supplement the primary analysis assessing for an overall dose-response, pairwise comparisons of each active-dose group versus placebo were performed as secondary analyses. Data were analysed using an intention-to-treat approach. In all cases, two-tailed p values of .05 or less were considered statistically significant with no adjustments made for multiple comparisons.

Tobacco withdrawal. Daily average negative affect, arousal, attention disturbance, and restlessness scores were computed from electronic diary random prompt data, and sleep disturbance was calculated using the electronic diary morning reports. For each individual, baseline symptom scores were established using the mean of the daily scores obtained for 1 week during stage 1. Withdrawal symptoms assessed following the target quit date were analysed as change from baseline with change scores greater than zero indicating worse withdrawal symptoms. Daily change scores for each of the first 2 weeks following the target quit date were analysed using generalized estimating equations (Diggle, Liang, & Zeger, 1994). For these analyses, withdrawal symptom score change from baseline was the dependent variable and patch dose was the independent variable. Linear contrasts were used to assess for a dose-response relationship and also to compare each active dose to placebo. For the primary analysis, daily change scores were included for each subject from the target quit date to the last day the subject was abstinent from tobacco. A secondary analysis was performed that included all data regardless of tobacco use status.

Nicotine toxicity and adverse events. Nicotine toxicity symptoms were collected during the evening report and summarized for the first 4 weeks of patch therapy. The percentage of subjects for whom the maximum toxicity severity rating was either moderate or severe was calculated according to patch dose, and each active-dose group was compared to placebo using Fisher's exact test. Adverse events that occurred during the first 4 weeks of patch therapy also were collected at each study visit and summarized according to patch dose, and each active-dose group was compared to placebo using Fisher's exact test.

Tobacco abstinence. Tobacco abstinence was assessed at each study visit with 7-day point-prevalence abstinence defined as no tobacco use for the previous 7 days and continuous abstinence defined as no tobacco use since the target quit date (Hughes, Keely, Niaura, Ossip-Klein, Richmond, & Swan, 2003). Tobacco use outcomes were analysed using an intention-to-treat approach that included an outcome for all randomized subjects. For this analysis, subjects who missed a visit and could not be contacted were classified as using tobacco for that assessment.

The endpoints of interest were 7-day point-prevalence and continuous tobacco abstinence at week 8 and at 6 months. Separate analyses were performed for each endpoint using logistic regression with tobacco abstinence as the dependent variable and nicotine patch dose as the independent variable.

At 8 weeks and 6 months, subjects reporting abstinence from tobacco provided a urine specimen for anabasine as biochemical confirmation of tobacco abstinence. For patients reporting the use of NRT, cotinine cannot be used to validate tobacco abstinence biochemically because it is a metabolite of nicotine. However, because nicotine replacement products do not contain the tobacco alkaloid

anabasine, urinary anabasine has been proposed as a biomarker of tobacco consumption that differentiates tobacco users from non–tobacco users who use NRT (Jacob, Yu, Shulgin, & Benowitz, 1999). In the present study, urine anabasine concentrations of less than 2 ng/ml indicated tobacco abstinence in subjects reporting no tobacco use. This concentration has been used by other investigators and has been confirmed by pilot data (Hatsukami et al., 2000; Moyer et al., 2002). All biochemical measurements were conducted in the Mayo Medical Laboratories.

Electronic diary compliance. Compliance with the electronic diary during the first 2 weeks of patch therapy was calculated as the percentage of completed prompts based on one morning report, 5 random prompts, and one evening report each day.

Results

Subjects

We conducted telephone prescreening on 115 ST users, 81 (70.4%) of whom were determined to be potentially eligible and invited to an informational meeting. Of these 81 potential subjects, 55 (67.9%) attended, were consented, and passed the initial study screen. Of the 55 subjects invited to enroll in the study, 42 (76.4%) met all screening criteria and were enrolled. Of the 26 who were prescreened but never consented to study, 18 did not show for the screen visit, 5 decided they were not interested, and 3 could not make all the visits. Of the 13 who were consented but not enrolled in the study, 4 did not show for the randomization visit, 3 could not stay for the 3 days of in-patient visits, 1 did not wish to use the electronic diary for the withdrawal data, 1 was not on a stable blood pressure medication dose, and 4 were excluded based on lab values. All enrolled subjects were male. All subjects used snuff (moist tobacco), 41 were White, and 1 was of Asian descent. The demographic characteristics of enrolled subjects were similar across the dose groups, with the notable exception that the 42 mg/day patch group used a higher average number of tins per week (Table 1).

Tobacco withdrawal

A dose-response relationship was observed with higher doses of nicotine patch therapy associated with decreased tobacco withdrawal symptoms (Figure 1). During week 1 of patch therapy, higher doses of nicotine patch therapy were associated with less decreased arousal (χ^2=6.87, p=.009), less negative affect (χ^2=3.85, p=.05), and less restlessness (χ^2=3.90, p=.048). Compared with subjects using placebo during week 1, those in the 63 mg/day dose group were found to have significantly less decreased arousal (χ^2=7.38, p=.007), less negative affect (χ^2=5.20, p=.023), less restlessness (χ^2=4.66, p=.031), and approached statistical significance for less attention disturbance (χ^2=3.76, p=.052). During week 2 of nicotine patch therapy, a dose-response relationship was observed for decreased arousal (χ^2=6.77, p=.009) (see Figure 1). Compared with placebo during week 2, the 63 mg/day dose was found to be associated with less decreased arousal (χ^2=4.66, p=.031).

No dose-response relationship was observed for sleep disturbance. Compared with placebo, only the 21 mg/day group was observed to have significantly less sleep disturbance compared with those using placebo during week 1 (χ^2=5.53, p=.019).

Nicotine toxicity and adverse events

A total of 26 subjects (62%) reported a moderate or severe nicotine toxicity symptom during the nicotine patch phase; overall, symptoms did not differ by dose group (Table 2). Of the individual toxicity symptoms assessed, nausea was reported more frequently in the 63 mg/day group than in the placebo group (p=.035). No other individual symptoms occurred more frequently in active-patch groups compared with placebo.

One subject in the 42 mg/day group reported vomiting, which he attributed to motion sickness during week 3 of patch therapy. The subject removed the patches, replaced them when the episode resolved, and completed the study on all patches without further events. One subject in the 63 mg/day group experienced nausea and vomiting during the in-patient phase, one patch was removed, and the subject completed the study with two patches without further incident. Another subject in the 63 mg/day group experienced nausea shortly after placing patch C during week 3 of patch therapy; the nausea improved after the subject removed the patch. The subject completed the rest of the study with two patches.

The other adverse events reported most frequently during study visits included upper respiratory tract infection (17%), vivid dreams (12%), insomnia (10%), irritability (7%), and erythema at the patch site (5%). None of these adverse events differed by dose group.

No serious adverse events such as death, life-threatening clinical events, myocardial infarction, hospitalization, or disability occurred in any patient during this study.

Tobacco abstinence

Only one subject (placebo group) discontinued study participation and was lost to follow-up. The subject

Table 1. Demographic characteristics of 42 smokeless tobacco users in a Phase II clinical trial of high-dose nicotine patch therapy.

Characteristic	Placebo (n=11)	21 mg (n=10)	42 mg (n=11)	63 mg (n=10)
Age, years				
Mean (*SD*)	38.0 (6.9)	34.1 (9.4)	34.0 (6.2)	36.6 (7.7)
Range	31–48	20–56	26–47	27–49
Marital status, number of subjects (percent)				
Married	9 (82)	9 (90)	7 (64)	7 (70)
Divorced	1 (9)	1 (10)	1 (9)	1 (10)
Never married	1 (9)	0 (0)	2 (18)	2 (20)
Other	0 (0)	0 (0)	1 (9)	0 (0)
Highest level of education, number of subjects (percent)				
High school graduate	2 (18)	2 (20)	1 (9)	0 (0)
Some college/technical school	7 (64)	5 (50)	6 (55)	5 (50)
4-year college degree or higher	2 (18)	3 (30)	4 (36)	5 (50)
Years of regular ST use				
Mean (*SD*)	16.8 (7.3)	16.1 (6.7)	18.7 (7.6)	16.2 (8.2)
Range	5–30	5–28	7–35	2–26
Average minutes one dip in mouth				
Mean (*SD*)	52.3 (40.1)	64.5 (38.1)	45.6 (27.6)	46.5 (25.6)
Range	10–120	15–120	7–120	15–90
Average dips per day				
Mean (*SD*)	11.3 (5.4)	12.4 (9.0)	13.8 (7.4)	12.6 (8.1)
Range	3–20	3–35	4–25	5–30
Average tins per week				
Mean (*SD*)	5.4 (1.6)	5.5 (1.8)	8.0 (4.3)	4.6 (1.8)
Range	3–8	3–7	4–20	3–8
Serum nicotine concentration, ng/ml				
Mean (*SD*)	49.2 (33.4)	41.8 (11.2)	44.0 (17.0)	47.5 (11.5)
Range	26–131	26–60	25–79	32–69
Serum cotinine concentration, ng/ml				
Mean (*SD*)	597 (480)	489 (285)	435 (195)	549 (195)
Range	211–1892	182–1184	152–763	258–802
FTQ-ST				
Mean (*SD*)	14.9 (2.1)	15.7 (1.9)	16.0 (2.4)	14.3 (1.9)
Range	11–18	12–18	12–19	10–17
Previous quit attempts, number of subjects (percent)				
None	1 (9)	3 (30)	2 (18)	1 (10)
1–2	5 (45)	5 (50)	1 (9)	3 (30)
3–5	3 (27)	2 (20)	3 (27)	4 (40)
6 or more	2 (18)	0 (0)	5 (45)	2 (20)

Note. FTQ-ST=Fagerström Tolerance Questionnaire–Smokeless Tobacco.

was assumed to be using tobacco for all analyses. Table 3 lists the self-reported and biochemically confirmed tobacco abstinence rates at 8 weeks (end of patch treatment) and 6 months. Due to failure of our assay to detect urine anabasine in the setting of high nicotine concentrations resulting from the nicotine patch therapy, we were unable to obtain biochemical confirmation of self-reported tobacco abstinence at 8 weeks. Therefore, only the 6-month outcome data were confirmed biochemically. Of the 18 subjects who self-reported abstinence at the 6-month telephone follow-up, 7 declined to provide a urine sample for biochemical confirmation. Of the 11 subjects who provided a urine sample, all were biochemically confirmed tobacco abstinent. We did not detect a significant dose-response for any abstinence endpoint.

Electronic diary compliance

Overall electronic diary compliance was 79%±12% (*Mdn*=80%; range=52%–100%). Compliance did not differ across dose group (p=.690).

Adequacy of blinding

In the placebo group, 5 of 11 subjects (45%) reported that they believed they had been assigned to placebo. Compared with an expected value of 25% if blinding was successful, this result was not significant (χ^2=3.33, p=.117). Among subjects assigned to an active-dose group, only 2 of 31 (6%) felt that they had been assigned to placebo. Compared with an expected value of 25% if blinding was successful, this result was significant (χ^2=5.69, p=.017).

Discussion

In this pilot clinical trial, we observed that for ST users who used at least 3 cans of ST per week, higher doses of nicotine patch therapy resulted in a greater reduction of withdrawal symptoms. The doses were well tolerated, and we observed few adverse events related to nicotine toxicity. We did not detect a significant dose-response for any abstinence endpoints. However, the present study was not designed to provide adequate statistical power for this analysis.

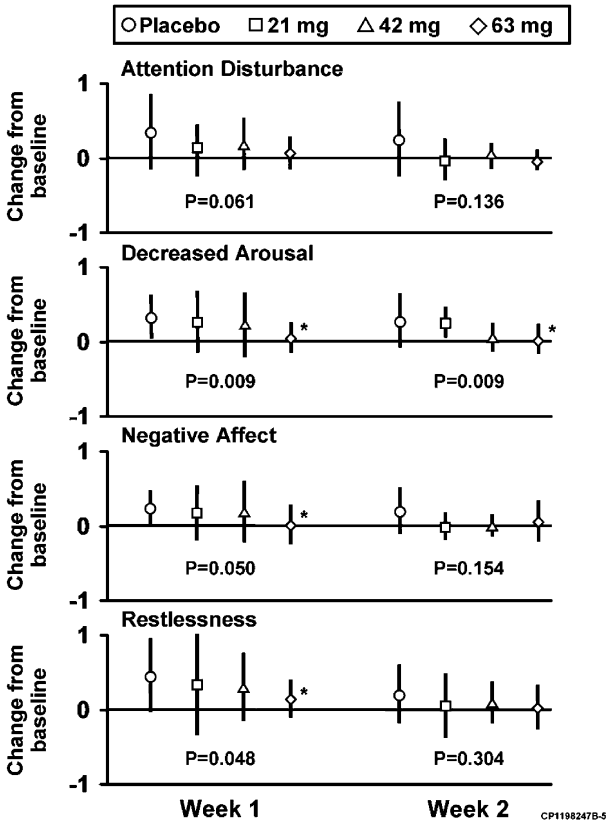

Figure 1. Tobacco withdrawal symptom change from baseline during week 1 and week 2 following target quit date according to nicotine patch dose. Withdrawal symptoms were analysed as change from baseline with change scores greater than zero indicating worse withdrawal symptoms. Daily change scores for each of the first 2 weeks following target quit date were analysed with change scores included for each subject from target quit date to the last day the subject was abstinent from tobacco. Data were analysed separately for weeks 1 and 2 following the target quit date using generalized estimating equations. For plotting purposes, the average change score for each week was calculated for each study subject using only data up to the last day the subject was abstinent from tobacco. The resulting weekly change scores are summarized according to nicotine patch dose. The *p* values presented correspond to a 1-degree-of-freedom linear contrast assessing for an overall dose-response. All 42 subjects were included in the analysis for week 1; however, 6 subjects (2 in placebo, 3 in 21 mg/day, and 1 in 63 mg/day) relapsed to tobacco during the first week and were excluded from the week 2 analysis. To supplement the dose-response analysis, linear contrasts also were performed to compare each active-dose group to placebo with an asterisk (*) used to denote groups found to be significantly different from placebo.

Our data suggesting a dose-response relationship, with higher doses of nicotine patches resulting in a greater reduction in withdrawal symptoms, is consistent with previous clinical trials in cigarette smokers (Dale et al., 1995; Paoletti et al., 1996; Tonnesen et al., 1999). The safety and tolerability of high-dose nicotine patch therapy in tobacco users also has been supported by previous research. Nicotine patch doses of 42–44 mg/day have been used in cigarette smokers (Dale et al., 1995; Fredrickson et al., 1995; Hughes et al., 1999). Dose-related adverse events ($p<.05$) occurring in at least 5% of subjects using the 42 mg patch have been categorized as abnormal dreams (33%), nausea (42%), dizziness (16%), headache (14%), cardiovascular events (8%), asthenia (8%), dyspepsia (8%), myalgia (8%), and vomiting (5%; Hughes et al., 1999). Doses up to 63 mg/day also have been used safely in selected cigarette smokers (Benowitz et al., 1998). In our own clinical experience with 24 ST users using a mean of 4.4 cans/pouches per week ($SD=2.6$), 7 subjects (29%) were treated with and tolerated nicotine patch doses ranging from 55 mg/day to 66 mg/day (Ebbert, Dale et al., 2004).

Previous trials have collected withdrawal data during study visits (Tonnesen et al., 1999) and/or using paper diaries (Dale et al., 1995; Jorenby et al., 1995). Most clinical assessments of withdrawal have relied on recall, asking subjects to average their withdrawal experiences over days or weeks (Hughes, Higgins, & Hatsukami, 1990; Piasecki et al., 2000). A methodological strength of the present study is that withdrawal data were collected using an electronic diary. This method provided multiple daily momentary assessments of withdrawal and circumvented some of the problems with paper diaries including poor compliance and hoarding (i.e., subjects complete all diaries for the week immediately prior to their clinic visit; Stone, Shiffman, Schwartz, Broderick, & Hufford, 2002). Substantial recall biases and errors are evident with paper diaries, even over short intervals (Stone et al., 1998), especially when assessing mood and other constructs that vary considerably over the course of the day. The electronic diary provided withdrawal assessments throughout the day at multiple times, thus circumventing the potential bias and assessment error.

The present study has several limitations. Incomplete blinding was suggested by the high percentage of subjects assigned to an active-dose group who accurately guessed that they were not receiving placebo. We speculate that subjects assigned to the 21 mg/day and 42 mg/day groups who were receiving both active and placebo patches may have been able to compare the appearance of the patches and determine that there were physical differences. Alternatively, subjects may have been able to discern that patches were active based on differences in skin reactions or symptom relief. Interestingly, although all 10 subjects assigned to the 63 mg/day dose perceived that they had been randomized to an active-patch group, only 3 (30%) felt that had received the highest dose. We propose that it is unlikely that the compromised blinding

Table 2. Nicotine toxicity symptoms reported during a Phase II clinical trial of high-dose nicotine patch therapy for smokeless tobacco users.[a]

	Number of subjects rating symptom as moderate or severe			
Symptom	Placebo (n=11)	21 mg (n=10)	42 mg (n=11)	63 mg (n=10)
Nausea	0	2	2	4*
Vomiting	0	0	2	1
Excessive saliva production	0	2	0	0
Abdominal pain	0	2	1	1
Diarrhea	2	3	3	1
Perspiration	1	4	2	2
Headache	3	5	3	3
Dizziness	1	0	2	0
Hearing disturbance	0	1	1	1
Visual disturbance	0	1	1	1
Mental confusion	1	1	1	0
Weakness	0	0	3	0
Feeling of exhaustion	2	4	3	0
Shortness of breath	0	0	1	1
Fainting spells (syncope)	0	0	0	0
Any symptom	6	8	6	6

Note. [a]Subjects rated nicotine toxicity symptoms each evening according to the maximum severity experienced that day using the response options of none, mild, moderate, or severe. Table entries are the number of subjects within the given dose group who reported symptom severity of moderate or severe at any time during the first 4 weeks of nicotine patch therapy.
*p=.035 for the comparison with placebo by Fisher's exact test.

would have resulted in the dose-response observed with tobacco withdrawal symptoms.

Another limitation of the present study is that a low percentage of patients provided biochemical confirmation at 6 months. Because abstinence was a secondary outcome, we used telephone follow-up to determine 6-month abstinence outcomes. To reduce subject burden, we asked only abstinent subjects to return for biochemical confirmation. This approach was problematic in that only 11 (61%) of the 18 subjects who reported abstinence on phone follow-up returned a urine sample for biochemical confirmation. Based on our previous experience with ST users and our extensive experience with cigarette smokers, it is unlikely that all of the subjects who self-reported abstinence but did not provide a urine sample would have failed biochemical confirmation had a urine sample been obtained. However, little is know about the effect of biochemical confirmation on treatment outcomes among ST users (Society for Research on Nicotine & Tobacco, 2002).

Finally, the sample size for our investigation was chosen to provide adequate statistical power to assess

Table 3. Tobacco abstinence rates at 8 weeks and 6 months among 42 smokeless tobacco users in a Phase II clinical trial of high-dose nicotine patch therapy.

					Logistic regression[b]	
	Placebo	21 mg	42 mg	63 mg	Odds ratio	p value
Point prevalence abstinence						
8 weeks						
Self-report	8/11 (73%)	4/10 (40%)	8/11 (73%)	7/10 (70%)	1.1	.742
6 months						
Self-report	4/11 (36%)	4/10 (40%)	5/11 (45%)	5/10 (50%)	1.2	.500
Biochemically confirmed[a]	2/11 (18%)	2/10 (20%)	3/11 (27%)	4/10 (40%)	1.5	.244
Continuous abstinence						
8 weeks						
Self-report	5/11 (45%)	4/10 (40%)	6/11 (55%)	7/10 (70%)	1.4	.216
6 months						
Self-report	3/11 (27%)	3/10 (30%)	5/11 (45%)	5/10 (50%)	1.4	.218
Biochemically confirmed[a]	2/11 (18%)	2/10 (20%)	3/11 (27%)	4/10 (40%)	1.5	.244

Note. [a]Subjects who self-reported abstinence via telephone follow-up at 6 months were asked to submit a urine sample for biochemical confirmation of tobacco abstinence. Of the 18 subjects who self-reported abstinence, 11 provided a urine sample and 7 declined to provide a urine sample. All subjects who provided a urine sample were biochemically confirmed to be tobacco abstinent. When calculating the rate of biochemically confirmed abstinence, subjects who self-reported abstinence from tobacco but declined to provide a urine sample were assumed to be using tobacco.
[b]For the logistic regression analysis, tobacco abstinence was the dependent variable, and nicotine patch dose was the independent variable. The odds ratios presented correspond to the increased likelihood of abstinence associated with a 21-mg increase in patch dose.

for an overall dose-response for the primary outcome of tobacco withdrawal. This sample size provides limited statistical power for comparing withdrawal symptoms for a single active-dose group versus placebo, and low statistical power to assess the secondary outcome of tobacco abstinence. Given the lack of statistical power for these secondary analyses, the findings from the pairwise comparisons of active-dose groups versus placebo and for abstinence endpoints should be interpreted with caution and nonsignificant findings should not be considered as evidence of no effect. Although our study was powered for the primary outcome of tobacco withdrawal rather than tobacco abstinence, nicotine withdrawal plays a key role in conceptualizations of nicotine dependence (American Psychiatric Association, 2000; Benowitz, 1992). Recent developments in the field emphasize withdrawal symptoms and other aspects of nicotine addiction as primary targets of treatment (NCI-NIDA Working Group, 2001).

Our data allow us to speculate on the potential for the increased efficacy of higher doses of nicotine patch therapy to increase long-term abstinence rates among ST users. A meta-analysis of 6 clinical trials (Dale et al., 1995; Hughes et al., 1999; Jorenby et al., 1995; Killen, Fortmann, Davis, Strausberg, & Varady, 1999; Paoletti et al., 1996; Tonnesen et al., 1999) comparing high-dose patch therapy to standard doses in cigarette smokers suggested a benefit of higher doses (OR=1.21, 95% CI=1.03–1.42; Silagy et al., 2004). The long-term goal of the current line of investigation is to study the potential benefits of appropriately tailored (i.e., heavier users receive higher doses) NRT for ST users on long-term abstinence rates. Recommendations for dosing nicotine patches up to 42 mg/day for ST users based on number of cans or pouches used per week have been published previously (Ebbert, Dale et al., 2004).

In conclusion, we observed a dose-response relationship between higher nicotine patch doses and decreased tobacco withdrawal symptoms in ST users using at least 3 cans of ST per week. Higher doses of nicotine patches were well tolerated and safe. Larger trials are needed to assess whether the dose-response relationship between higher doses of nicotine patch therapy and tobacco withdrawal symptom relief will translate into increased efficacy and improvement in long-term abstinence rates.

Acknowledgments

This project and manuscript was supported by National Cancer Institute grant R01 CA96881 awarded to Dr Jon O. Ebbert. The authors thank Donna Rasmussen, the staff of the Nicotine Research Program, and the staff of the Mayo GCRC for their hard work on this project and dedication to our ST users. They also thank the subjects who participated in this research.

References

Alguacil, J., & Silverman, D. T. (2004). Smokeless and other noncigarette tobacco use and pancreatic cancer: A case-control study based on direct interviews. *Cancer Epidemiology, Biomarkers & Prevention*, *13*, 55–58.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders*. (4th ed.). Washington, DC: Author.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders*. (text rev., 4th ed.). Washington, DC: Author.

Benowitz, N. L. (1992). Cigarette smoking and nicotine addiction. *The Medical Clinics of North America*, *76*, 415–437.

Benowitz, N. L., Porchet, H., Sheiner, L., & Jacob, P, 3rd. (1988). Nicotine absorption and cardiovascular effects with smokeless tobacco use: Comparison with cigarettes and nicotine gum. *Clinical Pharmacology and Therapeutics*, *44*, 23–28.

Benowitz, N. L., Zevin, S., & Jacob, P., 3rd. (1998). Suppression of nicotine intake during ad libitum cigarette smoking by high-dose transdermal nicotine. *Journal of Pharmacology and Experimental Therapeutics*, *287*, 958–962.

Connolly, G. N., Winn, D. M., Hecht, S. S., Henningfield, J. E., Walker, B., Jr., & Hoffmann, D. (1986). The reemergence of smokeless tobacco. *The New England Journal of Medicine*, *314*, 1020–1027.

Dale, L. C., Hurt, R. D., Offord, K. P., Lawson, G. M., Croghan, I. T., & Schroeder, D. R. (1995). High-dose nicotine patch therapy. Percentage of replacement and smoking cessation. *The Journal of the American Medical Association*, *274*, 1353–1358.

Diggle, P. J., Liang, K. Y., & Zeger, S. L. (1994). *Analysis of longitudinal data*. Oxford, U.K.: Clarendon Press.

Ebbert, J. O., Dale, L. C., Vickers, K. S., Gauvin, T. R., Bunge, N. E., & Hurt, R. D. (2004). Residential treatment for smokeless tobacco use: A case series. *Journal of Substance Abuse Treatment*, *26*, 261–267.

Ebbert, J. O., Rowland, L. C., Montori, V., Vickers, K. S., Erwin, P. C., Dale, L. C., & Stead, L. F. (2004). Interventions for smokeless tobacco use cessation. *Cochrane Database of Systematic Reviews* (3), CD004306.

Ellenhorn, M., & Barceloux, D. (1995). *Household products*. New York: Elsevier Science Publishing.

Fant, R. V., Owen, L. L., & Henningfield, J. E. (1999). Nicotine replacement therapy. *Primary Care*, *26*, 633–652.

Fiore, M. C., Bailey, W. C., Cohen, S. J., Dorfman, S. F., Gritz, E. R., Heyman, R. B., Holbrook, J., Jaen, C. R., Kottke, T. E., Lando, H. A., Mecklenbur, R., Mullen, P. D., Nett, L. M., Robinson, L., Stitzer, M., Tommasello, A. C., Villejo, L., & Wewers, M. E. (2000). *Treating tobacco use and dependence. Clinical practice guideline*. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service.

Fredrickson, P. A., Hurt, R. D., Lee, G. M., Wingender, L., Croghan, I. T., Lauger, G., Gomez-Dahl, L., & Offord, K. P. (1995). High dose transdermal nicotine therapy for heavy smokers: Safety, tolerability and measurement of nicotine and cotinine levels. *Psychopharmacology*, *122*, 215–222.

Hatsukami, D. K., Grillo, M., Boyle, R., Allen, S., Jensen, J., Bliss, R., & Brown, S. (2000). Treatment of spit tobacco users with transdermal nicotine system and mint snuff. *Journal of Consulting and Clinical Psychology*, *68*, 241–249.

Hatsukami, D. K., Jensen, J., Allen, S., Grillo, M., & Bliss, R. (1996). Effects of behavioral and pharmacological treatment on smokeless tobacco users. *Journal of Consulting and Clinical Psychology*, *64*, 153–161.

Howard-Pitney, B., Killen, J. D., & Fortmann, S. P. (1999). Quitting chew: Results from a randomized trial using nicotine patches. *Experimental and Clinical Psychopharmacology*, *7*, 362–371.

Hughes, J. R. (1993). Pharmacotherapy for smoking cessation: Unvalidated assumptions, anomalies, and suggestions for future research. *Journal of Consulting and Clinical Psychology*, *61*, 751–760.

Hughes, J. R., Higgins, S. T., & Hatsukami, D. K. (1990). Effects of abstinence from tobacco: A critical review. In: L. T. Koszlowski, H. M. Annis, H. D. Cappell, F. B. Glaser, M. S. Goodstat, Y. Israel, H. Kalant, E. M. Seelera, & E. R. Vingilis (Eds.), *Research advances in alcohol and drug problems* (pp. 317–398). New York: Plenum.

Hughes, J. R., Keely, J. P., Niaura, R. S., Ossip-Klein, D. J., Richmond, R. L., & Swan, G. E. (2003). Measures of abstinence in

clinical trials: Issues and recommendations. *Nicotine & Tobacco Research*, *5*, 13–25.

Hughes, J. R., Lesmes, G. R., Hatsukami, D. K., Richmond, R. L., Lichtenstein, E., Jorenby, D. E., Broughton, J. O., Fortmann, S. P., Leischow, S. J., McKenna, J. P., Rennard, S. I., Wadland, W. C., & Heatley, S. A. (1999). Are higher doses of nicotine replacement more effective for smoking cessation? *Nicotine & Tobacco Research*, *1*, 169–174.

Jacob, P., 3rd, Yu, L., Shulgin, A. T., & Benowitz, N. L. (1999). Minor tobacco alkaloids as biomarkers for tobacco use: Comparison of users of cigarettes, smokeless tobacco, cigars, and pipes. *American Journal of Public Health*, *89*, 731–736.

Jorenby, D. E., Smith, S. S., Fiore, M. C., Hurt, R. D., Offord, K. P., Croghan, I. T., Hays, J. T., Lewis, S. F., & Baker, T. B. (1995). Varying nicotine patch dose and type of smoking cessation counseling. *The Journal of the American Medical Association*, *274*, 1347–1352.

Killen, J. D., & Fortmann, S. P. (1997). Craving is associated with smoking relapse: Findings from 3 prospective studies. *Experimental and Clinical Psychopharmacology*, *5*, 137–142.

Killen, J. D., Fortmann, S. P., Davis, L., Strausberg, L., & Varady, A. (1999). Do heavy smokers benefit from higher dose nicotine patch therapy? *Experimental and Clinical Psychopharmacology*, *7*, 226–233.

Mattson, M. E., & Winn, D. M. (1989). Smokeless tobacco: Association with increased cancer risk. *National Cancer Institute Monographs*, *8*, 13–16.

Meddis, R. (1972). Bipolar factors in mood adjective checklists. *The British Journal of Social and Clinical Psychology*, *11*, 178–184.

Moyer, T. P., Charlson, J. R., Enger, R. J., Dale, L. C., Ebbert, J. O., Schroeder, D. R., & Hurt, R. D. (2002). Simultaneous analysis of nicotine, nicotine metabolites, and tobacco alkaloids in serum or urine by tandem mass spectrometry, with clinically relevant metabolic profiles. *Clinical Chemistry*, *48*, 1460–1471.

National Institutes of Health. (1986). *The health consequences of using smokeless tobacco: A report of the Advisory Committee to the Surgeon General*. (NIH Publication No. 86-2874). Bethesda, MD: U.S. Department of Health and Human Services, Public Health Service.

NCI-NIDA Working Group. (2001). *Meeting on pharmacologic approaches to nicotine addiction*. Washington, DC: Author.

Offenbacher, S., & Weathers, D. R. (1985). Effects of smokeless tobacco on the periodontal, mucosal and caries status of adolescent males. *Journal of Oral Pathology*, *14*, 169–181.

Paoletti, P., Fornai, E., Maggiorelli, F., Puntoni, R., Viegi, G., Carrozzi, L., Corlando, A., Gustavsson, G., Sawe, U., & Giuntini, C. (1996). Importance of baseline cotinine plasma values in smoking cessation: Results from a double-blind study with nicotine patch. *European Respiratory Journal*, *9*, 643–651.

Piasecki, T. M., Niaura, R., Shadel, W. G., Abrams, D., Goldstein, M., Fiore, M. C., & Baker, T. B. (2000). Smoking withdrawal dynamics in unaided quitters. *Journal of Abnormal Psychology*, *109*, 74–86.

Russell, J. (1980). A circumplex model of affect. *Journal of Personality and Social Psychology*, *39*, 1161–1178.

Severson, H. H. (1992). *Enough snuff: ST cessation from the behavioral, clinical, and public health perspectives*. (NIH Publication No. 93-3461). Bethesda, MD: National Cancer Instutute.

Severson, H. H. (2003). What have we learned from 20 years of research on smokeless tobacco cessation? *The American Journal of the Medical Sciences*, *326*, 206–211.

Severson, H. H., Andrews, J. A., Lichtenstein, E., Gordon, J. S., & Barckley, M. F. (1998). Using the hygiene visit to deliver a tobacco cessation program: Results of a randomized clinical trial. *Journal of the American Dental Association*, *129*, 993–999.

Shiffman, S., Engberg, J. B., Paty, J. A., Perz, W. G., Gnys, M., Kassel, J. D., & Hickcox, M. (1997). A day at a time: Predicting smoking lapse from daily urge. *Journal of Abnormal Psychology*, *106*, 104–116.

Shiffman, S., Hickcox, M., Paty, J. A., Gnys, M., Kassel, J. D., & Richards, T. J. (1996). Progression from a smoking lapse to relapse: Prediction from abstinence violation effects, nicotine dependence, and lapse characteristics. *Journal of Consulting and Clinical Psychology*, *64*, 993–1002.

Shiffman, S., Khayrallah, M., & Nowak, R. (2000). Efficacy of the nicotine patch for relief of craving and withdrawal 7–10 weeks after cessation. *Nicotine & Tobacco Research*, *2*, 371–378.

Shiffman, S., Paty, J. A., Gnys, M., Kassel, J. D., & Elash, C. (1995). Nicotine withdrawal in chippers and regular smokers: Subjective and cognitive effects. *Health Psychology*, *14*, 301–309.

Shiffman, S., Paty, J. A., Gnys, M., Kassel, J. A., & Hickcox, M. (1996). First lapses to smoking: within-subjects analysis of real-time reports. *Journal of Consulting and Clinical Psychology*, *64*, 366–379.

Silagy, C., Lancaster, T., Stead, L., Mant, D., & Fowler, G. (2004). Nicotine replacement therapy for smoking cessation. *Cochrane Database of Systematic Reviews* (3), CD000146.

Silverman, S., Jr., Gorsky, M., & Lozada, F. (1984). Oral leukoplakia and malignant transformation. A follow-up study of 257 patients. *Cancer*, *53*, 563–568.

Sinusas, K., Coroso, J. G., Sopher, M. D., & Crabtree, B. F. (1992). Smokeless tobacco use and oral pathology in a professional baseball organization. *Journal of Family Practice*, *34*, 713–718.

Society for Research on Nicotine and Tobacco. (2002). Biochemical verification of tobacco use and cessation. *Nicotine & Tobacco Research*, *4*, 149–159.

Stevens, V. J., Severson, H., Lichtenstein, E., Little, S. J., & Leben, J. (1995). Making the most of a teachable moment: A smokeless-tobacco cessation intervention in the dental office. *American Journal of Public Health*, *85*, 231–235.

Stockwell, H. G., & Lyman, G. H. (1986). Impact of smoking and smokeless tobacco on the risk of cancer of the head and neck. *Head and Neck Surgery*, *9*, 104–110.

Stone, A. A., Schwartz, J. E., Neale, J. M., Shiffman, S., Marco, C. A., Hickcox, M., Paty, J., Porter, L. S., & Cruise, L. J. (1998). A comparison of coping assessed by ecological momentary assessment and retrospective recall. *Journal of Personality and Social Psychology*, *74*, 1670–1680.

Stone, A. A., & Shiffman, S. (2002). Capturing momentary, self-report data: A proposal for reporting guidelines. *Annals of Behavioral Medicine*, *24*, 236–243.

Stone, A. A., Shiffman, S., Schwartz, J. E., Broderick, J. E., & Hufford, M. R. (2002). Patient non-compliance with paper diaries. *British Medical Journal*, *324*, 1193–1194.

Substance Abuse and Mental Health Services Administration. (2004). *Results from the 2003 National Survey on Drug Use and Health: National Findings*. Retrieved May 12, 2005, from www.oas.samhsa.gov/NHSDA/2k3NSDUH/2k3results.htm#ch4

Tonnesen, P., Paoletti, P., Gustavsson, G., Russell, M. A., Saracci, R., Gulsvik, A., Rijcken, B., & Sawe, U. (1999). Higher dosage nicotine patches increase one-year smoking cessation rates: Results from the European CEASE trial. *European Respiratory Journal*, *13*, 238–246.

U.S. Department of Health and Human Services. (2002). *Report on carcinogens*. (10th ed.). Rockville, MD: Author, Public Health Service, National Toxicology Program, Retrieved July 28, 2005, from http://ehp.niehs.nih.gov/roc/toc10.html

Walsh, M. M., Hilton, J. F., Masouredis, C. M., Gee, L., Chesney, M. A., & Ernster, V. L. (1999). Smokeless tobacco cessation intervention for college athletes: Results after 1 year. *American Journal of Public Health*, *89*, 228–234.

West, R. J., Hajek, P., & Belcher, M. (1989). Severity of withdrawal symptoms as a predictor of outcome of an attempt to quit smoking. *Psychological Medicine*, *19*, 981–985.

Winn, D. M. (1992). Smokeless tobacco and aerodigestive tract cancers: Recent research directions. *Advances in Experimental Medicine and Biology*, *320*, 39–46.

Winn, D. M., Blot, W. J., Shy, C. M., Pickle, L. W., Toledo, A., & Fraumeni, J. F., Jr. (1981). Snuff dipping and oral cancer among women in the southern United States. *The New England Journal of Medicine*, *304*, 745–749.