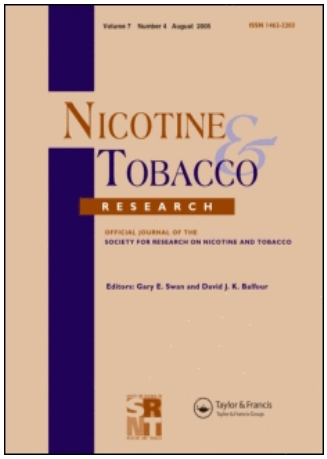

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Treating smokers before the quit date: Can nicotine patches and denicotinized cigarettes reduce cravings?

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Treating smokers before the quit date: Can nicotine patches and denicotinized cigarettes reduce cravings?

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The present study investigated whether treatment with the combination of denicotinized cigarettes and 21-mg nicotine patch for 2 weeks before a designated quit date could lessen cravings for smoking, thereby helping smokers abstain from smoking. The study was a randomized controlled clinical trial conducted at Roswell Park Cancer Institute, Buffalo, New York, in 2004 and 2005. Patients included 98 adult heavy smokers (using 20 or more cigarettes/day). Half of the subjects received 2 weeks of combination of denicotinized cigarettes (Quest 3) and 21-mg nicotine patch for 2 weeks before the quit date. The remaining smokers were switched to light cigarettes (Quest 1) during the 2 weeks before the quit date. After the quit date, all subjects received counseling for smoking cessation and were provided nicotine patches for up to 8 weeks after the quit date. Self-reported cravings for smoking, withdrawal symptoms, and smoking abstinence were measured at predetermined intervals using phone-based surveys and in clinical visits. The group that used denicotinized cigarettes and nicotine patch before quitting reported less frequent and less intense cravings for cigarettes in the 2 weeks before and after the designated quit date. Self-reported withdrawal symptoms and quit rates did not differ significantly between the groups. The use of a denicotinized cigarette combined with the nicotine patch appears to lessen cravings to smoke in the immediate postcessation period. A larger, better-powered study is needed to test if this treatment combination has merit for increasing quit rates.

Introduction

The rapid delivery of nicotine to the brain is one of the reasons many smokers find smoking pleasurable and find giving up smoking so difficult (Henningfield & Keenan, 1993; U.S. Department of Health and Human Services, 1988). However, if only the nicotine reinforced smoking behavior, the use of nicotine medications would make it possible for smokers to quit easily. Although nicotine medications have been shown to reduce withdrawal symptoms and increase the odds of quitting, most individuals who use them relapse back to smoking (Fiore et al., 2000).

Previous studies have demonstrated that smoking cigarettes that have very low levels of nicotine are still reinforcing for smokers (Shahan, Bickel, Badger, & Giordano, 2001; Shahan, Bickel, Madden, & Badger, 1999). The reinforcing effects of cigarette smoking in the absence of nicotine may be the result of past learning, whereby the repeated linked exposure of nicotine and smoke inhalation becomes associated with the act of smoking itself (Rose, Behm, Westman, & Kukovich, 2006). Thus the mere presence of smoke in the airway becomes a secondary reinforcer to the smoker because the sensory feel of the smoke becomes associated with the delivery of nicotine. This theory may help explain why very low nicotine delivery cigarettes reduce nicotine withdrawal symptoms (Buchhalter, Acosta, Evans, Breland, & Eissenberg, 2005; Buchhalter, Schrinel, & Eissenberg, 2001; Butschky, Bailey, Henningfield, & Pickworth, 1995; Gross, Lee, & Stitzer, 1997; Pickworth, Fant, Nelson, Rohrer, & Henningfield, 1999).

Smoking also becomes associated with many cues and triggers in the smokers' environment that serve as reminders to smoke (David et al., 2005; Due, Huettel, Hall, & Rubin, 2002); this helps explain why

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relapse to smoking is often associated with common smoking triggers such as drinking, stress, and socializing (Cummings, Jaen, & Giovino, 1985). Drug-seeking behavior may be extinguished better by nonrewarding drug administration than by discontinuation of drug use (Conkin & Tiffany, 2002). For example, in a rat model, removing the lever associated with cocaine injection does not extinguish the lever-pressing behavior; when the lever is returned to the chamber, the animal resumes lever pressing. However, if the lever is pressed and saline is injected instead of cocaine, lever pressing is extinguished (Koeltzow & Vezina, 2005). Another example is the administration of varenicline, a partial nicotine agonist, which seems to turn smoking into a nonrewarding experience and improve quit rates compared with placebo (Gonzales et al., 2006; Jorenby et al., 2006).

Based on these observations, we tested the hypothesis that combining steady-delivery nicotine replacement in the form of a nicotine patch with the sensory-motor reinforcing aspect of smoking without nicotine (i.e., Quest 3 cigarettes), compared with switching to light cigarettes (Quest 1), during the immediate precessation period would result in less cravings for a cigarette after quitting. We also tested a secondary hypothesis that less frequent cravings following cessation would increase quit rates, thereby favoring the combined patch plus Quest 3 over switching to light cigarettes during the precessation period.

Method

A randomized trial with 98 adult heavy smokers (using 20 or more cigarettes/day) was conducted in 2004 and 2005. Figure 1 provides a schematic of the study design. In the precessation part of the treatment, half the smokers in the trial received a very low nicotine yield cigarette (Quest 3, containing <0.05 mg of nicotine) along with a 21-mg nicotine patch for 2 weeks before quitting smoking. The other half were allowed to smoke a light cigarette (Quest 1 containing 0.6 mg of nicotine) for 2 weeks before the quit date. We deliberately chose to have all subjects switch from their usual cigarette brand to one of the Quest cigarette brands so that there was equivalence in the process of switching subjects away from their usual cigarette brand. Also, Quest 1 and Quest 3 cigarettes are identical in tar yield (10 mg, based on FTC method) and filter characteristics (no filter vents). During the 2 weeks before the quit date, subjects were asked to restrict themselves to smoking no more than one pack of the Quest cigarettes per day and not to smoke any other cigarettes except the Quest cigarettes we provided them.

After 2 weeks, all subjects were asked to stop smoking and received standard postcessation stop smoking treatment involving 8 weeks of 24-hour nicotine patch therapy (4 weeks of 21-mg patches, 2 weeks of 14-mg patches, and 2 weeks of 7-mg patches). Subjects were given their nicotine patches in 2-week increments, and all subjects participated in three 1-hr group cessation classes, plus individual counseling on

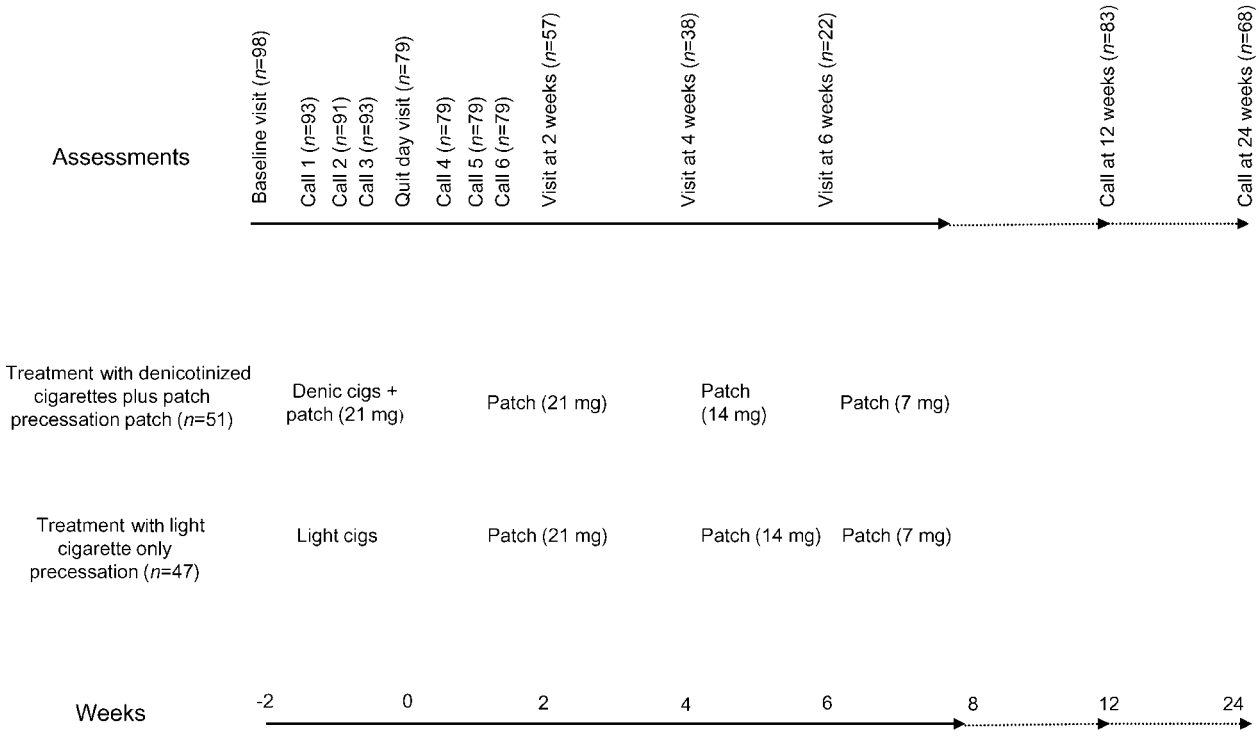

Figure 1. Study design of the randomized trial on denicotinized cigarettes (denic cigs) plus nicotine patch versus light cigarettes before the quit date (2004–2005).

subsequent clinic visits (each individual counseling session lasting about 20 min). The study protocol was approved by the Roswell Park Cancer Institute human subjects' research committee.

Recruitment of study subjects

Several methods were used to recruit subjects for this study. Flyers were posted around Roswell Park Cancer Institute to recruit employees and visitors who smoked. We also sent out a press release to local media and sent invitation letters to people who had previously attended the Roswell Park stop smoking clinic and were known to be smoking still. All promotional materials directed interested participants to contact a phone number to learn about the study. We received 150 calls from smokers interested in the study. Figure 2 shows the flow of subjects through different stages of the study.

Those who called the phone number were screened for eligibility for inclusion in the study. Inclusion criteria included currently smoking 20 or more cigarettes/day, age 18–65 years, commitment to complete the scheduled assessments, and for female smokers, willingness to avoid pregnancy during the study period. Exclusion criteria included active treatment for mental health conditions, current use of other stop smoking treatments, and contraindications for using the nicotine patch (i.e., recent heart attack, pregnancy). During the baseline visit, the subject's general health condition was assessed and eligibility for participation in the study confirmed.

Randomization to treatment conditions

When subjects called to enroll in the study, they were allowed to choose from one of six clinic group dates. Three of the groups were assigned randomly to the denicotinized cigarette plus patch precessation treatment, and three were assigned to the light cigarette precessation treatment. All groups received standard postcessation patch treatment and behavioral counseling. A total of 98 subjects were enrolled into the study; 51 were assigned to the denicotinized cigarettes plus patch precessation treatment group and 47 were assigned to the light cigarette only precessation treatment group. At the time of the first visit, subjects were told about the study and their assigned treatment group because there was no feasible way for blinding subjects or investigators to treatment group assignment.

Outcome measures

Outcome measures included self-reports of cigarette cravings, nicotine withdrawal symptoms, and smoking abstinence. These items were measured repeatedly

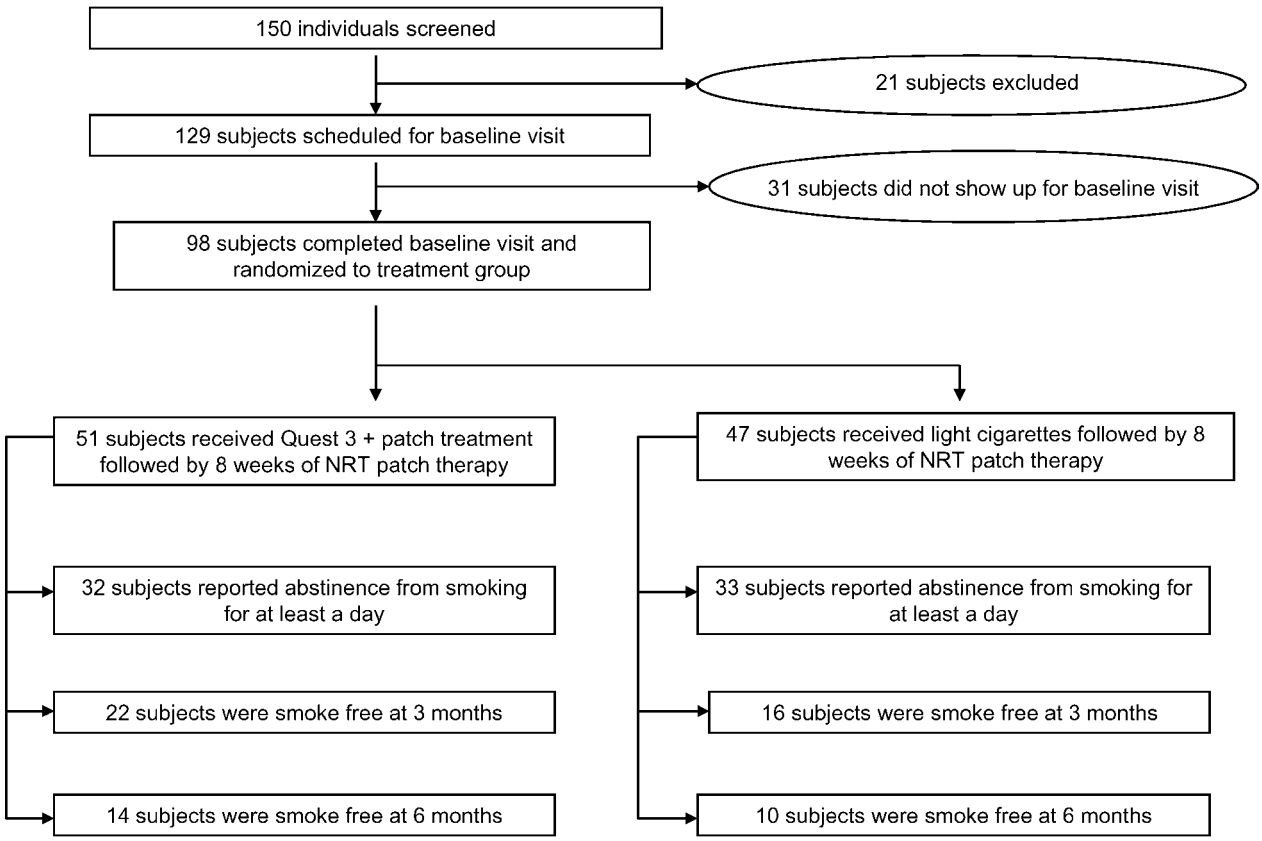

Figure 2. Flow of subjects through different stages of the study.

before and after the quit date. Efforts were made to reach participants within 48 hr of their originally scheduled appointment or phone call. These measures were obtained by asking subjects to report their experience during the 24 hr prior to the assessment and are described below:

Cravings index. The questions used for assessment of craving were adopted from the Questionnaire of Smoking Urges (Tiffany & Drobes, 1991) and included two items. These two items asked about the frequency and severity of cigarette cravings based on a 10-point scale on which 1 was the lowest score and 10 was the highest score. An index of cigarette craving was computed by multiplying the frequency and severity of craving scores at each assessment.

Self-reported craving for smoking in general was obtained at each of the four assessments (phone calls 1, 2, 3, and quit date visit) during the 2 weeks before the quit date, and at the four assessments (phone calls 4, 5, 6, and follow-up visit) during the 2 weeks after the quit date.

Withdrawal symptoms index. Self-reported withdrawal symptoms were obtained using the Minnesota Withdrawal Scale (Hughes & Hatsukami, 1986) during the four assessments during the 2 weeks before the quit date and at the four assessments during the 2 weeks after the quit date. Each of the assessments included questions about the following symptoms: anger, nervousness, distractibility, impatience, hunger, sleep problems, depression, and desire to smoke. Each of these items was given a score of 1 (lowest severity) to 5 (highest severity). The sum of the score to these eight items was used as a measure for severity of withdrawal from smoking and was considered as the secondary outcome measure (Hughes & Hatsukami, 1986). The Cronbach's alpha for the eight items in the withdrawal scale was .82.

Self-reported quit rate. Point prevalence of smoking abstinence after the quit date was assessed based on the self-report during the phone surveys scheduled 3 and 6 months after the quit date. Subjects who did not smoke during the 7 days prior to assessment were classified as quitters. Those who did not complete the survey were considered as smokers.

Evaluable subjects

The analysis was done in two subsets of participants, depending on how far along each participant made it in the study. The first set of analyses used data collected on all 98 study participants who consented to join the study and who were randomized into one of the two treatment groups. The second set of analyses was restricted to data collected on the 65 evaluable participants who (a) completed the baseline visit, (b) completed the quit date visit, (c) made a quit attempt of at least 24 hr (self-report) during the initial 2-week period following the quit date, and (d) completed at least four of the first six phone surveys scheduled during the 2-week periods before and after the quit date. These 65 subjects were eligible to continue the nicotine replacement therapy; the others were dropped from the study after 2 weeks following the quit date.

Comparison of characteristics of the 65 evaluable subjects with the other 33 subjects revealed that the former smoked fewer cigarettes per day at baseline (24.6 vs. 30.0, $p=.019$) and were less likely to live with a smoker (34% vs. 70%, $p=.001$) but were otherwise comparable on baseline characteristics. The proportion of evaluable subjects was similar for the denicotinized cigarette plus nicotine patch group compared with the subjects who switched to the Quest 1 light cigarettes before quitting (i.e., 63% vs. 70%, $p=.435$). After restriction of analysis to the 65 evaluable subjects, the results and conclusions remained the same. Therefore, we present the data for the larger sample of 98 subjects.

Data analyses

The study was designed to obtain four measures for craving and withdrawal during the 2 weeks before the quit date and four measures of those variables during the 2 weeks after the quit date for each participant. To take into account the dependent nature of the measurements, the two arms of the study were compared using linear mixed model analysis (Wright & Wolfinger, 1996). The outcome variable was placed as the dependent variable, the group assignment variable was placed as the independent variable, two other variables indicating the subject and the order of assessment of the response variable were considered in the constructed mixed linear model. The beta coefficient obtained for the group assignment variable and the p value for this coefficient represent the comparison of the two treatment arms. A negative value for the beta coefficient indicates a lower score of the response variable in the group treated with denicotinized cigarettes plus patch precessation.

Point prevalence of smoking abstinence was measured at 3 and 6 months after the quit date. These proportions were compared using a chi-square test between the two study arms.

Characteristics of subjects were measured at the baseline visit. As shown in Table 1, random assignment of the treatment led to two groups that were comparable on most characteristics, with the exception that those in the denicotinized cigarette plus nicotine patch precessation treatment group were slightly younger than those in the light cigarette only

Table 1. Comparison of selected demographic and tobacco use characteristics by treatment group.

Group	Denicotinized cigarettes plus patch precessation	Light cigarettes only precessation
Mean cigarettes/day (*SD*)	27.5 (1.5)	25.3 (1.1)
Mean FTND score (*SD*)	7.7 (0.3)	7.8 (0.3)
Mean combined craving score (*SD*)	60.06 (4.01)	65.09 (4.04)
Mean withdrawal score (*SD*)	18.42 (0.99)	20.70 (0.99)
Mean age, years (*SD*)	42.4 (1.5)	48.5 (1.2)
Gender		
Male	45%	43%
Female	55%	57%
Education, years		
<12	8%	6%
12	33%	43%
13–15	26%	38%
16+	33%	13%
Desire to quit		
Not at all	—	2%
A little	—	—
Somewhat	8%	15%
A lot	92%	83%
Smoker in house		
Yes	45%	47%
No	55%	53%
Tar content		
Regular	53%	53%
Light	37%	36%
Ultra-light	10%	11%
Attempts to quit in past year		
0	35%	28%
1	39%	36%
2+	25%	35%
Race		
White	86%	79%
Black	12%	17%
Other	2%	4%
Ethnicity		
Hispanic	4%	2%
Non-Hispanic	96%	98%
Income		
<$10,000	10%	13%
$10,000–$24,999	28%	23%
$25,000–$39,999	20%	36%
$40,000–$59,999	22%	11%
$60,000+	22%	17%
Marital status		
Never married	18%	19%
With partner	8%	13%
Married	53%	40%
Separated	18%	21%
Widowed	4%	6%

Note. Dashes indicate no responses in this category. FTND, Fagerström Test for Nicotine Dependence; *SD*, standard deviation. The only statistically significant group differences was for age (p=.002).

precessation treatment group. No other factors were significantly different between the two groups at the p<.05 level.

Results

Craving index

Figure 3 shows the difference between the two study groups in regard to the combined craving score. The group using the denicotinized cigarettes plus nicotine patch precessation treatment had lower combined craving score during the 2 weeks before (beta=−17, p<.001) and after (beta=−8, p=.013) the quit date.

Withdrawal symptoms index

Figure 4 shows the comparison of the two study arms in regard to the withdrawal score. The two study arms were similar in regard to the severity of withdrawal symptoms during the 2 weeks before (beta=0.74, p=.286) and after (beta=–1.05, p=.188) the quit date.

Self-reported quit rate

A shown in Figure 5, both study arms had comparable rates of self-reported point prevalence of smoking abstinence at the 3- and 6-month follow-ups. Differences in self-reported quit rates did not reach statistical significance.

As expected, quitters at 3 and 6 months, regardless of treatment group membership, had statistically significant lower average craving scores during the 2-week postcessation period (one-sided Mann–Whitney *U*-test p value=.05 for both cessation measures).

Discussion

Findings from this study indicate that combining use of denicotinized cigarettes plus a 21-mg nicotine patch for a brief period before quitting smoking can reduce cigarette cravings in the immediate postcessation period, compared with using the nicotine patch only after quitting. This result is compatible with the findings of Rose et al. (2006) that cravings were reduced in the denicotinized cigarette plus patch arm relative to usual brand plus patch.

The present study had a small sample size to start with and lost nearly one-third of the subjects because they were unable to remain smoke free for at least 24 hr after the designated quit date; thus it was not sufficiently powered to test for long-term differences in quit rates between treatment groups. The group treated with denicotinized cigarettes plus nicotine patch precessation had a slightly higher self-reported quit rate at 3 months (43% for denicotinized cigarettes plus patch vs. 34% for light cigarettes) and 6 months (28% vs. 21%, respectively), although the difference was not statistically significant at the p>.05 level. This self-reported quit rate differential is comparable with those of two other similar studies (Rose et al., 2006; Schuurmans, Diacon, van Biljon, & Bolliger, 2004). Rose et al. (2006) studied 98 subjects and found that the group treated with nicotine patch before the quit date had a significantly

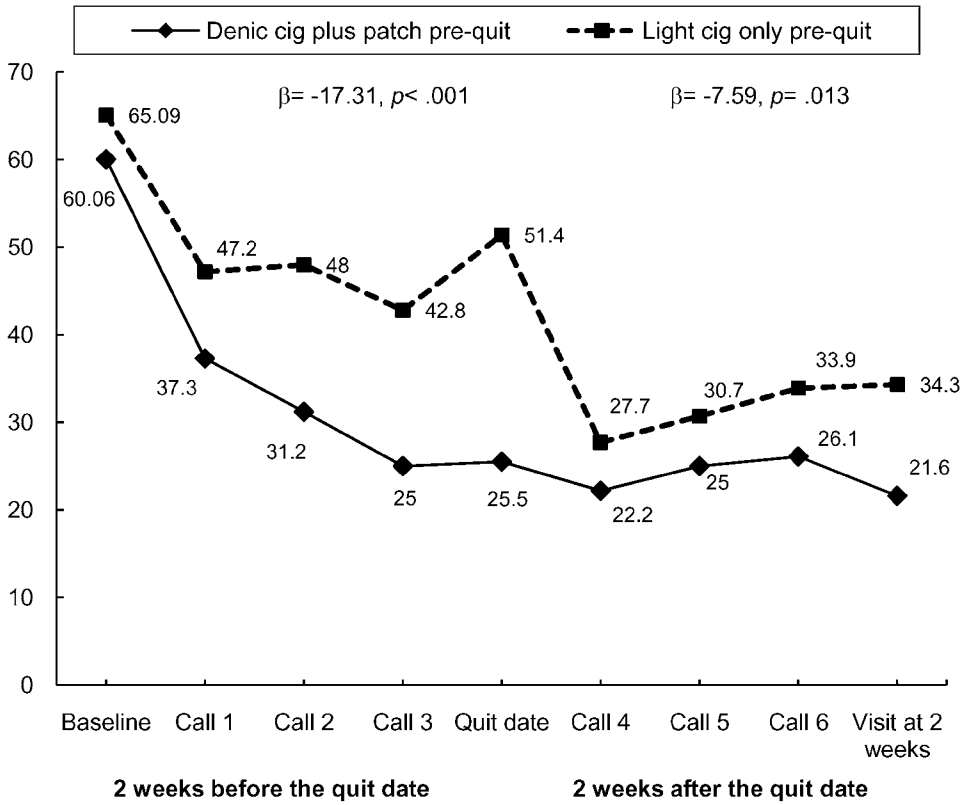

Figure 3. Combined craving score by treatment (N=98). Score=severity of craving × frequency of craving. Beta and p values obtained from mixed-model analysis.

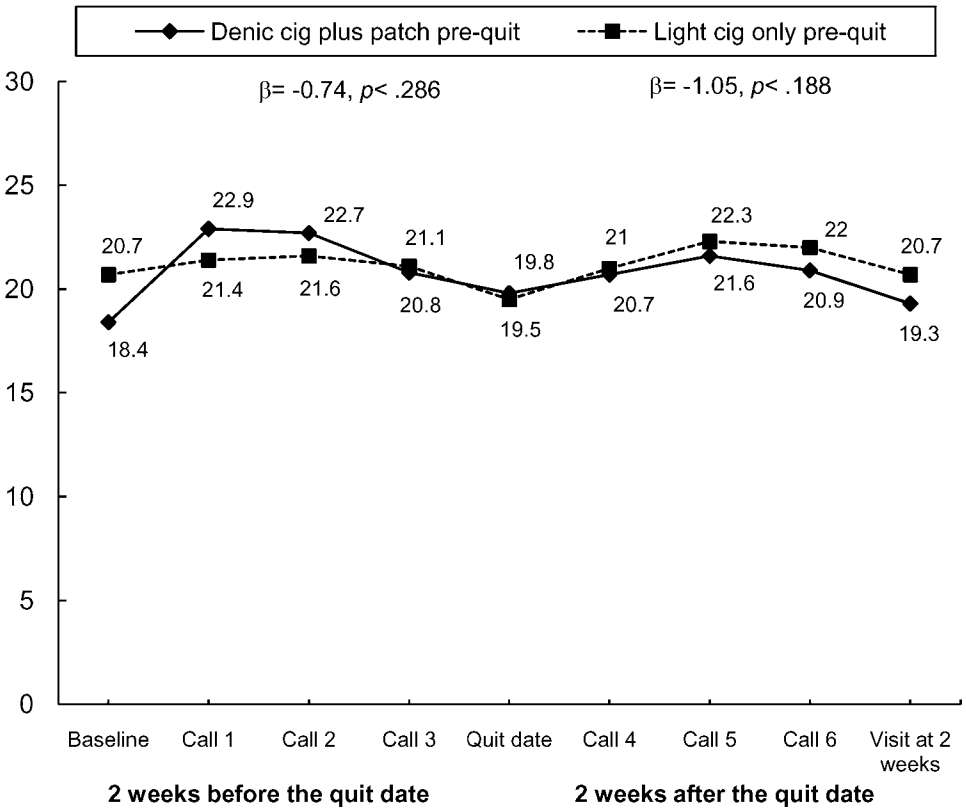

Figure 4. Withdrawal score by treatment (n=98). Score=sum of scores for anger+nervousness+distractibility+impatience+appetite+insomnia+depression+desire to smoke (Koeltzow & Vezina, 2005). Beta and p values obtained from mixed-model analysis (adjusted for baseline values).

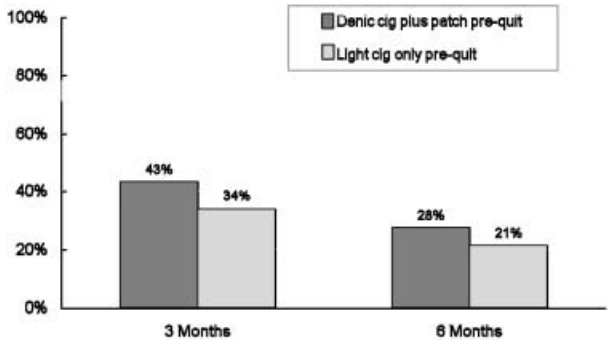

Figure 5. Self-reported quit rates by treatment arm at 3 and 6 months ($N=98$). Quitting defined as abstinence from smoking during the 7 days preceding the assessment. Nonsignificant p values obtained from chi-square test.

higher quit rate (50% vs. 20%) at 4 weeks. Schuurmans et al. (2004) studied a sample of 200 subjects and found that use of nicotine patch for 2 weeks before the quit date was associated with a significant increase (22% vs. 12%) in sustained abstinence at 24 weeks. Based on the effect size observed in the present study, we estimate that an adequately powered trial for smoking cessation would require a sample of about 430 subjects per treatment group.

Consistent with other published studies, we did not find evidence that combining the nicotine patch and denicotinized cigarette altered reports of nicotine withdrawal symptoms (Gonzales et al., 2006; Rose et al., 2006). Withdrawal symptoms may be related to decreased dopaminergic activity in the nucleus accumbens as a result of discontinuation of nicotine administration (Watkins, Koob, & Markou, 2000). Chronic exposure to nicotine may lead to neuron adaptations that can explain development of withdrawal symptoms when nicotine administration is discontinued. Nicotine replacement therapy has been shown to decrease the withdrawal symptoms and aid smoking cessation (Silagy, Lancaster, Stead, Mant, & Fowler, 2002). In the present study, subjects were receiving similar doses of nicotine either by the patch or by smoking the assigned light cigarettes, which could explain the similar Minnesota withdrawal scores (Hughes & Hatsukami, 1986) in both arms.

The Minnesota scale comprises different items that can be examined separately. One of the items measures the craving for smoking. The group treated with denicotinized cigarettes plus nicotine patch precessation had a significantly lower score for this single item of the scale during the 2 weeks before and after the quit date (data not shown). This finding confirmed our results from analysis of the craving scale presented in Figure 3.

Four of the items included in the withdrawal scale that were measuring anger, nervousness, distractibility, and impatience were highly correlated with a correlation coefficient of greater than .5. The sum of the score for these items could indicate negative affects and was found to be higher in the group treated with denicotinized cigarettes plus nicotine patch during the 2 weeks before the quit date. This finding is compatible with other instances of nonrewarding drug administration used for treatment of addiction that are likely to lead to frustration (Conklin & Tiffany, 2002).

The present study had some limitations. The 3- and 6-month quit rates are based on self-reported information and may overestimate actual quit rates. Both treatment arms received active treatment and clinical monitoring during the study period, which limits the extent to which group differences may exist in misreporting of smoking status. Those who self-reported no cigarettes smoked in the 7 days prior to the 6-month follow-up interview were asked to mail a saliva sample to the investigators for cotinine testing. Of the 21 samples requested, 13 were received (62%), and of these, 10 had salivary cotinine levels <15 ng/ml (77%). The fraction of received samples that had high cotinine values was not statistically different between the two treatment arms ($p=.70$).

Second, the study was not blinded for either the participants or the investigators, raising the possibility of information bias. As noted earlier, both groups received some form of active treatment and the clinical data collection for craving and other measures was based on self-reported information, which should reduce the potential for bias. Information from phone interviews was collected by an independent group of survey interviewers who were not familiar with the specifics of the study design or hypotheses being tested, which limits the likelihood of this type of bias as well.

Third, the present study does not provide information on other precessation treatments such as nicotine patch only, and further research is needed to determine the specific added value of denicotinized cigarettes as a precessation treatment over other possible treatments.

In summary, the findings from this research add to an increasing volume of research that suggests that use of the combination of denicotinized cigarettes plus nicotine patch before quitting can reduce craving for smoking in the immediate postcessation period, which may lead to higher long-term quit rates. However, whether this treatment combination can prevent relapse, thereby increasing long-term quit rates, still remains to be tested in a well-designed clinical trial.

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