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Varying Nicotine Patch Dose and Type of Smoking Cessation Counseling

[Original Contributions]

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Abstract

Objective: To compare the efficacy and safety of 22-mg and 44-mg doses of transdermal nicotine therapy when it is paired with minimal, individual, or group counseling to improve smoking cessation rates

Design: An 8-week clinical trial (4 weeks double-blind followed by 4 weeks open label) using random assignment of participants to both dose (22 or 44 mg) and counseling (minimal, individual, or group) conditions.

Participants: Daily cigarette smokers (greater or equal to 15 cigarettes per day for at least 1 year) who volunteered to participate in a study of smoking cessation treatment. A total of 504 participants were enrolled at two sites.

Intervention: Four weeks of 22- or 44-mg transdermal nicotine therapy followed by 4 weeks of dosage reduction (2 weeks of 22 mg followed by 2 weeks of 11 mg). Counseling consisted of a self-help pamphlet (minimal); a self-help pamphlet, a brief physician motivational message, and three brief (less than 15 minutes) follow-up visits with a nurse (individual); or the pamphlet, the motivational message, and eight weekly 1-hour group smoking cessation counseling visits (group). All participants returned weekly to turn in questionnaires and for assessment of their smoking status.

Main Outcome Measures: Abstinence from smoking was based on self-report, confirmed by an expired carbon monoxide concentration lower than 10 ppm. Withdrawal severity was assessed by means of an eight-item self-report questionnaire completed daily.

Results: Smoking cessation rates for the two nicotine patch doses and three levels of counseling did not differ significantly at either 8 weeks or 26 weeks following the quit date. Among those receiving minimal contact, the 44-mg dose produced greater abstinence at 4 weeks than did the 22-mg dose (68 percent vs 45 percent; P less than .01). Participants receiving minimal-contact adjuvant treatment were less likely to be abstinent at the end of 4 weeks than those receiving individual or group counseling (56 percent vs 67 percent; P less than .05). The 44-mg dose decreased desire to smoke more than the 22-mg dose, but this effect was not related to success in quitting smoking. Transdermal nicotine therapy at doses of 44 mg produced a significantly greater frequency of nausea (28 percent), vomiting (10 percent), and erythema with edema at the patch site (30 percent) than did a 22-mg dose (10 percent, 2 percent, and 13 percent, respectively; P less than .01 for each adverse effect). Three serious adverse events occurred during use of the 44-mg patch dose.

Conclusions: There does not appear to be any general, sustained benefit of initiating transdermal nicotine therapy with a 44-mg patch dose or of providing intense adjuvant smoking cessation treatment. The two doses and all adjuvant treatments produced equivalent effects at the 26-week follow-up, and the higher patch dose produced more adverse effects. Higher-dose (44-mg) nicotine replacement does not appear to be indicated for general clinical populations, although it may provide short-term benefit to some smokers attempting to quit with minimal adjuvant treatment.

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Smoking remains the leading preventable cause of illness and death in the United States, challenging the clinical and public health communities to address this issue more effectively. One of the more recent developments in national efforts to promote smoking cessation is the availability of transdermal nicotine therapy (the nicotine patch). More than two dozen clinical trials with the nicotine patch have been conducted to date. The results of these studies have been summarized in several different meta-analyses, [1-3] which all concluded that the patch is an effective aid to smoking cessation, doubling or tripling quit rates. Despite the relative efficacy of the patch, absolute cessation rates remain modest. One possible explanation of these modest cessation rates is that many smokers may be underdosed by the standard patch dose of 21 or 22 mg/d. Current nicotine patch doses typically replace less than 50 percent of the serum nicotine levels produced by smoking one pack of cigarettes per day. [4] It has been argued that replacing a greater percentage of baseline nicotine levels would result in more effective withdrawal suppression and better outcomes. [5] Hurt and colleagues [6] examined the issue of percentage of replacement and demonstrated that a greater percentage of nicotine replacement was associated with superior cessation outcomes (however, in a fixed dosing regimen, this may be confounded with lower initial smoking rates). This analysis was conducted with a limited number of participants, warranting replication with a larger sample. Of course, the safety of higher patch doses must also be evaluated prior to their general clinical use. While the nicotine patch has proved itself to be a very low-risk treatment for smoking cessation [7] and there are suggestions of a dose-response relationship, [8] concerns about potential nicotine toxicity need to be addressed if higher transdermal nicotine doses are to be used in general clinical practice.

Another reason for the modest long-term abstinence rates produced by the patch is that research has not yet identified the adjuvant treatments that, when combined with the nicotine patch, result in the highest long-term cessation rates. Extant clinical trials have used a variety of adjuvant therapies, ranging from minimal contact [9] to brief, individual follow-up modeled on the National Cancer Institute's How to Help Your Patients Stop Smoking program [6,10] to weekly group smoking cessation therapy. [11] Due to differences in study populations, patch treatment regimens, and other factors, it is difficult to compare adjuvant treatment efficacy across different trials. The meta-analysis conducted by Fiore and colleagues [3] provided an estimate of adjuvant treatment effectiveness by pooling effects across different studies. This analysis indicated that more intense adjuvant treatments produced higher absolute rates of smoking cessation.

Two different clinical trials reported by Fiore and colleagues [11] indicated superior cessation rates with group, compared with individual, smoking cessation counseling. These trials used similar (but not identical) populations, so caution must be used in generalizing the findings; the most robust test of adjuvant treatment requires participants to be assigned randomly to different treatments within the same study. In addition to varying nicotine patch dose, the study reported herein was designed around three different types of adjuvant treatments with an increasing level of intensity. The minimal treatment approximated a self-help program in which participants received a pamphlet prior to their quit date but no additional counseling. The individual contact treatment was a close approximation of the National Cancer Institute program. The group contact treatment was designed to be the most intense adjuvant, with 1 hour per week of group smoking cessation therapy during the 8 weeks of nicotine patch treatment.

By crossing the two initial nicotine patch dose levels (22 mg/d or 44 mg/d) with the three types of adjuvant treatment (minimal, individual, or group), the current study provided the opportunity to assess dose effects, counseling effects, and potential interactions between the two. Because of the consistent and robust increase in smoking cessation efficacy produced by a 21- or 22-mg patch relative to placebo, the current study compared the standard treatment (22 mg) with a higher dose (44 mg) without including a placebo condition. On the basis of previous work, it was hypothesized that larger nicotine patch doses would produce higher rates of smoking cessation, especially in more highly dependent smokers, and that more intense adjuvant treatments would produce higher rates of cessation.

METHODS

Subjects

Participants were recruited at two sites (Madison, Wis, and Rochester, Minn) by means of newspaper advertisements and local press releases. An initial telephone screening for inclusion and exclusion criteria was conducted, and qualified respondents were invited to a group orientation meeting at which study details were explained. Inclusion criteria required participants to be at least 20 years of age, smokers of at least 15 cigarettes per day for at least 1 year, and the only member of the household participating in the study. Exclusion criteria included allergy or hypersensitivity to transdermal adhesives; use of other nicotine-containing products, including forms of tobacco other than cigarettes; history of serious skin sensitivity; use of an investigational drug, as defined by the Food and Drug Administration, within the past 30 days; and recent (within 4 weeks) history of myocardial infarction, clinically significant angina pectoris, serious cardiac arrhythmias, balloon angioplasty, cardiac surgery, or stroke or other cerebrovascular accident. Pregnant or lactating women and women not using a medically accepted form of birth control were also excluded. Qualified participants provided informed consent and were scheduled for a medical screening visit, which included a physical examination and medical history, vital signs, an electrocardiogram (ECG), analysis of an expired carbon monoxide sample, blood chemistries and serum cotinine assay, and a urine pregnancy test for women of childbearing age. A total of 504 participants were enrolled, 252 at each site.

Persons who were deemed medically appropriate by a physician for study participation were randomly assigned to 22-mg or 44-mg transdermal nicotine treatment in a double-blind manner. All participants were also randomly assigned to one of the three types of counseling: minimal, individual, or group. All randomized participants established a quit date within 14 days of the medical screening visit.

Study Design

All participants reported to the study center on their designated quit date and once per week thereafter for 8 weeks. At each visit to the study center, data were collected on vital signs, expired air carbon monoxide, adverse events, concomitant medications, and self-reported smoking status for the previous week. Self-reported abstinence was considered confirmed by an expired carbon monoxide level lower than 10 ppm.

Every day during the trial participants completed a smoking withdrawal symptom questionnaire (daily diary) assessing eight withdrawal symptoms: desire to smoke, irritability/anger/frustration, anxiety/nervousness, difficulty concentrating, impatience/restlessness, hunger, awakening at night, and depression (modified Hughes and Hatsukami [12] items). All symptoms were rated on a scale of zero (none) to four (severe). Participants also reported any concomitant smoking on the diary form.

After 4 weeks of treatment, participants had a second physical examination, an ECG, blood chemistries and serum cotinine assay, and a urine pregnancy test for women of childbearing age.

Pharmacologic Intervention

Transdermal nicotine systems used in this study consisted of nicotine in a hydrogel matrix delivering either 22 or 11 mg/24 h through the skin (ProStep, Elan Pharmaceutical Research Corporation, Gainsville, Ga) or 22-mg-size patches of identical appearance but containing no nicotine. Each participant randomized to the 44-mg group wore two active 22 mg/24 h patches for the first 4 weeks of treatment, while each participant randomized to the 22-mg group wore one active 22 mg/24 h patch and one 22-mg-size placebo patch during the first 4 weeks. During weeks 5 and 6, participants in both groups each wore one 22 mg/24 h patch. During weeks 7 and 8, participants in both groups each wore one 11 mg/24 h patch. All patches were applied to nonhairy, nonirritated portions of the arms or torso, and application sites were changed daily.

Counseling Intervention

All participants were randomly assigned to one of three distinct types of counseling. Participants receiving minimal counseling were given a self-help pamphlet on smoking cessation (Clearing the Air [13]) during their initial medical screening visit. The physician conducting their physical examinations did not provide them with a motivational message on smoking cessation but did instruct them in the importance of not smoking while wearing a nicotine patch. At eight subsequent weekly study visits, participants receiving minimal counseling met with research staff only and had no contact with counselors. Research staff were instructed not to praise participants for abstinence or to engage in problem solving with participants. If participants asked direct questions, they were referred to their self-help pamphlet. Research staff were allowed to thank participants for attending weekly assessment visits (not contingent on smoking status) and warned participants of the danger of smoking while wearing a nicotine patch.

Participants receiving individual counseling were also given the self-help pamphlet at their medical screening visits, but it was accompanied by a motivational message from the examining physician designed in accordance with the program based on the National Cancer Institute publication How to Help Your Patients Stop Smoking. [10] In addition, a follow-up letter was mailed to participants in this group prior to their quit date to remind them of the importance of quitting smoking. As in the minimal counseling group, participants in the group receiving individual counseling reported to the study center for eight standard weekly assessments. However, 1, 2, and 4 weeks after their quit dates, participants in the individual counseling group each met briefly (less than 15 minutes) with a nurse to assess their progress. The nurse was trained to help participants identify high-risk situations and generate problem-solving strategies to deal with such situations; the nurse also provided praise and encouragement to participants.

Participants randomized to group counseling received the same intervention at the initial medical examinations as did those receiving individual counseling and reported to the study center for eight standard weekly assessments. In addition, group counseling participants received 1 hour of group smoking cessation counseling weekly for 8 weeks. The groups were conducted by trained smoking cessation counselors working from a detailed treatment manual. The group sessions were structured to provide coping skill training, identification of high-risk situations, emotional support, and information related to smoking cessation. In addition to working from a detailed treatment manual, counselors at both sites were observed by one of us (D.E.J.) to ensure uniform provision of treatment (treatment manuals are available from the corresponding author on request).

Biological Assays

Carbon monoxide levels were assessed by having participants take a deep breath and hold it for 15 seconds before exhaling into a carbon monoxide monitor (Bedfont Micro Smokerlyzer or Vitalograph Breathco Carbon Monoxide Monitor, Bedfont Scientific, Ltd, Upchurch, United Kingdom). Levels lower than 10 ppm

were considered to be confirmatory of self-reported abstinence. Blood samples for cotinine assays, collected during baseline smoking and while participants were receiving the maximum patch dose (week 4), were drawn into heparinized tubes and then centrifuged, and the plasma was separated. Plasma samples were stored in a freezer at a maximum temperature of -20 degrees C until analyzed. All cotinine analyses were conducted at the University of Wisconsin Hospital and Clinics Toxicology Laboratory using a fluorescence polarization immunoassay technique with a detection range of 50 to 4000 ng/mL.

Statistical Analysis

Baseline participant characteristics for the six conditions produced by patch dose group (22 mg vs 44 mg) and type of counseling (minimal vs individual vs group) and for population comparability between sites were evaluated by analysis of variance for continuous variables and by logistic regression analysis for categorical variables.

Comparative efficacy and safety analyses were based on intent to treat. Cessation efficacy was evaluated by hierarchical logistic regression modeling in which dose (22 mg vs 44 mg), counseling (minimal vs individual vs group), and site (Wisconsin vs Minnesota) main effects and interactions were tested at the end of each phase of the study (4, 8, and 26 weeks). At a significance level of P less than .05, the study had an 80 percent chance of detecting cessation differences as small as 10 percentage points between dose conditions and 12 percentage points between counseling conditions, assuming a 25 percent cessation rate in the least efficacious condition. At a minimum cessation rate of 50 percent, the detectable cessation differences were 12 and 15 percentage points, respectively.

Three separate sets of secondary efficacy analyses were conducted in which a fourth factor was added to the three-factor (dose, counseling, and site) logistic regression models. The first two sets of secondary analyses were conducted to test whether more heavily dependent smokers (as indexed by baseline number of cigarettes smoked per day [CPD] and scores on the Fagerstrom Tolerance Questionnaire [14] [FTQ]) would benefit more from the 44-mg dose.

Safety was evaluated by means of 2 X 2 ([22 mg vs 44 mg] X [adverse event occurrence vs absence]) chi square tests of independence. Withdrawal symptom data were collected daily during patch treatment, but for purposes of analysis a weekly mean was computed for each of the items at each of the 8 weeks of treatment. In addition, a mean composite score consisting of the mean of the eight ratings of adverse withdrawal effects was computed for each of the 8 weeks of treatment. The eight withdrawal symptom ratings and the composite score were analyzed in a three-factor analysis of covariance model consisting of a patch treatment factor (22 mg vs 44 mg), a counseling condition factor (minimal vs individual vs group), and a site factor (Wisconsin vs Minnesota). Two-tailed tests of statistical significance were used in all analyses.

RESULTS

Table 1 presents the baseline characteristics of participants in the six dose and counseling groups. One statistically significant difference was observed between the groups: participants in the 44-mg dose groups at the Minnesota site were older than those in corresponding groups at the Wisconsin site (47 vs 41 years; F [1,490]=10.43; P less than .01). Overall, the sample consisted mostly of older, white heavy smokers with some college education and a mean of three previous quit attempts.

		Mean (SD) Value at Baseline*									
Patch Dose	Counseling Type	Age, y	Sex, % Female	Race, % White	Education, y	Cigarettes/d	No. of Serious Quit Attempts	FTQ Score	Weight, kg	Serum Cotinine, ng/mL	Carbon Monoxide, ppm
22 mg	Minimal (n=85)	44.6 (11.72)	56.3	97.6	14.4 (2.38)	26.1 (8.86)	3.8 (4.06)	7.3 (1.73)	77.9 (17.33)	208.4 (97.16)	31.5 (13.59)
	Individual (n=80)	45.1 (10.98)	43.8	97.5	14.4 (2.47)	26.3 (8.39)	2.8 (2.05)	7.1 (1.82)	82.3 (21.11)	193.3 (89.69)	30.8 (12.97)
	Group (n=87)	44.2 (12.44)	55.2	97.7	13.9 (2.40)	27.8 (10.18)	2.6 (1.97)	7.4 (1.66)	75.5 (17.05)	189.3 (87.08)	29.0 (9.65)
44 mg	Minimal (n=84)	45.5 (12.15)	54.8	98.8	14.2 (2.20)	29.3 (12.65)	3.1 (3.46)	7.1 (2.08)	77.3 (16.94)	188.3 (105.02)	30.9 (12.02)
	Individual (n=86)	43.1 (11.59)	57.9	98.9	13.9 (2.38)	27.7 (10.16)	3.0 (2.51)	7.4 (1.99)	77.5 (17.94)	205 (88.57)	31.8 (13.32)
	Group (n=80)	43.01 (10.94)	52.5	97.5	13.8 (2.22)	28.1 (10.30)	2.8 (1.93)	7.4 (1.81)	78.3 (15.74)	200.8 (94.79)	30.7 (12.50)

*Computed using analysis of variance except for sex and race, for which logistic regression analysis was used. FTQ indicates Fagerström Tolerance Questionnaire.

Table 1. Baseline Patient Characteristics by Dose and Counseling Group

Safety

Table 2 presents the most common adverse effects reported during the double-blind portion of the study as a function of patch dose. The most frequently observed adverse effects included erythema at the site of patch application (50 percent of sample), itching (38 percent), and headache (29 percent). The two patch doses differed in the observed frequency of three adverse effects, all of which were more common with the 44-mg dose: nausea (28 percent vs 10 percent; P less than .001), vomiting (10 percent vs 2 percent; P less than .001), and erythema and edema at the site of patch application (30 percent vs 13 percent; P less than .01).

Symptom Reported	22-mg Dose (n=252)	44-mg Dose (n=252)	Probability
Headache	30	28	.62
Sleep problems	20	25	.16
Dreams or abnormal dreams	10	12	.57
Nausea	10	28	.001
Vomiting	2	10	.001
Gastrointestinal tract symptoms	7	10	.20
Musculoskeletal symptoms	16	19	.35
Itching	33	42	.06
Erythema	50	49	.79
Erythema and edema	13	23	.01
Erythema and vesicles	6	7	.72
Any of the above	83	87	.21
Serious adverse events†	0	1	.25

*Unless otherwise indicated, values are percentage of participants reporting one or more occurrences of the symptom during the first 4 weeks of patch therapy.

†Three serious adverse events requiring termination of patch treatment occurred during the first 4 weeks of the study among participants using the 44-mg dose. These are described in the text.

Table 2. Adverse Effects Reported as a Function of Nicotine Patch Dose During the 4-Week Double-blind Phase of the Study

Four participants experienced serious adverse events during the course of the clinical trial that mandated cessation of patch treatment. A 43-year-old white woman who smoked 20 cigarettes per day at baseline experienced transient visual impairment with field loss in the lower right quadrant of both eyes on day 3 of 44-mg treatment. The participant recovered without sequelae. A 70-year-old white woman who smoked 20 cigarettes per day at baseline experienced a right-hemisphere stroke on day 39 of treatment; she had received the 44-mg dose during the first 4 weeks of the study but was in the 22-mg dose phase at the time of the adverse event. On follow-up, this participant had recovered completely except for a mild weakness in her left forearm and hand. A 69-year-old white woman who smoked 35 cigarettes per day at baseline experienced a transmural inferior wall myocardial infarction on day 25 of 44-mg treatment. She recovered with mild compensated heart failure and no limitations to activity. Finally, a 59-year-old white man who smoked 30 cigarettes per day at baseline developed an urticarial reaction with symptoms of angioedema on day 19 of 44-mg treatment. He recovered without sequelae but required a course of high-dose oral

corticosteroid treatment. None of the serious adverse events were associated with concomitant smoking.

Cessation Efficacy

Participants were classified as abstinent if they had a self-report of no smoking (not even a puff) during the previous 7 days, confirmed by an expired carbon monoxide value lower than 10 ppm. Cessation efficacy was evaluated at three different time points: after 4 weeks of treatment (the end of the double-blind portion of the trial), after 8 weeks of treatment (the end of patch treatment), and 26 weeks after participants' quit dates. When data were collapsed across the dose and counseling conditions, 63 percent of participants were abstinent at 4 weeks, 54 percent at 8 weeks, and 28 percent at 26 weeks as determined by an intent-to-treat analysis; that is, participants who were lost to follow-up were considered to be smoking. The number of participants lost to follow-up was modest: 13.7 percent at 4 weeks, 21.4 percent at 8 weeks, and 16.3 percent at 26 weeks. There were no significant differences in number of participants lost to follow-up at any time point as a function of either dose or counseling condition.

Hierarchical logistic regression modeling of the 4-week cessation outcome revealed significant main effects for dose (P less than .05), counseling (P less than .05), and site (P less than .002) and a significant dose-by-counseling interaction (P less than .05); other two-way interactions and the three-way interaction involving site were statistically non-significant. The significant dose effect reflected overall abstinence rates of 60 percent for participants receiving 22 mg of nicotine and 67 percent for participants receiving 44 mg. The significant counseling effect reflected an overall abstinence rate of 56 percent for participants receiving minimal counseling compared with 66 percent for those receiving individual counseling and 68 percent for those receiving group counseling. The significant site effect reflected overall abstinence rates of 56 percent at the Minnesota site and 71 percent at the Wisconsin site. The significant dose-by-counseling interaction at 4 weeks was accounted for by the larger dose effect in minimal counseling than in individual or group counseling (45 percent for 22 mg vs 68 percent for 44 mg; chi square = 9.2; P less than .01); there were no significant differences in abstinence due to dose in the individual or group counseling conditions. Table 3 gives cessation rates by dose in each counseling condition.

	22-mg Dose			44-mg Dose		
Follow-up Point, wk	Minimal Counseling (n=85)	Individual Counseling (n=80)	Group Counseling (n=87)	Minimal Counseling (n=84)	Individual Counseling (n=88)	Group Counseling (n=80)
4 (End of double-blind)	45	71	66	68	61	71
8 (End of open label)	44	65	59	54	55	49
26 (End of follow-up)	26	34	26	26	30	25

Table 3. Smoking Cessation Rates (in Percentages) at 4, 8, and 26 Weeks as a Function of Initial Nicotine Patch Dose and Type of Counseling

Hierarchical logistic regression modeling of cessation outcome at the end of patch treatment (8 weeks after participants' quit days) revealed only a significant site effect (P less than .05) as reflected by overall abstinence rates of 48 percent at the Minnesota site and 60 percent at the Wisconsin site. Analysis of the 6-month cessation outcome revealed no significant main effects or interactions in the hierarchical logistic regression modeling. Overall abstinence declined to 28 percent of the sample, suggesting that relapse was a significant problem in all treatment groups following the end of treatment.

Outcomes were also examined for differential. impact on different types of participants. Because there were a priori reasons to predict that the 44-mg dose might be more effective with participants more

dependent on nicotine and potentially underdosed by a 22-mg patch, two sets of secondary analyses were conducted wherein participants' baseline CPDs or FTQ scores were added to the three-factor model (dose by counseling by site) tested initially. With CPD added to the hierarchical logistic modeling of the 4-week cessation outcome, the results were similar to the initial modeling results without CPD: a significant dose-by-counseling interaction (P less than .05) and significant main effects for counseling (P=.05) and site (P less than .01), as well as a significant main effect for CPD (P less than .05). No interactions of CPD with the other factors were statistically significant, and the dose main effect failed to attain statistical significance (P less than .09). Participants smoking fewer than 30 CPD were more likely to be abstinent at 4 weeks (66 percent vs 60 percent for the greater or equal to 30 CPD group). Participants smoking 30 or more CPD were significantly more likely to be abstinent at 4 weeks if they received individual or group counseling rather than minimal contact (65 percent vs 51 percent); this was not true of those smoking fewer than 30 CPD. The interaction of dose with minimal counseling was most pronounced in the group smoking fewer than 30 CPD, in which 49 percent of participants receiving the 22-mg dose were abstinent compared with 76 percent of those receiving 44 mg; for the group smoking 30 or more CPD, the respective percentages were 38 percent and 60 percent. Similar modeling in which FTQ scores were added instead of CPD revealed much weaker effects, with only a site main effect (P less than .02) for the 4-week outcome attaining statistical significance. Modeling of end-of-treatment and 26-week follow-up cessation outcomes for both sets of analyses (CPD and FTQ) failed to reveal any statistically significant main effects or interactions related to these two variables.

Another set of secondary hierarchical logistic regression models that added participant sex as a factor failed to reveal any main effects or interactions at any of the cessation outcome time points.

Withdrawal Suppression Efficacy

As in previous studies with transdermal nicotine therapy, [11] participants' self-reported withdrawal symptoms (eg, desire to smoke, anger, depression) showed an increase in severity from baseline during the first week following quitting, followed by a gradual reduction in severity. The one exception to this was the symptom desire to smoke, which had its highest weekly mean at baseline and declined in severity across the 8 weeks of treatment. Comparisons between the two dose groups during the first 4 weeks of treatment demonstrated that among those participants who were abstinent in a given week, the only reliable difference to emerge between the two dose groups was in ratings of desire to smoke. Figure 1 demonstrates that participants receiving the 44-mg dose reported less of a desire to smoke (Fs [1, 257]=5.84, 4.37, 6.37, 5.56; P less than .05) during the first 4 weeks of treatment. Once participants received identical nicotine replacement doses (beginning in week 5), this difference disappeared. When the same analyses were conducted using data from all participants (ie, including those who had smoked during a given week), the same pattern of results was observed.

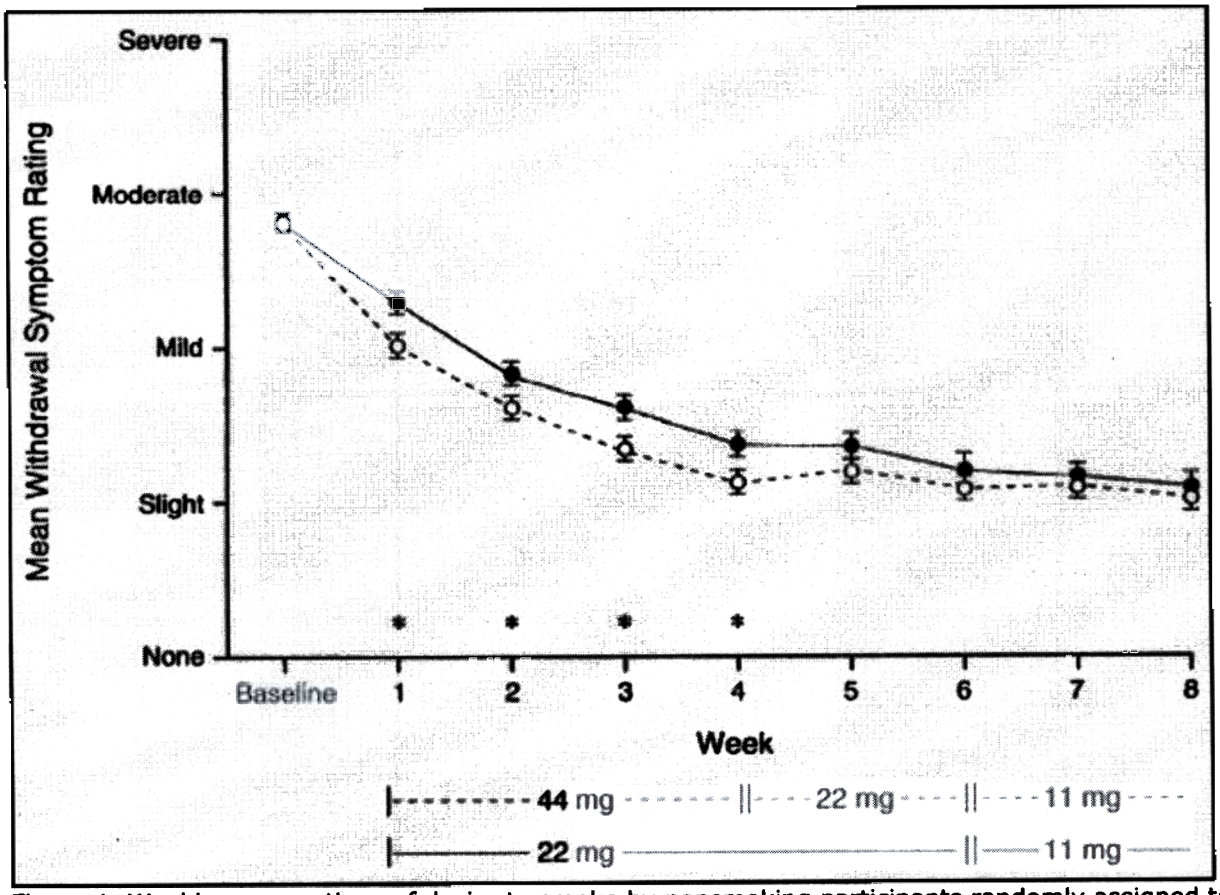

Figure 1. Weekly mean ratings of desire to smoke by nonsmoking participants randomly assigned to an initial nicotine patch dose of 44 mg (n=252) or 22 mg (n=252). Asterisk indicates P less than .05.

As with cessation efficacy, higher levels of nicotine replacement may have had a differential effect on certain subsets of participants. Comparisons of withdrawal suppression were conducted using modeling based on participant sex, CPD, and FTQ score, as with cessation efficacy. For all such comparisons, the only consistent differences observed were self-reports of less severe desire to smoke during the first 4 weeks among participants receiving the 44-mg dose; these differences did not persist beyond the first 4 weeks of treatment, did not differ reliably when analyzed as a function of sex or CPD or FTQ score, and were unrelated to cessation.

COMMENT

There does not appear to be any general, sustained benefit of initiating transdermal nicotine therapy with a 44-mg patch dose or of providing intense adjuvant smoking cessation treatment. The two patch doses produced different abstinence rates only during the initial 4-week treatment period among persons receiving minimal adjuvant treatment. Moreover, there were no long-term effects of patch dose even when subgroups of smokers were examined, such as highly dependent smokers or women. With 504 participants divided between the two dose groups, it appears unlikely that the failure to observe significant differences was due to inadequate statistical power. The pattern of long-term outcome was also highly similar across the two sites, suggesting that the findings are generalizable.

The impact of the larger dose on suppression of withdrawal was modest, being restricted to reports of less desire to smoke in the 44-mg group during the first 4 weeks of treatment. The significance of this finding is unclear because symptom severity is only modestly related to cessation success. [15] In the current study,

lessened desire to smoke was not reliably associated with greater cessation rates, even in the short term

The increased dose of transdermal nicotine did increase the likelihood of certain adverse effects. Of the three adverse effects observed more frequently in the 44-mg group, the two (nausea and vomiting) that are consistent with nicotine toxicity were observed across the initial 4-week treatment period. Additionally, among the four serious adverse events that required termination of patch treatment, three occurred among individuals receiving the 44-mg dose and one occurred in a participant originally assigned to the 44-mg dose who had titrated down to the 22-mg dose 11 days earlier. It is possible that these serious adverse events may have resulted, at least in part, from nicotine toxicity. Taken as a whole, it does not appear that doubling the nicotine patch dose results in a marked increase in adverse effects for most smokers. However, the increased risk of even a small number of adverse effects must be weighed against the lack of sustained cessation benefit. The current research provides little support for the clinical use of a larger nicotine patch dose.

Transdermal nicotine replacement therapy is a widely used treatment for smoking cessation, and it is important to establish the optimal adjuvant counseling treatment to accompany it. This study comprised three levels of adjuvant therapy intensity: a single self-help cessation pamphlet; four brief individual counseling sessions; and nine counseling sessions, eight of which involved hour-long group smoking cessation counseling. Despite dramatic differences in the length and intensity of counseling, there were no significant differences in long-term abstinence as a function of counseling intensity. It is possible, however, that even more intense treatments, such as inpatient treatment, [16] might have produced different results

Participants randomly assigned to the minimal contact condition showed the lowest initial abstinence rates (at 4 weeks). Indeed, the lowest published cessation rates among subjects using the nicotine patch were reported in a large clinical trial using a similar intervention. [9] However, the results reported herein probably overestimate the efficacy of a true self-help treatment. Participants were required to make a weekly site visit for assessment of adverse effects, and while these visits involved no explicit counseling, they may have had a nonspecific positive effect. Participants also received feedback on their carbon monoxide levels at each visit, which may have been motivating in the absence of formal counseling. These data raise a provocative question. A frequent finding in the smoking cessation field has been that more intense behavioral treatments produce superior outcomes, [3] but intensity is often confounded with increased overall contact time and more intense assessment procedures (eg, carbon monoxide monitoring). Given the lack of any sustained benefit of counseling intensity in the current study, in which participants were assigned randomly to treatment intensities, it will be important in future studies to demonstrate that superior long-term outcomes are the results of specific treatment content and not just nonspecific effects of increased contact time.

As with counseling, it is important to establish optimal dosing for nicotine replacement therapy. In this light, the differential effects of the two nicotine patch doses during the first 4 weeks of treatment are intriguing. It appears that the higher-than-usual dose of nicotine replacement was able to offset to some degree the reduced level of counseling treatment in the minimal contact condition. Superior suppression of the withdrawal syndrome does not seem to be a potential mechanism, since only one symptom showed a significant difference in severity between the two doses.

In sum, neither a 44-mg dose of transdermal nicotine nor intense adjuvant counseling appears to reliably increase long-term cessation rates beyond those produced by the usual 21- or 22-mg dose and brief counseling, which suggests that clinicians should not routinely use doses higher than currently recommended. Although there was evidence that the 44-mg dose produced superior short-term (4-week) outcomes among those receiving minimal adjuvant treatment, there was no evidence among any group at 8- and 26-week follow-ups of superiority of the 44-mg dose over the 22-mg dose. Suppression of the tobacco

withdrawal syndrome with a 44-mg dose appears to be similar to what has been observed with the 22-mg dose. [6,11] The results of this study yield little evidence that larger-than-usual doses of transdermal nicotine or intense adjuvant outpatient treatment will significantly boost long-term abstinence rates. Our results suggest a need for future research to identify specific subtypes of smokers who may show a superior treatment outcome as a result of different dosing regimens or more intense adjuvant treatment. [17]

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