Serum nicotine and cotinine levels during nicotine-patch therapy

We related serum nicotine and cotinine levels while subjects were smoking their usual numbers of cigarettes to levels while wearing a nicotine patch under carefully controlled, smoke-free conditions in a clinical research center. Twenty-four volunteers who needed intensive treatment for severe nicotine dependence were admitted to the clinical research center and were treated with a 22 mg transdermal nicotine patch each day and an intensive smoking-cessation program. Serum nicotine and cotinine levels, withdrawal symptoms, and hours and quality of sleep were noted. The steady-state serum nicotine and cotinine levels produced with the nicotine patch were lower than those observed when the subjects were smoking. Mean nicotine and cotinine levels were inversely related to mean withdrawal scores for the first 6 days. A fixed dose of transdermal nicotine will not be effective for all smokers. Individualization of therapy should be based on objective biologic measures such as serum cotinine and subjective assessment of withdrawal relief. (CLIN PHARMACOL THER 1993;54:98-106.)

Richard D. Hurt, MD, Lowell C. Dale, MD, Kenneth P. Offord, MS, Gary G. Lauger, MA, Leland B. Baskin, MD, George M. Lawson, PhD, Nai-Siang Jiang, PhD, and Peter J. Hauri, PhD *Rochester, Minn.*

Transdermal nicotine-replacement therapy represents an important addition to existing pharmacologic therapy in the treatment of patients with nicotine dependence.[1-8] Short-term efficacy is in part related to how well nicotine-withdrawal symptoms are relieved in the initial stages of smoking cessation.[9] It is important to show the efficacy of such therapy in relieving withdrawal symptoms, although withdrawal symptoms are subjective and quite variable both within and between individuals.

As with nicotine polacrilex, it is important to show that transdermal nicotine replacement can produce substantial blood levels of nicotine.[10] Early work showed significant salivary levels of nicotine after transdermal nicotine administration.[11] In the initial pharmacokinetic studies with a 22 mg nicotine patch, plasma nicotine and cotinine levels reached steady state within 7 days.[12] Plasma nicotine levels vary directly with dose, and 80% to 90% of the nicotine was absorbed from this patch, thus delivering approximately 22 mg/24 hr.[13]

To date, the best strategy for assessing dosage of nicotine with the transdermal patch has not been determined. To assess whether the principles of therapeutic drug monitoring were potentially applicable to this therapy, we studied subjects with severe nicotine dependence by relating serum nicotine and cotinine measurements while the subjects were smoking to levels achieved with a daily 22 mg (dose delivered) transdermal nicotine patch under carefully controlled smoke-free conditions in our clinical research center (CRC). We also correlated the subjects' subjective ratings of withdrawal, urges to smoke, and sleep quality to blood levels of nicotine and cotinine while in the CRC. The protocol was reviewed and approved by the Mayo Clinic Institutional Review Board.

METHODS

Subjects with severe nicotine dependence, based on Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) criteria,[14] were considered for the study. They were recruited by letter from a list of patients maintained at the Mayo Nicotine Dependence Center who needed intensive treatment for nicotine depen-

From the Division of Community Internal Medicine and Nicotine Dependence Center, the Section of Biostatistics, the Division of Thoracic Diseases and Internal Medicine, and the Section of Clinical Biochemistry, Mayo Clinic and Mayo Foundation.

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Reprint requests: Richard D. Hurt, MD, Mayo Clinic, 200 First St. SW, Rochester, MN 55905.

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Table I. Demographic features (n = 24)

	Mean	*SD*	*Range*	*No.*	*%*
Age (yr)	51.3	11.5	29-69	—	—
Height (cm)	165.0	10.0	152-187	—	—
Years smoked	33.7	9.5	17-50	—	—
No. cigarettes per day					
Current	33.2	13.1	16-70	—	—
Last 6 months	34.3	14.1	20-70	—	—
Average over years smoked	30.2	15.2	10-80	—	—
While smoking heaviest	43.8	16.4	20-80	—	—
Entry carbon monoxide (ppm)	30.6	12.0	8-55	—	—
Fagerström score	7.4	2.0	4-10	—	—
Fagerström score ≥7	—	—	—	14	58
Sex					
Female	—	—	—	18	75
Male	—	—	—	6	25

dence. Names on the list were from three sources: patients who requested inpatient treatment, referrals from physicians, and patients who had failed to stop smoking using existing interventions within the Mayo Nicotine Dependence Center. Thirty subjects were recruited and agreed to be screened for participation in the study. At the first screening visit, questionnaires were administered, cigarette smoking history was obtained, psychologic assessment was performed, and blood samples were drawn for laboratory tests, including nicotine and cotinine determination. At the second visit a physical examination was performed, and questionnaire and test results were reviewed. After the nature of the study had been explained, written informed consent was obtained from each eligible subject. Exclusionary criteria included the following: (1) history of recent (within 3 months) myocardial infarction, unstable angina, or serious cardiac arrhythmias; (2) mental impairment that would compromise the validity of subjective data; (3) pregnancy or nursing mothers; and (4) presence of significant chronic dermatoses. Four of the 30 subjects were excluded for the following reasons: (1) severe depression, (2) unstable angina, (3) active alcoholism, and (4) inability to cooperate with study requirements. Two subjects were approved and held as alternates. The 24 eligible subjects were hospitalized in four groups of six at the CRC of Saint Marys Hospital and Mayo Foundation. All subjects were instructed to continue smoking as usual up to the time of admission.

On admission to the CRC, a 22 mg nicotine patch was applied to the arm or upper forearm of each subject. Subsequently, the patches were changed each morning, and the site of application was rotated to different locations on the arms. Daily blood samples for analysis of nicotine and cotinine were drawn between 8 and 9 AM, immediately before patches were changed. Nicotine levels were determined by gas chromatography/mass spectrometry,[15] and cotinine levels were determined by liquid chromatography.[16]

Vital signs, carbon monoxide levels of expired air, and sleep logs were recorded each morning. A 15-item withdrawal symptom questionnaire was administered each evening. Subjects rated anxiousness or tension, compulsive eating, constipation, craving for a cigarette, difficulty concentrating, dizziness, drowsiness, headaches, heart palpitations or rapid heart rate, increased hunger, insomnia, irritability or impatience, nightmares, shakiness or tremors, and sweating. Each symptom was rated as absent, mild, moderate, or severe and scored as 0, 2, 4, and 8, respectively. A mean daily score for the 15 items was computed. Subjects also recorded the number of urges to smoke for each day on an urge questionnaire.

The subjects were provided an intensive smoking-cessation program, components of which included group therapy, daily lectures, exercise, and other supervised activities provided in the smoke-free, protected milieu of the CRC. A detailed description of this part of the study was published.[17] The subjects were monitored for 10 weeks after dismissal and continued to wear the 22 mg nicotine patch daily for 4 weeks, followed by 6 weeks of daily 11 mg patch therapy. The subjects were contacted at 6, 9, and 12 months to determine smoking status, and the 1-year biochemically validated stop rate was 29%.

RESULTS

All 24 participants completed all 14 days of the study. All subjects abstained from smoking during

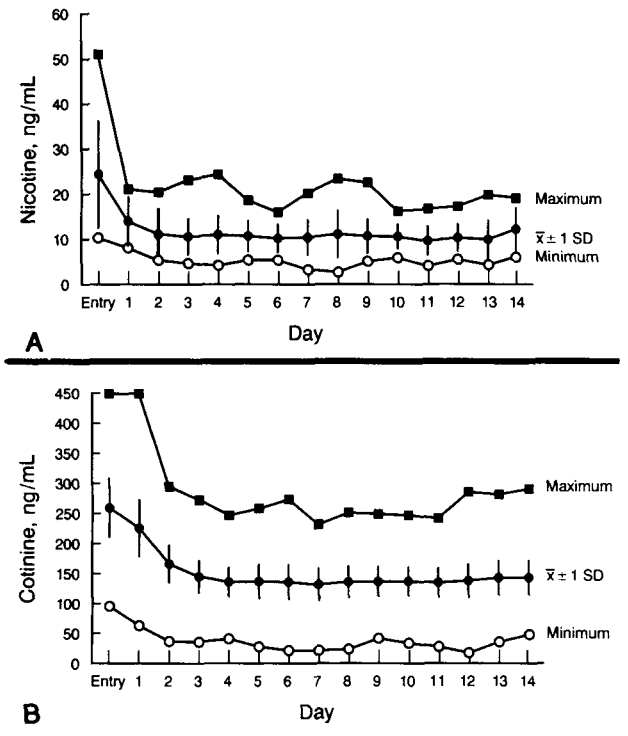

Fig. 1. Nicotine (**A**) and cotinine (**B**) levels as a function of days in the clinical research center. Blood samples were drawn each morning before subjects received new patches.

these 14 days with two exceptions—one subject smoked part of one cigarette in the bathroom on the fifth day of her stay, and another subject smoked part of a cigarette while taking part in an activity away from the CRC. Demographic features of the patients are shown in Table I. Of the 24 subjects, 22 had at least one disease known to be associated with or exacerbated by smoking. Chronic obstructive pulmonary disease was present in 14 subjects, arteriosclerosis obliterans in six, history of depression in five, coronary artery disease in four, alcoholism (recovering alcoholic) in four, cerebrovascular disease in three, peptic ulcer disease in two, and vocal cord leukoplakia in one.

Fig. 1 shows the serum nicotine and cotinine values for all subjects at entry (while smoking) and for each of the 14 days. During the first few days, the nicotine and cotinine levels reflected the combined effect of previous cigarette smoking and nicotine-replacement therapy. There was marked intersubject variation in nicotine and cotinine levels, with the entry levels ranging from 10.5 to 50 ng/ml and day 14 levels ranging from 4.5 to 18.1 ng/ml for nicotine and 94 to 444 ng/ml and 35 to 249 ng/ml for cotinine for the respective days. The subject in our study with the lowest levels of nicotine and cotinine both while smoking and when abstinent while receiving transdermal nicotine replacement was taking long-term maintenance anticonvulsant medication. Both nicotine and cotinine reached steady state on about day 3. For every day subsequent to entry, median levels for both nicotine and cotinine were significantly below that at entry ($p < 0.01$ by signed-rank test). For day 3 and beyond, the median percentage of entry-level value ranged from 41% to 53% for nicotine and from 46% to 53% for cotinine. For days 1 and 2, the median percentage of entry-level value was 64% and 53% for nicotine and 85% and 57% for cotinine. The daily serum levels did not indicate an accumulation of nicotine or cotinine.

When the reported amount of smoking at entry in cigarettes per day was compared with entry nicotine and cotinine values, no significant association was found. However, using Spearman rank correlation to relate entry smoking rate to nicotine and cotinine levels, we found several relationships of interest. For nicotine, all daily relationships were inverse and significant ($p < 0.05$) on 5 of the 13 days, as well as the average for days 2 through 7 and days 8 through 14 (Fig. 2). We observed a significant inverse relationship with cotinine levels for every day after entry ($p < 0.03$), including the average during the early and late periods (Fig. 2).

Fig. 3 shows the frequency of the maximum severity ratings over the 13 days for individual withdrawal symptoms. The symptoms that had the highest rating of severity were anxiety, insomnia, and craving, whereas those with the lowest rating were palpitations, sweating, and shakiness. For insomnia, as expected, the first day had the highest proportion of severe ratings. For days 6 through 14, more than 70% reported no insomnia for each of those nights. Over all 13 days, 63% (15 of 24) of subjects had at least one symptom score of severe on at least one day, 29% (7 of 24) had a moderate score as maximum, and 8% (2 of 24) had a mild score as maximum. When tabulated on a daily basis, there was a higher frequency of severe withdrawal symptoms during the first 5 days, and the trend was for improvement with time for total and individual symptoms.

Mean nicotine and cotinine levels showed a significant inverse relationship with mean withdrawal scores for the early period (Fig. 4).

Using Spearman rank correlation, we did not observe a significant association between the number of urges to smoke and the nicotine levels on individual

days or when averaged during the early and late periods. For 9 of 13 days, we observed a significant ($p \leq 0.03$) inverse relationship between cotinine levels and the number of urges to smoke, and there was a significant inverse relationship when averaged for the early (rank $r = -0.42$; $p = 0.041$) and late (rank $r = -0.49$; $p = 0.016$) periods.

Table II shows the changes from day 1 to day 14 for blood pressure, pulse rate, temperature, and weight. The mean weight increased. The mean blood pressure (systolic and diastolic) declined significantly (roughly 10% for each). The mean pulse rate declined roughly 15%, with no subject having an increased rate.

Analysis of the sleep logs showed sleep was poorer on the first night in the CRC, as would be expected when sleeping in a new place (Fig. 5). The slope of the linear regression of hours of sleep on days 3 through 14 for each subject was averaged over all subjects and compared to zero. There was no evidence of a significant trend, although 7 slopes were negative and 17 were positive. Every subject slept at least 6½ hours on 1 or more nights, and 11 of 24 never slept for less than 5 hours on any night.

No significant correlations were found when the hours of self-reported sleep for each subject were compared with nicotine and cotinine levels on the preceding and the following day. The rank correlations between hours of self-reported sleep and the number of urges to smoke reported on the following day were negative for 11 of the 14 days but significantly so only for day 10 (rank $r = -0.51$; $p = 0.019$); that is, the trend suggested that the better the subjects slept on a given night, the fewer urges they reported on the subsequent day.

Fig. 6 shows the subjects' perception of their sleep in the CRC in response to the question, "Compared with your own average over the last month, how well did you sleep last night?" The possible responses shown in Fig. 6 were assigned numeric values from 1 to 5 for regression analysis. For each subject for nights 3 through 14, we linearly regressed the score on night. The trend, although not statistically significant, was for better sleep with time (15 of 24 subjects had positive slopes; $p = 0.057$ by signed-rank test on the individual slopes). Using individual logistic regression, we assessed the trend for worse sleep (worse and much worse) against night and again found 15 of 24 subjects indicating improvement in sleep, four subjects had no change, and five subjects were worse ($p = 0.049$ by signed-rank test on the logistic regression slope coefficient).

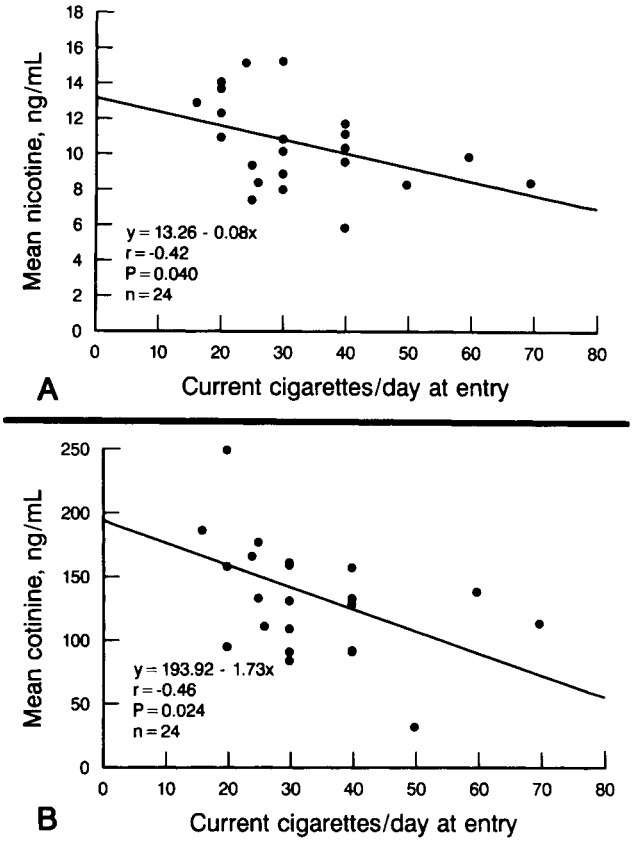

Fig. 2. Mean nicotine (**A**) and cotinine (**B**) levels during the last 7 days plotted against the cigarettes smoked per day before subjects entered the clinical research center. Blood samples were drawn each morning before subjects received new patches.

DISCUSSION

Our study is the first to compare nicotine and cotinine levels while subjects were smoking to daily levels for 2 weeks while subjects were wearing a 22 mg transdermal nicotine patch under carefully controlled smoke-free conditions. We observed marked intersubject variation in nicotine and cotinine levels, which points out the need for individualization of transdermal nicotine replacement therapy and the unlikeliness that a single dosing regimen will meet the needs of all patients. Intersubject differences in nicotine levels were to be expected and are thought to be the result of variability in nicotine pharmacokinetics.[18] We did find modest day-to-day within-subject variation in the steady-state levels for both nicotine and cotinine that was not thought to be of clinical significance. We observed no significant differences between sexes in the mean nicotine and cotinine levels.

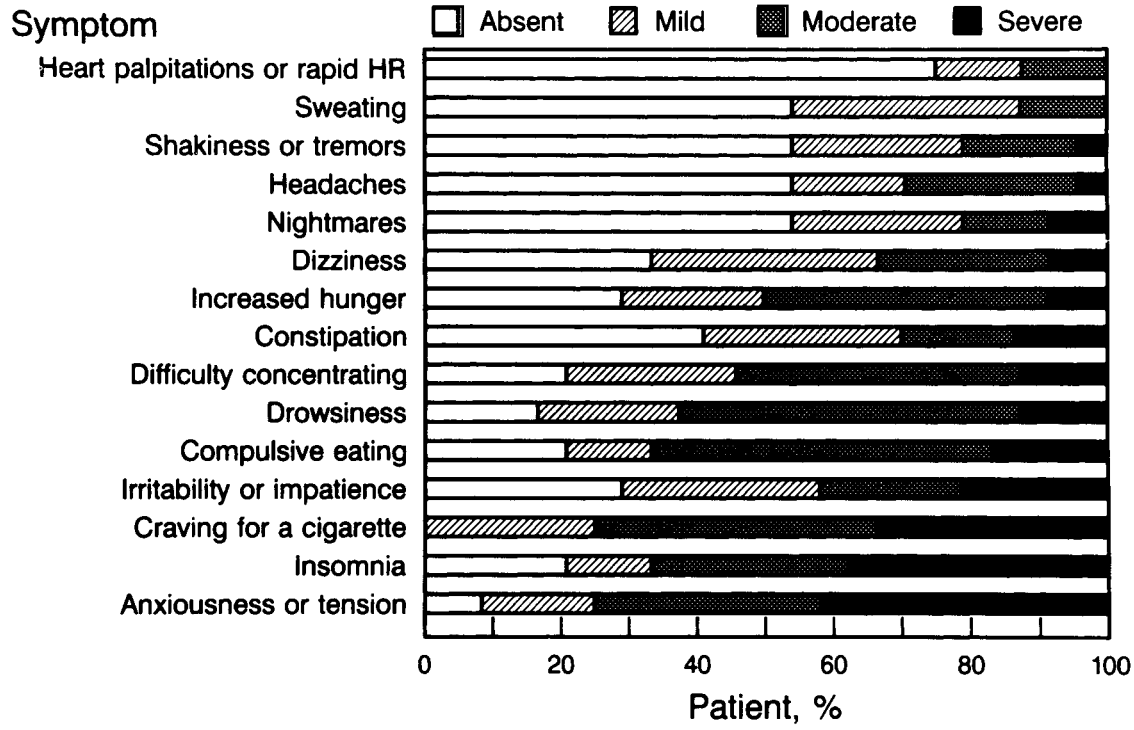

Fig. 3. For each subject and each of the 15 withdrawal symptoms, the maximum severity rating is shown for the entire stay in the clinical research center. Entries are percentages of subjects with the corresponding maximum severity rating. HR, Heart rate.

Our findings confirm that in subjects who are abstaining from smoking but receiving a single daily transdermal nicotine dose, a steady state of plasma nicotine and cotinine values is achieved by the third day. This finding is similar to that of Dubois et al.,[19] although in that study the subjects were not in a smoke-free environment, and all subjects were male. The mean steady-state trough levels of nicotine and cotinine observed in our subjects were similar to trough levels reported by Mulligan et al.[12] and Bannon et al.[13] for the same type of patch, but our subjects showed more intersubject variability. In addition, neither of these studies was performed in strictly controlled settings where abstinence from smoking was ensured. As in those studies, we observed no accumulation effect with continuous transdermal therapy in our subjects. We observed a steady decline in plasma cotinine levels until day 3, at which time the levels stabilized at a mean value of about 135 ng/ml, and there was a similar rate of decline in nicotine levels (Fig. 1). No subject had toxic levels or showed signs of nicotine toxicity, and only occasionally were daily levels at steady state above those present at entry for both nicotine and cotinine.

The steady-state levels of nicotine and cotinine achieved with a 22 mg transdermal patch in our subjects were much lower than the levels observed when the subjects were smoking their usual number of cigarettes just before transdermal-nicotine therapy was initiated ($p < 0.01$). The levels of cotinine at baseline were similar, although they were somewhat lower than those reported by Zeidenberg et al.[20] and more closely resemble the salivary cotinine levels reported by Daughton et al.[7] The percentage of nicotine replacement based on a denominator of the entry levels while smoking and numerator of trough levels for day 3 and beyond ranged from 41% to 53% for nicotine and 46% to 53% for cotinine. Using salivary measures of cotinine, Daughton et al.[7] found, as we did, that steady-state levels while subjects were wearing transdermal-nicotine patches were substantially lower than levels while subjects were smoking. Tønnesen et al.[8] reported the mean degree of nicotine substitution (based on salivary levels of cotinine compared with the calculated amount of nicotine contained in the cigarettes smoked) was less than 60% of the level when smoking after 1 week of transdermal nicotine therapy in 51 abstinent smokers. Neither of those studies was

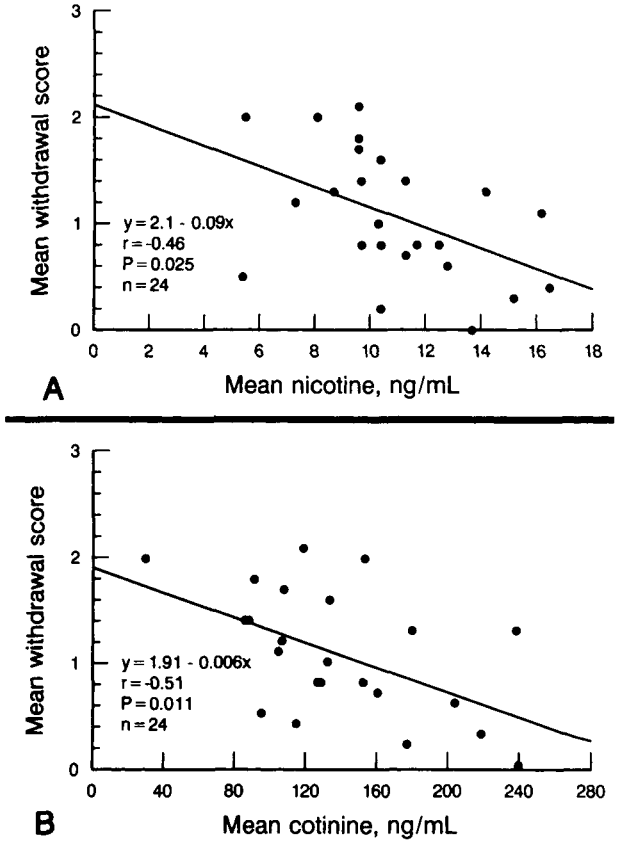

Fig. 4. Mean withdrawal score over first 6 days plotted against mean nicotine (**A**) and cotinine (**B**) values. Blood samples were drawn each morning before subjects received new patches. Withdrawal score for each day is averaged over 15 symptoms (see text for description).

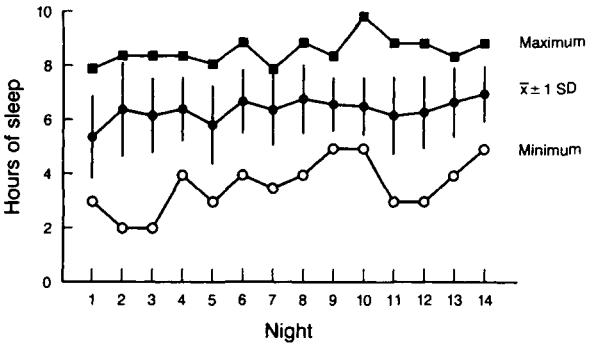

Fig. 5. Hours of sleep for each night in the clinical research center.

performed in a controlled research setting, and multiple measurements of serum levels were not obtained.

As expected, we observed an inverse relationship between withdrawal scores and serum cotinine levels. A similar trend was observed for serum nicotine levels, but this did not achieve statistical significance. Despite the replacement of nicotine by the patch, we observed that physiologic withdrawal symptoms still occurred and that urges to smoke were not suppressed by this treatment. This might be explained by the fact that the dose of nicotine was inadequate. In addition, it may be that other conditioned stimuli associated with smoking were absent and were missed by the subjects. On the other hand, withdrawal symptoms could have been lessened because of the smoke-free, protected, and supportive milieu. We observed that blood pressure and pulse rate declined. These changes in blood pressure and pulse are commonly observed during nicotine withdrawal and provide indirect evidence that the nicotine replacement in our subjects was not complete. There was a direct relationship between the number of cigarettes smoked per day before entry and withdrawal symptoms, although the number of cigarettes smoked per day before entry was inversely related to steady-state serum nicotine and cotinine levels. We speculate that the latter observation may be the result of the induction of the hepatic enzyme system in those who smoked more (higher number of cigarettes smoked per day at entry). Because of this observation, we are reluctant to use only the number of cigarettes smoked per day to determine the dose of nicotine-replacement therapy.

There is a need to better individualize the nicotine replacement dose on the basis of objective biologic measures in addition to the patient's subjective assessment of relief of withdrawal symptoms. Sole reliance on the relief of withdrawal symptoms is of concern because of the wide range of withdrawal symptoms for subjects receiving what would be considered to be a substantial dose of nicotine. In addition, the large intersubject variability of nicotine and cotinine levels leads to the conclusion that a fixed dose of transdermal nicotine will not be efficacious for all patients and may lead to underdosing those patients who may need higher doses of nicotine to control withdrawal symptoms while potentially overdosing others. This is a critical assessment because underdosing is likely to result in persistent withdrawal symptoms that may make relapse to smoking more likely.[21]

Consideration should be given to applying the principles of therapeutic drug monitoring to determine a therapeutic range of nicotine replacement therapy. Although a randomized controlled trial that uses different doses of transdermal nicotine will be needed to develop the therapeutic range and to confirm the

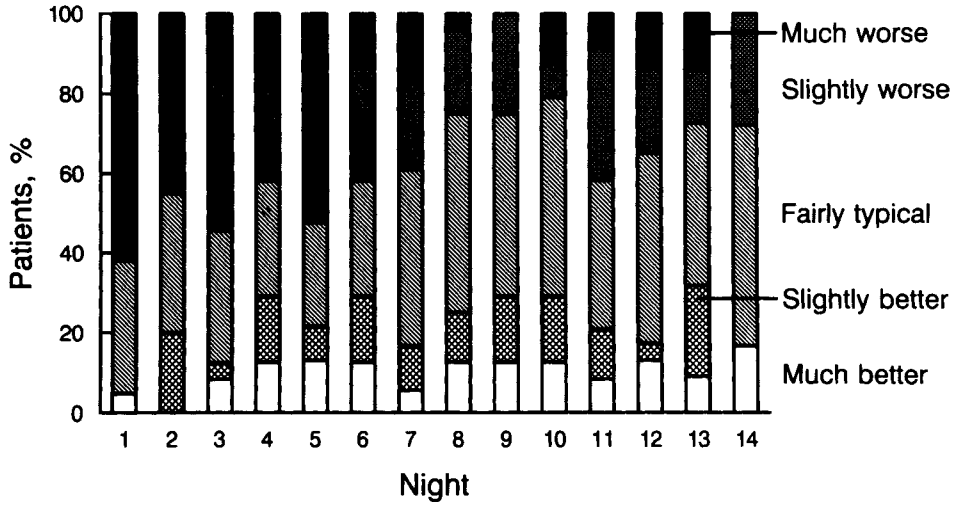

Fig. 6. Summary of responses to the question, "Compared with your own average over the last month, how well did you sleep last night?"

Table II. Changes from day 1 to day 14 (n = 24)*

Measurement	*Day 1*†	*Day 14*‡	Δ	*Positive* Δ	*Negative* Δ	Δ *of zero*	*p* Value§
Weight (kg)	69.3 ± 16.2	69.8 ± 16.6	0.6 ± 1.1	14	8	2	0.023
Systolic BP (mm Hg)	129 ± 17	115 ± 18	−14 ± 16	6	17	1	<0.001
Diastolic BP (mm Hg)	80 ± 8	72 ± 7	−7 ± 7	2	21	1	<0.001
Pulse rate (beats/min)	86 ± 8	75 ± 8	−13 ± 11	0	19	5	<0.001
Temperature (°C)	36.7 ± 0.4	36.4 ± 0.5	−0.3 ± 0.5	5	16	3	0.008

BP, Blood pressure.
*Unless otherwise indicated, entries are mean values ± SD. Δ is the difference of day 14 minus day 1. Positive Δ is the number of subjects with an increase; negative Δ is the number of subjects with a decrease; Δ of zero is the number of subjects with no change.
†Morning of first day in clinical research center.
‡Morning of fourteenth day in clinical research center.
§Two-tailed p value from paired t test of null hypothesis of mean change equal to zero.

usefulness of therapeutic drug monitoring in subjects being treated with the nicotine patch, our data provide insight into the basic issues. One consideration is to determine the amount of transdermal nicotine replacement therapy necessary to achieve the steady-state nicotine or cotinine levels the subject normally achieves while smoking, appreciating that the levels while smoking may vary. Because cigarette consumption varies during a 24-hour period, determining which level to target is a potential problem. If trough levels (i.e., first morning specimens) before smoking are used as a target, some subjects who have high levels while smoking during the day will be underdosed. Measuring levels at other times of the day will add to the variability, especially for nicotine levels. A starting point to address this issue would be to use as a target the cotinine level present in the first morning specimen after the subject had smoked the usual number of cigarettes in preceding days. The trough levels present in blood samples at steady state (after wearing a patch daily for 3 days *and* not smoking) would be used as the basis for adjusting the dose. The other alternative is to measure the subject's baseline levels while smoking at steady-state levels, that is, approximately 6 hours after rising, and to adjust the patch dose according to levels measured approximately 6 hours after a new patch is applied. The dose adjustment could be accomplished by combinations of varying sizes and delivery rates of patches, multiple patches, or duration of wearing time.[22]

Whether or not to use serum nicotine or cotinine values for monitoring the amount of nicotine replacement remains a question. Cotinine, although not thought to be psychoactive or addicting, is one of the

principal metabolites of nicotine. It is present in the blood of smokers in much higher concentrations than nicotine and has a longer half-life. Nicotine has a half-life of 2 hours, whereas cotinine levels decline in a log-linear fashion, with a half-life that averages around 20 hours. With this long half-life, there is much less within-day fluctuation in cotinine values, with levels of 250 to 300 ng/ml commonly observed in active smokers.[23] Many contend that because nicotine is the psychoactive substance and the absence of nicotine is responsible for nicotine withdrawal symptoms, nicotine levels should be used to determine replacement doses. Disadvantages of the use of serum nicotine for this purpose are its short half-life, larger differential between peak and trough levels while smoking, low levels compared to cotinine, and analytic difficulty for some laboratories. The longer half-life and consistency of steady-state levels of serum cotinine are the major reasons cotinine has been considered the biologic marker of choice for longitudinal studies,[24] and we favor its use for the purpose of monitoring nicotine replacement therapy.

Some investigators report that having subjects wear the patch for only the waking hours (16 hours per day) more closely resembles smoking behavior and that providing nicotine replacement therapy at night could disturb sleep.[25] The current study cannot conclusively deal with the question of sleep quality while the nicotine patch is worn. Switching from cigarette smoking to the patch is confounded by switching from sleeping at home to sleeping in the CRC. Also, we have no objective measure of sleep quality and quantity. Nevertheless, our subjective information does suggest quite strongly that sleep was not perceived to deteriorate during the 2 weeks that the nicotine patch was worn, even though the patch administered nicotine continuously for 24 hours per day. However, more objective data such as polysomnography or actigraphy are needed to confirm these findings.[26] Sleep disturbances that occur when subjects stop smoking during transdermal nicotine therapy could be the result of failure to adequately relieve withdrawal symptoms.

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