

## TRANSDERMAL NICOTINE AS MAINTENANCE THERAPY FOR ULCERATIVE COLITIS

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**Abstract Background.** Ulcerative colitis is largely a disease of nonsmokers. Having found previously that treatment with transdermal nicotine patches and mesalamine (5-aminosalicylic acid) has a beneficial effect on active colitis, we examined the value of transdermal nicotine for the maintenance of remission.

**Methods.** We treated 80 patients with ulcerative colitis in remission with either transdermal nicotine or placebo patches for six months in a randomized, double-blind study. Incremental doses of nicotine were given for the first three weeks to achieve a maintenance dose; most patients tolerated 15 mg for 16 hours daily. All patients were taking mesalamine preparations as maintenance treatment at entry into the study; this treatment was stopped once the maintenance dose of nicotine was achieved. Clinical, sigmoidoscopic, and histologic assessments were made at the beginning and the end of the study, or at relapse. Side effects and serum nicotine and cotinine concentrations were monitored throughout the study.

ULCERATIVE colitis is largely a disease of nonsmokers, and patients with ulcerative colitis who are exsmokers have usually acquired the disease within a few years after they stopped smoking.<sup>1-5</sup> Patients who smoke intermittently often experience improvement in their colitis symptoms during the periods when they are smoking.<sup>6,7</sup> Treatment with transdermal nicotine patches and mesalamine (5-aminosalicylic acid) has a beneficial effect on active colitis.<sup>8,9</sup> In a randomized, controlled trial, we studied the effect of transdermal nicotine, without mesalamine, on the maintenance of remission in patients with ulcerative colitis.

### METHODS

#### Patients

Two hundred fifty patients with ulcerative colitis (age, 18 to 70 years) were identified from departmental registers, and 80 eligible patients (70 in Cardiff, Wales, and 10 in Leigh, England) entered a six-month study. All were in clinical remission, as confirmed by rigid sigmoidoscopic examination. We excluded patients who had evidence of active disease on sigmoidoscopy or recent symptoms; had taken medication other than mesalamine for the maintenance of remission in the previous four weeks; had other medical problems, particularly of the cardiovascular system; were pregnant; were lactating; had previously received nicotine therapy for colitis; were current smokers; or declined to participate. The 80 patients remaining were randomly assigned to receive nicotine patches or placebo patches according to a predetermined random-allocation scheme, which was stratified according to center but not according to smoking history. The study

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**Results.** There was no significant difference in the number of relapses between the groups. Twenty-two patients in the nicotine group were prematurely withdrawn from the study, 14 because of relapse and 8 for other reasons, including side effects and protocol violations. In the placebo group, 20 patients were withdrawn prematurely, 17 because of relapse and 3 for other reasons. Among patients using 15-mg nicotine patches, serum nicotine and cotinine concentrations were lower than expected and may reflect poor compliance. Side effects were reported by 35 patients — 21 in the nicotine group and 14 in the placebo group — the most common of which were nausea, lightheadedness, and itching.

**Conclusions.** Transdermal nicotine alone was no better than placebo in maintaining remission of ulcerative colitis, and early withdrawal due to side effects was more common in the nicotine group. (N Engl J Med 1995;332:988-92.)

was approved by the ethics committees at both centers, and the patients gave written informed consent.

#### Nicotine Dose

The nicotine and placebo patches were identical in appearance, and the size of the patches was increased over a period of 18 days in an identical fashion in the two groups. The dose of nicotine was increased by 2.5 mg every three days until a maintenance dose of 15 mg daily was achieved. Most patients tolerated this dose, but if problems arose the dose was reduced to the maximal amount tolerated; thus, the maintenance dose was 5 mg in four patients, 7.5 mg in one, and 10 mg in eight. The patches were applied in the morning and removed at bedtime to ensure a nicotine-free period. After three weeks, when the maintenance dose had been achieved, the mesalamine preparation was tapered over a period of seven days. The maintenance dose of nicotine was continued throughout the trial. All changes in treatment were monitored by one physician at each hospital; none of the physicians were aware of the patients' treatment assignments.

#### Study Design

The patients were assessed clinically at the start of the trial and after 13 and 26 weeks, or at the time of early withdrawal from the study. At entry, all were in clinical remission, as confirmed by sigmoidoscopy, and all were taking mesalamine compounds (75 were taking mesalamine and 5 sulfasalazine). The effect of transdermal nicotine on the maintenance of remission was assessed by determining the number of patients who relapsed over a period of six months.

The patients were instructed to contact the study physician when clinical relapse occurred or if other difficulties arose. They were usually seen within 24 hours of the appearance of symptoms, and if relapse was confirmed by sigmoidoscopy, appropriate treatment was begun. All patients were contacted by telephone at weeks 1, 2, and 6 in order to deal with early difficulties and ensure compliance with treatment. They were also seen in the clinic at 13 and 26 weeks and if problems arose that could not be resolved on the telephone. During the week preceding the trial and during weeks 1, 2, 6, 13, and 26, the patients were asked to keep a diary in which they recorded stool frequency, the presence of blood in stool, general well-being, and the occurrence of nine common side effects of nicotine as well as any other side effects. Those completing the trial recommenced their usual treatment after the trial ended. Twelve weeks after the end of the trial, the patients were asked whether they had

a craving for nicotine or had started smoking again, if they were former smokers.

At entry into the trial, all patients underwent a sigmoidoscopic examination and rectal mucosal biopsy. Both procedures were repeated by the same physician at the end of the study or at the time a patient withdrew from the study. The appearance of rectal mucosa was graded visually according to previously published criteria<sup>10</sup>; only samples that were normal or showed edema (grades 0 and 1) were included. Relapse was considered to have occurred if the specimen revealed granular, friable mucosa (grade 2) or fulminating disease (grade 4). The biopsy specimens were stained with hematoxylin and eosin, and histologic activity was graded on the basis of the degree of infiltration of neutrophils<sup>9</sup>: a grade of 0 indicated the absence of neutrophils; 1, a small number of neutrophils in the lamina propria, with minimal infiltration of crypt epithelium; 2, prominent neutrophils in the lamina propria, with infiltration of more than 50 percent of crypts; 3, severe changes with crypt abscesses; and 4, florid acute inflammation with ulceration. The biopsy specimens were examined by someone who had no knowledge of the patients' treatment assignments. The severity of relapse was assessed clinically with the global score described by Truelove and Witts.<sup>11</sup> Serum nicotine and cotinine concentrations were measured initially and after 13 and 26 weeks of treatment, or at the time of withdrawal. Most serum samples were obtained 8 to 10 hours after a patch was applied, and they were stored at  $-20^{\circ}\text{C}$  until analysis.<sup>12</sup> To determine whether any patient had resumed smoking, breath carbon monoxide was measured with a Bedfont MicroSmokerlyzer at each clinic visit.

### Side Effects

Adverse effects were recorded at each clinical visit, during each telephone call, and at any other point during the trial if the physician was notified. They were graded as absent, mild, moderate, or severe; they were also designated as either serious or not serious, and the former always resulted in the withdrawal of the patient from the study.

### Statistical Analysis

The base-line characteristics of the patients in the two groups were compared by the Mann-Whitney test or unpaired t-test as appropriate. Changes in sigmoidoscopic and histologic grades from base line to 26 weeks, or on early withdrawal, were compared by a paired-samples Wilcoxon test, and any differences in the changes between groups were compared by the Mann-Whitney test. Analysis of covariance with adjustment for base-line differences was used to compare data obtained at 13 weeks, at 26 weeks, and on early withdrawal. The primary outcome — relapse — was examined according to intention-to-treat analysis and on the basis of the number of relapses. The Mann-Whitney test was used to compare the points at which patients in each group withdrew from the study. Differences in the severity of relapse in the two groups with respect to the clinical, sigmoidoscopic, and histologic scores were assessed by the Mann-Whitney, chi-square, and Fisher's exact tests. Differences in the numbers of side effects reported in the groups were assessed by the Mann-Whitney test or a two-tailed Fisher exact test when appropriate. Point and interval<sup>13</sup> estimates of the difference in the proportions of patients who withdrew and patients who had side effects are given. Nicotine and cotinine concentrations were log-transformed for analysis.

The sample size of 80 was based on the results of previous trials of maintenance therapy in colitis<sup>14</sup>; over a six-month period, 70 to 80 percent of patients given placebo might be expected to relapse, as compared with 20 to 30 percent of those given mesalamine. If nicotine is assumed to be as effective as mesalamine in averting 30 to 40 percent of the relapses over a six-month period, 76 subjects would be sufficient to achieve a power of 80 percent with a type I error of 0.05 in a placebo-controlled trial.

## RESULTS

### Base-Line Data

Eighty patients entered the trial, 40 in each group. At base line, the two groups were similar with respect

**Table 1. Base-Line Characteristics of 80 Patients with Ulcerative Colitis in Remission, According to Treatment Assignment.**

CHARACTERISTIC	NICOTINE (N = 40)	PLACEBO (N = 40)
<b>Demographic*</b>		
Sex (M/F)	22/18	18/22
Age (yr)	42±12	40±9
Height (cm)	168±9	171±8
Weight (kg)	71±15	75±12
Systolic blood pressure (mm Hg)	121±12	124±11
Diastolic blood pressure (mm Hg)	78±8	77±8
Heart rate (beats/min)	72±7	72±6
<b>Extent of disease (no. of patients)</b>		
Proctitis	21	16
Rectosigmoid involvement	4	10
Left-sided disease	5	7
Hepatic-flexure involvement	1	1
Colitis of the entire colon	9	6
<b>History of disease†</b>		
Age at diagnosis of colitis (yr)	30 (15–59)	30 (10–40)
Duration of disease (mo)	94 (11–311)	85.5 (4–320)
Time since last relapse (mo)	12 (3–85)	12.5 (3–50)
Duration of last relapse (wk)	4 (1–16)	3 (1–24)
No. of relapses in past year	1 (0–4)	1 (0–6)
<b>Smoking history (no. of patients)</b>		
Lifelong nonsmoker	22	24
Exsmoker	18	16
Onset of colitis before smoking cessation	2	3
Onset after cessation	15	11
Onset during cessation	1	2

\*Plus-minus values are means ±SD.

†Median values are shown, with ranges given in parentheses.

to blood pressure, extent of disease, smoking history, and features of colitis that may predict a relapse (Table 1). The patients in the nicotine group were taking a median daily dose of 1600 mg of mesalamine, and the patients in the placebo group were taking a median dose of 1400 mg. Sigmoidoscopic and histologic findings were similar at entry in the two groups. Twenty patients in each group had sigmoidoscopic grades of 0 or 1. With respect to histologic grades, 30 patients in the nicotine group and 33 in the placebo group had grades of 0; 7 and 1, respectively, had grades of 1; 0 and 5, respectively, had grades of 2; and 1 and 0, respectively, had a grade of 4. Biopsy specimens from three patients could not be evaluated.

### Outcome

Eighteen patients in the nicotine group and 20 in the placebo group completed the 26-week trial. There was no significant difference in the number of relapses between the groups (Table 2). Twenty-two patients in the nicotine group and 20 in the placebo group withdrew prematurely from the trial, 14 and 17, respectively, because of relapse. Eight patients in the nicotine group and three in the placebo group withdrew for other reasons: three at their own request (one given nicotine and two placebo), four because of an adverse event (three and one), and four because of a protocol violation (four and none). A larger percentage of patients in the nicotine group than in the placebo group withdrew prematurely from the trial (Fig. 1A), but this difference was not significant ( $P=0.28$  by the Mann-Whitney test). The time course of the relapses was almost identical in

the two groups (Fig. 1B). In both groups, the sigmoidoscopic and histologic grades worsened over the six months of the study, even in patients who completed the trial without a relapse, but there were no significant differences between the groups in terms of the numbers of patients who completed the trial. There was no significant difference between the groups in the severity of relapse according to clinical, sigmoidoscopic, and histologic scores. No characteristics were predictive of relapse, including the dose of mesalamine at enrollment, the number of relapses in the year preceding the study, the duration of remission, or smoking history. There were no significant differences in blood pressure, heart rate, or any hematologic or biochemical measurements within or between the two groups during the trial.

#### Nicotine Dose and Serum Nicotine and Cotinine Concentrations

Although most patients tolerated the 15-mg patches as maintenance therapy, some required a lower dose because of apparent side effects. This was true in both groups of patients. The dose was reduced at some point in eight patients given nicotine and five given placebo. The dose at withdrawal was submaximal in five patients in each group. Serum concentrations of nicotine and cotinine at 0, 13, and 26 weeks reflect the patients' treatment assignments (Table 3). During the study there was considerable variation in the concentrations among patients in the nicotine group, but the concentrations in individual patients were more consistent. The concentrations at relapse were lower than expected, but our analysis included two patients who had not worn a patch for three days before blood samples were taken. When the values for these two patients were excluded from the analysis, the concentrations were similar to those measured in patients who completed the study. There was no relation between the nicotine concentration and relapse.

#### Side Effects

Thirty-five patients reported a total of 59 side effects during the trial (21 in the nicotine group and 14 in the placebo group). More side effects were reported in the nicotine group than in the placebo group (37 vs. 22,  $P=0.18$  by the Mann-Whitney test). The pattern of reporting was not uniform: 16 side effects were reported

Table 2. Outcomes of the Two Groups of Patients.

OUTCOME	NICOTINE (N=40)	PLACEBO (N=40)	POINT ESTIMATE OF DIFFERENCE IN PROPORTIONS (95% CI)*
Withdrawal from trial	22	20	0.05 (-0.17 to 0.26)
Relapse	14	17	-0.08 (-0.28 to 0.14)
Other reasons†	8	3	0.13 (-0.03 to 0.29)
Completion of trial	18	20	

\*Point and interval estimates for the difference in proportions were calculated according to Mee.<sup>13</sup> CI denotes confidence interval.

†The following were other reasons for withdrawal: patient's request (one in the nicotine group and two in the placebo group), adverse event (three and one), and protocol violation (four and none).

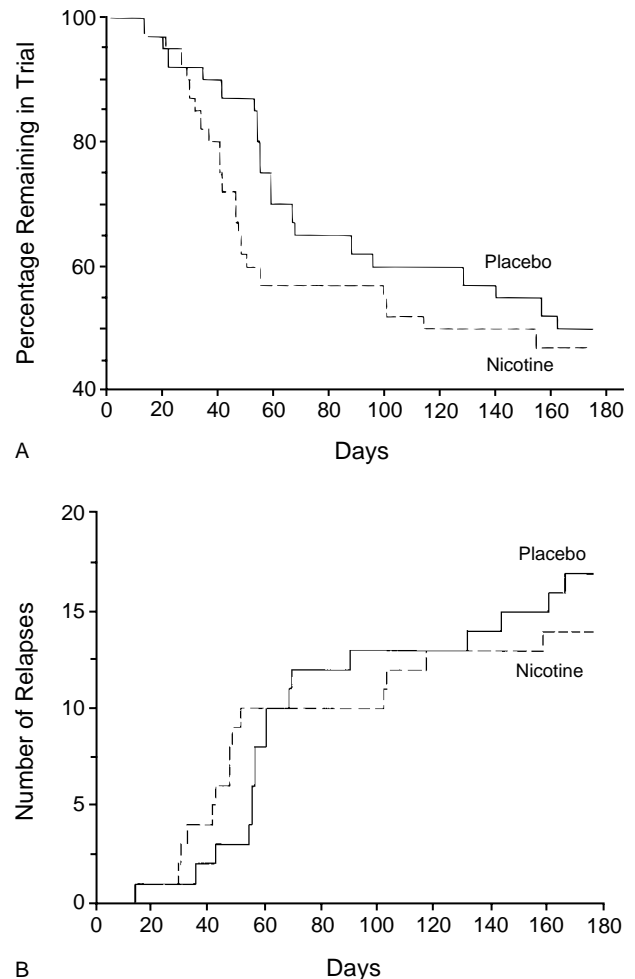


Figure 1. Outcome of the Six-Month Study, as Indicated by the Percentage of Patients Who Completed the Trial (Panel A) and the Number of Relapses (Panel B) in the Two Groups.

Patients withdrew from the trial because of relapse and for other reasons, which are listed in Table 2.

during the first two weeks, 10 during week 6, 9 during week 13, 8 during week 26, and 16 at other times. Four patients withdrew because of side effects: two patients using 5-mg nicotine patches had severe nausea and vomiting, one using 15-mg nicotine patches had profound bradycardia, and one patient in the placebo group had severe palpitations. The bradycardia occurred in a 40-year-old woman with influenza-like symptoms after six weeks of treatment with 15 mg of nicotine daily. Subsequent investigation showed a nodal bradycardia for which no cause could be found. Because the bradycardia did not revert to sinus rhythm when treatment with nicotine was stopped, a permanent pacemaker was implanted, and the patient subsequently made a full recovery. We could find no reports of a similar nature in the literature, and although nicotine is unlikely to have been the cause of this patient's bradycardia, the possibility cannot be excluded.

The most common side effects were nausea (12 pa-

**Table 3. Serum Nicotine and Cotinine Concentrations at Entry, after 13 and 26 Weeks, and at Relapse in Patients Using Nicotine or Placebo Patches.**

TIME	NO. OF PATIENTS	NICOTINE*	COTININE*
		ng/ml	
Week 0			
Nicotine	40	0.1 (0.04–0.45)	0.5 (0.06–4.30)
Placebo	40	0.1 (0.06–0.20)	0.3 (0.04–2.62)
Week 13			
Nicotine	22	7.8 (1.50–40.3)	76 (22–262)
Placebo	24	0.2 (0.04–0.91)	0.6 (0.07–4.77)
Week 26			
Nicotine	18	5.3 (1.10–26.7)	62 (23–163)
Placebo	20	0.2 (0.04–0.58)	0.6 (0.06–5.41)
At relapse†			
Nicotine	13	4.7 (0.2–108)‡	47 (1.3–1660)‡
Placebo	16	0.1 (0.05–0.24)	0.5 (0.05–4.05)

\*Geometric means are shown, with 95 percent fitted ranges given in parentheses.

†Nicotine and cotinine concentrations could not be measured at relapse in one patient in each group.

‡The range is very wide because the calculation includes values for two patients who had not worn patches for three days before blood sampling.

tients in the nicotine group and 2 in the placebo group,  $P=0.0035$  by the Mann–Whitney test), lightheadedness (4 and 6), and itching (5 and 0,  $P=0.055$  by Fisher's exact test). Patients in both groups reported various other side effects, which were transient. In the nicotine group, two patients had an unpleasant taste in their mouths, two had vivid dreams, and one patient each had facial boils, mouth ulcers, and headache. In the placebo group, two patients each had rash, headache, and fatigue and one patient each had vertigo, mouth ulcers, palpitations, and loin pain. In the nicotine group, lifelong nonsmokers reported more frequent and severe side effects than exsmokers, although the small numbers in each subgroup made analysis inappropriate. No patients experienced withdrawal symptoms or started smoking when nicotine was discontinued.

## DISCUSSION

Our chief finding is that transdermal nicotine is ineffective as maintenance therapy for ulcerative colitis, in contrast with our previous study, which showed it to be beneficial for active disease.<sup>9</sup> The findings are probably valid, since the number of patients studied was sufficient to show a clinically worthwhile difference, the study was double-blind, and randomization resulted in two well-matched groups. Blinding inevitably presents difficulties in clinical studies involving nicotine, but blinding appeared to be largely achieved. At the end of the study, patients and physicians were asked whether they could tell which treatment the patients had received. Sixty-two patients guessed, but only 33 were correct; physicians guessed correctly in 20 of 41 cases. Furthermore, 35 percent of the placebo group reported side effects during the study, and five patients in this group required a lower maintenance "dose" of placebo.

If one begins with the hypothesis that nicotine is effective in this clinical situation, then one needs to ad-

dress possible reasons for the failure of our study to show the effect. Serum concentrations of nicotine and cotinine were lower than those usually measured in studies of patients using 15-mg patches.<sup>15</sup> The serum concentration of cotinine, which has a half-life of 16 to 20 hours, should reflect the average intake of nicotine over a three-day period.<sup>16</sup> In our study the average daily intake of nicotine was 15 mg, which should produce cotinine concentrations of about 120 ng per milliliter; however, we recorded concentrations of 70 ng per milliliter.<sup>16</sup>

As compared with our previous study of acute colitis, we made several changes in the way we administered nicotine. We used transdermal nicotine alone rather than in addition to a dose of mesalamine. We limited the dose to 15 mg, instead of 25 mg. Treatment began with a dose of only 2.5 mg followed by a very slow build-up to a maintenance dose of 15 mg at three weeks. These changes were made to reduce the incidence of side effects and intolerance. The patch was worn only during the day and removed at bedtime rather than being left on until it was replaced by a new patch after 24 hours. It is not possible to say whether any of these changes influenced the efficacy of treatment. The lower serum concentrations of cotinine recorded during maintenance therapy could indicate poorer compliance with nicotine use during remission than during active disease. However, cotinine concentrations in patients who relapsed were similar to those in patients who completed the trial. In order to achieve serum concentrations of nicotine similar to those found in persons who smoke 20 cigarettes daily, patients would probably require a dose of 30 mg or more of transdermal nicotine, and such a dose would be less well tolerated in this group of nonsmokers.

If future work shows nicotine to be ineffective as maintenance therapy for ulcerative colitis, but effective for active disease, then the situation is analogous to that with corticosteroids. Although corticosteroids have repeatedly been shown to be effective for acute colitis,<sup>11</sup> they are of little or no value for the maintenance of clinical remission.<sup>17–19</sup> In contrast, mesalamine formulations are particularly valuable for the maintenance of remission but are also of value for acute colitis.<sup>10,14</sup> Nicotine may be more effective in reducing the acute neuromotor symptoms of active colitis than in suppressing the inflammatory process or the underlying abnormality responsible for the relapsing nature of the condition.

Further controlled studies of the therapeutic value of transdermal nicotine are required from other clinical centers, perhaps using higher doses alone and in combination with mesalamine, to establish its therapeutic role in this disease. Occasional therapeutic success with nicotine in individual patients is no substitute for carefully controlled, randomized studies of large numbers of patients.

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