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ARTICLE

Transdermal Nicotine for Mildly to Moderately Active Ulcerative Colitis

A Randomized, Double-Blind, Placebo-Controlled Trial

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Background: Ulcerative colitis is predominantly a disease of nonsmokers. Transdermal nicotine may help control clinical manifestations of this condition.

Objective: To determine the efficacy of transdermal nicotine for controlling clinical disease activity in active ulcerative colitis.

Design: Randomized, double-blind, placebo-controlled, single-center clinical trial.

Setting: Multispecialty group serving as an academic tertiary referral center.

Patients: 64 nonsmoking patients with mildly to moderately active ulcerative colitis despite the use of medication.

Intervention: Patients were stratified on the basis of smoking history, extent of disease, and concomitant medical therapy. After stratification, patients were randomly assigned to daily treatment with transdermal nicotine (n = 31) at the highest tolerated dose (11 mg for 1 week and then ≤ 22 mg for 3 weeks) or placebo (n = 33).

Measurements: Clinical features were assessed at baseline and 4 weeks by endoscopy, physician assessment, and a patient diary of daily symptoms. Serum concentrations of nicotine were determined by using gas chromatography and mass spectrometry, and plasma concentrations of cotinine were measured by using high-performance liquid chromatography.

Results: At 4 weeks, 12 of 31 patients (39%) who received nicotine showed clinical improvement compared with 3 of 33 patients (9%) who received placebo (P = 0.007). Four patients receiving nicotine discontinued therapy because of side effects (contact dermatitis [n = 2], nausea [n = 1], and acute pancreatitis [n = 1]). At week 4, the nicotine group had a mean (±SD) trough serum nicotine concentration of 11.3 ± 8.4 ng/mL and a mean trough plasma cotinine concentration of 192 ± 95 ng/mL.

Conclusions: Transdermal nicotine administered at the highest tolerated dosage (≤ 22 mg/d) for 4 weeks is efficacious for controlling clinical manifestations of mildly to moderately active ulcerative colitis.

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Ulcerative colitis is primarily a disease of nonsmokers [1-4]. Nonsmokers who have ulcerative colitis and begin smoking may go into remission [5]. These observations led to uncontrolled trials of nicotine administered through chewing gum [6] or a transdermal patch [7]. A controlled trial of 15 to 25 mg of transdermal nicotine for active ulcerative colitis reported that 49% of patients responded to nicotine, whereas only 24% responded to placebo [8]. A subsequent controlled trial of 15 mg of transdermal nicotine used to maintain remission of ulcerative colitis reported that 45% of patients receiving nicotine had remission compared with 50% of patients receiving placebo [9]. Finally, a controlled trial [10] showed a clinical response in 32% of patients with active ulcerative colitis who received 15 to 25 mg of transdermal nicotine and in 58% of patients who received oral prednisolone. These studies suggest that transdermal nicotine may be efficacious for active ulcerative colitis, but confirmatory placebo-controlled trials are needed. We conducted a 4-week placebo-controlled trial in which transdermal nicotine, 11 to 22 mg/d, was used to treat active ulcerative colitis.

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Study Design

Our study was a randomized, double-blind, placebo-controlled trial that used the highest tolerated dosage of transdermal nicotine (≤ 22 mg/d) in nonsmoking patients with mildly to moderately active ulcerative colitis. To ensure that the nicotine and placebo groups were similar, patients were assigned to 1 of 16 strata on the basis of concomitant medical treatment (mesalamine, sulfasalazine, and olsalazine; oral corticosteroids; both; or neither), smoking history (persons who formerly smoked or persons who never smoked), and extent of disease (extensive or left-sided only). Eligible patients were sent to the Nicotine Research Center of the Mayo Clinic in Rochester, Minnesota, for randomization and dispensing of study medication. In each stratum, patients were randomly assigned to treatment by a computer-generated randomization sequence that was developed from SAS software (SAS Institute, Cary, North Carolina) [11]. Nicotine and placebo transdermal patches, labeled only by an identifying letter, were placed in clear plastic bags without any treatment-identifying information and were dispensed by Elan Pharmaceutical Research Corp. To the staff of the Nicotine Research Center along with a key for breaking the randomization code. The staff of the Center then dispensed study medication to the patients. The staff was not involved in patient care or assessment of disease activity, and treatment allocation was concealed from the medical personnel involved in patient care or assessment of disease activity and from the patients.

Patients

From April 1993 to September 1995, 66 adult patients with mildly to moderately active ulcerative colitis were referred by colleagues at the Mayo Clinic for study enrollment. Active ulcerative colitis was diagnosed by the usual symptomatic, radiographic, and endoscopic criteria [12]. The Institutional Review Board of the Mayo Clinic approved the study, and all patients gave written informed consent.

Patients were classified as having never smoked or as having formerly smoked. Patients who had used products that contained nicotine within 3 months of study entry were excluded. To confirm patients' self-reported abstinence from nicotine products at study entry, CO concentrations in expired air [13] and serum nicotine and plasma cotinine concentrations were measured [14, 15].

During the trial, therapy with oral 5-aminosalicylate compounds (sulfasalazine, olsalazine, and mesalamine), oral corticosteroids (≤ 20 mg/d), topical corticosteroids, and topical mesalamine was continued at prestudy doses if the doses had not been changed during the 2 weeks preceding study entry. Patients who were receiving corticosteroids at a dosage greater than 20 mg/d and patients who were taking cyclosporine, 6-mercaptopurine, azathioprine, or methotrexate were excluded.

At the initial visit, the extent of colonic mucosal involvement was determined by using flexible sigmoidoscopy. Left-sided disease was defined as a demarcation between inflamed colonic mucosa and normal colonic mucosa (both shown by endoscopy) that was located less than 60 cm from the anal verge; in extensive disease, the demarcation extended more than 60 cm from the anal verge.

Assessment of Disease Activity

Each day, patients recorded the number of stools, any rectal bleeding, and any other symptoms coinciding with therapy that might represent adverse reactions. Patients were evaluated at study entry and after 4 weeks according to a previously described 13-point disease activity index that measured stool frequency, rectal bleeding, endoscopic findings, and the physician global assessment [16]. Clinical remission was defined as a disease activity index score of 0, and clinical improvement was defined as a decrease in the disease activity index of at least 3 points (or a decrease of $\geq$ 2 points if the baseline disease activity index was $\leq$ 3).

Colonic mucosal biopsy specimens were obtained at study entry and after 4 weeks, and histologic disease activity was assessed according to a previously described 5-point histologic disease activity index [17]. Endoscopic biopsy specimens were obtained from the site in the rectosigmoid colon that appeared to have the most severe inflammation. One pathologist blindly determined the histologic disease activity index scores in random order at one sitting. Histologic remission was defined as a histologic disease activity index score of 0, and histologic improvement was defined as a decrease in the histologic disease activity index of at least 1 point.

Transdermal Nicotine Patch

Transdermal nicotine and placebo patches (Elan Pharmaceutical Research Corp., Athlone, Ireland) were used in our study. The transdermal nicotine patches were dispensed in two sizes and doses: small (11 mg) and large (22 mg). Placebo patches identical in appearance to the nicotine patches were also dispensed in two sizes.

Patients were instructed to use the small patches for 7 days and then change to the large patches for 21 days. Patients who wore the larger patch and then developed intolerable side effects that lasted 3 consecutive days were instructed to resume using the smaller patch. Patients who wore the smaller patch and then developed intolerable side effects that lasted 3 consecutive days were instructed to discontinue patch therapy. The patients were instructed to apply fresh patches to the skin of the upper torso every 24 hours. Compliance was determined by review of patient diaries and by counting the number of used and unused transdermal patches at the week 4 visit.

Adverse Reactions to Nicotine

Intolerable adverse reactions (such as severe contact dermatitis, lightheadedness, dizziness, nausea, or vomiting) that occurred before week 4 were reported to the study coordinator; therapy was then changed as described in the preceding paragraph. At the week 4 visit, patients were specifically asked about the following adverse reactions: skin erythema or irritation or contact dermatitis, nausea or vomiting, headaches, sleep disturbance or violent or sexual dreams, diaphoresis or sweating, lightheadedness or dizziness, and shakiness or tremor. Tachycardia and hypertension were also noted.

Concentrations of Serum Nicotine, Plasma Cotinine, and Expired Air Carbon Monoxide

Serum nicotine and plasma cotinine concentrations were determined in venous blood by using standard assays [14, 15]. At study entry, blood samples were collected to confirm abstinence from products that contain nicotine. At the week 4 visit, blood samples were collected at the peak time (the time of maximum concentration, which occurs approximately 8 hours after the transdermal patch is placed on the skin), and at the trough time (the time just before application of the next transdermal patch). Blood samples were processed immediately after venipuncture, and serum and plasma were stored at

–20°C until assays were done.

Concentrations of CO in expired air were measured at study entry and at the week 4 visit by using a Vitalograph EC 50 monitor (Vitalograph, Inc., Lenexa, Kansas) [13]. The results of this assay confirmed the patients' self-reported abstinence from smoking (a concentration of 8 parts per million indicates recent smoking).

Statistical Analysis

The baseline characteristics of the treatment groups were compared by using the rank-sum test for continuous variables and the Fisher exact test for categorical variables. We also used the Fisher exact test to compare the percentage of patients in each group who had overall clinical improvement and remission. The Cochran-Mantel-Haenszel general association statistic was used to test for a difference between treatment groups on overall clinical improvement after simultaneous adjustment for the three stratification factors. For each treatment group, the changes from baseline to week 4 in the 13-point clinical disease activity index, the components of the clinical disease activity index (stool frequency, rectal bleeding, sigmoidoscopic findings, and physician global assessment), and the histologic disease activity index were compared to a score of 0 by using the one-sample signed-rank test. The changes in these scores in the nicotine group were compared with the changes in the placebo group by using the two-sample rank-sum test. When data at the week 4 visit were missing, the last-value-carried-forward technique was used. In all cases, two-tailed tests were used; *P* values less than 0.05 were considered statistically significant.

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Randomization

Sixty-six patients were randomly assigned to treatment, but 2 patients dropped out of the study before receiving any study medication: One decided not to participate in the study, and 1 was severely ill and required hospitalization immediately after randomization (in retrospect, this patient's ulcerative colitis was too severe to meet entry criteria). Before the randomization code was broken, we decided to exclude these patients from the analysis; thus, the analysis included only the 64 treated patients (31 in the nicotine group and 33 in the placebo group). Inclusion of the 2 excluded patients (intention to treat) did not change the results (presented below) for the primary study end point of clinical improvement or remission.

Demographic Characteristics

The groups did not significantly differ in demographic characteristics, concomitant drug therapy (Table 1), or disease severity (Table 2). Symptoms had occurred for a median of 228 days in the nicotine group and a median of 240 days in the placebo group. Only five patients (two in the nicotine group and three in the placebo group) were not receiving concomitant therapy at the start of the study. Most patients in both groups had chronically active ulcerative colitis that was resistant to first-line therapy.

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Table 1. **Patient Characteristics at Baseline***

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Table 2. **Disease Activity Index Scores at Baseline and Week 4***

Disease Activity

One patient in the nicotine group had a baseline disease activity index score of 3; all other patients had a baseline score greater than 3 points. After 4 weeks of therapy, the rate of clinical improvement in the nicotine group was significantly higher than that in the placebo group (12 of 31 patients [39%] compared with 3 of 33 patients [9%]; $P = 0.007$) (Figure 1, top left). However, the rates of clinical remission in the nicotine group (2 of 31 patients [6%]) and placebo group (0 of 33 patients [0%]) did not significantly differ ($P > 0.2$). Figure 1 also shows the rates of clinical improvement for both groups according to the three stratification variables: smoking status, concomitant therapy, and extent of disease. In an analysis that simultaneously adjusted for these stratification variables, treatment with nicotine was found to be associated with a rate of clinical improvement that was higher than the rate associated with placebo ($P = 0.006$).

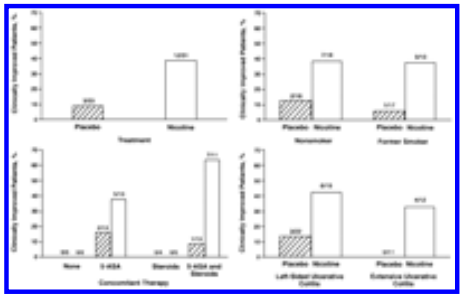

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Figure 1. **Percentage of patients with clinically improved ulcerative colitis at week 4.** The Fisher exact test was used to calculate all *P* values. Top left. According to treatment group ($P = 0.007$). Top right. According to treatment group and history of smoking status ($P = 0.125$ for the patients who never smoked and 0.061 for the patients who formerly smoked). Bottom left. According to treatment group (placebo group, diagonally striped bars; nicotine group, white bars) and concomitant therapy ($P > 0.2$ for the patients who received 5-aminosalicylate [5-ASA] and 0.008 for the patients who received both 5-aminosalicylate and steroids). Bottom right. According to treatment group and extent of disease ($P = 0.075$ for the patients with left-sided colitis and 0.093 for the patients with extensive colitis).

Figure 2 shows the mean (±SD) clinical disease activity index scores of the nicotine and placebo groups at baseline (7.2 ± 2.2 and 7.9 ± 1.9, respectively) and week 4 (5.1 ± 3.1 and 7.5 ± 2.1, respectively). Compared with scores in the placebo group, scores in the nicotine group showed significant improvement between baseline and week 4 ($P = 0.009$). In the nicotine group, scores significantly improved between baseline and week 4 ($P = 0.001$); in the placebo group, the change from baseline to week 4 did not significantly differ from a change of 0 ($P = 0.116$).

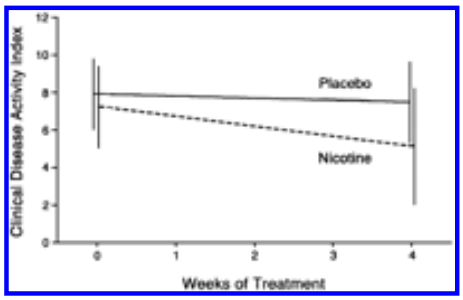

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Figure 2. **Mean scores on the ulcerative colitis clinical disease activity index for each treatment group at each study visit.** Vertical bars at 0 and 4 weeks represent SDs. *P* = 0.009 (two-sample rank-sum test) for scores in the nicotine group at week 4 compared with scores in the placebo group at week 4 (two-sample rank-sum test). *P* = 0.001 (one-sample signed-rank test) for scores in the nicotine group at baseline compared with those at week 4.

Table 2 summarizes the components of the clinical disease activity index (stool frequency, rectal bleeding, sigmoidoscopic findings, and physician global assessment) and the histologic disease activity index at baseline and week 4. Compared with the placebo group, the nicotine group showed significant improvement between baseline and week 4 in stool frequency, sigmoidoscopic findings, and physician global assessment but not in rectal bleeding or histologic disease activity. In the nicotine group, each of the four components of the clinical disease activity index significantly improved between baseline and week 4, but histologic disease activity did not. In the placebo group, neither the four components nor histologic disease activity significantly changed between baseline and week 4. In all analyses, the changes in disease activity indices were measured a second time with the inclusion of the two patients who withdrew from the study; in no cases did the findings change. Patient compliance during the study was high; 30 of 31 (97%) patients in the nicotine group and 32 of 33 (97%) patients in the placebo group wore the study medication patch as directed on at least 90% of the study days.

Adverse Reactions to Nicotine

Adverse reactions occurred significantly more frequently in the nicotine group than in the placebo group (Table 3). Four of 31 (13%) patients in the nicotine group and 0 of 33 (0%) patients in the placebo group had adverse reactions severe enough to necessitate discontinuation of nicotine therapy at or before their scheduled week 4 visit (*P* = 0.05). Reasons for discontinuation of nicotine therapy included contact dermatitis (*n* = 2), nausea in the first week of therapy with the 11-mg patch (*n* = 1), and acute pancreatitis later diagnosed as idiopathic acute relapsing pancreatitis (*n* = 1). Five of 31 (16%) patients receiving nicotine could not tolerate the 22-mg patch because of nondermatologic adverse reactions; they therefore reduced the nicotine dose to 11 mg. Of these 5 patients, all but 2 could complete the study by wearing the 11-mg patch. Except for dermatologic reactions, adverse reactions occurred during the first few days of use of the 22-mg patch and then subsided.

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Table 3. **Patients with Adverse Reactions**

Serum Nicotine and Plasma Cotinine Concentrations

No patients in either treatment group had elevated concentrations of serum nicotine or plasma cotinine at baseline, and no patients in the placebo group had elevated concentrations at the week 4 visit. In both groups, the concentrations of CO in expired breath at baseline and week 4 were both less than 8 parts per million; this finding validates the patients' self-

reported nonsmoking status. Table 4 shows the peak and trough concentrations of serum nicotine and plasma cotinine at 4 weeks in the nicotine group. Of the 31 patients receiving nicotine, 20 wore a 22-mg patch all day, 1 patient wore a 22-mg patch part of the day, and 3 wore an 11-mg patch part of the day or all day during the 3-day period that ended with the day of the week 4 visit. Six patients did not consistently wear their patches on each day in this 3-day period, and 1 patient did not return for follow-up at week 4. In an analysis restricted to the 24 patients who wore a nicotine patch for at least part of each of these 3 days, trends toward negative associations were seen between change in clinical disease activity (score at baseline minus score at week 4) and trough and peak serum nicotine concentrations (r = –0.36[*P* = 0.095] and –0.29[*P* = 0.178], respectively [Spearman rank correlation]). The change in clinical disease activity was not significantly correlated with the trough and peak plasma concentrations of cotinine.

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Table 4. **Peak and Trough Serum Nicotine and Plasma Cotinine Concentrations in 30 Patients after Use of Transdermal Nicotine Patches for 4 Weeks***

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A serendipitous observation that current smokers rarely develop ulcerative colitis [1] led to the investigation of nicotine as the active therapeutic moiety of smoking in ulcerative colitis [6-10]. However, the efficacy of transdermal nicotine for ulcerative colitis has remained unclear. One placebo-controlled trial of nicotine for active ulcerative colitis showed efficacy [8], and one placebo-controlled trial of nicotine for maintenance of remission of ulcerative colitis showed no efficacy [9].

Our placebo-controlled trial shows that transdermal nicotine at the highest tolerated dosage (≤ 22 mg/d) has a clinically significant therapeutic benefit in active ulcerative colitis after 4 weeks. Thirty-nine percent of the patients in our study who received nicotine improved clinically after 4 weeks of therapy compared with 9% of patients who received placebo. Significant improvement was seen not only in the 13-point clinical disease activity index but also in three of the four components of the index (stool frequency, sigmoidoscopic findings, and physician global assessment). In the nicotine group, the fourth component of the index, rectal bleeding, also significantly improved between baseline and week 4. A trend toward improvement in rectal bleeding was seen with nicotine when the week 4 index scores of the nicotine and placebo groups were compared. These results are particularly striking given the fact that the study patients had chronically active ulcerative colitis that was resistant to first-line therapy.

Our positive results are similar to those reported by Pullan and colleagues [8]. These researchers found that 49% of patients with active ulcerative colitis treated with transdermal nicotine at the highest tolerated dosage (≤ 25 mg/d for 6 weeks) improved compared with 24% of patients receiving placebo. Our results are also similar to those of Thomas and colleagues [10], who reported that 32% of patients with active ulcerative colitis improved after treatment with transdermal nicotine at the highest tolerated dosage (≤ 25 mg/16 hours for 6 weeks). Taken together, the results of these three controlled trials in 197 patients with active ulcerative colitis show that transdermal nicotine at the highest tolerated dosage (≤ 22 to 25 mg/16 to 24 hours) had a significant therapeutic benefit. Thus, a more definitive conclusion-that transdermal nicotine at dosages of 22 to 25 mg every 16 to 24 hours is efficacious for the treatment of active ulcerative colitis-seems reasonable.

In contrast, in another study by Thomas and colleagues [9], transdermal nicotine at a dosage of 15 mg/16 hours was not efficacious for maintaining remission of ulcerative colitis (45% of patients receiving nicotine and 50% of patients receiving

placebo had relapse). This result may have occurred because, like corticosteroids, nicotine is not beneficial for maintaining remission of ulcerative colitis or because the nicotine dosage used was too low. The latter seems more likely. In our study (which used ≤ 22 mg of nicotine per day), the mean trough serum nicotine and plasma cotinine concentrations at week 4 were 11.3 ± 8.4 ng/mL and 192 ± 95 ng/mL, respectively; in Pullan and colleagues' study (which used ≤ 25 mg of nicotine per day), the mean trough plasma nicotine and cotinine concentrations at week 6 were 8.2 ± 7.1 ng/mL and 120 ± 98 ng/mL, respectively. These findings are similar to those reported in active smokers with ulcerative colitis in remission, in whom the mean plasma nicotine and cotinine concentrations were 11 ± 7 ng/mL and 220 ng/mL, respectively [18]. In contrast, the study by Thomas and colleagues [9] that had negative results (nicotine dosage, 15 mg/16 hours) reported that the mean trough plasma nicotine and cotinine concentrations at week 26 were 5.3 ng/mL and 62 ng/mL, respectively.

All of the patients in our study who improved were receiving concomitant therapy with oral 5-aminosalicylate compounds (sulfasalazine, olsalazine, and mesalamine), with or without oral corticosteroids. Similarly, most patients in previous studies of transdermal nicotine for active ulcerative colitis also received concomitant therapy [7, 8]. Whether this finding is coincidental or whether nicotine and 5-aminosalicylate or corticosteroids exert synergistic effects remains to be determined. Future studies should establish whether transdermal nicotine is effective as monotherapy.

For other drugs used to treat active ulcerative colitis, including mesalamine and corticosteroids, both clinical response and remission rates increase from 4 to 16 weeks of therapy. It is possible that transdermal nicotine treatment of active ulcerative colitis for at least 6 to 8 weeks would result in rates of response and remission that are greater than those seen in our study. The duration of treatment required to achieve an optimal response should be investigated in future studies.

Our 4-week study did not show a statistically significant improvement in histologic ulcerative colitis disease activity in either the nicotine or placebo group; this finding contrasts with that of the 6-week study by Pullan and colleagues [8], in which patients receiving nicotine had significant histologic improvement. Several reasons may explain this discrepancy. First, histologic improvement may lag behind clinical and endoscopic improvement, and the 4-week treatment duration in our study may not have been long enough to allow histologic improvement to occur. Second, because biopsy specimens were obtained from the area of the colonic mucosa that contained the most severe endoscopically determined inflammation rather than from randomly selected areas of the rectosigmoid colon, there was probably a selection bias toward severe histologic inflammation. The histologic findings in our study may not accurately reflect the overall histologic disease activity in our patients.

In our study, adverse reactions to nicotine occurred frequently (77% of patients in the nicotine group); these reactions were severe enough to necessitate discontinuation of nicotine therapy in 13% of all nicotine recipients. The most frequent adverse reactions were dermatologic complications, nausea, and lightheadedness or dizziness. These findings are similar to those reported in other studies of transdermal nicotine used to treat ulcerative colitis [8, 9]. Because of the relatively high rate of adverse reactions in patients receiving nicotine, some degree of patient unblinding may have occurred during the study. Similarly, treatment with nicotine could have caused a beneficial psychoactive effect, although the psychoactive effects of nicotine largely depend on the route of administration; smoking results in mood elevation, and transdermal nicotine has minimal psychoactive effects [19, 20]. These factors may have positively influenced the subjective clinical outcomes of the nicotine group. We did not specifically ask either the patients or the medical personnel which treatment they thought the patient had received. However, all patients who improved clinically also had significant improvement in objective endoscopic outcomes. Thus, we do not believe that patient knowledge of treatment assignment or beneficial psychoactive effects from nicotine accounted for a major portion of the positive outcome of our study.

In contrast to ulcerative colitis, Crohn disease occurs more frequently in active smokers (relative risk, 4.8 compared with matched controls) [21]. This phenomenon of "opposite effects" of smoking on ulcerative colitis and Crohn disease remains unexplained, and it is unclear whether the adverse effect of smoking on Crohn disease results from nicotine or some other component of cigarette smoke. Additional studies are needed to determine whether transdermal nicotine therapy for either smoking cessation or treatment of intestinal inflammation in patients with Crohn disease is efficacious or detrimental.

In conclusion, our study shows that transdermal nicotine administered at the highest tolerated dosage (≤ 22 mg/d for 4 weeks) along with 5-aminosalicylate compounds, oral corticosteroids, or both reduces clinical activity but does not induce remission in nonsmoking patients with mildly to moderately active ulcerative colitis.

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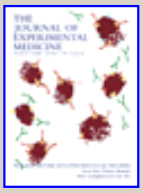

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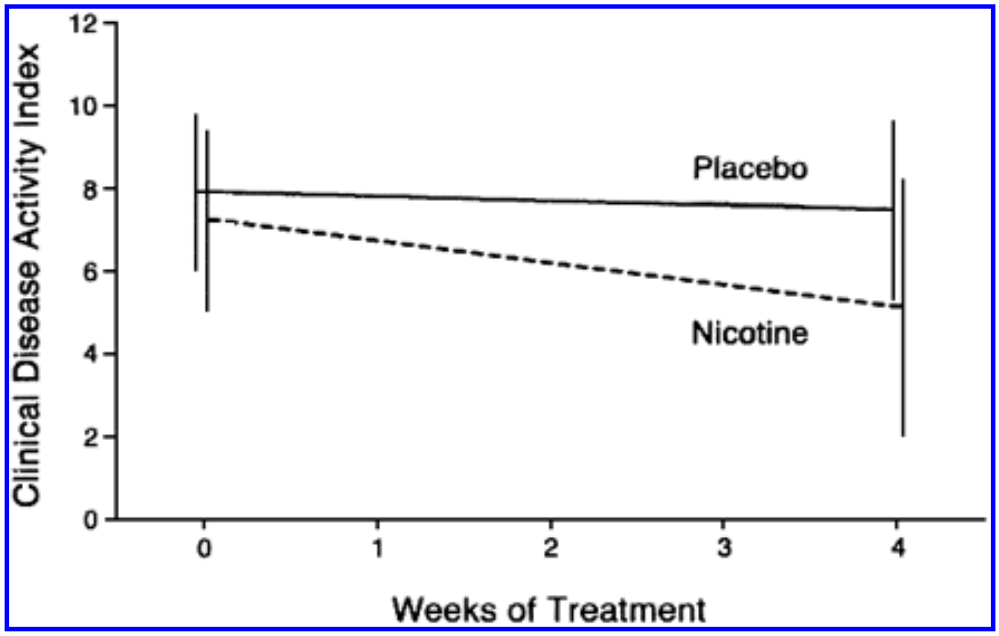

Figure 2. **Mean scores on the ulcerative colitis clinical disease activity index for each treatment group at each study visit.** Vertical bars at 0 and 4 weeks represent SDs. *P* = 0.009 (two-sample rank-sum test) for scores in the nicotine group at week 4 compared with scores in the placebo group at week 4 (two-sample rank-sum test). *P* = 0.001 (one-sample signed-rank test) for scores in the nicotine group at baseline compared with those at week 4.

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Table 4. **Peak and Trough Serum Nicotine and Plasma Cotinine Concentrations in 30 Patients after Use of Transdermal Nicotine Patches for 4 Weeks***

Patients	Nicotine Concentration				Cotinine Concentration			
	Patients	Trough Concentration	Patients	Peak Concentration	Patients	Trough Concentration	Patients	Peak Concentration
	n	*ng/mL*	*n*	*ng/mL*	*n*	*ng/mL*	*n*	*ng/mL*
All patients	29	11.3 ± 8.4†	27	12.2 ± 7.0	30	192 ± 95	27	203 ± 71
Patients using 22-mg patch‡	19	13.3 ± 9.6†	19	13.8 ± 7.4	20	226 ± 82	19	224 ± 73
Patients using 11-mg patch§	4	9.7 ± 3.4	4	8.6 ± 4.6	4	110 ± 63	4	149 ± 52
Other patients‖	6	6.1 ± 2.9	4	8.6 ± 4.8	6	131 ± 101	4	161 ± 17

* Thirty-one patients were assigned to the nicotine group. One patient, however, discontinued patch therapy on day 3 because of an adverse event and did not return for the week 4 visit.
† One patient's trough blood sample had a serum nicotine concentration of 122.4 ng/mL. This sample is assumed to have been contaminated and therefore is not included in the summary of trough nicotine concentrations presented in the table. If this sample is included, the mean (± SD) trough nicotine concentration for all 30 patients is 15.0 ± 21.9 ng/mL and the mean concentration for the 20 patients who used the 22-mg patch is 18.8 ± 26.1 ng/mL.
‡ These 20 patients reported wearing a 22-mg patch all day during each day of the 3-day period that ended with the day of the week 4 visit.
§ These four patients reported wearing a 22-mg patch for part of the day (n = 1) or an 11-mg patch for part or all of the day (n = 3) for 1 or more days of the 3-day period that ended with the day of the week 4 visit.
‖ These six patients reported not wearing a patch on 1 or 2 days of the 3-day period that ended with the day of the week 4 visit (three of these patients discontinued patch therapy at the week 4 visit because of adverse events).

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Table 3. **Patients with Adverse Reactions**

Reaction	Nicotine Group ($n = 31$)	Placebo Group ($n = 33$)	*P* Value*
	%		
Skin irritation, erythema, or contact dermatitis	58	12	<0.001
Lightheadedness or dizziness	29	3	0.005
Nausea	29	0	<0.001
Vomiting	6	0	>0.05
Headaches	10	0	>0.05
Sleep disturbance or violent or sexual dreams	6	3	>0.05
Stimulation of central nervous system	3	3	>0.05
Diaphoresis or sweating	3	0	>0.05
Shakiness or tremor	3	0	>0.05
Tachycardia	3	0	>0.05
Miscellaneous	23	15	>0.05
Any adverse reaction	77	30	<0.001

* By the Fisher exact test.