Effect of Treatment With Capsaicin on Daily Activities of Patients With Painful Diabetic Neuropathy

CAPSAICIN STUDY GROUP

OBJECTIVE— To establish the effects of topically applied capsaicin on daily activities in patients with painful diabetic neuropathy.

RESEARCH DESIGN AND METHODS— Investigators at 12 sites enrolled 277 men and women with painful peripheral polyneuropathy and/or radiculopathy in an 8-wk double-blind vehicle-controlled study with parallel randomized treatment assignments. Participants were unresponsive or intolerant to conventional therapy and were experiencing pain that interfered with functional activities and/or sleep. Either 0.075% capsaicin cream or vehicle cream was applied to the painful areas 4 times/day. A visual analogue scale of pain intensity and baseline measurements of the pain's interference with the ability to walk, work, participate in recreational activities, use shoes and socks, sleep, and eat were recorded at onset and at 2-wk intervals. A physician's global evaluation scale assessed changes in pain status from baseline.

RESULTS— Statistically significant differences are percentage of patients with improvement in favor of capsaicin versus vehicle: 69.5 vs. 53.4% with clinical improvement in pain status ($P = 0.012$), 26.1 vs. 14.6% with improvement in walking ($P = 0.029$), 18.3 vs. 9.2% with improvement in working ($P = 0.019$), 29.5 vs. 20.3% with improvement in sleeping ($P = 0.036$), and 22.8 vs. 12.1% with improvement in participating in recreational activities ($P = 0.037$).

CONCLUSIONS— The results from this study suggest that topical 0.075% capsaicin is effective for reducing pain in patients with painful diabetic neuropathy with subsequent improvement in daily activities, enhancing the quality of the patient's life.

Painful neuropathy is one of the most distressing complications of diabetes. Some patients with acute painful diabetic neuropathy may spontaneously experience marked improvement in 6–10 mo (1), however, when the neuropathic symptoms persist for ≥12 mo, the pain usually does not resolve spontaneously and may last for many years (2). The painful neuropathy often disrupts and reduces the overall quality of the patient's life. The effects of peripheral polyneuropathy may include severe dysesthetic burning, most often in the feet and ankles and to a lesser extent in the upper extremities, with nocturnal worsening, cutaneous contact discomfort, thermal hyperalgesia, paresthesias, insomnia, weight loss, anxiety, depression, and absenteeism from work (1). Drugs such as narcotic analgesics, tricyclic antidepressants, anticonvulsants, and phenothiazines have been used to treat painful neuropathy, but these drugs are not effective for many patients, and the side effects may become intolerable. There is a need for additional effective therapies.

Capsaicin (0.075%; Axsain, GalenPharma, Northbrook, IL) is a new topical medication for treatment of neuralgia. This drug has been used to treat postherpetic neuralgia (3–5) and postmastectomy pain syndrome (6) without the side effects associated with systemic drugs. This study was conducted to determine the effects of treatment with capsaicin on the daily activities of patients with painful diabetic neuropathy.

RESEARCH DESIGN AND METHODS

METHODS— Insulin-dependent (type I) and non-insulin-dependent (type II) diabetic patients with painful neuropathy were entered into this 8-wk, randomized, double-blind, vehicle-controlled, multicenter study. Entry criteria included men or nonpregnant women 18–85 yr of age with diagnosis of peripheral polyneuropathy or radiculopathy verified by a history of neuropathic pain, results of a neurological examination, and abnormal nerve conduction studies. The dysesthesia associated with the neuropathy, i.e., the unfamiliar unpleasant painful sensation described as being located superficially, was the pa-

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Table 1—*Demography*

	CAPSAICIN (*N* = 138)	VEHICLE (*N* = 139)
MEN (*N*)	71	68
WOMEN (*N*)	67	71
MEAN AGE (YR)	60.1 (27–92)	60.3 (22–81)

Age ranges in parentheses.

rameter used for evaluation of treatment outcome. Paresthesias were noted in characterizing the sensory neuropathy at the baseline visit. For acceptance into the study, subjects had to experience dysesthetic pain of moderate to severe intensity daily, interfering with daily activities or sleep unattributable to psychological origins. Patients were excluded from the study if there was another skin condition in the area affected by the neuropathy, if diabetes was not stable or well controlled (fasting blood glucose >10 mM or glycosylated hemoglobin >11% [normal range 5–8%]), or if they had another organic disease or disorder not under long-term control. Patients taking oral pain medication associated with neuropathy were enrolled in the study if the medication dosage was not expected to change during the study. New oral analgesic, antiinflammatory, or CNS-acting drugs were not allowed during the study. No attempts were made to change antidiabetic therapy or nutritional habits for the purpose of bringing the patient into tighter control. Topical medications previously applied to the treatment areas were discontinued for at least 7 days before the study.

Patients were evaluated at a pretreatment visit with respect to entrance criteria, and physical examinations and nerve conduction studies were performed. Patients were randomly assigned to receive either 0.075% capsaicin cream or vehicle cream. Patients applied the study drug 4 times/day to painful area associated with the neuropathy and returned to the clinic at 2, 4, 6, and 8 wk for safety and efficacy evaluations.

The effects of pain on the quality of life were evaluated by functional capacity scales, which the patients completed at the pretreatment visit and at each subsequent visit during the 8-wk treatment period. The functional capacity scales rated the interference of pain with working, sleeping, walking, participating in recreational activities, wearing shoes and socks, and eating. Patients indicated whether the amount of interference for each activity was severe, 4; moderate, 3; slight, 2; or none, 1. The physician's global evaluation (PGE) of change in pain status from baseline during the study by assessing any change as pain completely gone, +3; much better, +2; better, +1; same, 0; worse, −1; or much worse, −2. A visual analogue scale (VAS), consisting of a 100-mm line across which the patient marked the degree of pain, was used to assess pain intensity. The VAS for pain intensity was labeled *no pain* at one end and *worst possible pain* at the other end. PGE and VAS results were previously reported by Donofrio et al. (7). Safety evaluations were conducted at each visit during the treatment period and included an assessment of side effects, study drug application, and use of concomitant medications.

Twelve investigators at universities or in private practice participated in this study. Permission to conduct the study was obtained by each investigator from an institutional review board, and written informed consent was obtained

Table 2—*Diabetes and neuropathy characteristics*

	CAPSAICIN (*N* = 138)	VEHICLE (*N* = 139)
TYPE AND DURATION OF DIABETES MELLITUS		
TYPE I (%)	51 (16.5)	47 (18.6)
TYPE II (%)	49 (18.6)	53 (10.9)
TYPE AND DURATION OF PAINFUL NEUROPATHY		
POLYNEUROPATHY (%)	92 (3.7)	87 (4.6)
RADICULOPATHY (%)	5 (2.2)	9 (3.5)
BOTH (%)	3 (0.7)	4 (2.9)
PRETREATMENT PAIN SEVERITY (% OF PATIENTS)		
MODERATE	11	11
SEVERE	60	56
VERY SEVERE	29	33

Values are percentages of patients with mean duration (yr) in parentheses.
Type I, insulin-dependent diabetes mellitus; type II, non-insulin dependent diabetes mellitus.

Table 3—*Descriptors of dysesthesia and paresthesia*

	CAPSAICIN (*N* = 138)	VEHICLE (*N* = 139)
DYSESTHESIA		
BURNING	107	95
DULL ACHING	53	59
CRAMPLIKE	33	39
CUTTING	21	23
CRUSHING	6	9
OTHER	44	41
PARESTHESIA		
NUMBNESS	103	87
TINGLING	83	63
COLDNESS	54	51
OTHER	3	3

Table 4—*Pretreatment interference of pain with functional capacities*

	CAPSAICIN (*N* = 138)	VEHICLE (*N* = 139)
WORKING (%)		
SEVERE	38	33
MODERATE	34	36
MILD	12	10
NONE	16	21
SLEEPING (%)		
SEVERE	50	53
MODERATE	26	30
MILD	13	9
NONE	11	8
WALKING (%)		
SEVERE	50	54
MODERATE	33	21
MILD	8	11
NONE	9	14
PARTICIPATING IN RECREATIONAL ACTIVITIES (%)		
SEVERE	44	42
MODERATE	30	26
MILD	11	12
NONE	15	20
WEARING SHOES AND SOCKS (%)		
SEVERE	32	26
MODERATE	21	29
MILD	15	14
NONE	32	31
EATING (%)		
SEVERE	5	3
MODERATE	6	8
MILD	6	12
NONE	83	77

Values are percentages of patients.

from each patient before study procedures were initiated.

Categorical data derived from the functional capacity scales and PGE were analyzed with the Cochran-Mantel-Haenszel statistic (8). Demographic data were analyzed with Fisher's exact test and a *t* test. VAS was analyzed with analysis of variance. Results were analyzed at the pretreatment visit and at 2, 4, 6, and 8 wk of the treatment period. To determine whether the study results were affected by dropouts, a final-visit analysis was performed with data from all patients who completed at least one visit during the treatment period. All tests were two tailed at $P = 0.05$.

RESULTS— Of 277 patients entering the study, 139 were men, and 138 were women. The mean age of the patients was 60 yr with a range of 22–92 yr. There were 136 patients with type I and 141 with type II diabetes. Most patients were diagnosed with peripheral polyneuropathy (89%) with a mean duration of pain of 5 yr, and the remaining patients were diagnosed either with radiculopathy (7%) with a mean duration of pain for 3 yr or with both peripheral polyneuropathy and radiculopathy (4%) with a mean duration of pain of 2 yr. The intensity of dysesthetic pain was very severe in 31%, severe in 58%, and moderate in 11% of patients (Tables 1 and 2). There were no statistical differences between the capsaicin- and vehicle-treated groups concerning age, sex, race, type and duration of diabetes, type and duration of neuropathy, and severity of pain at the pretreatment visit ($P > 0.05$). The number of patients treated with ongoing systemic analgesic or CNS drugs, 77% in the capsaicin and 83% in the vehicle group, and the types and dosages of drugs used was not statistically different between treatment groups. The terms used by the patients in describing the dysesthesias and paresthesias are listed in Table 3. No significant difference between treatment groups was noted for the number or type of descriptors used.

Of the 58 patients who did not complete the study, 38 were in the capsaicin group, and 20 were in the vehi-

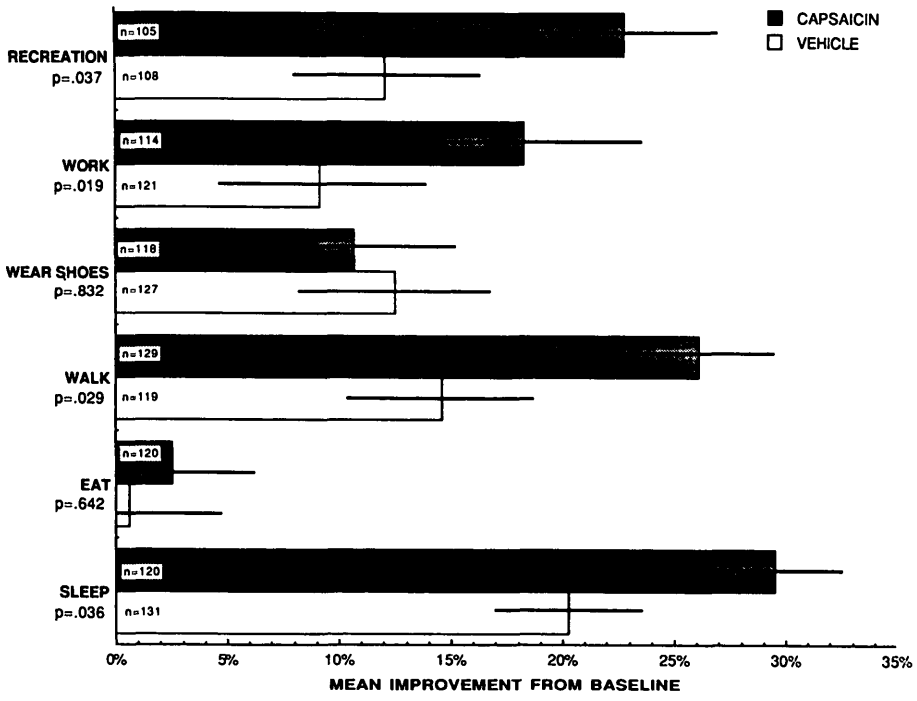

Figure 1—*Mean ± SE percentage of improvement in daily activities at final visit for capsaicin- and vehicle-treated patients.*

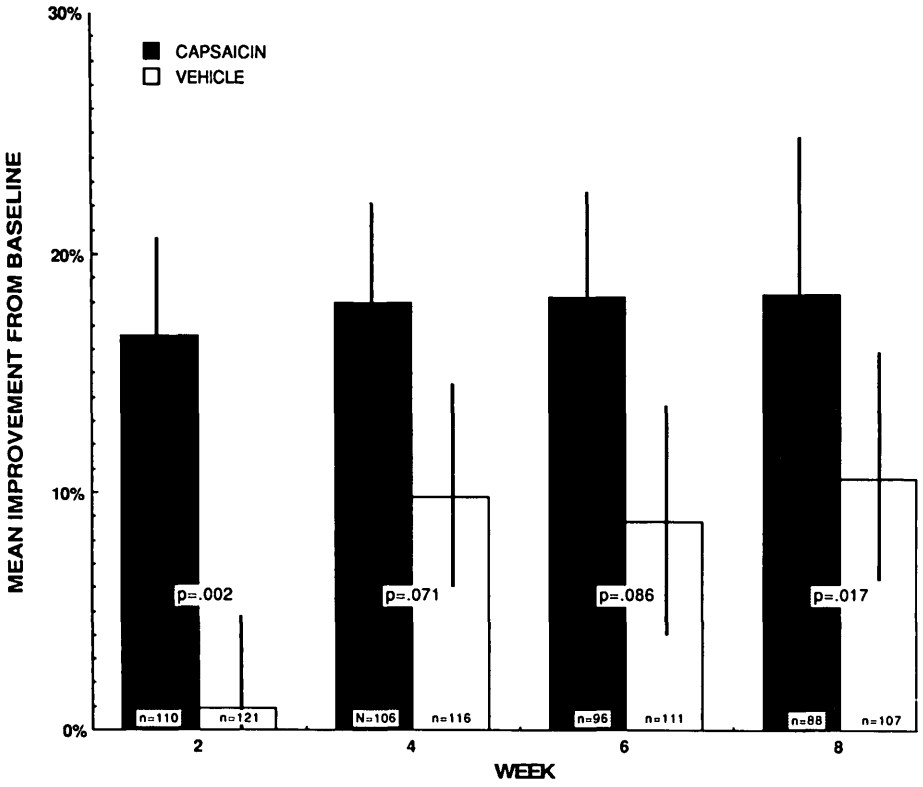

Figure 2—*Mean ± SE percentage of improvement in ability to work for capsaicin- and vehicle-treated patients at each visit.*

cle group. Twenty-five of 58 withdrew from the study before efficacy evaluations could be made at the 2-wk visit. The reasons for patients not completing the study included side effects (18 capsaicin, 5 vehicle), lack of compliance with dosage schedule (7 capsaicin, 6 vehicle), treatment failure (0 capsaicin, 2 vehicle), health-related problems (10 capsaicin, 5 vehicle), and other (3 capsaicin, 2 vehicle). After removal of patients without evaluatable data, the statistical comparability between treatment groups remained for the analysis of demographic parameters and diabetes and neuropathy characteristics.

Before the first application of study drug, patients indicated whether the pain associated with diabetic neuropathy interfered with selected functional capacities. A moderate or severe interference in functional activities was reported by 70% of the 277 patients for working, 79% for sleeping, 79% for walking, 71% for participating in recreational activities, 54% for wearing shoes and socks, and 12% for eating (Table 4). There were no statistical differences between the capsaicin and vehicle groups with respect to any of the pretreatment functional capacities ($P > 0.05$).

The overall improvement in functional capacities at the final visit is shown in Fig. 1. The improvement is reported as the percentage change from baseline. Patients in the capsaicin group showed significantly greater improvement in ability to work ($P = 0.019$), sleep ($P = 0.036$), walk ($P = 0.029$), and participate in recreational activities ($P = 0.037$) than those in the vehicle group. Eating, which showed little or no interference by painful neuropathy at baseline, was not affected by either capsaicin or vehicle during the study. Slight improvement in the ability to wear shoes and socks was reported in both groups but was not statistically significant.

Figures 2–5 show the weekly improvements in the ability to work, sleep, walk, and participate in recreational activities. By 2 wk, patients in the capsaicin group reported more improvement in ability to work (17 vs. 1%, $P = 0.002$), walk (16 vs. 6%, $P = 0.011$), and participate in recreational activities (17 vs. 2%, $P = 0.008$) than those in the vehicle group. Patients in both the capsaicin and vehicle groups showed similar improvements in ability to sleep at the 2-wk visit.

At the 4- and 6-wk visits, more improvement was reported by patients in the capsaicin group than by patients in the vehicle group for all four of these functional capacity scales. The differences in the capsaicin and vehicle groups were maintained at the 8-wk visit, when more improvement was reported by capsaicin patients than vehicle patients in ability to work (18 vs. 11%, $P = 0.017$), sleep (30 vs. 20%, $P = 0.031$), walk (27 vs. 15%, $P = 0.031$), and participate in recreational activities (24 vs. 13%, $P = 0.054$).

The PGEs for the 219 patients who completed the 8-wk study showed a statistically significant difference between the two treatment groups, i.e., 71.3% of the capsaicin-treated patients improved, and 51.3% of the vehicle-treated patients improved ($P = 0.007$). When added to the evaluations of patients who completed the study, analysis of the final-visit evaluations of patients who withdrew prematurely did not alter the statistical outcome, i.e., 69.5 and 53.4% improvement for capsaicin- and vehicle-treated patients, respectively ($P = 0.012$). The mean percentage decrease in pain intensity at the 8-wk visit, as measured by the visual analogue scales, was 40.1 and 27.8% for capsaicin- and vehicle-treated pa-

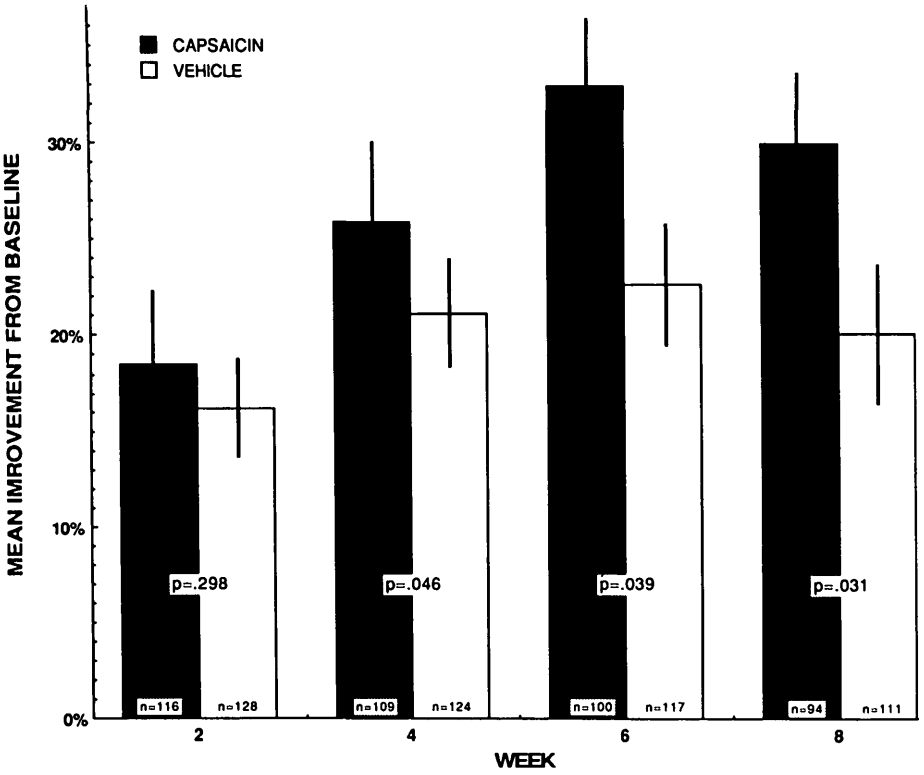

Figure 3—*Mean ± SE percentage of improvement in ability to sleep for capsaicin- and vehicle-treated patients at each visit.*

tients, respectively. This difference between treatment groups was statistically significant ($P = 0.014$). The subset of patients with radiculopathy was not large enough for meaningful statistical comment. The percentage of patients with radiculopathy who improved in the capsaicin group was greater than in the vehicle group (80 vs. 33%).

Side effects reported in this study included rash/erythema, dry skin, inhalation reactions, and exposure/irritation to other parts of the body (Table 5). Burning was the most frequently described side effect in both groups; it was reported by 63% of patients in the capsaicin group and 17% of patients in the vehicle group. Of those patients who reported burning sensations with application, 14 of the capsaicin-treated patients withdrew prematurely from the study because of this side effect. All but 4 of the capsaicin dropouts occurred during the first 2 wk of the study, indicating that this side effect is greatest in the first 2 wk, diminishes with time, and is not likely to be a problem with long-term use. By the end of the study, only 34 of 87 capsaicin-treated patients who initially experienced burning continued to experience any burning, also suggesting that this effect becomes tolerable or ceases with continued use. Side effects such as sedation, dry mouth, constipation, and neuromuscular reactions, generally associated with the systemic drugs used to treat painful diabetic neuropathy, were not reported in this study.

CONCLUSIONS — Diabetes is costly to society and to patients and their families. A study conducted by the Center for Economic Studies in Medicine (9) estimated that in 1987, there were 6,895,516 physician visits by diabetic patients in the working population in the United States, with an average time away from the job of 1.7 h/visit. The associated value of the lost earnings was $86.9 million or $63/event. This does not include the substantial direct costs associated with the delivery of health-care services, laboratory tests, and medications, nor does it include the costs related to hospitalization or nursing-home care in all age-groups. The total cost of diabetes in 1987 was estimated at $20.4 billion. Approximately 39% of this total was related to inpatient treatment in hospitals or nursing homes for the complications of diabetes, including diabetic neuropathy.

Patients entering this study reported that their overall quality of life was reduced because of the effects of their painful condition. During the 8-wk study, patients in the capsaicin group reported significant improvement in the ability to work compared with patients in the vehicle group. The clinical improvement in ability to work may translate into fewer workdays lost or greater productivity; however, the study was not designed to quantify these points. Patients treated with capsaicin were able to sleep better than patients treated with vehicle, an effect most likely related to the improved pain status. The significant improvements in walking and participating in recreational activities made by patients in the capsaicin group presumably allowed these patients to be more independent and enjoy social activities with family and friends. The interference of pain with eating was a minor problem for patients entering this study and, as expected, did not change as a result of treatment.

The patients receiving vehicle also reported improvement in functional capacities; however, the vehicle response rate was significantly lower than the capsaicin response rate for

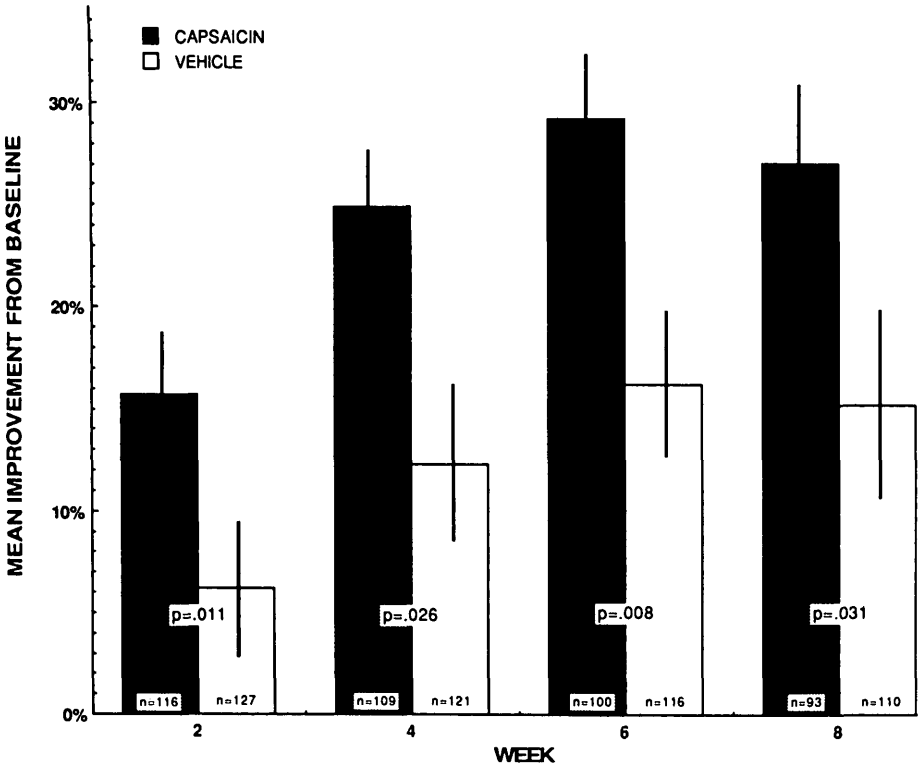

Figure 4—*Mean ± SE percentage of improvement in ability to walk for capsaicin- and vehicle-treated patients at each visit.*

sleeping, walking, working, and participating in recreational activities. Placebo responses in the range of 40–50% are not unexpected in pain studies and studies of medication applied topically with a vehicle cream. The mechanism of the vehicle response is unknown but could be associated with massaging the painful area as the cream is applied, because massage has been associated with a reduction in painful sensations (1).

Maintaining an ideal blinded design for a therapeutic agent with prominent side effects is always a challenge in clinical trials. Because the major side effect of capsaicin, i.e., burning, is a result of its action on the target cells of therapeutic benefit, i.e., C-nociceptive fibers, it is impossible to identify a perfect placebo, i.e., one that produces burning without affecting C-nociceptive fibers. Previous experience with capsaicin in double-blind studies confirmed that in addition to the capsaicin-treated patients who experienced burning sensations, patients treated with vehicle cream also reported burning (5,7). The investigators in this study realized that the certain identification of treatment assignment based on burning or lack of burning was impossible. Indeed, the results of this study showed that 51 of the capsaicin-treated patients did not experience burning and 23 of the vehicle-treated patients experienced burning.

To examine the possibility that the burning sensation side effect might influence or predict outcome, the PGEs of capsaicin-treated patients with burning and those without burning were compared. No statistically significant difference was found. Interestingly, the percentage of patients who improved was slightly higher in the group without burning than in the group with burning (76 vs. 66%, respectively).

The incidence of burning is greater in the capsaicin group, an action attributed to the drug's pharmacological activity. Although the burning sensation occurred in a significant portion of the capsaicin-treated patients during the first 2 wk of therapy, it was well tolerated by most and decreased or disappeared with continued application. The coughing observed in the capsaicin-treated patients was attributed to a dried residue of capsaicin at the application site, which became airborne and was inhaled. The risk of this occurring was minimized by applying an amount of cream that would rub into the affected area without resulting in a "caked" residue.

Capsaicin (0.075%) provided pain relief in patients with established painful diabetic neuropathy and increased their productivity, mobility, and ability to sleep and participate in recreational activities. This drug should be considered as an early therapeutic choice for patients with painful diabetic neuropathy, or those intolerant of other medications, because capsaicin is well tolerated in most patients and lacks the

Table 5—*Side effects*

	Capsaicin (N = 138)	Vehicle (N = 139)
Burning	87	23
Coughing/ sneezing	16	2
Accidental exposure/irritation to other parts of body	9	1
Rash/erythema	10	4
Dry skin	5	6
Increased pain	2	5
Other	6	8

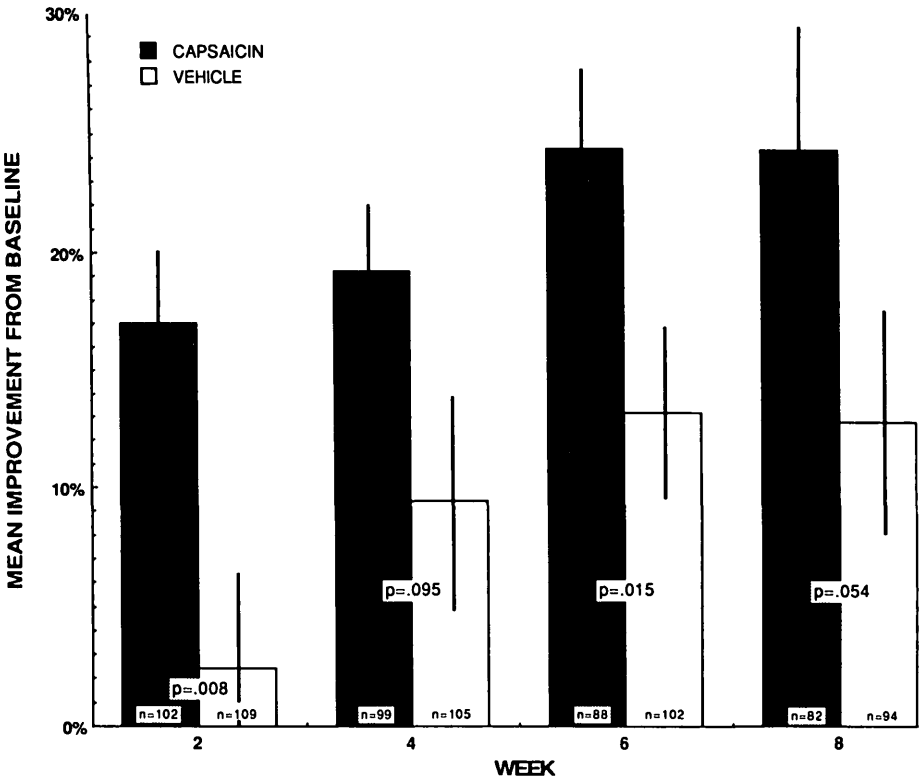

Figure 5—*Mean ± SE percentage of improvement in ability to participate in recreational activities for capsaicin- and vehicle-treated patients at each visit.*

untoward side effects of systemic medications.

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APPENDIX: THE CAPSAICIN STUDY GROUP

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