A COMPARISON BETWEEN THE EFFECTS OF 0.025% AND 0.075% CAPSAICIN ON PAINFUL DIABETIC NEUROPATHY

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WHITWORTH COLLEGE
Spokane, Washington

Spring 1996
We, the undersigned members of the committee
have read and approved the clinical research project

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ON PAINFUL DIABETIC NEUROPATHY

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I had the great fortune of having a splendid group of colleagues who continuously provided support and encouragement. I am very gratefully to them all.
To my loving children

Juan Cristobal
and
Maria de los Angeles
A COMPARISON BETWEEN THE EFFECTS OF 0.025% AND 0.075% CAPSAICIN ON PAINFUL DIABETIC NEUROPATHY

Abstract
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The purpose of this study was to determine the difference between two different strengths of topical capsaicin cream on relieving the pain associated with diabetic neuropathy. This quasi-experimental single blind and randomized drug study evaluated 15 diabetics with painful peripheral neuropathy during treatment with 0.025% or 0.075% capsaicin.

Neuropathy pain was assessed at baseline and at weeks 1, 3, 5, 7 and 8 by a vertical 100mm visual analog scale in which participants rated their most intense pain. Repeated measures analysis of variance showed no significant difference between the two available over-the-counter strengths of capsaicin (p=0.496) in relieving the pain associated with diabetic neuropathy. However, analysis of variance showed significant pain relief over time for both groups (p=0.000). Compliance with the study's treatment was evaluated by t-tests (t=0.520, df=1, p=0.612), and Pearson chi-square ($\chi^2=3.951$, df=5, p=0.557) methods, which showed no significant difference between the two groups. The study concluded that capsaicin's 0.025% regular strength cream is as effective as the 0.075% extra-strength in relieving diabetic neuropathy pain.
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Chapter I

Introduction

Diabetes mellitus, a syndrome of metabolic decompensation characterized by inappropriate hyperglycemia, affects fourteen million people in the United States (Harvey, 1996). Persons with either type I or type II Diabetes Mellitus are vulnerable to long-term complications associated with serious morbidity. These complications include retinopathy, nephropathy and neuropathy (Nathan, 1993).

Neuropathy, the most frequent complication of diabetes, is a peripheral nerve dysfunction that affects 30% of diabetics after ten years of the disease, 40% after twenty-five years, and 50% after fifty years (Herman & Greene, 1992). Hyperglycemia is thought to cause chemical changes in nerves, impairing the transmission of impulses. The National Institutes of Health (1995) states in their Diabetic Sourcebook, that hyperglycemia also causes damage to blood vessels reducing the flow of oxygen and nutrients to nerves. Among the symptoms caused by damaged nerves, pain may be the most difficult and distressing to manage (Dyck, 1992). The pain can be severe enough to interfere with sleep and activities-of-daily living, thus decreasing the quality of the patient's life (Pfeiffer, et al., 1993).

Painful diabetic neuropathy is difficult and challenging to manage, as it is often refractory to simple analgesics such as acetaminophen and Ibuprofen. Other oral pharmacologic agents are used with limited success due to unfavorable side effects. Additional treatments have included insulin pumps and physical therapy. Massage and the use of transcutaneous electric nerve stimulation units provides some relief to 25-
30% of the patients (Pfeiffer et al., 1993).

Attention has turned recently to Capsaicin, a topical medication introduced in 1987 as Zostrix, offering effective pain control. The increasing popularity of capsaicin can be attributed to its lack of systemic side effects and drug interactions. Capsaicin, the active ingredient derived from hot red peppers, is a substance P antagonist that can apparently block pain without affecting the sense of touch, pressure, or vibration (Cotton, 1990).

Statement of the Problem

Successful demonstration of topical capsaicin's effectiveness on painful diabetic neuropathy make its use attractive to many diabetics suffering from pain. Capsaicin is currently available over the counter in regular 0.025% and extra strength 0.075% concentrations. Although Vinik (1994) points out that the more expensive 0.075% concentration offers no significant advantage over the 0.025% concentration, there is no documented research comparing the two strengths. Clinical trials directly comparing the two strengths of capsaicin would provide increased knowledge with regards to the degree of effectiveness each strength has for particular pain characteristics. This knowledge would in turn assist clients to decide which strength to use initially. Since the extra-strength capsaicin is more expensive, determining equally effective pain relief with regular capsaicin will also help clients who may not be able to afford the stronger cream.

Statement of the Purpose

The purpose of this quasi-experimental study was to determine the difference in
efficacy between topical application of capsaicin cream 0.025% and 0.075% strength in relieving pain associated with diabetic neuropathy.

**Background and Significance**

Uncontrolled diabetes leads to complications of retinopathy, neuropathy and nephropathy and contributes to other complications such as lower extremity amputation, retinal detachment, and end stage renal failure (Lorber, 1994). Diabetes not only impacts the lives of patients, their families, and their cost for health care, but also affects other related health problems and the cost of health care nationally. The total annual health care costs generated by all diabetics is $14 billion (U.S. Preventive Services Task Force, 1996).

Tight glycemic control with maintenance of glucose levels below 130 has demonstrated to be the best treatment in prevention of diabetic complications (Diabetes Control and Complications Trial, 1993). Unfortunately, even in the setting of tight glycemic control, diabetic neuropathies may ensue.

Distal symmetrical polyneuropathy is the most prevalent of all diabetic neuropathies. Approximately 12% of diabetics develop this condition at the onset of their diabetes, and nearly 60% after 25 years of the disease. Distal symmetrical polyneuropathy is characterized by varying syndromes of pain and sensory loss. Diabetic neuropathy pain is commonly described as ranging from a deep aching such as a toothache to superficial and burning. The pain may be stabbing or tearing, and it worsens at night (Herman & Greene, 1992). Pain in diabetic neuropathy usually occurs 5-10 years after the start of diabetes (Harvey, 1996), and may last for more than one
year in 45% of the patients. The pain is an extremely unpleasant complication that often occurs without evidence of other neurologic impairment. To date, the treatment has been frustrating and often unsuccessful (Lorber, 1994). Capsaicin is now available as a treatment option without a prescription. In recommending it to their patients, primary care providers need to know about capsaicin's safety, efficacy and available therapeutic dosages. Currently, it is unknown by providers which strength has the greatest proved safety and therapeutic value. Research findings will assist the provider to adequately treat patients who are suffering from diabetic pain by recommending the appropriate dose, in order to improve the quality of the patient's life.

Clinical Literature Review

This section explains the pathophysiology of diabetic neuropathy and its associated pain. The mechanisms of capsaicin's action is also explained.

Diabetic neuropathy.

The 1988 consensus conference on diabetic neuropathy developed the following conceptual definition of diabetic peripheral neuropathy: "Diabetic neuropathy is a descriptive term meaning a demonstrable disorder, either clinically evident or subclinical, that occurs in the setting of diabetes mellitus without other causes for peripheral neuropathy. The neuropathic disorder includes manifestations in the somatic and/or autonomic parts of the peripheral nervous system" (Asbury & Porte, 1990). The three major types of diabetic neuropathy are: distal symmetrical polyneuropathy, focal neuropathy, and autonomic neuropathy (Lorber, 1994). For the purposes of this study, only distal symmetrical polyneuropathy is discussed.
The cause of distal symmetrical polyneuropathy remains unclear, but it is currently believed to result from abnormal neural metabolism and/or generalized neural ischemia (Lorber, 1994). Current and accruing evidence implies that the axon is the initial site of damage. Patients with diabetic neuropathy have thickened neural capillaries and widened capillary basement membranes. These changes suggest that alterations in blood-nerve barrier allows the access of toxic substances to the nerve, producing the neuropathy. Nerve conduction studies support this hypothesis of nerve damage (Walker, 1991).

Other factors contributing to the manifestation of diabetic polyneuropathy include hyperglycemia and hypoxia. Hyperglycemia causes a thickening of the capillary basement membrane which eventually results in decreased tissue perfusion and hypoxia to the nerves (Walker, 1991). The contribution of hyperglycemia to the pathogenesis of polyneuropathy is currently explained by the following three hypotheses:

1. The sorbitol and myo-inositol abnormality hypothesis suggests that hyperglycemia causes slowing of nerve conduction (Walker, 1991). Glucose is normally converted to sorbitol, a sugar alcohol, by aldose reductase. Hyperglycemia leads to high levels of sorbitol, which accumulate in nerves, causing functional damage to neural membranes (Walker, 1991).

2. Current research indicates that nerve fibers in animals and humans with diabetes have low amounts of myo-inositol. Myo-inositol is a substance which determines how nerve cells use energy to maintain an adequate balance of salts. This
balance is what enables the cell to conduct impulses (National Institutes of Health, 1994).

3. Hyperglycemia speeds up the normal process of protein aging, weakening the collagen support in nerve tissues. There is a strong possibility that the above three processes may be linked, and investigations of their relationships are in process (NIH, 1994).

Although the exact physiologic reason for the pain of diabetic neuropathy is unclear, it is thought that the breakdown of myelinated nerve fibers and axonal atrophy may play a role in the production of pain (Kahn & Weir, 1994). Pain is also thought to result from hyperactivity of damaged axons (Ross, Taylor, & Aaron, 1993).

**Clinical presentation of painful diabetic neuropathy.**

The presentation and progression of pain in individual patients is unforeseeable. Some pain syndromes are self-limiting, needing only rest as a therapeutic intervention. Other pain characteristics may be so severe that they disable the person from performing their activities-of-daily living. The pain, characterized by sensory malfunction, is worst in the lower extremities. Pain is accompanied by sensory loss; there may be tingling and hypersensitivity to normally painless stimuli (dyasthesia). The pain is worse at night, often hindering sleep. The description of pain ranges from deep rooted and aching, to superficial and burning. Severe burning pain is often manifested by weight loss, depression, impotence and anorexia (Ross, Taylor, & Aaron, 1993).

The diagnosis of distal symmetric polyneuropathy is usually based on history and physical examination, but should be carefully differentiated from pain of non-
diabetic origins. To confirm the diagnosis of painful neuropathy, simple tests for peripheral nervous system function are used. Some of these tests are distal temperature sensation, distal pinprick or pressure sensation, and distal vibratory sensation (Lorber, 1994).

**Current treatment available for painful diabetic neuropathy.**

The management of diabetic neuropathy begins with stringent control of blood glucose. Unfortunately, while tight glycemic control may prevent the neuropathy from worsening, it has not consistently improved existing pain. Initial therapy might be aimed at simple measures such as warm baths, pressure stockings, analgesics and anti-inflammatory drugs (Ross, Taylor, & Aaron, 1993). Additional treatments have included vitamins, selective serotonin re-uptake inhibitors, and transcutaneous electric nerve stimulation units. In addition to the use of capsaicin, other oral pharmacologic methods are commonly used in attempts to control pain, but are usually not consistently effective (Ross, Taylor, & Aaron, 1993). For example, phenytoin or carbamazepine used in anticonvulsant doses for shooting or stabbing pains make diabetic control more difficult. Amitriptyline, prescribed for deep aching pains, needs to be monitored closely for the possibility of autonomic nervous system side effects (Walker, 1991).

As described in the literature, treatment for painful neuropathy is often ineffective or related to adverse effects. Because of ongoing tests confirming the safe and effective use of capsaicin, primary care providers can more confidently recommend its use to improve their patient's quality of life.
Review of relevant clinical research

In this review, recent published research about capsaicin's effect on painful diabetic neuropathy was examined to recognize the strengths and weaknesses in the research, and to evaluate research needs.

The Gen Derm© Corporation (Lincolnshire, IL) announced to readers of "Clinical Diabetes, 1994", the "proven efficacy of capsaicin (Zostrix™) 0.075% topical analgesic cream in relieving the burning, throbbing, lancinating pain of diabetic neuropathy." The two page advertisement is based on the results of three studies demonstrating the efficacy of capsaicin to reduce the pain of neuropathy.

Capsaicin is derived from red peppers, and appears to deplete Type C nerve fibers of substance P and other neurotransmitters which transmit pain signals in diabetic neuropathy. By its mechanism of action, capsaicin greatly diminishes responses to noxious stimuli. Initially pain may increase during the first 2-3 weeks of application, due to released substance P from the nerve terminals, but continued use depletes the nerve terminals, leading to loss of the pain sensation (Clarke, 1993).

The Capsaicin study group (1991) studied the effect of treatment with capsaicin on daily activities of patients with painful peripheral neuropathy. Results of the double-blind, placebo controlled, eight week trial in 277 patients with painful diabetic neuropathy demonstrated the effectiveness of 0.075% topical capsaicin cream. Pain relief was accomplished in 75% of patients receiving capsaicin with a subsequent improvement in activities-of-daily living, enhancing their quality of life. Of the placebo group, 45% reported pain relief. Of the 277 initial subjects, 219 completed the study.
Efficacy of treatment was based on the 252 subjects who used the treatment for at least the first two weeks. The cause of early withdrawal from the study was attributed mainly to the burning sensation upon application of the cream.

Scheffler, Sheitel and Lipton (1991) also support capsaicin as effective in managing painful diabetic neuropathy. Their eight week, double blind, vehicle controlled study reports that 90% of the patients receiving capsaicin showed improvement in pain status. Patients were randomly assigned to either treatment with capsaicin 0.075% or to a placebo cream. Several variables were controlled or blocked by imposing restrictions and requirements to the study. Pain was initially assessed by both the patient and the investigator, and improvement in pain status was assessed with a pain evaluation scale used by the researchers. Five of the initial 54 patients dropped the study due to poor compliance and adverse burning experienced by capsaicin. The significant difference in pain control between the two groups was pronounced at the eighth week, with 90% response in the treatment group and 50% in the control group. Clinical improvement in daily activities was also measured, with significant positive results in favor of capsaicin.

The desensitization to painful stimuli by capsaicin raised concerns for its safety when used in disorders associated with loss of sensation. A study by Tandan, Lewis, Budger and Tries (1992) examined the effects of 0.075% capsaicin cream on sensory function in painful diabetic neuropathy. Results of the eight week study in 22 patients demonstrated no significant change in warmth and vibration thresholds, although cold thresholds were reduced by both the experimental and placebo treatments. The results demonstrated no adverse effects of capsaicin in sensory function, even with preexisting
neuropathic sensory dysfunction. A limitation to the study was the small sample size, limiting the ability to generalize these findings.

The conclusions drawn from research studies that capsaicin 0.075% cream is safe and effective led to a number of other clinical trials. The results from these investigations supported that capsaicin is not only effective in painful diabetic neuropathy, but also in post-herpetic neuralgia, arthritis, and trigeminal neuralgia (Tandan, et al., 1992). Capsaicin has recently also been found useful in the treatment of some of the symptoms of psoriasis (Zhang & Wan Po, 1994).

The literature review makes it clear that several physiologic processes occurring with diabetes may lead to neuropathy and it's common symptomatic manifestation (pain) which has been difficult to treat. The literature also documents the rationale for the use of capsaicin to effectively treat the pain of neuropathy. As primary care providers strive to effectively treat their patients with capsaicin, they need the fundamental knowledge of the medication's potency-related effectiveness.

**Research Hypothesis**

1. Participants in the group receiving capsaicin 0.075% will show statistically significant greater pain relief as measured by the Visual Analog Scale, in comparison to the participants in the group receiving capsaicin 0.025%.

**Definition of Terms**

For the purpose of this study, the following conceptual definitions were used:

1. **Pain**- Pain is an unpleasant sensory and emotional experience, and is whatever the experiencing person says it is (McCaffery & Beebe, 1989). Pain can be measured

2. **Diabetic Neuropathy**- Peripheral nerve dysfunction occurring in diabetics, and characterized by a group of clinical syndromes that include pain (Herman & Greene, 1992).

3. **Visual Pain Analog Scale (VAS)**- A tool used to measure perceived pain intensity. It consists of a 10 cm long vertical line with anchor words at either end: no pain, or worse pain felt. Patients mark at any point on the line to indicate the intensity of their pain (McGuire, 1984).

Refer to Appendix C for VAS.

**Significance to Nursing**

Many diabetic patients with symptomatic diabetic neuropathy seek treatment for their pain in primary care settings. When making treatment decisions, primary care providers need to consider the established effectiveness of the medication in relation to its potency in order to implement care with more confidence. Because capsaicin is available over the counter in two concentrations, nurses and diabetic educators will also benefit from knowledge about the particular effectiveness of each strength. A patient's decision on which strength to purchase may be based largely on economic impact, and primary care providers may be able to influence their decision in a way that results in optimal pain control.
Chapter II

Methods of Study

The purpose of this study was to determine the difference in efficacy between topical application of capsaicin 0.025% and 0.075% cream in relieving pain associated with diabetic neuropathy.

Type of Design

A quasi-experimental single blind randomized time series research design was used for this study. Burns and Grove (1994) explain that quasi-experimental designs provide substitute means for examining causality when one of the following criteria is missing: random sampling, control groups, and manipulation of the treatment. The design was appropriate for this study because the independent variables (capsaicin's two strengths) were manipulated to cause an effect on the dependent variable (pain), but a control group was lacking. One group received 0.025% capsaicin (Zostrix), and another group received 0.075% capsaicin (Zostrix HP). Pain related data (rated visual analog scale) were collected initially and throughout the study.

Setting for Study

A physician's diabetic and endocrinology specialty practice in the Northwest provided the setting for this study. In this site, 220 clients are treated per month. Approximately 31% of the diabetic clients have painful diabetic neuropathy, and 60% have asymptomatic neuropathy. The participants in the study were seen either in the physician's office or at their homes.
Population and Sample

The subjects for this study were all diabetic persons with pain due to diabetic neuropathy. The target population were patients with painful diabetic neuropathy in the Inland Empire. The sample for this study was obtained from a review of over 500 patient charts located at a diabetologist's office. Letters of invitation to participate in the study were sent out to 156 diabetics with painful diabetic neuropathy. Five of the letters were returned to sender. Of the remaining 151 letters, 45 inquired further about the study. Twenty-nine of the 45 met the established criteria and agreed to participate by completing a questionnaire that included demographic, medical and pain information. The remainder of the participants that had originally expressed interest were not symptomatic enough for the study, or were discouraged by the inconvenience of the application of capsaicin. One potential subject was already using capsaicin.

Subjects who participated in this research met the following criteria:

1. Participants were men or non-pregnant, non-lactating women over 18 yrs of age.
2. Participants had diabetes mellitus with an established diagnoses of neuropathy. In this study, neuropathy was confirmed by the researcher's physical examination findings. This entailed non-invasive sensation and vibratory testing of the area affected by neuropathy.
3. Participants had moderate to severe pain, as rated on a standard pain scale, and were able to utilize and understand a standard pain scale.
4. Participants who manifested skin conditions in the affected area were excluded.
5. Participants were willing to discontinue all other topical agents during the study.
6. Participants agreed to comply with the experimental treatment.

7. Participants were physically and mentally able to read English, respond to questions, and give informed consent to participate.

Instrumentation

The instruments identified for use with this investigation included the pain scale instrument, and the data collection tool. The pain scale instrument used was the visual analog scale (VAS), a vertical line, deemed to be a sensitive and reliable technique to measure pain intensity. (McCaffery & Beebe, 1989). The VAS was developed almost 60 years ago (McGuire, 1984) and is routinely used to measure the intensity of subjective experiences such as pain, fatigue and dyspnea (Gift, 1989). Validity for the VAS has been established by comparing responses on the visual analog scale to other methods of measurement such as the McGill Pain Questionnaire (Gift, 1989). Price, McGrath, Rafii, and Buckingham (1983) established high reliability for the VAS (r=0.97).

A structured interview was used to collect all pertinent data for this study. This method was likely to result in a higher response rate than the use of a mail questionnaire (Appendix A)(Burns & Grove, 1994). The initial researcher-conducted interview was used to collect demographic data, such as age, gender, and medical conditions. The VAS was included in every interview. Follow-up contacts consisted of mail-back questionnaires (Appendix B) which addressed any change in the subject’s medical condition, and their pain level per the VAS (Appendix C).

Data Collection Procedure

Prior to the initiation of the formal research study, the following conditions were
evaluated: the timing of the initial and follow-up interviews, the researcher's technique in collecting the data, and the comfort of the physical environment.

The research protocol began by arranging the date, time and location for the interview of consenting participants. A baseline pain assessment and determination of peripheral diabetic neuropathy was obtained by the researcher, as well as any demographic data from the interview guide. The determination of peripheral diabetic neuropathy consisted of sensation and vibratory testing of the extremities involved. Conditions outlined in the consent form were followed; that is, the need for participants to stop any current use of topical agents, and directions on how to use the cream that they received. Participants were randomly assigned to each study group by the researcher drawing numbers randomly from a hat. Follow-up interviews were done the first week after initiation of the study, and every two weeks thereafter to evaluate the response to capsaicin cream. The follow-up interviews included the VAS to determine the intensity of the pain. The study concluded after eight weeks.

Data Analysis Plan

This research study examined the difference in effectiveness of capsaicin 0.025% and 0.075% cream on the pain from diabetic neuropathy. The demographic information collected in the initial interview provided data on the attribute characteristics of the sample. Narrative and descriptive statistics were used to analyze these nominal data, by the use of frequencies and percents.

T-tests were used to compare ages, duration of DM, duration of neuropathy, duration of pain between the two groups, and the mean intensity of pain at the initial
baseline interview. T-tests were also used to compare rates of compliance with
treatment between the groups. Fisher exact two-tail tests and Pearson chi-square were
used to compare the groups with respect to sex, type of diabetes, and other
demographic characteristics. Scores on the VAS were calculated by a metal millimeter
ruler to provide interval level data, which was analyzed by repeated measures of
Analysis of Variance (ANOVA), to determine the difference in pain relief between the
two groups.

**Human Subjects Protection**

The proposal to conduct this study was submitted for approval to the:

1. Clinical Project Committee, Intercollegiate Center for Nursing Education, Spokane,
   Washington.
3. The participant's physician.

The institutional Review Board Approval Form is displayed in Appendix E.

Several methods were used to ensure the protection of human subjects in this
study. Subjects were informed of the purpose and duration of the study. Risks and
benefits were explained in the consent form. The risks and inconveniences involved
with the participation in this study were:

1. A possible initial (2-3 weeks) warm stinging or burning sensation on the application of
capsaicin cream. This discomfort was to become less severe, and disappear the
   longer the cream was used.
2. Possibility of adverse effects to capsaicin besides the burning sensation, although
none are known presently.

3. The cost of capsaicin after the conclusion of the study will be high, but adequate pain relief might be established and outweigh the cost.

4. The inconvenience of having to apply the cream four times daily.

Confidentiality was ensured throughout the study by the use of identification numbers on data collection instruments. Participant's names were in the sole possession of the researcher and their physician, and kept locked in a secure safe. Subject's names were not mentioned in data analysis, and will remain anonymous throughout the discussion of results in publication.

Participants were provided with information regarding the researcher's phone number to contact for questions, or in the event of any problem associated with the study. Subject participation in this study was voluntary and subjects were free to withdraw at any time.

The benefit to the participant was the potential relief of neuropathy pain. The information gathered from the study was used to establish, and hopefully generalize, the effectiveness of the two strengths of capsaicin.

Written consent was obtained after full explanation of the study and after questions were answered. No one was pressured to participate. The informed consent appears in Appendix D.

Limitations of the study

Limitations of this study occurred through both internal and external threats to validity. The main limitation to this study was the limited sample size (n=15), impeding
generalization of the findings. A larger sample size would provide a more representative sample of the population. Limitations also included factors that may have potentially affected the outcome of the study. For example, extraneous variables, such as other methods for coping with pain and the potential for other physiologic conditions causing the pain were difficult to control. Also, although compliance was measured at regular intervals, actual poor compliance with treatment regimen may have occurred in either group. There is also the possibility of spontaneous pain relief in some patients.
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CHAPTER III

Manuscript prepared for submission to the

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ABSTRACT

The purpose of this study was to determine the difference between two different strengths of topical capsaicin cream on relieving the pain associated with diabetic neuropathy. This quasi-experimental single blind and randomized drug study evaluated 15 diabetics with painful peripheral neuropathy during treatment with 0.025% or 0.075% capsaicin.

Neuropathy pain was assessed at baseline and at weeks 1, 3, 5, 7 and 8 with a vertical 100mm visual analog scale in which participants rated their most intense pain. Repeated measures analysis of variance showed no significant difference between the two available over-the-counter strengths of capsaicin (p=0.496) in relieving the pain associated with diabetic neuropathy. However, analysis of variance showed significant pain relief over time for both groups (p=0.000). Compliance with the study's treatment was evaluated by t-tests (p=0.612), and Pearson chi-square (p=0.557) methods, which showed no significant difference between the two groups. The study concluded that capsaicin's 0.025% regular strength cream is as effective as the 0.075% extra-strength in relieving the pain associated with diabetic neuropathy.
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Introduction

Diabetes Mellitus, a complex syndrome of metabolic dysregulation, affects 14 million people in the United States (Harvey, 1996). A hallmark of diabetes is its propensity to cause numerous longterm complications associated with serious morbidity (Nathan, 1993). Peripheral neuropathy, a nerve dysfunction caused by hyperglycemia, is the most frequent and debilitating of these complications. The prevalence of peripheral neuropathy is 8% in recently diagnosed diabetics, and rises to 50% after 25 years of the disease (Wright, 1994). The clinical presentation of peripheral neuropathy reflects the underlying nerve damage, as individuals with the condition report burning, tingling, numbness and other symptoms. Among these symptoms, pain is the most difficult and distressing to manage (Harvey, 1996). The pain is often severe enough to interfere with sleep, work, and activities-of-daily living, thus decreasing the quality of the patient's life (Pfeiffer, et al., 1993).

Although rigorous diabetic control may prevent the progression of neuropathy, existing pain may ensue, making its treatment an eminent challenge to care providers (Ross, Taylor, & Vinik, 1993). Whereas the use of simple analgesics and other oral pharmacologic agents have resulted in limited success due to unfavorable side effects, recent use of topical capsaicin cream is demonstrating effectiveness without systemic side effects (Cotton, 1990).
Capsaicin, the active ingredient derived from hot red peppers, is available as an over-the-counter topical medication in regular (0.025%) and extra strength (0.075%) concentrations (Basha, 1991). Although Vinik (1994) points out that the more expensive 0.075% concentration offers no significant advantage over the 0.025% concentration, there is no documented research directly comparing the two strengths. Watson (1994) states that "Topical capsaicin appears safe but is quite expensive. The optimal concentration remains unknown".

This study compared the effectiveness of the two strengths of capsaicin cream on diabetic neuropathy pain. Another purpose of this study was to determine if the difference in effectiveness is worth the additional cost of extra-strength capsaicin.

Review of the Literature

Diabetic Neuropathy

One of the most frequent and chronic complications of diabetes is distal symmetrical polyneuropathy, also known as peripheral neuropathy (Lorber, 1994). Although the basis of distal symmetrical polyneuropathy remains unclear, theories include abnormal neural metabolism and/or generalized neural ischemia (Lorber, 1994). Hyperglycemia leads to decreased tissue perfusion and hypoxia by causing a thickening of neural capillary basement membranes (Walker, 1991). This alters the blood-nerve barrier, allowing access of toxic substances to the nerve. The toxic substances are thought to damage the axon, producing the neuropathy. Nerve conduction studies support this hypothesis of nerve damage (Brooks & Francisco, 1992).
There is less agreement on how hyperglycemia contributes to the pathogenesis of polyneuropathy.

1. The sorbitol and myo-inositol abnormality hypothesis suggests that hyperglycemia causes slowing of nerve conduction, as a result of excess sorbitol accumulation in nerve fibers; the high levels of sorbitol damage neural membranes. Glucose is normally converted to sorbitol, a sugar alcohol, by aldose reductase (Walker, 1991).

2. Current research indicates that nerve fibers in animals and humans with diabetes have low amounts of myo-inositol. Myo-inositol plays a role in how nerve cells use energy to maintain an adequate balance of salts. This balance is what enables the cell to conduct impulses (National Institutes of Health, 1994).

3. Hyperglycemia speeds up the normal process of protein aging, weakening the collagen support in nerve tissues. The above three processes may be linked, and investigations of their relationships are in process (NIH, 1994).

Although the exact physiologic reason for the pain of diabetic peripheral neuropathy is unclear, it is thought that the breakdown of myelinated nerve fibers and axonal atrophy may play a role in the production of pain (Kahn & Weir, 1994). Pain is also thought to result from hyperactivity of damaged axons (Ross, Taylor, & Vinik, 1993).

Clinical presentation of painful diabetic neuropathy

The manifestation and progression of pain in individual patients is unforeseeable. Self-limiting pain syndromes may respond only to rest as a therapeutic
intervention, but other pain characteristics are so severe that they disable the person from performing activities-of-daily living. The pain of peripheral neuropathy, accompanied by a distal sensory loss in a stocking-glove pattern is worse in the lower extremities. There may be tingling and hypersensitivity to normally painless stimuli (dyasthesia), particularly at night, which may become physically and emotionally disabling. Description of pain ranges from deep rooted and aching, to superficial and burning. Severe burning pain is frequently associated with weight loss, anorexia, depression, and impotence (Ross, Taylor, & Vinik, 1993).

Distal symmetric polyneuropathy is usually diagnosed based on history and physical examination, but should be carefully differentiated from pain of non-diabetic origins. Tests to confirm the diagnosis of painful neuropathy include distal temperature sensation, distal pinprick or pressure sensation, and distal vibratory sensation (Lorber, 1994). These sensations may be spared early in the disease, but as the neuropathy progresses, there is loss of sensation and deep tendon reflexes (Harvey, 1996).

Treatment available for painful diabetic neuropathy

The primary management of diabetic neuropathy is stringent control of blood glucose. This can prevent the neuropathy from worsening, but unfortunately it has not consistently improved existing pain. Initial therapy includes simple measures such as warm baths, pressure stockings, transcutaneous electric nerve stimulation units, analgesics, and anti-inflammatory drugs (Ross, Taylor, & Vinik, 1993). Other oral pharmacologic methods are commonly used in attempts to control pain, but are usually not consistently effective, and are associated with systemic adverse effects (Ross,
Taylor, & Vinik, 1993). For example, phenytoin or carbamazepine used in anticonvulsant doses for shooting or stabbing pains make diabetic control more difficult. Amitriptyline, prescribed for deep aching pains, needs to be monitored closely for the possibility of autonomic nervous system side effects (Walker, 1991).

Ongoing tests are confirming the safe and effective use of capsaicin, the ingredient derived from hot peppers. Capsaicin is available as a topical cream that depletes type C nerve fibers of substance P and other neurotransmitters which transmit pain signals in diabetic neuropathy. By its mechanism of action, capsaicin greatly diminishes responses to noxious stimuli. Initially pain may increase during the first 2-3 weeks of application, due to released substance P from the nerve terminals, but continued use depletes the nerve terminals, leading to loss of the pain sensation (Clarke, 1993).

The Capsaicin Study Group (1991) studied the effect of treatment with capsaicin on daily activities of patients with painful peripheral neuropathy. Results of the double-blind, placebo controlled, eight week trial in 277 patients demonstrated the effectiveness of 0.075% topical capsaicin cream. Pain relief was accomplished in 75% of patients receiving capsaicin with a subsequent improvement in activities-of-daily living, enhancing their quality of life. Of the placebo group, 45% reported pain relief. Of the 277 initial subjects, 219 completed the study. Efficacy of treatment was based on the 252 subjects who used the treatment for at least the first two weeks. The main reason for early withdrawal from the study was the burning sensation upon application of the cream.
Scheffler, Sheitel and Lipton (1991) also support capsaicin as effective in managing painful diabetic neuropathy. Their eight week, double blind, vehicle-controlled study reports that 90% of the patients receiving capsaicin showed improvement in pain status. Patients were randomly assigned to either treatment with capsaicin or to a placebo cream. Several extraneous variables were controlled or blocked by imposing restrictions and requirements to the study. Pain was initially assessed by both the patient and the investigator, and improvement in pain status was assessed with a pain evaluation scale used by the researchers. Five of the initial 54 patients dropped the study due to poor compliance and adverse burning experienced by the use of capsaicin. The significant difference in pain control between the two groups was pronounced at the eighth week, with 90% response in the treatment group and 50% in the control group. Clinical improvement in daily activities was also significant, with positive results in favor of capsaicin.

Because capsaicin desensitizes painful stimuli, concerns were raised for its safety when used in disorders associated with loss of sensation. A study by Tandan, Lewis, Budger and Fries (1992) examined the effects of 0.075% capsaicin cream on sensory function in painful diabetic neuropathy. Results of the eight week study in 22 patients demonstrated no significant change in warmth and vibration thresholds, although cold thresholds were reduced by both the experimental and placebo treatments. The results demonstrated no adverse effects of capsaicin in sensory function, even with preexisting neuropathic sensory dysfunction. A limitation to the study was the small sample size, limiting the ability to generalize these findings.
A number of other clinical trials support that capsaicin is not only effective in painful diabetic neuropathy, but also in post-herpetic neuralgia, arthritis, and trigeminal neuralgia (Tandan, et al., 1992). Capsaicin has recently also been found useful in the treatment of some of the symptoms of psoriasis (Zhang & Wan Po, 1994).

In summary, previous investigations have demonstrated that diabetic neuropathy is a common manifestation which has been difficult to treat. The research literature also proposes rationale for the use of capsaicin as an effective treatment for the pain of neuropathy, as it is not associated with any systemic adverse effects. Capsaicin cream is currently available in two strengths, but there is no documented research directly comparing those two strengths. Primary care providers striving to effectively treat their patients with capsaicin need the fundamental knowledge of the medication’s potency-related effectiveness. This study aimed to provide this information.

Research Design and Methods

A quasi-experimental, single blind, time-series research design was used to determine the difference in efficacy between topical application of capsaicin 0.025% and 0.075% cream in relieving pain associated with diabetic neuropathy. One study group received 0.025% capsaicin (Zostrix), and another received 0.075% capsaicin (Zostrix HP). Pain related data were collected initially and throughout the study by the use of a rated visual analog scale. The hypothesis for the study was as follows:

1. Participants in the group receiving capsaicin 0.075% will show statistically significant greater pain relief as measured by the Visual Analog Scale, in comparison to the participants in the group receiving capsaicin 0.025%.
Setting/Sample

The setting for this study was provided by a physician's endocrinology practice in the Northwest United States. The participants in the study were seen either in the physician's office or at their homes. The sample for this study was obtained from a review of over 400 patient charts located at the endocrinologist's office. Letters of invitation to participate in the study were sent to 156 diabetics with painful diabetic neuropathy. Forty-five subjects inquired further about the study, and twenty-nine who met the established criteria agreed to participate. The remainder were not symptomatic enough to participate in the study, or expressed that the frequent application of capsaicin would be an inconvenience. One potential subject was already using capsaicin and could not be included in the study.

Of the original 29 participants, fifteen have completed eight weeks of study. Three subjects have not completed the study, and eleven withdrew prematurely. Efficacy analysis for this study was based on 15 participants who completed the eight weeks. Seven were assigned to the 0.025% group, and eight to the 0.075% group. Of the eleven who dropped out of the study, six belonged to the 0.025% group and 5 to the 0.075%. Five participants terminated the study prior to the second or third week because of "intolerable" burning on application of capsaicin, two of which also reported intense redness. One subject dropped out of the study because of severe coughing and sneezing which persisted in-between applications. Four reported never initiating the cream due to other health related problems.

Participants in this research met the following criteria:
1. Participants were men or non-pregnant, non-lactating women over 18 yrs of age, who had diabetes mellitus with an established diagnoses of peripheral neuropathy. Non-invasive sensation and vibratory testing of the affected neuropathy area was performed by the researcher to confirm the neuropathy.

2. Participants had moderate to severe pain, as rated on a standard pain scale, and were able to utilize and understand the standard pain scale (see Appendix C).

3. Participants agreed to comply with the treatment protocol.

4. Participants who manifested skin conditions in the affected area were excluded.

5. Participants were physically and mentally able to read English, respond to questions, and give informed consent to participate.

Procedure

Consenting participants were randomly assigned into one of the two study groups after initial history and evaluation were obtained. Participants received a copy of their signed consent form with instructions on how to contact the researcher in the event of side effects and any concerns. Participants were provided with the blinded capsaicin cream. All participants were informed of the possible burning discomfort on application of capsaicin for the initial 2-3 weeks, and the rationale for continued and regular use of the cream (four times daily) for it to be effective. Participants were told that use of simple analgesics was acceptable during the study for any burning discomfort of the cream. Verbal and written instructions were provided on how to apply the cream and avoid contact with their eyes and mucous membranes (Appendix D).
Pain was assessed at baseline and at weeks 1, 3, 5, 7 and 8 with a visual analog scale for pain intensity. Participants rated their pain in a vertical 100mm scale according to when their pain was most intense. At week eight, participants were seen again, and sensation and vibratory testing were repeated.

**Data Analysis**

Narrative and descriptive statistics were used to analyze the attribute characteristics of the sample. T-tests were used to compare ages and duration of DM, duration of neuropathy, and duration of pain between the two groups. Fisher Exact Two-tail tests or Pearson Chi-square were used to compare the groups with respect to sex, type of diabetes, and other demographic characteristics. Scores on the VAS were calculated by a metal millimeter ruler to provide interval level data, which were then analyzed by an Analysis of Variance (ANOVA) to determine the difference in pain relief between the groups. Since compliance would greatly influence pain response, a t-test compared the compliance rates between the two groups, prior to use of the ANOVA analysis.

**Results**

A description of sample characteristics is presented in Table 1. No statistically significant differences were found between the two groups with respect to sex, age, type of diabetes, duration of diabetes, and duration of neuropathy. Only the presence of other medical conditions was somewhat significant between the groups. However, none of the participants that completed the eight weeks of the study reported any significant problems with their medical condition that affected their use of the cream.
Participants' pain characteristics were assessed prior to initiation of the study, and Chi-square testing showed no statistically significant difference between the two study groups. Refer to table 2 for reported pain attributes.

Follow-up questionnaires included assessment of compliance and side effects with medication use. Since compliance with medication use was thought to greatly influence the results of the study, tests were performed to demonstrate equivalence between the groups. There was no statistically significant difference between the groups with respect to compliance (T-test \( P=0.612 \), Pearson chi-square \( P=0.557 \)). Figure 1 shows compliance means between the groups at each follow-up during the study.

The most commonly occurring side effect for both groups was burning. One participant in the 0.025% group and two spouses applying the cream to participants in
the 0.075% group reported self-limiting cough and sneezing. Some participants reported mild and self-limiting erythema. There was no significant difference between the groups (Pearson chi-square P=0.720) with regards to side effects from capsaicin. Table 3 lists a brief description of reported side effects.

Table 3 about here

Dramatic and statistically significant pain reduction was noted over time at each follow-up period for both groups (ANOVA p=0.001). However, one participant in each of the groups reported no improvement in pain and quit the study at the end of the eight weeks. The participant in the extra-strength group did show pain relief for his original burning pain, but not for his electric shock-type pain (the most bothersome for him). Figure 2 shows linear progression of the means in pain scores for each group.

Hypothesis testing

The hypothesis for the study stated that there will be statistically significant greater pain relief in participants of the group receiving capsaicin 0.075% as per VAS, in comparison to the participants in the group receiving capsaicin 0.025%. Analysis of Variance by repeated measures failed to reject the null hypothesis, as findings demonstrated no significant statistical difference across time between the two groups in respect to pain relief. Table 4 summarizes the ANOVA findings in relation to pain relief.
At the end of the eight weeks of study, vibration retesting per biothesiometer, showed improvement in more than two of four readings for four participants in the regular strength group and for three in the extra-strength group. Two of four readings worsened in two participants from the 0.075% group. The rest of the participants did not show any changes with regards to sensation.

Discussion and Implications

Results from this study revealed no significant difference in pain relief between the two strengths of capsaicin cream. Nevertheless, capsaicin did offer significant pain relief to both groups (0.025% and 0.075%) of diabetics with painful peripheral neuropathy (based on the group means). Results were based on analysis of a standard pain visual analog scale rated by the participants at periodic intervals. Of 15 randomly assigned participants who completed eight weeks of the study, seven received 0.025% capsaicin and eight received 0.075% capsaicin. The two study groups demonstrated no significant difference with respect to demographic data, pain characteristics, compliance with the treatment, and side effects. Note that duration of diabetes and neuropathy portray the known duration but may not truly reflect the actual duration.

Several threats to internal validity existed. The study did not strictly restrict participants from using other methods of coping with pain, and a large majority did use
simple analgesics; some were using central nervous system acting medications such as antidepressants. There is the possibility that repeated use of the VAS influenced subjects' ratings of their pain. Since the VAS was used in repeated measures, the possibility exists that participants may have answered in a pre-conditioned or haphazard manner. The rationale for the use of the 100mm metal ruler was to reduce the possibility of error. Some of the subjects mentioned a preference for a 0-10 scale, which may have influenced findings.

Although the intent of the study was only to compare the effectiveness between the two strengths of capsaicin, other interesting findings occurred. A particular observation was the drop out rate prior to the first two to three weeks (time it usually takes for the treatment to start working). The burning caused by the application of the cream was one of the major causes for this drop out rate. Three of the participants in the 0.025% group and two of the 0.075% group reported an improvement in the "numb" feeling that was so bothersome initially. No relationship was made by the researcher with regards to the sensation and vibration studies except for the documentation of neuropathy.

Limitations

The main limitation to this study was the small sample size (n=15), impeding generalization of the findings. Limitations in the design also included a non-random selected sample. Another limitation was that extraneous variables, such as other methods for coping with pain and the potential for other physiologic conditions causing the pain, were difficult to control. An additional limitation included the lack of double
Although compliance was checked at regular intervals, actual poor compliance with treatment regimen may have occurred in either group.

Conclusions

Although capsaicin was effective in relieving the pain associated with diabetic neuropathy, there was not any significant difference between the 0.025% and 0.075% strengths. The results imply that the regular strength capsaicin can be just as effective as the extra-strength. Care providers can confidently recommend the lesser strength capsaicin to diabetics with neuropathy pain, especially if cost of medication is an issue. Since the side effects of the two strengths appeared equally distributed between the groups, persons who feel they are not experiencing pain relief with the regular strength might opt to try the extra-strength. Further research should be done with larger samples to investigate the difference in effectiveness between the cream's strengths with a stricter control of extraneous variables and a close follow-up of side effects.
References


### Table 1 - Between Group Participant's Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Capsaicin 0.025% Group n=7</th>
<th>Capsaicin 0.075% Group n=8</th>
<th>Statistic Analysis</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>4(57%)/3(43%)</td>
<td>4(50%)/4(50%)</td>
<td>Chi²:Fisher Exact test</td>
<td>1.0</td>
</tr>
<tr>
<td>Age</td>
<td>45-82 Mean=62±14</td>
<td>42-82 Mean=69±13</td>
<td>T-test</td>
<td>0.302</td>
</tr>
<tr>
<td>Type of DM* (I/II)</td>
<td>5(71%)/2(29%)</td>
<td>7(87%)/1(13%)</td>
<td>Chi²:Fisher Exact test</td>
<td>0.569</td>
</tr>
<tr>
<td>Years w/DM</td>
<td>3-29yrs Mean=13.4±9</td>
<td>3-15yrs Mean=9.8±4</td>
<td>T-test</td>
<td>0.325</td>
</tr>
<tr>
<td>Other medical conditions</td>
<td>4 none</td>
<td>1 heart</td>
<td>Pearson Chi-Square</td>
<td>0.064</td>
</tr>
<tr>
<td></td>
<td>1 heart</td>
<td>2 Htn</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 multiple med conditions**</td>
<td>5 multiple conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration neuropathy</td>
<td>2-15yrs Mean=5.7±5</td>
<td>1-11yrs Mean=3.6±3.6</td>
<td>T-test</td>
<td>0.425</td>
</tr>
</tbody>
</table>

*Type I DM indicates insulin-dependent diabetes mellitus; Type II indicates non-insulin-dependent diabetes mellitus.

**Multiple medical conditions refers to more than two medical conditions in addition to DM.
Table 2 - Between Group Participant's Pain Characteristics

<table>
<thead>
<tr>
<th>Duration of pain</th>
<th>Capsaicin 0.025% Group n=7</th>
<th>Capsaicin 0.075% Group n=8</th>
<th>Statistic Analysis</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-20yrs Mean 5.6±7</td>
<td>0.5-10yrs Mean=2.6±3</td>
<td>T-test</td>
<td>0.297</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Past medication used for pain</th>
<th>Capsaicin 0.025% Group n=7</th>
<th>Capsaicin 0.075% Group n=8</th>
<th>Statistic Analysis</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes/No</td>
<td>4(57%)/3(43%)</td>
<td>3(37%)/5(63%)</td>
<td>Chi²:Fisher Exact test</td>
<td>0.619</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ongoing use of systemic medications for pain control</th>
<th>Capsaicin 0.025% Group n=7</th>
<th>Capsaicin 0.075% Group n=8</th>
<th>Statistic Analysis</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>2 analgesics plus CNS med.</td>
<td>5 analgesics plus CNS med</td>
<td>Pearson Chi-Square</td>
<td>0.328</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location of pain</th>
<th>Capsaicin 0.025% Group n=7</th>
<th>Capsaicin 0.075% Group n=8</th>
<th>Statistic Analysis</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 toes-ankle 2 up to knees</td>
<td>6 toes-ankle 2 up to knee</td>
<td>Chi²:Fisher Exact test</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pattern of pain</th>
<th>Capsaicin 0.025% Group n=7</th>
<th>Capsaicin 0.075% Group n=8</th>
<th>Statistic Analysis</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 worse at noc 1 pain=day&amp;noc</td>
<td>5 worse @ noc 3 day &amp; noc</td>
<td>Chi²:Fisher Exact test</td>
<td>0.569</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sleep interfered by pain</th>
<th>Capsaicin 0.025% Group n=7</th>
<th>Capsaicin 0.075% Group n=8</th>
<th>Statistic Analysis</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 yes 2 no</td>
<td>5 yes 3 no</td>
<td>Chi²:Fisher Exact test</td>
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<table>
<thead>
<tr>
<th>Pain description</th>
<th>Capsaicin 0.025% Group n=7</th>
<th>Capsaicin 0.075% Group n=8</th>
<th>Statistic Analysis</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 type A pain 1 type B pain</td>
<td>5 type A pain 3 type C pain</td>
<td>Pearson Chi-Square</td>
<td>0.133</td>
<td></td>
</tr>
</tbody>
</table>

*CNS med refers to the use of antidepressants or anticonvulsants for attempts at pain relief. Toes-ankle indicates that the pain was limited only to the foot; up to knees indicates that pain was experienced from toes to knees. A pain = burning, tingling, pins & needles type pain; B pain = electric and shock like shooting pains; C pain = combination of A & B type pain.
<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Capsaicin 0.025% (n=7)</th>
<th>Capsaicin 0.075% (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None reported</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Burning for &lt;2 weeks</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Burning for &gt;2 weeks</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Self-limited coughing &amp; sneezing</td>
<td>1</td>
<td>2 (spouses)</td>
</tr>
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</table>
Table 4.-Summary of ANOVA with repeated measures for pain

<table>
<thead>
<tr>
<th>Source of Variance</th>
<th>SS</th>
<th>DF</th>
<th>MS</th>
<th>F</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Between Groups¹</td>
<td>1.110</td>
<td>1</td>
<td>1.110</td>
<td>0.055</td>
<td>0.818</td>
</tr>
<tr>
<td>Error between</td>
<td>260.398</td>
<td>13</td>
<td>20.031</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within Groups²</td>
<td>101.258</td>
<td>5</td>
<td>20.252</td>
<td>6.457</td>
<td>0.000</td>
</tr>
<tr>
<td>Error within</td>
<td>203.854</td>
<td>65</td>
<td>3.136</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within Groups³</td>
<td>13.881</td>
<td>5</td>
<td>2.776</td>
<td>0.885</td>
<td>0.496</td>
</tr>
<tr>
<td>Error within</td>
<td>203.854</td>
<td>65</td>
<td>3.136</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹Evaluates for group differences for all time periods together
²Evaluates for pain change overtime for both groups
³Evaluates for pain change between groups over time (one time period to the next)
Figure 1 - Compliance with use of treatment

Treatment Compliance

Means for each follow up evaluation

<table>
<thead>
<tr>
<th>Time interval</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>2.5</th>
<th>3</th>
<th>3.5</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 week</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>7 week</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>5 week</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>3 week</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 week</td>
<td></td>
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</tbody>
</table>

Capsaicin

- 0.075%
- 0.025%
Figure 2-Pain score means during the study
APPENDICES
APPENDIX A

DATA COLLECTION INSTRUMENT

INITIAL INTERVIEW GUIDE
Data Collection Instrument: Initial Interview guide

PARTICIPANT # _______________   DATE________________

AGE __________

MALE or FEMALE

1. TYPE OF DIABETES:
   Insulin dependent __________
   Non-insulin dependent __________

2. AGE AT ONSET OF DIABETES: __________ NEUROPATHY: __________

3. HOW LONG HAVE YOU HAD NEUROPATHY PAIN? ________________

   WHAT HAVE YOU TRIED TO RELIEVE THE PAIN?
   ____________________________________________________________________
   ____________________________________________________________________
   ____________________________________________________________________

   What medications have you used to treat the pain?
   Do you know the name of them?
   ____________________________________________________________________
   ____________________________________________________________________
   ____________________________________________________________________

   Which of the medicines has helped relieve your pain?
   ____________________________________________________________________

5. WHAT MEDICATIONS DO YOU CURRENTLY TAKE?
   ___________   ___________   ___________
   ___________   ___________   ___________
6. DO YOU HAVE ANY OTHER MEDICAL PROBLEMS?

7. ABOUT YOUR PAIN
   A. WHERE IS YOUR PAIN?

   B. DESCRIBE YOUR PAIN:

   C. HOW LONG DOES IT LAST?

   D. WHAT MAKES YOUR PAIN WORSE?

   E. WHAT TIME OF THE DAY IS YOUR PAIN THE WORST?

   Morning_____ Mid-day_____ Night_____

   MARK THE AREA IN THE SCALE PROVIDED THAT YOU FEEL DESCRIBES
   YOUR PAIN.

   For the Researcher:

   Do Results of Vibration and Sensation Testing confirm Peripheral Neuropathy?
APPENDIX B

DATA COLLECTION TOOL

FOLLOW-UP INTERVIEW GUIDE
Data Collection Tool: Follow up Interview Guide

DATE__________________ Participant's number:__________

1. Follow up # _______ after the initial interview

2. Are there any changes in your medical condition:
   Yes      No
   If yes, explain below
   ____________________________________________________________

3. Are there any changes in your medications?
   Yes      No
   If yes, write below
   ____________________________________________________________

4. How often are you applying the ointment? _________________

5. Are you having any side effects? __________________________

6. MARK THE AREA IN THE SCALE PROVIDED THAT YOU FEEL DESCRIBES YOUR PAIN.
APPENDIX C

VISUAL ANALOG SCALE FOR PAIN
Pain Visual Analog Scale

Worst Pain

No Pain
APPENDIX D

INFORMED CONSENT
A Comparison between the Effects of 0.025% and 0.075% topical Capsaicin in the Relief of Painful Diabetic Neuropathy

Informed Consent

A. Invitation to participate
My name is Mercedes Gonzalez-Aller and I am a graduate student at the Intercollegiate Center for Nursing Education (ICNE). I am inviting you to participate in a study to determine the effectiveness of capsaicin 0.025% cream compared to capsaicin 0.075% cream in relieving the pain of diabetic neuropathy. The Washington State University Institutional Review Board (IRB) has approved the use of human subjects for this study. Your participation in this study is voluntary.

B. Purpose of the Study
Capsaicin cream is being used to treat pain from diabetic neuropathy and other painful conditions. The purpose of this study is to determine the difference in relieving the pain of diabetic neuropathy by comparing two different strengths of capsaicin. You have been asked to participate because you may be able to help determine if there is a difference, and in doing so, you will help other diabetics with pain decide which strength to use.

C. Explanation of the study protocol
If you agree to participate in this study, you will be asked to sign this consent form. On the first day of the study you will be asked to provide information about yourself, such as age, gender, pain level, and medical status. The following conditions will not allow you to participate in the study: Any skin breakdown in the affected area, and if applicable, pregnancy or lactation. Your participation in this study will require you to apply a cream to the painful area four times a day. The cream will be provided to you without charge. You may receive either the 0.025% or the 0.075% capsaicin cream, but you will not know which it is. You will be asked to provide information about your level of pain every two weeks for the duration of the study (12 weeks), by completing a questionnaire which will take about 5 minutes of your time. You will also be asked to make a visit to the Doctor's office 8 weeks after the study and at the end of the study.

D. Potential risks and discomforts
You may experience a burning sensation with the application of the cream, which should disappear within the first two weeks. You may find that applying the cream four times a day is an inconvenience, but for the cream to work, its repeated use is necessary.

Your participation in this study is voluntary, and you may withdraw from the study at any time. If you choose not to continue, your relationship with your physician will not be affected.
E. Potential benefits
   There is no payment for your participation in this study. The cream will be provided to you, free of charge. The potential for the cream to help relieve your pain is good. Because creams that are applied to the skin are safer than systemic medications, confirming the effectiveness of this cream may help other diabetics obtain pain relief without systemic complications.

F. Confidentiality
   The information obtained for this study will be strictly confidential, and used only for research purposes. All questionnaires will be identified with a number. Your name will not be a part of any data. Your identification number and personal data will not be available to anyone other than myself and my research committee. The results of this study may be published in group form with data combined from other participants. Names will not be identified, and data will remain anonymous.

G. Withdrawal from the study
   Your participation is voluntary and you are free to withdraw from the study at any time. Your decision to not participate will not prejudice your relationship with your physician or clinic.
   Participant's Initials ________

H. Contact Information
   If you have any questions, or concerns regarding the study, you may contact me at ICNE, W 2917 Fort George Wright Drive Spokane, WA 99204. In the event of any problem associated with the study, you may contact me at 483-1479 or contact my advisor Lorna Schumann at 324-7285.

I. Informed Consent
   I,________________________ fully understand the purpose of this study, what is required of me, and the possible risks involved. I understand that participating in this study is fully voluntary and that I may withdraw at any time. I give permission to Mercedes Gonzalez-Aller to use the information obtained from the study for research purposes. I understand that the researcher and her committee will maintain the privacy and confidentiality of the information I provide.
   I have read and understand the conditions of the study, and have been given a chance to ask questions. Answers to my questions have been provided to my satisfaction. I have received a copy of this form.

   Participant's Signature ________________________________ Date __________

   Researcher Signature ________________________________

APPENDIX E

DIRECTIONS ON HOW TO APPLY THE CREAM
ZOSTRIX (CAPSAICIN)

DIRECTIONS

Zostrix topical cream relieves pain by depleting Substance P, a chemical messenger in nerve cells that transmits pain signals. When Zostrix depletes Substance P at the site of application, less pain is felt. Zostrix will not interfere with the oral medications you are taking.

For maximum pain relief, you must apply the cream regularly and frequently, to prevent Substance P from building up in nerve cells again. Because it takes time to deplete Substance P, relief occurs gradually.

- Apply to the painful area four times a day, regularly.

- Apply only enough cream to cover the area, and gently massage into the skin until absorbed and until no residue remains. Avoid thick application. Dried residue may cause coughing and sneezing.

- Do not apply to open or irritated skin.

- Wash hands thoroughly after use to avoid spreading cream to other sensitive areas of the body. If the cream gets in your eyes, it will cause a burning sensation, but there are no reports of any harmful effects. Flush your eyes with water.

- A burning sensation may be felt with initial use of Zostrix, but subsides with regular use. Continue to use the cream as directed in order to obtain maximum relief and minimize the burning sensation.
APPENDIX F

INSTITUTIONAL REVIEW BOARD APPROVAL
September 28, 1995

MEMORANDUM

TO: Mercedes Gonzallez-Aller, ICNE (5291)
FROM: Dr. Paul Whitney, Chair, Institutional Review Board
SUBJECT: Review of Human Subjects Protocol

Your Human Subject Review Summary Form and additional information provided for the proposal entitled "A Comparison Between the Effects of 0.025% and 0.075% Topical Capsaicin in the Relief of Painful Diabetic Neuropathy," OGRD #NF was reviewed for the protection of the subjects participating in the study. Based on the information received from you, the IRB has approved your human subjects protocol on September 28, 1995.

The IRB approval indicates the IRB's belief that the Human Subjects protocol as presented in the Human Subjects Review Summary Form by the investigator, is designed to adequately protect the subjects participating in the study. This approval does not relieve the investigator from the responsibility of providing continuing attention to ethical considerations involved in the utilization of human subjects participating in the protocol. This approval is valid for one year from approval date. If any significant changes are anticipated in the study please notify the IRB before implementation.

In accordance with federal regulations, this approval must be kept by the researcher for THREE years after completion of the research.