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Review Article

Clinical Outcomes Utilizing the Combined Electrochemical Treatment for Peripheral Neuropathy: A Retrospective Study from a Western Clinic

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Abstract

Treatment of peripheral neuropathy has been confined to papering over symptoms with medications such as gabapentin and pregabalin, both of which have high side effect profiles approaching 40%. The Combined Electrochemical Technique (CET), co-developed and popularized by the first author, has been shown to safely and effectively treat peripheral neuropathies of all causes. Retrospective results from the first experiences with CET to treat neuropathy are presented.

The data strongly suggest that CET is safe and effective in the treatment of peripheral neuropathy in as many as 70-80% of cases. Long term data revealed that more than 50% of patients had sustained benefits for at least one year. Patients with depression and vascular disease appeared to do as well as patients without these co-morbidities. Sleep and quality of life assessments demonstrated improvements in 70-80% of patients. Almost 70% of patients recorded some sort of functional improvement. There were no adverse events noted in this series.

Prospective studies have also confirmed the efficacy of this technique. The potential benefits of CET to the health care system are substantial. Although these outcome measures are subjective and a function of other independent variables, results strongly suggest that CET is an effective treatment for parameters which matter most to patients.

Introduction

Morbidity associated with diabetic and other neuropathies is a major reason patients seek medical care and represents a major cost to patients and society [1,2]. Peripheral neuropathy occurs as a result of basic pathologic processes from injury or disease. The incidence of neuropathy increases with age and its prevalence is growing. In fact, the prevalence of peripheral neuropathy may be as high as 8% in the United States. The course of neuropathy is often progressive. To date, most treatments have focused on reduction of symptoms [3] and, in the case of diabetes, control or slowing of the progression of the underlying disease.

The Combined Electrochemical Treatment (CET) has been utilized over the past eight years for the treatment of many chronic pain states, and most popularly for peripheral neuropathy. The technique was first formally described in 2008 [4] and more recently [5-7] a prospective study has confirmed earlier results [8]. CET has been described under various names in the literature, including the Integrated Block and the Combined Electrochemical Block (CEB). Practitioners who have had extensive experience with the protocol have recently agreed to utilize the term CET.

A basic science foundation has been established for this treatment in earlier publications [9]. This paper will present

retrospective outcome data from a single clinic, which confirms data published previously as to the efficacy of the CET in reversing the chronic disease process of peripheral neuropathy.

The Electrical cell Signaling Treatment (EST) component is the integral part of the CET. It is administered after the chemical (local anesthetic) injections. Neuropathy is a multi-faceted and complex condition and requires a comprehensive and varied-parameter EST approach. Traditional electrotherapy devices (TENS, interferential, and middle frequency) are simplistic and limited electronically and do not effectively deliver the various required mechanisms of action necessary for nerve regeneration and long term treatment success.

The device used in our CET protocol [10] is capable of continuously varying and delivering simultaneous modulation (AM and FM) of the electronically generated signal frequencies, the amplitude of the Electromagnetic Fields (EMF), and the impulse variations necessary to ensure accurate neuron activity without accommodation. The system program and signal frequencies will also produce required metabolic muscle work when indicated. Continuous changes in the electronic signaling values are applied at specific incremental steps, which are mathematically calculated to produce harmonic resonance and vibratory effects on the cells 'membranes'.

Methods (Study Design)

Structure

The CET protocol has been implemented at the Neuropathy and Pain Centers of America since 2008, with refinements ongoing to mid-2009 when the current protocol was optimized. Prior to beginning a course of treatment, each patient was given a full informed consent regarding the risks and benefits of the procedure. This explanation included the fact that both aspects of care - the local anesthetic blocks and Transcutaneous Electrical Stimulation (CET is classified as a TENS) were both FDA approved interventions. Each patient signed a statement indicating their understanding of these principles.

This is a review of 112 charts dating from August 2008 to July 2013. Each patient reviewed in this study received the same treatment protocol; treatment was completed at the same clinic and personally performed or overseen by the author. Data was collected from a review of the electronic medical records.

Each chart was analyzed and organized according to demographic, baseline and outcome data related to a patient's treatment using the Combined Electrochemical Treatment (CET). Each category of outcome data had a different number of patients studied since not all data points were obtained from each patient in this retrospective review. When a data point could not be obtained from the chart and not been provided by the patient, it was not included in the "n" for that specific outcome measure. Therefore, "n" varied as subsets of total number in the review (141) from outcome to outcome. The kind of demographics and outcome data recorded for each patient are listed in table 1. Ages varied from 37 to 80 years, but most patients were over 65 years old with nearly an equal number of males and females.

Demographics
• Type of neuropathy present
• Age of the patient
• Length of time neuropathic symptoms present prior to treatment
Pre & Post Treatment Data
• Symptom score (0-10)
○ NRS (pain score, 0-10)
○ Numbness (converted to 0-10)
• Functional capabilities
• Presence of co-morbidities - vascular disease & depression
• Sleep quality - interruption or not
• Quality of Life
• Neural scan score, defined in text
• Relevant medication usage (Narcotics, Lyrica, Neurontin)

Table 1: Demographics and Pre/Post Treatment Data Collected.

Earlier posters [4,5] and publications [6], have described the protocol in detail. Patients were administered two combined electrochemical blocks per week (Monday, Friday) to each ankle. A third EST treatment only was done on the third day (Wednesday). Of the charts reviewed, 112 patients underwent at least 5 CETs. Thirty patients of the original number reviewed were not included since the number of CETs was less than five. The average number of CETs was between 12 and 13 and ranged from five to 26. The protocol required that, after the patient's progress had plateaued (or no improvement after 6 CETs), CETs were discontinued and several weeks of EST treatment only were provided prior to discharge.

Each patient's chart consisted of a short term outcome data recorded just after treatment had been completed. Data was then compared to the patients' recorded assessments prior to treatment. All long term outcome measurements were reassessed in follow-up interviews, which were conducted between three months to four years after treatment had been completed. The patients were contacted and interviewed to gauge the effectiveness of their treatment long term; the contact times varied following discharge. All parameters were tabulated in either graphs and or tables presented in the results section.

Patients presenting with neuropathy were queried to rate their pain, dysesthesias and/or numbness. The well-known Numeric Rating Scale (NRS) (range 0 to 10) was applied to represent all of these symptoms together. Following treatment each patient was asked how much improvement in symptom relief was achieved as a percentage.

Study outcome measures - Subjective

Neuropathy is much more complex and is more difficult to both characterize and quantify than chronic pain. Neuropathy

symptoms present in multiple ways, including pain, dysesthesias and numbness. Therefore, it is less straight forward to accurately determine the amount of symptom relief with which each patient might experience after an intervention or series of interventions. For the purposes of Numerical Rating Scale (NRS) classification, patients for whom pain was not the dominant symptom were asked to combine their pain, dysesthesias and numbness in to one number (0 to 10), if more than one of these three symptoms were present. Symptom relief for each patient was assessed using this measurement. Relief of symptoms was defined as any reduction in pain, dysesthesias and/or numbness. Patients were asked to provide a percentage of relief following treatment. Percentage improvement in pain, numbness and/or dysesthesias was and recorded as overall symptomatic relief. The number for each 25% interval symptom relief was tabulated and recorded.

Functional improvement was self-defined by each patient. Improvement was defined as the increased ability to function in any way. This included, but was not limited to, a patient's ability to walk and/or perform activities of daily living more easily. Each patient was his/her own control for this outcome measure.

Patients were queried if the neuropathy had interrupted their sleep. Criteria was documented as 1) interrupted regularly, 2) sometimes, 3) not interrupted, or 4) interrupted by a health factor other than neuropathy symptoms. Tabulation of the data revealed that the "sometimes" category (2) was quite small, so it was combined with the "interrupted regularly" category (1). If sleep was interrupted by something other than neuropathic symptoms, that patient's response was not included in the particular "n" for that tabulation.

The influence of neuropathic symptoms on each patient's quality of life was defined as any interruption in the patient's well-being and ability to perform daily activities. Improvement in this parameter was assessed post treatment. Only patients who reported an initial decrease in this measure were assessed.

Many patients presented with various co-morbidities. This review recorded two major co-morbidities: depression and peripheral vascular disease. All patients who presented with these co-morbidities were analyzed as a subset to determine treatment effectiveness for patients with these additional medical issues. Co-morbidity reduction was measured only as a "yes" (any reduction realized) or "no" (no reduction).

The physician's staff asked each patient if they were satisfied with their treatment. Satisfaction could include any combination of pain reduction, sleep improvement, functional improvement and overall quality of life improvement. All 112 patients who received treatment were included in this outcome measure.

Study outcome measures - Long term

Our goal was the determination of the long term effectiveness of the treatment protocol with regards to the previous measures. The follow-up time period ranged from 6 months to >4 years post treatment. It proved difficult to accurately measure all specific outcome measures and progress in all patients. Data which could be collected was not always the same for all patients. Many were able to provide detailed accounts of their treatment, but some patients in this older population could not. Patients were specifically asked whether the treatment had been to their satisfaction and had provided some form of persistent relief. We focused on the patients' overall wellbeing and level of continued symptom improvement, including whether symptom relief during sleep and quality of life improvement, and function.

Objective study outcome measure: Epidermal nerve fiber density

The Epidermal Nerve Fiber Density (ENFD) is a skin punch biopsy measuring the density of unmyelinated a-delta and c fibers in the epidermis; it can be used as an anatomic measure of nerve regeneration and may provide objective measure of small fiber nerve regeneration [11,12] the patient's progressive improvement.

Results - Short term

The average symptom relief is tabulated in (Figure1). Symptom relief as function of type of neuropathy was also tabulated (Figure 2). Over 82% of patients experienced relief of pain, numbness and/or dysesthesias. The symptom relief appeared to be independent of the cause of neuropathy.

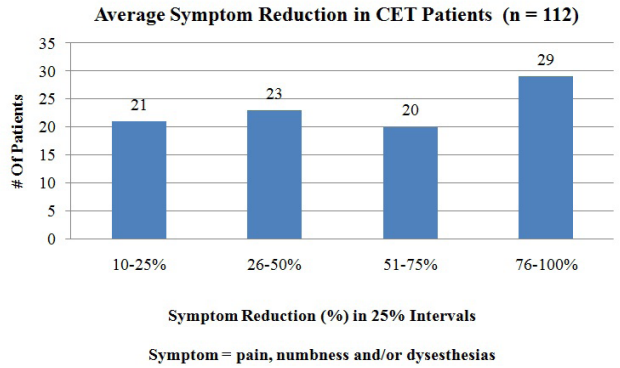

Figure 1: Average Symptom Reduction using CET by 25% increments.

Patients were asked what their overall symptom (pain and/or numbness and/or dysesthesias) reduction was, if any, at the end of treatment. The number of patients who reported this sensory symptom decrease was recorded in intervals of 25%-82.4% of patients reported some decrease in symptoms (> 0%) and 64.2% reported an improvement of over 25%.

Depression and peripheral vascular disease were co-morbid conditions considered in this review. Patients with

Type of Neuropathy	Number of Patients	Percent Improved	Percent not improved	Average % Pain Reduction
Diabetic	56	82.1	17.86	49.6
Idiopathic	40	80.0	20	47.1
Toxic	6	83.3	16.6	42.5
Chemotherapy	9	88.8	11.1	52.1
HiV/AIDs	1	100	0	100
Other	6	100	0	100

Figure 2: overall symptom relief by neuropathy type.

these co-morbidities were treated as subsets to determine if the effectiveness of the treatment varied in these conditions (Figure 3). The percentage of this subset of patients who reported symptom reduction was 86.7%. The percentage of patients who had an overall satisfaction from treatment was 80.0%. Both percentages were higher than the outcome measures for all patients (both with and without these two co-morbidities).

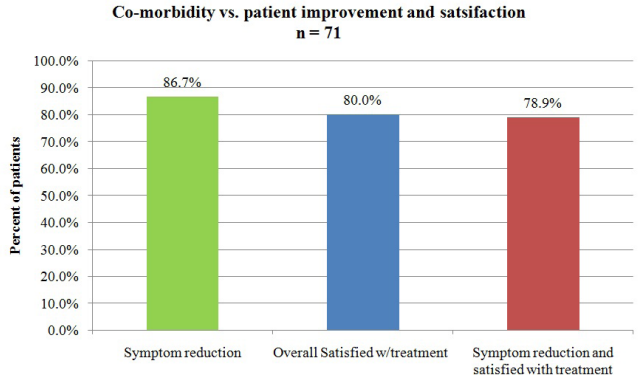

Figure 3: Co-morbidities (Depression + Vascular disease).

The duration of time patients had been aware of their neuropathic symptoms varied widely, since a definitive treatment has not previously existed for the treatment of peripheral neuropathy. The scatter graph in (Figure 4 indicates that there did not seem to be a correlation between the length of time a patient has had symptomatic peripheral neuropathy and the magnitude of their response to treatment.

The length of symptoms present in years vs. the percent of symptom reduction experienced immediately post treatment (n=107) is presented in figure 4. No correlation between prior length of symptoms and percent of symptom reduction could be found, suggesting that the length of time a patient has had neuropathy may not be a factor in their ability to respond to treatment.

73 of 106 (68.9%) patients recorded functional improvement. The parameter of sleep interruption or disturbance was tabulated. Of 59 patients who initially noted sleep disturbance, 41 (69.5%) had an improvement in their quality of sleep post treatment 79 patients who initially noted a diminution in their quality of life at the beginning of treatment were reassessed following treatment. 65 (82.5%) of patients noted an improvement immediately post treatment.

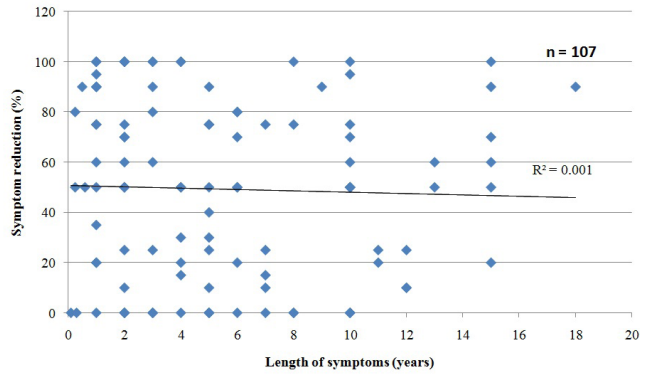

Figure 4: Symptom reduction vs. length of symptoms prior to treatment.

All patients were asked about their overall satisfaction following treatment. Of the 105 patients who responded, 79 (75.2%) were pleased with their treatment and the outcome. In all cases, there were no adverse outcomes recorded; minor or major, temporary or permanent.

Results - Long term

We were able to retrospectively obtain long term follow up information from 32 patients (22.7% of the total number studied, 141). 53% of the patients contacted noted that symptom improvement and satisfaction achieved during the treatment had been maintained. Very few patients returned during this time period, so we had anticipated much more than a 53% retention rate. Many patients who were treated for peripheral neuropathy were suffering from medical illnesses other than those which caused the neuropathy or either co-morbidity assessed (depression and vascular disease). In many cases, patients complaining of no long term symptom relief stated that it was often not clear to them whether the treatment had given them long term benefit because of interference from the negative effects of other co-morbid conditions.

Discussion

Effectiveness of the Combined Electrochemical Treatment (CET)

The data strongly suggest that CET is safe and effective in the treatment of peripheral neuropathy in as many as 70-80% of cases. Of the 112 patients recorded for NRS improvement, 82.4% of them reported a decrease in symptoms and 61% reported an improvement of over 50%. Some of the variability in clinical outcomes reflects patient variability in genetic makeup and disease state, although the data suggest that improvement can be obtained in a variety of underlying disease settings. Despite study limitations, the data show favorable outcomes in multiple aspects of the peripheral neuropathic disease state, and support data from an earlier prospective study [5]. Improvements appear to be independent of the cause of the neuropathy (Table 2), suggesting a final common pathology for the various causes of peripheral neuropathy.

Many patients suffer from co-morbidities associated with peripheral neuropathies and other causes of peripheral neuropathies. Many studies linking chronic pain and depression have found that improvement in pain leads to an improvement in depression, but it is often difficult to determine which comes first. Persistent afferent input activates and sensitizes Wide Dynamic Range (WDR) neurons and these ascend to higher centers in the limbic system including the amygdala, anterior cingulate gyrus and insula, all of which place crucial roles in the emotional and affective aspects of pain [10]. From the data analyzed in this study, it appears that the two co-morbidities considered were not significant factors in patient outcomes. In depression, it is possible that the improvement of the altered input to the WDR neurons may have had a salutary effect of the patients' emotional response to neuropathy. In vascular disease, a primary healing element of the electric cell signaling device (provided by the Sanexas Corporation) utilized in the study is the increase of blood flow. Thus, these two associations are not unexpected.

	NRS Improved	NRS No Change	Totals
Neural scan Improved (+ NS score)	16	11	27
Neural scan w/o change or worse 0/- NS score	4	3	7
Totals	20	14	34

Table 2: Neural scan Score vs. Symptom Improvement.

McNamara's Odds Ratio = 2.75

The length of time that a patient presents with any kind of chronic disease and attendant symptomatology is usually a factor in regards to the prognosis for the efficacy of any form of therapy. It is intuitive that the earlier a chronic disease process can be treated, the better the anticipated outcome. Anecdotal evidence from more recent patients treated at this clinic have supported this supposition; one patient with only a three week history of idiopathic neuropathy had complete symptom resolution after only two CETs and nine EST sessions. However, the data presented in (Figure 4) reveal that for this series, there was no correlation between the duration of time a patient had symptoms and the chances of obtaining symptomatic relief. Several reasons for this apparent lack of correlation include the specific cause of the neuropathy. Ongoing disease control in some diabetic neuropathy patients who initially improved showed regression some months after treatment stopped; a check of their Hgb A1C revealed that it was greater than 8. The disease process can cause recurrence of the peripheral neuropathy. Lifestyle changes, and disease control, are of paramount importance in maintaining improvement in symptoms.

Improvement in function - usually related to mobility, balance, and increased ability to lead their lives as they were previously able - is crucial in older patients to maintaining better states of health. Increased functional ability also has related salutary health benefits. One patient, morbidly obese and in his late 40s, was able to walk for two hours each day after his neuropathy symptom reversal; his weekly weight loss of 16 pounds could be directly attributable to the calories expended daily from exercise.

Sleep and quality of life assessments demonstrated improvements in the 70-80% of patients. Although these outcome measures are subjective and a function of other independent variables, results strongly suggest that CET is an effective treatment for parameters which matter most to patients. Likewise, overall satisfaction with the treatment protocol (75.2%) was significant since the treatment process involves two to three months of three visits to the clinic per week; a majority of these visits involved potentially painful ankle injections. As expected, during the course of treatment, many patients experienced increased pain with injections as their peripheral nerves would begin to heal and better carry out the function for which they were designed - reporting acute (a-delta) pain.

Long term effectiveness was documented in greater than 50% of patients. It was our experience that many patients treated for neuropathy were able to reduce their usage of Gabapentin, Lyrica, or even narcotics.

There were no follow-up "wellness" programs offered to patients who underwent the protocol. Ongoing patient engagement and cooperation in such areas as diet, lifestyle, and perhaps even a maintenance program of periodic EST treatments could be crucial in maintaining the benefits of the neuropathic treatment protocol. Future studies will be designed for more robust long term follow-up data comparison.

Study limitations

The study of outcomes in neuropathy is complicated by the greater number of symptoms and signs which must be measured. Many of the signs and symptoms were considered, but some were not. Several screening measures for peripheral neuropathy include Semmes Weinstein Monofilament Examination (SWME), Rydel-Seiffer measurement of vibration, and the thermal threshold testing [14,15]. SWME and vibration, for example, were not quantitatively measured in this study. (Current protocols now use pre- and post-treatment measurements of the Rydel-Seiffer method, termed vibration perception threshold. Vibration perception threshold can be an important tool in tracking outcomes and is considered by some to be one of the most sensitive measures of peripheral neuropathy [16]. Furthermore, some of the other measurement outcomes had to be quantified, e.g., sleep, as either interrupted or not interrupted. In this case, our classification

may not be sensitive enough to fully measure disruption and improvements in sleep.

Patients were treated with a variable number of CETs (minimum 5) during our early experience with the protocol. The average number of treatments was 12 to 13. CETs were discontinued when patients' symptoms plateaued; they were then treated with another six EST treatments over the final 2 -3 weeks, reevaluated, and discharged. This practice was utilized since there is evidence that the electronic signaling can help to stimulate the ongoing healing process after the CETs have been discontinued. Many patients exhibited progress even after all treatment ceased. The wide variation in the number of CETs in the protocol reflect both a learning curve on the part of the first author and individual responses (or lack thereof) to treatment. Current protocol permits the number of CETs to be as high as while average number needed are somewhat less than that. The optimal treatment protocol requires further study and the number of CETs per patient will likely need to be individualized according to patient response.

The data management technique of combining pain, dysesthesias and numbness into one measure (NRS) could be subject to criticism. Patients were asked to consider the NRS as a "discomfort score" if symptoms other than pain (dysesthesias, numbness) were a more significant manifestation of the peripheral neuropathy. A plurality of patients sought care for pain or dysesthesias. However, pain scores of "0" for patients with only numbness would have skewed the data and could have been misleading in terms of outcomes, since many patients with numbness and dysesthesias only were also improved [5]. More exact measurement tools await all researchers who deal with the variety of symptoms of peripheral neuropathy.

According to Sadosky [13], the most common comorbid conditions are sleep disturbance or insomnia (43.8%), depressive symptoms (41.1%), and anxiety (35.7%). In this review only two of these most common comorbidities were recorded: depression and sleep disturbance. There are many other co-morbid conditions which could have been considered, for example headache/migraine, fibromyalgia (mild/moderate/severe only), chronic fatigue syndrome (overall only), and chronic low back pain [17]. Their influence on outcomes can be considered in future studies.

Long term data, done by telephone follow-up, was more difficult than anticipated. These limitations were outlined in the section above where results were presented for clarity of that section.

No consistent objective testing was considered in this review. Neuropathic symptoms are classified into positive symptoms, (pain, dysesthesias and paresthesia), and negative symptoms (loss or impairment of sensory quality, numbness, dry skin, gait instability, fall risk, incontinence, and erectile dysfunction). Involved sensory nerve fibers include afferent c-fibers, efferent c-fibers, and unmyelinated and myelinated a-delta fibers. The diagnostic functional tests, which, can assess each of these fibers include; A-delta NCS, Sudoscan (efferent c-fibers by measuring sweat function) and anatomic studies (epidermal nerve fiber density biopsies (c and unmyelinated a-delta). This study did not feature the consistent use of any rigorous objective testing, although A-delta NCS testing was used in a subset. Future studies are planned that will incorporate all three.

This study was retrospective and thus not as robust as prospective studies. In addition, uniform data could not be abstracted from each of the 112 patients. Prospective studies are being undertaken at this time, which should increase the robustness of the data and increase confidence in the outcome comparisons.

Safety

There were no adverse events noted in this series, nor have any significant complications been reported in thousands of cases across the country. Infection is a complication which could be possible when multiple injections are utilized; however, care was taken not to inject at the same site each time. Even in diabetic patients (highest risk for infection), no infections were observed. On the contrary, skin appearance in those patients who had venous stasis, scaling and other manifestations of neuropathy or peripheral circulation compromise often improved early on in treatment.

Injections close to the five nerves which traverse the ankle sometimes produced paresthesias; however, these nerves proved to be quite forgiving and nerve pain did not persist after the first day.

Cost savings

The benefits of CET to the health care system are substantial. According to Sadosky et al., [17] the annualized direct and indirect costs per diabetic patient with neuropathy varies from about $8000 per year (mild cases) to $21,000 (severe cases). These patients utilize a disproportionately high percentage of health care resources, with excess costs associated with diabetic neuropathy being about $6000 [18]. By comparison, a course of CET may range from between $5000 and $8000 as a one-time cost only. These cost comparisons alone are a reason to aggressively pursue further studies of CET in the treatment of diabetic and all peripheral neuropathic states, irrespective of co-morbidities present. The cost effectiveness of this treatment concept will be more extensively analyzed in other work soon to be republished.

Conclusion

Results of this retrospective study support the conclusions of Cernak et al., [8] regarding the safety and effectiveness of CET for the treatment of diabetic and other peripheral neuropathies. The effectiveness of the protocol does not seem to depend on the type of neuropathy nor on how long the

patients have had symptoms. The truly remarkable finding is the high percentage and variety of symptom reversals for this chronic disease; based on the literature, there is strong evidence that the CET protocol is truly producing healing of the neuropathies, a chronic disease state, which is a rarity in the management of chronic diseases.

Data suggest that all types and severity of neuropathy are potentially treatable with the combined electrochemical therapy protocol. The length of time that a patient has had symptoms does not appear to have any relationship to predicted outcome (improvement), although further studies with higher "n" values may show otherwise.

The CET requires further study with more robust and rigorously controlled prospective studies. The future appears bright for using "energy medicine" approach to healing.

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