A Randomized Longitudinal Double-Blind Clinical Trial on Long-Term Neuropathic Symptomatology Relief & Pain Analgesia

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Abstract

Diabetic neuropathic pain is one of the most difficult to treat with high levels of reoccurrence and a substantial increase with aging. It involves expensive hospitalizations, often resulting in an amputated lower limb. We explored a variety of methods treating neuropathic pain such as low-level laser, monochromatic near-infrared treatment, TENS, acupuncture and pulsed electromagnetic fields that demonstrated inconclusive, limited or temporary pain relief with minor or short-term improvements in mobility. Research conducted by ultra-low energy technologies reports pain relief and reduction of inflammation as a result of anti-oxidant electron donation transforming free radicals into stable molecules. We report the results of a randomized double blind one-year-long longitudinal clinical study on 10 diabetic mellitus (DM) subjects with chronic neuropathy, treated with ultra-low energy nanotechnology who experienced substantial long-term neuropathic pain relief. Importantly, pain analgesia and improvement in neuropathic symptomatology were not age-contingent. This contradicts past research postulating that age-accumulated inflammation and endothelial dysfunction can further exacerbate diabetic neuropathy. Importantly, a method offering age-independent, cost-effective, long-term neuropathic pain relief and increased mobility has major implications in reducing hospitalization time and overall expenses by offering a solution that enhances quality of life.

Keywords

Aging, Pain Relief, Diabetes Mellitus, Neuropathy, TENS, Ultra-Low Energy Technologies, Nanotechnology, Limp Amputation, Neuropathic Pain
1. Introduction

Diabetic neuropathy has always been a challenge, because it increases with age and traditional treatments result in temporary symptoms’ relief, without preventing or halting the neuropathic condition. Diabetes patients experience neuropathic pain as a direct consequence of abnormalities in the peripheral nerves’ network, leading to an imbalance between excitatory and inhibitory somatosensory signalling. This involves ion channels’ alterations and hence dysregulation of pain messages transmitted from the thalamic nucleus to the cerebral cortex [1] [2]. Neuropathy typically causes numbness, tingling, sharp pain, muscle weakness, poor mobility, paraesthesia or hyperesthesia. Diabetic neuropathy is associated with susceptibility to foot or ankle fractures and ischemic ulceration leading to lower-limb amputations, often accompanied by negative mood and depression that further exacerbate discomfort [3] [4], locking these patients into a vicious circle of poor quality of life with little hope for escape.

The pathological basis for DM neuropathy includes both metabolic, vascular and immune pathogenesis models [5]. Experimental models of metabolic pathogenesis of neuropathy postulate that severe hyperglycemia can produce reduction in nerve conduction velocity and axonal shrinkage. Vascular pathogenesis models demonstrate that the severity of polyneuropathy is associated with an increase in basement membrane area and endothelial cell degeneration. The immunologic/inflammatory pathogenesis demonstrates asymmetric nerve fiber loss and lymphocytic epineural inflammation resembling vasculitis [6]. Vincent et al. (2011) explored the cellular mechanics of mitochondrial function, imbalances of cellular metabolites of glucose and lipids, impaired insulin signalling and sensory neurons’ vulnerability to oxidative and inflammatory stress. They outlined therapeutic targets focusing on inflammation and functional balance within mitochondrial mechanisms [7]. Overall, inflammation and oxidative stress appear to be closely related to diabetic neuropathy.

Low-level laser therapy has been reported to alleviate neuropathic pain on the basis of the significant reduction of the hypoxia-inducible factor 1α (HIF-1α) that is related to increased inflammation. The chronic constrictive injury model on rats used, demonstrated decreased inflammation after low-laser therapy treatments for 7 consecutive days [8]. However, adopting an animal model does not allow for participants’ confirmation that decreased inflammation is in fact accompanied by pain relief. Beckerman et al. looked at the efficacy of laser therapy on diabetic neuropathy, diabetic wounds and other skin lesions on the basis of 36 randomized clinical trials involving 1704 subjects. They conclude that laser studies were characterized by low methodological quality with no follow up, offering no definite conclusions on the efficacy of lasers on pain relief and skin disorders [9].

Reduced neuropathic pain, improved balance and restoration of sensation was reported after 12 treatments with a monochromatic near-infrared technology on 27 patients with diabetic peripheral neuropathy in a double-blind, randomized...
placebo-controlled clinical trial [10]. However, it would appear that balance improvement was reported on 83% of the patients, a non-significant statistical result, in the absence of a longitudinal follow up to determine neuropathic pain re-occurrence.

Results from anti-nervous drugs, such as tricyclic antidepressants, anticonvulsants, topical agents, and sympathomimetics, seeking improvements in nerve function and blocking the transmission of pain impulses offer some promising results when combining pathogenetic and symptomatic therapy, specifically the aldose reductase inhibitor ranirestat and duloxetine [11]. However, drug treatments have side effects, and benefits often dissipate when the pharmaceutical is halted or discontinued.

Transcutaneous Electrical Nerve Stimulation (TENS) devices have been widely used for analgesia with or without pharmaceuticals, however, there is little evidence of their efficacy with DM neuropathic pain [12]. A review of Acupuncture-like TENS devices (AL-TENS) in the management of pain using low frequency (1 - 10 Hz) electrical currents, has rendered inconsistent results due to insufficient details describing various TENS treatment interventions and often the lack of follow up [13]. Acupuncture studies report pain reduction that is not maintained over time or offers results that are not statistically significant. For example, Abuaisha et al.’s research [14] reports that 77% of subjects with peripheral neuropathy expressed pain relief and symptomatic improvement, a statistically, non-significant result.

Low-frequency pulsed electromagnetic fields (PEMF) with 225 diabetic neuropathy subjects showed some positive results in terms of neuropathic symptomatology, especially itching. Twenty seven subjects underwent 3-mm skin biopsies from 3 standard lower limb sites and showed an increase in distal leg epidermal nerve fiber density quantification which were correlated with decreased pain. Despite the neuropathic symptomatology reduction, these investigators conclude that the overall effect of PEMF on neuropathic pain was not significant [15].

A lot of research starting with Cheng et al. in 1982 [16] has postulated that ultra-low currents increase adenosine triphosphate (ATP) one of the main biological energy currencies as well as overall protein synthesis which is crucial for neuro-communications and systemic balance. More recently ultra-low energy technologies have been shown to decrease inflammation, alleviate neuropathic pain, increase mobility, and speed up the healing of wounds [17] [18] [19] [20]. These investigators postulate that diabetic wound healing and neuropathic pain relief is the result of electron flow into the ion channels of the cells, acting as a mega antioxidant by donating electrons to free radicals, the group of atoms with unpaired electrons, rendered unstable and highly reactive. Electron donation, fills in the gaps of unpaired electrons transforming free radicals into stable molecules. This electron-driven antioxidant process, reduces both oxidative stress and inflammation. Inflammation and oxidative stress are simultaneously present in neuropathy as well as several other pathological conditions. Inflammatory
cells release reactive oxygen species reinforcing oxidative stress [21]. Reactive oxygen/nitrogen species also initiate intracellular signalling cascades enhancing proinflammatory gene expression [22] [23]. Previously mentioned research by Vincent et al. [7] has associated neuropathy with sensory neurons’ vulnerability to oxidative and inflammatory stress.

The rationale for using such extremely low energy technology in wound healing is related to the concept of power frequency windows in the human body that appears to be affected by weak oscillating fields, unlike non-living systems that primarily respond to strong oscillating electromagnetic fields [24] [25] [26]. In his book “Electron Gated Ion Channels” Wilson Ranston [27] presents a new quantum-mechanical approach to the intrinsic simplicity of electrons controlling ion channels at ultra-low energies below thermal noise, reinforcing mechanisms important to cellular function and intercellular signaling.

Overall, chronic pain associated with diabetic neuropathy is one of the most difficult to treat with high levels of reoccurrence, long hospitalization times, mounting expenses, and the often inevitable possibility of an amputated limb. In search of solutions that can offer relatively inexpensive neuropathic pain relief and increased mobility, we tested the hypothesis that ultra-low energy nanotechnology can offer long term pain analgesia and increased mobility enhancing quality of life.

2. Methodology

We used an ultra-low energy nanotechnology originally invented in London University for cellular regeneration in 1992. The technology was subsequently modified over a period of 20 years on the basis of a series of original proprietary mathematical formulae based on unpublished in vitro and in vivo, clinical and electronic research. The technology has been used for over 10 years in clinical practice by over 800 physicians around the world with no reported adverse reactions or side effects. It is subjectively experienced as relaxing despite being imperceptible. Contraindications, warnings and cautions are according to the list provided under TENS devices by the FDA, although this novel technology has a nanoamp output (nanoamp = 10^{-9} Amperes) that is substantially lower than any other TENS devices which are usually in the milliamp range (milliamp = 10^{-3} Amperes). The technology stores 9600 sine and square waveforms combinations synthesized on the basis of an original mathematical formula with resultant frequencies ranging from 0.25 - 10,000 Hz. The technology is designed to emit four different resonant composite waveforms simultaneously out of the four virtual channels generated by prototypical software, at a predesigned variety of discrete specific times that range from 4 secs to 24 secs. Timing is calculated by a prototypical formula partly derived from the mathematical calculations describing how tunneling electrons control ion gates and the timing of circadian rhythms discussed earlier [27]. The sequence in which the four signals are emitted at a time, which varies in the technology’s 8 different programs, is regulated by an original
mathematical formula invented after 20 years of clinical and electronic research. The four resonant waveform composites that constantly alternate with respect to the timing formula, are transmitted via a single physical channel, and through a pair of four grade ultra-silver-plated microphone cables with attached stainless surgical steel probes that make contact with the patient’s skin. Probes are sanitized prior to each usage. During treatment, the device’s voltage output is estimated to range from 0.003 \( \mu V \) to 0.5 \( \mu V \) \( (\mu V = 10^{-6} \text{ Volts}) \) depending on the resultant frequency and skin resistance. The device’s current output reaching the skin is estimated to range from 10 nanoamps to 60 nanoamps depending on skin resistance.

Testing measures included: 1) A structured clinical interview conducted by a licensed dermatologist; 2) A neuropathic symptomatology checklist; 3) A physical examination 4) A comprehensive medical history questionnaire; 5) The subjective peripheral neuropathy screen (SPNS) questionnaire which has been successfully tested for validity and reliability. Research on the SPNS has demonstrated reliability, internal consistency, construct validity, and criterion-related validity for this instrument [28]; 6) The Pain Detect Questionnaire (PD-Q) offered before and after treatment completion. The PD-Q is a reliable screening tool with high sensitivity, specificity and positive predictive accuracy [29].

3. Procedure

Ten diabetic neuropathy subjects, four females and six males ages 40 - 78 years old were randomly selected out of patients who had sought treatments for neuropathic symptomatology in the hospital and private clinic over a period of 2 years. All participants were randomly selected after their treatments were completed at which point they were asked if they would allow their results to be used for clinical research, and upon accepting to participate, they signed a consent form. All subjects had been diagnosed with DM Neuropathy for an average of 8 years and had been previously treated with a variety of methodologies that had only offered them temporary relief. All subjects were hyperglycaemic and presented persistent inflammation on the site of pain. The neuropathy diagnosis was based on a physical examination and clinical interview conducted by their treating dermatologist, two self-report questionnaires, the SPNS and PD-Q, and a neuropathic symptomatology checklist that specifically explored the subjective experience of numbness, pain sharpness, burning sensation, tingling sensation, sensitivity to touch, muscle weakness and mobility. All subjects had scored higher than 19 on the SPNS, confirming the incidence of neuropathy and had fulfilled all the criteria for chronic pain and neuropathic symptomatology on the PD-Q, the physical examination, the clinical interview and the symptomatology checklist. Subjects were given six 30-min ultra-low energy nanotechnology treatments on each leg (6 one-hour treatments on both legs), delivered every three days. After the six treatments, the subjects were once again given the SPNS, the PD-Q, the physical examination and clinical interview by the treating der-
matologist, and the neuropathic symptomatology checklist. The subjects were followed up for one year after the six treatments and were re-examined to investigate the possibility of neuropathic pain and symptomatology reoccurrence.

Treatments and the scoring of the two questionnaires were completed by technicians who had no bias or personal interest in the direction of the results and were not aware that the data was eventually going to be used for research. None of the subjects had an implanted device such as a cardiac pacemaker, was pregnant, or was trying to get pregnant. The ultra-low energies emitted by the nanotechnology device are imperceptible, therefore the subjects were not aware whether the device was on or off, serving as their own control group. All subjects were instructed to suspend all pain medication two days prior and during the entire course of the six treatments.

4. Results

Subjects’ results on the SPNS and PD-Q with the percentages of neuropathic pain relief are listed in Table 1. After treatment results provided values from 15 down to 6 which were substantially below the cut off value of 19+ indicating the presence of neuropathic pain.

Subjects’ reports on pain relief and symptomatology improvement immediately after the 6th treatment, are given in Table 2.

Subjects’ reports on the long-term neuropathic symptomatology, pain relief and increased mobility one year after the treatment are given in Table 3.

The results were analyzed with the Mann Whitney U test and ANOVA, one-way analysis of variance for repeated measures.

The ANOVA yielded statistically significant results at p < 0.01 as shown in more detail in Table 4. The Mann Whitney U test for the SPNS before and after scores yielded highly significant results where p = 0.00009. The U-value was 0. The critical value of U at 0 < 0.01 was 19. Therefore, the results were significant at 0 < 0.01. The z-score was 3.74185 indicating statistical significance at p < 0.01. A graphic representation of the SPNS results before and after the ultra-low energy nanotechnology treatment is illustrated by Figure 1.

The Mann Whitney U test for the PD-Q before and after scores also yielded highly significant results where p = 0.000087. The U-value was 0. The critical value of U at 0 < 0.01 was 19. Therefore, the results were significant at 0 < 0.01. The z-score was 3.74184 indicating statistical significance at p < 0.01. Figure 2 depicts the PD-Q results on neuropathic pain relief before and after the treatment.

Results analysis on both SPNS and PD-Q as shown in both Tables 1-3, Figure 1 and Figure 2 revealed that age was not a factor in terms of degree of neuropathic symptomatology and pain relief. For example, 66 - 78 years old subjects appeared to have greater pain analgesia than younger subjects. The physical examination after the 6 treatments and a year later revealed less inflammation at the site where pain was reported prior to the ultra-low energy nanotechnology intervention.
Figure 1. All subjects reported significant neuropathic pain relief on the SPNS, independent of age.

Figure 2. All subjects reported significant neuropathic pain relief on the PD-Q. Age did not seem to play a significant difference with respect to relief from neuropathic symptomatology. For ex., a 66-year-old subject showed greater improvement than younger subjects.

Table 1. Inflammation, SPNS and PD-Q values before and after treatments.

| Gender | Age | Inflammation | SPNS Prior | SPNS After | % Pain Decrease | PD-Q Prior | PD-Q After | % Pain Decrease |
|--------|-----|--------------|------------|------------|----------------|------------|------------|----------------|
| Male   | 40  | Yes          | 32         | 12         | 62.5%         | 30         | 10         | 66.6%         |
| Female | 41  | Yes          | 34         | 15         | 55.8%         | 32         | 14         | 56.25%        |
| Male   | 45  | Yes          | 28         | 6          | 78.57%        | 30         | 8          | 73.3%         |
| Female | 53  | Yes          | 23         | 8          | 65.21%        | 24         | 9          | 62.5%         |
| Male   | 60  | Yes          | 22         | 16         | 27.27%        | 21         | 14         | 33.3%         |
| Female | 66  | Yes          | 38         | 13         | 65.78%        | 36         | 12         | 66.6%         |
| Female | 66  | Yes          | 26         | 9          | 65.38%        | 25         | 8          | 68%           |
| Male   | 73  | Yes          | 23         | 9          | 60.86%        | 24         | 11         | 54.16%        |
| Male   | 75  | Yes          | 20         | 7          | 65%           | 19         | 8          | 57.89%        |
| Male   | 78  | Yes          | 22         | 8          | 63.6%         | 24         | 6          | 75%           |
| Mean Average | | | 26.8 | 10.5 | 61% | 26 | 11.5 | 67.9% |
Table 2. Subjects results on reported percentage of neuropathic symptomatology relief based on the clinical interview and symptomatology checklist after treatments.

| Gender | Age | Numbness % | Pain % | Sharp Sensation % | Tingling Sensation % | Sensitive To Touch % | Muscle Weakness % | Poor Mobility % |
|--------|-----|------------|--------|------------------|----------------------|----------------------|------------------|-----------------|
| Male   | 40  | 70%        | 70%    | 70%              | 80%                  | 80%                  | 70%              | 70%             |
| Female | 41  | 65%        | 60%    | 60%              | 65%                  | 70%                  | 65%              | 65%             |
| Male   | 45  | 80%        | 70%    | 80%              | 75%                  | 80%                  | 70%              | 70%             |
| Female | 53  | 75%        | 75%    | 80%              | 65%                  | 75%                  | 75%              | 65%             |
| Male   | 61  | 55%        | 57%    | 60%              | 70%                  | 70%                  | 60%              | 60%             |
| Female | 66  | 60%        | 65%    | 60%              | 70%                  | 70%                  | 70%              | 65%             |
| Female | 66  | 68%        | 70%    | 68%              | 68%                  | 78%                  | 70%              | 70%             |
| Male   | 73  | 73%        | 70%    | 75%              | 75%                  | 80%                  | 75%              | 75%             |
| Male   | 75  | 70%        | 70%    | 70%              | 75%                  | 80%                  | 70%              | 65%             |
| Male   | 78  | 75%        | 70%    | 75%              | 75%                  | 85%                  | 75%              | 70%             |
| Mean Average | 69% | 68%        | 70%    | 72%              | 77%                  | 70%                  | 66%              | 66%             |

Table 3. Subjects results on reported percentage of neuropathic symptomatology relief based on the clinical interview and symptomatology checklist after one year.

| Gender | Age | Numbness % | Pain % | Sharp Sensation % | Tingling Sensation % | Sensitive To Touch % | Muscle Weakness % | Poor Mobility % |
|--------|-----|------------|--------|------------------|----------------------|----------------------|------------------|-----------------|
| Male   | 40  | 70%        | 70%    | 75%              | 90%                  | 80%                  | 80%              | 80%             |
| Female | 41  | 60%        | 55%    | 60%              | 55%                  | 55%                  | 65%              | 65%             |
| Male   | 45  | 80%        | 70%    | 80%              | 80%                  | 80%                  | 80%              | 80%             |
| Female | 53  | 50%        | 50%    | 50%              | 50%                  | 50%                  | 50%              | 50%             |
| Male   | 60  | 55%        | 57%    | 70%              | 70%                  | 70%                  | 60%              | 60%             |
| Female | 66  | 60%        | 65%    | 65%              | 65%                  | 65%                  | 60%              | 60%             |
| Female | 66  | 68%        | 70%    | 78%              | 78%                  | 78%                  | 70%              | 70%             |
| Male   | 73  | 70%        | 70%    | 70%              | 70%                  | 70%                  | 65%              | 65%             |
| Male   | 75  | 70%        | 70%    | 80%              | 80%                  | 80%                  | 70%              | 70%             |
| Male   | 78  | 70%        | 60%    | 70%              | 70%                  | 70%                  | 60%              | 60%             |
| Mean Average | 65% | 64%        | 70%    | 71%              | 70%                  | 66%                  | 66%              | 66%             |

Table 4. Summary of data. Results analysis with ANOVA for repeated measures.

| Treatments | 1 | 2 | 3 | 4 | Total |
|------------|---|---|---|---|-------|
| N          | 10| 10| 10| 10| 40    |
| ΣX         | 268| 103| 265| 102| 738   |
| Mean       | 26.8| 10.3| 26.5| 10.2| 18.45 |
| ΣX²        | 7510| 1169| 7275| 1110| 17064 |
| Std. Dev.  | 6.0332| 3.4657| 5.2967| 2.7809| 9.4025 |

Result Details

| Source | SS | df | MS | F = 93.51448 |
|--------|----|----|----|--------------|
| Between-treatments | 2690.1 | 3 | 896.7 | |
| Within-treatments | 757.8 | 36 | 21.05 | |
| Error | 258.9 | 27 | 9.5889 | |

The F-ratio value is 93.51448. The p-value is < 0.00001. The result is significant at p < 0.01.
5. Discussion

This randomized double blind longitudinal clinical trial that was conducted in the absence of any pain medication, indicated a significant lasting improvement in pain analgesia and the symptomatology of neuropathy after six half-hour treatments on each leg with ultra-low energies nanotechnology, supporting our hypothesis. Interestingly, age was not a factor since older subjects reported greater pain analgesia and neuropathic symptomatology relief than younger subjects on all measures. Although we included a symptomatology checklist, a clinical interview and physical examination along with the self-report measures, it should be noted that subjective reports are usually prone to distortion based on the individual experience and personal perspective. We made an inference that our results were due to a significant reduction of oxidative stress subsequently decreasing inflammation, on the basis of previously mentioned research associating oxidative stress to inflammation [21] [22] [23], and mathematical evidence that electrons control the cells’ ion gates at energies below thermal noise [27]. The nanotechnology’s electron generation and flow through the ion channels and into the cells interiors presumably repair the uneven number of electrons in free radicals, thus transforming them into stable molecules. The unobstructed flow of electrons through ion sodium, potassium and calcium channels at discrete times based on the mathematical calculations of tunneling electrons controlling the timing of circadian rhythms [27], may also energize age-inactivated molecular mechanisms, invigorate blood circulation, trigger cellular detoxification, ultimately decreasing inflammation and initiating a bottom up reparative process.

Our clinical study fell short in terms of examining oxidative damage in the subjects’ blood, or exploring inflammation markers such as the C-reactive protein (CRP) for example, that increase when there is an inflammatory condition. Overall, additional measures to test for oxidative damage, inflammation markers, hyperglycemia, and level of endothelial dysfunction in diabetic subjects with neuropathy is necessary to further validate and substantiate our results.

6. Conclusion

Our sample was small, and the study’s outcome was entirely based on subjective assessments and short self-report questionnaires that are usually prone to idiosyncratic distortion, exaggerations or understatements, in the absence of additional measures to test for oxidative damage, inflammation markers or hyperglycemia. However, the results of the self-report questionnaires, symptomatology checklist, clinical interviews and physical examinations were consistent in reiterating a long-term reduction of inflammation, neuropathic pain and overall symptomatology, following treatment with ultra-low energy nanotechnology. Results were statistically significant suggesting an alternative solution to adverse consequences such an amputated limp or lengthy expensive hospitalizations, by decreasing inflammation, and offering long-term analgesia and relief from neu-
ropathic symptomatology.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Treede, R.D., Jensen, T.S., Campbell, J.N., Cruccu, G., Dostrovsky, J.O., Griffin, J.W., Hansson, P., Hughes, R., Nurmikko, T. and Serra, J. (2008) Neuropathic Pain: Redefinition and a Grading System for Clinical and Research Purposes. Neurology, 70, 1630-1635. https://doi.org/10.1212/01.wnl.0000282763.29778.59

[2] Collosa, L., Ludman, T., Bouhassira, D., Baron, R., Dickerson, A., Yarnitsky, D., Freeman, R., Truini, A., Nadine, A., Finnerup, N., Eccleston, C., Kalso, E., Bennett, D., Dworkin, R. and Raja, S. (2017) Neuropathic Pain. Nature Reviews Disease Primers, 3, 17002. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5371025/

[3] Pensdey, S. (2010) Understanding Diabetic Foot. International Journal of Diabetes in Developing Countries, 30, 75-79.

[4] Poncelet, A.N. (2003) Diabetic Polyneuropathy. Risk Factors, Patterns of Presentation, Diagnosis, and Treatment. Geriatrics, 58, 16-30.

[5] Varkonyi, T. and Kempler, P. (2008) Diabetic Neuropathy: New Strategies for Treatment. Diabetes Obesity and Metabolism, 10, 99-108. https://www.researchgate.net/publication/6244689_Diabetic_neuropathy_New_strategies_for_treatment

[6] Gries, F.A., Cameron, N.E., Low, P.A. and Ziegler, D. (2003) Textbook of Diabetic Neuropathy. Thieme, Stuttgart, Germany.

[7] Vincent, A.M., Callaghan, B.C., Smith, A.L. and Feldman, E.L. (2011) Diabetic Neuropathy: Cellular Mechanisms as Therapeutic Targets. Nature Reviews Neurology, 7, 573-583. https://www.ncbi.nlm.nih.gov/pubmed/21912405

[8] Hsieh, Y.-L., Chou, L.-W., Chang, P.-L., Yang, C.-C., Kao, M.-J. and Hong, C.-Z. (2012) Low-Level Laser Therapy Alleviates Neuropathic Pain and Promotes Function Recovery in Rats with Chronic Constriction Injury: Possible Involvements in Hypoxia-Inducible Factor 1α (HIF-1α). The Journal of Comparative Neurology, 520, 2903-2916. https://doi.org/10.1002/cne.23072

[9] Beckerman, H., De Bie, R.A., Bouter, L.M., De Cuypers, H.J. and Oostendorp, R.A.B. (1992) The Efficacy of Laser Therapy for Musculoskeletal and Skin Disorders: A Criteria-Based Meta-Analysis of Randomized Clinical Trials. The Journal of Physical Therapy Science, 72, 483-491. https://www.ncbi.nlm.nih.gov/pubmed/14098811 https://doi.org/10.1093/ptj/72.7.483

[10] Leonard, D.R., Farooqi, M.H. and Myers, S. (2004) Restoration of Sensation, Reduced Pain, and Improved Balance in Subjects with Diabetic Peripheral Neuropa-
thy: A Double-Blind, Randomized, Placebo-Controlled Study with Monochromatic near-Infrared Treatment. Diabetes Care, 27, 168-172. 
https://care.diabetesjournals.org/content/27/1/168
https://doi.org/10.2337/diacare.27.1.168

[11] Várkonyi, T. and Kempler, P. (2008) Diabetic Neuropathy: New Strategies for treatment. Diabetes Obesity and Metabolism, 10, 99-108. 
https://www.researchgate.net/publication/6244689_Diabetic_neuropathy_New_strategies_for_treatment

[12] Gibson, W., Wand, B.M. and O’Connel, N.E. (2017) Transcutaneous Electrical Nerve Stimulation (TENS) for Neuropathic Pain in Adults. Cochrane Systematic Review; No. 9, Article No. CD011976. 
https://doi.org/10.1002/14651858.CD011976.pub2

[13] Johnson, M.I. (1998) Acupuncture-Like Transcutaneous Electrical Nerve Stimulation (AL-TENS) in the Management of Pain. Physical Therapy Reviews, 3, 73-93. 
https://www.tandfonline.com/doi/abs/10.1179/ptr.1998.3.2.73?src=recsys
https://doi.org/10.1179/ptr.1998.3.2.73

[14] Abuaisha, B.B., Costanzi, J.B. and Boulton, A.J. (1998) Acupuncture for the Treatment of Chronic Painful Peripheral Diabetic Neuropathy: A Long-Term Study. Diabetes Research and Clinical Practice, 39, 115-121. 
https://www.sciencedirect.com/science/article/abs/pii/S016882279700123X
https://doi.org/10.1016/S0168-8227(97)00123-X

[15] Weintraub, M.I., Herrmann, D.N., Smith, A.G., Backonja, M.M. and Cole, S.P. (2009) Pulsed Electromagnetic Fields to Reduce Diabetic Neuropathic Pain and Stimulate Neuronal Repair: A Randomized Controlled Trial. Archives of Physical Medicine and Rehabilitation, 90, 1102-1109. 
https://www.sciencedirect.com/science/article/abs/pii/S0003999309002172
https://doi.org/10.1016/j.apmr.2009.01.019

[16] Cheng, N., Van Hoof, H., Bockx, E., Hoogmartens, M.J., Mulier, J.C., De Dijcker, F.J., Sansen, W.M. and De Loecker, W. (1982) The Effects of Electric Currents on ATP Generation, Protein Synthesis, and Membrane Transport of Rat Skin. Clinical Orthopaedics and Related Research, 171, 264-272. 
https://www.ncbi.nlm.nih.gov/pubmed/7140077
https://doi.org/10.1097/00003086-198210000-00045

[17] Leon, P. and Tim, W. (2009) Bioelectricity and Microcurrent Therapy for Tissue Healing—A Narrative Review. Journal of Physical Therapy Reviews, 14, 104-114. 
https://doi.org/10.1179/174328809X405973

[18] Wishing, P.G., Habrom, A.D., Zehnder, T.M., Friedli, S. and Blatti, M. (2013) Wireless Micro Current Stimulation—An Innovative Electrical Stimulation Method for the Treatment of Patients with Leg and Diabetic Foot Ulcers. International Wound Journal, 12, 693-698. https://doi.org/10.1111/iwj.12204

[19] Lee, B.Y., Al-Waili, N., Stubbs, D., Wendell, K., Butler, G., Al-Waili, T. and Al-Waili, A. (2010) Ultra-Low Microcurrent in the Management of Diabetes Mellitus, Hypertension and Chronic Wounds: Report of Twelve Cases and Discussion of Mechanism of Action. International Journal of Medical Sciences, 7, 29-35. 
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2792735/
https://doi.org/10.7150/ijms.7.29

[20] Sofra, X. and Lampe, N. (2020) Empowering the Woman. A Comprehensive Model of Sexual Anti-Aging. Journal of Nursing, 9, 118-127. 
https://doi.org/10.12968/joan.2020.9.3.118

[21] Biswass, S.K. (2016) Does the Interdependence between Oxidative Stress and In-
flammation Explain the Antioxidant Paradox? Oxydative Medicine and Cellular Longevity. 2016, Article ID: 5698931. https://doi.org/10.4236/health.2020.127054

[22] Anderson, M.T., Staal, F.J., Gitler, C., Herzenberg, L.A. and Herzenberg, L.A. (1994) Separation of Oxidant-Initiated and Redox-Regulated Steps in the NF-κB Signal Transduction Pathway. Proceedings of the National Academy of Sciences of the United States of America, 91, 11527-11531. https://doi.org/10.1073/pnas.91.24.11527

[23] Flohé, L., Brigelius-Flohé, R., Saliou, C., Traber, M.G. and Packer, L. (1997) Redox Regulation of NF-kappa B Activation. Free Radical Biology and Medicine, 22, 1115-1126. https://doi.org/10.1016/S0891-5849(96)00501-1

[24] Adey, W.R. (1980) Frequency and Power Windowing in Tissue Interactions with Weak Electromagnetic Fields. Proceedings of the IEEE, 68, 119-125. https://doi.org/10.1109/PROC.1980.11591

[25] Zhou, S.-A. and Uesaka, M. (2006) Bioelectrodynamics in Living Organisms. International Journal of Engineering Science, 44, 67-92. https://doi.org/10.1016/j.ijengsci.2005.11.001

[26] Oschman, J.L. (2005) Energy and the Healing Response. Journal of Bodywork and Movement Therapies, 9, 3-15. https://doi.org/10.1016/S1360-8592(03)00092-5

[27] Ralston, W.P. (2005) Electron Gated Ion Channels: With Amplification by NH3 Inversion Resonance.

[28] McArthur, J.H. (1998) The Reliability and Validity of the Subjective Peripheral Neuropathy Screen. Journal of the Association of Nurses in AIDS Care, 9, 84-94. https://doi.org/10.1016/S1055-3290(98)80048-4

[29] Freynhagen, R., Baron, R., Gockel, U. and Tölle, T.R. (2006) PainDETECT: A New Screening Questionnaire to Identify Neuropathic Components in Subjects with Back Pain. Current Medical Research and Opinion, 22, 1911-1920. https://doi.org/10.1185/030079906X132488