Nerve Reviver research summary

Our product development road map has been anchored in clinical research. Through the aggregation of the below cited research studies we have formulated our therapy protocols and modalities. We have always believed that proper pain management and therapeutic results are harnessed within a combinational approach to therapy, and that each individual modality will provide an incremental benefit towards A) lowering the pain scale B) providing long-term therapeutic results. Thus when all modalities are used in combination and adjunctively, maximum results prevail.

Nerve Reviver LED Therapy	Nerve Reviver Cold Laser
Nerve Reviver LED Vibration Unit	Wand Nerve Rebuilder Medical Unit

LED - LOW LEVEL LIGHT THERAPY RESEARCH SUMMARY

Desmet KD et al. Clinical and Experimental Applications of NIR-LED Photobiomodulation. Photomedicine and Laser Surgery. 2006, 24(2): 121-128.·

• NIR-LED light represents a novel, noninvasive, therapeutic intervention for the treatment of numerous diseaseslinked to mitochondrial dysfunction.

• In addition, it has been demonstrated that up to 50% of NIR light is absorbed by mitochondrial chromophores,including cytochrome c oxidase

• Human studies using NIR-LED light therapy have demonstrated greater amounts of epithelialization for woundclosure and accelerated healing of skin grafts

• Genes that were down-regulated in NIR-LED light–treated mice include cytokine receptors, interleukin-1,interleukin-10, and macrophage inflammatory protein–2. A decrease in these genes encoding for proteins associatedwith the inflammatory response results in a decrease in pain, which in turn increases the ability oftissue-regenerating proteins to facilitate wound closure.

• NIR-LED light treatment produced a significant reduction in left and right buccal pain (48% and 39%,respectively)

DiDuro J. Neuropathy Patient Satisfaction High with Infrared LED Care.

Proceedings of The 10th AnnualConference of the North American Association for Laser Therapy. 2010.

• 77 patients were surveyed during a course of multimodal care that included IR therapy • After an average of 9.6 visits, 90.1% of patients were satisfied with their care

Medicine. 2000, 27: 427-437

• LLLI caused potent dilation in the laser-irradiated arteriole, which led to marked increases in the arteriolar blood flow.

• As a consequence of these changes, the blood flow (Q) showed a rapid initial increase even

at ~1 minute after LLLI (increase in the early phase), and continued to increase till 30 minutes after LLLI (increase in the

• In conclusion, we have shown that laser irradiation at a wavelength of 830 nm is a potent dilator of the arteriole and consequently causes a marked increase in blood flow in the rat microvascular bed. Nitric oxide seems partly involved in the vasodilation that occurs in the early phase.

Ishiguro M, Ikeda K, and Tomita K. E ect of Near-Infrared Light-Emitting Diodes on Nerve Regeneration. JOrthop Sci. 2010, 15:233-239.

• Our histological study suggests that irradiation with LEDs is advantageous to nerve regeneration. • In this study, LEDs at a wavelength of 660 nm e ectively promoted peripheral nerve regeneration in our rat model. We propose that this is due to the antioxidative e ect induced by LEDs.
• In the 1-mm section, we observed a significant (approx.. 230%) increase in the LED group compared to that for the controls

Lohr NL et al. Enhancement of Nitric Oxide Release From Nitrosyl Hemoglobin and Nitrosyl Myoglobin by Red/Near Infrared Radiation: Potential Role in Cardioprotection.

• The use of far red and near infrared light (R/NIR) can reduce infarct size, protect neurons from methanol toxicity, and stimulate angiogenesis.
• These data suggest that this light source facilitates the release of nitric oxide from nitrosyl heme proteins. • In combination these data suggest that the ability of R/NIR light to liberate nitric NO from tissue stores contributes to cardioprotection and that nitrite, by potentially increasing the size of these NO stores

DeMott TK, Richardson JK, Thies SB, Ashton-Miller JA. Falls and gait characteristics among older persons with peripheral neuropathy. Am J Phys Med Rehabil 2007; 86:125-132.

• Thirteen of 20 (65%) subjects fell, and 6 of 20 (30%) subjects sustained a fall-related injury during the year of observation.
• Injuries resulting from falls cost $6 billion per year in the United States.

Whelan HT, et al. DARPA soldier self care: rapid healing of laser eye injuries with light emitting diode technology. Presented at the RTO HFM Symposium on Combat Casualty Care in Ground Based Tactical Situations: Trauma Technology and Emergency Medical Procedures. 2004.

• Photobiomodulation by light in the red to near infrared range (630-1000 nm) using low energy lasers or light emitting diode (LED) arrays has been shown to accelerate wound healing, improve recovery from ischemic injury and attenuate degeneration in the injured optic nerve.
• The prolonged e ect of brief NIR-LED treatment implies that it induces a cascade of events leading to the stimulation of gene expression, protein synthesis, and oxidative metabolism.
• Assessment of the severity of the laser burn in LED treated and untreated animal demonstrated a greater that 50% improvement in the degree of retinal healing at 1 month post-laser in the LED-treated monkey. • The results of this study and others suggest that photobiomodulation with red to near infrared light augments recovery pathways promoting neuronal viability and restoring neuronal function following injury.

Harkless LB, DeLellis S, Carnegie DH, Burke TJ. Improved foot sensitivity and pain reduction in patients with peripheral neuropathy after treatment with monochromatic infrared photo energy- MIRE. Journal of Diabetes Care and Its Complications 2006; 20:

81-87.
• Prior to treatment with MIRE, of the 10 tested sites (5 on each foot), 7.1 +/- 2.9 were insensitive to the monofilament 5.07, and 2078 patients (93%) exhibited loss of protective sensation defined by Medicare as a loss of sensation at two or more sites on either foot.
• After treatment, the number of insensate sites on both feet decreased to 2.4F2.6, an improvement of 66%. • After MIRE treatment, the mean pain level was reported to be 2.4 +/- 2.1, a mean reduction of 4.8 points, or 67%.

DeLellis SL, Carnegie DH, Burke TJ. Improved sensitivity in patients with peripheral neuropathy: e ects of monochromatic infrared photo energy. Journal of the American Podiatric Medical Association 2005; 95(2): 143-147.
• After treatment, the mean ± SD number of insensate sites on both feet was 2.3 ± 2.4, an improvement of 71%.

• In the case of diabetic peripheral neuropathy, there have been no reports of either spontaneous reversal of this condition or e cacy of any nonsurgical intervention.
• A significant proportion of patients, more than 75%, had well-defined peripheral neuropathy, a condition that would be the least likely to spontaneously reverse or to respond to pharmacologic treatment.

Demura S, Yamaji S, Ikemoto Y. E ect of linear polarized near-infrared light irradiation on flexibility of shoulder and ankle joints. Journal of Sports Medicine and Physical Fitness 2002; 42(4): 438-435. • Ranges of shoulder and ankle motions become greater with infrared irradiation, and is e ective as a warming up method.
• 10% improvement in ankle and shoulder ROM was seen after a single treatment.
• The e ect of therapy is greater in subjects with lower joint ROM than those with higher.

M.T. Wong-Riley, H.L. Liang, J.T. Eells, B. Chance, M.M. Henry, E. Buchmann, M. Kane, and H.T. Whelan, Photobiomodulation directly benefits primary neurons functionally inactivated by toxins: role of cytochrome oxidase. J Biol Chem 2005; 280 (6): 4761–4771.
• Evidence has indicated that near-IR light treatment can prevent cell death (apoptosis) in cultured neuronal cells. • Recent reports have ascribed the ability of specific wavelengths of light to promote cellular proliferation to the activation of mitochondria, the energy-producing organelles within the cell.
• Near-IR treatment can also augment mitochondrial function and stimulate antioxidant protective pathways in specific neurons that o er protection against neuronal degeneration.
• 670nm light pretreatment for 5 minutes (30 J/cm2) twice a day over 3 days attenuated the deficits in locomotor behavior induced by a single injection of MPTP.
• MPTP has the added advantage in that it poisons the very process thought to account for the beneficial actions of near-IR light—namely, mitochondrial energy production.

Ying R, Liang HL, Whelan HT, Eells JT, Wong-Riley MT. Pretreatment with near-infrared light via light-emitting diodes provided added benefit against rotenone and MPP+ induced neurotoxicity. Brain Research 2008; 1243: 167-168.
• The goal was to test our hypothesis that pretreatment with near-infrared light (NIR) via light-emitting diode (LED) had a greater beneficial e ect on primary neurons grown in media with rotenone or MPP+ than those with or without LED treatment during exposure to poisons.
• Results indicate that pretreatment with NIR-LED significantly suppressed rotenone- or MPP+-induced apoptosis in both striatal and cortical neurons ($P<0.001$), and that pretreatment plus LED treatment during neurotoxin exposure was significantly better than LED treatment alone during exposure to neurotoxins. • The mechanism of NIR-LED action is

the up-regulation of cytochrome c oxidase activity and the production of adenosine triphosphate (ATP).

Wong-RileyMT,BaiX,BuchmannE,WhelanHT.Light-emittingdiodetreatmentreverse the e ect of TTX on cytochrome oxidase in neurons. Neurochemistry 2001; 12(14): 3033-3037.

• Light treatment with a light emitting diode array at 670 nm (LED) is therapeutic in stimulating cellular events involving increases in cytochrome oxidase activity.
• 50% of near infrared light is absorbed by mitochondrial chromophores such as cytochrome c oxidase, which is the terminal enzyme of the electron transport chain. Cytochrome oxidase is an integral membrane protein. • The prolonged e ect of a brief LED treatment implies that it induces a cascade of events leading to the stimulation of gene expression, protein synthesis, and oxidative metabolism.
• LED treatment at the parameters used significantly reversed the detrimental e ect of TTX on neuronal cytochrome oxidase activity.t was 2.3 ± 2.4, an improvement of 71%.

Gutierrez EM, Helber MD, Dealva D, Ashton-Miller JA, Richardson JK. Mild diabetic neuropathy a ects ankle motor function. Clinical Biomechanics 2001; 16: 522-528.

• Diabetic neuropathy leads to a decrease in rapidly available ankle strength which impairs balance recovery among older women. Younger women demonstrate similar ankle strength but superior balance recovery compared to older women without neuropathy.
• Others have found that ankle strength is important to balance. Wolfson et al also noted that ankle strength in nursing home residents with a history of falls was about one tenth that of controls, and that loss of balance during sensory organization test correlated with decreased ankle plantar and dorsiflexion strength. • Furthermore, decreased ankle strength has been prospectively identified as a risk factor for falls by Sorock and Labiner.

Bulgher D. Forward of Proceedings of the Second International Conference on Near-Field Optical Analysis: Photodynamic Therapy and Photobiology 2001.

• Astronaut and cosmonaut experiences have indicated that normal healing of superficial skin wounds is retarded similar to the delayed healing observed during long-term submerged operations on submarines. Photodynamic therapy using near infrared (NIR) light has been shown to enhance wound repair via several molecular mechanisms, involving absorption by cytochrome C in the mitochondria, enhancement of intracellular signalling, gene expression and subsequent cytokine secretions.

WhelanHT.TheuseofNASAlight-emittingdiodenear-infraredtechnologyforbiostimulation. Proceedings of the Second International Conference on Near-Field Optical Analysis: Photodynamic Therapy and Photobiology 2001. 32-39.

• Optimal LED wavelengths include 680, 730 and 880 nm
• Near-IR induced a thirty percent increase in the rate of wound closure in these animal models. • Light-emitting diodes (LEDs) developed for NASA crewed spaceflight experiments o er an e ective alternativeto lasers.Thesediodescanbemadetoproducemultiplewavelengths,andcanbe arranged in large, flat arrays allowing treatment of large wounds.
• 20% reduction in pain observed when LEDs used on Navy SEAL subjects

Caviness J, Esquilin J, Whelan H. E ect of NASA light-emitting diode on wound healing aboard submerged submarines. Proceedings of the Second International Conference on Near-Field Optical Analysis: Photodynamic Therapy and Photobiology 2001.

• It is an accepted condition of service aboard U.S. Navy submarines that wounds, burns, and

lacerations heal more slowly during submerged operations at sea than they would normally heal if not on board the submarine. • The actual analysis of the photographs showed 40% faster healing for the injury treated for 10 days.

Whelan HT, et al. E ect of NASA light-emitting diode irradiation on molecular changes for wound healing in diabetic mice. Journal of Clinical Laser Medicine and Surgery 2003; 21(2): 67-74.

• The use of NASA light-emitting diodes (LED) for light therapy will greatly enhance the natural wound healing process, and more quickly return the patient to a preinjury/illness level of activity.
• In our study, type 2 diabetic mice with excisional skin wounds were treated with LEDs at individualwavelengthsof 680nm,730nm,and880nmat4J/cm2and50mW/cm2.LED treatment produced increased healing rates, compared to surgical controls.
• 25% decrease in wound size in treatment group compared to surgical controls.

Whelan HT, et al. E ect of NASA light-emitting diode irradiation on wound healing. Journal of Clinical Laser Medicine and Surgery 2001; 19(6): 305-314.

• LED produced in vitro increases of cell growth of 140–200% in mouse-derived fibroblasts, rat-derivedosteoblasts, andrat-derivedskeletalmusclecells,andincreasesingrowthof 155–171% of normal human epithelial cells.
• LED produced improvement of greater than 40% in musculoskeletal training injuries in Navy SEAL teammembers, anddecreasedwoundhealingtimeincrewmembersaboardaU.S.Naval submarine. LED produced a 47% reduction in pain of children su ering from oral mucositis.

Zhang R, et al. Near infrared light protects cardiomyocytes from hypoxia and reoxygenation injury by a nitric oxide dependent mechanism. J Mol Cell Cardiol 2009; 46(1)

• Our results demonstrate that exposure to NIR at the time of reoxygenation protects neonatal rat cardiomyocytes and HL-1 cells from injury.
• The protective e ect of NIR is related to NO
• NIR increases NO, partially independent of NOS
• Mitochondria have been identified as trigger and e ector organelles in cardioprotection by ischemic and pharmacologic preconditioning and postconditioning [46]. COX (complex IV) is the terminal component of the electron transport chain, oxidizing its electron donor cytochrome c and reducing oxygen to water. It has been recognized as a photoreceptor in the NIR range with absorption peaks at 680, 760 and 820 nm, and implicated to be directly involved in photobiomodulation [14,15,48,49]. NIR at 670 and 830 nm partially reversed COX activity in primary neurons after inhibition with KCN, an inhibitor of complex IV. These actions resulted in preserved cellular ATP content and decrease in neuronal death [14].

Swislocki A, et al. A randomized clinical trial of the e ectiveness of photon stimulation on pain, sensation, and quality of life in patients with diabetic peripheral neuropathy. Journal of Pain and Symptom Management 2010; 39(1): 88-99.

• Significant decreases, over time, were found in some pain quality scores, and significant improvements in sensation were found in patients who received the treatment.
• 76.2% of IR therapy group reported improvement compared to 53.4% of the placebo group. (Treatment group nearly 23% more likely to report decreased pain than placebo)

Prendergast JJ, Miranda G, Sanchez M. Improvement of sensory impairment in patients with peripheral neuropathy. Endocrine Practice 2004; 10: 24-30.

• All patients obtained improvement in sensory impairment in comparison with baseline CPT measures, and 16 of the 27 patients achieved normal sensory responses in all nerve fiber subpopulations.

• The SWM test is widely used, and the failure to sense the SWM 5.07 is clinically recognized as highly predictive of foot ulceration and lower extremity amputation
• Average reduction in VAS pain scale was from 8 to 3.
• In the medical literature, however, no evidence suggests that DPN spontaneously reverses.
• Because enhanced circulation is produced by some near-infrared devices as well as the ATS system, a microcirculatory increase seems to be the most plausible mechanism of action with respect to improvement in sensory perception noted in this study

Leonard DR, Farooqi MH, Myers S. Restoration of sensation, reduced pain, and improved balance in subjects with diabetic peripheral neuropathy. Diabetes Care 2004. 27: 168-172.
• Nearly 50% pain reduction noted after 12 treatments
• At entry 90% of subjects reported substantial balance impairment, after treatment this decreased to 17%.

Powell MW, Carnegie DE, Burke TJ. Reversal of diabetic peripheral neuropathy and new wound incidence: the role of MIRE. Adv Skin Wound Care 2004; 17: 295-300.
• After reversal of diabetic peripheral neuropathy following treatment with infrared therapy, only 1 in 68 patients studied developed a new diabetic foot wound.
• This was an incidence of 1.5% compared to 7.3% in the diabetic population

Powell MW, Carnegie DH, Burke TJ. Reversal of diabetic peripheral neuropathy with phototherapy (MIRE) decreases falls and the fear of falling and improves activities of daily living in seniors. Age and Ageing 2006; 35: 11-16.
• Overall, reversal of peripheral neuropathy in a clinician's o ce and subsequent use of MIRE™ at home was associated with a 78% reduction in falls, a 79% decrease in balance-related fear of falling and a 72% increase in ADLs.

Kochman AB, Carnegie DH, Burke TJ. Symptomatic reversal of peripheral neuropathy in patients with diabetes. Journal of the American Podiatric Medical Association 2002; 92(3): 125-130.
• On the basis of Semmes-Weinstein monofilament values, 48 subjects (98%) exhibited improved sensationafter6 treatments,andallsubjectshadimprovedsensationafter12treatments.
• After 12 MIRE treatments, 9 of 12 (75%) subjects with type 1 diabetes converted from impaired hot- versus - cold sensation to an intact ability to discriminate hot from cold (Table 1), and 4 of 11 (36%) subjects with type 2 diabetes were able to discriminate hot versus cold after 12 MIRE treatments.

Arnall DA et al. The restorative e ects of pulsed infrared light therapy on significant loss of peripheral protective sensation in patients with long-term type 1 and type 2 diabetes mellitus. Acta Diabetol 2006; 43: 26-33.
• PILT improved PPS even in patients with long-standing chronic neuropathies whose initial pre-study sensation was not measurable with a 200-g SWM. PILT significantly improves PPS.

LASER THERAPY RESEARCH

Ihsan MFR. Low-level laser therapy accelerates collateral circulation and enhances microcirculation. Photomedicine and Laser Surgery 2005; 23(3): 289-294.
• The results indicated that LLLT accelerated collateral circulation and enhanced microcirculation

and seemed to be unique in the normalization of the functional features of the injured area, which could lead to occlusion of the regional blood vessels.
• Numerous collateral blood vessels proliferated the area, with marked increases in the diameters of the original blood vessels.
• Low-level lasers also activate ATP, ATPase, and the conversion of adenosine triphosphate to adenosine.Adenosine stimulatestheconversionofcAMPtonitricoxide(NO)orthevascular endothelial growth factor (VEGF). • Adenosine, Growth Hormone, Fibroblast Growth Factor, and VEGF are angiogenic factors and promote new vessel growth in the same manner

Schindl A et al. Low-intensity laser irradiation improves skin circulation in patients with diabetic microangiopathy. Diabetes Care 1998; 21(4): 580-584.
• The data from this first randomized double-blind placebo-controlled clinical trial demonstrate an increaseinskin microcirculationduetoathermiclaserirradiationinpatientswithdiabetic microangiopathy.

Karu TI, Pyatibrat LV, Afaanasyeva NI. Cellular e ects of low power laser therapy can be mediated by nitric oxide. Lasers in Surgery and Medicine 2005; 36: 307-314.
• NO2 is involved in the radiation-induced mesenteric arteriolar vasodilatation and the subsequent increase in the microcirculatory blood flow. Irradiation at di erent wavelengths induces vasodilatation in blood-perfused vessels but not in saline-perfused ones. It was suggested that NO2–hemoglobin might serve as a light-sensitive store of NO2 in red blood cells from which it was released by irradiation

VIBRATION THERAPY RESEARCH

Maloney-Hinds C, Petrofsky JS, Zimmerman G. The e ect of 30 Hz vs. 50 Hz passive vibration and duration of vibration on skin blood flow in the arm. Med Sci Monit 2008; 14(3): 112-116.
• 5-minutes of 30 Hz or 50 Hz vibration produced significant increases in SBF. Clinically, 50 Hz has additional benefits because SBF increased more rapidly and did not result in vasoconstriction during the recovery period. • The fifth minute of vibration yielded the greatest increases in flow with a mean of 360% in the 30 Hz group and a mean of 511% in the 50 Hz group.
• Clinically these increases (in blood flow) would be beneficial to many populations especially those withdiabetes. Overtime,TypeIIdiabetescanleadtoautonomicnervoussystemdamagewhich can lead to circulatory problems which can lead to ulcerations. Methods which may increase circulation may aid in wound healing in these populations.

Bovenzi M, Gri n MJ, Ru ell CM. Acute e ects of vibration on digital circulatory function in healthy men. Occupational and Environmental Medicine 1995; 52: 834-841.
• Acute vibration can induce significant changes in the blood flow and skin temperature

Figueroa A, Vicil F, Sanchez-Gonzalez MA. Acute exercise with whole-body vibration decreases wave reflection and leg arterial sti ness. Am J Cardiovascular Dis 2011; 1(1): 60-67.
• Whole-body vibration exercise (WBV) acutely decreases brachial-ankle pulse wave velocity (baPWV), an index of systemic arterial sti ness.
• The decrease in wave reflection magnitude was due to vasodilation of peripheral arteries.
• Thus, the prolonged decrease in leg PWV after WBV exercise could be attributed mainly to the local e ect of vibration on the leg arteries.

Otsuki T, Takanami Y, Aoi W, Kawai Y, Ichikawa H, Yoshikawa T. Arterial sti ness acutely decreases after whole-body vibration in humans. Acta Physiol 2008; 194: 189-194.

• WBV acutely decreases arterial sti ness.
• WBV is feasible not only in healthy humans but also in vulnerable populations such as elderly nursing home residents and immobilized patients, such as those with osteogenesis imperfect.
• Increased arterial sti ness is an independent risk factor for the development of atherosclerosis and cardiovascular disease.
• Previous studies have demonstrated that pharmacological inhibition of nitric oxide synthase increased arterial sti ness in humans, suggesting that nitric oxide participates in the regulation of arterial sti ness. • The mechanical influences of WBV on artery may be related to endothelial function and to the acute decreases in arterial sti ness.

Zhang Q, Ericson K, Styf J. Blood flow in the tibialis anterior muscle by photoplethysmography during foot-transmitted vibration. Eur J Appl Physiol 2003; 90: 464-469.

• This made it possible to detect a relative increase in MBF of 20% during an acute vibration exposure. • The ease of use and simplicity of equipment for measurements of MBF by PPG are unrivalled by other methods. • In the present study, MBF increased with time of exposure to vibration and it did not return to the baseline immediately after vibration.

Stewart JM, Karman C, Montgomery LD, McLeod KJ. Plantar vibration improves leg fluid flow in perimenopausal women. Am J Physiol Regul Integr Comp Physiol 2005; 288: 623-629.

• The results suggest that plantar vibration serves to significantly enhance peripheral and systemic blood flow, peripheral lymphatic flow, and venous drainage.

• However, calf blood flow increased during plantar stimulation in the upright position (from 1.2 +/- 0.2 at 0 Hz, to 1.6 +/- 0.4 at 15 Hz, and to 1.8 +/- 0.4 ml per 100 ml per min at 45 Hz)
• This represents 33% increase in blood flow at 15 Hz vibration and a 50% increase at 45 Hz.

Yamada E et al. Vastus lateralis oxygenation and blood volume measured by near-infrared spectroscopy during whole body vibration. Clin Physiol Funct Imaging 2005; 25: 203-208.

• The way to reduce TPR (total peripheral resistance) during vibration would be opening more capillaries or dilating some vessels or both. This would increase the total surface area of the micro-vessels in the muscles. Thus, the gas and material metabolism between the blood and the muscle fibres would be improved. This gives at least a hint to the mechanism for various potential benefits associated with vibration training.
• As a reaction of compensation, more capillaries are probably opened in order to keep a necessary level of cardiac output needed for the body, resulting in more e cient gas and material metabolism between the blood and muscle fibres. This might be one of the reasons for the various potential beneficial e ects of vibration training.

Herrero AJ, et al. Whole-body vibration alters blood flow velocity and neuromuscular activity in Friedrich's ataxia. Clin Physiol Funct Imaging 2010.

• The results of this study suggest that higher frequencies (30 Hz) produce a greater increase in blood flow velocity and rate of perceived exertion.
• Moreover, this study provides evidence that a high frequency of vibration (30 Hz) generated moreneuromuscular activationthanalowfrequency(10Hz).Increasingfrequencyproduced

systematic increases in leg blood flow velocity, EMG and RPE. These findings suggest that greater frequencies may be used during WBV treatment to elicit a greater neuromuscular stimulus.

Lythgo N, Eser P, de Groot P, Galea M. Whole-body vibration dosage alters leg blood flow. Clin Physiol Funct Imaging 2009; 29: 53-59.
• Compared to the non-vibration bouts, frequencies of 10–30 Hz increased mean blood cell velocity by approximately 33% (P<0Æ01) whereas 20–30 Hz increased peak blood cell velocity by approximately 27% (P<0Æ01).
• Vibration may lead to an increase in shear forces at the vascular endothelium due to the inertia of the blood. • Endothelial-derived vasodilators such as nitric oxide and prostaglandins are thought to be released as a response to increased shear forces at the vascular endothelium.

Kerschan-Schindl et al. Whole-body vibration exercise lead to alterations in muscle blood volume. Clinical Physiology 2001; 21(3): 377-382.
• The mean blood flow velocity in the popliteal artery increased from 6.5 to 13.0 cm s -1 and its resistive index was significantly reduced.
• This study showed that WBV doubled blood flow to the legs.
• The results indicate that low-frequency vibration does not have the negative e ects on peripheral circulation known from occupational high-frequency vibration.

Trans T, Aaboe J, Henriksen M, Christensen R, Bliddal H, Lund H. E ect of whole body vibration exercise on muscle strength and proprioception in females with knee osteoarthritis. The Knee 2009; 16: 256-261. • This study showed that the WBV-exercise regime on a stable platform yielded increased muscle strength, while the WBV-exercise on a balance board showed improved threshold for detection of passive movement (TDPM), a measure of proprioception.
• Vibrations elicit a response called “tonic vibration re fl ex”, including activation of muscle spindles, mediation of the neural signals by Ia a erents, and activation of muscle fi bres via large α-motor neurons. The tonic vibration reflex is also able to cause an increase in recruitment of the motor units through activation of muscle spindles and polysynaptic pathways.

• It is well known that the input of proprioceptive pathways (Ia, IIa and probably IIb) play an important role in the production of isometric contractions.

Sanduo B et al. E ect of whole-body vibration exercise on balance in women with fibromyalgia syndrome: a randomized controlled trial. The Journal of Alternative and Complementary Medicine 2012; 18(2): 158-164. • Women with FM may increase their mediolateral stability index (MLSI) by engaging in a 6-week traditional exercise program with supplementary WBV. This may have implications for falls prevention in this patient group. • After the intervention period participants who exercised with WBV improved postural balance (MLSI) by42.63% witheyesopenand25.57%witheyesclosed.
• Large improvements in balance were found, which may indicate that WBV training can have a relatively quick and positive influence on the proprioceptive system in FM.

Bogaerts A, Verschueren S, Delecluse C, Claessens AL, Boonen S. E ects of whole body vibration training on postural control in older individuals: a 1 year randomized controlled trial. Gait and Posture 2007; 26: 309-316. • Whole body vibration training was associated with reduced falls frequency on a moving platform when vision was disturbed and improvements in the

response to toes down rotations at the ankle induced by the moving platform. • Thus, whole body vibration training may improve some aspects of postural control in community dwelling older individuals.
• The mechanical stimuli are transmitted to the body where they stimulate the primary endings of the muscle spindles which in turn activate alpha-motor neurons resulting in muscle contractions. Previous studies have shown that WBV is associated with increases in lower limb muscle strength which is essential for postural stability. Because WBV provides a strong sensory stimulus that activates the muscle spindles, it might also enhance proprioception.

Cheung WH et al. High-frequency whole-body vibration improves balancing ability in elderly women. Arch Phys Med Rehabil 2007; 88: 852-857.
• WBV was e ective in improving the balancing ability in elderly women. This also provides evidence to support our user-friendly WBV treatment protocol of 3 minutes a day for the elderly to maintain their balancing ability and reduce risks of fall.
• Movement velocity improved from 14.96 in the control group to 53.49 in WBV group
• Maximum point excursion improved from 3.36 to 18.84
• Because these functional parameters involve the ability to recruit muscle fibers, muscular adaptation, and neuromuscular coordination, these improvements indicate that WBV would be e ective in enhancing neuromuscular rehabilitation.

Gusi N, Parraca JA, Olivares PR, Leal Alejo, Adsuar JC. Tilt vibratory exercise and the dynamic balance fibromyalgia: a randomized controlled trial. Arthritis Care and Research 2010; 62(8): 1072-1078. • Based on ITT analysis, the dynamic balance of the vibration group improved by 36% as compared with baseline, whereas that of the control group was unchanged.
• Changes in performance on timed up-and-go and Tinetti-test (for body balance and total score) were significantly better for the WBV+ compared to the control group (p = 0.029 for timed up-and go, p = 0.001 and p = 0.002 for Tinetti body balance and total score respectively). In fact, subjects of the WBV+ group improved significantly on the timed up-and-go test (p = 0.008), whereas no change was observed in the controls. • 27.5% improvement in timed get-up and go

Spiliopoulou SI, Amiridis IG, Tsiganos G, Economides D, Kellis E. Vibration e ects on static balance and strength. Int J Sports Med 2010; 31: 610-616.
• After vibration training, postural sway significantly decreased in both directions for the vibration group in all tasks • See graphic on next page:

Pang MYC. Whole body vibration therapy in fracture prevention among adults with chronic disease. World Journal of Orthopedics 2010; 1(1): 20-25.
• WBV therapy is also proposed to have potential therapeutic e ects on muscle strength and other important sensorimotor functions such as postural control

Bruyere O et al. Controlled whole body vibration to decrease fall risk and improve health-related quality of life of nursing home residents. Arch Phys Med Rehab 2005; 86: 303-307.
• After 6 weeks, the vibration intervention group improved by a mean standard deviation of 2.4 +/- 2.3 points on the gait score compared with no score change in the control group (P _.001).
• The intervention group improved by 3.5 +/- 2.1 points on the body balance score (40% increase) comparedwitha decreaseof0.3_1.2pointsinthecontrolgroup(P_.001).
• Timed get up and go test time decreased by 11.0 +/- 8.6 seconds in the treated group (43%improvement) comparedwithanincreaseof2.6+/-8.8secondsinthecontrol

group (P _.001).
• The intervention group had significantly greater improvements from baseline on 8 of 9 items on the SF-36 compared with the control group.

Bautmans I, Van Hees E, Lemper JC, Mets T. The feasibility of whole body vibration in institutionalized elderly persons and its influence on muscle performance, balance, and mobility: a randomized controlled trial. BMC Geriatrics 2005; 5(17)
• In nursing home residents with limited functional dependency, six weeks static WBV exercise is feasible, and is beneficial for balance and mobility.
• 27.5% increase in timed get up and go test
• 25.7% increase in 30 second chair stand balance test

ELECTROSTIMULATION RESEARCH

Julka IS, Alvaro M, Kumar D. Beneficial e ects of electrical stimulation on neuropathic symptoms in diabetes patients. Journal of Foot and Ankle Surgery 1998; 37(3): 191-198.
• Forty-one (76%) patients reported a 44.0 ± 4.0% subjective improvement in their neuropathic pain. The overall improvement in pain was also significant on an analog scale of 10 (p < .01), and correlated well with the percent amelioration data (12 =.65). These data suggest an e ectiveness of electrotherapy in managing neuropathic pain as an adjunct to the analgesics.
• A significantly higher incidence of ulcers of feet was seen in the treatment failure group (p < .03). Four of the 10 patients in the treatment failure group and 2 of 24 electrotherapy responders had ulcers .

Kumar D, Marshall HJ. Diabetic peripheral neuropathy: amelioration of pain with transcutaneous electrostimulation. Diabetes Care 1997; 20(11): 1702-1705.
• In the electrotherapy group (n = 18), symptomatic improvement was seen in 15 (83%) cases, 3 of which were completely asymptomatic.T
• The pain score declined from 3.17 ± 0.12 to 1.44 ± 0.25 (P < 0.01) and the posttreatment pain scores were considerably lower (P < 0.03), indicating a substantial treatment e ect over and above any placebo influence. • Patients in the electrotherapy group reported greater reduction in symptoms (52 ± 7% vs. 27 ± 10% in control subjects, P < 0.05) on an analog scale.

Dubinsky RM, Miyasaki JM. Assessment: e cacy of transcutaneous electric nerve stimulation in the treatment of pain in neurologic disorders (an evidence-based review). Neurology 2010; 74: 173-176. • TENS should be considered in the treatment of painful diabetic neuropathy
• Two Class II studies compared TENS to TENS-sham, and 1 Class III study compared high-frequency muscle stimulation to TENS in the relief of pain associated with mild diabetic peripheral neuropathy (distal symmetric neuropathy, excluding patients with mononeuropathies and plexopathies).
• A modest reduction in VAS was found for TENS compared to TENS-sham, and a larger proportion felt benefit with the high frequency muscle stimulation compared to TENS.

Hamza et al. Percutaneous electrical nerve stimulation: a novel analgesic therapy for diabetic neuropathic pain. Diabetes Care 2000; 23: 365-370.
• Compared with the pain VAS scores before active (6.2 ± 1.0) and sham (6.4 ± 0.9) treatments, pain scores after treatment were reduced to 2.5 ± 0.8 and 6.3 ± 1.1, respectively.
• 60% reduction in pain noted with TENS.

• Active PENS treatments produced significant pain relief, increased levels of mood and physical activity, and improved quality of sleep compared with the sham treatments during the course of the 3-week treatment period. • Although the precise mechanism of PENS-induced analgesia is not known at this time, it appears to be related to both neural modulation and an increase in endogenous opioid-like substances (e.g., dynorphins, endorphins, enkephalins) within the central nervous system.
• Interestingly, both Cameron et al. and Mo et al. have reported that peripheral electrical stimulation can normalize the changes in nerve conduction velocity when using an experimental diabetic rat model. • Walsh et al. also observed a decrease in nerve conduction latency and mechanical pain threshold when TENS was applied directly over the nerve.
• In addition, clinical studies have suggested that the use of electrotherapy in diabetic patients produces decreases in mechanical pain threshold, a local vasodilatory e ect, and enhanced wound healing.

Somers DL and Clemente FR. Contralateral high or a combination of high and low-frequency transcutaneous electrical nerve stimulation reduces mechanical allodynia and alters dorsal horn neurotransmitter content in neuropathic rats. The Journal of Pain 2009; 10(2): 221-229.
• Daily, high frequency or a combination of high- and low-frequency TENS reduced mechanical (P < .001), but not thermal allodynia in the right hind paw when compared with untreated CCI rats.
• Daily high frequency TENS elevated the dorsal horn synaptosomal content of GABA bilaterally (P < .014) and a combination of high- and low-frequency TENS elevated the dorsal horn content of aspartate (P < .001), glutamate (P < .001) and glycine (P < .001) bilaterally over that seen in untreated CCI rats.
• The present findings support a contralateral approach to the application of TENS and suggest that distinct strategies for TENS application may di erentially alter neurotransmission in the central nervous system.

Reichstein L, Labrenz S, Ziegler D, Martin S. E ective treatment of symptomatic diabetic polyneuropathy by high-frequency external muscle stimulation. Diabetologia 2005; 48: 824-828.
• This pilot study shows, for the first time, that HF can ameliorate the discomfort and pain associatedwithDSP,andsuggeststhatHFismoreeectivethanTENS.
• Subgroup analysis revealed that HF was more e ective than TENS in relieving the symptoms of non-painful neuropathy(HF100%,sevenoutofseven;TENS:44%,fouroutofnine;p<0.05)and painful neuropathy (HF: 69%, nine out of 13; TENS: 25%, three out of 12; p<0.05).

Kloth LC. Electrical stimulation for wound healing: a review of evidence from in vitro studies, animal experiments, and clinical trials. Lower Extremity Wounds 2005; 4(1): 23-44.
• Electrically induced acceleration of the closure of wounds caused by nonischemic diabetic neuropathy has been demonstrated in 4 studies, including 2 randomized controlled clinical trials.

• In a randomized controlled trial, Lundeberg et al evaluated the e ect of biphasic asymmetric PC onwoundhealing. Sixtyfourpatientswithchronicdiabeticneuropathicfootulcerswere randomized to receive either active ES (parameters not given) or sham control ES for 20 minutes twice a day for 12weeks in addition to standard wound care. Polarity of the treatment electrode was changed each session. After 12 weeks, there was a statistically significant treatment e ect based on the closure of 42% of wounds in the active ES group compared to 15% of the controls.
• Baker et al 144 conducted a randomized trial involving 80 individuals with diabetes and 114 open

wounds.Wounds wererandomizedtobetreatedeitherwithsymmetricalorbiphasicasymmetrical PC plus standard care or with standard care alone. The authors demonstrated that both waveforms combined with standard care enhanced the wound-healing rate by nearly 60% over control wounds treated with only standard care.

Jin DM, Xu Y, Geng DF, Yan TB. E ect of transcutaneous electrical nerve stimulation on symptomatic diabetic peripheral neuropathy: a meta-analysis of randomized controlled trials. Diabetes Research and Clinical Practice 2010; 89: 10-15.

• The reductions in mean pain score were significantly greater in TENS group than in placebo TENS group in 4 weeks and 6 weeks follow-up.
• TENS therapy was associated with significantly subjective improvement in overall neuropathic symptoms in 12 weeks follow-up.
• It is reported that the annual cost of DPN together with its complications in the US varies between 4.6 billion and 13.7 billion dollars.
• Kumar et al. reported that 16.6–36% of patients in TENS group even had complete pain relief. • A clinical study, which evaluated the e ect of the di erent frequency of the electrical stimulus of TENS on the postoperative pain, illustrated that TENS at mixed (2 Hz and 100 Hz) frequencies of stimulation produced a slightly greater analgesic e ect than either low (2 Hz) or high (100 Hz) frequencies alone. It implies that the stimulation frequency played an important role in TENS treatment.
• Experimental study has demonstrated that electrical stimulation could improve endoneurial blood flow and normalize deficits in nerve conduction velocity. Several clinical studies showed that a good clinical response with improvement of peripheral circulation was achieved in the stimulated field, and that may be related to the increased endogenous opioid-like substances (e.g. endorphins, encephalin) within the central nervous system, which inhibit the transmission of painful stimuli by closing the 'gate' to pain transmission by C fibres.

Somers DL and Somers MF. Treatment of neuropathic pain in a patient with diabetic neuropathy using transcutaneous electrical nerve stimulation applied to the skin of the lumbar region. Physical Therapy 1999; 79: 767-775.

• For several reasons, such an alternative electrode placement might be desirable when TENS is used to treat people with painful diabetic neuropathy.
• First, large diameter myelinated nerve fibers may be damaged in the painful extremities of people with severe diabetic neuropathy. Because activation of large-diameter myelinated nerve fibers is believed to be the mechanism by which high-frequency TENS produces analgesia the modality may be more e ective for people with severe neuropathy if it is delivered through undamaged peripheral nerves.
• Another reason to consider not placing the electrodes on the painful extremity is the concern for integument integrity. Because vascular insu ciency so often a ects the extremities of people with diabetes skin breakdown is a common occurrence and an important concern. Although there is no evidencethatTENScausesskin breakdown,themostprevalentsideeectofTENSwhenusedfor pain relief is skin irritation. • Consequently, it may be desirable to avoid placing the TENS electrodes on an involved extremity of a person with diabetes. Such a strategy also may be prudent when diabetic neuropathy results in diminished pain and temperature sensation, a frequent occurrence in the a ected limb of people with diabetic neuropathy. • Following 20 minutes of TENS on the first day
of treatment, the patient reported a 38% reduction in intensity of pain. After 17 days, the patient reported no pain following 20 minutes of TENS and that she could sleep through the night.

Wikstrom SO, Svedman P, Svensson H, Tanweer AS. E ect of transcutaneous nerve stimulation on microcirculation in intact skin and blister wounds in healthy volunteers. Scand J Plast Reconst Hand Surg 1999; 33: 195-201.

• The mean blood flow increased by 40% during low frequency TENS and by 12% during high frequency TENS. • The microcirculatory blood flow, measured as red blood cell velocity (RBC-V) in 5–14 individual capillaries in each wound, was assessed before and during 45 minutes of TENS (2 Hz and 100 Hz). Mean RBC-V increased by 23% during low frequency TENS (n = 6) and by 17% during high frequency TENS (n = 8).

Khalil Z, Merhi M. E ects of aging on neurogenic vasodilator responses evoked by transcutaneous electrical nerve stimulation: relevance to wound healing. Journal of Gerontology 2000; 55A (60): B257-B263. • Using the healing endpoint as the time when full wound contraction occurred, the active group required 14.7 +/- 0.2 days for complete healing, a significant improvement over the sham group (21.8 +/- 0.3 days). • We contend that low-frequency TENS can improve the vascular response of old rats. In addition, wound healing in aged rats can be accelerated by peripheral activation of sensory nerves at low-frequency electrical stimulationparameters.