

Review

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Review

Mechanisms of Action of Low-Frequency Pulsed Magnetic Fields in Peripheral Nerve Regeneration

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Abstract

Peripheral nerve regeneration remains one of the most difficult clinical problems in neuropathy management, and no currently approved treatment reliably restores nerve structure once damage has occurred. Low-frequency pulsed magnetic fields (LFPMFs) have attracted interest primarily as an analgesic modality, culminating in FDA clearance of a magnetic peripheral nerve stimulation (mPNS) device for painful diabetic neuropathy. However, accumulating preclinical data suggest that LFPMFs may act on the biological determinants of nerve repair, not merely on pain transmission. This review organizes those mechanisms chronologically. Early effects center on the endoneurial microvasculature: LFPMF exposure promotes release of FGF-2 and VEGF from endothelial cells, drives arteriolar dilation, and stimulates capillary neogenesis, restoring oxygen delivery to ischemic nerve segments. These vascular changes are especially relevant in diabetic neuropathy and peripheral vascular disease, where endoneurial ischemia drives progressive fiber loss. Later effects involve Schwann cell proliferation, downregulation of neuroinflammatory cytokines, upregulation of BDNF, NGF, and GDNF, and acceleration of axonal sprouting through calcium-dependent intracellular signaling. Notably, the Brown et al. trial of high-intensity mPNS reported a 53% reduction in numbness—a finding that cannot be explained by analgesia alone and raises the possibility that clinical-grade devices may drive structural regeneration. Whether the regenerative mechanisms identified with lower-power devices translate to, or are amplified by, high-intensity mPNS remains an open and important question.

Keywords: low-frequency pulsed magnetic fields; LFPMF; nerve regeneration; microvascular; angiogenesis; Schwann cells; myelin sheath; neurotrophic factors; peripheral vascular disease; diabetic neuropathy

1. Introduction

Neuropathy is common, often inadequately treated, and carries a substantial burden for patients and healthcare systems alike. Whether the cause is diabetes, trauma, chemotherapy, or ischemic vascular disease, the shared clinical problem is the same: peripheral nerves that have been damaged do not reliably heal, and the treatments available address symptoms rather than the underlying structural deficit. Current pharmacological options for neuropathic pain—anticonvulsants, serotonin-norepinephrine reuptake inhibitors, opioids—provide only partial and often poorly tolerated relief. Nothing in routine clinical use promotes the axonal regrowth, remyelination, and target reinnervation that would constitute genuine recovery.

Low-frequency pulsed magnetic fields (LFPMFs)—electromagnetic fields delivered at 0.5 to 100 Hz—have moved from experimental curiosity to clinical reality faster than most would have predicted a decade ago. In a prior publication, we described the mechanisms by which LFPMFs, implemented clinically as magnetic peripheral nerve stimulation (mPNS), produce neuronal blockade and central nervous system reconditioning to relieve chronic neuropathic pain [1,2]. The subsequent FDA clearance of an mPNS device for painful diabetic neuropathy was a significant milestone, not least because it occurred in a patient population that has historically responded poorly

to available therapies [2]. What that clearance also did, however, was draw attention to a question that the pain literature had largely not asked: are the effects of LFPMFs on peripheral nerves limited to modulating pain transmission, or do they extend to the cellular and structural processes of nerve repair?

The answer, as this review will argue, is that they likely do. The physical advantage of magnetic over electrical stimulation—tissue penetration without attenuation by the high-impedance stratum corneum—gives LFPMFs access to endoneurial vessels and nerve fibers that surface electrical modalities cannot reach [1]. This makes them potentially well suited to addressing the two core obstacles to peripheral nerve regeneration: ischemia of the endoneurial microvasculature and failure of Schwann cell-mediated remyelination. We review the evidence for each in sequence, from early vascular effects through to later cellular and molecular events, and consider what existing clinical data tell us about whether these mechanisms operate at the field intensities used in current practice.

1.1. Characteristics and Comparative Benefits of LFPMFs

1.1.1. Frequency and Field Properties

LFPMFs are characterized by their operating frequency (0.5 to 100 Hz), pulsed rather than continuous waveform delivery, and field strengths spanning from 0.05 mTesla in wound-healing applications to up to 1.6 Tesla in mPNS devices designed to produce action potentials in peripheral nerves [1,3]. The pulsed nature of the field is critical to its biological effects: the time-varying magnetic field induces localized electric fields in conductive biological tissues in accordance with Faraday's law, enabling interaction with ion channels, cell membranes, and intracellular signaling cascades without direct tissue contact [1].

In the context of nerve regeneration, the field strength and frequency determine which cellular populations are most affected. Lower intensities (1 to 100 mT) at frequencies of two to 50 Hz have been demonstrated to exert robust effects on endothelial cells, Schwann cells, and neural progenitors, making them relevant to the microvascular and remyelination events discussed below [3–5]. Higher field strengths employed by mPNS devices primarily target larger myelinated axons for conduction blockade and functional reconditioning. The critical distinction between regenerative LFPMF applications and analgesic mPNS is therefore one of field intensity and clinical intent, though the same fundamental electromagnetic principles underlie both.

1.1.2. Benefits of Magnetic Stimulation Modalities

Polson was the first to report magnetic stimulation of peripheral nerves in 1982, demonstrating the painless nature of magnetic stimulation and the ability of these fields to stimulate deep nerves [20]. A magnetic field can penetrate tissues far more deeply than electric fields, which are heavily attenuated by the high-resistance stratum corneum and underlying tissues. The magnetic field also provides a broader and more homogeneous field distribution, passing through tissues relatively uniformly regardless of tissue type or resistance. In addition, LFPMF therapy is entirely non-invasive, requiring no skin contact and eliminating concerns about electrode placement or skin irritation [1].

2. Early Mechanisms: Microvascular Changes and Peripheral Vascular Effects

2.1. Endoneurial Microcirculation and Initial Vascular Response

The earliest detectable response to LFPMF exposure in neural tissues involves changes in the microvasculature. Peripheral nerves depend on a delicate endoneurial blood supply for oxygen delivery, waste removal, and the transport of neurotrophic factors. Injury or ischemia of this microvasculature is a central pathophysiological feature of diabetic neuropathy and other neuropathic conditions. Restoration of endoneurial perfusion is therefore a prerequisite for meaningful nerve regeneration.

Bragin and colleagues demonstrated that LFPMF stimulation produces significant dilation of cerebral arterioles in vivo, with baseline arteriolar diameter increasing from a mean of 26.4 micrometers to 29.1 micrometers following magnetic field exposure, along with measurable increases in tissue oxygenation [5]. Smith and colleagues similarly documented microcirculatory enhancement following PEMF exposure, identifying improvements in blood flow velocity and capillary density [6]. These vascular changes appear to be mediated in part through modulation of voltage-gated calcium channels on vascular smooth muscle and endothelial cells, leading to vasodilation and increased capillary recruitment [4].

At the molecular level, LFPMF exposure has been shown to promote the release of vascular endothelial growth factor (VEGF) and fibroblast growth factor-2 (FGF-2) from endothelial cells, both of which are potent drivers of angiogenesis [4]. Tepper and colleagues demonstrated in a landmark study that electromagnetic field exposure significantly increased in vitro and in vivo angiogenesis through endothelial release of FGF-2, providing a molecular basis for the observed neovascularization in magnetically treated tissues [4]. The formation of new capillary networks within and adjacent to injured nerve segments creates the hemodynamic foundation necessary for subsequent Schwann cell migration and axonal growth.

2.2. Effects in Peripheral Vascular Disease and Ischemic Neuropathy

Peripheral vascular disease (PVD) represents an important comorbidity in patients with neuropathy, particularly those with diabetes mellitus. Ischemia caused by arterial insufficiency compounds the direct metabolic damage to peripheral nerves and severely limits the regenerative capacity of the nerve microenvironment. LFPMFs have demonstrated meaningful effects on vascular remodeling in models of ischemic limb disease that are directly relevant to this population.

Guo and colleagues investigated the effects of PEMF therapy in a model of acute hindlimb ischemia in streptozotocin-induced diabetic rats and found that PEMF-treated animals exhibited significantly greater blood perfusion recovery by laser Doppler imaging compared to controls [7]. Immunofluorescent analysis confirmed higher neovascular density in PEMF-treated limbs, measured by CD31 expression and alkaline phosphatase staining [7]. These findings are consistent with PEMF's capacity to stimulate collateral vessel formation in ischemic territories, directly addressing the vascular component of diabetic neuropathy.

In the context of diabetic peripheral neuropathy (DPN), VEGF expression in sciatic nerve tissue is paradoxically elevated in a pathological manner, contributing to abnormal vascular permeability and progressive nerve fiber loss rather than beneficial angiogenesis. Hu and colleagues demonstrated that 15 Hz PEMF treatment in STZ-induced diabetic rats led to a reduction in pathological VEGF immunostaining in sciatic nerve tissue and a corresponding attenuation of demyelination and axon enlargement [8]. This suggests that LFPMF therapy may help normalize dysregulated vascular signaling in the diabetic nerve environment, shifting the balance from pathological toward physiologically appropriate angiogenesis.

The clinical relevance of these vascular effects is supported by the randomized controlled trial by Tassone and colleagues, which found that PEMF therapy improved skin perfusion pressure in patients with diabetic distal symmetric peripheral neuropathy, in addition to reducing pain scores [9]. The improvement in skin perfusion pressure served as a surrogate measure of microvascular function and suggested that the observed clinical benefits extended beyond neuronal blockade to include genuine vascular enhancement in the affected extremities.

Together, these early vascular events establish a permissive environment for nerve regeneration by restoring oxygen and nutrient delivery to ischemic nerve segments, reducing edema through normalized vascular permeability, and creating the capillary infrastructure through which Schwann cells, macrophages, and regenerating axons will subsequently navigate.

3. Later Mechanisms: Schwann Cell Activation, Myelin Regeneration, and Axonal Repair

3.1. Wallerian Degeneration and the Regenerative Microenvironment

Following peripheral nerve injury, Wallerian degeneration proceeds distal to the site of injury, involving the breakdown of the myelin sheath and axonal debris by Schwann cells and recruited macrophages. This process, while destructive, is an essential prerequisite for regeneration because it clears inhibitory myelin-associated proteins and converts Schwann cells to a repair phenotype capable of supporting axonal regrowth. The Schwann cell repair phenotype is characterized by upregulation of p75 neurotrophin receptor, downregulation of myelination-associated genes, formation of Bands of Büngner to guide regenerating axons, and secretion of neurotrophic factors [10].

LFPMFs appear to interact with this regenerative microenvironment at multiple levels. The early microvascular changes described above facilitate macrophage recruitment and debris clearance, while direct electromagnetic effects on Schwann cells and axonal membranes accelerate the transition from degeneration to active repair. Sisken and colleagues provided foundational evidence that low-level PEMF exposure at two Hz significantly increased neurite outgrowth in dorsal root ganglion cultures and produced a 22% increase in the *in vivo* nerve regeneration rate following sciatic nerve crush injury in rats, without affecting the initial delay period of Wallerian degeneration [3]. This suggests that LFPMFs act primarily on the reparative phase rather than on the degenerative events immediately following injury.

3.2. Schwann Cell Proliferation and Myelination

Schwann cells are the principal mediators of peripheral nerve regeneration and remyelination. Their proliferation, migration along the denervated nerve segment, and ultimate re-ensheathment of regenerating axons are rate-limiting steps in functional recovery. Pulsed magnetic fields have been shown to exert direct stimulatory effects on Schwann cell biology.

Liu and colleagues investigated the effects of pulsed magnetic field exposure on Schwann cells in culture and identified an optimal intensity of 2.0 mT, at which cells exhibited significantly enhanced proliferation by EdU labeling assay with relatively low apoptosis [11]. Moreover, PMF-treated Schwann cells showed increased gene expression and secretion of neurotrophic factors including BDNF, GDNF, and VEGF, as measured by RT-PCR and ELISA, suggesting that magnetically stimulated Schwann cells actively remodel the regenerative environment to support axonal growth [11].

Piotrkowska and colleagues, in a comprehensive 2025 review of PEMF therapy in peripheral nerve regeneration, confirmed that PEMF-induced Schwann cell activation reduces inflammation and promotes the expression of genes associated with myelination and neurotrophin signaling [10]. Key genes upregulated in PEMF-treated Schwann cells include those encoding nerve growth factor (NGF), BDNF, and transforming growth factor beta (TGF- β), while pro-inflammatory cytokines such as interleukin-1 β (IL-1 β) and tumor necrosis factor-alpha (TNF- α) are suppressed [10]. The anti-inflammatory effect of LFPMFs on the Schwann cell microenvironment is important because sustained neuroinflammation impairs both myelination and axonal elongation.

PEMF exposure has also been demonstrated to promote myelin repair in animal models of demyelinating disease. In a chronic cuprizone mouse model of demyelination, low-field magnetic stimulation promoted myelin repair and cognitive recovery, supporting the capacity of magnetic fields to drive active remyelination rather than simply preserving existing myelin [12]. This finding has direct relevance to the pathophysiology of diabetic neuropathy and other neuropathies in which progressive demyelination contributes to slowing of nerve conduction and impaired sensory function.

3.3. Axonal Sprouting and Neurite Outgrowth

The stimulation of axonal sprouting is a central mechanism by which LFPMFs promote structural nerve regeneration. Multiple preclinical studies have demonstrated accelerated axonal regeneration in PEMF-exposed animals following various types of nerve injury. Orgel and colleagues reported that PEMF treatment approximately doubled the rate and quality of peripheral nerve regeneration in a rat sciatic nerve transection model, with histological evidence of increased fiber-containing axis cylinders and larger fiber diameters in PEMF-exposed animals compared to controls [13].

The morphometric analyses performed in these studies have consistently identified greater regeneration indices, increased myelinated axon counts, and higher axon density in magnetically treated groups. Liboff and colleagues confirmed a statistically significant improvement in regeneration indices in PEMF-stimulated rats following sciatic nerve section and allograft interposition, accompanied by increased activity of NAD-specific isocitrate dehydrogenase and acetylcholinesterase at motor end plates, indicating functional maturation of regenerated motor axons [14].

The cellular mechanism underlying axonal sprouting likely involves LFPMF-induced changes in intracellular calcium signaling through transient receptor potential canonical (TRPC) channels. Electromagnetic field exposure has been shown to upregulate TRPC1 expression and increase intracellular calcium peak amplitude in neural stem cells, which in turn activates the proneural transcription factors NeuroD and Ngn1, promoting neuronal differentiation and neurite outgrowth [15]. The activation of calcium-dependent signaling cascades by LFPMF exposure may thus provide the intracellular second-messenger system through which electromagnetic stimulation is transduced into axonal growth responses.

The delayed repair model studied by Piotrkowska and colleagues further demonstrated that PEMF improved peripheral nerve regeneration even when treatment was initiated following a one-month delay after injury, suggesting that LFPMFs retain regenerative efficacy even in subacute neuropathy and not merely in the acute post-injury period [10]. This has significant clinical implications for patients presenting with established chronic neuropathy, such as those with long-standing diabetic neuropathy.

3.4. Neurotrophic Factor Upregulation

Neurotrophic factors are essential mediators of axonal survival, elongation, and target reinnervation. BDNF, NGF, and GDNF each play distinct roles in promoting the survival of specific neuronal populations and guiding regenerating axons toward their target tissues. The upregulation of these factors in response to LFPMF exposure represents a key mechanism linking electromagnetic stimulation to structural nerve repair.

Liu and colleagues demonstrated that pulsed magnetic field exposure of Schwann cells in vitro increased both messenger RNA expression and protein secretion of BDNF, GDNF, and VEGF in a dose-dependent manner [11]. These findings were complemented by Stachowiak and colleagues, who showed that extremely low-frequency electromagnetic field (ELF-EMF) therapy significantly elevated plasma levels of BDNF and VEGF in post-stroke patients undergoing rehabilitation, with BDNF levels positively correlated with functional recovery indices [16]. While this study examined central rather than peripheral nerve repair, the commonality of BDNF-dependent regenerative mechanisms across nervous system compartments suggests translatable relevance.

The Fan and colleagues comprehensive review of magnetism-based approaches in peripheral nerve regeneration confirmed that PEMF increases the expression and secretion of multiple neurotrophic factors by Schwann cells, and that these factors act in an autocrine and paracrine fashion to create a pro-regenerative milieu throughout the injured nerve segment [12]. NGF serves as a critical chemoattractant that guides regenerating axonal growth cones toward target tissues, while GDNF supports the survival of motor neurons and promotes the reinnervation of muscle end plates.

3.5. Mesenchymal Stem Cell Priming and Cell-Based Synergies

A further dimension of LFPMF-mediated nerve regeneration involves the priming of mesenchymal stem cells (MSCs) toward a neural regeneration-supportive phenotype. Wang and colleagues investigated the effects of low-frequency PEMF pretreatment on bone marrow-derived MSCs (BMSCs) and found that pre-conditioned cells exhibited faster proliferation and greater mRNA expression of neural-supportive growth factors including BDNF and NGF compared to untreated BMSCs [17]. When PEMF-pretreated BMSCs were injected into animals with crush injury of the mental nerve, they achieved significantly higher myelinated axon counts, greater axon density, and improved retrograde labeling of trigeminal ganglion neurons compared to injection of untreated BMSCs [17].

These findings suggest that LFPMFs may be applied not only as a standalone therapeutic modality but also as a preparatory or adjunctive treatment to enhance the efficacy of cell-based therapies for nerve regeneration. The ability of magnetic fields to upregulate the neural differentiation potential of stem cells in the absence of exogenous growth factors represents a clinically attractive property that may reduce the regulatory complexity associated with growth factor administration.

4. Clinical Evidence and Applications

4.1. Pain Management and Structural Outcomes

The translational pathway from preclinical nerve regeneration studies to clinical application of LFPMFs is actively being defined. The most robust clinical evidence to date pertains to the analgesic effects of mPNS in painful diabetic neuropathy, where clinical response rates of 60 to 75% for immediate pain relief have been documented across multiple randomized controlled trials [1,2]. The sustained pain relief observed beyond the treatment period, persisting for months following completion of the treatment protocol, is consistent with neuroplastic reconditioning but may also reflect a structural regenerative contribution [1].

The study by Weintraub and colleagues, which enrolled 225 subjects with stage II or III diabetic peripheral neuropathy across 16 academic and clinical sites, found that while the tested low-intensity PEMF dosimetry did not achieve the primary pain endpoint, neurobiological markers of regeneration were affected, including changes in epidermal nerve fiber density (ENFD) [18]. The authors concluded that higher dosimetry was likely needed to achieve full regenerative effects, and that the biological signal observed in ENFD supported continued investigation of PEMF for structural nerve repair.

The randomized controlled trial by Tassone and colleagues examined twice-daily PEMF therapy over 18 weeks in 182 subjects with confirmed diabetic distal symmetric peripheral neuropathy and found significant reductions in pain alongside improvement in skin perfusion pressure, suggesting measurable enhancement of peripheral microvascular function in addition to symptomatic pain relief [9]. Kapural and colleagues further documented one-year follow-up outcomes in a large multisite cohort treated with the mPNS protocol, confirming durable pain reduction and continued improvement over the observation period [19].

4.2. Treatment Parameters and Optimization

The efficacy of LFPMF therapy for nerve regeneration depends on the same core parameters as its analgesic applications: field frequency and intensity, pulse characteristics, treatment duration, and treatment frequency. For regenerative endpoints, lower field strengths (1 to 100 mT) in the 2 to 50 Hz range have the strongest preclinical support. Clinical protocols are less well standardized than the mPNS pain protocol, which specifies three daily treatments followed by three weekly treatments in month one, then bi-weekly in month two and monthly maintenance thereafter [1,2].

Emerging applications of LFPMF therapy for nerve regeneration include post-surgical neuropathy, post-traumatic neuropathy, post-amputation stump pain, and phantom limb pain. The

extension to overactive bladder via sacral (S3) nerve stimulation and to osteoarthritic applications has been explored in pilot studies, suggesting a broad regenerative utility that extends beyond peripheral sensory neuropathy [1]. Future biomaterials engineering will explore differently sized coils for distinct anatomical applications.

4.3. Safety Considerations

LFPMF therapy has an excellent safety record with a significant clinical advantage over many pharmacological treatments. The electromagnetic fields are non-ionizing; therefore, no charge buildup occurs under the skin, and their low frequencies and field strengths do not cause thermal damage or tissue injury [1,20]. Clinical trials have documented few adverse events or side effects. The most commonly reported side effects are mild and transient, including temporary tingling or warmth at the treatment site. No serious adverse events have been consistently linked to LFPMF therapy in well-conducted clinical trials.

Contraindications are few. The most significant is the presence of implantable cardioverter-defibrillators or other active implanted medical devices. Pregnant women are typically excluded as a precautionary measure. Devices are not placed over the head or the heart. The favorable safety profile makes LFPMF therapy accessible to many patients for whom conventional pharmacological treatments are not well tolerated.

5. Discussion

Taken together, the preclinical literature reviewed here describes a logical and internally consistent sequence of events. LFPMFs first act on the endoneurial vasculature—dilating arterioles, releasing angiogenic factors, and driving new capillary formation—before Schwann cells, working in an improved microenvironment, begin the slower work of debris clearance, remyelination, and neurotrophic support. The sequence matters clinically because it implies that the timing, duration, and dosimetry of LFPMF treatment may need to be matched to the biological phase being targeted, and that single-timepoint outcome assessments may miss meaningful effects that emerge weeks to months after treatment begins.

What the preclinical data do not yet tell us is how well any of this translates to patients—particularly patients treated with the higher-intensity clinical devices now in use. Almost every mechanistic study reviewed here used field strengths orders of magnitude below those of the mPNS device cleared by the FDA. That is not a minor technical detail; it is a fundamental gap in the translational chain. It is entirely possible that the cellular mechanisms active at 2 mT are suppressed, overwhelmed, or qualitatively altered at 1.6 Tesla. It is equally possible that they are amplified. We simply do not know, and that uncertainty should be front of mind when interpreting the clinical data.

5.1. Field Intensity and the Gap Between Regenerative and Analgesic Devices

Every mechanistic study cited in this review used a low-power PEMF device, typically operating between 0.05 and 100 mT. These are the devices for which cellular and molecular mechanisms—angiogenesis, Schwann cell activation, neurotrophic upregulation, axonal sprouting—have been worked out in animal models and cell culture. The clinical mPNS devices now being used in patients operate at up to 1.6 Tesla: field strengths roughly four orders of magnitude greater. At those intensities, the primary biological event is direct action potential generation in myelinated nerve fibers, which is qualitatively different from the subthreshold membrane modulation that underlies the regenerative effects described above [1,2]. Whether the regenerative mechanisms identified at low field strengths survive, are amplified, or are simply irrelevant at clinical mPNS intensities is not currently known.

There are arguments on both sides. Higher field strengths generate stronger induced electric fields in tissue, which could in principle produce more robust activation of the ion channels and signaling cascades underlying angiogenesis and Schwann cell activation. Deeper tissue penetration

with stronger devices might also reach nerve segments that lower-power coils cannot. On the other hand, the sheer magnitude of the field at 1.6 Tesla may overwhelm the subtle membrane modulation effects that seem to drive regenerative responses at low intensities, producing a fundamentally different cellular environment. The honest answer is that we do not yet have the experimental data to choose between these possibilities, and designing studies that can answer this question should be a priority for the field.

Against that uncertainty, there is one clinical finding that deserves particular attention. In the Brown et al. trial of the mPNS device for painful diabetic neuropathy, patients reported a 53% reduction in numbness [2]. That is not a pain outcome. Numbness is what happens when sensory nerve fibers stop functioning—the progressive loss of fiber density and conduction that defines the structural progression of diabetic neuropathy. It is difficult to attribute a 53% improvement in numbness to neuronal blockade or central sensitization reversal; those mechanisms do not restore sensation. The more plausible explanation is that something restorative is happening at the level of the peripheral nerve fiber itself. Whether the mechanism is microvascular, directly trophic, or something else entirely, this finding should not pass without comment in the regeneration literature. It is, at minimum, a signal worth following with purpose-designed endpoints.

6. Future Directions and Research Needs

While significant progress has been made in understanding the mechanisms and potential clinical applications of LFPMFs in nerve regeneration, several important research questions remain. A more thorough understanding of the cellular and molecular mechanisms underlying LFPMF effects will be required to rationally optimize treatment parameters and identify patient populations most likely to benefit. Future research should focus on RCTs evaluating the use of mPNS for osteoarthritic and perioperative applications, and studies examining structural nerve regeneration endpoints such as ENFD, nerve conduction velocity, and quantitative sensory testing.

The potential for combination therapies is particularly intriguing. LFPMFs could be combined with pharmacological treatments, cell-based therapies, growth factor administration, regenerative-type injections, or physical rehabilitation to achieve synergistic effects. Research into such combinations could lead to novel treatment paradigms providing superior outcomes to any single therapy alone. Expanded duration follow-up studies are needed to confirm whether mPNS can provide a permanent “reset” of the pain processing and nerve regeneration system. The longest mPNS follow-up study is currently at one year [19].

Future research should also focus on patient populations with specific neuropathic subtypes most amenable to LFPMF-mediated regeneration, including chemotherapy-induced neuropathic pain, post-viral neuropathy including long COVID-related conditions, and chronic pain with significant central sensitization. Cost-effectiveness analyses will be important to establish the health-economic value of LFPMF therapy relative to established pharmacological and interventional options.

7. Conclusions

The preclinical case for LFPMF-mediated peripheral nerve regeneration is stronger than the clinical literature currently reflects. The mechanistic sequence—early microvascular restoration via FGF-2 and VEGF-driven angiogenesis, followed by Schwann cell activation, myelin reconstitution, and neurotrophic factor upregulation—is internally coherent and supported by multiple independent lines of evidence across different animal models and cell systems. For patients with diabetic neuropathy and peripheral vascular disease in particular, where endoneurial ischemia is a central driver of nerve fiber loss, the early vascular effects of LFPMFs address a mechanism that current pharmacological treatments do not.

The clinical translation of these findings is at an early stage but not without signal. A 53% reduction in numbness in the Brown et al. mPNS trial, improvements in epidermal nerve fiber density in the Weintraub study, and sustained gains in skin perfusion pressure with PEMF therapy are

individually modest but collectively point in the same direction. Confirming whether any of these effects reflect true structural nerve regeneration will require trials designed with that question in mind: longer follow-up, biopsy-based ENFD measurement, nerve conduction studies, and quantitative sensory testing as primary outcomes. The safety profile of LFPMF therapy creates room to ask those questions without undue risk to patients. The answer would matter considerably, both for the millions of people living with treatment-resistant neuropathy and for our broader understanding of electromagnetic effects on neural tissue.

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Abbreviations

The following abbreviations are used in this manuscript:

BDNF	Brain-Derived Neurotrophic Factor
BMSC	Bone Marrow-Derived Mesenchymal Stem Cell
DPN	Diabetic Peripheral Neuropathy
DSPN	Diabetic Symmetric Peripheral Neuropathy
ENFD	Epidermal Nerve Fiber Density
FDA	Food and Drug Administration
FGF-2	Fibroblast Growth Factor-2
GDNF	Glial Cell Line-Derived Neurotrophic Factor
LFPMF	Low-Frequency Pulsed Magnetic Field
mPNS	Magnetic Peripheral Nerve Stimulation
MSC	Mesenchymal Stem Cell
NGF	Nerve Growth Factor
PEMF	Pulsed Electromagnetic Field
PVD	Peripheral Vascular Disease
STZ	Streptozotocin
TENS	Transcutaneous Electrical Nerve Stimulation
TGF-β	Transforming Growth Factor Beta
TRPC1	Transient Receptor Potential Canonical 1
VEGF	Vascular Endothelial Growth Factor

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