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# Veterinary applications of pulsed electromagnetic field therapy

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ABSTRACT

Pulsed electromagnetic field (PEMF) therapy can non-invasively treat a variety of pathologies by delivering electric and magnetic fields to tissues via inductive coils. The electromagnetic fields generated by these devices have been found to affect a variety of biological processes and basic science understanding of the underlying mechanisms of action of PEMF treatment has accelerated in the last 10 years. Accumulating clinical evidence supports the use of PEMF therapy in both animals and humans for specific clinical indications including bone healing, wound healing, osteoarthritis and inflammation, and treatment of post-operative pain and edema. While there is some confusion about PEMF as a clinical treatment modality, it is increasingly being prescribed by veterinarians. In an effort to unravel the confusion surrounding PEMF devices, this article reviews important PEMF history, device taxonomy, mechanisms of action, basic science and clinical evidence, and relevant trends in veterinary medicine. The data reviewed underscore the usefulness of PEMF treatment as a safe, non-invasive treatment modality that has the potential to become an important stand-alone or adjunctive treatment modality in veterinary care.

## 1. Introduction

Pulsed electromagnetic field (PEMF) therapy is a non-invasive, non-thermal treatment that involves pulsing electromagnetic fields in tissue to promote healing (Strauch et al., 2009). PEMF devices have been approved by the U.S. Food and Drug Administration (FDA) to treat non-union fractures and cleared to treat post-operative pain and edema, osteoarthritis, and plantar fasciitis. Implementation of PEMF therapy in veterinary medicine is increasing. Pathologies that are often treated with PEMF devices include bone fractures, inflammation and arthritis, pain, edema, and chronic wounds. Though there is a growing body of basic and clinical evidence in support of PEMF treatment as a therapeutic modality, veterinary practitioners and animal owners report significant confusion about PEMF devices largely due to the number of different types of devices and the varying amounts of evidence that support each type of device. This lack of clarity regarding the PEMF modality is furthered by poor dissemination of data on mechanisms of action and a wide variety of unsubstantiated claims that are used for marketing purposes. In an effort to unravel the confusion surrounding PEMF devices, this article reviews important PEMF history, device taxonomy, mechanisms of action, basic science and clinical evidence, and relevant trends in veterinary medicine. The goal of this overview is to provide readers with a clearer understanding of the PEMF treatment modality, with an emphasis on recent PEMF technologies that are rooted in basic science and clinical research and are well-positioned to augment veterinary care.

## 2. History

Electromagnetic field devices have been used therapeutically for more than a century and for a variety of applications (Fig. 1) (Strauch et al., 2009). Historically, most devices have had a wide range of operating modes and were largely promoted without scientific evidence or validation. The era of modern PEMF technologies began in the 1930s when a vacuum tube-based diathermy machine, a radio-frequency electromagnetic device used to deliver heat deep into tissue, was adapted to produce little to no heat. This was accomplished by reducing the duty cycle of the diathermy device, or the percentage of the electromagnetic signal's on-off cycle in which the signal is active, to about 4%. These new non-thermal devices were purported to have therapeutic effects in wound healing and treatment of pain, though via unknown mechanisms at the time.

Commercial distribution of these “non-thermal diathermy” devices started in 1950 (Al-Mandeel and Watson, 2008). In parallel work during the 1970s, clinician researchers began to employ direct electrical currents to treat non-union fractures, using electrodes surgically implanted

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**Fig. 1.** 1920's era fischer diathermy machine.
This device is an example of an early pulsed electromagnetic field technology that was used for therapeutic heating of tissue. This device was developed and sold by Fischer & Co in the early 1920's.

**Fig. 2.** Modern bone growth stimulator.
This device is an example of a modern bone growth stimulator device use for treating non-union fractures. When in use, the device is positioned such that the two coil panels are on opposite sides of the fractured bone. Because of the weak fields generated by these devices, they are often used for several hours per day for weeks or months.

in bone (Paterson et al., 1977). By the late 1970s, implanted electrodes were being replaced with non-invasive inductive antennas (Bassett et al., 1977). During that period PEMF was successfully used to treat delayed and non-union fractures in Beagles and, shortly thereafter, humans. After extensive clinical research, by the early 1980s low-powered PEMF devices called bone growth stimulators (BGS) were approved by the U.S. FDA for human use (Fig. 2) (Bassett et al., 1982). Subsequently, in the 1990's, a next generation class of PEMF devices was developed for treating soft-tissue instead of bone. These devices were solid-state and smaller, improving upon the cumbersome large vacuum tube models.

The growing body of research and clinical evidence supporting PEMF therapy in the 1980's and 1990's also fostered greater understanding of mechanisms of action (Pilla, 2006). Scientists began to develop PEMF devices with waveforms designed, a priori, to modulate specific biological processes. For example, one device termed “targeted PEMF” was successfully developed to reduce inflammation and has become a FDA-cleared therapy for treating postoperative pain and edema (Fig. 3) (Pilla, 2013). Non-targeted PEMF systems, also readily available, were not specifically configured to a known biological target, and thus demonstrated a wide range of technical specifications and

**Fig. 3.** Targeted pulsed electromagnetic field device.
This targeted PEMF device consists of a single loop antenna and battery-powered pulse generator. The targeted PEMF waveform was designed to reduce inflammation in soft tissue. Characteristics of the waveform, such as the long burst width and the high frequency 27.12 MHz carrier wave, result in very efficient delivery of electric field to tissue, and, therein, beneficial clinical effects with small doses of treatment.

clinical effectiveness. Although devices without FDA clearance are utilized in human and veterinary care, this review will concentrate on FDA-cleared devices, as they are supported by basic science and clinical research studies that help illustrate relevant areas of clinical application and therapeutic utility in veterinary medicine.

### 2.1. Taxonomy

PEMF is a type of electrotherapy that employs an active electromagnetic waveform that is typically delivered via an antenna to treat an area of tissue on a subject. Many different types of PEMF devices have been developed both for research and clinical applications. These technologies are differentiated by (1) the shape and strength of the electromagnetic waveforms they emit, (2) the size and geometry of antennas used, and (3) the duration and frequency of treatment application. These variables combined determine the strength of the magnetic and electric fields generated by each device and, ultimately, whether the devices provide safe and efficacious therapy.

To showcase the intricacy of these variables, Fig. 4A shows the shape of the waveform used in the original BGS device to promote healing of non-union fractures. Fig. 4B illustrates the very different waveform used in the targeted PEMF device referenced above, which has been successfully used to treat pain and inflammation (Pilla et al., 2011). Furthermore, the strength of the magnetic fields generated by PEMF devices can vary dramatically from less than one Gauss to several thousand Gauss. Obviously, not all PEMF signals are alike. Consequently, this substantial variability in device parameters underscores the necessity of rigorous animal and human research for the sake of validating individual PEMF therapies for specific clinical applications.

PEMF waveforms, in the configurations cleared for human use by the FDA, were designed to penetrate completely through tissue of all types, allowing for effective non-invasive delivery of the therapy. These PEMF devices differ significantly from other forms of electrotherapy

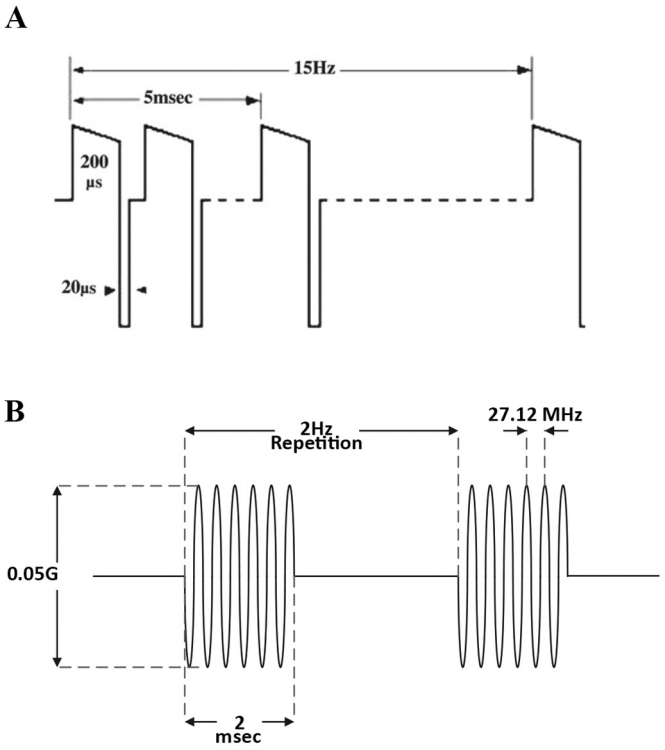


**Fig. 4.** Waveform differences between PEMF devices.
The waveform from a bone growth stimulator device consists of 5 millisecond bursts.
of asymmetrical, rectangular, biphasic waves repeating at 15 Hz. Devices with this waveform are capable of delivering an electric field of approximately 5 V per meter. B. The waveform from a targeted PEMF device consists of a shortwave 27.12 MHz carrier sine wave that is pulse-modulated with bursts of two milliseconds repeating at 2 Hz. The targeted PEMF device generates a small magnetic field of 0.05 gauss and a relatively large electric field strength of more than ten volts per meter.

such as transcutaneous electrical stimulation (TENS). In contrast to PEMF which uses an inductive antenna, TENS units require electrodes to be placed in contact with the skin. Because of this difference in the delivery of energy, TENS units drive current along the surface of the skin and cannot reach deeper tissue, whereas PEMF devices are able to deliver therapy to deeper targets (Claydon et al., 2011).

The strongest basic science and clinical research evidence supporting the use of PEMF therapy has been generated in the pursuit of regulatory approval by the U.S. FDA. Devices with FDA clearance or approval fall into two primary categories (see Table 1): non-invasive bone growth stimulators, and nonthermal shortwave diathermy PEMF devices (which encompass targeted PEMF devices). Additionally, a select few manufacturers have conducted basic and clinical research to demonstrate the utility of their devices, though they have not sought regulatory approval by the FDA.

Shortwave nonthermal diathermy devices (Table 1) that are FDA-cleared for use in treating superficial soft tissue all operate using a shortwave 27.12 MHz carrier wave frequency. However, other key waveform parameters such as pulse width and pulse frequency are varied for devices within this class. As mentioned earlier, these waveform parameters determine the strength of the magnetic and electric fields generated by a device, and therein its safety and efficacy. Note that PEMF devices and the electromagnetic fields that they emit have both electric field and magnetic field components that are measureable. For example, the waveform for one type of device, we can refer to as "Device A", has a pulse width of 100 microseconds and a pulse frequency of 1000 Hz. The waveform for another type of device, we can refer to as "Device B", has a pulse width of 2 milliseconds and a pulse frequency of 2 Hz. The difference in waveforms yields a 7-fold greater electric field strength for Device B as compared to Device A and this difference has meaningful consequences for treatment efficacy (see *Osteoarthritis* and Table 2 below). In this overview, PEMF technologies that use waveforms similar to Device A, or those that use waveforms not specifically designed to evoke specific biological effects, are referred to as non-targeted PEMF devices. Technologies that are similar to Device B, are referred to as targeted PEMF devices, because their waveforms are specifically designed to efficiently deliver energy to tissue and modulate biological signaling cascades. For additional specificity, devices that are described below will be identified as low frequency (≤1000 Hz carrier frequency), often indicating biological effects stemming from delivery of magnetic fields, or high frequency (> 1000 Hz carrier frequency), indicating biological effects stemming from delivery of electric fields.

**Table 1**
FDA-regulated PEMF devices.

| Device type | Product code | Example indications |
|---|---|---|
| Bone Growth Stimulator | LOF | Treatment of fracture non-unions Adjunct to lumbar spinal fusion surgery Adjunct to cervical fusion surgery Treatment of congenital pseudarthrosis |
| Shortwave Nonthermal Diathermy PEMF | ILX | Adjunctive use in the palliative treatment of post-operative pain and edema in superficial soft tissue |

**Table 2**
Outcome comparison for PEMF treatment of knee osteoarthritis.

| Device type | Waveform | Prescribed dose | VAS pain score |
|---|---|---|---|
| Non-targeted PEMF | 27.1 MHz, 100 µs pulse width, 1000 Hz pulse frequency | 12 h daily | −25.4% |
| Targeted PEMF | 27.1 MHz, 2 ms pulse width, 2 Hz pulse frequency | 15 min twice daily | −38.4% |

Bagnato et al., 2016; Nelson et al., 2013.

### 2.2. Mechanisms of action

#### 2.2.1. Faraday's law of induction

Michael Faraday was one of the most influential scientists in history, a major contributor to the study of electromagnetism and electrochemistry. His main discoveries include the principles underlying electromagnetic induction, diamagnetism and electrolysis. In the 1830s, Faraday proposed the equations that describe how a time-varying (pulsing) electromagnetic field will induce an electrical field in a nearby conductor, like copper or tissue. This principle, Faraday's Law, is the physical mechanism underlying many PEMF devices that have non-invasive biological effects (Fig. 5). As mentioned earlier, the

$$\mathcal{E} = N\frac{d\Phi_B}{dt}$$

**Fig. 5.** Faraday's law of induction.
Faraday's Law of Induction is a basic law of electromagnetism that predicts how a time varying magnetic field will interact with an electric circuit to produce electromotive force. The law states that the induced electromotive force in any closed circuit is equal to the rate of change of the magnetic flux enclosed by the circuit. In the figure, ε represents the electromotive force, *N* represents the number of turns in the coil, $d\,\Phi_B$ represents the magnetic flux, and *dt* represents time. Many PEMF devices operate by inducing electromotive force in conductive targets such as tissues of the human body.

characteristics of the electromagnetic pulse (i.e., frequency, duration, amplitude) determine the magnitude of the magnetic and electrical fields delivered to the tissue, and therein, efficacy and safety.

#### 2.2.2. PEMF biophysics

The biophysical and cellular mechanisms through which PEMF therapies influence biology are complex and remain an ongoing area of research focus. However, significant progress has been made in identifying some of the pathways that are relevant to the more widely used PEMF technologies.

For targeted PEMF, the BGS and some non-targeted PEMF devices, increased calcium ion ($Ca^{2+}$) signaling has been identified as a critical factor underlying the observed biological and clinical effects of PEMF treatment (Brighton et al., 2001; Pilla et al., 2011). Release of intracellular $Ca^{2+}$, driven by PEMF exposure, leads to increased binding of $Ca^{2+}$ to calmodulin (CaM) and a variety of downstream signaling pathways related to metabolism, inflammation, apoptosis, vascular tone, and others.

Research studies focused on mechanism have demonstrated that targeted PEMF induces downstream production of nitric oxide (NO), one of the few known gaseous signaling molecules. Dr. Louis Ignarro and colleagues characterized the role of nitric oxide in biology, particularly in reference to its cardiovascular effects. They were later awarded the Nobel Prize in Physiology or Medicine for their research (Ignarro, 1990; Ignarro et al., 1987; Ignarro et al., 1981). In addition to its function as a vasodilator, nitric oxide can potently influence cells of the immune system and the nervous system, making it an important signaling molecule for organism homeostasis (Bogdan, 2001; Calabrese et al., 2007). Targeted PEMF treatment has been shown to result in production of low concentrations of nitric oxide, which are associated with diminished inflammation and enhancement of vasodilation (Bragin et al., 2014; Pilla et al., 2011; Pilla, 2012; Strauch et al., 2009). As mentioned earlier, targeted PEMF was designed specifically to manipulate this pathway and can do so more efficiently than the BGS or non-targeted PEMF devices that produce weaker electric fields (Pilla et al., 2011; Pilla, 2012).

In the context of the BGS, several studies have found that PEMF exposure increased expression of bone morphogenetic proteins 2 and 4, induced osteogenesis, and promoted differentiation of osteoblast cells, all of which are consistent with bone repair (Bodamyali et al., 1998; Petecchia et al., 2015; Tsai et al., 2009). For targeted PEMF, upregulation of nitric oxide production been found to reduce inflammatory gene expression in immune cells, reduce programmed cell death, and promote dilation of blood vessels and enhanced circulation (Bragin et al., 2014; Pena-Philippides et al., 2014; Rasouli et al., 2012; Rohde et al., 2010; Rohde et al., 2015). These results are consistent with reductions in pain, swelling, and inflammation that have been observed clinically.

#### 2.2.3. Nitric oxide signaling

When increased concentrations of free calcium ions ($Ca^{2+}$) are present in the cytoplasm, $Ca^{2+}$ binds with CaM. $Ca^{2+}$/CaM binding activates the constitutive nitric oxide synthase (cNOS), which, in turn, produces short-bursts of nitric oxide (NO). NO is then able to bind to soluble guanylyl cyclase and increase production of cyclic guanosine monophosphate (cGMP). The upregulation of NO and cGMP are known to activate endogenous anti-inflammatory responses, enhance blood flow and increase production of growth factors required for repairing tissue. After injury, pro-inflammatory cytokines, such as interleukin-1beta, are quickly released, initiating a complex inflammatory cascade. This response helps ward off infection and reduces use of the affected area. Simultaneously an anti-inflammatory cascade is initiated to ensure that the pro-inflammatory process does not become overactive and result in unnecessary tissue damage and serves to initiate healing and return to homeostasis. Triggering of the CaM/cNOS/NO pathway rapidly reduces the production of pro-inflammatory factors and increases production of cGMP, which drives the release of the growth factors that support neovascularization, tissue regeneration, and tissue remodeling. Targeted PEMF, specifically, has been well-characterized in accelerating this endogenous pathway. Interestingly, the response to treatment is only observed in injured tissues. The targeted PEMF technologies do not themselves cause bone growth or tissue regeneration outside of the context of injured tissue. This characteristic is likely part of the reason that these technologies are not associated with any known side-effects nor adverse events when used within clinical guidelines and indications for use.

#### 2.2.4. Heat shock proteins

A number of studies have also found that PEMF treatment can increase the expression of heat shock proteins (HSP), a class of inducible proteins that are expressed under conditions of stress and have been associated with a number of cytoprotective and anti-apoptotic effects (Goodman et al., 1994; Robertson et al., 2007). In particular, HSP70 proteins, a family of intracellular chaperones that are important for assisting in the process of protein folding, have repeatedly been found to be induced by non-thermal PEMF treatment (DiCarlo et al., 1999; Rodriguez de la Fuente et al., 2009; Rodriguez-De la Fuente et al., 2012).

#### 2.2.5. Adenosine receptor expression

Separately, PEMF (low frequency) has also been linked to cell membrane adenosine receptor expression. Cadossi and colleagues have reported that PEMF exposure results in increased expression of the $A_{2A}$ and $A_{3A}$ adenosine receptors in a variety of cells and tissues (Varani et al., 2017). Activation of these receptors by endogenous adenosine is associated with reductions in prostaglandins and inflammatory cytokines, again consistent with the published clinical findings of reduced pain and inflammation.

In contrast to drug therapies, it is becoming clear that PEMF interventions likely operate via a few biological cascades rather than one narrow signaling pathway. As research into PEMF mechanisms of action continues to unfold, the gained knowledge will be helpful for further optimization of device engineering, treatment dosing, and exploration of new clinical indications.

### 2.3. Basic science and clinical evidence

#### 2.3.1. Bone healing

Early PEMF technologies were developed specifically to treat non-union fractures (Bassett et al., 1977). This type of PEMF, BGS (low frequency), is currently in use for that purpose and is an established approach in the orthopedic surgery community. Other indications beyond non-union fracture treatment have emerged including spinal fusion and congenital pseudarthrosis (Table 1).

BGS therapy is a long-term treatment, often used for 8 or more hours per day for several months. This extended treatment cycle is necessary, in part, because the BGS, originally developed in the 1970s, employs a waveform that slowly deposits energy into tissue over time (Pilla et al., 2011). Even in the face of inefficient energy delivery to a target bone or tissue, randomized controlled clinical trials (RCT) carried out to assess the efficacy of BGS interventions have found reductions in both pain and risk of radiographic fracture non-union (Assiotis et al., 2012; Bassett et al., 1982; Mooney, 1990; Shi et al., 2013). Authors of a recent meta-analysis on electrotherapies for bone healing, which also included direct current and capacitive coupling devices, reported that "Patients treated with electrical stimulation as an adjunct for bone healing have less pain and are at reduced risk for radiographic non-union; functional outcome data are limited and requires increased focus in future trials" (Aleem et al., 2016).

A small number of veterinary-specific studies have demonstrated evidence of clinical utility for BGS devices. For example, in one study canines were treated with a BGS device (low frequency) or sham for 1 h

per day after transverse mid-diaphyseal tibial osteotomy (Inoue et al., 2002). BGS treatment, when compared with sham, was associated with faster recovery of load-bearing ability, increased bone formation, and greater mechanical strength of the healing bone. Additionally, a case study in canines with Legg-Calvé-Perthes disease, a necrotic condition of the femoral head, found that treatment with a non-targeted PEMF mat (low frequency) for two months resulted in full recovery and avoidance of surgical intervention. However, this was a case study and requires replication in a controlled trial (Pinna et al., 2014).

#### 2.3.2. Osteoarthritis

A non-targeted PEMF device (high frequency) was recently shown to improve pain and increase function in a RCT involving patients with knee osteoarthritis (Bagnato et al., 2016). An earlier study, investigating a targeted PEMF device therapy (high frequency) for knee osteoarthritis also showed significant reductions in pain (Nelson et al., 2013). The comparable study design and clinical populations in these trials lend to a meaningful comparison of use and effectiveness for the non-targeted and targeted PEMF devices. The results show that after one month of treatment, the targeted PEMF device, developed explicitly to reduce inflammation, produced a more pronounced reduction in the visual analog scale for pain (VAS) and did so at significantly lower doses (12 h daily vs. 30 mins daily) (Table 2). As mentioned above, a key driver for this difference in efficacy is the device waveform, which for the targeted PEMF device generates an electric field 7 times stronger than that of the non-targeted PEMF device.

Veterinary-focused research studies have also demonstrated benefits of PEMF treatment for osteoarthritis. A non-targeted PEMF device (low frequency) was found to lessen clinical signs of osteoarthritis in dogs after 20 18-minute treatments (Pinna et al., 2012). While this study lacked a sham device control group, the PEMF treatment was compared to treatment with firocoxib, a non-steroidal anti-inflammatory drug, and PEMF treatment was found to outperform drug treatment in long term follow up. Another study found that a non-targeted PEMF device (low frequency) applied for 1 h on 9 consecutive days reduced osteoarthritis pain in dogs as assessed by their owners. Animal owners who provided self-report of clinical data in this study, however, were not blinded, which underscore a need for study replication with a more rigorous design (Sullivan et al., 2013).

#### 2.3.3. Inflammation, pain, and edema

The acute inflammatory cascade that occurs after tissue injury, whether surgical or traumatic in origin, is an important part of the recovery process to fight infection, promote tissue remodeling, and initiate healing. High levels of inflammation, both acute and chronic, often contribute to pain and edema at the site of injury. Several studies support the effectiveness of PEMF and targeted PEMF as treatments for inflammation, pain and swelling.

Basic science studies conducted by Kubat and colleagues found that non-targeted PEMF treatment (high frequency) was able to induce gene expression changes associated with resolution of inflammation in human cells (Kubat et al., 2015). Another non-targeted PEMF device (high frequency) study reported that continuous PEMF treatment for 7 days after breast surgery resulted in significantly lower VAS pain scores and fewer narcotic pain pills taken (Rawe et al., 2012).

Four double-blind, randomized, controlled human trials have been conducted using targeted PEMF (high frequency) in patient populations who underwent breast augmentation, bilateral mastectomy and reconstruction, breast reduction, and transverse rectus abdominus breast reconstruction, respectively (Heden and Pilla, 2008; Rohde et al., 2010; Rohde et al., 2015). In all of these studies, targeted PEMF therapy (as compared with sham treatment) was observed to significantly reduce both pain and narcotic pain medication use following these surgical procedures. The magnitude of the clinical effects observed in a study involving breast reduction surgery patients was particularly notable (Rohde et al., 2010). Targeted PEMF was applied for 20 min every 4 h after surgery and was found to reduce pain by 50%, reduce the concentration of the inflammatory cytokine interleukin-1beta at the wound site by 40% and, importantly during this period of opioid crises, reduce the use of narcotic pain medication by 50%.

PEMF devices have been applied in veterinary trials to assess efficacy of post-operative pain reduction. In a controlled study, a non-targeted PEMF device (low frequency) was applied with or without morphine to female dogs after ovariohysterectomy for 20 min every 40 min over a period of 6 h after surgery. This study failed to find a benefit of PEMF alone when compared to untreated controls (Shafford et al., 2002). A more recent randomized, sham-controlled study evaluated the effects of a targeted PEMF device (high frequency) therapy in dogs with acute intervertebral disc extrusion and paraplegia being treated with spinal decompression surgery. Targeted PEMF treatment was applied for 15 min every 2 h for two weeks then twice daily for four weeks. Treated dogs exhibited significant reductions in surgical incision site pain, lower concentrations of inflammatory biomarkers, and improved proprioceptive function compared to controls (Zidan et al., 2018).

#### 2.3.4. Soft tissue wound healing

Clinical studies examining the effects of PEMF therapy on soft tissue and wound healing have demonstrated that treatment accelerated the healing of chronic wounds such as pressure sores and diabetic leg and foot ulcers. FDA-cleared or -approved PEMF devices are reimbursed by Centers for Medicare and Medicaid services as safe, effective treatments for chronic wounds and several studies support the effectiveness of PEMF for this indication (Kloth et al., 1999; Mayrovitz and Larsen, 1995; Salzberg et al., 1995; Stiller et al., 1992; Strauch et al., 2007). In a RCT conducted with paraplegic veterans with sacral ulcers, a single 30 min non-targeted PEMF treatment (high frequency) every weekday for a month resulted in 64% wound closure in the active treatment arm as compared to a 7% increase in wound size in sham treatment arm (Kloth et al., 1999).

To investigate how PEMF therapy enhanced wound repair, experiments were carried out to examine potential treatment effects on vascular function, an important aspect of wound healing. A study by Roland and colleagues found that non-targeted PEMF treatment accelerated the growth of new blood vessels by 5-fold in an arterial loop transfer in rats (Roland et al., 2000). In a subsequent trial, native arterial blood supply to a rodent tissue flap was cut off and PEMF was applied to enhance vascular performance. Whereas the sham treatment cohort had virtually complete flap failure, animals treated with PEMF twice daily for 30 min over 8 weeks exhibited significant vascularization and virtually complete flap survival (Weber et al., 2004). These data provide proof of principle that PEMF interventions are effective at promoting wound healing in part because of enhanced vascularization and associated tissue perfusion and oxygenation, all of which are important for wound repair.

#### 2.3.5. Psychiatric & neurological disorders

Development of drug therapies for psychiatric and neurological disorders has been remarkably unsuccessful. Lack of effective treatment is most obvious for conditions like major depressive disorder, brain trauma, stroke, Alzheimer's disease, and a number of other severe disorders.

Preliminary research studies have demonstrated the utility of several PEMF therapies for addressing some of the unmet treatment needs for these conditions affecting the brain. PEMF appears to be an advantageous therapeutic strategy, particularly because the electromagnetic fields generated by the devices are able to penetrate the head and reach the brain tissue being targeted. In vitro studies and studies in animals have demonstrated that PEMF can promote healing in models of stroke, traumatic brain injury, brain cancer, and Alzheimer's disease (Arendash et al., 2010; Grant et al., 1994; Mukthavaram et al., 2015; Pena-Philippides et al., 2014; Rasouli et al., 2012). Many of these

technologies are in the process of transitioning into Phase I and II clinical trials in humans to assess safety and efficacy.

PEMF treatment may have valuable applications in the treatment of small and large animal mood and behavioral disorders. This is supported by studies showing that targeted PEMF can reduce inflammatory cytokine production in the brains of laboratory animals after brain injury (Rasouli et al., 2012). Inflammatory tone is believed to be an important driver of behavior in both animals and humans (Haroon et al., 2012). Additional research in humans has found that other forms of electromagnetic intervention can effectively reduce clinical signs of depression (Pascual-Leone et al., 1996; Rohan et al., 2014). While PEMF may be useful tool for veterinary treatment of behavioral disorders, this is a new area of investigation and research studies focused on specific conditions will need to be carried out before any conclusions are drawn.

### 2.4. Safety

The known dangers of non-ionizing electromagnetic fields and radiofrequency fields are due to thermal effects (e.g., heating caused by microwave radiation). The Institute for Electrical and Electronics Engineers Standards for Radio Frequency Electromagnetic Field Exposure concluded that "A review of the extensive literature on radiofrequency biological effects, consisting of well over 1300 primary peer reviewed publications published as early as 1950, reveals no adverse health effects that are not thermally related". Non-invasive, non-thermal PEMF technologies have a long history of clinical use. Since the late 1990s, PEMF devices are estimated to have delivered over 3,000,000 treatments without reports of side effects or significant adverse events. Underscoring this point, two general reviews of clinical PEMF use found no evidence of significant adverse events nor side-effects in the literature reviewed (Guo et al., 2011; Guo et al., 2012).

### 2.5. Current trends in veterinary medicine

Both small and large animal veterinary practices are adapting to the currently evolving animal care landscape. Unsurprisingly, the priorities of pet owners and large animal caretakers are critical drivers of change and include preference for non-invasive, non-toxic, at-home treatments that are as feasible and well-tolerated as possible. There is also increasing emphasis on rehabilitation for chronic conditions and post-operative recovery and "prehabilitation" to reduce the risk of injury or chronic disease, or to condition an animal before surgical repair, competition or work.

Animal wellness is also an underlying theme for many of the new initiatives that are being adopted by leading veterinary practices. For example, recent research innovations have led to the development of validated instruments for measuring acute and chronic pain in dogs and cats, lending to pain-management care focused on improving quality of life (Brondani et al., 2011; Wiseman-Orr et al., 2006). Another effort, led by Dr. Martin Becker of Fear Free$^{SM}$, aims to reduce animal anxiety during veterinary visits, improving the experience for both animals and pet owners and also fostering improved compliance and quality of care.

The heightened focus on animal wellness and evolving priorities of pet owners have also contributed to veterinary treatment plans involving multiple modalities of therapy applied simultaneously or in sequence. Combined modes of treatment can include drugs, surgical intervention, device therapy, nutrition, exercise, manual therapy and behavior change, and are intended to both optimize clinical outcomes and minimize adverse effects of treatment. Multipronged treatment plans are particularly valuable for vexing yet common conditions such as osteoarthritis-associated pain, in which NSAIDs, steroid drugs, or opiates are prescribed but can be poorly tolerated and are ill-suited as long-term solutions for symptom management. In contrast, because of the multiple signaling pathways at work, PEMF not only address pain but has been shown to promote resolution of pathology by promoting blood flow, secretion of growth factors, and other pathways that can contribute to healing.

Apart from pharmacologic agents, a number of non-invasive devices have been developed and clinically implemented to treat inflammatory conditions and pain in both humans and animals. These technologies rely upon electromagnetic and mechanical stimulation of tissue to reduce symptomatology and promote healing. As these technologies represent a non-pharmaceutical alternative or adjunct to NSAIDs, they have been dubbed NPAID® or non-pharmaceutical anti-inflammatory devices.

PEMF devices, described above, provide a non-invasive form of treatment, both in-office and at home, that has been repeatedly found to be safe, effective, and affordable. These characteristics are attractive for both monotherapy and as an adjunct to traditional standard of care. PEMF is commonly used adjunctively with NSAIDs and steroidal drugs to augment clinical benefit or to facilitate administration of lower doses of drugs, underscoring the trend towards multimodal treatment.

Many veterinary practices also use Class III or IV lasers as an in-office treatment for strains, sprains, osteoarthritis, and wound healing. Some lasers have also been shown to reduce both pain and inflammation (Pryor and Millis, 2015). The risk of retinal and thermal tissue damage from these devices, however, generally restricts their use to certified medical professionals. Lastly, though not anti-inflammatory in mechanism, therapeutic ultrasound, which relies on high frequency sound wave treatment of tissue, also has a long history of veterinary use and is gaining further traction as research demonstrates its utility in treating stiffness, pain, and wounds (Kavros et al., 2008; Morishita et al., 2014; Zhang et al., 2016).

## 3. Conclusions

Early PEMF devices lacked systematic evidence. Natural skepticism of the utility of PEMF was compounded by unscrupulous marketing, unsubstantiated claims, and unproven, unregulated devices. However, in the last 30 years, clinicians and scientists have developed a significant volume of research involving cell models, animals, and humans demonstrating the biological effects and clinical value of PEMF treatment for a variety of conditions. Advancement of this field has significance for both human and veterinary medicine, particularly in the areas of pain management, mitigation of inflammation, bone healing, and wound healing. The most rigorous and compelling research has been conducted on devices that are regulated by the FDA.

Here we have reviewed PEMF history, regulatory status, and key studies and cases that illustrate clinical utility. These data underscore the usefulness of PEMF treatment as a safe, non-invasive treatment modality that has the potential to become an important stand-alone or adjunctive treatment modality in veterinary care. As the field of veterinary medicine continues to mature, further development and implementation of PEMF and other NPAID technologies will serve an important role in multimodal treatment strategies that aim to maximize animal wellness.

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## Declaration of interest

JSG declares no conflicts of interest. SH and BTG are paid consultants of Assisi Animal Health.

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