

HOW PEMF WORKS

Orthofix Pulsed Electromagnetic Field Technology for Bone Growth Therapy devices

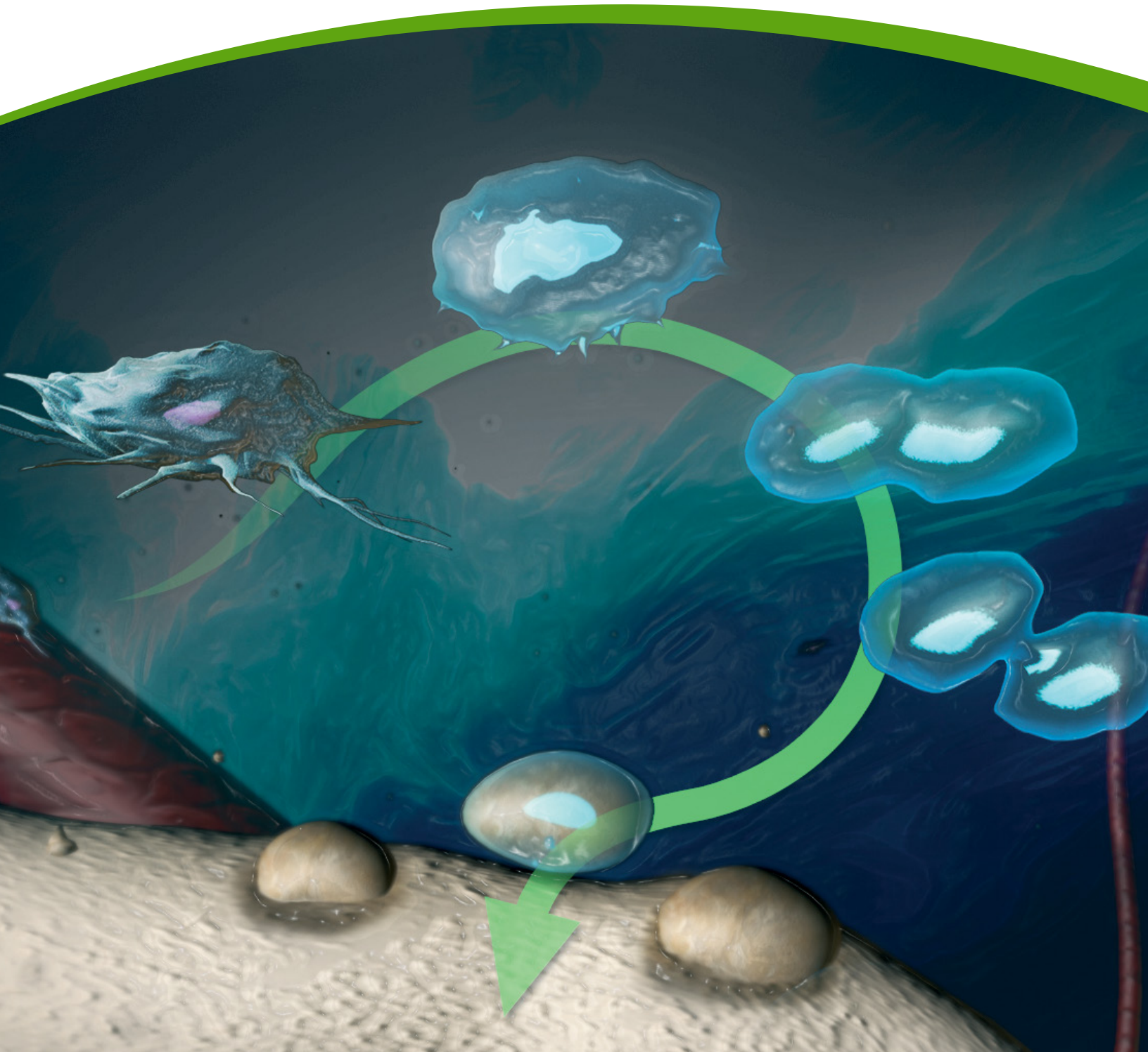


Table of Contents

- 2 How PEMF Stimulates Bone Healing
- 3 PEMF Impacts Bone Healing at a Molecular, Cellular and Tissue Level
- 4 PEMF at the Molecular Level
- 5 PEMF at the Cellular Level
- 6 PEMF at the Tissue Level
- 7 Four Phases of Bone Healing
- 9 Spinal Fusion
- 10 Fracture Healing
- 11 References
- 13 Glossary
- 14 Brief Prescribing Information

How PEMF Stimulates Bone Healing

How does PEMF affect spinal fusion?

A successful spinal fusion depends on many complex healing processes. In patients with conditions and risk factors that can lower fusion success rates, pulsed electromagnetic field (PEMF) stimulation helps create an environment conducive to healing. PEMF stimulation is a safe, noninvasive treatment prescribed by a physician to promote spine fusion success, or to treat a failed lumbar fusion with the goal of avoiding a revision surgery.¹⁻⁵

How does PEMF affect fracture healing?

When human bone is bent or broken, it generates an electrical field. This low level electrical field stimulates fracture healing.⁶⁻⁸ For years it has been known that bone tissue is deposited in regions of negative charge and absorbed in areas of positive charge.⁹ PEMF induces a negative electrical field at the fracture site which supports the natural healing process and stimulates fracture repair.⁶

In some patients this healing process is impaired or absent, and the fracture results in a nonunion. Electromagnetic stimulation has been shown to dramatically increase the speed and completeness of bone healing in large or slowly healing fractures.¹⁰



CervicalStim™ Device



SpinalStim™ Device



PhysioStim™ Device

The Orthofix® CervicalStim™, SpinalStim™, and PhysioStim™ devices help promote bone healing by providing 360 degrees of PEMF coverage.^{11, 12}

Orthofix Bone Growth Therapy Stimulators use a unique PEMF signal to create a conducive environment for bone healing.**

PEMF Impacts Bone Healing at a Molecular, Cellular and Tissue Level

Molecular Level

Within 10 minutes of PEMF exposure, signaling pathways are activated.¹³

Cellular Level

PEMF stimulates bone cells to proliferate, differentiate, and mineralize.^{14, 15}

**360°
Coverage
at Bone
Healing Site^{11, 12}**

Tissue Level

PEMF has been shown to improve the quality of bone tissue and enhance bone preservation.¹⁶⁻¹⁸

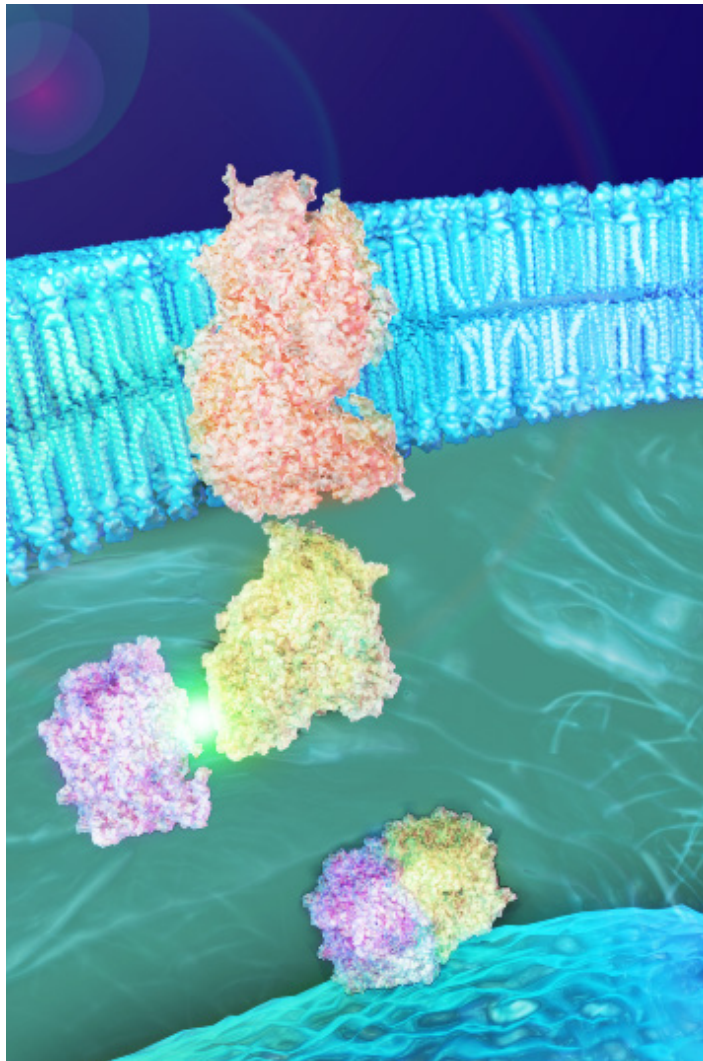


PEMF at the Molecular Level

Research on the Molecular Impact of PEMF Demonstrates:

- Exposure of a bone-forming cell (osteoblast) to PEMF generates an electric field gradient across the cell membrane¹⁹
- Following this activation, bone cells recognize PEMF with an immediate intracellular response^{13, 20}
- Similar to growth factors (PTH and Insulin), PEMF activates signaling pathways within minutes¹³
- Activating cellular signaling pathways with PEMF results in cell growth, proliferation, and differentiation¹³⁻¹⁵

PEMF Activates Signaling Pathways^{13, 15, 21}

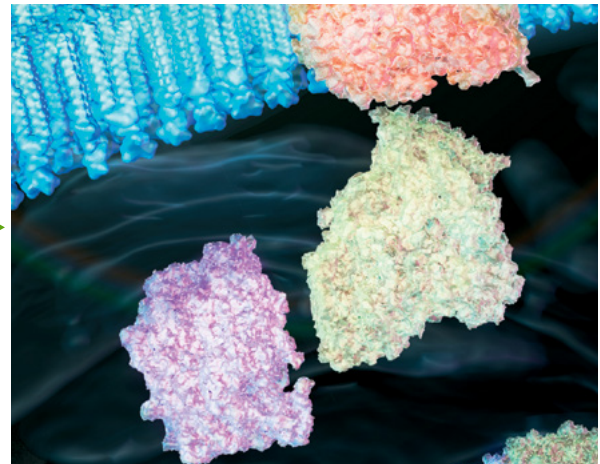


PEMF at the Cellular Level

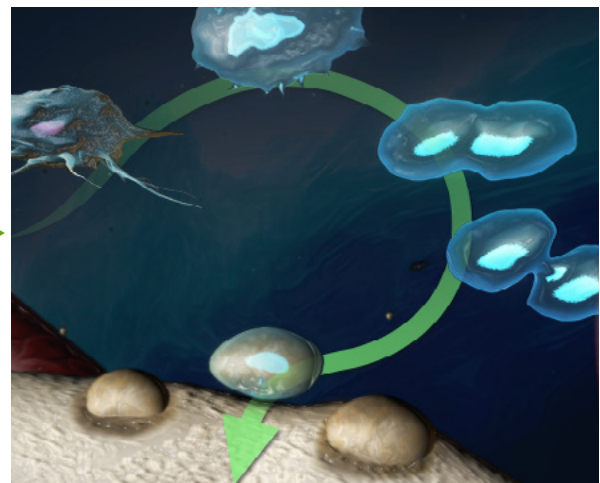
Research at The Cleveland Clinic, New York University and the University of California, San Francisco have significantly advanced our understanding of how PEMF stimulates tissue repair at the cellular level:

- PEMF shows an early anti-inflammatory effect²²
- PEMF treatment causes a significant increase in expression for genes involved in proliferation, differentiation, and mineralization¹⁴
- The use of PEMF and BMP-2 together has been documented to have an additive effect on cell growth and proliferation, which suggests that each intervention utilizes a separate intracellular signaling pathway^{13, 14, 23}

PEMF activates signaling pathways¹³



Bone cell growth and proliferation is enhanced¹⁴



PEMF at the Tissue Level

The application of PEMF has been documented to have a significant effect on bone tissue in animal studies completed at the Cleveland Clinic.^{16-18, 24}

PEMF Increases Bone Volume and Quality^{17, 18}

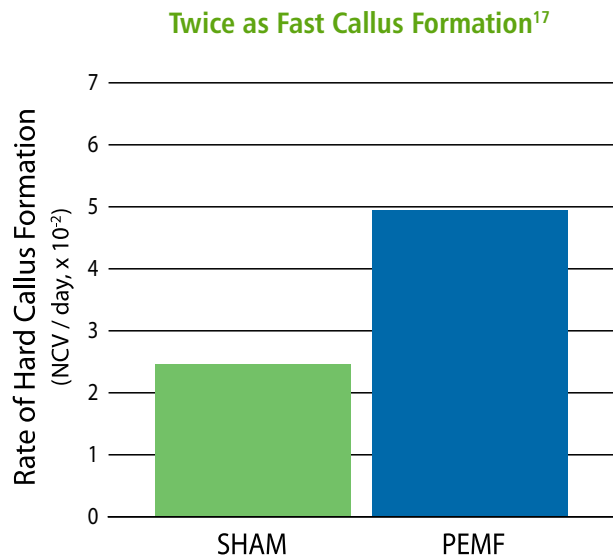
- In a fibular fracture model (rat osteotomy), the group treated with PEMF was shown to have a 2-fold increase in bone volume 13-20 days postoperatively compared with the control group. A histological comparison between osteotomy sites revealed the bone quality was better in sites treated with PEMF.

PEMF Slows Bone Resorption in a Pre-Clinical Disuse Model¹⁶

- A separate study also utilizing a fibular fracture model (rat osteotomy) reported the group treated with PEMF experienced a 75% preservation of bone volume at the distal fibular end in comparison to controls.

PEMF Mitigates Bone Loss in a Pre-Clinical Osteoporosis Model²⁴

- In an osteoporosis reversal rodent model it was shown that specific PEMF signals were able to mitigate the bone loss similarly to bisphosphonate (alendronate) treated animals.



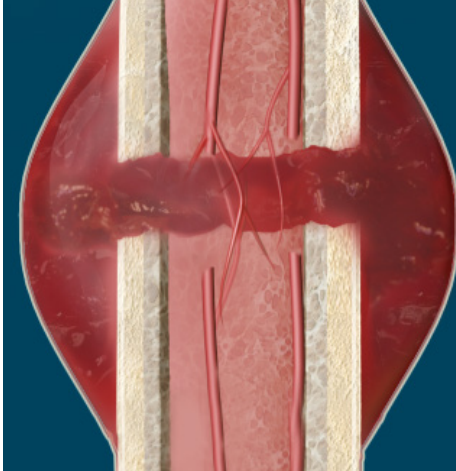
Notes:

- Significantly faster rate of callus formation for PEMF
- NCV = Normalized Callus Volume

PEMF has been shown to improve the quality of bone tissue and enhance bone preservation.^{** , 16, 17}

Four Phases of Bone Healing

Phase 1: Hematoma

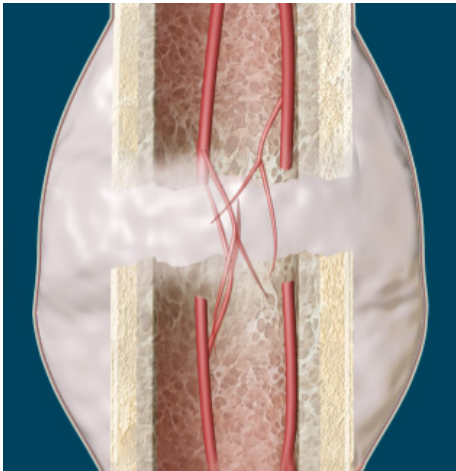


- When a bone breaks, blood vessels in the bone and periosteum are torn and hemorrhage, and a hematoma (blood clot) forms at the fracture site.
- Tissue at the site becomes swollen and painful in response to inflammatory factors.
- New blood vessels begin to form to reestablish the blood supply.

PEMF Benefit

- PEMF stimulates an increase in blood vessel production.⁷

Phase 2: Formation of Soft Callus

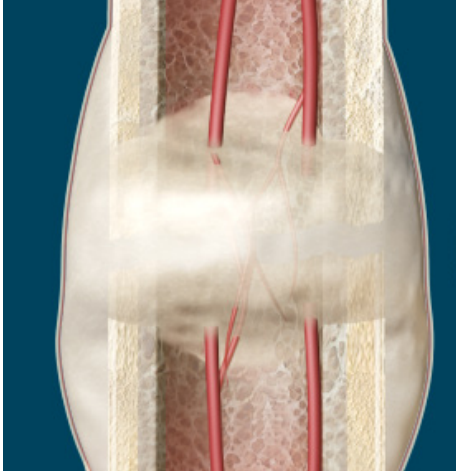


- Inflammatory factors attract cells to the site.
- Cells remove the hematoma and bone debris.
- For healing to progress at this stage, the inflammatory response must cease.
- Cells begin reconstructing the bone by laying down matrix. Proteins and mineralization factors produced by the osteoblasts (bone forming cells) begin to consolidate into what is known as a soft callus.

PEMF Benefit

- PEMF amplifies calcium flux, which activates signal transduction pathways.²⁵
- Activated pathways increase the production of growth factors.¹⁰
- These growth factors promote healing by increasing the number and activity of osteoblasts.¹⁰

Phase 3: Formation of Hard Callus

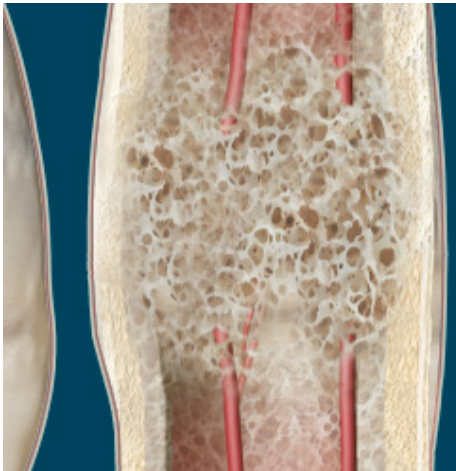


- Osteoblasts mineralize the matrix, converting soft callus into hard callus.

PEMF Benefit

- PEMF treatment increases mineralization of this matrix and calcification of fibrocartilage.^{10, 17}

Phase 4: Remodeling



- Woven bone is remodeled into stronger lamellar bone by the orchestrated action of osteoblast bone formation cells and osteoclast bone resorption cells.
- Eventually, the fracture callus is remodeled into a new shape which closely duplicates the bone's original shape and strength.

PEMF Benefit

- PEMF stimulates remodeling activity by increasing the rate of osteoblast activity.¹⁰

Spinal Fusion

Clinical studies have validated the effectiveness of Orthofix PEMF devices¹⁻⁵

Patients undergoing interbody lumbar spinal fusion treated with PEMF in a prospective, double-blinded, randomized, controlled trial had significantly higher fusion rates than patients without adjunctive PEMF treatment.^{1,3}

- 195 patients (98 PEMF group/97 placebo control group): Among consistent users⁺, fusion success rates were 92% in the PEMF group compared with 68% in the control group ($P < 0.001$).

PEMF is a safe and effective alternative to surgical treatment for patients with established spinal pseudarthrosis.²

- A prospective, multi-center, open trial was conducted on 100 patients where at least 9 months elapsed following spine fusion surgery with 3 months of no progressive healing shown on radiographs. These patients had risk factors such as revisions, multilevel fusions, and smoking. An overall fusion success rate of 67% was reached in this population of previously failed patients.

Patients undergoing cervical fusion treated with PEMF in a prospective, controlled, randomized clinical trial had significantly higher fusion rates than patients without adjunctive PEMF treatment.^{4,5}

- 323 patients (163 PEMF group/160 control group): There was a fusion success rate of 84% in the PEMF group compared with 69% in the control group ($P = 0.0065$). The fusion success rate in patients age 50 and above in the PEMF group was 81% compared with 56% in the control group ($P = 0.004$).

⁺Consistent users were patients wearing the device 2 or more hours per day.

PEMF has been proven to be a safe and effective noninvasive treatment to improve overall spinal fusion healing success rates.¹⁻⁵

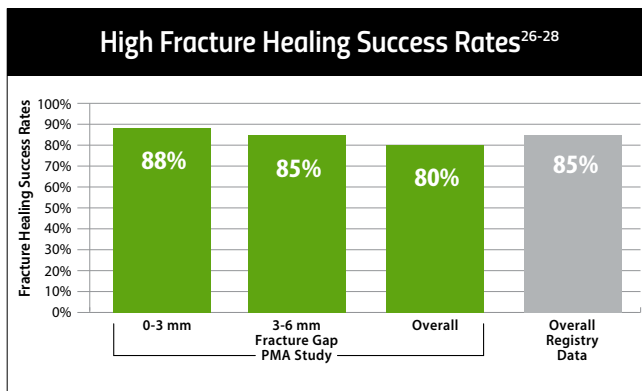
Fracture Healing

Clinical studies have validated the safety and effectiveness of Orthofix PEMF devices:

In a prospective clinical trial, Garland et al confirmed the effectiveness of PEMF on fracture nonunions. A nonunion was defined as a fracture that failed to demonstrate both clinical and radiographic union at least nine months after the original insult.^{26, 27}

When the PEMF unit was worn for 3 hours per day, there was an overall healing success rate of 80% in long bone nonunions without any additional surgery required. The results of the study also show that the success rate for fracture gaps 0-3mm was 88%, and the success rate for fracture gaps 3-6mm was 85%.^{26, 27}

In addition to the prospective clinical trial proving the safety and effectiveness for fracture nonunion, Orthofix conducted a 4-year follow-up on those patients who were prescribed the PhysioStim device. After PMA approval was received, a Patient Registry was conducted. Both the long term follow-up and the registry confirm the high healing success rate reported in the original PMA study.²⁸



Healing Success in Common Nonunion Sites ²⁸	
Femur	84.2%
Fibula	91.4%
Metatarsal	90.9%
Tibia	89.0%

PEMF has been proven to be a safe and effective noninvasive treatment to improve overall nonunion fracture healing success rates.²⁶⁻²⁸

References

1. Mooney V. Pulsed electromagnetic fields: an adjunct to interbody spinal fusion surgery in the high risk patient. *Surg Technol Int* 1993, 2:405-410
2. Simmons JW Jr, Mooney V, Thacker I. Pseudarthrosis after lumbar spine fusion: nonoperative salvage with pulsed electromagnetic fields. *Am J Orthop*. 2004;33(1):27-30
3. PMA P850007/S6. February 1990
4. Foley KT, Mroz TE, Arnold PM, et al. Randomized, prospective, and controlled clinical trial of pulsed electromagnetic field stimulation for cervical fusion. *Spine J*. 2008;8(3):436-442
5. PMA P030034. December 2004
6. Bassett, CA. Fundamental and practical aspects of therapeutic uses of pulsed electromagnetic fields (PEMFs). *Crit Rev Biomed Eng*. 1989; 17(5):451-529
7. Yen-Patton GP, et al. Endothelial cell response to pulsed electromagnetic fields: stimulation of growth rate and angiogenesis in vitro. *J Cell Physiol*. 1988 Jan; 134(1): 37-46
8. Zoltan, JD. Electrical Stimulation of Bone: An Overview. *Seminars in Orthopaedics*, Vol 1, No 4 (December), 1986: 242-252
9. Bassett CA. A biophysical approach to craniofacial morphogenesis. *Acta morphologica Neerlando-Scandinavica*. 1972;10(1):71-86
10. Barnes F, Greenebaum B. *Biological and Medical Aspects of Electromagnetic Fields*. CRC Press, 2007
11. Zborowski M, Androjna C, Waldorff EI, Midura RJ. Comparison of therapeutic magnetic stimulation with electric stimulation of spinal column vertebrae. *IEEE Transactions on Magnetics*, Vol. 51, No. 12, December 2005, 5001009. Erratum in *IEEE Transactions on Magnetics*, Vol. 53, No. 2, February 2007, 9700101
12. Data on file. Field mapping analysis conducted by M. Zborowski, Ph.D., Cleveland Clinic
13. Schnoke M, Midura RJ. Pulsed electromagnetic fields rapidly modulate intracellular signaling events in osteoblastic cells: comparison to parathyroid hormone and insulin. *J Orthop Res*. 2007;25(7):933-40
14. Selvamurugan N, Kwok S, Vasilov A, Jefcoat SC, Partridge NC. Effects of BMP-2 and pulsed electromagnetic field (PEMF) on rat primary osteoblastic cell proliferation and gene expression. *J Orthop Res*. 2007;25(9):1213-20
15. Selvamurugan N, He Z, Rifkin D, Dabovic B, Partridge NC. Pulsed Electromagnetic Field Regulates MicroRNA 21 Expression to Activate TGF- Signaling in Human Bone Marrow Stromal Cells to Enhance Osteoblast Differentiation. *Stem cells international*. 2017 Apr 23;2017. doi.org/10.1155/2017/2450327
16. Ibiwoye MO, Powell KA, Grabiner MD. Bone mass is preserved in a critical-sized osteotomy by low energy pulsed electromagnetic fields as quantitated by in vivo micro-computed tomography. *J Orthop Res*. 2004;22(5):1086-93

17. Midura RJ, Ibiwoye MO, Powell, KA, et al. Pulsed electromagnetic field treatments enhance the healing of fibular osteotomies. *J Orthop Res.* 2005;23:1035-46
18. Androjna C, Fort B, Zborowski M, Midura R. Pulsed electromagnetic field treatment enhances healing callus biomechanical properties in an animal model of osteoporotic fracture. *Bioelectromagnetics.* 2014; 35(6): 396-405
19. Panagopoulos DJ, Karabarbounis AK, Margaritis LH. Mechanism for action of electromagnetic fields on cells. *Biochem Biophys Res Commun.* 2002;298:95-102
20. Vincenzi F, Targa M, Corciulo C, Gessi S, Merighi S, Setti S, Cadossi R, Goldring MB, Borea PA, Varani K. Pulsed Electromagnetic Fields Increased the Anti-Inflammatory Effect of A2A and A3 Adenosine Receptors in Human T/C-28a2 Chondrocytes and hFOB 1.19 Osteoblasts. *PLOS ONE* 2013; 8(5):e65561
21. Brighton CT, Wang W, Seldes R, Zhang G, Pollack SR. Signal Transduction in Electrically Stimulated Bone Cells. *Journal of Bone and Joint Surgery* 2001; 83A(10): 1514-1523.
22. Miller SL, Coughlin DG, Waldorff EI, Ryaby JT, Lotz JC. Pulsed electromagnetic field (PEMF) treatment reduces expression of genes associated with disc degeneration in human intervertebral disc cells. *Spine J* 2016;16:770e6
23. Schwartz Z, Simon BJ, Duran MA, Barabino G, Boyan BD. Pulsed Electromagnetic Fields Enhance BMP-2 Dependent Osteoblastic Differentiation of Human Mesenchymal Stem Cells. *Journal of Orthopaedic Research* 2008; 26:1250-1255
24. Androjna C, Waldorff EI, Ryaby JT, Zborowski M, Midura RJ. "Optimizing Pulsed Electromagnetic Field (PEMF) Signals to Reduce Bone Loss Associated with Osteoporosis", Poster category: Bone - Osteoporosis, Metabolic Bone Disease, Biomarkers (PS2-110), Poster #: 1670, March 19-22, 2017, ORS (Orthopaedic Research Society), San Diego, California, USA
25. Spadaro J, Bergstrom W. In Vivo and In Vitro Effects of a Pulsed Electromagnetic Field on Net Calcium Flux in Rat Calvarial Bone. *Calcif Tissue Int.* 2002; 70:496-502
26. Garland DE, Moses B, Salver W. Fracture healing: Long-term follow-up of fracture nonunions treated with PEMFs. *Contemp Orthop.* 1991;22(3):295-302
27. PMA P850007. February 1986
28. Orthofix patient registry. PMA P850007/S20. Data on file

**The results of preclinical studies may not be indicative of human clinical trials.

Glossary

- OSTEOBLASTS- bone forming cells
- OSTEOCLASTS- cells that break down bone, involved in remodeling
- GROWTH FACTOR- a substance (typically a protein or a hormone) that stimulates growth of a cell population and stimulates maturity of the cell.
- PROLIFERATION- increase cell population/number of cells
- DIFFERENTIATION- maturity of the cells; only mature cells can be active/result in bone formation.
- CYTOKINE- protein signaling molecules involved in the inflammatory response.

Brief Prescribing Information

Full prescribing information can be found in product labeling on our patient education website www.BoneGrowthTherapy.com or by calling Patient Services at 1-800-535-4492.

Caution: Federal law (USA) restricts this device to sale by or on the order of a physician.

SpinalStim™ Device:

The SpinalStim device is indicated as a spinal fusion adjunct to increase the probability of fusion success and as a nonoperative treatment of salvage of failed spinal fusion, where a minimum of nine months has elapsed since the last surgery. Cardiac pacemakers may be adversely affected by exposure to pulsed electromagnetic fields. Use of this device is contraindicated where the individual has an implanted cardiac pacemaker. The safety and effectiveness of this device has not been established for individuals lacking skeletal maturity. The safety of this device for use on patients who are pregnant or nursing has not been established. Rare instances of reversible minor discomfort have been reported.

CervicalStim™ Device:

The CervicalStim device is indicated as an adjunct to cervical fusion surgery in patients at high risk for non-fusion; there are no known contraindications. Do not use this device if you have a cardiac pacemaker or defibrillator. Remove the device prior to any imaging procedures. The safety of this device for use on patients who are pregnant or nursing has not been established. Adverse effects may include increased pain, numbness and tingling, headache, migraines and nausea; these effects may or may not be directly related to use of the device.

PhysioStim™ Device:

The PhysioStim device is indicated for the treatment of an established nonunion acquired secondary to trauma, excluding vertebrae and all flat bones, where the width of the nonunion defect is less than one-half the width of the bone to be treated. A nonunion is considered to be established when the fracture site shows no visibly progressive signs of healing.

Use of this device is contraindicated where the individual has synovial pseudarthrosis. Demand type pacemaker operation may be adversely affected by exposure to pulsed electromagnetic fields. The safety and effectiveness of this device has not been established for individuals lacking skeletal maturity or individuals with a nonunion secondary to, or in connection with, a pathological condition. The safety of this device for use on patients who are pregnant or nursing has not been established. Rare instances of reversible minor discomfort have been reported.

PROVEN SUCCESS

Pulsed Electromagnetic Field (PEMF)



CERVICALSTIM™
SPINAL FUSION THERAPY



SPINALSTIM™
SPINAL FUSION THERAPY



PHYSIOSTIM™
BONE HEALING THERAPY

