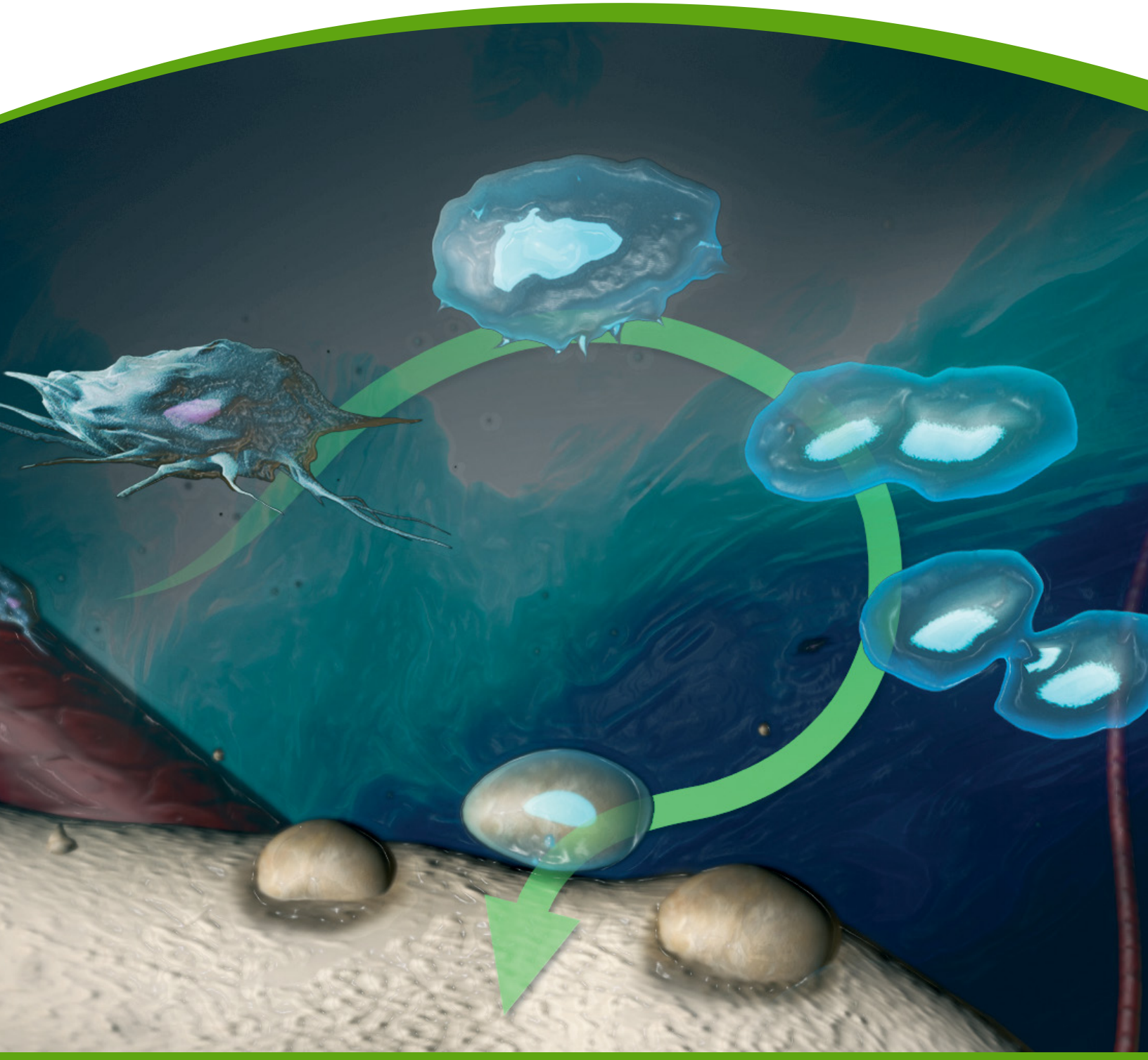
HOW PEMF WORKS

Orthofix Pulsed Electromagnetic Field Technology for Bone Growth Therapy devices



ORTHOFIX®

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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

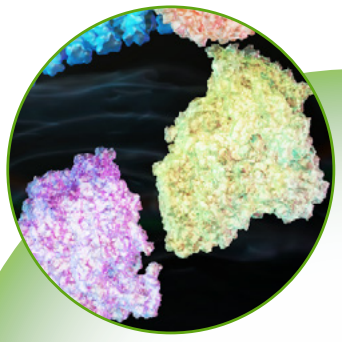
The Orthofix® CervicalStim™, SpinalStim™, and PhysioStim™ devices help promote bone healing by providing 360 degrees of PEMF coverage.[11, 12]

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

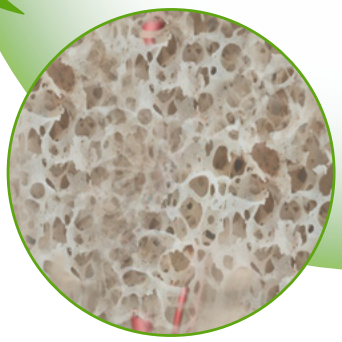
Within 10 minutes of PEMF exposure, signaling pathways are activated.[13]



Cellular Level

PEMF stimulates bone cells to proliferate, differentiate, and mineralize.[14, 15]

360° Coverage at Bone Healing Site[11, 12]



Tissue Level

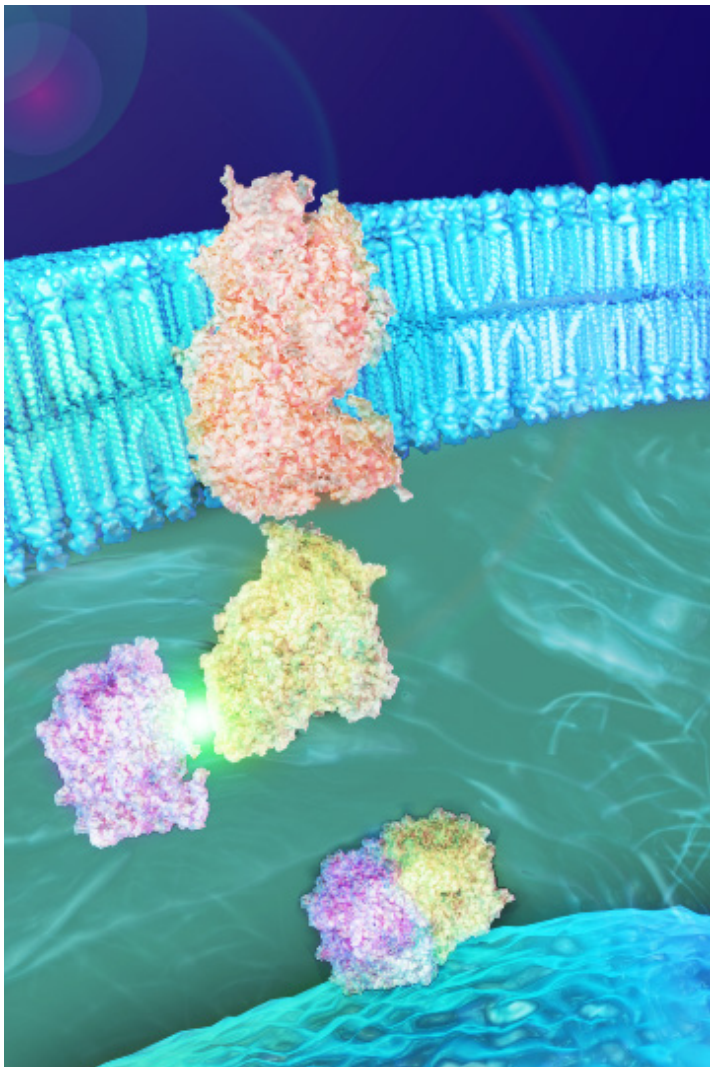
PEMF has been shown to improve the quality of bone tissue and enhance bone preservation.[16-18]

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 membrane[19]
- 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 minutes[13]
- Activating celluar signaling pathways with PEMF results in cell growth, proliferation, and differentiation[13-15]

PEMF Activates Signaling Pathways[13, 15, 21]

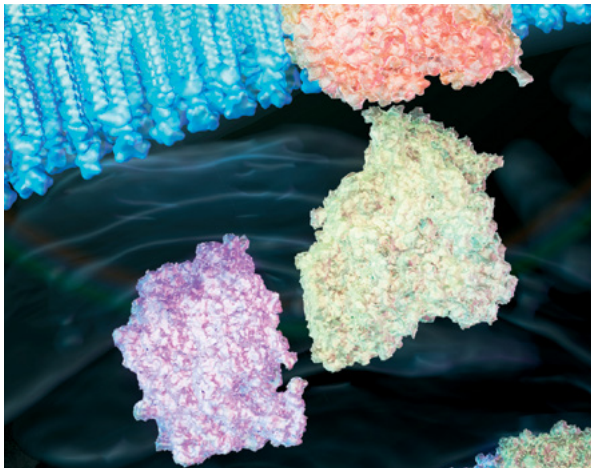


PEMF at the Cellular Level

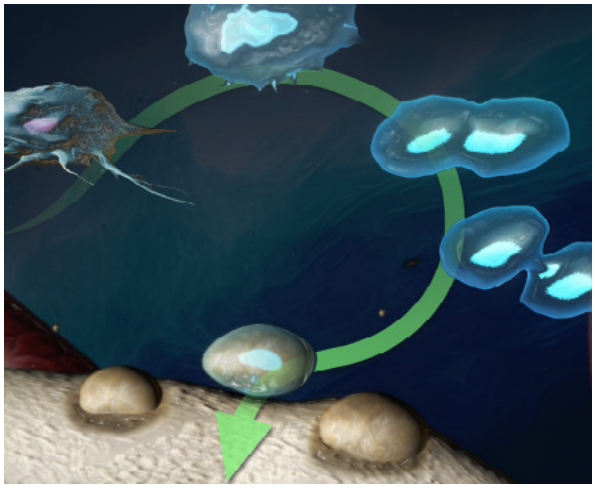
Research at The Cleveland Clinic, New York University and the University of California, San Francisco have significantly advanced our understanding of how PEMF stimulates tissue repair at the cellular level:

- PEMF shows an early anti-inflammatory effect[22]
- PEMF treatment causes a significant increase in expression for genes involved in proliferation, differentiation, and mineralization[14]
- 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 pathways[13]



Bone cell growth and proliferation is enhanced[14]



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.

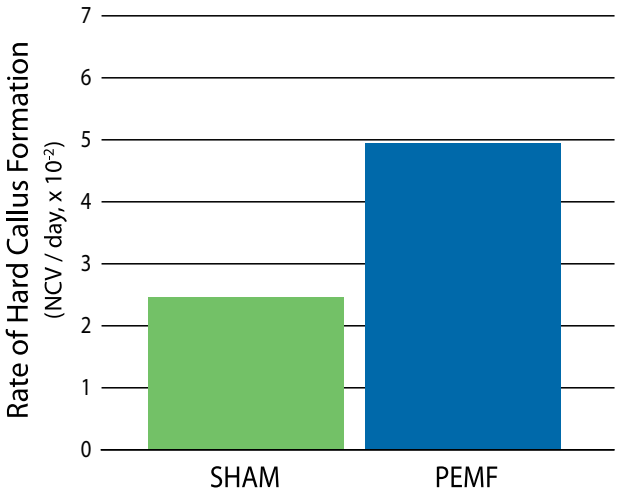
PEMF Slows Bone Resorption in a Pre-Clinical Disuse Model[16]

- 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 Model[24]

- 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.

Twice as Fast Callus Formation[17]



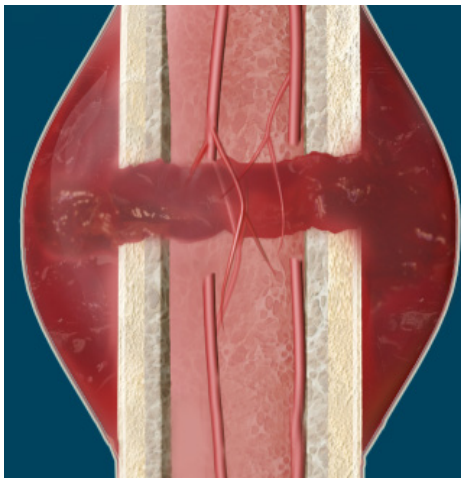
Notes:

- 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

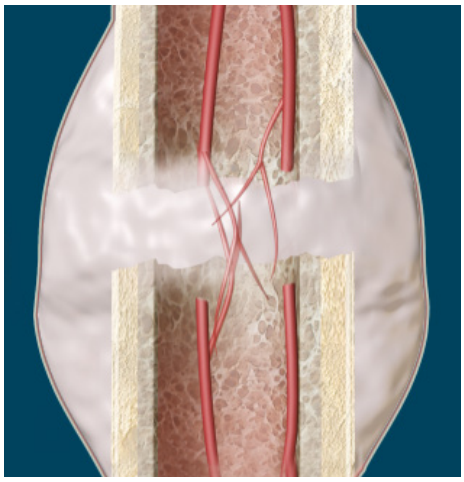


- When a bone breaks, blood vessels in the bone and periosteum are torn and hemorrhage, and a hematoma (blood clot) forms at the fracture site.
- Tissue at the site becomes swollen and painful in response to inflammatory factors.
- New blood vessels begin to form to reestablish the blood supply.

PEMF Benefit

- PEMF stimulates an increase in blood vessel production.[7]

Phase 2: Formation of Soft Callus

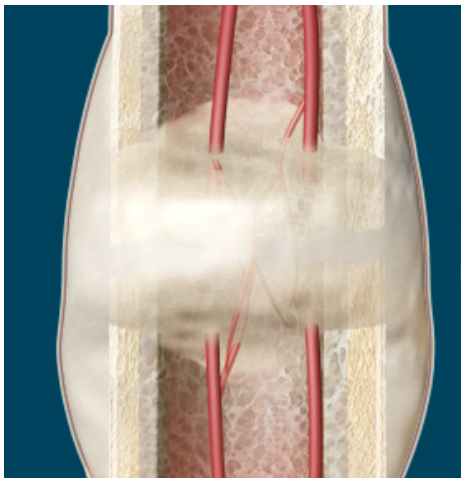


- Inflammatory factors attract cells to the site.
- Cells remove the hematoma and bone debris.
- For healing to progress at this stage, the inflammatory response must cease.
- Cells begin reconstructing the bone by laying down matrix. Proteins and mineralization factors produced by the osteoblasts (bone 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

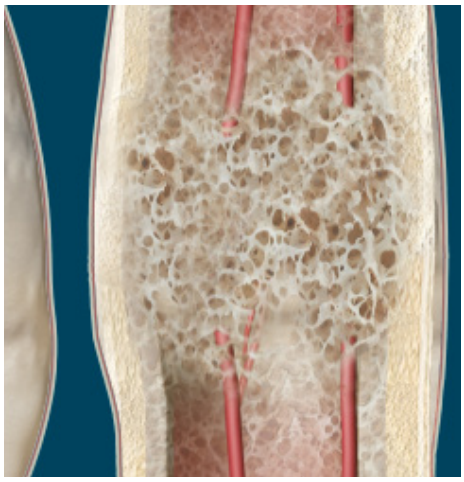


- Osteoblasts mineralize the matrix, converting soft callus into hard callus.

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 devices[1-5]

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

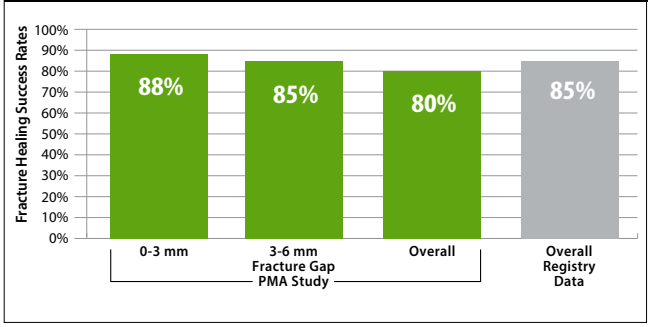
Clinical studies have validated the safety and effectiveness of Orthofix PEMF devices:

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]

High Fracture Healing Success Rates[26-28]



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]

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**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™
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