

Appendix D

Appendix D

Detailed Study Summaries: Studies from RS Medical's Petition (Part I) and Studies from the BGS Group's Literature Search (Part II)

Part I: Papers Cited in RS Medical's Petition

1 Jenis et al., 2000

Citation	Prospective Comparison of Effect of Direct Current Electrical Stimulation and Pulsed Electromagnetic Fields on Instrumented Posterolateral Lumbar Arthrodesis L.G. Jenis, H.S. An, R. Stein, and B. Young Journal of Spinal Disorders, 13(4): 290 – 296, 2000
Intended Use	<input checked="" type="checkbox"/> Lumbar spinal fusion
Stimulation Type	<input checked="" type="checkbox"/> PEMF <input checked="" type="checkbox"/> Implanted stimulation device (direct current)
Commercial Device Name(s)	SpinalStim 8212 (PEMF)
Overall Study Design	<input checked="" type="checkbox"/> Randomized, concurrent control, prospective Three arms: standard therapy, standard plus implanted DC stimulation, standard plus PEMF stimulation
# Patients	61 22, standard therapy 22, standard + PEMF 17, standard + implanted DC
Selection Criteria	Inclusion: <ul style="list-style-type: none"> • To undergo posterolateral lumbar or lumbosacral fusion w/ instrumentation and autogenous iliac crest bone graft. • Age between 18 and 75. Exclusion: <ul style="list-style-type: none"> • Previous interbody fusion surgery. • Preoperative infection. • Depressed immune system. • Regional conditions affecting bone metabolism. • Systemic diseases including renal disease, uncontrolled diabetes, metastatic carcinoma. • Implanted pacemaker, defibrillator, or dorsal column stimulator.
Methods	All received surgery using posterior lumbar approach, bilateral intertransverse process fusion, and insertion of pedical screws. All were fitted with a rigid lumbosacral orthosis for 10-12 weeks. Those randomized to the SpinalStim were trained on care and use. They were instructed to use it for at least 2 hours each day on at least 90% of the first 150 consecutive days after surgery. A device printout was obtained to determine the extent of patient compliance. Those randomized to DC stimulation had the stimulation device placed at the time of surgery. The exact nature of the stimulation pattern, strength, etc. were not described.

	<p>Patients were followed for one year. At three and 12 months, there were anteroposterior radiographs to assess the density of the fusion bone mass. At twelve months, additional views were taken to determine the level of arthrodesis. The radiographic analysis was carried out by an independent observer not involved in the patient care. Clinical outcome was also assessed at 12 months by evaluating function and pain levels as assessed by an independent questionnaire. The questionnaire and its grading criteria were not described.</p>
Success/Failure Criteria	<p>Radiographically, the degree of fusion was graded on a 3-point scale: 1 if there were obvious pseudoarthrosis in the fusion mass and discontinuity between the transverse processes, 2 if there were possible pseudoarthroses with areas of lucency, and 3 if there was solid arthrodesis with trabecular bridging bone.</p> <p>The clinical evaluation resulted in one of four classifications: excellent for full return to activity, no analgesics and no significant pain; good for return to most activities, minimal analgesics, and minimal pain; fair if there were significant activity limitations, moderate analgesic requirements, and moderate pain; or poor if there was no return to preoperative activity, heavy analgesic requirements, and significant pain.</p>
Results	<p>Radiologic Effectiveness:</p> <ul style="list-style-type: none"> • Standard therapy: Grade 1: 4.7%, Grade 2: 14.3%, Grade 3: 81% • PEMF: Grade 1: 5.0%, Grade 2: 30%, Grade 3: 65% • Implanted DC: Grade 1: 0%, Grade 2: 38.9%, Grade 3: 61.1% • No significant difference among groups. <p>Clinical Effectiveness:</p> <ul style="list-style-type: none"> • Standard therapy: Excellent 43%, Good 43%, Fair 14%, Poor 0% • PEMF: Excellent 35%, Good 50%, Fair 10%, Poor 5% • Implanted DC: Excellent 32%, Good 37%, Fair 31% • No significant difference among groups. <p>Other Effectiveness:</p> <p>The authors detected trends toward greater bone mass density in the electrically stimulated patients, but the differences were not statistically significant.</p> <p>Safety:</p> <p>Two wound infections in each treatment group. One epidural hematoma in the standard therapy group. No complications directly attributed to the stimulation devices.</p>
Potential Sources of Bias	<p>Observer bias in the radiological assessments could not be completely eliminated, because the implantable stimulation device would be visible on the x-rays.</p> <p>There is a possibility of bias in the clinical evaluations, but there is not enough information on the scoring system to either confirm or rule out such bias.</p>
Other Limitations of the Study	<p>This study had a very specific focus: to determine if electrical stimulation provided any additional benefit when spinal fusion surgery was completed using a specific technique and rigid instrumentation. The authors note that the technique alone tends to provide very good results. The applicability of these results to other uses of electrical bone growth stimulation in which good results may not be as routine is unclear.</p> <p>This study only looked at only one form of non-invasive stimulation and did not give detailed information on the nature of the implanted stimulation. Both of these limitations make it difficult to apply these results to other types of stimulation devices.</p> <p>The reproducibility of the results is also difficult to assess because little information is given about the questionnaire used to determine clinical outcomes. The authors do not provide the specific questions, any information on validation studies, the scoring system that was used.</p>

2. Linovitz et al., 2002

Citation	<p>Combined Magnetic Fields Accelerate and Increase Spine Fusion. A Double-Blind, Randomized, Placebo-Controlled Study</p> <p>R.J. Linovitz, M. Pathria, M. Bernhardt et al.</p> <p>Spine 27(13): 1382-1389, 2002</p>
Intended Use	<input checked="" type="checkbox"/> Lumbar spinal fusion
Stimulation Type	<input checked="" type="checkbox"/> Combined magnetic field
Commercial Device Name(s)	SpinaLogic
Overall Study Design	<p><input checked="" type="checkbox"/> Randomized, concurrent control, prospective</p> <p>Control group was a placebo-controlled group that used an inactive sham device. Clinicians and patients were both unaware of device activity status.</p>
# Patients	<p>243 enrolled (201 evaluable)</p> <p>Placebo: 118 (97 evaluable)</p> <p>Active Device: 125 (104 evaluable)</p>
Selection Criteria	<p>Inclusion:</p> <ul style="list-style-type: none"> • Underwent primary noninstrumented intertransverse fusion of one or two vertebral levels between L3 and S1. • At least 18 years of age. • Some autograft bone, with or without allograft material. • Device first used within 30 days of surgery. <p>Exclusion:</p> <ul style="list-style-type: none"> • Use of instrumentation. • Prior fusion surgery of any type. • Malignancy. • Metabolic bone disease. • Severe osteoporosis. • Spondylitis. • Implanted cardiac pacemaker. • Pregnancy.
Methods	<p>Patients were enrolled and randomized within 30 days of surgery.</p> <p>After enrollment, patients received either an active or placebo stimulation device. The device contained an internal timer and microprocessor control to limit the amount of time the stimulation could be delivered and also provided a compliance record.</p> <p>Clinical and radiographic follow-up was done at 3, 6, and 9 months after surgery. Routine radiographic imaging included anteroposterior, lateral, and oblique views. CT scans were completed at 9 months. The primary endpoint was fusion status at 9 months. The evaluation was completed by a three-reviewer panel, none of whom knew whether the patient had been treated with an active or a placebo device.</p>
Success/Failure Criteria	<p>The fusion was graded as 0, no fusion; 1, minimal fusion; 2, moderate fusion; and 3, solid fusion. The criteria for assigning each of the grades include the amount of continuity in the fusion mass and whether or not there is motion within the mass. Those with grade 0 or 1 (with motion in the fusion mass) are considered to be failures, and those with grade 2 or 3 (no motion in the fusion mass) are considered successes. Analysis was repeated for both the fully evaluable patients and under intention-to-treat rules, with patients who dropped out</p>

	considered as failures.
Results	<p>Effectiveness:</p> <p>The active treatment group had a 64% fusion success rate at 9 months, as compared to 43% success in the placebo group. This difference was statistically significant ($P = 0.003$ by Fisher's exact test). When stratified by gender, the difference was statistically significant for women, but not for men. When withdrawn patients were included and handled as failures, the results remained statistically significant overall, and for women as a subgroup.</p> <p>A secondary endpoint was a repeated measures analysis looking at the rate of healing. The results support the hypothesis of more rapid healing in the stimulated patients.</p> <p>Safety:</p> <p>The authors do not comment on the presence or absence of any complications or adverse events.</p>
Other Limitations of the Study	<p>The study was limited to primary, noninstrumented fusion surgeries and combined magnetic field stimulation. The results may not be applicable to revision surgeries, instrumented surgeries, other intended uses, or other stimulation types.</p> <p>The authors report that the patient population was relatively older than in most studies, but the impact of the age difference is not clear.</p>

3. Mooney, 1990

Citation	<p>A randomized double-blind prospective study of the efficacy of pulsed electromagnetic fields for interbody lumbar fusions</p> <p>V. Mooney</p> <p>Spine 15(7): 708-712, 1990</p>
Intended Use	<input checked="" type="checkbox"/> Lumbar spinal fusion
Stimulation Type	<input checked="" type="checkbox"/> PEMF
Commercial Device Name(s)	Specific device model not named, but study was in cooperation with American Medical Electronics.
# Patients	<p>Total enrolled: 206</p> <p>Total completing study: 195</p> <p>Active device group: 107 assigned, 98 completed</p> <p>Placebo device: 99 assigned, 87 completed</p>
Selection Criteria	<p>Inclusion:</p> <ul style="list-style-type: none"> • Age at least 18 years old. • Initial attempt at interbody spinal fusion, anterior or posterior approach, with or without internal fixation. <p>Exclusion:</p> <ul style="list-style-type: none"> • Trauma. • Inflammatory condition of the spine. • Severe osteoporosis. • Metabolic problems (e.g., diabetes or renal dysfunction). • Metastatic cancer.
Methods	<p>All patients underwent a surgical interbody fusion procedure. The nature of the graft varied among patients (autogenous, cadaverous, or both) as did the presence or absence of internal fixation.</p> <p>All patients were fitted for a brace that incorporated a PEMF stimulation unit. Neither the</p>

	<p>patient nor the clinician knew if the stimulation unit was active or inactive. Patients were instructed to use the brace for at least 8 hours a day. Compliance was monitored internally by the device, but patients did not know this.</p> <p>The timing of follow-up assessments was not specified, only that the surgeon "identified the radiographic status at the time of union." The radiographic analysis was based on an estimate of the percent of graft assimilation. The initial evaluation was made by the surgeon, and then confirmed by the radiologist. If these two observers disagreed, an independent orthopedic surgeon was used. This independent observer could cause a patient initially classified as a success to be converted to a failure, but could not cause a patient initially classified as a failure to be reclassified as a success.</p> <p>There was also an assessment of clinical outcome, with patients classified as having an excellent, good, fair, or poor outcome. The methods for making the clinical assessments were not given.</p>
Success/Failure Criteria	Patients were classified as a success if the radiographic analysis indicated that the fusion was at least 50% assimilated.
Results	<p>When all patients completing the study are considered, the success rate in the active treatment group was 81/98 (82.7%), and in the placebo group, 64.9%. However the success rate they use for statistical analysis is the success rate for the 64 patients from the active group who consistently used the device more than four hours, which was 59/64 (92.2%). When they compare the success rate of consistent users to the overall rate of success in the placebo group, they found the difference to be statistically significant ($P < 0.005$). The author did not identify the specific statistical test used. It is unclear why they did not compare consistent users of the active device with consistent users of the placebo device, in whom the success rate was 67.9%.</p> <p>The author presented several subgroup analyses of the results for consistent users in both the active and inactive groups in an effort to identify factors associated with the disease or the surgical procedure which might promote better or worse outcomes. There were some suggestive differences, especially among the patients in the placebo group, but none were statistically significant, perhaps due to sample size limitations.</p> <p>Safety:</p> <p>There were few complaints and adverse reactions overall, with similar results between the two treatment groups. The main complaint was finding the brace bulky or uncomfortable (13.1% in each group). Other reported problems include two cases of minor skin rash in the active group (1.9%), one report in each treatment group (1%) of pain while using the device, and a complaint listed as "other" in the placebo group. No patient in either group reported insomnia, fainting, nausea/diarrhea, or polymenorrhea.</p>
Potential Sources of Bias	<p>The author acknowledges the possibility that site-to-site variations in radiologic interpretation might affect the results, but there was no analysis of differences in success rate by site. This could be significant, because two sites enrolled a disproportionate number of patients.</p> <p>There are possible sources of bias related to the analysis itself. First, a larger number of patients were excluded from the active study arm than from the placebo arm. The reasons given for exclusion include medical problems, not undergoing the surgery, requirements for repeat surgery, incompletion secondary to alcohol dependency, and patients lost to follow-up. Many of these reasons for exclusion are suggestive of poor outcomes, and patients were disproportionately excluded from the active treatment group. Had they been included, the difference in the two treatment groups may not have been as large.</p> <p>Also, the choices of statistical comparisons raise some questions. Comparing the compliant group of active patients with the entire placebo group provides a more favorable comparison than if the compliant patients in each treatment arm had been compared. Some of the benefits of consistent use may be related to use of the brace alone, rather than the stimulation provided.</p>
Other Limitations of	The study only evaluated PEMF stimulation devices.

the Study	The results from this study may not apply to other types of spinal fusion procedures or other uses for electrical stimulation.
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4. Simmons, 1985

Citation	Treatment of Failed Posterior Lumbar Interbody Fusion (PLIF) of the Spine with Pulsing Electromagnetic Fields J.W. Simmons Clinical Orthopedics and Related Research No. 193, March 1985, pp 127 – 132
Intended Use	<input checked="" type="checkbox"/> Lumbar spinal fusion
Stimulation Type	<input checked="" type="checkbox"/> PEMF
Commercial Device Name(s)	Bi-Osteogen system manufactured by Electro-Biology, Inc.
Overall Study Design	<input checked="" type="checkbox"/> Patient as own control, prospective
# Patients	13
Selection Criteria	Inclusion criteria: Patients defined as having a failed posterior lumbar interbody fusion (PLIF) procedure, with attempted fusion of no more than two levels, located between L3 and S1. For the PLIF procedure to be considered a failure, the last surgical intervention had to be at least 18 months before enrollment. Exclusion criteria: Bone gap > 1 cm or inadequate bone stock.
Methods	No new surgical procedures were performed. Patients were instructed to use the device 8-10 hours a day. Treatment could occur during one session (e.g., overnight) or during multiple sessions, each at least one hour long. No information was given on how patient compliance was assessed. The patient was evaluated on day 0, then at monthly intervals for 4 months, then at the end of the 12-month treatment period. Pre- and post-treatment radiographs were assessed by an independent observer, but the author does not state that the observer was blinded as to treatment status.
Success/Failure Criteria	The main endpoint was the extent of bony fusion throughout the nonunion site.
Results	Thirteen male patients were selected for the study, with a mean interval between the last surgical intervention and the onset of treatment of 40 months (range of 18 to 101 months). Of these 13, 11/13 (85%) showed significant increase in bone density in the nonunion site, and 10/13 (77%) showed solid bony fusion throughout the intervertebral disk space. The authors do not comment on any complications or adverse events.
Potential Sources of Bias	There is some potential for selection bias in this study group. It is notable that only male patients were enrolled. The reasons for this selection pattern and the implications of a male-only population are not clear. However, the pattern suggests that study population may not be representative of all patients with failed procedures. Observer bias is also possible, given that the author did not appear to mask the treatment status of the patients when the films were sent for evaluation.
Other Limitations of the Study	The major limitation of this study is that it did not include a concurrent control group. The author gives two justifications for this decision. First, he states that "by any statistical means, the most one could expect is one spontaneous fusion in this period." However, this assertion seems to be based on the length of follow-up reported in other stories, rather than a rigorous time-to-event analysis. The actual basis for the author's statistical assertion is completely

	<p>unclear. Second, he states that on the basis of his clinical experience, the use of the orthosis without stimulation would be unlikely to have an effect. Again, the data underlying this assertion are not given.</p> <p>Beyond the study design problems, the study is limited by the inclusion of only PEMF stimulation and evaluation of the stimulation only for interbody fusion procedures.</p>
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5. Simmons et al., 2004

Citation	<p>Pseudarthrosis After Lumbar Spine Fusion: Nonoperative Salvage with Pulsed Electromagnetic Fields</p> <p>J.W. Simmons, V. Mooney, and I. Thacker</p> <p>American Journal of Orthopedics, pp. 27-30, January 2004</p>
Intended Use	<input checked="" type="checkbox"/> Lumbar spinal fusion
Stimulation Type	<input checked="" type="checkbox"/> PEMF
Commercial Device Name(s)	Spinal-Stim, manufactured by Orthofix, Inc.
Overall Study Design	<input checked="" type="checkbox"/> Patient as own control, prospective
# Patients	100 with consistent device use (authors are not clear if some enrolled and then were excluded for poor compliance).
Selection Criteria	<p>Inclusion:</p> <ul style="list-style-type: none"> • Radiographic documentation of pseudoarthrosis and clinical symptoms indicative of pseudoarthrosis at nine months or more after the last surgical intervention. • No radiographic evidence of progressive healing for 3 months. <p>Exclusion:</p> <ul style="list-style-type: none"> • Cardiac pacemaker • Spinal trauma • Spondylitis • Paget's disease • Severe osteoporosis • Metastatic cancer • Uncontrolled diabetes • Renal dysfunction
Methods	<p>Baseline information was gathered on previous treatments, medical history, pain assessment, activity level, and most recent imaging studies.</p> <p>Patients were instructed to use the device for at least two hours a day for at least 90 days. Compliance could be verified using a monitor internal to the device. The duration of the overall follow-up period was not defined.</p> <p>Fusion success was determined by radiologic assessment. The investigator's assessment was confirmed by an independent radiologist who was blinded as to treatment status. If the two assessments disagreed, and the investigator rated the patient as a fusion success, an independent orthopedic surgeon provided the final review.</p> <p>Clinical outcome was rated as excellent, good, fair, or poor on the basis of pain intensity, medications taken, and return to activity.</p>
Success/Failure Criteria	<p>Radiologic success criteria for the graft were to be at least 50% assimilated.</p> <p>Clinical outcome classifications were based on criteria that had been previously published. Only the reference to the previous paper was given.</p>

Results	<p>Patients started using the PEMF device at a mean of 18.7 months after surgery (range 9 months to 12.5 years). The mean duration of treatment was 8.3 months (range 3 to 21 months).</p> <p>The overall fusion success rate was 67%. The success rates were similar regardless of the type of procedure (interbody vs. posterolateral), the type of graft (autograft, allograft, or mixed), and whether or not instrumentation was used in the surgery. Smoking status also did not have a significant effect on fusion success. There were trends toward higher success rates in patients under 50 years of age and in females, but these differences were not significant by a one-sided Fisher's exact test.</p> <p>There was a trend toward better clinical outcomes in patients who were classified as a radiologic success. Of those with successful fusion, 42/67 (62.7%) had a good or excellent outcome, as compared to 10/33 (30.3%) of those without successful fusion. The authors did not comment on the statistical significance of this difference.</p> <p>The authors do not comment on the presence or absence of adverse reactions or complaints.</p>
Potential Sources of Bias	<p>There is the potential for some selection bias, as this was an open trial that appears not to have required evaluation of all potentially eligible patients. At least some of the inclusion criteria are subjective in nature. There is no full accounting of the number of patients who enrolled, only the number of patients "who consistently used the device." Some bias may have entered the study if those who did not complete the required treatment time were qualitatively different.</p> <p>The use of a panel of reviewers, some of whom were blinded as to treatment status, limits the potential for observer bias for the main outcome, radiological success.</p> <p>It is not possible to evaluate the potential for bias in the clinical assessment, because the methodology is not included.</p>
Other Limitations of the Study	<p>This study only addresses PEMF stimulation in the context of failed lumbar spine fusion.</p>

6. Abeed et al., 1998

Citation	<p>Capacitively Coupled Electrical Stimulation Treatment: Results from Patients with Failed Long Bone Fracture Unions</p> <p>R.I. Abeed, M. Naseer, and E.W. Abel</p> <p>Journal of Orthopedic Treatment 12(7): 510-513, 1998</p>
Intended Use	<p><input checked="" type="checkbox"/> Non-Union fracture long bones</p>
Stimulation Type	<p><input checked="" type="checkbox"/> Capacitive coupling</p> <p>Appears to have been developed by the researchers. It was designed to produce a constant six-volt peak-to-peak symmetrical sine wave at a frequency of 62 kHz.</p>
Commercial Device Name(s)	<p>Not applicable.</p>
Overall Study Design	<p><input checked="" type="checkbox"/> Patient as own control, prospective</p>
# Patients	<p>16</p>
Selection Criteria	<p>All patients met the criteria for non-union: minimum of nine months from the original injury and no radiologic sign of progressive healing for at least three consecutive months.</p> <p>No exclusion criteria were listed.</p>
Methods	<p>The patients were fitted with the device and instructed in its use. The device was to be used continuously each day until the low-battery signal occurred, after about 7-8 hours. The plates were to be removed when stimulation was not occurring, and then repositioned after replacing batteries the next day. There was no specific means to verify compliance with the prescribed regimen.</p>

	Patients were recalled at 4-week intervals for evaluation. Radiographs (4 views) were taken after 12 weeks. Stimulation was stopped when significant healing was noted or at 30 weeks maximum.
Success/Failure Criteria	Healing was defined as the presence of bone trabeculae across the full width of the fracture line on all four views.
Results	<p>The 16 patients included 13 with previous surgical interventions and three who had been treated by casting alone. Five of the patients had active infections at the time stimulation was initiated.</p> <p>The success rate was 11/16. The chief determinant of treatment success or failure appeared to be the interplate distance. In all successful cases, the interplate distance was 60 mm or less. The authors hypothesized that distances above 60 mm do not result in sufficient current to stimulate bone growth.</p> <p>Factors such as age, number of prior surgical procedures, presence of metal at the fracture site, and presence of infection did not result in significantly different healing rates.</p>
Potential Sources of Bias	<p>Selection bias is possible in this study. The selection criteria were not clearly described in the paper, and the authors do not state that the study enrolled consecutive patients. Therefore, it is likely that some patients were considered for the study but eliminated for unstated reasons.</p> <p>Observer and outcome bias are probably not significant in this study, because the success criteria are clearly defined. However, it should be noted that the observations were most likely made by the treating physician rather than by an independent observer.</p>
Other Limitations of the Study	<p>The sample size in this study is relatively small, which limits the ability to detect differences in outcome due to other factors and their overall confidence in the results.</p> <p>There is no concurrent control group, so it is not possible to compare the effectiveness of their stimulation approach to that of other treatments.</p> <p>The results apply only to long-bone fractures treated with capacitively coupled electrical stimulation.</p>

7. Adams et al., 1992

Citation	<p>Treatment of Scaphoid Nonunion with Casting and Pulsed Electromagnetic Fields: A Study Continuation</p> <p>B.D. Adams, G.K. Frykman, and J. Taleisnik</p> <p>J Hand Surg., 17A:910-914, 1992</p>
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture other bones <i>scaphoid</i>
Stimulation Type	<input checked="" type="checkbox"/> PEMF
Commercial Device Name(s)	EBI Bi-Osteogen System, Electro-Biology, Inc.
Overall Study Design	<input checked="" type="checkbox"/> Patient as own control, retrospective
# Patients	<p>54 patients</p> <ul style="list-style-type: none"> • 51 males • 3 females • Average age 26 yr (range 14 to 46 yr) • Average time from injury to treatment was 35 mo (range 6 – 241 mo)
Selection Criteria	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Scaphoid fracture at least 6 months old and a standardized protocol of treatment had to be followed.

	<ul style="list-style-type: none"> No operation performed during or just before initiation of PEMF treatment. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Carpal instability was the only specific exclusion criterion. The authors note that none of the cases had significant angulation at the non-union site or periscaphoid arthritis.
Methods	<ul style="list-style-type: none"> External PEMF coils were centered over the scaphoid and attached to either a long arm thumb spica cast or a short arm thumb spica cast. To be included in the final analysis, all patients had to be treated until the fracture healed or for a least a 3 month period. All patients were examined 1 – 33 months after treatment stopped for an average follow-up of 8.5 months. Plain radiographic evaluation was the standard method used for the initial assessment of non-union as well as for the final determination of healing status. Anteroposterior, lateral, and scaphoid views were available for each case.
Success/Failure Criteria	<ul style="list-style-type: none"> Plain radiographic evaluation was the standard method used for the final determination of healing status.
Results	<ul style="list-style-type: none"> Non-unions healed in 69% (37/54) cases. Average duration of electrical stimulation in healed group was 4 months (range 2.5 – 9 mo). In the failed cases, the average time from injury to initiation of treatment was 50 mo (range 6 to 241 mo); in the healed cases, the average time from injury to initiation of treatment was 27 mo (range 6 to 170 mo). Among fractures that were more than 60 months old, 2/7 healed (29%), as opposed to 30/41 (73%) that were less than 60 months old. The authors do not show whether this result is statistically significant.
Potential Sources of Bias	<p>There are potential sources of observer bias:</p> <ul style="list-style-type: none"> It is unclear who read the radiographs, but presumably it was the treating physicians. The criteria for determining healing from the radiographs are not mentioned, so there may have been some subjectivity in the analysis. Excluding the patients with poor compliance from the analysis is not consistent with modern intention to treat rules.
Other Limitations of the Study	<ul style="list-style-type: none"> More sophisticated imaging would have a more accurate diagnostic value than plain x-rays, and the authors felt their success rate may have been overestimated. The need for a prospective, randomized, multicenter study comparing several alternative methods of treatment for scaphoid union is suggested by the authors.

8. Bassett et al., 1981

Citation	Treatment of Ununited Tibial Diaphyseal Fractures with Pulsing Electromagnetic Fields C.A.L. Bassett, S.N. Mitchell, and S.R. Gaston The Journal of Bone and Joint Surgery, 63-A:511-523,1981
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture long bones <i>tibia</i>
Stimulation Type	<input checked="" type="checkbox"/> PEMF
Commercial Device Name(s)	Manufacturer: EBI Electro-biology, Inc.
Overall Study Design	<input checked="" type="checkbox"/> Patient as own control, prospective
# Patients	125 (127 ununited fractures)

Selection Criteria	<ul style="list-style-type: none"> • Patients had ununited fractures that had not changed radiographically for a minimum of 4 months prior to starting treatment. • Both “hypertrophic” and “atrophic” non-unions were included. • Exclusion: psuedoarthroses with a fluid filled gap.
Methods	<ul style="list-style-type: none"> • The device was applied with the non-union centered within the confines of a coil-placement block on the cast with confirmation of positioning done by x-ray. • Patients were instructed to apply voltage for a cumulative total of 10 hr/day with no segment less than 1 hr. • Non-weight bearing was a critically important feature, and the patients were advised to not to do this; this was persistently reinforced to the patients. • The plaster cast was applied at an angle to minimize force on the lesion site. • Radiographs were made at 4-6 week intervals without cast removal. • Once Stage-I healing was observed (see below), the leg was placed in a short cast and impactive axial compressive exercises were begun; the intensity and repetitions was determined based on the type of fracture with the goal being to produce adequate impactive loading rates equal to maximum endogenous voltages in the bone. • Once Stage-II healing was observed (see below), the cast, crutches, and coils were discontinued. • The cast was then replaced with a molded fiberglass support. • Once Stage-III healing was complete, the support was removed; at this time.
Success/Failure Criteria	<ul style="list-style-type: none"> • Evidence of healing was based on changes in the fracture gap and the dense bone flanking it specifically: <ul style="list-style-type: none"> • Stage-I healing: an increase in radiographic density (fuzziness) in the tissues in the gap and a patchy loss of density in the sclerotic bone can be documented (usually 1-3 mo after onset of treatment). • Stage-II healing: occurs at or before the time of partial weight-bearing and is indicated by the appearance of consolidated bone-stress lines that bridge the fracture gap in at least three distinct locations on the anteroposterior and lateral radiographs. • Stage-III healing: Continuity of the medullary canal across the non-union site is evident; the fracture was considered to be healed at this point (implied to be the level required for a patient to be considered a success). • Stage-IV healing: radiographic evidence of further remodeling.
Results	<p>Effectiveness</p> <ul style="list-style-type: none"> • Overall success rate 87%. • Failure rate 13% - includes all fractures for which healing did not occur regardless of cause for failure. Causes included poor patient compliance, gap greater than 1 cm, and interposition of soft tissues into the gap. • Average treatment length = 5.2 mo (range 2-22 mo); the average is slightly elevated due to treatment optimization over the years as the study progressed. <p>Safety:</p> <ul style="list-style-type: none"> • Report mentions that the total clinical investigations have spanned 7 years and are supported by toxicology and teratology studies, which were submitted for FDA review. • The 10 V of current applied to the coils is non-hazardous even if the coils are inadvertently immersed in water.
Potential Sources of Bias	<ul style="list-style-type: none"> • The authors do not state whether consecutive patients were offered participation in the study, so there is some possibility of selective enrollment. • Not all patients followed the same treatment regimen; the treatment changed significantly over time, yet all data were generally lumped together. • It appears that radiographs were evaluated for healing by the treating physicians rather than by independent observers, so there is some potential for observer bias.
Other Limitations of the Study	<ul style="list-style-type: none"> • Patient cooperation (non-weight bearing and use of coils 10 hr/day) was required for usual progress to occur and depended upon reporting of patient.

	<ul style="list-style-type: none"> The study reports on fractures in a specific bone using only one type of limitation.
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9. Benazzo et al., 1995

Citation	Use of Capacitive Coupled Electric Fields in Stress Fractures in Athletes F. Benazzo, M. Mosconi, G. Beccarisi, and U. Galli Clinical Orthopaedics and Related Research, 310: 145-149, 1995
Intended Use	<input checked="" type="checkbox"/> Other ___ Stress Fractures _____
Stimulation Type	<input checked="" type="checkbox"/> Capacitive coupling
Commercial Device Name(s)	Bioelectron, Inc.; battery-powered coupling device generator supplying current conveyed by 2 wires to stick on hydrogel capacitively coupled electrodes place on either side of the fracture.
Overall Study Design	<input checked="" type="checkbox"/> Case series, uncontrolled, prospective
# Patients	25 fractures; 21 patients 17 male 4 female Aged 17-29 yr old (average 21.8 years)
Selection Criteria	<ul style="list-style-type: none"> Athletes competing at least on regional level. Training at least 3X/week. No performance-enhancing drugs. Injury sustained during training and competition. Injury detected by radiography, scintigraphy, and computed tomography. No systemic disorders.
Methods	<ul style="list-style-type: none"> Treatment ran round the clock beginning at time of diagnosis. Treatment continued until fracture healed or improved, as monitored bi-weekly by radiograph or until no additional progress was noted at 3 such evaluations. Checked apparatus at each visit for functionality. No device failures were observed. Some patients were immobilized in a plaster cast for comfort. Results were assessed by 4 variables: time of disappearance of pain, time of complete return to sports activities, radiographic evidence of union, negative scintigraphy.
Success/Failure Criteria	Patients were classified as: <ul style="list-style-type: none"> Healed Improved (incomplete healing on radiographs, but marked decrease in pain) Not healed (no healing seen on radiographs; although there may have been reduction of pain)
Results	<ul style="list-style-type: none"> Time from symptom onset, diagnosis, and beginning of treatment ranged from 7 days (fracture of fifth metatarsal) to 730 days (tarsal navicular fracture) – average for all fractures 147.5 days; average for navicular fracture 223.9 days. Average length of stimulation time was 51.9 days. Analysis of radiographic and clinical data showed that 22 fractures (88%) healed, 2 fractures (8%) improved, and 1 fracture (4%) was not healed. No safety information given.
Potential Sources of	<ul style="list-style-type: none"> The authors admit that this study was performed as an open study, as opposed to a

Bias	<p>single or double-blind, or a case control study because of the rarity of stress fractures in intensively trained athletes. Therefore, it would have been difficult to recruit a sufficient number of patients for single or double-blind trials or case control studies.</p> <ul style="list-style-type: none"> • The sample group consisted of relatively young patients (average 21.8 yr) that were very fit. • “Many of the stress fractures should or could have been classified as pseudoarthroses on account of the duration of the symptomatology before diagnosis. However, consideration was directed solely to the mechanism responsible (repeated microtraumas) and not to the length of time between symptom appearance and diagnosis.” • It is unclear who made the diagnosis and interpreted the radiographs.
Other Limitations of the Study	<ul style="list-style-type: none"> • Only capacitive coupling was used. • The results for stress fracture may not be directly applicable to other acute traumatic injuries.

10. Brighton and Pollack, 1985

Citation	<p>Treatment of Recalcitrant Non-Union with a Capacitively Coupled Electric Field C.T. Brighton and S.R. Pollack The Journal of Bone and Joint Surgery, 67-A: 577-585, 1985</p>
Intended Use	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Non-Union fracture long bones <input checked="" type="checkbox"/> Non-Union fracture other bones <i>clavicle, carponavic</i>
Stimulation Type	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Capacitive coupling <p>The device was developed by the researchers. The power source produced a constant five-volt peak to peak, 60 kHz, symmetrical sine-wave signal. The amount of current produced by the power source, as measured at the level of the patient’s skin, ranged from 7.1 to 10.5 mAmp. Power source was a 9V battery that the patient changed every day.</p>
Commercial Device Name(s)	Not applicable.
Overall Study Design	<input checked="" type="checkbox"/> Patient as own control, prospective
# Patients	<p>20 patients; 22 fractures 11 female 9 male average age 38.4 yr; range 16 – 62 yr</p> <ul style="list-style-type: none"> • average duration of non-union 3.3 yr • 71 operations in 17/20 patients (average 3.7) • 9 non-unions treated previously with both bone-graft and electrical therapy • 4 non-unions treated previously with bone-graft alone • 4 non-unions treated previously with electrical therapy <ul style="list-style-type: none"> ◦ these 17 were considered recalcitrant • 5 non-unions treated previously with bone-graft or electrical therapy were considered to be routine
Selection Criteria	<ul style="list-style-type: none"> • Well-established non-union (a fractured bone in which all roentgenographically demonstrable reparative processes had ceased but bone continuity had not been restored). • Non-union was diagnosed from routine anteroposterior, lateral, and both oblique roentgenograms on which there were no progressive signs of healing of the non-union callus over a 3 month period. This criterion was applied to 20/22 non-unions after 12 mo had elapsed after original injury. • Each patient had to be willing and able to return for periodic follow-up examinations; the capacitive coupling was applied only with the informed consent of the patient after its experimental nature had been fully explained.

Methods	<ul style="list-style-type: none"> • Non-unions were a consecutive series treated by one of the authors. • During the entire electrical treatment and until each non-union was determined to be either healed or a failure, the involved extremity was immobilized in a plaster cast. • Patients seen monthly; at each visit, the device and cast were inspected. • At the end of 12 weeks, the cast was removed, and roentgenograms were made of the limb. • Results at this point usually showed the beginnings of healing, so the cast immobilization and capacitive coupling were continued in most patients until the non-union was determined to be either healed or a failure of treatment. • The capacitively coupled electrical field was applied for an average of 24.8 weeks (12 – 46 week range) in 22 non-unions; an additional 5-12 weeks of cast immobilization was required for 7 of the patients.
Success/Failure Criteria	<ul style="list-style-type: none"> • A non-union was considered to be healed only when bone trabeculae were seen to cross the full width of the fracture line on all four roentgenograms. • A non-union was considered to be a failure when the bone trabeculae did not cross the full width of the fracture line on all 4 roentgenograms and it failed to show progression in healing over a 3 month period on all 4.
Results	<p>The average duration of non-union before enrolling in the study was 3.3 years. Most of the patients (17/20) had been treated by various surgical means before entering the study.</p> <p>Effectiveness:</p> <ul style="list-style-type: none"> • 17 (77.3%) of the non-unions healed. • 5 (22.7%) failed to heal. • No significant difference between healing in routine and recalcitrant unions. • Average duration of treatment was 24.8 weeks; 22.5 weeks in 17 non-unions that healed and 32.6 weeks in non-unions that failed to heal. <p>Safety: No complications were encountered in any of the patients throughout the course of therapy except for a slight skin rash under the electrodes in one patient.</p>
Potential Sources of Bias	There is potential for observer bias because no mention is made of an independent observer examining the roentgenograms.
Other Limitations of the Study	<ul style="list-style-type: none"> • The conclusions are limited to capacitive coupling device that may not be directly applicable to commercial devices. • It is impossible to determine with certainty the role of electrical stimulation in these patients, because it was part of an overall treatment regimen that incorporated other treatment modalities. A randomized study would have been needed to fully clarify the role of stimulation in these patients. • The study was probably too small to detect any statistically significant differences in healing between subgroups.

11. Brighton et al., 1995

Citation	<p>Tibial Nonunion Treated with Direct Current, Capacitive Coupling, or Bone Graft</p> <p>C.T. Brighton, P. Shaman, R.B. Heppenstall, J.L. Esterhai, Jr., S.R. Pollack, and Z.B. Friedenber</p> <p>Clinical Orthopaedics and Related Research, 321: 223-234, 1995</p>
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture long bones <i>tibia</i>
Stimulation Type	<input checked="" type="checkbox"/> Capacitive coupling <input checked="" type="checkbox"/> Implanted stimulation device – <i>direct current</i> <input checked="" type="checkbox"/> Other <i>bone graft surgery</i>
Commercial Device Name(s)	Not applicable.
Overall Study Design	<input checked="" type="checkbox"/> Case series, uncontrolled, retrospective
# Patients	<p>271</p> <ul style="list-style-type: none"> • Direct current – 167

	<ul style="list-style-type: none"> • Capacitive coupling – 56 • Bone graft surgery – 48 <p>Average age 35.4 yr Males:females – 3:1 Average duration of non-union 23.5 months</p>
Selection Criteria	<ul style="list-style-type: none"> • Well-established non-union, defined as a fractured bone in which all radiographically demonstrable healing had ceased but bony continuity had not been restored. • Diagnosis of non-union was made by reviewing routine anteroposterior, lateral, and both oblique radiographs in which no progressive signs of healing of the callus were seen during a 3 month period. • Also, each non-union had to be of a minimum 9 month duration, and each patient had to be willing and able to return for periodic follow-up examinations. <p>Exclusions:</p> <ul style="list-style-type: none"> • Draining osteomyelitis of the nonunion was a cause for exclusion from treatment with direct current or bone graft surgery but not capacitive coupling.
Methods	<p>Treatment regimens</p> <ul style="list-style-type: none"> • Direct current – 4 cathodes were inserted percutaneously into the non-union site, 20 microamps were applied to each cathode 24 hr/day for 12 weeks; all patients wore a non-weightbearing cast for all 12 weeks. • Capacitive Coupling – Capacitor plates/electrodes were applied to the skin through windows cut in a cast; a 60 kHz , 5 V peak to peak symmetrical sine wave signal was applied continuously for 24 hr/day for 12-24 weeks. • Bone graft surgery – conventional surgery using autogenous iliac bone accompanied by internal or external fixation. <p>Logistic regression was used to compare the 3 methods.</p> <ul style="list-style-type: none"> • The heal rate of the 3 treatment methods of tibial non-union were compared, and the fitted model was used to identify risk factors adversely affecting the healing on non-unions. • Independent variables included: <ul style="list-style-type: none"> ○ Treatment type ○ Gender ○ Osteomyelitis ○ Prior electrical treatment ○ Prior bone graft ○ Fracture condition ○ Non-union type ○ Fracture type ○ Presence/absence of metal ○ Fracture location • Differences in composition among the 3 treatment groups were analyzed for statistical significance using the Chi-squared test with Yate's correction added for small numbers.
Success/Failure Criteria	<ul style="list-style-type: none"> • All patients were observed to end point: healed or failed. • Healed – all 4 radiographic views showed bony trabeculae spanning the full width of the non-union gap. • Failed – all 4 radiographic views taken serially during a 3 month period showed that healing had ceased (no progressive changes in the callus), yet bony continuity had not been restored.
Results	<ul style="list-style-type: none"> • Significant differences were observed among the treatment groups for: <ul style="list-style-type: none"> ○ type of fracture ○ type of nonunion ○ history of osteomyelitis

	<ul style="list-style-type: none"> ○ history of electrical treatment ○ history of bone graft surgery ○ location of surgery ○ presence of metal. <ul style="list-style-type: none"> • With no risk factors present, there were no differences in the heal rate among the 3 treatment methods at 10 mo duration of non-union (99% for direct current, 96% for capacitive coupling, 99% for bone graft surgery). • As more risk factors were added, the heal rate decreased significantly, regardless of the treatment method. • At 70 months duration of non-union, the chance of healing, was predicted by the fitted model to be 91% with direct current, 90% with bone graft surgery, and 71% with capacitive coupling. <p>No safety information is given.</p>
Potential Sources of Bias	<p>Selection bias is a concern in this study for the following reasons:</p> <ul style="list-style-type: none"> • Patients were not randomly assigned to treatment groups • The selection criteria differed for the three methods in that active infection precluded some treatments, but not others. <p>It is unclear who read the radiographs to determine whether the treatment healed or failed, so there may be some observer bias.</p> <p>The study was retrospective, did not incorporate randomization, and did not involve a double-blind protocol.</p>
Other Limitations of the Study	<p>The study only addresses capacitive coupling and implanted direct current devices. Because of the retrospective nature of the study, there is the potential for time-drift effects and uncontrolled variables in patient treatment.</p>

12. Garland et al., 1991

Citation	<p>Long-term Follow-up of Fracture Nonunions Treated with PEMFs D.E. Garland, B. Moses, and W. Salyer Contemporary Orthopaedics , 22(3):295-302, 1991</p>
Intended Use	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Non-Union fracture long bones <input checked="" type="checkbox"/> Non-Union fracture other bones <input checked="" type="checkbox"/> Other: Failed joint fusion procedures
Stimulation Type	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> PEMF
Commercial Device Name(s)	<p>The specific device is not named, but it is likely from American Medical Electronics since one of the authors (B.M.) is a clinical research associate with the company.</p>
Overall Study Design	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Patient as own control, prospective
# Patients	<p>181 patients - 139 patients completed the study 193 fractures – 149 fractures in patients who completed the study 118 males, average age 38 yr (range 13 – 76 yr) 63 females, average age 49.2 yr (range 14 – 83 yr)</p>
Selection Criteria	<ul style="list-style-type: none"> • A non-union was defined as a fracture or an arthrodesis that failed to demonstrate both clinical and radiographic union at least nine months after the original injury. • Established non-unions that underwent a bone grafting procedure or internal fixation became candidates for PEMF treatment if evidence of healing was not apparent radiographically by 3 months after the procedure or if no radiographic progression of healing occurred during the 3 month period.
Methods	<ul style="list-style-type: none"> • Patients were asked to use a PEMF stimulation device for a minimum of 8 hr/day for 6 mo or until union. • An independent panel of 3 orthopedists reviewed all radiographs at the termination

	<p>of treatment.</p> <ul style="list-style-type: none"> • Investigators rated each subject for motion at the fracture site, tenderness, pain, and the requirement for casting. • Some patients were evaluated for long-term effects over a four-year period.
Success/Failure Criteria	<ul style="list-style-type: none"> • A successful rating indicated that at least two of the three panelists rated the subject's final radiographs as showing cortical bridging and/or trabecular bridging with major modification of the radiolucent gap on any radiographic view and that the overall callus showed progression from baseline. • Patients were determined to be clinically healed if they were non-casted, without motion at the fracture site, and had absent or minimal pain at the non-union site.
Results	<p>139 patients (149 fractures) who completed the 12 week PEMF treatment were ranked according to daily use time:</p> <ul style="list-style-type: none"> • 13 patients (14 fractures) averaging less than 3 hr/day had a success rate of 35.7%. • 126 patients (135 fractures) averaging more than 3 hr/day had a success rate of 80%. • Confidence interval tests showed this difference to be statistically significant. <p>Subsequent analysis of results was confined to patients who received over 3 hr/day treatment; no statistically significant difference was noted with increasing treatment times beyond 3 hr/day.</p> <ul style="list-style-type: none"> • Tibial non-unions had a success rate of 74%. • No statistically significant difference in the success rate of non-unions with fracture gaps up to 1 cm. The overall healing rates are given but not the confidence intervals. • 90 patients (97 fractures) who averaged more than 3 hr/day PEMF therapy and were originally classified as healed were reevaluated clinically and radiographically at 4 years following treatment. 89 (92%) maintained a solid union. <p>The authors reported that there were no long-term adverse effects attributable to PEMF by either the physicians or the patients.</p>
Potential Sources of Bias	<ul style="list-style-type: none"> • There were 131 investigators at 74 sites involved in this study, and the patient selection may not have been uniform among all the investigators. • The long-term follow-up data did not handle patients lost to follow-up as failures, as would be expected by modern intention-to-treat rules.
Other Limitations of the Study	<p>The authors apparently looked only at one stimulation device even though this study involved patients at 74 sites; the assumption is that the same device was used.</p> <p>The sample size may have been too small for the subgroup analyses to have shown significant differences.</p>

13. Bassett et al., 1977

Citation	<p>A Non-Operative Salvage of Surgically-Resistant Pseudarthroses and Non-Unions by Pulsing Electromagnetic Fields; a Preliminary Report</p> <p>C.A.L. Bassett, A.A. Pilla, and R.J. Pawluk</p> <p>Clinical Orthopaedics and Related Research No. 124, May 1977, pp. 128 – 143.</p>
Intended Use	<p>Non-Union fracture long bones</p> <p>Non-Union fracture other bones</p> <p>Other pseudarthroses, pathological acquired lesions</p>
Stimulation Type	PEMF
Commercial Device Name(s)	Designed/fabricated by ElectroBiology, Inc.

Overall Study Design	Patient as own control, prospective
# Patients	29: 12 congenital pseudarthroses, 14 acquired pseudarthroses, 3 "pathological lesions"
Selection Criteria	<ul style="list-style-type: none"> • Previously treated by one or more unsuccessful surgical attempts. • Amputation recommended for most by at least one qualified orthopedist prior to acceptance into study. • Majority with satisfactory axial and rotary alignment of proximal and distal fragments.
Methods	<ul style="list-style-type: none"> • Coil applied to external surface of cast under radiographic guidance to ensure centering over pseudarthroses and pulsing electromagnetic field at right angles to long axis of bone. • Plastic box attached to cast to allow patient to remove and replace the coil. • Measurements taken to allow calculation of field strength in order to produce a "given voltage" in bones. • Pulse patterns monitored at each office visit to ensure proper voltage. • Treatment conducted at home by patient for 12 – 16 hours daily for three to six months. • Radiographs taken through plaster at monthly intervals. • Non-weightbearing for non-unions of lower extremities, with exception of patients who had been ambulatory on "mechanically stable" lesions immediately prior to coil therapy. • Children under 10 monitored bi-monthly for recurrence of pseudarthroses, retreated at first sign (radiographic or clinical) of recurrence.
Success/Failure Criteria	Presumed to be radiographic and/or clinical evidence of healing, though this is not defined. No specific safety data were presented.
Results	<ul style="list-style-type: none"> • 73% (9/11, one not followed long enough for analysis) of congenital pseudarthroses with radiographic evidence of healing. • 76% (10/13, one not followed long enough for analysis) of acquired pseudarthroses with radiographic evidence of healing. • 100% (3/3) of pathological lesions with evidence of healing.
Potential Sources of Bias	<ul style="list-style-type: none"> • Non-RCT design • Small number of subjects • Selection Criteria not clearly defined, especially for pathological lesion group • No exclusion criteria noted • Outcome criteria not defined
Other Limitations of the Study	<ul style="list-style-type: none"> • Per the authors, this is a preliminary analysis and report. • PEMF only, therefore unable to make comparisons to other techniques. • Per the authors "throughout the study the pulse parameters employed have evolved as the specificity of pulse informational requirements became better defined," thus this does not appear to have been standardized from the outset.

14. Cheng et al., 1985

Citation	<p>Treatment of Non-Union, Congenital Pseudarthroses and Benign Cystic Lesions Using Pulsed Electromagnetic Fields</p> <p>N. Cheng, H. Van Hoof, P.H. Delpport, M.J. Hoogmartens, and J.C. Mulier</p> <p>Department of Orthopaedic Surgery, University Hospital, Pellenberg, Belgium</p> <p>Reconstruct. Surg. Traumat. 19: 118 - 122 (1985)</p>
Intended Use	<p>Non-Union fracture long bones</p> <p>Other: congenital pseudarthroses, benign cystic lesions</p>
Stimulation Type	<p>PEMF</p> <p>Authors termed it the "Bassett device." A magnetic field of about 2 gauss induces a flow of current in bone of about 1.0 – 1.5 mV/cm².</p>
Commercial Device Name(s)	N/A ("Bassett device")
Overall Study Design	Case series, uncontrolled, prospective

# Patients	63; of these: <ul style="list-style-type: none"> • 50 non-union (28 tibiae, 10 femurs, 8 humeri, 2 ulnae, 2 radii) • 4 delayed union (1 femur, 3 tibiae), • 3 congenital pseudarthroses (1 ulna, 2 tibiae) • 3 benign cystic lesions (1 ilium, 2 femurs) • 2 failed knee arthrodeses • 1 failed synostosis between ulna and radius
Selection Criteria	No criteria enumerated; categories not specifically defined, excepting note that "most patients had reached a stage where initial or further operation was inevitable." Some were amputation candidates.
Methods	Using Bassett device, coils were placed on the outer surface of a plaster cast and fed a specific pulsed current. A magnetic field induced flow of current in the bone. Treatment applied for 14 hours daily. No details were given regarding the frequency of follow-up, the total duration of follow-up, nor the methods used to evaluate success or failure.
Success/Failure Criteria	"Clinical and radiological evidence of union," not otherwise defined.
Results	Radiologic and clinical union in: <ul style="list-style-type: none"> • 78% (22/28) of tibial non-unions • 60% (6/10) of femoral non-unions • 25% (2/8) humeral non-unions • 50% (1 of 2) radial non-unions • 0% (0/2) ulnar non-unions • 100% of delayed unions • 33% (1/3) congenital pseudarthroses • 33% (1/3) benign cystic lesions 59% (37/63) overall The authors do not comment on the reasons for the substantial variability in results, depending on the location of the nonunion. The authors do not provide any specific information on safety, except to note that the treatment is safe in their opinion.
Potential Sources of Bias	<ul style="list-style-type: none"> • Non-RCT design • Selection/exclusion criteria not defined • Treatment protocol not defined, apart from daily use of the device • Radiologic and clinical evidence required to be considered healed not defined
Other Limitations of the Study	PEMF only, therefore unable to make comparison with other techniques.

15. Sharrard, 1990

Citation	A Double-Blind Trial of Pulsed Electromagnetic Fields for Delayed Union of Tibial Fractures W.J.W. Sharrard The Journal of Bone and Joint Surgery, Vol. 72-B, No. 3, May 1990
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture long bones; all tibial shaft fractures
Stimulation Type	<input checked="" type="checkbox"/> PEMF Author-built. Pulses of electric current passed through two coils of copper wire, producing pulses of magnetic flux in fracture region and pulses of electric induction in the bone. Bursts of 20 individual quasi-rectangular-shaped pulses, at 15-Hertz intervals, were followed by a sharper reverse form. (In the placebo- units, the coils were short-circuited.)
Commercial Device Name(s)	Not applicable.
Overall Study Design	<input checked="" type="checkbox"/> Randomized, concurrent control, prospective

# Patients	48 patients. Two (both placebo) left the study, and one (placebo) tampered with the PEMF device; these three were dropped from the analysis
Selection Criteria	<p>Inclusion:</p> <ul style="list-style-type: none"> • Fracture not united after at least 16 weeks, not more than 32 weeks of treatment with a plaster cast. • After reduction, fracture ends were apposed over at least 50% of their surfaces, in acceptable alignment, with no distraction. • Fracture shows two or three of the criteria of fracture severity at the time of the injury that fall into the moderate or severe categories (specified by measurements). The 5 criteria of severity are: fracture displacement; fracture angulation; comminution; size of skin wound; severity of injury to soft tissue. The purpose of this requirement was to select for a high liability of delayed union or non-union. • Over 18 years of age <p>Exclusion:</p> <ul style="list-style-type: none"> • Fracture located within 5 cm of ankle or knee. • Surgery to fracture (other than to wound or to reduce fracture) excluded, to make previous treatments as uniform as possible. • Treatment by internal or external stabilizing pins. • Gap greater than .5 The RBI Carpet Market Report for. • Patients with any severe, generalized disease, including bone disease such as Paget's disease. • Patients receiving systemic steroid treatment. • Severely atrophic bone with spindle-shaped bone ends. • Fractures with marked hypertrophy.
Methods	<p>Initial assessment was made of clinical mobility (measured with a goniometer), pain with and without pressure (measured by patient pointing to heights on a visual analogue scale), and infection (measured by the number of dressings needed per day). Radiographs taken parameters recorded so future radiographs could be made under the same conditions.</p> <p>Patients were assigned randomly with double-blind precautions to active and placebo units. Patients were supplied with indistinguishable active or dummy PEMF units. They were instructed to apply the treatment 12 hours a day, no individual session for less than one hour (most patients used sleeping time) and to put no weight on fractures. Antibiotics and analgesics allowed.</p> <p>After 12 weeks, the cast was removed, and the initial assessments were repeated. Radiographs were assessed independently and blindly by a radiologist and an orthopedic surgeon.</p>
Success/Failure Criteria	The orthopedic surgeon and the radiologist classed radiographs into different categories by degree of healing, but both agreed on radiographs classed as united and radiographs classed as showing no improvement.
Results	<p>After 12 weeks, the improvements in movement, pain, tenderness, and infections were not statistically significant. The radiologist's assessment of radiographic evidence showed significantly greater improvement in the experimental group ($p = 0.002$ by Fischer's exact test). The orthopedic surgeon's assessment also showed significantly greater improvement with the PEMF ($p = 0.02$).</p> <p>Age distribution in the two groups was significantly different, but analyses of subjects above and below 35 years of age showed differences between active and control groups only slightly above p values of .05. (The small samples might account for these values.)</p>

	Comparison of radiological and clinical data showed that absence of movement at the fracture is not a reliable indicator of union, which is probably why the clinical data did not show statistical significance.
Potential Sources of Bias	Clinical criteria were more subjective than radiographic data, but the inclusion of both led to discovery about the weakness of some clinical evaluations, especially that the absence of movement does not indicate union.
Other Limitations of the Study	A larger sample might have produced significance below the .05 level in the test for age effects on healing.

16. Sharrard et al., 1982

Citation	The Treatment of Fibrous Non-union of Fractures by Pulsing Electromagnetic Stimulation W.J.W. Sharrard, M.L. Sutcliffe, M.J. Robson, and A.G. Maceachern The Journal of Bone and Joint Surgery, Vol. 64-B, No. 2, 1982
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture long bones; large majority tibia <input checked="" type="checkbox"/> Non-Union fracture other bones: ankle, knee, one capitellum (ball of humerus)
Stimulation Type	<input checked="" type="checkbox"/> PEMF
Commercial Device Name(s)	Authors built system described by Bassett et al. 1977; external coils taped to plaster cast produced 1 to 1.5 millivolts of induced current in bone, driven by 5-millisecond bursts from a generator, repeated at 15 hertz.
Overall Study Design	<input checked="" type="checkbox"/> Patient as own control, prospective
# Patients	52 subjects with 53 non-unions, 35 male, 17 female.
Selection Criteria	Inclusion: <ul style="list-style-type: none"> • Fibrous non-union in an appendage, indicated by movement at the fracture, pain and tenderness, and by radiographic evidence • At least six months since last surgery, 12 months since injury. • For past three months, no radiological evidence of bone growth at fracture. Exclusion: <ul style="list-style-type: none"> • Surgery to fracture site after beginning PEMF treatment • No very young children were in sample. However, subjects were as young as 13. • Two subjects excluded because synovial pseudoarthrosis suspected (non-union was highly mobile and painless).
Methods	Patients self-administered treatment 12 to 16 hours a day, at home, usually during sleep. When there was clear radiological evidence of loss of density at bone ends and increased density in the gap, axial compression exercises were given with gradually greater weight-bearing. PEMF was discontinued when there was no clinical movement at fracture, no pain or tenderness, and radiographs showed bony tissue crossing at least half the width of the fracture.
Success/Failure Criteria	Union: No clinical movement at fracture, no pain or tenderness. Failure: Failure of union one year after PEMF initiated
Results	71.1% of cases (38) achieved union, suggesting that PEMF is helpful in cases of non-union. Age, direction of the line of the fracture, sepsis (occurring in slightly less than half the cases, usually before PEMF), and severity of fracture (about half were simple, half major or compound) did not appear to affect results. Width of the fracture affected results: all 4 cases with gaps over 5 mm failed to unite, and cases of gaps over 2 mm showed larger proportion of failure than narrower gaps. Hypertrophic (enlarged, or with more bridging tissue?) non-unions, as seen radiographically,

	<p>united more often (21/25) and faster (median 5 ½ months) than intermediate cases (13/21; 7 months) and atrophic cases (4/7; 7 ½ months).</p> <p>A screw in the fracture site was associated with failure in the 3 cases where it occurred, but plates with screws away from the fracture site did not appear to inhibit bone growth.</p> <p>Tibia are said to have responded better than other bones to PEMF (but there were very small samples of other bones).</p> <p>Safety: no negative side effects noticed.</p>
Potential Sources of Bias	Assessment criteria were for the most part subjective and might be difficult to replicate.
Other Limitations of the Study	<p>Statistical analysis was not attempted.</p> <p>Not enough cases were included of non-tibia fractures or of screws in the fracture site to show convincingly that these factors inhibited bone growth in response to PEMF.</p>

17. Delima and Tanna, 1989

Citation	<p>Role of Pulsed Electromagnetic Fields in Recalcitrant Non-unions</p> <p>D.F. Delima and D.D. Tanno</p> <p>Journal of Postgraduate Medicine, 1989, 35 (1)</p>
Intended Use	<input checked="" type="checkbox"/> Non-union or delayed-union fracture long bones
Stimulation Type	<p><input checked="" type="checkbox"/> PEMF</p> <p>Author-built. A pair of coils received from a generator produced a rectangular wave form, in unstable, continuous equal mark space mode, with a frequency of 40 Hertz. The driving current was either "between 12 volts in the upper extremity and 30 volts in the lower extremity" (according to the Material and Methods section) or "either 40 volts for the lower extremity and 25 volts for the upper extremity" (according to the Discussion section). In any case, the purpose was to deliver pulses that did not mimic the biological response to injury.</p>
Commercial Device Name(s)	Not applicable.
Overall Study Design	<input checked="" type="checkbox"/> Patient as own control, prospective
# Patients	29
Selection Criteria	<p>Inclusion:</p> <ul style="list-style-type: none"> • Non-unions or delayed unions. • Patients had varying histories. The injuries were between 0 and 3 months old in two patients, between 4 and 9 months old in 7 patients, between 9 and 24 months in 18 patients, and over 24 months old in 1 patient. • The sample probably comprised every non-union or delayed union the authors could find.
Methods	<p>Patients were kept on a strictly non-weight-bearing regimen and were stimulated 16-18 hours a day. Radiographs were taken at 8 weeks and 3 months. When calcification and haziness of the fracture gap and a decrease in sclerosis of the fracture margins developed, axial compression exercises were introduced. When mature lamellar bone was seen bridging the gap in at least two sites, the patient was allowed partial weight bearing. No mention of compliance.</p>
Success/Failure Criteria	Not given.
Results	<p>Overall success rate of 82.14%, although the electrical current was not designed to evoke the specific biological response involved in healing.</p> <p>All gaps less than 1 cm in width united successfully. The three patients with gaps of more</p>

	<p>than 2 cm were classed as failures.</p> <p>All 9 infected fractures with a rigid fixation united successfully. All 4 infected fractures with poor, unstable fixation failed.</p> <p>Younger age did not seem to predict success.</p>
Potential Sources of Bias	<p>About a third of the injuries were 9 months old or less, and were therefore quite likely to heal spontaneously without electrical stimulation. Only one was over two years old. This weakens considerably the point the authors seem to be making that their particular method of electrical stimulation is capable of promoting bone growth. The one dropout was not counted in calculating the 82.14% success rate.</p> <p>Details about assessment criteria are vague, and success is not specifically defined.</p>
Other Limitations of the Study	<p>As in most studies with a small, highly varied sample, the results are anecdotal, and there is no attempt to apply statistics. One purpose of the paper may be to publicize this method in India.</p> <p>The results apply largely to the author's own device rather than commercially available devices.</p>

18. Ito and Shirai, 2001

Citation	<p>The Efficacy of Ununited Tibial Fracture Treatment Using Pulsing Electromagnetic Fields H. Ito and Y. Shirai J. Nippon Med. Sch. 2001: 68(2)</p>
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture long bones, all tibias
Stimulation Type	<input checked="" type="checkbox"/> PEMF <p>Author-built, resembling system used by Bassett: two external electromagnets fastened to plaster cast, driven by a generator, 5-ms burst quasi-rectangular pulses at intervals of 15 Hertz, producing 1 to 1.5 my of induced current in the bone.</p>
Commercial Device Name(s)	Not applicable.
Overall Study Design	<input checked="" type="checkbox"/> Patient as own control, prospective
# Patients	30
Selection Criteria	<p>Inclusion:</p> <ul style="list-style-type: none"> • Delayed union or non-union tibial fractures
Methods	<p>Patients instructed to use PEMF 8 hours a day and not to bear weight. Used at patients' homes, mainly during sleep. Clinical and radiological assessment every 6 weeks. Cast changed to PTB cast and brace as indicated clinically. PEMF discontinued when no clinical mobility and not more than slight tenderness at fracture site.</p>
Success/Failure Criteria	<p>Union defined by radiographic confirmation in two planes showing bony trabecular crossing at least half the width of the fracture.</p>
Results	<p>Union achieved in 25 of 30 cases. Median time to achieve was 8.6 months (4 to 16 months). Healing rate did not correlate with age or gender, presence of surgical hardware, length of time injured, orientation of the fracture, or number of previous operations. Failures include non-unions and dropouts. All 8 hypertrophic non-unions healed and all 15 sclerotic non-unions. 4 of 6 necrotic cases and 3 "defective non-unions" failed to heal.</p>
Potential Sources of Bias	<p>The finding that healing occurred in spite of the presence of surgical hardware was not fully informative because the authors did not distinguish between screws at the site of the fracture (which Sharrard found impeded healing) and screws elsewhere holding plates on the fracture.</p> <p>About a third of the sample had been injured more recently than 9 months ago, thus were delayed unions, and might have healed spontaneously without PEMF. This may have</p>

	<p>produced a higher proportion of successes than in many other studies.</p> <p>The criterion for success, that trabecular bone reached at least halfway across the fracture gap, was a lower standard than in many studies, and might have resulted in a report of faster healing times than in many studies.</p> <p>There was no test for compliance, hence the electrical dosage might have been less than it appeared to be, or it might have been more than actual dosages in other studies that did not test compliance.</p> <p>Criteria for assessments were not given. Radiographs do not seem to have been read by independent parties, or read blind. Thus initial condition of fractures may not be comparable with injuries described the same way in other studies, and the potential for bias in defining union exists.</p> <p>Precise definitions of hypertrophy, sclerotic, and necrotic are not given, as in most studies, and may not be the same as in other studies.</p>
Other Limitations of the Study	<p>Statistical analysis was not attempted, probably because of the small sample, which limits the value of the findings about effects of PEMF on subjects with various characteristics.</p> <p>Does not demonstrate the value of other types of PEMF, or other methods of electrical stimulation of bone.</p>

19. Madronero et al., 1988

Citation	<p>Pulsed Electromagnetic Field Treatment Failure in Radius Non-United Fracture Healing I. P. Madronero and F. J. Manso J. Biomed. Eng., 1988, Vol 10</p>
Intended Use	<input checked="" type="checkbox"/> Non-Union and delayed union fracture long bones, radius only
Stimulation Type	<input checked="" type="checkbox"/> PEMF Author-built. Not specified. Described by Guillen and Madronero, J Biomed Eng, 1985, 7.
Commercial Device Name(s)	Not applicable.
Overall Study Design	<input checked="" type="checkbox"/> Patient as own control, prospective
# Patients	10
Selection Criteria	<p>Inclusion:</p> <ul style="list-style-type: none"> • Delayed unions and non-unions. • Radius only, to be sure of pseudo-piezoelectric biopotential absence. <p>Exclusion:</p> <ul style="list-style-type: none"> • One patient excluded because of insomnia anxiety.
Methods	PEMF given at doses up to 2.3 G (as described by Guillen and Madronero), until bone consolidation occurred.
Success/Failure Criteria	Success: radiological evidence presence of bone callus, pseudoarthrotic resolution. Absence of spontaneous pain or pain under pressure. Absence of movement at fracture.
Results	<p>Six patients with implanted metallic plates secured with screws failed to achieve consolidation. Four patients without implanted plates secured with screws achieved bone consolidation. P = .01 by Fischer exact test. Authors suggest because negative polarization of the fracture is diminished because metal plate conducts electricity, and electrical contact introduced by screws causes polarization to be equal throughout its area.</p> <p>Safety: no biochemical or hematological abnormalities were found in patients throughout study.</p>
Potential Sources of	This is a small sample size, and the authors do not appear to have ruled out the possibility

Bias	<p>that factors such as the extent of the original injury may be the cause of the difference between the patients with and without metal.</p> <p>Longest PEMF treatments (presumably the cases in which union did not occur) were only six months. Other studies have reported that it required as long as 16 months for some fractures to achieve union under PEMF, and treatments are often extended over 40 months before non-union is considered permanent. Thus the failures with metal plates in this study might have healed after six months.</p> <p>Details of radiological measurements not given. (Perhaps in Guillen and Madronero.) Apparently not done by independent parties. It would be impossible to mask the presence of metallic instrumentation on the x-rays.</p> <p>Details of treatment, such as number of hours a day PEMF given, other treatments concurrently, not given. (Perhaps in Guillen and Madronero.) If different patients followed different regimes, this could have biased results.</p> <p>It was not reported whether the small samples with and without metal plates also differed in the degree of blood flow (hypertrophic, atrophic) to bones, which would affect healing.</p> <p>Compliance was not tested; hence patients with metal plates and screws may have used PEMF less than other patients.</p>
Other Limitations of the Study	<p>The study does not shed light on the value of other types of PEMF equipment, or on other methods of electrical stimulation of bone.</p> <p>This study looked at a relatively short period of treatment compared to other studies.</p>

20. Marcer et al., 1984

Citation	<p>Results of Pulsed Electromagnetic Fields (PEMFs) in Ununited Fractures after External Skeleton Fixation</p> <p>M. Marcer, G. Musatti, and C.A.L. Bassett</p> <p>Clin. Orthop. 190-260-65 (1984)</p>
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture long bones
Stimulation Type	<input checked="" type="checkbox"/> PEMF
Commercial Device Name(s)	Not clear, but it seems to be implied that only cases were chosen using EBI Bone Healing System.
Overall Study Design	<input checked="" type="checkbox"/> Patient as own control, retrospective
# Patients	147
Selection Criteria	<p>Inclusion:</p> <ul style="list-style-type: none"> Records of patients whose fractures had been treated both with external skeleton fixation and with PEMF. <p>Exclusion:</p> <ul style="list-style-type: none"> Additional surgery had not been attempted when PEMF added to treatment.
Methods	<p>“Recommended” treatment time was 10 hours a day, which were usually logged at night. There is no mention of a compliance monitor.</p> <p>Follow-up intervals and duration were not uniform for this retrospective analysis.</p>
Success/Failure Criteria	Success if all of the following are present: no detectable motion or tenderness, no pain on weight-bearing, no further need for external support, and radiographic evidence of bone bridging of the gap.
Results	Healing occurred in 73% of cases. The authors comment that this is about the same result as is to be had from other methods for treating ununited fractures (77%), but they note that their study included a number of serious cases (66% open fractures, an average of 3.3 failed operations, 1/3 had history of infections).

	<p>The proportion of successes was higher in tibia fractures (75%), compared to 31% in femur fractures and 38% in humerus fractures. Gap size correlated with success. In successful cases, the “average gap” (the average width where the gap was not uniform, and the width in other cases) ranged from 4 to 8 mm, while in failures the range was 9 to 12 mm.</p> <p>Age, length of disability, complexity of the fracture, number of failed operations, and whether injuries were open or closed did not appear to affect the outcome. Presence of infection at the time of PEMF treatment is said to appear to make no difference (70% success) but there were only 5 cases. There was a nearly equal distribution of atrophic, oligotrophic, and hypertrophic lesions in the healed and failed groups – although all 15 fractures classified as hypertrophic healed successfully.</p> <p>Some failures were probably due to mistakes in the external fixation, especially with humerus fractures. The percentage of poor fixation technique was 3.5 times higher among failures than among successes, and all 8 humerus failures were associated with wrong placement of pins, while all 5 humerus successes showed good fixation technique. Fixation was judged inadequate if less than 5 pins were used, if pins failed to engage to cortices, when there was disintegration around the pins (shown by radiographic translucence, or when an inadequate reduction accompanied less than two external bars. However, there was no data on fixation technique in about a third of the total cases.</p> <p>Safety: The authors note that PEMF seems to be compatible with the metal of the fixation framework, “and no untoward results were reported.”</p>
Potential Sources of Bias	<p>These past cases, seen by different physicians at different times, and unevenly reported, were probably treated differently in ways that were not identified in this study. Correlations between healing or failing to heal and other characteristics are therefore likely to be subject to unknown sources of bias. In a third of the cases, for instance, researchers were unable to judge whether mistakes had been made in external fixation technique, although the criteria for mistakes were well specified. Compliance is not mentioned.</p> <p>It is not clear if the same person or persons assessed all the X-rays, but it is not stated that the assessments were blind (with regard to success of healing). Only 15 of the 147 fractures were classed as hypertrophic, a much lower number than is usual in studies.</p> <p>No statistical analysis was done, and many assertions were not backed up by any figures, or were based on extremely small samples – correlations within 15 humerus cases, 15 cases of hypertrophy, 5 cases of infection. The authors compare their healing rate of 73% to the rate using other methods of treating non-union (77%), but do not give a source for the latter figure. They note that their study contains a high proportion of severe cases, but do not compare their data on severity with data from other studies.</p> <p>Because of these problems, most of the statements about features of the fractures that predicted success or failure are not very useful.</p>
Other Limitations of the study	<p>It is not clear whether all these patients used the EBI Bone growth unit. A paragraph in Materials and Methods describes the EBI device and its use as if the authors themselves applied it as part of the research. It is probable that all patients used this instrument, and thus the findings are limited to its efficacy, in association with external skeletal fixation.</p>

21. Meskens et al., 1990

Citation	<p>Treatment of Nonunion Using Pulsed Electromagnetic Fields: A Retrospective Follow-up Study</p> <p>M.W.A. Meskens, J.A.E. Stuyck, H. Feys, and J.C. Mulier</p> <p>Acta Orthopédica Belgica Vol. 56, 2, 1990</p>
Intended Use	<p><input checked="" type="checkbox"/> Non-Union fracture long bones</p>
Stimulation Type	<p><input checked="" type="checkbox"/> PEMF</p> <p>Author-built. Based on Bassett.</p>

Commercial Device Name(s)	Not applicable.
Overall Study Design	<input checked="" type="checkbox"/> Patient as own control, retrospective
# Patients	34
Selection Criteria	<p>Inclusion:</p> <ul style="list-style-type: none"> Absence of signs of continuing consolidation on X-rays after at least 24 months since injury <p>Exclusion:</p> <ul style="list-style-type: none"> Patients operated on for nonunion within 4 months of the study were excluded
Methods	<p>Patients used PEMF attached to cast, warned not to bear any weight. PEMF was given 14 hours per day first 3 months. Next 3 months, 10 hours per day. After that, only at night. X-rays taken "regularly." As soon as X-rays showed bone growth, partial weight-bearing exercises axial compression. Mobilization and partial weight-bearing started when patient able to support half his body weight, progressing to full weight-bearing without crutches. PEMF given average 11.5 months. Range 3 months to 43 months.</p>
Success/Failure Criteria	Success: bridging and disappearance of the gap on X-ray. Disappearance of movement at the fracture. Disappearance of pain and pain on percussion of fracture.
Results	<p>Even though all patients were at least 24 months past injury, their success rates were similar to those from studies with shorter periods since injury.</p> <p>After 43 months, complete consolidation in 67.6% of patients. When patients with a gap wider than half the width of the bone with a true synovial non-union (pseudoarthrosis) were excluded, success rate 76.6%.</p> <p>Femur success rate 77.8%, tibia 73.3 %, femur 77.8%, humerus 20%. (This may be because humerus fractures are difficult to immobilize rigidly.) Hypertrophic success rate 75%, atrophic 0%, and neither 80%. Authors suggest hypertrophy may be a contraindication for PEMF.</p> <p>Differences not important: Initial open fracture 75%, closed fracture 61% - not a large difference. Not comminuted 76%, comminuted 58%, not a major difference. Initial therapy for treating fracture did not seem to have a clear influence. Surgery 70% success rate, plaster or external fixation only, 60%.</p>
Potential Sources of Bias	<p>Radiographic bridging and disappearance of the gap, hypertrophy, and atrophy are not defined precisely, which make comparison of rates of healing a bit problematic.</p> <p>Observer bias is also possible, as there is no indication that the x-rays were reviewed by an independent reviewer.</p> <p>Compliance was not tested; hence patients in certain categories may have received larger doses than patients in contrasting categories.</p>
Other Limitations of the Study	<p>Small sample size, which is probably why statistics were not used. The comparisons of success rates with various factors are not very useful for this reason.</p> <p>The suggestion that hypertrophy is a contraindication for PEMF is surprising, given the small difference in success rates between hypertrophic fractures (75%) and non-hypertrophic but not atrophic (80%).</p> <p>The patients were seen over two years, and may have had somewhat different treatments.</p> <p>The study focuses of PEMF, is not informative about other methods of electrical stimulation, or other forms of PEMF equipment.</p>

Citation	Pulsing Electromagnetic Fields in the Treatment of Non-union of Fractures J.M. Caullay and T.S. Mann Journal of the Royal College of Surgeons in Edinburgh, 27(2): 102-107, 1982
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture long bones <i>tibia</i>
Stimulation Type	<input checked="" type="checkbox"/> PEMF
Commercial Device Name(s)	Model name not given; made by Electro-Biology International.
Overall Study Design	<input checked="" type="checkbox"/> Patient as own control, prospective
# Patients	4 patients 64 yr old male with non-union of tibial fracture; infection 55 yr old male with non-union of tibial fracture; infection 4 yr old male with congenital pseudoarthrosis 4 yr old sex not reported with congenital pseudoarthrosis
Selection Criteria	<ul style="list-style-type: none"> • Selection Criteria not reported.
Methods	<ul style="list-style-type: none"> • The apparatus was placed over the fracture site, on the external surface of a well-molded, snug fitting plaster cast or brace; the patients were instructed on use of the equipment and how to ensure it was functioning properly. • Treatment was continued 12-16 hr daily for a total of about 1600 hours, depending on progress. • Weight-bearing was forbidden until evidence of union was present. • Determination of healing was made both radiologically and clinically.
Success/Failure Criteria	<ul style="list-style-type: none"> • Specific criteria are not given. Mention is only made of healing based on clinical and radiographic findings.
Results	<ul style="list-style-type: none"> • 64 yr old man - after 3 months, signs of healing were present; after 18 months, healing had taken place. • 55 yr old man - bony union took place after 4 months of treatment. • 4 yr old male - healed after 1600 hr stimulation. • 4 yr old sex not reported - healing of a McFarland bypass graft occurred 9 months after treatment.
Potential Sources of Bias	<ul style="list-style-type: none"> • The potential for selection bias seems very high. • No mention is made of the radiological or clinical criteria for healing nor does the paper mention who read the radiographs or performed the clinical evaluation, so observer bias cannot be ruled out.
Other Limitations of the Study	<ul style="list-style-type: none"> • With a sample size of only 4, two very different etiologies, and no clear selection criteria, it is hard to draw any significant conclusions from these findings The authors acknowledge the limitations of the small sample size. • The study was limited to one PEMF stimulation device.

23. DeHaas et al., 1986

Citation	The Canadian Experience with Pulsed Magnetic Fields in the Treatment of Ununited Tibial Fractures W.G. De Haas, A. Beaupre, H. Cameron, and E. English Clin Orthop Relat Res, 208: 55 - 58, 1986
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture long bones <i>tibia</i>

Stimulation Type	<input checked="" type="checkbox"/> PEMF Custom built system at the University of Calgary; produces a 1 Hz quasi square wave signal with a 150-300 Gauss flux density at the fracture site.
Commercial Device Name(s)	Not applicable.
Overall Study Design	<input checked="" type="checkbox"/> Patient as own control, prospective
# Patients	56 patients Time from injury to start of treatment: 6 months to 13 years 38 patients had undergone one or more surgical procedures 17 cases had active infections 6 cases had internal metallic fixation devices
Selection Criteria	<ul style="list-style-type: none"> • Tibial fractures that had remained ununited for at least 6 months. • Fractures that remained ununited after 6-9 months of immobilization were classified as "delayed union." • Fractures that remained ununited after 9 months of immobilization or longer, without any radiologic changes occurring during the last 2 months of treatment were classified as "non-unions."
Methods	<ul style="list-style-type: none"> • The magnet was mounted on a long leg cast with its pole pieces supported in slots at the level of the fracture site. • Stimulation was applied for 18-20 hours daily for 3 – 10 weeks. • Most patients were treated at home. • After treatment, cast immobilization was continued until the fracture united. • Healing was assessed clinically and radiologically; in case of any doubt, tomograms were taken.
Success/Failure Criteria	<ul style="list-style-type: none"> • No specific criteria were given in the paper.
Results	<ul style="list-style-type: none"> • All patients with delayed union healed with an average time of 4.6 months. • 37/44 (84%) patients in the non-union healed with an average time of 5.5 months. • The patient with the pseudoarthrosis failed to heal. • The patient with the congenital pseudoarthrosis required a bone graft and eventually healed; no breakdown of the union was observed during a 4 year follow up period. • 14/17 (82.3%) patients with infection present healed. • All 6 cases with internal metallic fixation devices healed. • No side effects were observed in any of the patients; the only complication consisted in stress fractures in 5 cases which all healed with further electrical stimulation and immobilization.
Potential Sources of Bias	<ul style="list-style-type: none"> • The actual selection method was not cited (serial, random, etc). • It is unclear who read the radiographs or did the clinical assessment. • No specific criteria were cited that defined healing.
Other Limitations of the Study	<ul style="list-style-type: none"> • The authors indicate that the apparatus is very bulky and its use is limited to the tibia; although; fractures of the humerus and distal femur have also been treated. • They also state that the prolonged immobilization by casting is not economically feasible or handled well by the patient.

	<ul style="list-style-type: none"> • Some of the ununited tibiae were in poor alignment, and although union occurred, the results were considered cosmetically unsatisfactory. • The study used only PEMF stimulation.
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24. Brighton et al., 1981

Citation	A Multicenter Study of the Treatment of Non-Union with Constant Direct Current C.T. Brighton, J. Black, A.B. Friedenber, J.L. Esterhai, L.J. Day, and J.F. Connolly The Journal of Bone and Joint Surgery, 63-A: 2-13, 1981
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture long bones <input checked="" type="checkbox"/> Non-Union fracture other bones
Stimulation Type	<input checked="" type="checkbox"/> Other <i>Constant Direct Current</i> Non-commercial; field-effect transistors and resistors in circuit with a 7.5 V battery, such that constant current was delivered regardless of changing resistance; surgically implanted percutaneously.
Commercial Device Name(s)	Not applicable.
Overall Study Design	<input checked="" type="checkbox"/> Patient as own control, prospective
# Patients	Study I: University of Pennsylvania 186 patients Average duration of non-union was 2.7 yr post injury 134 (72%) had previous surgical procedures (average 2.2) Study II: Participating Investigators (12) 79 patients Average duration of non-union was 3.3 yr post injury 49 (62%) had previous surgical procedures
Selection Criteria	<ul style="list-style-type: none"> • Each patient had a well-established non-union, defined as all demonstrable reparative processes had ceased in a fractured bone and bone continuity had not been restored. • Diagnosis of non-union was based on serial roentgenograms. • Initially, diagnosis was made on the absence of visibly progressive signs of healing on serial roentgenograms made over a 5 mo period; later determined that diagnosis could be made off of 3 sets of roentgenograms made at monthly intervals over a 3 mo period. • The criterion of no progressive signs of healing was not met by 81% of the patients until after 12 mo post-injury. • The patient had to be willing and able to return for periodic follow-up examinations.
Methods	<ul style="list-style-type: none"> • Device cathodes were surgically implanted percutaneously under local or general anesthesia. • A plaster cast was applied; cast remained applied during entire course of electrical treatment. • Current was monitored monthly by a physician. • Current was applied continuously for 9 weeks in the first 7 patients in the Pennsylvania series; all subsequent patients at that site and all the participating investigators' sites had current applied for 12 weeks.

	<ul style="list-style-type: none"> • After 12 weeks, the cast and device were removed and roentgenograms were made with the limb out of plaster. • The cast was reapplied and immobilization occurred for another 12 weeks without electricity. • This complete process was carried out once in 160 Pennsylvania patients; 2x in 18 patients; 3x in 6 patients; 4x in 4 patients; and 5x in 1 patient. • This complete process was carried out once in all of the participating investigators' patients.
Success/Failure Criteria	<ul style="list-style-type: none"> • Visible signs on healing on roentgenograms; no specific criteria mentioned that defined "healed" or "failed to heal."
Results	<ul style="list-style-type: none"> • Of the 189 Pennsylvania non-unions, 149 (78.8%) achieved solid bone union. • In the beginning of the study, 11 consecutive non-unions of larger bones (tibia, femur, humerus) failed to unite with one cathode; therefore, 4 cathodes were used after that on non-unions involving these bones; the results improved dramatically. • Of the remaining 178 patients, 149 (83.7%) achieved solid bone healing after one round of treatment; 18 patients underwent two round of treatment and 14/18 (77.8%) achieved healing; 6 patients underwent three rounds of treatment and 4/6 (66.7%) healed; 4 patients underwent 4 rounds of treatment and 2/4 healed (50%); 1 patient underwent 5 rounds of treatment and did not achieve healing (0%). • Of the 43 Pennsylvania patients with a previous infection (osteomyelitis), 32 (74.4%) achieved solid bone union. • Of the 22 non-unions with plates and screws; 14 (63.6%) achieved healing; of the 8 non-unions that were plated, 5 (62.5%) achieved healing; of the 2 non-unions with intramedullary rods, 1 (50%) healed. • No correlation was shown between duration of non-union and result up to 40 months; beyond 40 months, no conclusion could be drawn due to too few numbers. • Of the 80 Participating Investigator (PI) non-unions, 58 (72.5%) achieved solid bone union. • The duration of the non-union and the result achieved by electrical treatment failed to show any correlation. • When the results of the Pennsylvania series and the PI series were compared statistically, there was no difference between the two groups. • Complications of the electrical treatment were minor and there was no deep infection resulting from this procedure in patients without previous osteomyelitis. The authors demonstrated that the use of constant direct current in the treatment of non-union is safe.
Potential Sources of Bias	<ul style="list-style-type: none"> • At all sites there was some potential for observer bias, because (1) there was no indication of an independent observer reading x-rays, (2) the radiologic criteria which they used to define "healed" non-union were not clearly defined, and (3) it would be impossible to mask the presence of the implanted electrodes.
Other Limitations of the Study	The study was limited to an implanted constant direct current device and may not be applicable to noninvasive stimulation devices.

25. Holmes, 1994

Citation	<p>Treatment of Delayed Unions and Nonunions of the Proximal Fifth Metatarsal with Pulsed Electromagnetic Fields</p> <p>G.B. Holmes, Jr.</p> <p>Foot & Ankle International, 15(10):552 – 556, 1994</p>
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Intended Use	<input checked="" type="checkbox"/> Non-Union fracture other bones <i>metatarsal</i>
Stimulation Type	<input checked="" type="checkbox"/> PEMF
Commercial Device Name(s)	Name not given; cited as an external coil device which provided PEMF.
Overall Study Design	<input checked="" type="checkbox"/> Patient as own control, retrospective
# Patients	9 patients Mean duration of treatment prior to PEMF was 2.8 months
Selection Criteria	Inclusion: <ul style="list-style-type: none"> Only fractures that were classified as Jones fractures or diaphyseal stress fractures and further subclassified as delayed union or non-union according to the criteria by Torg et al. 1984 and Torg 1990 were included in this study. Exclusion: <ul style="list-style-type: none"> Acute fractures treated with PEMF.
Methods	<ul style="list-style-type: none"> Follow-up information was obtained by direct interview with the patient or questionnaire to the treating physician or podiatrist. Pre and post-treatment radiographs were also available for review. Patients were treated with an external coil device which provided PEMF. The daily coil usage goals were 8 – 10 hours/day. The device was positioned over the foot and a short leg non-weightbearing cast, short leg weightbearing cast, or weightbearing postoperative shoe was applied.
Success/Failure Criteria	<ul style="list-style-type: none"> Completion of healing was determined by radiographic evidence of trabecular bridging across the fracture line, pain-free gait, and the achievement of ambulation without a cast, walking boot, or postoperative wooden shoe.
Results	<ul style="list-style-type: none"> All fractures healed with a mean healing of 4 months (range 2 to 8 months). No further interventions were necessary and there were no recurrences of symptoms or re-fractures. Of the 3 patients who received the short leg non-weightbearing cast, healing was accomplished in 3 months. Of the 6 patients that received either a short leg weightbearing cast or weightbearing postoperative shoe, healing was accomplished in a mean time of 4.5 months.
Potential Sources of Bias	<ul style="list-style-type: none"> It is unclear who interpreted the radiographs. If it was the study's author, this may represent a source of bias.
Other Limitations of the Study	<ul style="list-style-type: none"> The author indicates that a double-blind prospective trial would be optimal. The author indicates that the best study will involve the direct comparison of results of electrical stimulation, prolonged immobilization, inlay bone graft, and axial screw fixation. These results only pertain to one type of stimulation device and one application (Jones fractures).

26. Beckenbaugh, 1985

Citation	Noninvasive Pulsed Electromagnetic Stimulation in the Treatment of Scaphoid Nonunion R. D. Beckenbaugh Orthopedic Transactions 9:444 (Fall 1985)
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture scaphoid bones of wrist

Stimulation Type	<input checked="" type="checkbox"/> PEMF
Commercial Device Name(s)	Not given.
Overall Study Design	<input checked="" type="checkbox"/> Patient as own control, prospective
# Patients	21
Selection Criteria	<p>Inclusion:</p> <ul style="list-style-type: none"> • Non-union of scaphoid established from 6 months to 4 years. <p>Exclusion:</p> <ul style="list-style-type: none"> • Cases of significant angulation or associated carpal collapse patterns, as shown tri-spiral tomography, excluded. PEMF is contraindicated for these conditions.
Methods	Not described.
Success/Failure Criteria	“union”
Results	<p>60% success rate. 9 of 10 patients with long arm cast healed, but only 6 of 11 patients with short arm cast. Duration of disability period did not affect success.</p> <p>In cases of non-union of a nondisplaced fracture of the scaphoid, PEMF resulted in a healing rate of 90%. Author recommends this should be the primary treatment of choice in these cases.</p>
Potential Sources of Bias	Not enough information.
Other Limitations of the Study	Not enough information, except that it applies only to PEMF.

27. Colson et al., 1988

Citation	<p>Treatment of Delay and Non-Union of Fractures Using Pulsed Electromagnetic Fields D.J. Colson, J.P. Browett, N.J. Fiddian, and B. Watson J. Biomed. Eng. Vol 10, 1988</p>
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture long bones, 22 of 33 were tibias
Stimulation Type	<input checked="" type="checkbox"/> PEMF Peak magnetic field of 0.8 mT. The stimulating waveform consists of a train of five quasi-rectangular pulses, each 300 microsecond duration, separated by 1500 microseconds. The pulse train is itself pulsed at 50 Hz.
Commercial Device Name(s)	Not applicable.
Overall Study Design	<input checked="" type="checkbox"/> Patient as own control, prospective
# Patients	32, with 33 fractures
Selection Criteria	<p>Inclusion:</p> <ul style="list-style-type: none"> • Consecutive patients at St. Bartholomew’s Hospital, London with long-bone fractures treated with PEMF; apparently all that have been treated in this way at this hospital. • PEMF was given only with difficult fractures, usually with non-union of at least 5 months, or considered likely to have delayed or non-union likely with conventional treatment.
Methods	Surgery was used to correct wide gaps, gross movement at the fracture site requiring internal fixation, and synovial pseudoarthroses before the treatment was instituted.

	<p>Device fastened to cast. There was no expert technical help in fitting the coils or subsequent patient reviews. Coils were not separated by the size of their diameters (which is wrong physically: it should be by the width of their radii), because coils of this size are not feasible for treating fractured limbs. In any case, limbs are not homogeneous and will complicate the electric fields produce.</p> <p>Patients were instructed strictly no weight bearing. Patients used the device at home, 12 to 15 hours a day. Patients were to test coils daily to see if the unit was working.</p> <p>There was strict non-weight-bearing on lower limbs until definite radiological signs of bridging, and then partial weight-bearing was allowed.</p> <p>Stimulation continued until there was full radiological and clinical evidence of union. If union was not achieved within one year, the therapy was discontinued.</p>
Success/Failure Criteria	The authors do not provide the specific radiologic and clinical criteria for assessing successful union.
Results	<p>All 19 fractures that were treated with PEMF and surgery united within 9 months (mean and median 6 months). 12 of the 14 fractures treated with PEMF alone united within 10 months (mean and median 6 months). (Note: Total success rate of 94%)</p> <p>One failure was an extremely obese patient whose cast was not stabilizing the fracture, and who dropped out. The other was a patient who went abroad, was bearing weight, and whose unit was found to be nonfunctional when he returned. Another possible complicating factor was that he had a low-grade infection throughout. He was given surgery and healed within a year without more PEMF.</p>
Potential Sources of Bias	<p>The criteria for initiating PEMF therapy appear to be less stringent than those used in other studies.</p> <p>Assessment details are not given. Information not given on radiography, number of views, frequency, who read radiographs, creating the possibility of observer bias.</p> <p>Compliance with hours unit was used, whether unit was checked daily, and whether weight-bearing was avoided, was not monitored, so may have been different than in other studies.</p>
Other Limitations of the Study	<p>Limited to PEMF stimulation.</p> <p>This is a relatively small study, without a control group.</p>

28. Beigler et al., 1994

Citation	<p>Multicenter Nonunion Clinical Investigation of the Regentek OL1000 Bone Growth Stimulator</p> <p>D. Beigler, et al. (17 investigators or institutions)</p> <p>White Paper, 1994.</p>
Intended Use	<p><input checked="" type="checkbox"/> Non-Union fracture long bones</p> <p><input checked="" type="checkbox"/> Non-Union fracture other bones: scaphoid (wrist), malleolus, metacarpal, capitate (wrist), metatarsal</p>
Stimulation Type	<input checked="" type="checkbox"/> Combined magnetic fields
Commercial Device Name(s)	Regentek OL1000 Bone Growth Stimulator
Overall Study Design	<input checked="" type="checkbox"/> Patient as own control, prospective
# Patients	112 with 116 fractures

Selection Criteria	<p>Inclusion:</p> <ul style="list-style-type: none"> • Nonunion acquired secondary to trauma. • No clinical or radiographic evidence of union at least nine months after injury. • No surgical intervention within three months before entering study. • No radiographic evidence of healing within at least three months before entering study (determined by the independent review panel). • Radiographic evidence of skeletal maturity or at least 18 years of age. <p>Exclusion:</p> <ul style="list-style-type: none"> • Written informed consent not provided. • Fracture gap greater than half the diameter of the bone. • Fracture involved a vertebrae, flat bone, or was a pathological fracture. • Congenital or true synovial pseudoarthrosis. • Nonunion was due to a failed fusion of spine, skull, or joint. • Concurrent pregnancy. • Demand-type pacemaker near the treatment site, including fractures of hand, wrist, arm.
Methods	Not given.
Success/Failure Criteria	<p>Clinically no pain or motion at fracture.</p> <p>Three or more cortices bridged on radiograph. Final outcome verified by an independent review panel composed of two orthopedic surgeons and one musculoskeletal radiologist.</p>
Results	<p>Effectiveness:</p> <p>51 of 116 (44%) fractures healed, 33 of 116 fractures did not heal (2 eventually amputated), and 32 did not complete treatment. (16 voluntarily withdrew, 5 were reported to be noncompliant, 8 withdrew due to study protocol violations, 1 hospitalized for pre-existing condition, 1 incarcerated, 1 geographically relocated.</p> <p>Of the 84 fractures that completed treatment, 51 fractures healed and 33 did not heal.</p> <p>Safety:</p> <p>Toxicological studies on isolated cells and on animals were performed to evaluate the safety of combined static and dynamic magnetic fields. There were no significant adverse findings which could be associated with chronic exposure to the combined fields.</p> <p>Additional Findings:</p> <p>In vitro and in vivo studies were conducted to determine whether application of these magnetic fields in animal models would stimulate bone healing. Findings: a combined static and dynamic field like the one produced by Regentek OL1000 had a statistically significant stimulatory effect on bone healing. In vivo studies on chick embryo femurs showed significant effect on bone development.</p>
Potential Sources of Bias	The authors give 60.7% overall success rate, by excluding a significant number of patients, including patients more likely to have relatively poor outcomes.
Other Limitations of the Study	<p>The relatively high withdrawal rate is not well-explained.</p> <p>The study applies only to combined fields, and specifically a single commercial device.</p>

29. Mueller and Thomas, 1979

Citation	Treatment of Non-Union in Fractures of Long Bones M.E. Muller and R.J. Thomas Clinical Orthopaedics and Related Research, No. 138, 1979
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture long bones, excluding non-unions of femoral neck
Stimulation Type	<input checked="" type="checkbox"/> None. Internal or external fixation, electrical stimulation.
Commercial Device Name(s)	Not applicable.
Overall Study Design	<input checked="" type="checkbox"/> Patient as own control, retrospective
# Patients	113
Selection Criteria	Inclusion: <ul style="list-style-type: none"> • Patients treated for non-unions following long bone fractures at two clinics in Berne, Switzerland between 1967 and 1976. Most were referred from other clinics; the average case had undergone one previous operation. • At least 8 months disability period.
Methods	Uninfected fractures (90) were fixed with a medullary nail or a plate applied under pressure to exert compression, or in four cases with external fixation. In atrophic cases, decortication and cancellous bone grafting were also used. Infected fractures (24) were usually treated with external fixation which could be tightened to exert compression, and usually with surgical decortication and cancellous grafting.
Success/Failure Criteria	Healing of the non-union, irrespective of complications. There was no cut-off date. No details are given, but radiographs were clearly taken.
Results	All 90 (100%) of the uninfected fractures healed, 82 with one operation and the majority within 6 months of surgery. Of the 24 infected cases, 23 healed (96%). 15 healed without further operation, and the others required additional procedures. One patient had been referred for amputation, requested additional treatment first, but eventually accepted amputation. The authors state that, "experience over 20 years has shown that non-union is rarely an unsolvable problem." Note: The authors say that early surgery leads to extremely good outcomes.
Potential Sources of Bias	The selection of patients appears to be based on referral patterns from other clinics. It is not possible to assess the types of bias that may have been introduced at the referring clinics. The criteria for success are vague, raising the potential of some observer bias.
Other Limitations of the study	This study does not provide any information on electrical stimulation.

30. Nelson et al., 2003

Citation	Use of Physical Forces in Bone Healing F.R.T. Nelson, C.T. Brighton, J. Ryaby, B.J. Simon, J.H. Nielson, D.G. Lorch, M. Bolander, and J. Seelig Journal of the American Academy of Orthopaedic Surgeons, Vol. 11, No. 5, 2003
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture long bones <input checked="" type="checkbox"/> Non-Union fracture other bones <input checked="" type="checkbox"/> Lumbar spinal fusion

Stimulation Type	<input checked="" type="checkbox"/> Capacitive coupling <input checked="" type="checkbox"/> PEMF <input checked="" type="checkbox"/> Combined magnetic fields <input checked="" type="checkbox"/> Implanted stimulation device <input checked="" type="checkbox"/> Modified PEMF
Commercial Device Name(s)	Only Spinal-Stim mentioned.
Overall Study Design	This is a review of research on the use of direct current stimulation, pulsed electromagnetic field, modified electromagnetic field, capacitive coupling, combined magnetic fields, and ultrasound in bone healing.
# Patients	Not applicable.
Selection Criteria	Not applicable.
Methods	Not applicable.
Success/Failure Criteria	Authors criticize most studies for recording only presence or absence of healing as the end point, instead of outcomes such as return to work or other specific activities.
Results	<ol style="list-style-type: none"> (1) DC stimulation is approved for use with nonunions and with spinal fusion. Implanted DC eliminates the problem of patient compliance. Not useful with synovial pseudoarthrosis. (2) PEMF is recommended as an adjunct to standard fracture management, including of nonunions, failed fusions, and congenital pseudoarthrosis. Contraindications are a fracture gap greater than 5 mm, suspected or documented synovial pseudoarthrosis, and severe devascularization. Gossling added together cases from a number of studies and reported that PEMF shows as high rates as surgery in healing nonunions, higher rates in healing infected nonunions and closed fractures, but lower rates than surgery in healing open fractures. Dosage correlates with healing rate. (3) Capacitive coupling is indicated for nonunions of long bones and the scaphoid and as an adjunct treatment in spinal fusions. Skin reaction, a problem, is usually mild. Risk factors that adversely affect healing rate include long disability period, prior bone graft surgery, prior electrical stimulation, open fracture, osteomyelitis, comminuted or oblique fracture, and atrophy. When 2 to 5 of these risk factors are present, capacitive coupling has been shown to be less effective than DC stimulation or bone graft, but with 6 or all 7 risk factors, all three methods yield poor results. Not useful with synovial pseudoarthrosis. (4) Modified PEMF (as Spinal-Stim), developed to reduce energy requirements, is recommended for fracture nonunions, especially as an adjunct to spinal fusion surgery, and as a nonsurgical treatment to salvage a failed spinal fusion. Dosage correlates with healing rate. Not effective with synovial pseudoarthrosis. (5) Combined magnetic fields (CMFs) have been shown to be effective in healing nonunions and as adjunctive stimulation for primary spinal fusion. Further research may establish usefulness in osteoarthritis and neuropathy. Not useful with synovial pseudoarthrosis. (6) Low intensity ultrasound has been approved for stimulating healing in fresh fractures and in nonunions. Not effective with synovial pseudoarthrosis.
Potential Sources of Bias	It is impossible to evaluate all possible sources of bias in the studies on which the review is based.
Other Limitations of the Study	It does not include direct clinical experience.

Citation	Treatment of Surgically Resistant Non-Unions with Pulsed Electromagnetic Fields B.T. O'Connor Reconstr. Surg. Traumat., Vol. 19, 1985
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture long bones
Stimulation Type	<input checked="" type="checkbox"/> PEMF
Commercial Device Name(s)	EBI Bi-Osteogen System
Overall Study Design	<input checked="" type="checkbox"/> Patient as own control, retrospective
# Patients	54
Selection Criteria	Inclusion: <ul style="list-style-type: none"> Cases of long bone non-union (one case congenital, others acquired) that were referred to author's clinic. Many are said to have been referred because multiple previous interventions had failed. 89% had disability times of over 9 months.
Methods	The affected area was generally immobilized in a cast. In 2 cases, patients had either internal fixation or external fixation that was sufficiently immobilizing to dispense with a cast. The unit was placed on the cast centered over the non-union. Patients were told to use equipment for 12 hours a day, and not to bear any weight. The author says that subjects applied PEMF for "at least 10 hours a day." When the non-union was clinically stable with radiographic evidence of substantial bony bridging, they began axial compression exercises. Monthly reviews included X-rays through the cast. After 3 months the cast was replaced or discarded, depending on progress. No compliance monitor was mentioned.
Success/Failure Criteria	Success based on radiographic evidence. If there is no radiographic evidence of improvement between 6 and 12 months, treatment is stopped.
Results	At time of writing, 32 cases completed, 22 still undergoing therapy. Two patients withdrawn for non-compliance were not included in success rate calculations. Of the 30 who have completed therapy, 83% have reached protected or full function. In 5 of these cases, union was achieved with the help of surgery after the PEMF treatment began. The 5 failures among the completed cases were due to one request for amputation by the patient; an intact fibula causing distraction of the bone ends of a tibial fracture; poor bone quality due to steroid therapy; and no known causes in two cases. Of the 22 ongoing cases, 8 have been in treatment over 9 months, 4 from 7-9 months, and 3 from 4-6 months. Of successful cases, 2 cases healed in less than 4 months, 36% required 4-6 months, and 32% required 7-9 months to heal. Tibial and femoral fractures heal more easily under this method than humeral fractures, perhaps because the latter are harder to immobilize completely.
Potential Sources of Bias	The success rate of 83% reflects only those patients who have completed treatment. Many of those still undergoing treatment may be less likely to achieve a good outcome (under treatment for over nine months). Failure criteria are vague, as the author states that if there is no radiographic evidence of healing, treatment is discontinued "between 6 and 12 months." Continuing treatment would place subjects in the ongoing-treatment group rather than in the failure group, so this vagueness would make it possible to make the treatment program appear more successful than it was.

	<p>Five of the completed-treatment cases involved surgery after PEMF was started, but they are nevertheless counted in the PEMF success rate.</p> <p>Selection Criteria are not given other than focus on long bone non-unions. The exact criteria for classifying a patient as nonunion are not given, but they may not have been as rigorous as in other studies (some with disability periods under 9 months).</p> <p>Two patients withdrawn for noncompliance were not included in the calculation of success rate, which is not consistent with modern intention-to-treat analysis rules.</p> <p>Safety issues were not discussed.</p>
Other Limitations of the study	The study focuses only on treatment with the EBI Bi-Osteogen system.

32. Scott and King, 1994

Citation	<p>A Prospective, Double-Blind Trial of Electrical Capacitive Coupling in the Treatment of Non-Union of Long Bones</p> <p>G. Scott and J.B. King,</p> <p>The Journal of Bone and Joint Surgery, Vol. 76-A, No. 6, June 1994</p>
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture long bones
Stimulation Type	<input checked="" type="checkbox"/> Capacitive coupling
Commercial Device Name(s)	Orthopak bone-growth stimulator (Bioelectron). Placebo units adjusted to give no electrical current except during brief (less than 30 sec) daily check of the equipment and battery, when they gave a current 1/5 to 1/10 the therapeutic dose.
Overall Study Design	<input checked="" type="checkbox"/> Randomized, concurrent control, prospective
# Patients	23 volunteers (advertised for). Patients with non-union of long bones were difficult to find. One patient in each group was dropped for consistent noncompliance.
Selection Criteria	<p>Inclusion:</p> <ul style="list-style-type: none"> • Non-union of long bone. • At least 9 months since injury. • No radiographic or clinical signs of progress toward healing for at least 3 months prior. • Continuous immobilization during the last 3 months with no other form of treatment if the injury duration was > 9 months, or continuously if the injury was less than 9 months. <p>Exclusion:</p> <ul style="list-style-type: none"> • Synovial pseudoarthrosis, recognized by excessive mobility or by a cold cleft between hot fragments on a technetium methylene-diphosphonate bone scan. • Gap or bone defect of more than half the width of the bone. • Any generalized disorder of bone metabolism. <p>The excluded traits might make the fracture unsuitable for treatment by electrical stimulation.</p>
Methods	<p>Patients were fitted randomly with active or placebo units. The distributions of ages, presence of metal plates, and types of non-union (atrophic etc.) are quite similar.</p> <p>Patients continued the plaster cast or brace support worn during the last 3 months (so that the only new variable would be the electrical stimulation). Holes were cut in plaster casts to place the surface electrodes. Patients were allowed to bear weight because most patients had been allowed this before the study, in order not to introduce new variables. Patients were taught to use equipment.</p> <p>Evaluations were held every 3 months (or sooner if problems arose) and radiographs were</p>

	<p>made, as in the initial evaluation, anteroposterior, lateral, and two oblique. If no healing had taken place by 6 months, a patient was withdrawn from the study and offered an alternative form of treatment. If the patient wanted to continue, his code was broken and he was given active treatment if he had been on placebo.</p> <p>There was a readout on the units indicating compliance with the regime.</p> <p>All patients were seen a minimum of 6 months after treatment was discontinued, to verify that late failure had not occurred.</p>
Success/Failure Criteria	<p>A non-union that was still healing, or had not begun to heal, at 9 months was classified as not having healed. A non-union was defined as healing but not yet healed if there was less pain, less motion, and a definite increase in callus. Lack of healing was defined as the absence, or cessation before union, of any clinical or radiological improvement. Union was not defined.</p>
Results	<p>Effectiveness:</p> <p>0 of the 10 fractures in the placebo group had healed by the endpoint of 9 months, compared with five of the 11 in the active group. At the most recent follow-up evaluation (after 83 months), 6 of 10 patients in the active group had a solid union, compared with 0 in the placebo group. This is a significant difference ($p = 0.0004$ by Fischer exact test for small sample size). Adding in the two dropped noncompliant subjects as failures, the difference is still significant ($p = 0.02$).</p> <p>Six placebo patients later chose active treatment, and two achieved unions, one rapidly in 6 weeks, the other, who had an infection, more slowly in 14 weeks. Two others showed partial healing (specified). Two showed no healing.</p> <p>There seemed to be no correlation between originally open or closed fractures and success.</p> <p>A patient with a Kuntscher nail in a femoral fracture failed to unite after electrical treatment, but a locked intramedullary nail in a femoral fracture and interfragmentary screws in a tibial fracture united after electrical treatment.</p> <p>Safety:</p> <p>Two patients had allergic reactions to the electrode discs on the skin, treated successfully with hydrocortisone ointment and adjustment of position of discs.</p>
Potential Sources of Bias	<p>The strict selection criteria and the randomization scheme minimized the potential for selection bias. However, the sample was too small to achieve equal distribution of all relevant traits. There were more tibial fractures in the placebo group, and more femoral fractures in the active group. There were more hypertrophic and atrophic fractures in the active group, and far more oligotrophic fractures in the placebo group, which probably favored the placebo group, in spite of which that group healed significantly less well.</p> <p>The cutoff period of 9 months might have excluded some slower-healing placebo group fractures from the success category.</p> <p>The definition of union was not specified.</p>
Other Limitations of the Study	<p>The authors note that it was difficult to find a large sample of non-union long bone fractures. They believe that is because most delayed unions were being treated with electrical stimulation.</p> <p>This study focuses on the capacitive coupling technique, but did not describe the waveform used.</p>

33. Sedel et al.

Citation	<p>Results of Non Unions Treatment by Pulsed Electromagnetic Field Stimulation L. Sedel, P. Christel, J. Duriez, R. Duriez, J. Evrard, C. Ficat, J. Caauchois and J. Witvoet Acta Orthop.. Scand. Suppl. 196:81-91 (1982)</p>
Intended Use	<p><input checked="" type="checkbox"/> Non-Union fracture long bones or clavicle</p>

Stimulation Type	<input checked="" type="checkbox"/> PEMF
Commercial Device Name(s)	Unit from Electro-Biology Inc.
Overall Study Design	<input checked="" type="checkbox"/> Patient as own control, retrospective
# Patients	39
Selection Criteria	<p>Inclusion:</p> <ul style="list-style-type: none"> • Patients treated with PEMF for bone non-union at four orthopedic departments in Paris. No other details are given about selection. Disability periods ranged from 2 months to 14 years (mean 11 months).
Methods	Units were attached to plaster casts in the usual way.
Success/Failure Criteria	Not given.
Results	<p>31 cases healed (about 80% counting as failures 2 dropouts who were not analyzed in the article.) Authors mention that about 2/3 of the successful unions were strong, with a large callus, while about a third were weak, with thin or curved bones, or in one case healing of one forearm bone and not the other. (One case was congenital; one success re-fractured, then healed during PEMF.)</p> <p>Tibias healed best, as in other studies.</p> <p>The 2 dropouts mentioned above are not described.</p> <p>Safety of the unit was not discussed.</p>
Potential Sources of Bias	<p>Criteria for success are extremely vague, leading to the potential for observer bias.</p> <p>Selection Criteria for this retrospective study are not given, other than that subjects were patients of the authors and received PEMF. It is not clear that all PEMF cases in a given time period were included. The inclusion of cases with disability periods as short as 2 months suggests that the criteria were less rigorous than in other studies. Some cases might have healed spontaneously, without PEMF.</p>
Other Limitations of the study	<p>As a multi-site retrospective study, there was less uniformity in overall patient management.</p> <p>The results apply only to PEMF stimulation.</p>

34. Simonis et al., 1984

Citation	<p>The Treatment of Non-union by Pulsed Electromagnetic Fields Combined with a Denham External Fixator</p> <p>R.B. Simonis, C. Good, and T.K. Cowell</p> <p>Inquiry, 13(4): 255-60, 1984.</p>
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture long bones, tibia, ulna, radius <input checked="" type="checkbox"/> Non-Union fracture of knee, one case
Stimulation Type	<input checked="" type="checkbox"/> PEMF
Commercial Device Name(s)	St. Thomas' Hospital bone stimulator. Generator produces current running for 3 ms every 40 ms. Runs to two coils attached to Denham External Fixator rather than plaster cast.
Overall Study Design	<input checked="" type="checkbox"/> Patient as own control, prospective
# Patients	15
Selection Criteria	<p>Inclusion:</p> <ul style="list-style-type: none"> • First fifteen consecutive patients treated with combination of Denham External Fixator and PEMF. This is the standard treatment for long bone non-union at St. Thomas' Hospital.

Methods	<p>Patients were surgically fitted with Denham External Fixator, described by Edge and Denham, 1981, one or more external rods attached to the bone by screws, which can be tightened to compress the fracture. Plates, staples, or screws crossing fracture site were removed because they would have prevented compression. The advantage of the fixator over a plaster cast is that it compresses the fracture, joints are not immobilized as in a cast, and infected wounds can easily be dressed.</p> <p>PEMF was applied. No details are given.</p> <p>Monthly reviews were made when fixator was tightened, and antero-posterior, lateral, and two oblique radiographs taken. PEMF was stopped and partial weight-bearing allowed when fracture line had filled in and compression had become difficult. Weight borne was then increased over a month to full weight, and then fixator was removed. If movement of the fracture was detected under stress, the fixator was re-applied.</p>
Success/Failure Criteria	Not clear.
Results	<p>Effectiveness:</p> <p>Results (87% success within 8 months, average 4 months) compare favorably with PEMF studies using plaster casts rather than external fixation. Patients exhibited long periods since injury, from 12 months to 55 months, so it is unlikely that they would have spontaneously healed during this time.</p> <p>Two infected, atrophic non-unions failed to unite. One case, in which compression was not possible for technical reasons, had not united after 9 months. The other was developing promising union when over-tightening of the fixator at 3 months caused a re-fracture.</p> <p>Six of the eight atrophic cases united successfully.</p> <p>Safety:</p> <p>Danger of overtightening the fixator, causing re-fracture, was illustrated. No safety issues were directly related to electrical stimulation.</p>
Potential Sources of Bias	<p>By including all subjects fitted with a fixator and given PEMF, rather than selecting among them, the researchers guarded against selection for a high success rate, but might also have included recent non-unions that could have healed spontaneously without PEMF. However, all patients had long disability times – 11 months was the shortest – consistent with strict criteria for defining nonunion.</p> <p>Criteria for assessments were not clearly defined, raising the potential for observer bias. Initial hypertrophy or atrophy was not precisely defined. All fractures were classed as either one or the other, with no intermediate category, which is most unusual.</p> <p>The criteria for success (union) were not defined, so are not easily compared with other studies using casts instead of fixation, and were possibly quite subjective. The article does not state how many people read the radiographs and how independent they were from the research project.</p>
Other Limitations of the Study	<p>Without a control group, this study does not distinguish between the contributions of rigid external fixation and PEMF. With no internal compliance monitor, it is even more difficult to assess the contribution of PEMF stimulation.</p> <p>The very small sample size leaves open the possibility of high success due to factors not considered in the study. Statistical analysis was not attempted.</p>

35. Dhawan et al., 2004

Citation	<p>The Effect of Pulsed Electromagnetic Fields on Hindfoot Arthrodesis: A Prospective Study S.K. Dhawan, S.F. Conti, J. Towers, N.A. Abidi, and M. Vogt The Journal of Foot & Ankle Surgery, 43 (2): 93 – 96, 2004</p>
Intended Use	Elective hindfoot arthrodesis

Stimulation Type	PEMF
Commercial Device Name(s)	EBI Medical
Overall Study Design	Randomized, concurrent control, prospective
# Patients	64 total patients, of these, <ul style="list-style-type: none"> • Control group received standard surgical procedure and included 76 joints in 38 feet: 37 subtalar joint fusions (33 primary, 4 revisions of failed prior arthrodeses), 19 primary talonavicular fusions, and 21 primary calcaneocuboid joint fusions. • Study group received standard surgical procedure plus PEMF and included 68 joints in 32 feet: 27 subtalar joint fusions (22 primary, 5 revisions of failed prior arthrodeses), 23 talonavicular arthrodeses (20 primary, 3 revisions), 19 calcaneocuboid fusions (17 primary, 2 revisions).
Selection Criteria	Inclusion criteria: All patients who underwent elective triple arthrodesis or subtalar arthrodesis performed by one surgeon between March 1993 and March 1996. Exclusion criteria: Patients with systemic disease such as rheumatoid arthritis, diabetes mellitus, and patients on oral corticosteroids.
Methods	<ul style="list-style-type: none"> • All patients underwent triple or isolated subtalar arthrodesis using standard surgical technique. • All patients were kept non-weightbearing in a short leg cast until all joints showed evidence of radiographic consolidation. • Casts of all patients changed at intervals corresponding with radiographic evaluation. • Study group received an external PEMF device 10 days after surgery which was used 12 hours daily until radiographic union was noted to have occurred. • Standardized plain radiographs (anteroposterior, lateral, and oblique views) taken preoperatively and postoperatively at intervals of 2 weeks, 6 weeks, and 12 weeks, then every 3 weeks up to 27 weeks or until radiographic union. • All radiographs reviewed by a senior musculoskeletal radiologist who was blinded to the use of the PEMF device; particular parameters defined for review were joint apposition (adequate/inadequate), quality of bone (low/normal) stages of bone graft incorporation (none/partial/complete), stages of bone graft maturation (none/partial/complete), time to fusion (in weeks), and the presence or absence of joint fusion (yes/no).
Success/Failure Criteria	<ul style="list-style-type: none"> • Each joint was analyzed separately for radiographic evidence of fusion. • For each joint which successfully fused, time to fusion was calculated.
Results	<p>Controls:</p> <ul style="list-style-type: none"> • 37 subtalar – 33 union, 4 nonunion; average time 14.5 weeks • 19 talonavicular – average time 17.6 weeks • 21 calcaneocuboid – average time 17.7 weeks <p>PEMF:</p> <ul style="list-style-type: none"> • 22 subtalar – average time 12.9 weeks • 20 talonavicular – average time 12.2 weeks • 19 calcaneocuboid – average time 13.1 weeks <p>Difference in fusion time reached statistical significance for the talonavicular and calcaneocuboid joints.</p>
Potential Sources of Bias	<p>All study patients participated as part of elective procedures; thus the overall population is self-selected.</p> <p>Patients opting for elective procedures are generally insured and may seek medical care for their problems at an earlier stage of illness and may therefore represent the “best case scenario.”</p> <p>Assessment of radiographic studies for union is open to a certain amount of subjectivity.</p>

Other Limitations of the Study	<p>This study demonstrated effectiveness of the PEMF device alone in the setting of very specific joint fusions. Thus no generalizations may be made to other situations which might benefit from pulsed electromagnetic field therapy, or to other devices.</p> <p>The authors also mention that because of the infrequent intervals of assessment, the determination of time to fusion is therefore relatively coarse.</p>
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36. Frykman et al., 1986

Citation	<p>Treatment of Nonunited Scaphoid Fractures by PEMF and Cast. G.K. Frykman, J. Taleisnik, G. Peters, R. Kaufman, B. Helal, V.E. Wood, and R.S. Unsell <i>J. Hand Surg (Am)</i> 1986 May 11(3): 344-9</p>
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture other bones (<i>Scaphoid</i>)
Stimulation Type	<input checked="" type="checkbox"/> PEMF
Commercial Device Name(s)	Bi-osteogen.
Overall Study Design	<input checked="" type="checkbox"/> Case series, uncontrolled, retrospective
# Patients	<p>44 Cases total; non-united scaphoid fractures of at least 6 mo duration.</p> <ul style="list-style-type: none"> • 41 males, 3 females, ages ranged from 14-46 y.o. <p>No allocation to treatments as this was a retrospective descriptive study of previous patients who were treated with PEMF.</p>
Selection Criteria	<ul style="list-style-type: none"> • Non-united scaphoid fracture of 6 months duration. • No history of surgical intervention during or just prior to PEMF treatment. • No scaphoid collapse. • No degeneration of periscaphoid joints.
Methods	<p>Retrospective reviews of patients who met above criteria and underwent the following treatment:</p> <p>PEMF coils centered over scaphoid fracture, attached to either long-arm thumb spica or short arm thumb spica casts. PEMF according to previously cited standardized protocol (not detailed in paper).</p> <p>Radiologic review by authors.</p>
Success/Failure Criteria	<p>Success: Treatment was stopped either when fracture was healed or determined to be non-healed. Radiologic criteria used.</p> <p>Failure: Non-union of scaphoid fracture as judged radiographically.</p>
Results	<p>Mean duration of PEMF with casting: 4.3 months, with a range of 2.5 to 9 months.</p> <p>% healed with short arm spica cast with PEMF: 75%</p> <p>% healed with long arm spica cast with PEMF: 92%</p> <p>% healed with proximal scaphoid fracture: 62.5%</p> <p>% healed with middle or distal scaphoid fracture: 86%</p> <p>% healed with avascular necrosis prior to treatment: 89%</p> <p>% healed with previous bone grafting: 73%</p> <p>The authors conclude PEMF is a reliable alternative to treat non-united scaphoid fractures. In this retrospective case review, one patient whose fracture did not resolve had synovial pseudoarthrosis at 132 months post-fracture. Three other patients whose fractures did not resolve had dorsal intercalated segment instability.</p> <p>No statistical analysis was done; the %'s listed above are raw percentages.</p>

	No safety data were reported in this study.
Potential Sources of Bias	<p>Lost to follow-up: Three patients were lost to follow-up after immobilization cessation and removal of electrical coils for unknown reasons. Initially, the authors cited that 50 patients were reviewed; it is unclear what happened to six of the patients that were not included in this paper.</p> <p>Inadequate treatment: Three patients received inadequate treatment of 2 months or less. Two patients had poor compliance and were considered failures; authors stated that due to compliance issues, these patients should have been dropped from study.</p> <p>Criteria not clearly stated: This was a retrospective study and there was no method to confirm for patient compliance.</p> <p>Lack of independent assessment: There were no independent criteria for radiographic and clinical indications of union.</p> <p>Lack of controls: There were no patients reviewed who had their fractures simply immobilized for comparable periods of time.</p>
Other Limitations of the Study	<p>While the rates of success were cited for patients with pre-existing conditions, the N for each pre-existing condition was too small to draw meaningful conclusions. The contribution of other chronic illness to the study outcome was not addressed, even though the population included a number of elderly patients. The authors acknowledge that the union rates were better than other published studies of simple long-term immobilization but it would be difficult to justify comparisons without knowing the populations used for the other published studies.</p> <p>The authors state this treatment is safe and effective; however, there are no direct measurements of safety.</p>

37. Heckman et al., 1981

Citation	<p>Nonunion Treatment with Pulsed Electromagnetic Fields. J.D. Heckman, A.J. Ingram, R.D. Loyd, J.V. Luck, Jr., and P.W. Mayer Clin Orthop Relat Res. 1981 Nov-Dec;(161):58-66</p>
Intended Use	<p><input checked="" type="checkbox"/> Non-Union fracture long bones <input checked="" type="checkbox"/> Non-Union fracture other bones</p>
Stimulation Type	<input checked="" type="checkbox"/> PEMF
Commercial Device Name(s)	<p>ElectroBiology, Inc. Fabrication of electrostimulation coils custom fit to each patient. Exact specifications of the signal generated by coils were determined by the manufacturer; the specifications varied as the technology improved and with the anatomical location of the non-union.</p>
Overall Study Design	<input checked="" type="checkbox"/> Case series, uncontrolled, retrospective
# Patients	174 patients who were previously treated by one or more of the five authors of this paper.
Selection Criteria	<p>Excluded: congenital pseudoarthroses, fresh fractures, failed fusions, any patient believed to have true (synovium lined) pseudoarthrosis, patient with fracture gap \geq than 1 cm.</p> <p>Included:</p> <p>Patients with fracture \geq 6 months prior to treatment initiation. Made up of 2 groups:</p> <ul style="list-style-type: none"> • Patients with clinical signs of non-union (pain and false motion at fracture site). Normal course of union arrested, and documented by serial x-rays \geq 2 months apart.

	<ul style="list-style-type: none"> Patients in whom fracture healing was so slow that implanted fixation devices were threatened with fatigue failure prior to full bony union. <p>149 patients (153 non-united fractures) were followed and treated for a minimum of 3 – 4 months. Patients were equally divided amongst the authors.</p> <p>Median age: 36.6 y.o.; range of years was between 16 y.o. and 81 y.o.</p> <p>Average time from fracture to start of pulsed electromagnetic stimulation was 30.2 months (range was 6 months to 37 months).</p> <p>29 fractures had a history of infection. 26 fractures were actively infected.</p> <p>130 patients had no surgery within 3 months of treatment. 19 patients had some form of associated surgery within 3 months of treatment.</p> <p>87% of fractures treated were in long bones. 8/19 patients with history of recent surgeries had a bone graft done.</p>
Methods	<p>For all patients, after coil was made, attempt was made to have <i>complete immobilization</i> of the fracture ends. This was sometimes done by internal fixation devices, more frequently by casting. All patients with lower extremity non-unions were instructed <i>not to bear weight</i> on the affected limb.</p> <p>For most, but not all patients, symmetrical pair of coils was applied to plaster cast. Occasionally, one coil was used. Coils were parallel to each other and centered directly over the fracture site and maintained in place by use of a centering key on the cast surface; center was confirmed by x-ray.</p> <p>Intercoil distances measured to ensure compliance with manufacturer recommendations.</p> <p>Patients given instructions re: removal and application. <i>Patients instructed to apply coils for ≤ 12 hours per day.</i></p> <p><i>Follow-up occurred at monthly intervals by radiography</i> to assess fracture, to check cast for adequate immobilization, assess degree of patient compliance with use of coils. After 3 months of electromagnetic stimulation, all patients were evaluated clinically and radiographically out of their casts.</p> <p>Clinical evaluation included assessment of pain and mobility at fracture site.</p>
Success/Failure Criteria	<p>Goal of this study was to 1) define the length of treatment time needed to ascertain efficacy or failure of the treatment; 2) identify the overall success rate of this treatment modality; 3) identify variables which might affect the outcome of treatment and thus refine the indications for the use of electromagnetic stimulation; and 4) identify any short term side effects and complications of treatment.</p> <p>Clinical criteria: Decreased pain and mobility at fracture site with manipulative stress was considered positive signs of fracture healing.</p> <p>Radiographic criteria: Fuzziness and clouding at fracture site and decreased density or softening of the sclerotic bone ends at the fracture site were early signs of healing. Later signs of healing included trabecular bridging of the fracture gap. Signs of healed fracture site included remedullarization of the bone.</p>
Results	<p>96/149 (64.4%) of the original patients showed union at average of 11.1 months</p> <p>At 3 months follow-up after start of treatment: 17/149 (11.4%) patients were healed; 83/149 (55.7%) in process of healing, 49/149 (32.9%) unchanged.</p> <ul style="list-style-type: none"> At 8 months follow-up after start of treatment: 16/17 remained healed; 1 had recurrent motion and pain after trial of weight bearing. <p>72/83 patients who had not healed by 3 months treatment healed satisfactorily <i>between 3 months and 1 year later</i>. 11/83 failed to heal further than initially noted at 3 months.</p> <p>41/49 patients who were clinically and radiographically unchanged at 3 months failed to heal; 8/49 patients healed at 7.4 months follow-up.</p>

	<p><i>Healing rates differed between bones</i> in this order: tibia, femur, and humerus. Other bones insufficiently represented to correlate rates of healing.</p> <p>History of or active <i>infection had no effect</i> on healing rates.</p> <p>17/19 patients who had surgery within 3 months of the start of surgery healed with treatment; 2/19 did not.</p> <p>Of the 96 healed patients, the average age was 34.2 y.o. (range: 16-74 y.o.)</p> <p><i>A larger portion of the patients who failed to heal were treated earlier in this study.</i></p> <p><i>Side effects:</i> 2 patients had mild pain at fracture site after coil application; this did not interfere with device use. 1 patient developed headaches after 3 months and had to discontinue use. 1 patient developed limb swelling.</p>
<p>Potential Sources of Bias</p>	<ol style="list-style-type: none"> 1) Coil manufacturer had different specifications over time. Patients at the start of the study had different machines than those at the beginning of the study. This was noted by the authors. Earlier machines may have correlated with higher failure rate. 2) There was no mention of independent compliance measures in the study; compliance may have contributed to the difference in outcomes. 3) Lost to follow-up: 25 patients were lost to this retrospective study because they a) failed to return for follow-up evaluation, b) could not comply with use of the device for a minimum of 3 months, c) refused to use the device as instructed, or d) had mechanical problems with the device which hindered continued use. 4) Unclear whether there were any patients who had chronic illnesses that might have affected the outcome. The presence of chronic illnesses that affect healing or vascularization may have contributed to the difference in outcomes. 5) No description of quantitative or semi-quantitative measures of clinical criteria for bone healing; for instance, mobility can be measured quantitatively, but no angle measurements were done. Pain can be assessed on a subjective pain scale, but no measurements were done. 6) Different bones had different healing rates. However, the majority of bones included in this study were precisely the bones the authors state are the best suited for this type of treatment. Overall rates may not be particularly meaningful if attempting to treat any other bone than the tibia. 7) Patients who had a recent history of surgery were more likely to heal with this treatment. Their presence in this study can skew true rates of healing and times needed to resolve fracture.
<p>Other Limitations of the Study</p>	<p>The authors acknowledge that it is difficult to differentiate between non-union and delayed union that will heal without further intervention.</p> <p>The authors acknowledge that some bones are more likely to heal with this treatment than others. This may be due to inadequate immobilization for bones other than the tibia. It is also more likely that true pseudoarthroses develop more frequently on the humerus than the tibia but it is difficult to determine whether a pseudoarthrosis is present with current non-invasive techniques.</p> <p>Authors acknowledge the positive effect of recent surgery on healing, particularly bone grafting. It is difficult to pinpoint whether these fractures would have healed without further electromagnetic stimulation</p> <p>Authors also acknowledge healing rates might be affected by patient age.</p> <p>As time goes on, there may have been different selection criteria for candidates to undergo electromagnetic stimulation treatment.</p>

38. Gossling et al., 1992

Citation	Treatment of Ununited Tibial Fractures: A Comparison of Surgery and Pulsed Electromagnetic Fields (PEMF) H.R. Gossling, R.A. Bernstein, and J. Abbott Orthopedics 1992 Jun; 15(6): 711-9.
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture long bones
Stimulation Type	<input checked="" type="checkbox"/> PEMF
Commercial Device Name(s)	N/A
Overall Study Design	<input checked="" type="checkbox"/> Other <i>Review</i>
# Patients	This is a review of 44 articles of tibial fractures. The numbers of patients is not reported; the numbers of fractures is reported.
Selection Criteria	Inclusion: any papers on the tibia, written in English and accessible via Medline with key descriptors listed in Methods. Exclusion: any papers not referring to the tibia. Tibial ununited fractures: 14 articles on primary surgical treatment and 28 articles on PEMF treatment were reviewed.
Methods	Literature search between 1977 and 1987 via Medline. Key descriptor words were: delayed nonunion, nonunion, electromag, electrostim, electric, direct current, ununited, and stimulate. A subset of papers with data on tibias was selected if adequate data were retrievable for analysis. Data on the following parameters were used in the study: number of fractures, age of fracture, number of previous surgical procedures, number of fractures that healed, time to heal, infection and whether the original fracture was open or closed. Whether a fracture was deemed 'delayed union' or 'ununited' depended upon the judgment of the physician reporting the study. No analysis of safety done.
Success/Failure Criteria	Success is dependent upon the paper being analyzed in this review; it is author dependent. The authors of this paper do not describe whether the criteria for success or failure are similar between papers.
Results	Success rates of primary surgery and PEMF treatment of ununited tibial fractures are equivalent. Furthermore, the success rates of PEMF after multiple surgeries remained high. <i>The overall success rate of PEMF-treated fractures is approximately 70-80%.</i> Tibia Ununited Fractures: Overall success rate for surgical treatment of 569 ununited tibial fractures was 82% (range: 70-100%). 90% (range: 77% - 100%) of nonunions healed; 79% (range: 70%-94%) of delayed unions healed. 75% unspecified fractures healed. Successful Surgical Procedures: According to one study, the initial success rate for primary surgery is 88%; for 2 nd surgery is 66%, for 3 rd surgery is 64%, for 4 th surgery is 50%. Other studies show similar drops with successive surgeries. Initial success rate for primary surgery on ununited fractures is high; rates drop dramatically as successive surgeries are performed. One study suggests that the number of previous surgeries does not significantly affect the success rate of PEMF to heal tibial nonunions. "Controlled" Studies with PEMF: In one study, 45% more PEMF treated fractures had progressed to healing than did placebo treated fractures. (p = 0.04) In another study, the healing rate of the PEMF group was 88% and was equal to, or better than, the healing rate of bone grafted 83% fractures.

	<p>Infection: In surgically treated ununited fractures, the heal rate in the infected population was 21% lower than the heal rate in the non-infected population (69% vs. 90%).</p> <p>In the PEMF treated fractures, the infected heal rate was only 6% lower than the non-infected rate (81% vs. 87%). Treatment with PEMF yields results comparable to, or better than, surgery.</p> <p>Closed vs. Open Fractures: The rate of healing for open fractures was 89% for surgery and 78% for PEMF. In closed fractures, PEMF stimulated 85% healing vs. 79% in surgically treated cases.</p> <p>Fracture location: Insufficient data to discuss implication of fracture location on healing rates.</p> <p>No safety data.</p>
Potential Sources of Bias	<ol style="list-style-type: none"> 1) No consensus exists about what constitutes a 'ununited fracture' as compared to a 'nonunited fracture'. 2) Age of fracture from initial injury for delayed union overlaps with non-union. 3) Many PEMF studies included patients with a history of multiple failed surgeries prior to PEMF treatment. 4) Unclear how authors dealt with differences in definition, baseline status of patients, differences in clinical or radiographic criteria used in the different papers. 5) Unclear whether PEMF was administered in comparable ways in all the reviewed studies.
Other Limitations of the Study	<p>Insufficient data to discuss implication of fracture location on healing rates.</p> <p>The authors mention the absence of reported complication and high efficacy; however, there is no mention of what criteria any paper used to judge safety.</p>

39. Goodwin et al., 1999

Citation	<p>Double-Blind Study of Capacitively Coupled Electrical Stimulation as an Adjunct to Lumbar Spine Fusions</p> <p>C.B. Goodwin et al.</p> <p>Spine, Vol 24, no 13, 1999</p>
Intended Use	<input checked="" type="checkbox"/> Lumbar spinal fusion
Stimulation Type	<input checked="" type="checkbox"/> Capacitive coupling
Commercial Device Name(s)	SpinalPak, Bioelectron, Inc.
Overall Study Design	<input checked="" type="checkbox"/> Randomized, concurrent control, prospective, double-blind, 28 different investigators
# Patients	<p>337:</p> <p>20 have missing documents, 63 withdrew or dropped, 34 are still undergoing treatment, and 41 have not yet undergone final radiographic review. Hence, only 179 are reported here.</p> <p>85 receiving stimulation, 94 not receiving.</p>
Selection Criteria	<p>Inclusion:</p> <ul style="list-style-type: none"> • Must have surgeries within following range: one or two level fusion, posterior lumbar interbody fusion, anterior lumbar interbody fusion, posterolateral fusion, autograft, allograft, or a mixture of graft materials, and any type of internal fixation except interbody fusion cages. <p>Exclusion:</p> <ul style="list-style-type: none"> • Pathological spinal processes, as tumors, infections

	<ul style="list-style-type: none"> • Spinal fractures • Systemic diseases as diabetes, osteoporosis, that might affect fusion <p>Randomly assigned to treatment groups. Breakdown shows histories and severity of two groups is quite comparable.</p>
Methods	<p>Patients instructed to use stimulator 24 hours a day until healing occurred. Compliance monitored.</p> <p>Stimulation was discontinued at 9 months if still not healed. Patient returned at 12 months for final assessment.</p>
Success/Failure Criteria	<p>Success required both clinical and radiological success.</p> <p>Clinical success: outcome rated excellent or good: resumption of normal or modified activities, no pain or occasional pain, no medication or occasional medication.</p> <p>Radiological: Fusion documented as solid both by the investigator and by a blinded independent radiologist. Disagreements were resolved by a second blinded independent reviewer. Specific criteria for success.</p>
Results	<p>84.7% active successful, 64.9% placebo successful. $P = 0.0043$</p> <p>Capacitive coupling was especially beneficial for patients with degenerative disc disease (86.5% to 57.4%).</p> <p>Previous controlled studies have not included posterolateral fusions, whereas a majority of the 137 were of this type. Benefit from stimulation was significant ($p = 0.006$). Smaller subsamples (types of injury, risk factors) did not reach statistical significance, but all showed advantage for stimulation.</p> <p>Blind follow-up of 119 or 208 patients completed more than 2 years before; no significant difference between 2 groups.</p> <p>Safety: 9 subjects dropped from study for skin irritation</p>
Potential Sources of Bias	<p>Slightly over half subjects originally enrolled are not analyzed in this study. Vague reasons for dropping or not completing assessment leave much room for selection bias. Drop-outs were not counted as failures, as is consistent with modern intention-to-treat rules.</p> <p>Randomized assignment to treatment groups produced very evenly balanced groups on risk factors.</p> <p>Rigorous success criteria and the use of independent reviewers limit the potential for observer bias.</p>
Other Limitations of the Study	<p>Study not finished.</p> <p>Applies only to this equipment and to these types of fusion.</p>

40. Meskens et al., 1988

Citation	<p>Treatment of Delayed Union and Nonunion of the Tibia by Pulsed Electromagnetic Fields. A Retrospective Follow-Up.</p> <p>M.W.A. Meskens, J.A.E. Stuyck, J.C Mulier</p> <p>Bull. Hosp. Joint Dis. Orthoped. Inst., 48(2): 170 – 175, 1988</p>
Intended Use	<p><input checked="" type="checkbox"/> Non-Union fracture long bones</p>
Stimulation Type	<p><input checked="" type="checkbox"/> PEMF</p> <p>Described as being the same system as Bassett, 1977.</p>
Commercial Device Name(s)	<p>Not applicable.</p>
Overall Study Design	<p><input checked="" type="checkbox"/> Patient as own control, retrospective</p>

# Patients	57
Selection Criteria	<p>Inclusion:</p> <ul style="list-style-type: none"> • Original injury at least 6 months earlier. • No progress toward bony union over a two-month interval. • No surgery in 4 months prior to treatment. <p>Exclusion: (implemented "in later years").</p> <ul style="list-style-type: none"> • Presence of a gap larger than half the bone width at the side of the nonunion. • Hypermobility nonunion with uncontrollable motion. • True synovial pseudoarthrosis. • Non-cooperative patient.
Methods	<p>The EM coils were incorporated into the plaster cast. Patients were instructed to operate the device for 14 hours a day for the first 3 months, then 10 hours a day for the next 3 months. If therapy was needed beyond six months, it was to be used during sleeping hours only. There was no weightbearing until signs of healing were identified, then a progressive rehabilitation schedule began.</p> <p>Radiographs were taken at regular intervals, and the device was checked every 6-8 weeks. It appears that radiographs were interpreted by the treating physician. Patients were also evaluated clinically.</p>
Success/Failure Criteria	<p>To be considered a success, patients had to meet all of these criteria:</p> <ul style="list-style-type: none"> • Mechanical stability on clinical testing • Absence of local tenderness • Obliteration of the fracture gap on radiographs
Results	<p>Overall, 75% of the lesions healed, after an average of 10 months. If the four patients with either a large fracture gap or synovial pseudoarthrosis are excluded, the success rate is 81%. Other risk factors such as the length of previous disability, number of previous interventions, or presence of infection did not have a significant effect on the results (statistical methods not given).</p> <p>In the 25% of patients deemed failures, treatment went on for an average of 11 months. The authors do not state the criteria for classifying a case as a failure, but presumably it was lack of progress on the radiographs.</p> <p>The authors do not comment on safety issues.</p>
Potential Sources of Bias	<p>The minimum of six months from injury and the lack of progress over two months are both less stringent criteria than were used in other studies.</p> <p>There is a potential for observer bias because of the lack of an independent reviewer.</p>
Other Limitations of the Study	<p>The lack of a control group makes it difficult to know how much of the effect was from the electrical stimulation and how much from the rigorous immobilization and progressive rehabilitation.</p> <p>The study only evaluated PEMF stimulation in the tibia.</p>

41. Fontanesi et al., 1983

Citation	<p>Treatment of Delayed Union and Pseudarthrosis by Low Frequency Pulsing Electromagnetic Stimulation</p> <p>F. Fontanesi, F. Giancetti, R. Rotini (Reggio Emilia), and R. Cadossi (Modena)</p> <p>Italian Journal of Orthopedics and Traumatology 9(3): 305-318, 1983.</p>
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Intended Use	Non-Union fracture long bones Non-Union fracture other bones Other: established pseudarthrosis
Stimulation Type	PEMF
Commercial Device Name(s)	Biostim
Overall Study Design	Patient as own control, prospective
# Patients	33 patients with 35 fractures
Selection Criteria	Inclusion: patients with fractures affected by either delayed union or established pseudarthrosis. Exclusion: None.
Methods	<ul style="list-style-type: none"> • Stabilization of fracture, by conventional plaster (16 cases), "functional" plaster (not defined) (10 cases), external fixation (5 cases), or internal fixation (4 cases). • Weightbearing allowed in certain cases. • Coils placed over center of pseudarthrosis parallel and opposite each other, perpendicular to axis of bone segment involved; placement determined by AP/lateral radiographs; coils held in place by elastic bandages. • Stimulation for minimum of 12 hours daily for at least 60 days. • Patients recalled every 60th day for clinical and radiological assessment.
Success/Failure Criteria	Clinical and radiographic union, not otherwise defined.
Results	Radiological and clinical union in 31 of 33 cases or 88.5%, average time to union 4 – 6 months.
Potential Sources of Bias	<ul style="list-style-type: none"> • Study is non-RCT. • Inclusion criteria somewhat vague; source of study participants is unclear; no notable exclusion criteria. • No clearly stated measurement of either clinical or radiographic success/failure.
Other Limitations of the Study	Study deals only with PEMF, thus not able to make comparisons to other modalities. No safety information noted. Patients seen only at 60 day intervals.

42. Hinsenkamp et al., 1985

Citation	Treatment of Non-Union by Pulsing Electromagnetic Field: European Multicenter Study of 308 Cases M. Hinsenkamp, J. Ryaby, and F. Burny Reconstr. Surg. Traumat., 19: 147 – 151, 1985
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture long bones <input checked="" type="checkbox"/> Non-Union fracture other bones
Stimulation Type	<input checked="" type="checkbox"/> PEMF
Commercial Device Name(s)	No specific device name given; device manufactured by Electro-Biology, Inc.
Overall Study Design	<input checked="" type="checkbox"/> Patient as own control, retrospective
# Patients	308 total cases of non-union <ul style="list-style-type: none"> • 80.6% of the non-unions had undergone a surgical procedure before stimulation; mean time between last surgery and PEMF = 18 months. • Age breakdown: N = 235 <ul style="list-style-type: none"> ○ 0 – 20 yr 41 ○ 21 – 30 yr 62 ○ 31 - 40 yr 44 ○ 41 – 50 yr 31

	<ul style="list-style-type: none"> ○ 51 – 60 yr 27 ○ ≥ 61 yr 30 • Sex breakdown: N = 267 <ul style="list-style-type: none"> ○ 187 males ○ 80 females • Closed versus Open: N = 245 <ul style="list-style-type: none"> ○ 111 Closed ○ 134 Open • Type of non-union: N = 156 <ul style="list-style-type: none"> ○ 82 Hypertrophic ○ 74 Atrophic • Location: N = 272 <ul style="list-style-type: none"> ○ 19 humerus ○ 16 ulna ○ 55 femur ○ 148 tibia ○ 34 other
Selection Criteria	<ul style="list-style-type: none"> • Delayed union and congenital pseudoarthrosis were avoided. • Used data on 308 cases of non-union treated by stimulation units distributed by Electro-Biology, Inc. in different European Orthopedic Centers on record.
Methods	<ul style="list-style-type: none"> • The unit was fixed on both sides of the limb, facing the non-union. • Stimulation was applied 12 hr/day in one or more sequences. • Treatment was applied at home by the patients themselves. • The mean time from the injury to the treatment was 3 years.
Success/Failure Criteria	<ul style="list-style-type: none"> • No specific criteria for healing or failure to heal were given.
Results	<p><i>Fractures healed by category:</i></p> <ul style="list-style-type: none"> • By age: <i>no significant difference</i> <ul style="list-style-type: none"> ○ 0 – 20 yr 28/41 (68.2%) ○ 21 – 30 yr 52/62 (83.9%) ○ 31 – 40 yr 35/44 (79.5%) ○ 41 – 50 yr 19/31 (61.3%) ○ 51 – 60 yr 21/27 (77.8%) ○ ≥ 61 yr 19/30 (12.9%) ○ Combined 174/235 (74%) • By sex: <i>no significant difference</i> <ul style="list-style-type: none"> ○ Male 145/187 (77.5%) ○ Female 48/80 (60%) ○ Combined 193/267 (72%) • Closed versus Open: <i>no significant difference</i> <ul style="list-style-type: none"> ○ Closed 83/111 (74.7%)

	<ul style="list-style-type: none"> ○ Open 97/134 (72.4%) ○ Combined 180/245 (73.5%) • Type of non-union: <i>significant difference</i> <ul style="list-style-type: none"> ○ Hypertrophic 72/82 (87.8%) ○ Atrophic 43/74 (58.1%) ○ Combined 115/156 (73.7%) • Location: <i>significant differences</i> <ul style="list-style-type: none"> ○ Humerus 14/19 (73.7%) ○ Ulna 7/16 (43.8%) ○ Femur 36/55 (65.5%) ○ Tibia 117/148 (79.1%) ○ Other 25/34 (73.5%) ○ Combined 199/272 (73.2%) • No information on device safety was given.
Potential Sources of Bias	<ul style="list-style-type: none"> • It is unclear who read the results or performed the examinations on these patients. The assumption is that the authors used existing interpretations since this is a retrospective study and no mention was made of clinical or radiograph exams by the authors themselves. • It is also unclear how the total 308 cases were chosen. All categories examined included a subset of the initial 308. No indication is given as to why data for all categories were not included in this study.
Other Limitations of the Study	<ul style="list-style-type: none"> • The conclusions from these data pertain to non-unions treated by this device only.

43. Bassett et al., 1978

Citation	Repair of Non-Unions by Pulsing Electromagnetic Fields C.A.L. Bassett, S.N. Mitchell, L. Norton, and A.A. Pilla Acta Orthop. Belg., 44(5): 706 – 724, 1978
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture long bones
Stimulation Type	<input checked="" type="checkbox"/> PEMF
Commercial Device Name(s)	No device name given; manufactured by Electro-Biology, Inc.
Overall Study Design	<input checked="" type="checkbox"/> Patient as own control, prospective
# Patients	<p>220 patients initially with congenital and acquired non-unions.</p> <ul style="list-style-type: none"> • 108 cases were used in this study as those were the only ones for whom data were available. • In the acquired non-unions: <ul style="list-style-type: none"> ○ 52 tibial non-unions. <ul style="list-style-type: none"> ▪ 54% had been operated on an average of 4x. ▪ 50% had been infected or were actively draining. ○ 10 femur non-unions. ○ 5 ulna-radii non-unions. ○ 3 humerus non-unions.

	<ul style="list-style-type: none"> • 32 congenital pseudoarthrosis of the tibia and 3 of forearm bones were treated in the total 108 cases.
Selection Criteria	<ul style="list-style-type: none"> • Initially only included congenital and acquired lesions in which amputation had been recommended. • As the investigation proceeded over 3 years and no untoward effects occurred, patient selection was modified to include patients with unoperated non-unions, 9 months to a year after injury. • Later, delayed unions were included 4-9 months after fracture.
Methods	<ul style="list-style-type: none"> • Two coils were placed on the external surface of a cast, brace, or extremity; the coils were wired together facing each other, with the non-union centered; the diameter of the coils was precisely fitted to each patient. • Patients treated themselves at home 12-16 hr/day. • Patients with non-unions in weight-bearing bones were instructed not to bear weight until radiographic evidence of union was present. • Monthly follow-up exams were analyzed (without plaster removal for at least 3 months). • X-rays were analyzed for evidence of revascularization (fuzziness of sharp or sclerotic bone margins flanking the non-union) and for increasing radiographic density in the gap region. • Complete calcific osseous bridging of the gap at the cortical margins of the lesion was generally present at 3 months and preceded progressive loading of the extremity. • Compression exercises were begun in lower extremities at about 3 months. • Some form of external support was used by patients with lesions of the lower extremity.
Success/Failure Criteria	<ul style="list-style-type: none"> • Criteria for success included radiographic obliteration of the radiolucent lines, mechanical stability on clinical testing, no local tenderness, and function with or without an external protective splint. • Complete corticalization and modularization was a late feature of success but rarely was complete in most of these cases until 1-2 yr after treatment. • In congenital lesions of the tibia, the same criteria were applied with the additional requirement that lesions should not recur throughout the period of active skeletal growth.
Results	<ul style="list-style-type: none"> • 87/108 (81%) obtained functional union. • 88% tibial non-unions healed. • 70% femur non-unions healed. • 80% ulna-radial non-unions healed. • 66% humerus non-unions healed. • Average time of treatment of tibial non-unions was 5 months. • For a 6 month period, 28/29 (96%) tibial non-unions healed. • 2 patients re-fractured after treatment had been discontinued and weight-bearing had begun for a month; 1 patient had fallen and the other prematurely discontinued the use of the external protective splint. • 25 out of 32 patients with congenital pseudoarthrosis had end results available for analysis.

	<ul style="list-style-type: none"> ○ 19/25 (76%) achieved functional union. ○ All 19 were tibial non-unions. ○ Treatment time ranged from 53 days to 2 yr. ● No untoward effects as a result of PEMF were observed in any of the healed congenital pseudoarthrosis patients who required nightly stimulation and who were all less than 6 years of age. ● No detrimental side effects were observed in any patient.
Potential Sources of Bias	<ul style="list-style-type: none"> ● There is no indication who analyzed or interpreted the radiographs or clinical data.
Other Limitations of the Study	<ul style="list-style-type: none"> ● The authors mentioned that others have suggested that a double-blind study would be better, but they claim that it would have been too difficult. ● These results only pertain to one type of stimulation device. ● No indication is made of the results from the patients who had been infected or had an active infection and patients who had prior surgeries.

44. Boyd et al., 1961

Citation	<p>Observations on Non-Union of the Shafts of the Long Bones, with a Statistical Analysis of 842 Patients</p> <p>H.B. Boyd, S.W. Lipinski, and J.H. Wiley</p> <p>The Journal of Bone and Joint Surgery, 43-A(2): 159-168, 1961</p>
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture long bones
Stimulation Type	<input checked="" type="checkbox"/> None
Commercial Device Name(s)	Not applicable.
Overall Study Design	<input checked="" type="checkbox"/> Case series, uncontrolled, retrospective
# Patients	842
Selection Criteria	Patients referred for operative treatment of nonunion of one or more long bones.
Methods	<p>All patients were treated with operative treatment that included some form of bone graft. Casting or other forms of immobilization were used where indicated.</p> <p>Patients were followed clinically to evaluate the success of the procedure. If the initial procedure failed, the surgeons either re-operated or amputated the limb if there was recurrent infection and poor prognosis for an eventual successful outcome.</p>
Success/Failure Criteria	The exact criteria for determining success or failure of a given procedure were not described in the paper.
Results	<p>A total of 842 patients underwent 919 operations (1013 grafting procedures). Of these, 790 (94%) eventually obtained union. Most, 739 (88%), had a successful outcome after the first procedure.</p> <p>Factors that predisposed to nonunion were open fractures with internal fixation, infection, interruption of the blood supply, multiple fractures, and lack of contact between the bone ends.</p> <p>The specific type of bone graft used did not seem to alter the outcome to any significant extent.</p>
Potential Sources of Bias	This is a retrospective review of clinical experience, so no effort was made to recruit a representative population. Over 80% of the patients had received previous surgical interventions before their referral, so the population may be biased toward difficult-to-treat cases.

	There is the potential for some observer or outcome bias, as these patients were evaluated for success by the operating surgeon, and no specific criteria were given in the paper.
Other Limitations of the Study	This paper is useful only for providing a set of historical controls for comparison, because no form of electrical stimulation was used. Another potential limitation is the fact that all treatments were completed before 1959. Evolution in surgical practice and available devices might result in a different outcome under current standard therapy.

45. Bassett et al., 1974

Citation	Augmentation of Bone Repair by Inductively Coupled Electromagnetic Fields C.A.L. Bassett, R.J. Pawluk, and A.A. Pilla Science 184: 575-577, May 1974
Intended Use	<input checked="" type="checkbox"/> Other: Healing of surgically induced osteotomies in dogs
Stimulation Type	<input checked="" type="checkbox"/> PEMF
Commercial Device Name(s)	Not applicable.
Overall Study Design	<input checked="" type="checkbox"/> Other: Animal study with bilateral surgical lesions. An untreated contralateral leg served as the control.
# Patients	39 evaluable animals <ul style="list-style-type: none"> • 20 using the 2 mv/cm device • 19 using the 20 mv/cm device
Selection Criteria	None specified.
Methods	Bilateral transverse fibular osteotomies were performed. The animals were fitted with coils after surgery. One side was active and the contralateral side served as a control. Twenty-eight days after surgery, the osteotomies were dissected and analyzed. The primary analysis was physical test for load stiffness. The secondary test was a histological analysis.
Success/Failure Criteria	No firm success or failure criteria were defined.
Results	In the first set of animals, there was little difference in load stiffness and there was a variety of healing patterns. In the second set of animals, 13 were subjected to a uniform stimulation pattern, and 10 showed much larger gains in stiffness for the stimulated bones. In 90% of the specimens from these animals, the physical behavior was consistent with radiologic and histologic results.
Limitations of the Study	The chief limitations of the study are the use of animals rather than humans and the use of surgically-induced lesions. Both of these factors limit the applicability of these results to the human clinical situation. The load stiffness analysis is also quite different from the endpoints used to evaluate effectiveness in human studies.

46. ZumBrunnen and Brindley, 1968

Citation	Nonunion of the Shafts of the Long Bones – A Review and Analysis of 140 Cases J.L. ZumBrunnen and H.H. Brindley JAMA, 203(9): 121 – 124, 1968
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture long bones
Stimulation Type	<input checked="" type="checkbox"/> Other surgical treatment, non-surgical treatment, or amputation
Commercial Device Name(s)	Not available.

Overall Study Design	<input checked="" type="checkbox"/> Patient as own control, retrospective
# Patients	120 patients/140 non-unions
Selection Criteria	<ul style="list-style-type: none"> Records from patients with long bone non-unions during a 20 yr period at 3 hospitals were used in order to study the issue of failure of long bones to unite following fracture.
Methods	<ul style="list-style-type: none"> 146 surgical procedures were performed on 123 of the 140 long bones that failed to unite. Preoperative preparation of the joints and soft tissue was performed and deemed critical in treating non-union. Different types of bone grafts were employed.
Success/Failure Criteria	<ul style="list-style-type: none"> Clinical records, pertinent roentgenograms, and therapeutic results were reviewed and analyzed, but no specific criteria for non-union or union were given.
Results	<ul style="list-style-type: none"> One fracture united during the preoperative preparation phase. Surgery was refused or not indicated in 8 cases. 9 patients had undergone multiple surgical procedures and severe complications made amputation the operation of choice. Union was obtained in 104/122 (85%) cases with an average time of 5.5 months. Union was achieved in 67% of cases involving the humerus and 89% in cases involving the ulna. 20 of the nonunited bones required second operations; 6 failed to unite and 14 united. Union was attempted a third time in 3, with failure in 2.
Potential Sources of Bias	<ul style="list-style-type: none"> It is unclear how the patients were selected for this study. No indication is made as to who read the radiographs or who evaluated the clinical information.
Other Limitations of the Study	This study does not directly address electrical stimulation of any type.

47. Bassett et al., 1982

Citation	C.A.L. Basset, S..N. Mitchell, and S.R. Gaston Pulsing Electromagnetic Field Treatment in Ununited Fractures and Failed Arthrodeses JAMA, 247 (5): 623 - 628, 1982
Intended Use	Non-Union fracture long bones Other: failed arthrodeses
Stimulation Type	PEMF
Commercial Device Name(s)	Not specified.
Overall Study Design	Case series, uncontrolled, prospective Case series, uncontrolled, retrospective
# Patients	> 6,000 enrolled, of these 1,078 who reached a final endpoint are included in this analysis.

Selection Criteria	<p>Inclusion:</p> <ul style="list-style-type: none"> • Referral to study by treating orthopedic surgeons of patients with ununited fractures or failed arthrodeses. • Direct patients of authors at Columbia-Presbyterian with ununited fractures or failed arthrodeses. • Inclusion in analysis required endpoint of either healing or failure. <p>Exclusion:</p> <ul style="list-style-type: none"> • Gap of > 1 cm between the bone segments. • Radiographic evidence of pseudoarthrosis.
Methods	<p>Study Protocol:</p> <ul style="list-style-type: none"> • Application of a snug plaster cast to control motion. • Measurement of the cast diameter at the level of the nonunion to establish intercoil distance and appropriate “driving” voltage for each patient’s pulse generator. • Placement of the parallel coils under roentgenographic control. • Treatment at home for 10 to 12 hours daily. • Strict non-weight-bearing during early phases of treatment for unstable lesions in the lower extremity. • Assessment of the lesion in plaster with standardized roentgenograms at monthly intervals. • Graded, protected rehabilitation, once roentgenographic and clinical evidence of early union was established. <p>Follow-up obtained either as outpatients at Columbia-Presbyterian, or for patients treated at other facilities by letter, telephone communication, standardized prescription and follow-up forms, and roentgenograms.</p> <p>Analysis divided into three geographic categories: Columbia-Presbyterian Medical Center, other US treatment centers, and International. Study authors are at Columbia; PEMFs were used at other US centers and internationally in consult with study authors.</p> <p>Analysis was further broken down by fracture site, joint type, and length of disability time prior to inclusion in the study group.</p>
Success/Failure Criteria	<p>Healing defined as:</p> <ul style="list-style-type: none"> • roentgenographic evidence of “cortical bridging, trabecular bridging, or both, with major modifications of the radiolucent gap” • clinical evidence of “no motion at the old fracture site on stress, no local tenderness, no pain on ambulation, and no further plaster immobilization.” <p>Failure not specifically defined.</p>

<p>Results</p>	<p>1,007 cases of ununited fractures analyzed, 71 cases of failed arthrodeses analyzed.</p> <p>Key results:</p> <ul style="list-style-type: none"> • Of a total of 1,078 patients, 834 healed and 244 failed; overall success rate = 77%. • Overall success rate for 220 Columbia patients = 81%; for 233 International patients = 79%; for 625 US patients = 76%. • Of 1,007 ununited fractures, 658 (65%) involved tibia. • Success rate for tibial fractures was identical (82%) for three geographic locations. • Success decreased slightly with increasing length of previous disability in Columbia and International groups. • Success more likely in tibial lesions than in femoral lesions; upper extremity lesions less successful than lower extremity with exception of carpal navicular (16 of 19 = 84% united). • Previous disability time for tibial and femoral lesions exceeded 24 months in 265 (31%) of 845 patients. • For 71 failed arthrodeses, 20 (87%) of 23 healed at Columbia, 33 (79%) of 42 healed in US, 5 (83%) of 6 healed in International; overall 82% success. <p>Also noted are:</p> <ul style="list-style-type: none"> • Cases with ununited fracture with infection = 294 of 845 in Columbia and US. 81% overall success rate at Columbia for healing in cases with infection; 72% success for US cases with infection; no mention made in this case for International. • 92% success rate for patients (38 of 845) who received operative repair (grafting) (Columbia and US) within one month of starting PEMFs. • 100% success for patients (28 of 845) considered failures after initial PEMFs, with subsequent bone grafting followed by further PEMF treatment. <p>No specific safety information given, apart from stating that PEMF treatment carries a negligible to nonexistent risk.</p> <p>No analysis is undertaken of the failures. No complications or adverse events are noted.</p>
<p>Potential Sources of Bias</p>	<p>Study design is not a randomized controlled trial; in fact, authors argue against the need for a randomized controlled trial because of high success rates in non-randomized controlled trial studies done to date and "unassailable evidence in controlled tissue culture and animal studies" that the technique is effective.</p> <p>No mention made of standardization of interpretation of roentgenographic evidence, or of who was doing the interpretation.</p> <p>No mention of patient compliance with the treatment protocol (i.e., length of time per day, observance of strict non-weightbearing).</p> <p>The majority of patients enrolled were not included in the analysis. Without clear criteria for defining when a patient must be classified as a failure, this practice raises the potential for bias being introduced during analysis.</p>
<p>Other Limitations of the Study</p>	<p>This study focused specifically on PEMF under two very specific circumstances, thus results cannot be applied to other types of stimulation devices or to other situations where bone growth stimulation could be beneficial.</p>

48. Bassett and Becker, 1986

Citation	Generation of Electric Potentials by Bone in Response to Mechanical Stress C.A. Bassett and R.O. Becker Science, 137:1063-1064, 1968
Intended Use	<input checked="" type="checkbox"/> Other
Stimulation Type	<input checked="" type="checkbox"/> Other
Commercial Device Name(s)	Not applicable.
Overall Study Design	<input checked="" type="checkbox"/> Other
# Patients	Not applicable.
Selection Criteria	Not applicable.
Methods	<ul style="list-style-type: none"> • Initial observations were made on fresh feline fibulae. <ul style="list-style-type: none"> ○ Drying was prevented as was electrode movement during deformation of bone. ○ One electrode was placed on the posterior aspect and the other one opposite on the anterior aspect at midshaft. ○ Stress was applied so that the thin fibula bowed.
Success/Failure Criteria	<ul style="list-style-type: none"> • A change in electric potential was the measure of success.
Results	<ul style="list-style-type: none"> • Initial observations were made on fresh feline fibulae; stress was applied so that the thin fibula bowed (concave posteriorly) and the posterior electrode instantly became negative with respect to the anterior electrode while the stress was being applied. • Once the deforming force was removed, the bone immediately returned to its normal shape and the anterior electrode briefly became negative before returning to a state of isopolarity. • Equal deformation in the opposite direction induced a reverse polarity of the same size. • The amplitude and potential was dependent on the rate and magnitude of the bony deformation; whereas, the polarity was determined by the direction of bending. • Fresh specimens of cat fibula, rat femur, and bullfrog tibiofibula demonstrated the same phenomenon. • The potentials were not dependent on cell viability as freeze-thawed and air-dried specimens behaved like the fresh specimens except that the amplitude was decreased approximately 25%. • No potentials were detected when wood, polyethylene strips or fresh tendo Achilles from the cat were deformed in a variety of ways. • Decalcified bone lost its capacity to generate potentials in response to stress. • When the organic fraction of the cat fibula was removed, it became so fragile that it fractured before significant deformation could occur.
Potential Sources of Bias	<ul style="list-style-type: none"> • No indication is given as to numbers of animals used in the study or magnitudes of responses (quantified data).

Other Limitations of the Study	<ul style="list-style-type: none"> This study in and of itself does not establish the relationship between cellular activity in bone and the concentration of charge.
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49. Bassett et al., 1982

Citation	<p>Treatment of Therapeutically Resistant Non-Unions with Bone Grafts and Pulsing Electromagnetic Fields</p> <p>C.A.L. Bassett, S.N. Mitchell, and M.M. Schink</p> <p>J Bone Joint Surg Am, 64(8):1214 – 1220, 1982</p>
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture long bones <input checked="" type="checkbox"/> Non-Union fracture other bones
Stimulation Type	<input checked="" type="checkbox"/> PEMF <input checked="" type="checkbox"/> Other <i>bone graft</i>
Commercial Device Name(s)	Bi-Osteogen Systems 204, Electro-Biology, Inc.
Overall Study Design	<input checked="" type="checkbox"/> Case series, uncontrolled, retrospective
# Patients	<p>83 adult patients</p> <p>Average 1.5 yr between fracture and treatment.</p> <p>24/83 (29%) had history of infection; 14 (17%) actively draining.</p> <p>Average number of prior operations = 2.4.</p> <p>Group A: 38 patients in whom bone grafts were combined with PEMF; in all but 3 patients, local conditions of the non-union (gap at fracture site > 1 cm, synovial pseudoarthrosis, or a significant mal-alignment requiring surgical correction) had contraindicated the use of PEMF alone.</p> <p>Group B – 45 patients in whom concomitant bone-grafting and application of PEMF followed a previous failure to secure union with electromagnetic fields alone.</p> <p>Group A median age = 35 yr.</p> <p>Group B median age = 32 yr.</p> <p>Group A: 18 tibia, 12 femur, 4 humerus, 2 radius/ulna, 2 misc.</p> <p>Group B: 27 tibia, 13 femur, 4 humerus, 0 radius/ulna, 1 misc.</p>
Selection Criteria	<ul style="list-style-type: none"> The patients were, in part, a subset of a previously reported series (Bassett et al. 1982) together with patients identified from a computer search of all patients treated with PEMF until 1981 at Columbia-Presbyterian Medical Center. The series consists of an inclusive and consecutive, unselected group of patients who had bone grafts and PEMF used concomitantly.
Methods	<ul style="list-style-type: none"> Records and serial radiographs, generally made at 1-2 month intervals, were available for all patients. No patients were lost to follow-up. 38 (46%) of the patients were followed by the authors; whereas, 45 (54%) were analyzed by the authors based on reports and radiographs supplied to them. Patients were treated with bone-grafting and PEMF under two formats: <ul style="list-style-type: none"> Group A – 38 patients in whom bone grafts were combined with PEMF; in all but 3 patients, local conditions of the non-union (gap at fracture site > 1 cm, synovial pseudoarthrosis, or a significant misalignment requiring

	<p>surgical correction) had contraindicated the use of PEMF alone.</p> <ul style="list-style-type: none"> ▪ The median length of time from fracture until the beginning of treatment was 16 months. ▪ A total of 100 operations had occurred in this group prior to bone graft/PEMF; 33 involved unsuccessful bone graft. <p>○ Group B – 45 patients in whom concomitant bone-grafting and application of PEMF followed a previous failure to secure union with electromagnetic fields alone.</p> <ul style="list-style-type: none"> ▪ The median length of time from fracture until the beginning of treatment was 17 months. ▪ A total of 101 operations had occurred in this group prior to bone graft/PEMF; 38 involved unsuccessful bone graft. ▪ 8 patients had obtained bone union with electromagnetic fields but has sustained a re-fracture, usually because of reduced cortical diameter; bone grafting was done to increase the local bone mass in this area. <ul style="list-style-type: none"> • 24/83 (29%) patients in both Groups A and B had a history of infection; 14/83 (17%) were actively draining at time of treatment. • All patients had a graft with fresh autogenous cortical-cancellous or cancellous iliac bones, except for one patient who received a preserved allogeneic cortical graft. • Only small cancellous chips were used in patients with an actively draining wound. • No patient with internal or external skeletal fixation was excluded. • In most patients, the primary immobilization was an appropriate plaster cast. • 2-4 weeks after bone-grafting, coils specifically made and measured for each patient were applied to the surface of the cast under radiographic control. • Pulse-generators produced a 5 msec-wide burst of 200 µsec-wide pulses, repeating at 15 Hz. • Patients applied treatment for 10 hr/day. • Strict non-weight-bearing was observed for the involved limb during the postoperative period for patients with an unstable non-union in the lower extremity. • Monthly assessment of the fracture site with standardized radiographs. • Graded, protected rehabilitation was initiated once radiographic and clinical evidence of early union was established.
<p>Success/Failure Criteria</p>	<ul style="list-style-type: none"> • A non-union was judged to be healed when there was both clinical and radiographic evidence of union, as determined by: <ul style="list-style-type: none"> ○ No detectable motion or tenderness on physical examination ○ No pain on weight-bearing ○ No further requirement for external support ○ Osseous bridging of the gap defect present on the radiograph ○ All criteria had to be met in order to be considered healed
<p>Results</p>	<ul style="list-style-type: none"> • Group A: Healed non-unions overall 33/38 (87%) <ul style="list-style-type: none"> ○ Tibia 16/18 (89%) ○ Femur 11/12 (92%) ○ Humerus 3/4 (75%) ○ Radius/ulna 2/2 (100%)

	<ul style="list-style-type: none"> ○ Misc. ½ (50%) ● Group B: Healed non-unions overall 42/45 (93%) <ul style="list-style-type: none"> ○ Tibia 26/27 (96%) ○ Femur 12/13 (92%) ○ Humerus ¾ (75%) ○ Radius/ulna 0/0 ○ Misc. 1/1 (100%) ● Median time to heal was 4 months in both groups; Group A range 2 to 10 months; Group B range 2 to 12 months. ● 35 (95%) of patients in both groups who had no history of bone-grafting healed ● 42/48 (87%) who had previous bone-grafting healed. ● 12/14 (86%) of patients with active infection healed. ● 10/10 (100%) of patients with history of infection healed. ● No complications of surgery or of the use of PEMF were reported in this group of patients.
Potential Sources of Bias	<ul style="list-style-type: none"> ● The authors were the ones who analyzed the radiographs and clinical data instead of an outside observer.
Other Limitations of the Study	<ul style="list-style-type: none"> ● The authors noted the need for more studies on humeral non-unions due to the resistance of these types of non-unions to attempts to unite. ● PEMF should not be used alone on bone with a reduced cortical diameter. ● No statistical analyses were performed on these data. ● The two groups chosen represent very specific applications of bone-grafting and PEMF together.

50. Bose, 2001

Citation	Outcomes After Posterolateral Lumbar Fusion with Instrumentation in Patients Treated with Adjunctive Pulsed Electromagnetic Field Stimulation B. Bose Adv. Ther. 18(1):12 - 20, 2001
Intended Use	<input checked="" type="checkbox"/> Lumbar spinal fusion
Stimulation Type	<input checked="" type="checkbox"/> PEMF
Commercial Device Name(s)	Spinal-Stim®; Orthofix, Inc.
Overall Study Design	<input checked="" type="checkbox"/> Patient as own control, prospective
# Patients	52 patients (4 lost to follow-up). Mean age = 50.0 ± 13.2 yr (18-76 range). 54.2% male. 45.8% female. Majority presented with herniated nucleus pulposus and had one or more diagnosis. Nearly 60% had undergone at least one spinal surgery prior.
Selection Criteria	<ul style="list-style-type: none"> ● No selection criteria were given.
Methods	<ul style="list-style-type: none"> ● 52 patients underwent posterolateral spine fusion with instrumentation and were treated adjunctively with PEMF stimulation.

	<ul style="list-style-type: none"> • Iliac crest bone augmented with freeze-dried corticocancellous granules were used in all but 3 patients. • Large pieces of Gelfoam were placed over the bony fusion mass to form a barrier between it and the muscle. • The dura was also covered in Gelfoam and a large fat graft was placed over the Gelfoam before closure. • Patients were mobilized 1 day after surgery in a Boston Overlap Brace. • All patients received PEMF stimulation within 4 weeks after surgery. • The PEMF device was placed externally over the fusion site which allowed mobility during the day. • The patients were instructed to use the device at least 4 hr/day until the fusion site was considered healed; compliance was monitored daily by a built-in component recorder. • Patients were asked to return for routine clinical and radiographic evaluation each month for the first 6 months and at 9, 12, and 24 months. • An independent orthopedic surgeon evaluated radiographs taken in anteroposterior and lateral flexion and extension. • An independent abstractor compiled information retrospectively on diagnosis, age, sex, smoking status, graft material, previous fusion surgery, pain, activity level, and occupational status. • Pain was assigned a qualitative scale and clinical assessment was based on pain, physical activity level, and occupational status. • Descriptive statistics were employed.
Success/Failure Criteria	<ul style="list-style-type: none"> • A fusion was judged to be a success if at least two-point bridging, no radiolucency, and intact hardware were present. • A fusion was judged to be a failure if any of these criteria were not met.
Results	<ul style="list-style-type: none"> • The outcome analysis included 48 patients; 4 were lost due to follow-up. • Fusion succeeded in 47/48 (98%) patients; 1 patient developed pseudoarthrosis. • 23/39 (59%) patients returned to work. • 7/7 (100%) who did not work prior to surgery healed. • 32/45 (71%) reported improvement in pain; 12/45 (27%) showed no improvement, and 1/45 (2%) worsened; before treatment pain was not available for 3 patients. • 21/48 (44%) were able to return to an increased level of activity; 22/48 (46%) resumed their previous activity level, and 5/48 (10%) returned to light activity from moderate activity before treatment. • Overall clinical assessment was excellent for 2/48 (4%); good for 38/48 (79%); fair for 8/48 (17%). • No patient reported any significant complication or adverse event; follow-up radiographs showed no abnormal changes in the surgical area of the spine.
Potential Sources of Bias	<ul style="list-style-type: none"> • No indication was made as to how these patients were selected for this study. <p>No concurrent control group was used .</p>
Other Limitations of the Study	<ul style="list-style-type: none"> • The applicability of PEMF as an adjunct treatment for lumbar fusion surgery applies only to this specific device.

Part II: Select Summaries of Studies from the BGS Opposition Group's Literature Search

Section A: Additional Clinical Reports for On-Label Uses

1. Godley, 1997

Citation	Nonunited Carpal Scaphoid Fracture in a Child: Treatment with Pulsed Electromagnetic Field Stimulation. D.R. Godley Orthopedics, 1997 Aug; 20(8); 718-9
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture other bones (<i>scaphoid</i>)
Stimulation Type	<input checked="" type="checkbox"/> PEMF
Commercial Device Name(s)	Electro-Biology, Inc (Parsippany, NJ)
Overall Study Design	<input checked="" type="checkbox"/> Other <i>Case Study</i>
# Patients	1 patient, with non-union of wrist scaphoid fracture after 10 wks of casting
Selection Criteria	Not available.
Methods	Patient treated with long arm thumb spica cast with PEMF for ten hours per day, every day for two months. Then the patient was switched to a short arm thumb spica cast with PEMF for ten hours per day every day for one month. Investigators cite inconsistent use of wrist splint thereafter. A follow-up radiograph was done five months post-splint removal.
Success/Failure Criteria	This was a case study, no criteria established. Report was only observational. Investigators noted the union of the scaphoid fracture.
Results	Statistical analysis not available for this study. No comments regarding safety. Investigators cited cost savings over bone grafting and/or conventional treatments. Union of scaphoid fracture was achieved in 9 weeks. Investigators noted that the patient suffered no hospitalization, no missed school, no infection at site of fracture and regained full range of motion.
Potential Sources of Bias	Outcome bias: unclear or subjective assessment criteria; if there are subjective components, lack of an independent observer to make the assessments; if different treatment groups, treatment assignment not masked; lack of clear control group.

2. Barker et al., 1984

Citation	Pulsed Magnetic Field Therapy for Tibial Non-Union. A.T. Barker, R.A. Dixon., W.J. Sharrard., and M.J. Sutcliffe Lancet 1984 May 5; 1 (8384): 994-6
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture long bones
Stimulation Type	<input checked="" type="checkbox"/> PEMF
Commercial Device Name(s)	Not applicable. (custom made plaster casts with EMF stimulator)
Overall Study Design	<input checked="" type="checkbox"/> Randomized, concurrent control, prospective
# Patients	17 total patients 9 in treatment group 8 in control group (1 left group because not compliant)
Selection Criteria	Inclusion: o 1 year of nonunion (range of 12-39 months in treatment group; range of 13-

	<p>133 months in control group);</p> <ul style="list-style-type: none"> • no surgery to treat fracture; • fracture is ≥ 5 cm from joint; • mobility at fracture site; • complete width fracture; • no improvement from previous radiographs; and • patient is ≥ 18 y.o. (range of treatment group between 19-72 y.o.; range of control group between 19-41 y.o.) <p>Exclusion:</p> <ul style="list-style-type: none"> • Gap at fracture site of >0.5 cm; • presence of internal fixation; • bone disease; • severe bone sepsis with constitutional effects; • steroid use; • external fixator. • Exclusion after study started included non-compliance to treatment regimen.
Methods	<p><i>Stimulation</i> according to Bassett and described by Barker and Lunt: 1.5mT peak, 5 msec bursts, 15Hz frequency. Coils to provide electromagnetic pulses are custom fit around the cast of each patient.</p> <p><i>Recommended treatment protocol:</i></p> <p>12-16 hr every day with minimum session length of 1 hr; and minimum total daily stimulation of 10hr.</p> <p>To be considered compliant, the patient could miss no more than 7 days in each 6 week period, not more than 14 days in each 24 week period where machine was used for 6 hours or less. Compliance was measured by implanted clocks.</p> <p>Patients had full clinical exams every 6 weeks for 48 weeks, the duration of the study.</p> <p>Patients were not weight bearing while fully immobilized.</p> <p>At end of treatment period, patients had a full exam with the removal of their plaster cast; 2 independent observers checked mobility at fracture site with goniometers; 2 independent observers assessed stress radiographs for each patient; pain at the fracture site was assessed on a pain scale. Observers were blinded.</p> <p>Stimulation was discontinued when the fracture was united. After union, the leg was splinted, patient started on exercises for 6 weeks.</p>
Success/Failure Criteria	<p><i>Authors were looking clinically and radiographically for united fractures.</i> Assessment of the fracture was done by two independent observers and involved mechanical stress radiographs and goniometer measurements. When no movement was detected during stressing and stress radiographs looked stable, the fracture was deemed united.</p>
Results	<p>5/9 patients treated with PEMF had united fractures at 24 weeks. 7/9 patients treated with PEMF had united fractures at 48 weeks.</p> <p>5/7 control patients had united fractures at 24 weeks.</p> <p>2/7 control patients got switched after 24 weeks to PEMF and 1/7 was united by 36 weeks.</p> <p>95% confidence interval is 33% to (-) 61%. PEMF treated patients may have done up to 33% better than untreated controls – or up to 61% worse.</p> <p>There were no differences between control and treatment groups for pain and tenderness at the fracture sites.</p>

	The authors state that no patient suffered adversely from this treatment.
Potential Sources of Bias	<p>One of the control patients left the trial and was not counted in the result. Noncompliance was cited as reason.</p> <p><i>Randomization process was not described.</i> Also, participants were moved from control to treatment group when deemed that fractures were not healing. However, their "crossover" results were not included.</p> <p><i>Control and treatment groups were not very similar at the start of this study.</i> For instance, age ranges were dissimilar as were the lengths of time since their initial injury. The fracture locations were not adequately noted. It is unclear whether the baselines were truly identical; it is unclear whether the groups were matched.</p>
Other Limitations of the Study	<p><i>Authors state that it is possible that simple immobilization and conservative treatment may be responsible for the results seen with this study.</i> Conservative regimes (non-weight bearing immobilization) may be the underlying cause for fracture resolution.</p> <p>The small size of the study means that the differences between groups would have to be very large in order for the study to detect an effect.</p> <p>There were no direct measures of device or treatment safety. There were no adverse effects noted, but it is unclear whether this information was solicited from patients.</p>

3. Brighton and Pollack, 1984

Citation	Treatment of Nonunion of the Tibia with a Capacitively Coupled Electrical Field C.T. Brighton and S.R. Pollack Journal of Trauma, 24(2): 153-55 (Feb. 1984)
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture tibia
Stimulation Type	<input checked="" type="checkbox"/> Capacitive coupling Driven by 5 V peak to peak current at 60 kHz
Commercial Device Name(s)	Not available.
Overall Study Design	<input checked="" type="checkbox"/> Case report
# Patients	1
Selection Criteria	Recalcitrant nonunion after 10 months, 2 surgeries.
Methods	10-12 hours daily treatment "electromagnetic stimulation" for 7 months. Clinical improvement, but still radiographic nonunion. 6 months later, capacitive coupling equipment applied. Healing had begun 12 weeks later. At the end of another 12 weeks, the fracture was healed.
Success/Failure Criteria	Not specified.
Results	Nonunion healed after 6 months of treatment
Potential Sources of Bias	Anecdotal.

4. Cundy and Patterson, 1996

Citation	A Ten-Year Review of Treatment of Delayed Union and Nonunion with an Implanted Bone Growth Stimulator P.J. Cundy and D.C. Patterson Clinical Orthopedics and Related Research. (259): 216-22 (Oct. 1990)
Intended Use	<input checked="" type="checkbox"/> Non-Union or delayed-union fractures, bone not specified

Stimulation Type	<input checked="" type="checkbox"/> Implanted DC stimulation device Constant DC of 20 mu amp. (usual dosage in these studies)
Commercial Device Name(s)	Not applicable.
Overall Study Design	Ten-year follow-up of patients in a nonrandomized multi-center (30) clinical trial in Australia.
# Patients	Originally 81 patients; 84 fractures. 36 were unlocatable, 7 had died, 1 refused to cooperate but relatives said bone was healed and patient was pleased. 37 remaining (40 implants, 38 fracture sites) were reviewed.
Selection Criteria	Not available.
Methods	Not available.
Success/Failure Criteria	Clinical and radiographic evaluation.
Results	All fractures completely healed. Safety: No harmful effects from electrical stimulation found.
Potential Sources of Bias	Huge loss to follow-up make results difficult to interpret.
Other Limitations of the Study	Applies only to implanted stimulation devices.

5. Unpublished report

Citation	Summarized in G. Scott and J.B. King, A Prospective, Double-Blind Trial of Electrical Capacitive Coupling in the Treatment of Non-Union of Long Bones, Journal of Bone and Joint Surgery, Vol 76-A: 820-26 (1994)
Intended Use	<input checked="" type="checkbox"/> Bones not specified
Stimulation Type	<input checked="" type="checkbox"/> Direct Current <input checked="" type="checkbox"/> PEMF <input checked="" type="checkbox"/> Capacitive Coupling
Commercial Device Name(s)	Not given.
Overall Study Design	<input checked="" type="checkbox"/> Patient as own control, prospective
# Patients	Total: 64 29 had direct current 17 had PEMF 18 had capacitive coupling.
Selection Criteria	Not clear.
Methods	Not given.
Success/Failure Criteria	Not given.
Results	19 of the 29 patients given direct current (66%) healed. 13 of the 17 patients given PEMF (76%) healed after 5 to 18 months. 13 of the 18 patients given capacitive coupling (72%) healed.
Potential Sources of Bias	Obviously, patients may have been selected differently and managed differently. Lengths of treatment, bones involved, severity are not given for all three studies. They may not be

	comparable.
Other Limitations of the Study	This unpublished study was not subjected to peer review.

6. Rogozinski et al., 1996

Citation	Efficacy of Implanted Bone Growth Stimulation in Instrumented Lumbosacral Spinal Fusion A. Rogozinski and C. Rogozinski Spine. 21(21): 2479-83 (Nov. 1996)
Intended Use	<input checked="" type="checkbox"/> Lumbar spinal fusion
Stimulation Type	<input checked="" type="checkbox"/> Implanted DC stimulation device
Commercial Device Name(s)	EBI SpF-2T Produces a constant direct current of 20 + 2 mA (10mA per cathode).
Overall Study Design	<input checked="" type="checkbox"/> Randomized, concurrent control, prospective
# Patients	94 patients; one experimental patient moved, lost to follow-up at 3 months, counted in analysis as a failure.
Selection Criteria	Inclusion: <ul style="list-style-type: none"> • Judged in need of surgery (by the same two surgeons) after at least 6 months conservative treatment. • A positive response to provocative discography (using the double-needle technique). Consecutive patients May 1990 to May 1991 (26) control. Consecutive patients May 1991 to June 1992 (42) experimental. Consecutive patients June 1992 to December 1992 assigned randomly to either group. (15 control, 11 experimental)..
Methods	A minimum of 6 months spent on conservative treatment before surgery was considered. All surgery performed by the same two surgeons working together. All patients received posterolateral fusions incorporating bone graft, and fixation with Rogozinski spinal rod system. A sequential compression device applied to lower extremities and continued until patients were able to mobilize independently. Suture removal and reexamination 10 days after surgery, at which time most were advised to begin a walking program, 1 mile a day at first. Physical exam and serial radiographs at 6 weeks, 3 months, 6 months 12 months. Annually thereafter. If fusion appeared solid radiographically at 12-16 weeks, a reconditioning program begun for most patients. Follow-up evaluation Dec 1993, average period for all patients 20.5 months. Average for controls 22.5 months. Experimental 19 months.
Success/Failure Criteria	Fusion determined radiographically by surgeons. Solid union: trabeculated bone mass with no movement on stress views and no loss of fixation. Anteroposterior and 2 lateral views. Endpoint apparently Dec. 1993, longer after surgery for controls than for experimental group.
Results	96% experimental had solid fusion, versus 85% control (p = 0.02). Success rates higher in experimental than control patients in various high-risk categories, such as smoking, multiple-level fusions, previous back surgery.
Potential Sources of Bias	Radiographs assessed by the surgeons who are doing the study, apparently not blinded. There is significant potential for selection bias. Compliance not an issue with implanted units. One dropout counted as a failure, in experimental group.

Other Limitations of the Study	Results do not apply to noninvasive bone growth stimulators.
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7. Zoltan and Ryaby, 2000

Citation	Combined Magnetic Fields for Non-Union Treatment J. Zoltan and T. Ryaby Paper presented at International Society for Fracture Repair, Hong Kong, September 2000
Intended Use	<input checked="" type="checkbox"/> Non-Union fractures except spine
Stimulation Type	<input checked="" type="checkbox"/> Combined magnetic fields
Commercial Device Name(s)	Not available.
Overall Study Design	<input checked="" type="checkbox"/> Comparison with historical controls
# Patients	2370 patients. Treated by many physicians in a registry process as required by FDA. Collected December 1994 to December 1998.
Selection Criteria	Inclusion: <ul style="list-style-type: none"> • Non-union at least 2 months from injury (median 6.3 months).
Methods	30 minutes a day treatment.
Success/Failure Criteria	Determined by each physician based on radiographic data and clinical evaluation. Specific criteria were not given.
Results	Overall 75% success rate, average healing time of 4.9 months. Estimated 25% would have healed without stimulation, which gives $p = 0.001$ by Fischer's exact test. Outcomes varied with bone. 89.7% for carpal metacarpal. 57.2% for humerus. Outcomes varied with time from injury to start of treatment. Shorter time, better success rate, statistically significant.
Potential Sources of Bias	Use of estimated rates from historical controls is not well justified. The criterion of nonunion is lax, and the fractures were relatively fresh, making this a non-challenging population. Assessment by each physician, not by independent assessors. Very different management regimes.
Other Limitations of the Study	Results do not apply to PEMF or capacitive coupling. This paper was not subject to peer review.

8. Wahlstrom, 1984

Citation	Stimulation of Fracture Healing with Electromagnetic Fields of Extremely Low Frequency (EMF of ELF) O. Wahlstrom Clinical Orthopaedics and Related Research (186): 293-301 (June 1989)
Intended Use	Fresh fractures of the tibia
Stimulation Type	Alternating magnetic field with frequency 1-1000 Hz (noise) but most amplitude in "middle and lower" frequencies. Developed by authors. Coil fixed on outside of cast at fracture site. Treatment lasted 4 weeks. Battery pack could be carried in pocket. Batteries changed every week and device checked.
Overall Study Design	Randomized, concurrent groups, prospective
# Patients	32 (2 were dropped after a week because of faulty cables) <ul style="list-style-type: none"> • 15 with stimulation

	<ul style="list-style-type: none"> • 15 without stimulation
Selection Criteria	Inclusion: <ul style="list-style-type: none"> • women 50-70 • articular Colles fracture • after reduction, dorsal angulation less than 10 degrees
Methods	After reduction, fractures were put in casts and immobilized for 4 weeks, during which treatment took place.
Success/Failure Criteria	Scintigrams taken measuring how much accumulation of injected Tc-MDP in fracture, at 1 week, 2 weeks, 4 weeks, and 8 weeks after the injury. High activity and then a drop-off indicates faster healing. No clinical, radiographic, or return to normal activity types of data were reported, although roentgenograms were taken after 1, 2, and 4 weeks, to make sure that angulation was no more than 10 degrees.
Results	Experimental group showed higher activity than control group during first two weeks ($p < 0.05$, $p < 0.01$), then dropped off to normal values, while the control group had high activity much longer. This is taken as evidence of faster healing in the experimental group.
Potential Sources of Bias	<p>Selection in two groups randomized, and very similar fractures required in all subjects. However, other characteristics that might affect healing (i.e., smoking and diseases), were not taken into account.</p> <p>This population was quite different from most study populations in that the fractures were fresh rather than delayed or nonunion.</p> <p>The measurement of Tc-MDP is an objective test that limits the potential for observer bias.</p>
Other Limitations of the Study	Measurement of Tc-MDP cannot be compared with clinical and radiographic assessments in other studies.

9. Sharrard, 1994

Citation	A Double-Blind Trial of PEMFs for Delayed Tibial Union: Clinical Follow-up J. Sharrard Paper, 16 th Annual Meeting of the Bioelectromagnetics Society, Copenhagen, 1994
Intended Use	Delayed union fracture of long bones
Stimulation Type	PEMF
Methods	After an average of 2 years following the beginning of treatment, follow-up of double-blind study which initially assessed success at 12 weeks.
Results	Healing without surgical treatment had occurred in 85% of treatment group, 36% of control. $P = 0.001$.
Other Limitations of the Study	Not a peer-reviewed publication.

10. Dunn and Rush, 1984

Citation	Electrical Stimulation in Treatment of Delayed Union and Nonunion of Fractures and Osteotomies C. William and G.A. Rush III Southern Medical J. 77 (12): 1530-34 9Dec. 1984)
Intended Use	Nonunion long bones, hand
Stimulation Type	PEMF, Implanted DC
Overall Study Design	Case series, retrospective

# Patients	52 patients <ul style="list-style-type: none"> • 17 treated by implanted stimulation device. • 35 treated by PEMF.
Selection Criteria	<ul style="list-style-type: none"> • (Implant group) All the patients treated at the authors' hospital for nonunion of fracture by implanted DC, from 1979 on (apparently only for one year), who are now available for final analysis of results. • (PEMF group) All the patients treated with electrical stimulation from February 1980 on, when the authors began to use PEMF.
Methods	Not specified.
Success/Failure Criteria	If fracture had not united by 12 months, treatment considered a failure. Exact criteria for determining union were not given.
Results	Almost exactly equal proportions healed by the two methods. Authors recommend using PEMF when infected wound is draining.
Potential Sources of Bias	The criteria for using one treatment method or another may have been different, so there is some potential for selection bias. There is no mention of blinded independent assessments, so observer bias is possible.
Other Limitations of the Study	The results do not address differences among various types of noninvasive stimulation devices.

11. Paterson et al., 1980

Citation	Treatment of Delayed Union and Nonunion with an Implanted Direct Current Stimulator D.C. Paterson, G.N. Lewis, and C.A. Cass Clinical Orthopaedics and Related Research, 148:117 – 127, 1980
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture long bones <input checked="" type="checkbox"/> Other <u>Delayed Union fracture long bones</u>
Stimulation Type	<input checked="" type="checkbox"/> Implanted stimulation device
Commercial Device Name(s)	Osteostim S12, Telectronics Pty. Ltd., Australia
Overall Study Design	<input checked="" type="checkbox"/> Patient as own control, prospective
# Patients	84 cases 47 delayed fractures 37 non-union fractures 64 male 20 female Age range: 5 to 81 yr (mean = 30 yr) 44 patients had one or more operation 10 patients had 3 or more operations 15 fractures had infection present at the time of electrical stimulation
Selection Criteria	<ul style="list-style-type: none"> • Strict criteria were used for case selection and included clinical, radiologic, and nuclear scan evidence of at least delayed union of fractures of long bones not less than 12 weeks from the initial injury. • Surgical confirmation of lack of union at the time of implant surgery was mandatory. • <i>Non-union</i>-is defined as when bone healing had ceased, where the fracture is mobile

	<p>clinically and where well-defined radiologic features are present; fracture has not united within 12 months.</p> <ul style="list-style-type: none"> • <i>Delayed union</i>-is defined as when the possibility of bone healing still persists, even though clinically and radiologically the fracture is non-united; fracture has not united within 6 months.
Methods	<ul style="list-style-type: none"> • Two surgical techniques were used; cathode was threaded across fracture site or coiled into the form of a helix across fracture site (majority). • The anode and stimulator pack were inserted surgically, the wound closed, and a usual immobilization technique for that particular fracture was applied. • The implanted generator was removed anywhere from 3–6 months after implantation. • Minimal postoperative pain was a significant feature of this procedure. • 5 patients had a second stimulator inserted to achieve union. • Plemister cancellous grafting was used in conjunction with bone growth stimulation in 11 patients. • Cancellous grafting was added in 3 other patients at the direction of the surgeon.
Success/Failure Criteria	<i>Bone union</i> is defined as the time when it is considered safe either clinically or radiologically, or both, to remove all plaster immobilization and allow full weight-bearing.
Results	<ul style="list-style-type: none"> • Time from injury to implant varied from 3 months to 7.5 yr; average time = 10 months; for 60% more than 6 months elapsed. • 72/84 (86%) cases were successfully treated. • Time to achieve union ranged from 12 to 36 weeks with an average of 16 weeks. • 36/44 (82%) of patients who had a previous operation healed successfully. • 7/10 (70%) of patients who had 3 or more previous operations healed successfully. • 13/15 (87%) had infection present at time of stimulation. • 10/11 (91%) cases with Plemister cancellous grafting healed successfully. • Complications were infrequent and insignificant; no infection at the fracture site resulted directly from the operative procedures.
Potential Sources of Bias	<ul style="list-style-type: none"> • It is unclear who evaluated the radiographs or who performed the clinical evaluation on these patients.
Other Limitations of the Study	<ul style="list-style-type: none"> • The authors separate cases based on delayed and non-union fractures, but the success rate data presented was for the combined population. • It is really not clear how often the radiographs were taken or a clinical evaluation was performed during the treatment phase.

12. Friedenberg et al., 1971

Citation	Healing of Nonunion of the Medial Malleolus by Means of Direct Current: A Case Report Z.B. Friedenberg, M.C. Harlow, and C.T. Brighton J Trauma, 11(10): 883-885, 1971
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture other bones <i>medial malleolus</i>
Stimulation Type	<input checked="" type="checkbox"/> Other <i>Direct Current</i>
Commercial Device Name(s)	Non-commercial; power source was a 7.5 V battery with resistors and field effect transistors designed to produce a constant current of 10 μ amps.
Overall Study Design	<input checked="" type="checkbox"/> Case report

# Patients	1
Selection Criteria	This was a case report from a woman who sustained a bimalleolar fracture of her right ankle, was treated, and returned to the hospital approximately 14 months later with pain and swelling; roentgenograms revealed a non-union of the medial malleolar fracture and slight displacement.
Methods	<ul style="list-style-type: none"> • Under local anesthesia, a small incision was made over the non-union site. • A small hole was made in the non-union defect, and the cathode was inserted into the hole. • The wire was fastened to surrounding tissue and brought out through another hole in the skin. • The anode was placed on the surface of the skin and held in place by tape. • A short-leg non-weight-bearing cast was applied. • The cathode and anode wires were brought through a small window in the cast and attached to the power pack which was taped to the outside of the cast. • Current was checked daily initially and then weekly. • At 3 weeks the cast was changed. • The patient was kept non-weight-bearing with the battery pack on for 9 weeks. • Roentgenographic examination of the non-union revealed bony trabeculae crossing the defect at which time the current was discontinued, the wires were removed, and the patient was started on crutch-walking with partial weight-bearing. • Two weeks later, full weight-bearing was commenced.
Success/Failure Criteria	Success occurred when roentgenographic examination of the non-union revealed bony trabeculae crossing the defect.
Results	<ul style="list-style-type: none"> • The patient's nonunion healed, and there were no problems from the wire insertion.
Potential Sources of Bias	<ul style="list-style-type: none"> • It is possible that the 9 week immobilization in a non-weight-bearing cast may have contributed to the healing of the non-union. • It is also possible that the operation performed to insert the cathode into the non-union may have done something to stimulate healing. • No indication is made as to who read the roentgenographs or performed the clinical evaluation so the assumption is that it was one or more of the authors.
Other Limitations of the Study	<ul style="list-style-type: none"> • This report involved only one patient and one type of device on one type of fracture (non-union), so no general conclusions can be reached. • The device used was invasive rather than non-invasive.

13. Longo, 2000

Citation	Successful Treatment of Recalcitrant Nonunions with Combined Magnetic Field Stimulation J.A. Longo, III Surgical Technology International VI, 2000: 397-403
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture long bones <input checked="" type="checkbox"/> Non-Union fracture other bones
Stimulation Type	<input checked="" type="checkbox"/> Combined magnetic field
Commercial Device Name(s)	Orthologic 1000 bone growth stimulator
Overall Study Design	<input checked="" type="checkbox"/> Patient as own control, prospective

# Patients	<p>20 patients</p> <p>Average number of surgical procedures prior to stimulator initiation was 2.1 procedures.</p> <p>10 patients had 2 or more surgical procedures to enhance fixation or union.</p> <p>6 patients had 3 or more surgical procedures prior to stimulation.</p>
Selection Criteria	<ul style="list-style-type: none"> • Fractures were classified as non-unions if there was no clinical or radiographic evidence of union at least 6 months after the injury, and there was no radiographic evidence of progression of healing within 3 months prior to the initiation of the Orthologic 1000 stimulator. • 3 patients were treated prior to 6 months as the author felt there was no chance of normal healing with these patients.
Methods	<ul style="list-style-type: none"> • The Orthologic 1000 was applied to the non-union site for 30 min/day by the patient. • Casting and bracing were continued after the Orthologic 1000 application to control symptoms and discontinued as clinical symptoms allowed. • No attempt was made to modify brace or orthosis usage or modify activity level from that prior to the use of the stimulator. • Clinical and radiographic evaluations were performed monthly during the treatment until union was evident. • Long term follow-up after clinical and radiographic determination of union was available on 17 patients (19 non-unions) for an average length of follow-up after union of 10.4 months. • 10 patients had at least 1 year follow-up and 6 patients had greater than 2 yr follow-up.
Success/Failure Criteria	<ul style="list-style-type: none"> • Clinical union was determined by the absence of rest or activity related bone pain, and absence of bone pain related to manual stress examination. • Radiographic union was defined when at least three of four cortices were bridged by trabecular (calcified) bone as determined by evaluation of AP and lateral radiographs and occasionally additional oblique views to evaluate healing around metallic hardware.
Results	<ul style="list-style-type: none"> • 23/23 (100%) non-unions healed. • Average time from the date of injury to the initiation of the stimulation was 389 days (range 129 to 1069 days). • Duration of treatment averaged 6 months (range 4 to 9 months) with greater than 90% compliance with daily treatment. • No safety data were given.
Potential Sources of Bias	<ul style="list-style-type: none"> • No indication was made as to how these patients were selected. • No indication was made as to who performed the clinical and radiographic evaluations.
Other Limitations of the Study	<ul style="list-style-type: none"> • Even though long-term follow-up was available on 16 patients, no data were presented on the long-term effectiveness of the treatment. • The study applies to only one form of stimulation.

Section B: Clinical Reports of Off-Label Uses

1. Comorosan et al., 1993

Citation	The Effect of Diapulse Therapy on the Healing of Decubitus Ulcer S. Comorsan , R. Vasilco, M. Arghiropol, L. Pasteru, V. Jieanu, and S. Stelea Rom. J. Physiol. 1993 Jan-Jun; 30(1-2): 41-5
Intended Use	<input checked="" type="checkbox"/> Other <i>Healing of decubitus ulcers</i>
Stimulation Type	<input checked="" type="checkbox"/> PEMF
Commercial Device Name(s)	Diapulse (V = 117, freq = 27.12 mHz, 65 microsec freq, 80-600 pulses per sec; wattage ranges from 293 to 975 watts)
Overall Study Design	<input checked="" type="checkbox"/> Randomized, concurrent control, prospective
# Patients	20 patients in treatment group 5 patients in control group (conventional treatment) 5 patients in placebo control group (sham treatment)
Selection Criteria	Patients were in terminal stages of life, chronically ill, neurologically impaired. 16 patients had stage II ulcers, 14 patients had stage II ulcers. Decubitus ulcer locations included: buttocks, sacrum, knee, coxal, back, heel, leg. Primary diagnoses included: Cerebrovascular accident, spinal cord trauma, Alzheimer's disease, systemic arteriosclerosis.
Methods	Authors state random assignment to either of three groups. No description of how they accomplished the randomization. Control group received conventional treatment consisting of H ₂ O ₂ cleansing, talcum powder application, application of methylene blue, and tetracycline use. Diapulsed group received a local PEMF application to each ulcer directly through dressings; each treatment was 30 min, twice per day at 6 hr intervals, @600 pps. Each patient also received a hepatic application at 400 pps for 20 minutes every day. Conventional dressing changes and antimicrobial treatment was also used on this group. Placebo control group was treated the same as the Diapulsed group with a nonfunctioning Diapulse unit. Study was semi-double blinded; the standard therapy control group was obvious because they did not receive any PEMF treatment. Clinical observations by caregivers were used to assess the state of decubitous wounds. The study lasted 5 weeks.
Success/Failure Criteria	Treatment success was a healed ulcer. Levels of success were described on a scale as follows: Excellent =completely healed Very good = 75-95% healed Good = 50-75% healed Fair = 25-50% healed Poor = <25% healed No improvement = unhealed (treatment failure)
Results	Authors state use of Diapulse resulted in good to excellent healing of decubitus ulcers in a shorter amount of time. The mean length of time to healing of stage II wounds was 3.28 weeks; the mean length of time to healing of stage III wounds was 4.87 weeks. There was no statistical analysis of data.

	The authors did not directly measure safety of Diapulse treatments.
Potential Sources of Bias	<p>There was no independent assessment of wounds included in study. Given small numbers of patients with different chronic conditions, it was difficult to determine whether the groups were even similar enough to warrant comparison after treatment.</p> <p>There may have been some differences in staff care since the placebo control group did better than the controls.</p> <p>Randomization did not result in groups that were well matched for type, location, and size of decubitus ulcers. Stage II ulcers in the control groups were larger, on average, than stage II ulcers in the Diapulse group.</p> <p>There was no control for the subjective clinical assessment of wounds. There was no independent blinded assessment of wounds.</p>
Other Limitations of the Study	<p>The authors state that they do not know if hepatic applications were useful</p> <p>While it looks like Diapulsed decubitus ulcers healed faster, this was not a well-controlled, properly randomized study. It is unclear how much better, if at all, decubitus ulcers will heal with Diapulse treatments.</p>

2. Tabrah et al., 1990

Citation	<p>Bone Density Changes In Osteoporosis-Prone Women Exposed to Pulsed Electromagnetic Fields (PEMFs)</p> <p>F. Tabrah, M. Hoffmeier, F. Gilbert, S. Batkin, and C.A.L. Bassett</p> <p>Journal of Bone and Mineral Research 5(5): 437 – 442, 1990</p>
Intended Use	<input checked="" type="checkbox"/> Other: Increasing bone density in uninjured bones
Stimulation Type	<p><input checked="" type="checkbox"/> PEMF</p> <p>A 380 microsecond quasirectangular wave was followed by a 6 ms quasitriangular wave when measured with a standard coil probe placed centrally in the air between the coils. The amplitude of the leading edge of the quasirectangular wave was 12.5 mV. Pulses were repeated at 72 Hz. The peak value of the B field was measured at 2.85 mT in 380 microseconds, resulting in an electric field of 7.5 t/sec.</p>
Commercial Device Name(s)	Not specified.
Overall Study Design	<input checked="" type="checkbox"/> Patient as own control, prospective
# Patients	20
Selection Criteria	<p>Inclusion:</p> <p>Postmenopausal women from a previous longitudinal bone density study for whom detailed clinical data and forearm bone density measurements were available.</p> <p>Exclusion:</p> <p>Concurrent use of gold, hormone replacement, corticosteroids, anticonvulsant agents, fluorides, major tranquilizers, or cytotoxic agents.</p> <p>Previous use of more than 400 units of vitamin D per day.</p> <p>Kidney or liver disease or hypercalcemia</p>
Methods	<p>Participants applied PEMF treatment to their non-dominant forearms for 10 hours per day over 12 weeks. The coils were placed so that the distal edge was at the radiocarpal junction and the proximal edge was just proximal to the midradial shaft.</p> <p>Bone density was measured in both arms at 0, 6, 9, 12, 18, 24, 36, and 48 weeks. Bone density was measured using single-photon absorption densitometry.</p>

	<p>X-rays were also taken at the baseline and at week 48, as well as blood chemistry tests (SMA12 and complete blood count).</p> <p>Statistical analysis was carried out using the Pearson product-moment correlation.</p>
Success/Failure Criteria	This was an exploratory type study, so no specific success criteria were established.
Results	<p>The bone density of the midshaft of the radius, which the authors describe as the area of maximum exposure, increased significantly during the 12-week exposure period ($r = 0.78$), but the density of the distal portion of the radius was unchanged ($r = 0.09$).</p> <p>During the time from the end of stimulation to the end of follow-up at 48 weeks, there was a significant reduction in bone density in the midshaft of the radius, ($r = 0.96$) and in the distal portion of the radius. At the end of the follow-up period, the bone density in the midshaft was lower on average than it had been at baseline, although the authors did not determine if the difference in means was significant.</p> <p>The authors also found an unexpected change in bone density in the unexposed, "control" arm. Although there was no significant change in bone density in the contralateral arm during the exposure period, there was a significant reduction in density of the radial mid-shaft during the post-exposure follow-up period. The authors were unable to explain the effect on the contralateral arm.</p> <p>The authors note that there was no apparent change in bone density visible on x-rays taken at the end of the study.</p> <p>The authors note that there were no significant complaints or clinical problems in any of the subjects, but that one subject dropped out of the study for "personal reasons." There were no significant changes on the SMA12 or the CBC.</p>
Potential Sources of Bias	<p>The authors selected these subjects from a larger study population, but the exact selection criteria are not given. The authors describe them as "matched for age and treatment history," but it is unclear with whom they were matched. It is quite possible that they are not a representative sample.</p> <p>It is unclear who performed the bone density measurements, and whether they were blinded as to treatment status.</p>
Other Limitations of the Study	This study raises a number of questions that could not be answered from the available data, including questions about how the magnetic fields were interacting with bones not directly stimulated and questions about whether the post-use reduction in bone density is permanent.

3. Rispoli et al., 1988

Citation	<p>The Use of Low Frequency Pulsing Electromagnetic Fields in Patients with Painful Hip Prostheses</p> <p>F.P. Rispoli et al.</p> <p>J Bioelectricity 7 (2) 1988-89</p>
Intended Use	Poor bone growth around hip prostheses
Stimulation Type	PEMF with low frequency. Only info on signal was a waveform which seemed to show a 10 msec frequency
Commercial Device Name(s)	Igeastimulator, Howmedica, New York
Overall Study Design	Patient compared with self, prospective
# Patients	45
Selection Criteria	<p>Inclusion:</p> <ul style="list-style-type: none"> 6 months since non-cemented primary or revision press-fit hip prosthesis

	<ul style="list-style-type: none"> • Pain in the hip • Walking possible only with crutches and for a short time • X-rays show low mineral content around prostheses
Methods	Stimulator on cast. Received calcitonin, Vit D, non-steroidal anti-inflammatories. Used stimulator for 60 days, at least 6 hours a day. Compliance monitored.
Success/Failure Criteria	Evaluated after 4 months by surgeons. 4-point scales (0 to 3) for pain, ability to walk, and radiological evidence. A maximum of 9 points were possible if the patient was completely pain-free, could walk all day without support, and compact bone was present all around the prosthesis and trabecular bone in the intertrochanteric region. 0 points were assigned if there was no improvement in 4 months.
Results	<p>Among patients who stimulated fewer than 360 hours, eight had less than 4 points, and 2 had 4 points or more. Among patients who stimulated more than 360 hours, 3 had less than 4 points, and 29 had 4 points or more.</p> <p>“The group of patients considered here, the biological and biomechanical problems involved, the extremely slow progression of the disease toward healing, and the unsatisfactory response to standard treatments make it very difficult to obtain a satisfactory result. . . . our data suggest a beneficial effect of PEMF.”</p>
Potential Sources of Bias	<p>Some of the areas of assessment were open to subjective assessments by either the patients or the surgeons.</p> <p>Without a true control group, it is hard to assess the true effect of the PEMF treatment.</p>
Comments	This seems to be a PEMF device with an atypical signal.

4. Steinberg et al., 1989

Citation	<p>Osteonecrosis of the Femoral Head; Results of Core Decompression and Grafting with and without Electrical Stimulation</p> <p>M. Steinberg et al.</p> <p>Clinical Orthopedics and Related Research (249); 199-208 (Dec. 1989)</p>
Intended Use	Nonunion of hip: Avascular necrosis of femoral head
Stimulation Type	Implantable electrical stimulator DC
Commercial Device Name(s)	Osteostim, Telectronics, Englewood, CO or Orthofuse (DuPuy, Warsaw, Indiana)
Overall Study Design	Randomized, concurrent controls, third arm retrospective
# Patients	<p>171 patients</p> <ul style="list-style-type: none"> • 42 treated with decompression and grafting alone • 74 treated with decompression, grafting, and supplemental electrical stimulation • 55 treated without surgery, retrospective review
Selection Criteria	<p>Inclusion:</p> <ul style="list-style-type: none"> • Minimum follow-up time of two years. • Younger individuals with established non-traumatic AVN of the femoral head. <p>Exclusion:</p> <ul style="list-style-type: none"> • Cases so far advanced it was considered useless to try save the femoral head.
Methods	<p>All patients on partial weight bearing with crutches for 6 months. If both hips operated on, instructed to use 4-point gait. Evaluated each 3 months first year, each 6 months for second and third years.</p> <p>Retrospective cases: mean follow-up period was fairly short because a number (apparently</p>

	79%) required surgery within 6 months to 2 years.
Success/Failure Criteria	Clinically, pre- and post-operative and at each evaluation using Harris scores. Roentgenographic progress anteroposterior and lateral pre and post operative and at evaluations scored 0 to VI.
Results	Clinically, electrically stimulated cases slightly better than non-electricity but the difference was not statistically significant. Roentgenographic progression was less in the electrically stimulated cases than for those without, but the difference was not statistically significant. In the retrospective review of non-surgery cases, there was roentographic progression found in 92% of cases.
Potential Sources of Bias	Prospective analysis groups were randomized, and apparently closely matched, so there is little evidence of selection bias. The retrospective cases started without surgery, which suggests that some were less severe than the experimental and control groups. This was not made clear.
Other Limitations of the Study	It is difficult to compare scores from the retrospective groups and the two prospective groups. The study does not apply to noninvasive stimulation devices.

5. Brighton et al., 1981

Citation	A Multicenter Study of the Treatment of Non-Union with Constant Direct Current C.T. Brighton et al. J Bone and Joint Surgery, 63-A: 2-13 (1981)
Intended Use	Nonunion fractures of long bones, clavicle, wrist, malleolus
Stimulation Type	DC partially implanted
Commercial Device Name(s)	Not specified.
Overall Study Design	Patient with self, prospective
# Patients	269
Methods	Electrical stimulation and immobilization in cast. No bone-graft surgery. Apparently different surgeons managed patients differently.
Results	DC ineffective if inadequate electricity (one 10-microampere cathode instead of four 20-microampere cathodes. "Given proper electrical parameters and proper cast immobilization, a rate of bone union comparable to that seen with bone-graft surgery was achieved." However, they found it difficult to identify a comparable retrospective sample of bone-graft patients.
Other Limitations of the Study	Extremely varied sample, and no good comparison. Results do not apply to noninvasive stimulation devices.

Section C: Reviews, Non-clinical Studies, etc.

1. Byers et al., 1998

Citation	Effect of Pulsed Electromagnetic Stimulation on Facial Nerve Regeneration J.M. Byers, K.F. Clark, and G.C. Thompson Arch Otolaryngol Head Neck Surg. 1998 Apr; 124(4): 383-9
Intended Use	<input checked="" type="checkbox"/> Other (<i>regeneration of facial nerve in rats</i>)
Stimulation Type	<input checked="" type="checkbox"/> PEMF
Commercial Device Name(s)	Not specified; Custom designed to fit around rat cages
Overall Study Design	<input checked="" type="checkbox"/> Randomized, concurrent control, prospective
# Patients	28 total rats 12 allocated to experimental treatment, 2 rats with sham operations 12 allocated to control group, 2 rats with sham operations
Selection Criteria	Not stated.
Methods	<p>Left facial nerve cut in the tympanic section of the fallopian canal in 24 rats; then, nerve ends were re-approximated without sutures to maximize regeneration potential in both experimental and control groups. Four rats underwent sham surgeries where the facial nerve was not cut. 12 rats were randomly allocated to the control group; 12 to the experimental group; 2 rats with sham operations were allocated to each group.</p> <p>Treatment protocol: Exposure to pulsed electromagnetic stimulation (0.4 mT at 120 Hz, for 4 hours everyday, 5 days per week for 8 weeks.</p> <p>Control protocol: Handled in identical manner without stimulation.</p> <p>Evaluation methods:</p> <p>At 2 week intervals post-transection, nerve regeneration was evaluated with electroneurography (compounded action potentials, or CAP). Investigators also quantitatively measured the force of whisker and eyelid movements. Facial movements were subjectively assessed by three independent, blinded observers and rated at 1,2,3,5, and 8 weeks post-transection. Histologic evaluation of regenerated nerves done at 10 weeks; the operated side and unoperated side was sectioned and quantitatively compared for each rat.</p> <p>Dependent variables were analyzed with 2-way ANOVA with 1 between groups and 1 repeated measures variable.</p>
Success/Failure Criteria	<p>Nerve regeneration was reflected in greater negative deflection of the depolarization phase of muscle fibers, in measurements of CAPs at 2 weeks post-transection, in greater force of eye and whisker movements after electrical stimulation.</p> <p>The authors were looking for differences in time to nerve regeneration between control and experimental rats. They were also looking for differences in histologic criteria between control and experimental rats.</p>
Results	<p>The authors concluded that pulsed electromagnetic stimulation enhances early regeneration of transected facial nerves in rats.</p> <p>By 2 weeks, the study showed statistically significant differences between the experimental and control groups. The experimental group showed a higher CAP values, as measured by electroneurography. The return of electrical activity as a percent of normal uncut nerve activity was sooner and greater in the treated vs. control rats. The mean force of eye closure and whisker movement was greater in the treated vs. control rats at 4 weeks. The authors noted an improvement in facial nerve function, facilitated by electromagnetic stimulation.</p>

	<p>Differences in CAPs, in mean force of eye closure and whisker movement, in subjective assessment of rat facial movements were all significantly different ($p < 0.05$). There were no statistically significant differences in the quantitative histological examination of regenerated facial nerves.</p> <p>While these studies show a significant positive effect of pulsed electromagnetic stimulation on the regeneration of rat facial nerves, the range of the effect is yet undetermined.</p> <p>The magnitude of the effect was undetectable by 8 weeks; control animals looked similar to experimental animals.</p> <p>The study did not directly address safety.</p>
Potential Sources of Bias	<p>There was no definition of "well-approximated ends" when facial nerves were transected and replaced within the fallopian tract.</p> <p>No ranges were noted for normal CAP values or for the force of whisker or eyelash movements.</p> <p>Investigators were not blinded to which rats were getting treatment.</p>
Other Limitations of the Study	<p>There was a lack of more sensitive functional measurements for the facial nerve in rats.</p> <p>Pulse frequency was not the same type of wave used in other PEMF studies.</p> <p>The authors speculate that electromagnetic fields may actually cause facial muscles to be more sensitive or more hyperactive.</p>

2. Darendeliler et al., 1997

Citation	<p>Effects of Static Magnetic and Pulsed Electromagnetic Fields on Bone Healing M.A. Darendeliler, A. Darendeliler, and P.M. Sinclair Int J Adult Orthodon Orthognath Surg 1997; 12(1): 43-53</p>
Intended Use	<input checked="" type="checkbox"/> Other <i>mandibular postgonial area of the 2wk old guinea pig</i>
Stimulation Type	<input checked="" type="checkbox"/> PEMF <input checked="" type="checkbox"/> Other (<i>compared to static magnetic field</i>)
Commercial Device Name(s)	<p>EBI Bone Healing System, model 1020, Control Unit to provide power to two coils arranged in a Helmholtz configuration.</p> <p>Static magnetic field: Neodimium magnets.</p>
Overall Study Design	<input checked="" type="checkbox"/> Nonrandomized concurrent control, prospective
# Patients	<p>30 Hartley guinea pigs, 2 weeks old, approximately 240g.</p> <p>12 in PEMF group.</p> <p>12 in static magnetic fields (SMF) group.</p> <p>6 in non-placebo control.</p>
Selection Criteria	All guinea pigs underwent bilateral mandibular osteotomy.
Methods	<p>When not undergoing a treatment regimen, guinea pigs were housed for 16 hours per day in 12" x 12" cases and fed ad libitum. During the 8 hours that animals were undergoing treatment, they were housed in individual cages with their heads centered in the area of the magnetic field, while still having some degree of comfort and freedom.</p> <p>PEMF group: Animals kept in presence of uniform pulsed electromagnetic field generated by two coils arranged in a Helmholtz configuration for 8 hours per day.</p> <p>SMF group: Animals kept in presence of static magnetic field (SMF) produced by neodimium magnets for 8 hours per day.</p> <p>Control group: Animals kept in experimental cages for 8 hours per day without PEMF or SMF.</p>

	Tetracycline given to all animals 1 day prior to surgery to provide an initial bone marker. Animals were sacrificed at 9 days, the day previously determined to be an appropriate time to evaluate bone healing. The mandible of each animal was removed, fixed with 10% formaldehyde, decalcified with EDTA, and embedded with paraplast. Transverse 10 micrometer cross sections were cut and stained with hematoxylin and eosin.
Success/Failure Criteria	Describe characteristics the patient has to have to be considered a treatment success. There may be multiple levels of success. The criteria may include radiologic, clinical, or both. Histologic examination of ostomy areas show different stages of ossification between the three groups. Expected is that the PEMF group will show more advanced stages of ossification than will the control group.
Results	All animals gained weight and there was no difference in weight gain between the three groups. At the end of 9 days, bone healing in the SMF and PEMF groups were significantly more advanced than in the control group. Osteotomy areas in control groups were filled with connective tissues and only a few new bony islands. Healing process was deemed to be at the cellular repair blastema stage. Osteotomy areas in the PEMF and SMF groups were almost completely filled with new bone. New bone formation seemed to be slightly more advanced and consistent in the SMF group. However, no quantitative histomorphometric analysis could be undertaken because of the complex nature of the healing process. No percentages were given.
Potential Sources of Bias	4 animals died, all were from the SMF group. It is unclear if this indicates adverse effects from the static magnetic fields used in the study. Investigators were not blinded to which animals were in which groups.
Other Limitations of the Study	There was no way to do quantitative histomorphometric analysis on sections. Authors state this is due to the complex nature of the healing process.

3. Otter, 1998

Citation	Effects of Electromagnetic Fields in Experimental Fracture Repair M. Otter Clinical Orthopaedics and Related Research No 355S, October 1998
Intended Use	Various
Stimulation Type	<input checked="" type="checkbox"/> Pulsed capacitive coupling <input checked="" type="checkbox"/> PEMF
Commercial Device Name(s)	Various.
Overall Study Design	Review of what's known about how pulsed electromagnetic fields work, as of 1998.
# Patients	Not applicable.
Selection Criteria	Not applicable.
Methods	Not applicable.
Success/Failure Criteria	Not applicable.
Results	Endogenous electric fields in bone tissue are complex and still not well understood. It is hypothesized that mechanically induced electric fields could be an intermediate signal

	<p>through which bone cells sense the functional demands of bone growth. Electrical currents and fields have widely varying effects on different types of tissue and cell.</p> <p>Negative results of electromagnetic stimulation on several animal models have been reported:</p> <ul style="list-style-type: none"> • Akai, Yabuki, Tateishi, and Shiraski. Mechanical properties of the electrically stimulated callus: An experiment with constant DC in rabbit fibulae. Clin. Orthop. 188: 293-302, 1984. • Colson, Browett, Fiddian, Watson. Treatment of delayed and nonunion of fractures using pulsed electromagnetic fields. J Biomed Eng, 10:301-304, 1988. • Law, Annan, McCarthy et al. The effect of induced electric currents on bone after experimental osteotomy in sheep. J Bone Joint S 67B:463-469, 1985. • Miller, Burchardt, Enneking, Tytkowski, Electromagnetic stimulation of canine bone grafts. J. Bone Joint Surg 66A, 693-698, 1984. <p>The review raises the continuing question of how specific waveform characteristics affect the biologic results (p S92). The complexity of the pulsed electromagnetic fields (PEMF and pulsed capacitive coupling) may have ensured clinical success, but have significantly hampered efforts to understand how they work. We don't even know if it is the applied field or the induced field which is stimulating the healing response. Pulses induce electric fields spanning an extremely wide spectrum, and we don't know which are most effective.</p> <p>PEMF strengths have been set to mimic the frequency potentials recorded during impact loading of bone, since endogenous locomotion-induced fields cannot be imitated successfully (because the signal is attenuated by relaxation processes in the bone). Thus the evidence for these settings is "circumstantial," but they seem to work.</p> <p>The authors present some clues to optimal signals. Induced fields at frequencies lower than 120 Hz are probably optimal in causing bone remodeling. Seem to peak at 15 to 30 Hz. It is probably the induced field, not the imposed magnetic flux density, that is important. Extremely low-frequency sinusoidal electric fields, <150 Hz, are effective at encouraging bone growth. At 15 Hz, induced fields of no more than 1 mV/m caused remodeling, and higher and lower frequencies were less effective. The effectiveness of these low-frequency components suggests that endogenous electric fields are an important part of the effect of electric stimulation in accelerating healing. But it's also hypothesized that higher frequencies may be useful in maintaining bone mass (p S95-96).</p>
Potential Sources of Bias	<p>The authors do not present their methodology for deciding which studies to include in their review.</p> <p>There is also a possibility of the authors opinions affecting the interpretations presented.</p>
Other Limitations of the Study	<p>Not enough information is given to independently assess the quality of all the research studies.</p>

4. Emani et al., 1999

Citation	<p>No Effect of Low-Intensity Ultrasound on Healing Time of Intramedullary Fixed Tibial Fractures</p> <p>A. Emani, M. Petren-Mallmin, and S. Larsson.</p> <p>Journal of Orthopaedic Trauma, 13(4): 257-57 (May 1999)</p>
Intended Use	<p><input checked="" type="checkbox"/> Fracture tibia shafts</p>
Stimulation Type	<p><input checked="" type="checkbox"/> Ultrasound</p>
Commercial Device Name(s)	<p>SAFHS 2A Sonic Accelerated Fracture Healing System, Exogen Inc., Piscataway, NJ.</p> <p>The treatment head emitted an ultrasound signal composed of a burst width of 200</p>

	microseconds, containing 1.2-megahertz sine waves, with a repetition rate of one kilohertz, and a spatial average temporal intensity of 30 milliwatts per square cm.
Overall Study Design	<input checked="" type="checkbox"/> Randomized, concurrent control, prospective, double-blinded
# Patients	32 patients: 15 active ultrasound (12 Grade I closed fractures, 3 open fractures); 17 placebo (16 Grade I closed fractures, 1 open fracture). Other traits were balanced as much as possible: age, side of fracture, whether smoker, whether fibula also fractured, diameter of nail.
Selection Criteria	Patients at Uppsala University Hospital were invited to participate over about a 2-year period Inclusion: <ul style="list-style-type: none"> Treated for a closed or open primarily shaft tibial fracture with a closed reduction and a reamed and locked intramedullary (intra-marrow) nail. Exclusion: <ul style="list-style-type: none"> Younger than 16 years. Radiographs showed severe comminution or open physes. Fracture was a "Gustilo-type Grade II or III open fracture." If there were multiple fractures or other injuries. If alcoholism, drug abuse, neuropathy, arthritis, or malignant disease were present. Patients receiving steroids, anticoagulant therapy, anti-inflammatory drugs, or disphosphonate therapy.
Methods	After surgery, 28 were allowed to bear full weight, and 4 were allowed only partial weight-bearing. Ultrasound was started three days after surgery. During daily treatment sessions, an alignment fixture was used to set the treatment head module on the exact fracture site, as indicated by a permanent marker. All patients used device 20 min. daily for 75 days. Compliance was monitored by the unit, and it automatically turned off after 20 min. Patients also kept logs to encourage compliance. Compliance data showed the two groups to be very similar in time spent on treatment (23.4 hours active group, 22.3 hours placebo group). Radiographs taken every third week until healing, and at 6 and 12 months.
Success/Failure Criteria	Union: Radiological bridging of three cortices; i.e., disappearance of cortical gap as a result of callus formation. All radiographs assessed blinded and independently by a radiologist and an orthopedic surgeon. Two anteroposterior and two lateral radiographs taken, from somewhat different views (so 4 views in all) with exposure setting and leg positions held constant.
Results	Healing time was not significantly different in active and placebo groups ($p = 0.40$). These results were different from two previous double-blind, randomized, concurrent control studies, in which the same low-intensity ultrasound device significantly reduced healing time in cast-treated tibial fractures and cast-treated distal radial fractures. The assessments by the surgeon and by the radiologist independently show the same pattern of faster healing by the placebo group than by the active group. It looks rather like a trend that might reach significance in a larger sample. In other words, the ultrasound may inhibit healing in this sample. The authors compare their results with Heckman et al.'s similar study. Heckman et al. treated their subjects with a cast, without surgery or internal fixation, and found significantly shorter healing times in the active than the placebo group. Heckman et al.'s

	<p>placebo subjects had much longer healing times than placebo patients in this study, perhaps because the surgical reaming in this study promoted bone growth, and the fixation held the fractures more immobile in this study than the casts in Heckman's study did.</p> <p>The authors do not explain the difference between the results, but note that the main difference between the two studies is the presence of a statically locked, fixed nail in the bone marrow through the fracture site in their subjects. They note that an animal study showed that the presence of wires in the bone marrow in fractures of rat femora did not seem to diminish the healing effect of ultrasound, but point out that wire is far less stabilizing than a statically locked nail.</p>
Potential Sources of Bias	<p>This was a carefully done study with no obvious sources of bias.</p> <p>It was not explained if patients were recruited consecutively, but relevant factors in the two groups seem to have been well balanced. Compliance was well monitored, and was similar in both groups (slightly more treatment was taken on average in the placebo group). Assessment was defined and done blindly and independently by a musculoskeletal radiologist and an orthopedic surgeon.</p>
Other Limitations of the Study	<p>These results are not directly applicable to any form of electrical stimulation.</p>

5. Heckman et al., 1994

Citation	<p>Acceleration of Tibial Fracture Healing by Non-Invasive, Low-Intensity Pulsed Ultrasound</p> <p>J.D. Heckman MD et al.</p> <p>The Journal of Bone and Joint Surgery 76(1): 26-34 (1994)</p>
Intended Use	<p><input checked="" type="checkbox"/> Fresh fractures of the tibial shaft</p>
Stimulation Type	<p><input checked="" type="checkbox"/> Low-intensity Pulsed Ultrasound</p>
Commercial Device Name(s)	<p>Device not named, but one author is from Exogen, Inc. another from Health Products Development, Inc.</p> <p>Signal was composed of a burst width of 200 microseconds containing 1.5 megahertz sine waves, with a repetition rate of one kilohertz and a spatial average-temporal average of 30 milliwatts per sq cm.</p>
Overall Study Design	<p><input checked="" type="checkbox"/> Randomized, concurrent control, double-blind, prospective, multi-institutional (17 sites)</p>
# Patients	<p>67 fractures; 33 treated with ultrasound, 34 with a dummy device</p>
Selection Criteria	<p>Inclusion:</p> <ul style="list-style-type: none"> • Participation offered to all patients meeting criteria seen at these institutions over about a 4-year period. • Skeletally mature. • Non-pregnant. • Had closed or Grade I open tibial shaft fracture that was primarily transverse, short oblique, or short spiral, and could be treated effectively with closed reduction and immobilization in a cast. <p>Exclusion:</p> <ul style="list-style-type: none"> • Over 75 years of age. • Radiographs showed length of fracture line more than twice diameter of fractured shaft. • Radiographs showed the displacement was more than half the width of the

	<p>shaft.</p> <ul style="list-style-type: none"> • Radiographs showed the gap was more than 0.5 The RBI Carpet Market Report for. • Fractures with persistent shortening of more than 1 cm after reduction. • Fractures with a large butterfly fragment – larger than twice the diameter of the shaft. • Pathological fractures. • Comminuted fractures with fragments of more than 1 cm in length. • Patients receiving steroids, anticoagulants, anti-inflammatory medicines, calcium-channel blockers, diphosphonate therapy. • History of thrombophlebitis or vascular insufficiency. • Recent history of alcoholism or nutritional deficiency. <p>Statistical analyses (Fischer exact test, chi sq test, analysis of variance) for the differences in the two groups of various traits that might affect results did not find significant differences.</p>
Methods	<p>The 64 closed fractures (31 active, 33 placebo) were treated with closed reduction and immobilization in an above-the-knee cast. The 3 Grade I open fractures were treated with debridement and the wounds were allowed to heal.</p> <p>A plastic fixture to hold and align the device was inserted into a window in the cast. Treatment was given daily for 20 min., starting 7 days after the fracture. When investigator thought the fracture was sufficiently stable, a short cast or brace was substituted, and later, a splint or brace. The first 42 patients enrolled in the study were instructed not to bear weight during the first eight weeks, but the other 54 were allowed to bear weight according to the investigator's clinical judgment.</p> <p>Compliance was monitored by the unit. Patients also kept logs of treatment to encourage compliance. The units automatically turned off after 20 minutes.</p> <p>Treatment was continued for 20 weeks or until the investigator believed the fracture was sufficiently healed. Anteroposterior and lateral radiographs were taken at 4, 6, 8, 10, 12, 14, 20, 33, and 52 weeks after the fracture. The same exposure setting and leg positioning device were used each time.</p> <p>The end point was a healed fracture.</p>
Success/Failure Criteria	<p>Union, judged clinically (no movement, no pain), and radiographically by 2 parameters (below). All radiographs were assessed in independent, blind reviews by the PI and by the independent radiologist.</p> <p>Parameter (1) 3 of the 4 cortices bridged: None – no cortical bridging; Initial – periosteal reaction at the gap was first noted; Intermediate – increase in density or size of the initial periosteal reaction; Complete – the periosteal reaction completely bridged the gap. On each radiograph at each evaluation 4 cortices (2 on the anteroposterior radiograph, 2 on the lateral) were evaluated for the amount of cortical bridging.</p> <p>Parameter (2) Endosteal healing. Amount was quantified as: None – no change; Initial – fracture line less distinct; Intermediate – marked consolidation of the fracture line; Complete – fracture line replaced by a zone of increased density formed of endosteal callus.</p> <p>Follow-up was 2 years for all 56 fractures, and 4 years for 23 of the fractures.</p>
Results	<p>All fractures healed, but those treated with ultrasound healed on average in 96 days, while those without ultrasound healed on average in 154 days (p = 0.0001). Intermediate points were also reached on average in a shorter time by the actives than by the placebos. This confirms findings of other human and animal studies that ultrasound can accelerate normal healing. The p value was 1-sided because faster healing with</p>

	<p>ultrasound had been hypothesized at the beginning of the study.</p> <p>Only 37 of the subjects (about half) were asked about their smoking histories. The results favored the active group: 11 of the active group were smokers, compared to 9 who were not smokers; while 13 of the placebo were smokers, as against only 5 who were not smokers. Smokers would heal more slowly than non-smokers. However, the smoking histories of the other 30 subjects is not known.</p>
Potential Sources of Bias	<p>Difficulty of combining results from 17 different sites. Consecutive selection of subjects, the large sample, and random assignment to treatment groups guarded against selection bias. Rigorous selection criteria assured treatment groups would be similar in factors other than treatment, and the statistical tests confirmed this. The unusually rigorous quantification of assessments must have helped to lessen the lack of comparability of assessments among 17 different sites. The use of the same two blinded assessors of the radiographs prevented outcome bias due to differences in assessment at the 17 different sites.</p> <p>31% of the subjects (30, 31 fractures) were lost before the end of the study, which leaves room for selection bias. 12 should have been counted as failures, but adding them in would only have strengthened the result as they were mainly in the placebo group.</p> <p>Safety: One patient in the active group reported muscle cramping at one week, which went away without treatment by two weeks. One placebo patient had swelling in the cast at the 6-week follow-up visit that went away by the next visit. No patients had noticeable edema at the site of the window or skin irritation at the site of the treatment head. Patients found the device easy to use.</p>
Other Limitations of the Study	<p>These findings do not apply to electrical stimulation devices or to healing of nonunion fractures.</p>

6. Albert and Wong, 1991

Citation	<p>Electrical Stimulation of Bone Repair S.F. Albert and E. Wong Clinics in Podiatric Medicine and Surgery, Vol. 8, No. 4, 1991</p>
Intended Use	Not specified.
Stimulation Type	<input checked="" type="checkbox"/> Capacitive coupling, Conductive coupling <input checked="" type="checkbox"/> PEMF <input checked="" type="checkbox"/> Constant direct current, Pulsed direct current
Commercial Device Name(s)	Not stated.
Overall Study Design	Survey of natural healing process of bone, conventional treatment of fracture, and electrical stimulation methods.
# Patients	Not applicable.
Selection Criteria	Not applicable.
Methods	Not applicable.
Success/Failure Criteria	Determined in the studies reviewed, not the review itself.
Results	<p>Brighton reports dose levels below 5 muA do not produce enhanced bone growth. 5-20 muA therapeutic doses, 20 muA optimal. Above 20 muA, necrosis and bone destruction.</p> <p>Bassett reports an induced voltage of 1-5 millivolts per cm of bone is needed to cause calcification across the gap in the final phase.</p>
Potential Sources of Bias	Selection of studies to review, and the authors' opinions modifying the interpretation of results.

Other Limitations of the Study	It is not possible to assess the quality of the individual studies.
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7. Brighton, 1991

Citation	Advanced Clinical Applications of Electromagnetic-Field Effects: Bone and Cartilage C.T. Brighton In <i>Electromagnetics in Biology and Medicine</i> , San Francisco Press, Inc., 1991
Intended Use	Not specified.
Stimulation Type	PEMF, DC, capacitive coupling
Commercial Device Name(s)	Not specified.
Overall Study Design	Summary of literature on electrical stimulation to promote bone growth, as of 1991, and recommendations for use (a textbook).
# Patients	Not applicable.
Selection Criteria	Not applicable.
Methods	Not applicable.
Success/Failure Criteria	Not specified.
Results	<p>Results from DC, PEMF, and capacitive coupling seem to be essentially the same: 74% - 79% non-unions healed. Tibia is most successfully healed, followed by femur and humerus.</p> <p>A double-blind study comparing conventional treatment and PEMF (Barker et al., Lancet, 1984) had 9 patients with and 7 with dummy units, 5 tibiae healed in each group. But dummy units were putting out a very low-amplitude signal.</p> <p>Carefully analyzed study by Brighton et al. showed heal rate was the same for DC, capacitive coupling, and bone-graft surgery, when severity of fractures were matched.</p> <p>Sharrard's double-blind, careful study, but delayed unions (16-32 weeks post-fracture) significantly more likely to heal with PEMF than with a dummy unit.</p> <p>Studies reporting treatment of congenital pseudoarthrosis show combined lower heal rate (58%) than for acquired severe fractures. Results better where there is good bone stock, as opposed to where bone tapered to a point. Cancellous bone graft usually needed to provide good bone before electrical stim is given.</p> <p>Failed arthrodesis (fusion surgery) of joints often not healed with electric stim alone, and cancellous bone graft + fixation and elec is probably best route.</p> <p>Studies have shown that DC significantly augments bone grafting during spinal fusion. It is not known if electricity alone can produce an equally high fusion rate.</p> <p>Avascular necrosis of the femoral head (which typically progresses to severe degenerative arthritis, total hip replacement) appears to improve to a limited degree, or at least progress more slowly than expected, in some cases, with elect stimulation. Recommended along with core decompression and bone graft surgery.</p> <p>Many studies have shown the electric stimulation can prevent or reverse osteoporosis in animals.</p> <p>It is not known yet if congenital inequality of limb length can be cured or helped with electric stimulation of the growth plate cartilage in the shorter limb.</p> <p>It is not known yet if degenerative arthritis can be helped by electric stimulation of the articular cartilage.</p>

Conclusions	A limitation of this review is a lack of direct comparisons between capacitive coupling and PEMF or combined fields.
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8. Gudas and Cann, 1991

Citation	Nonunions and Related Disorders C.J. Gudas and J.E. Cann Clinics in Podiatric Medicine and Surgery 8 (2); 321-39 (Apr. 1991)
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture bones of the foot
Stimulation Type	<input checked="" type="checkbox"/> PEMF <input checked="" type="checkbox"/> Constant DC implanted <input checked="" type="checkbox"/> Constant DC percutaneous (semi-invasive)
Commercial Device Name(s)	EBI for DC implanted and PEMF. Percutaneous DC not in production.
Overall Study Design	Review of management of nonunion, delayed union, mal-alignment of bones of the foot
# Patients	Not applicable.
Selection Criteria	Determined by authors of original studies.
Methods	Determined by authors of original studies.
Success/Failure Criteria	Determined by authors of original studies.
Results	All three systems give comparable results, 80-90% success rate with "properly selected patients," with strict immobilization, aiming current at the fracture zone. Healing 3-6 months. Poor results with synovial pseudoarthrosis: the lining of the false joint must be removed for electricity to be effective. Poor results with a gap greater than 1/2 diameter of bone near the fracture. Not to be used with pacemakers. This high success rate compares favorably with autogeneous cancellous bone grafting for nonunions (figures not given). With mal-alignment, synovial pseudoarthrosis, or significant bone defect, surgery is better. Safety: No known deleterious effects.
Potential Sources of Bias	Selection of studies used for the review might introduce bias.
Other Limitations of the Study	Does not apply to capacitive coupling or combined field stimulation.

9. Fitzsimmons et al., 1994

Citation	Combined Magnetic Fields Increased Net Calcium Flux in Bone Cells R.J. Fitzsimmons, J.T. Ryaby, F.P. Magee, and D.J. Baylink Calcified Tissue International, 55: 376 - 380, 1994
Intended Use	Other: To determine the threshold of detection in which cells can respond to an EMF
Stimulation Type	Combined magnetic field
Commercial Device Name(s)	Not available.
Overall Study Design	Controlled non-clinical study
# Patients	None
Selection Criteria	Not available.
Methods	Cells grown from human osteosarcoma cell line TE-85 or SaOS-2 were prepared in a very specific manner. Cultured cells were then exposed to CMF by placing them in the center of a Helmholtz coil apparatus.

Success/Failure Criteria	Not available
Results	<ul style="list-style-type: none"> • Calcium flux increased during CMF exposure, but reverted to control levels following CMF exposure (statistically significant at $p < 0.0001$). • Increase in net calcium uptake was frequency dependent, with maximum uptake occurring at 16.3 Hz. <p>When exposed to CMF at 16.3 Hz in the presence of calcium, TE-85 cell cultures demonstrated increased calcium uptake over increasing lengths of exposure (statistically significant at $p < 0.0001$ at all time points except 10 min).</p>
Potential Sources of Bias	Not available.
Other Limitations of the Study	In vitro study, results may not necessarily extrapolate to humans

10. Brighton et al., 2001

Citation	Signal Transduction in Electrically Stimulated Bone Cells C.T. Brighton, W. Wang, R. Seldes, G. Zhang, and S.R. Pollack The Journal of Bone and Joint Surgery, 83-A (10): 1514-1522, 2001
Intended Use	<input checked="" type="checkbox"/> Other: Effects of electrical stimulation on cell proliferation and signaling.
Stimulation Type	<input checked="" type="checkbox"/> Capacitive coupling <input checked="" type="checkbox"/> PEMF <input checked="" type="checkbox"/> Combined magnetic field <p>Capacitive coupling via a custom-built system. The cell cultures were exposed to a 60-Hz sine wave with an output of 44.81 V peak to peak. This created a calculated field strength of 2.0 V/m and a current density of 300 microamps per cm.</p>
Commercial Device Name(s)	PEMF: Manufactured by EBI. CMF: OL 1000, Orthologic.
Overall Study Design	<input checked="" type="checkbox"/> Controlled cell culture study.
# Patients	No applicable.
Selection Criteria	The authors used MC3T3-E1 osteoblastic cells from mice.
Methods	<p>Before reaching confluence, the osteoblasts were subcultured into 35-mm tissue culture dishes or modified Cooper dishes (for use with capacitive coupling). Cells were grown until two days post-confluence, and the growth medium was changed just prior to beginning each experiment.</p> <p>The subcultured cells were placed into the experimental incubators with either an active or inactive stimulation device. The stimulation devices were left in place for 30 minutes, two hours, six hours, or twenty-four hours. Between 6 and 10 dishes were used for each run of a given set of exposure conditions. Cells were harvested for quantitative DNA preparations 24 hours after the start of the stimulation. Each set of exposure conditions was repeated 2, 3, or 4 times, for as many as 40 culture dishes per condition.</p> <p>To investigate possible signal transduction mechanisms, the investigators repeated the experiments with various chemical inhibitors that can affect calcium levels within the cells. The inhibitors selectively block different forms of calcium release and signaling.</p> <p>Statistical analysis included one-way analysis of variance and the Tukey-Kramer multiple-comparison test for significant differences between groups.</p>
Success/Failure Criteria	There was no specific definition of success and failure, but the quantitative DNA analysis was used as a marker of cell proliferation. Increased cell proliferation was seen as cellular evidence for the effect of electrical stimulation on bone growth in vivo.

	Patterns of cell growth inhibition were used to infer something about the mechanism(s) by which electrical stimulation prompts growth of bone cells.
Results	<p>All three methods of electrical stimulation resulted in significantly increased bone-cell DNA per dish when compared to unstimulated controls ($p < 0.05$).</p> <p><i>There is evidence that capacitive coupling is qualitatively different from the other two stimulation methods.</i></p> <p>The results for the three stimulation methods were similar for up to six hours of stimulation. Beyond six hours of stimulation, the DNA level in the cultures stimulated with PEMF or combined fields leveled off. However, the DNA levels in the cultures stimulated by capacitive coupling continued to increase in a linear fashion. When stimulation continued for 24 hours, the cultures stimulated by capacitive coupling had 123% more DNA than the controls and 63% more than the cultures stimulated by magnetic fields. Both of these results are statistically significant ($p = 0.006$).</p> <p>Additional evidence for a qualitative difference among the stimulation methods comes from the experiments with chemical inhibitors. The effects of both PEMF and combined fields were blocked by inhibitors that affect the ability of the cell to release intracellular calcium stores. The effect of capacitive coupling was not affected by these inhibitors; instead its effect was blocked by inhibitors that disrupt the function of intramembrane calcium channels that bring extracellular calcium into the cell.</p> <p>These different cellular mechanisms are consistent with the time curves seen in this experiment. The intracellular stores of calcium can be exhausted more quickly, leading to a plateau in the cellular response.</p>
Potential Sources of Bias	<p>The authors do not explain how they determined the optimal coil and electrode placement for the cell culture dishes. They may or may not have been scaled to provide the best replication of in vivo stimulation patterns and field strengths.</p> <p>The authors do not state that the technicians conducting the quantitative DNA analysis were blinded as to the stimulation status of the culture dishes. This leads to the possibility that small differences in handling of the cultures and DNA isolation might have influenced results, somewhat. It is unlikely that such differences would be able to fully explain the magnitude of effects seen in this study.</p>
Other Limitations of the Study	<p>This study looked at cells in culture. Different or additional mechanisms may be involved when the stimulation is applied to organized bone tissue in vivo.</p> <p>The capacitive coupling device used is not a commercially distributed device.</p>

11. Simonian and Trumble, 1994

Citation	Scaphoid Nonunion P. Simonian and T. Trumble Journal of the American Academy of Orthopaedic Surgeons, 2(4): 185-91 (Jul. 1994)
Intended Use	<input checked="" type="checkbox"/> Non-Union fracture scaphoid
Overall Study Design	Review of techniques of scaphoid nonunion diagnosis and description and treatment.
Results	The efficacy of electrical stimulation is difficult to evaluate objectively because of the many variables associated with scaphoid fractures.
Potential Sources of Bias	Bias in the selection of papers and the authors' interpretation are possible.
Other Limitations of the Study	As a review, it does not include sufficient information to independently assess the quality of the individual studies.

12. Bassett, 1989

Citation	Fundamental and Practical Aspects of Therapeutic Uses of Pulsed Electromagnetic
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	Fields (PEMFs) C. Andrew, and L. Bassett Critical Reviews in Biomedical Engineering 17(5): 451-529 (1989)
Intended Use	Various
Stimulation Type	PEMF
Results	This long review contains material suggesting what might go wrong with different electric signals. Key assertions: <ul style="list-style-type: none"> • In the section on Biological Principles, it gives lab examples suggesting that only certain kinds of signals and fields produce tissue growth. • In the section on Safety, it emphasizes that we don't know the safety hazards under all circumstances. Certain time-varying electric fields (not PEMFs) may have caused malformation of embryos, but those findings were not replicated in another study. • A PEMF generator, producing pulses substantially different from those in clinical usage, affects male scent-marking behavior and gonad size in Sprague Dawley rats prenatally exposed. • In an FDA-sponsored study, spermatogenesis was mildly reduced in mice continually exposed for 42-280 days after birth.
Potential Sources of Bias	Author' opinions may have affected the selection of studies and the interpretations presented.
Other Limitations of the Study	As a review, it is difficult to independently assess the quality of the individual studies cited.

13. Gershuni et al. 1993

Citation	Symposium: Recent Advances in Electrical Stimulation D. Gershuni et al. Contemporary Orthopedics 26 (6): 609 (1993)
Intended Use	Various
Stimulation Type	DC, PEMF, capacitive coupling
Overall Study Design	Not applicable. Review.
Results	Brighton mentions using DC in a rabbit tibia; some cell necrosis noted when current was increased to 30 microamps, excessive necrosis at 50 microamps. 20 microamps believed optimal in humans.
Other Limitations of the Study	As a review, it is not enough information to allow an independent assessment of the quality of individual studies cited.

14. Cole, 1989

Citation	Diagnostic and Therapeutic Technology Assessment (DATTA) H. Cole JAMA 261(6) (1989)
Overall Study Design	Report of independent panel.
Results	A majority (20/29) felt safety of noninvasive elec stim was established. Less than half (10/28) felt effectiveness was established, because of lack of well-controlled studies.

15. Bodamyali et al., 1998

Citation	Pulsed Electromagnetic Fields Simultaneously Induce Osteogenesis and Upregulate Transcription of Bone Morphogenetic Proteins 2 and 4 in Rat Osteoblasts in Vitro. T. Bodamyali, B. Bhatt, F.J. Hughes, V.R. Winrow, J.M. Kanazler, B. Simon, J. Abbott, D.R. Blake, and C.R. Stevens Biochem Biophys Res Comm 250, 458-461(1998)
Intended Use	<input checked="" type="checkbox"/> Other <i>PEMF stimulation of cultured osteoblasts</i>
Stimulation Type	<input checked="" type="checkbox"/> PEMF Helmholtz coil pair and waveform generator designed to mimic the field used by EBI, Inc.
Commercial Device Name(s)	Not available.
Overall Study Design	<input checked="" type="checkbox"/> Other <i>examined effects on tissue cultured osteoblast cells</i>
# Patients	This study used only primary culture rat osteoblasts.
Selection Criteria	N/A Used Rat Calvarial osteoblasts (RCOB) – this is a primary tissue culture cell line, not an established osteoblast cell line.
Methods	PEMF were generated by use of a Helmholtz coil pair and waveform generator designed to mimic the field used by EBI Inc, Parsippany, NJ. Rat calvarial osteoblast cells were obtained from neonatal (3 day old rats) and isolated by sequential collagenase digestion according pre-established protocol. Earlier passaged cells were used for bone nodule formation studies. Four test groups were used to determine the results of PEMF exposure; one group was a control. The test groups consisted of a) 15 min PEMF; b) 15 min PEMF exposure, followed by 15 min outside of field; c) 30 min PEMF exposure and d) 60 min PEMF exposure. Control and PEMF treated cultures (n=6 for each treatment) was allowed to grow for 3 weeks following either no PEMF (control group) or PEMF according to the above mentioned time frames. Cultures were then fixed and stained and the total number and sizes of nodules in a 10mm ² area was counted. The results were expressed as a mean number and \pm SD. Total RNA from control and PEMF-exposed osteoblasts were isolated, quantified, and reverse transcribed using sense and antisense primers for BMP2 and BMP4. Internal reverse transcription controls were run at the same time as samples for BMP2 and BMP4. Gels were analyzed quantitatively; the intensities of BMP2 and BMP4 specific bands were expressed as a percentage of the intensity of GAPDH specific fluorescence.
Success/Failure Criteria	PEMF treatment will cause induction of bone nodules and will cause increased levels of BMP2 and BMP4 in cultured osteoblast cells, mirroring the results seen when PEMF is used in vivo and in other cultured osteoblast systems. BMPs, which belong to the family of transforming growth factor beta family and which induce ectopic bone formation, may play a role in the transduction of electrical signals to biological signals. PEMF is hypothesized to induce BMP2 and BMP4 activity prior to any osteogenic effect.
Results	PEMF induces more and larger bone-like nodules in rat calvarial osteoblast cultures (RCOB). The increases in numbers and sizes were significant. The effect was maximal by 6 hours. PEMF exposure resulted in increases in both BMP2 and BMP4 mRNA levels in a time dependent manner, in cultured osteoblasts. BMP4 reached a maximal level of approximately four fold increase over control, unexposed levels by 30 min. BMP4 levels then decreased slightly by 60 min. BMP2 reached a maximal level after approximately

	<p>60 min; its relative levels of increase were less than that seen for BMP4, due to its initially higher levels. Continuous exposure resulted in greater increases.</p> <p>In other studies, exposure of cultured osteoblasts to recombinant BMP2 results in the auto-induction of more BMP2 mRNA transcription and translation. Increases in BMP2 was also concomitant with increases in BMP3 and BMP4 mRNA.</p> <p>The authors hypothesize that PEMF may act like BMP2 in inducing BMP4.</p>
Potential Sources of Bias / Other Limitations of the Study	<p>While the authors hypothesize that PEMF might act like BMP2 in causing the increase of BMP4 mRNA, it is unclear that there have been any studies done to indicate that the effect is direct. Furthermore, BMP2 is also induced in this system so PEMF may act via BMP2, instead of directly on BMP4, as hypothesized. Also, continued PEMF treatment (up to 60 min) resulted in a decrease of BMP4 while still causing the increase of BMP2. It would be difficult to say that either BMP2 or PEMF, one of which is increasing and the other of which is continuously applied, actually cause the increase of BMP4.</p> <p>The authors suggest that the whole picture of osteogenesis in response to PEMF may involve other BMPs as well as other local factors in vivo. This is the perpetual problem with the use of cell culture systems, despite their ease of use.</p> <p>Researchers were not blinded to which cultures received which treatment.</p>

16. Cook et al., 2001

Citation	<p>Acceleration of Spine Fusions with a Low Intensity Pulsed Ultrasound Device S.D. Cook, L.S. Salkeld, J.P. Ryaby, and T.S. Whitecloud Spine 1: 246-54 (Jul-Aug. 2001)</p>
Intended Use	<input checked="" type="checkbox"/> Lumbar spinal fusion <i>in dog model</i>
Stimulation Type	<input checked="" type="checkbox"/> Other <i>low intensity pulsed ultrasound device</i>
Commercial Device Name(s)	A "standard" device which delivered a low level acoustic pressure wave signal with an intensity of 30mW/cm sq at the skin.
Overall Study Design	<input checked="" type="checkbox"/> Animal as own control, prospective
# Patients	8 adult mongrel male dogs
Selection Criteria	Animal model – used all 8 mongrel male dogs. Authors did not use any female dogs.
Methods	<p>The authors used 8 mongrel male dogs. Each dog was fused bilaterally with autogenous bone graft harvested from both iliac crests at L2-L3 and L5-L6 levels.</p> <p>Animals were treated with an active ultrasound unit placed over one fusion site while a placebo unit was placed over the other fusion site. Ultrasound treatments consisted of one 20 minute treatment per day until sacrifice at six and 12 weeks. Three animals were sacrificed at 6 weeks and 5 animals at 12 weeks.</p> <p>CT and MRI studies were done to determine the presence and quality of spinal fusion. A 0-5 grading scale was used; 0 meant no evidence of fusion and 5 meant complete fusion.</p> <p>After CT and MRI studies, each fusion mass underwent torsional mechanical testing.</p> <p>Each fusion mass was examined for histological evidence of bone formation, graft incorporation, and degree of remodeling.</p>
Success/Failure Criteria	<p>Radiographic evidence of spinal fusion.</p> <p>Histologic evidence of spinal fusion.</p> <p>Torsional evidence of spinal fusion.</p> <p>Criteria for histologic or radiographic evaluation not specified in a quantitative manner.</p>
Results	At 6 weeks post-operation, new bone formation was noted. At sites which received ultrasound treatment, the fusion mass was contiguous with the facets. Fusion masses were not contiguous at control sites. At 12 weeks, nearly complete fusion was found at

	<p>ultrasound treated sites.</p> <p>Mean radiographic scores for ultrasound treated sites were higher than those for placebo controlled sites. Mean stiffness was also higher for ultrasound treated sites vs. placebo controlled sites at 12 weeks. Histologically, graft incorporation and new bone maturity was advanced in ultrasound treated sites vs. placebo controlled sites.</p> <p>The authors conclude that low intensity pulsed ultrasound therapy stimulated early new bone formation and autologous graft incorporation, resulting in an earlier spinal fusion.</p>
Potential Sources of Bias	<p>No method of evaluation was blinded.</p> <p>Unclear what criteria was used for radiographic evaluation.</p> <p>It was unclear whether upper or lower sites were consistently either ultrasound treated or placebo treated; or whether ultrasound treatment was randomly placed per animal.</p>
Other Limitations of the Study	<p>There is no validation of rating scale.</p> <p>Radiographic scores overlapped significantly between control and experimental group values. It is difficult to state the significance of the authors' findings.</p> <p>This study does not directly address noninvasive electrical stimulation.</p>

17. Glazer et al., 1997

Citation	<p>Use of Electromagnetic Fields in a Spinal Fusion: A Rabbit Model. P.A. Glazer, M.R. Heilmann, J.C. Lotz, and D.S. Bradford ISSLS June 2-6, 1997.</p>
Intended Use	<input checked="" type="checkbox"/> Lumbar spinal fusion <i>in rabbit model</i>
Stimulation Type	<input checked="" type="checkbox"/> PEMF
Commercial Device Name(s)	Unspecified.
Overall Study Design	<input checked="" type="checkbox"/> Randomized, concurrent control, prospective
# Patients	20 New Zealand white rabbits; 10 to placebo control group, 10 to PEMF group.
Selection Criteria	20 New Zealand white rabbits, unknown sex of rabbit, unknown ages of rabbits.
Methods	<p>10 New Zealand white rabbits were randomly assigned to undergo spinal fusions using either 1) autologous bone grafts with electromagnetic fields or 2) autologous bone grafts without electromagnetic fields.</p> <p>A plastic constraint cage was used to focus PEMF over the rabbit's lumbar spine for 4 hours per day. The control group was placed in PEMF cages, but the units were not activated.</p> <p>Animals were sacrificed at 6 weeks. Vertebral segments were tested for flexion in a hydraulic materials testing machine.</p> <p>Histologic examination was performed; it is unknown whether this evaluation was blinded.</p> <p>Vertebral masses were examined radiographically by blinded evaluator.</p>
Success/Failure Criteria	<p>Radiographic evidence of fusion; unspecified criteria.</p> <p>Histologic evidence of fusion; unspecified criteria.</p> <p>Torsional and load bearing measurement.</p>
Results	<p>Rate of pseudoarthrosis decreased from 40% to 20% with PEMF. Biomechanical analysis showed that PEMF resulted in statistically Significant increases in stiffness (35%), area under the load displacement curve (37%), and load to failure of the fusion mass (42%). Qualitative histologic assessment showed increased bone formation in those fusions exposed to PEMF.</p>

	The authors use the results of this study to further study biologic enhancement of spinal arthrodesis by using PEMF.
Potential Sources of Bias	It is unclear whether animal handlers were blinded to control and experimental groups. It is also unclear whether histologic examination was done blinded. There are no p-values mentioned to signify statistical significance. The criteria for histologic and radiographic determination of bone growth and/or fusion are not specified.
Other Limitations of the Study	Number of animals in this study is small; it is difficult to tell whether there was enough of a difference between the experimental and control groups since there were no confidence interval or ranges mentioned.

18. Sharrard, 1984

Citation	Treatment of Congenital and Infantile Pseudarthrosis of the Tibia with Pulsing Electromagnetic Fields W.J. Sharrard Orthopedic Clinics of North America, 15(1) 143 – 162 (1984)
Intended Use	Non-Union fracture long bones
Stimulation Type	PEMF
Commercial Device Name(s)	None named
Overall Study Design	Case series, uncontrolled, retrospective (meta-analysis of case series studies carried out by Bassett et al. and Sutcliffe et al.; unclear whether as prospective studies in the originals)
# Patients	34 and 49 in two studies
Selection Criteria	<ul style="list-style-type: none"> • Inclusion - congenital pseudarthrosis of the tibia
Methods	<ul style="list-style-type: none"> • Immobilization. • Application of coils according to measurement of the cast and radiographic location of the nonunion. • +/- prior surgical treatment for alignment, grafting.
Success/Failure Criteria	<ul style="list-style-type: none"> • Success defined as radiographic and clinical union. • Additional success criteria in Bassett: +/- need for further bracing after union to allow complete establishment of medullary canal. • Failure defined as nonunion.
Results	<p>Bassett: 70.6% success disregarding re-fracture.</p> <ul style="list-style-type: none"> • 17 of 34 “full healing” without re-fracture over a period of 1 – 7.5 years. • 7 of 34 “union with function,” 4 with later re-fracture. <p>Sutcliffe: 71% success disregarding re-fracture.</p> <ul style="list-style-type: none"> • 14 of 38 with EMF alone. • 7 of 38 with EMF followed by bone graft and further EMF treatment. • 6 of 38 surgery followed by EMF. <p>No safety information noted.</p>
Potential Sources of Bias	<ul style="list-style-type: none"> • Not-randomized, controlled trials. • Widely varying ages, degree of disability, site of nonunion, number of previous surgeries, +/- internal fixation. • Length of PEMF treatment was not standardized and varied widely before a case was classified as a failure or treated with adjunct treatments. • No standardization technique noted for reading of radiographs, and indeed comparison is being made across different studies.

Other Limitations of the Study	This paper is a retrospective analysis of results obtained by other researchers. Its intended purpose is to generalize a set of recommendations, based on the author's experience and the data from the two studies analyzed, pertaining to treatment of the type of lesions studied. It is not specifically looking at the effectiveness of PEMF treatment.
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19. Turner et al., 1992

Citation	Patient Outcomes After Lumbar Spinal Fusions J.A. Turner, M. Ersek, L. Herron, J. Haselkorn, D. Kent, M.A. Ciol, and R. Deyo JAMA, 268(7): 907-11 (Aug. 19, 1992)
Intended Use	<input checked="" type="checkbox"/> Other <i>Review of Lumbar Spinal Fusions</i>
Stimulation Type	<input checked="" type="checkbox"/> Other <i>No electrical stimulation; review of surgical procedure</i>
Commercial Device Name(s)	Review of lumbar spinal fusions without other interventions
Overall Study Design	<input checked="" type="checkbox"/> Other <i>Literature review</i>
# Patients	47 articles were reviewed
Selection Criteria	Review of literature between 1966 and 1991 reporting spinal fusion outcomes. Search done via MEDLINE for English-language journals only, bibliography review, and expert consultation. Articles were selected only if they reported at least 1 year of follow-up data to be able to allow for the classification of clinical outcomes for at least 30 patients. Excluded were foreign language journal articles, and search terms: child, cervical vertebrae, spinal tuberculosis, spinal neoplasm, scoliosis, and case reports.
Methods	MEDLINE was searched from 1966 through April 1991 for English-language journal articles including spinal fusion and human and excluding child, cervical vertebrae, spinal tuberculosis, spinal neoplasm, scoliosis, and case report. Articles were also identified from bibliographies of articles and book chapters, and by suggestions from six spine surgeons from 3 countries. Any information identifying authors, institutions, journal, year of publication was removed before review. Two clinicians independently reviewed each article according to the following criteria: 1) ≥ 1 yr of follow-up data for at least 30 adults who underwent lumbar spinal fusion for specified indications other than fracture, infectious disease, ankylosing spondylitis, neoplasm, congenital or adolescent idiopathic scoliosis, kyphosis, or achondroplasia; 2) outcome data that are classifiable into pre-determined definitions of either excellent, good, fair, and poor or satisfactory and unsatisfactory. Differences between groups were subject to ANOVA and Student's t tests. Regression analyses were performed to look at associations between variables. A meta-analysis could not be done because of the lack of randomized trials and incomplete reporting of data and statistical analyses.
Success/Failure Criteria	The authors' goals were to address the uncertainties about benefits, risks, and predictors of success of lumbar spinal fusions for specific disorders. They sought to address the following 5 questions: 1) what diagnoses and other patient characteristics predict outcomes? 2) what are the rates of satisfactory clinical outcomes? 3) which low back disorders are better treated by laminectomy and fusion than by laminectomy alone? 4) what relationships exist among fusion techniques and technical and clinical outcomes? 5) what are the types and rates of complications?
Results	The authors reviewed 47 articles. Of these 47 articles, there were no randomized trials. For many back disorders, there was no advantage for fusion over surgery without fusion. Patients undergoing surgery with fusion often had complications. Approximately 68% of patients had a satisfactory outcome after fusion; however, the range was large (16-

	<p>95%). Prospective vs. retrospective studies had worse outcomes. Clinical outcomes were worse in studies with a greater number of previously operated patients. The most common complications were pseudoarthrosis and chronic pain at graft donor site.</p> <p>Of the 47 articles, only four were prospective, 18 were retrospective, and 25 could not be classified. Prospective studies reported fewer satisfactory outcomes.</p> <p>In only 7 studies were outcomes independently assessed; others were assessed by or dependent upon the operating surgeon.</p> <p>Most articles gave little details regarding patient characteristics. Most articles did not rigorously define their patient selection criteria. Satisfactory outcomes were less frequent in patients with any prior back surgeries. Most researchers did not follow up all patients, and follow-up periods were relatively short for many patients.</p> <p>Only 4 studies compared surgery with and without fusion; all involved disk herniation. Furthermore, fusion techniques varied widely. Satisfactory outcomes were somewhat associated with single level fusions. Satisfactory outcome were associated with solid arthrodesis. Only one study found fusion to have better outcomes than laminectomy.</p> <p>The most common complications included instrumentation failure and bone graft donor site chronic pain.</p> <p>The authors' analysis did not support the superiority of any fusion procedure over others for clinical outcomes. Surgical methods may be less important than patient selection in determining clinical outcome.</p>
Potential Sources of Bias Other Limitations of the Study	<p>Compiling results from this collection of papers is of questionable value. No articles were randomized controlled trials. The authors concede that non-randomized comparisons may be misleading because groups may differ in ways that affect outcome.</p> <p>The authors note the wide range in satisfactory outcomes. Patients with poorer outcomes may be less likely to return for follow-up.</p> <p>The authors note that most studies had the operating surgeon also doing the outcome ratings.</p>
Other Limitations of the Study	<p>This review does not address the contribution of electrical stimulation to healing of lumbar fusions.</p>

20. Zhuang et al., 1997

Citation	<p>Electrical Stimulation Induces the Level of TGF-β1 mRNA in Osteoblastic Cells by a Mechanism Involving Calcium/Calmodulin Pathway.</p> <p>H. Zhuang, W. Wang., R.M. Seldes, A.D. Tahernia, H. Fan, and C.T. Brighton <i>Bioch Biophy Res Comm</i> 237: 225-229 (1997)</p>
Intended Use	<p><input checked="" type="checkbox"/> Other <i>Electrical Stimulation Mechanisms of action</i></p>
Stimulation Type	<p><input checked="" type="checkbox"/> Capacitive coupling</p>
Commercial Device Name(s)	<p>Not available.</p>
Overall Study Design	<p><input checked="" type="checkbox"/> Other <i>experiments on osteoblast cell line</i></p>
# Patients	<p>Used cultured cells, no patients.</p>
Selection Criteria	<p>Used cultured osteoblast cells, MC3T3-E1. These are clonally derived. As with any cultured cell line, it is unclear how faithfully these cells reflect osteoblasts in vivo.</p>
Methods	<p>Authors used a clonal osteoblastic cell line, MC3T3-E1. These cells were grown to confluency in tissue culture dishes and then subjected to capacitively coupled 60kHz sine wave signal for 30 min to 24 hours. 24 hours after the beginning of stimulation, both the media and cells were harvested.</p>

	<p>Inhibitors of capacitively coupled electric field induced osteoblast proliferation, W7 and verapamil, were used in this experiment. Polyclonal TGF-β1 antibodies were also used to detect the active form of TGF-β1 released from cells into the media.</p> <p>Cells were harvested and used to check for proliferation, mRNA and DNA synthesis.</p> <p>DNA content was quantified by measuring its fluorescence, via a spectrophotometer, at 458 nm. Total DNA was used to standardize the results while ^3H-thymidine uptake was used to determine proliferation.</p> <p>Total RNA was isolated from the osteoblastic tissue culture cells. One microgram of RNA was reverse transcribed to complementary DNA (cDNA) and assessed for TGF-β1 mRNA expression via a quantitative PCR amplification method, using two internal controls.</p>
Success/Failure Criteria	<p>Authors wished to determine if there is any causal relationship between electrical stimulation and TGF-β1 activity.</p>
Results	<p>The authors establish that, along with cell proliferation in response to a capacitively coupled electric field stimulation, osteoblast cells also induce the transcription of TGF-β1 mRNA. However, no causal relationship between TGF-β1 activity and osteoblast cell proliferation was established.</p> <p>The authors found that a capacitively coupled electric field increases proliferation of MC3T3-E1 cells. There was an 18.7% increase in ^3H-thymidine uptake in the 24 hour electrically stimulated group vs. a non-electrically stimulated group. ($p < 0.05$). This looked similar to MC3T3-E1 cells that were treated with anti-TGF-β1 antibodies, which showed proliferation to the same extent without electrical stimulation.</p> <p>The authors also found that a capacitively coupled electric field induces TGF-β1 mRNA and activity. There was a 38.8% increase of TGF-β1 activity in the 24 hour electrically stimulated group. The increase in activity was due to an increase in TGF-β1 mRNA synthesis, as determined by quantitative PCR. TGF-β1 mRNA was induced by 2 hours of electrical stimulation.</p> <p>Verapamil and W7 blocked capacitively coupled electric field-induced proliferation of osteoblast cells and also blocked the increase of TGF-β1 mRNA. The authors take this to mean that the increased proliferation and increased TGF-β1 might share the same mechanism. The authors hypothesize a role for cytosolic calcium-activated calmodulin axis since both cell proliferation and the increase in TGF-β1 mRNA synthesis upon capacitively coupled electrical stimulation is blocked by verapamil and W7.</p> <p>Capacitively coupled-induced proliferation of MC3T3-E1 cells does not depend on increased TGF-β1 activity. Anti-TGF-β1 antibodies failed to block electrical stimulation-induced cell proliferation but does block TGF-β1 activity. Therefore, the authors conclude that the increased proliferation of MC3T3-E1 cells was not due to the increased activity of TGF-β1.</p> <p>The authors do not know what role TGF-β1 plays in the proliferative response of bone cells to capacitively coupled electrical stimulation.</p>
Potential Sources of Bias / Other Limitation of the Study	<p>The authors showed two different results for the induction of TGF-β1 mRNA with capacitively coupled electrical stimulation. In figure 2B, they showed de novo induction of TGF-β1 mRNA after 2 hours of capacitively coupled electrical stimulation. In figure 3A and 3B, it looks like TGF-β1 mRNA was already present even at $t=0$ min. While this gel did show no increase with verapamil and W7 added, the authors did not give an explanation for induction of TGF-β1 mRNA de novo at the transcriptional level in one instance and not the other.</p> <p>Researchers were not blinded to which cultures were exposed to capacitively coupled electrical stimulation.</p>

	While there is no direct contribution of increased TGF- β 1 mRNA (and activity) to increased proliferation of bone cells, its role in vivo cannot be ruled out. TGF- β 1 has many roles and also induces the transcription of several other growth factors, it is possible that the effects of TGF- β 1 may be observed further downstream and with longer experimental time frames.
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21. Yonemori et al., 1996

Citation	Early Effects of Electrical Stimulation on Osteogenesis K. Yonemori, S. Matsunaga, Y. Ishidou, S. Maeda, and H. Yoshida Bone, 19(2): 173 – 180 (1996)
Intended Use	Other: Humeri of young male New Zealand white rabbits
Stimulation Type	<ul style="list-style-type: none"> • Direct current stimulation by Kirshner wire insertion • PEMF • PEMF plus Kirshner wire • Kirshner wire • Intramedullary drilling
Commercial Device Name(s)	PEMF: generator manufactured by Institute of Physical and Chemical Research (Wako, Saitama, Japan)
Overall Study Design	Nonrandomized concurrent control, prospective
# Patients	105 rabbits 51 allocated to each study group
Selection Criteria	Weight 2 – 3 kg
Methods	<ul style="list-style-type: none"> • DC group: 1 mm hole drilled in anatomical neck of humerus, 1 mm Kirshner wire (acting as cathode) then inserted into marrow, sutured in place; stimulation applied continuously during 14 days • PEMF group: rabbit immobilized with both humeri at equal distance from the electromagnetic coil which generated a 2 gauss electromagnetic field and was applied for 14 days, during 12 hours per day • PEMF + Kirshner wire: Same as above, with the addition of a 1 mm Kirshner wire, inserted into the humerus at the greater tuberosity • Kirshner wire group: Kirshner wire inserted into marrow, left in place during 14 days without further treatment • Intramedullary drilling: Bone marrow of the humerus drilled by a Kirshner wire 1 mm diameter, which was removed after drilling.
Success/Failure Criteria	Not available.
Results	Area of new bone growth was compared at various sites within each sample. <ul style="list-style-type: none"> • K wire with direct current stimulation: osteogenesis most active at the tip of the inserted K wire. • K wire with PEMF stimulation: uniform osteogenesis around the K wire, therefore not at the same site as DC with wire. • Intramedullary drilling and K wire alone showed osteogenesis, but much less than previous two. • PEMF alone showed little osteogenesis. • Alkaline phosphatase activity, an indicator of osteoblasts and osteogenesis, increased in the DC and PEMF + K wire groups at 7 and 14 days following surgery.
Other Limitations of the Study	Animal study, therefore results may not be applicable to humans.

22. Jervey and Friedman, 1990

Citation	Electrical Stimulation: Current Concepts and Indications C. Jervey and R.J. Friedman Contemporary Orthopaedics, 20(1): 61 – 65, 1990
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Intended Use	<i>Review Article</i>
Stimulation Type	<input checked="" type="checkbox"/> Capacitive coupling <input checked="" type="checkbox"/> PEMF <input checked="" type="checkbox"/> Implanted stimulation device
Commercial Device Name(s)	Not available.
Overall Study Design	<input checked="" type="checkbox"/> Other Review
# Patients	Not available.
Selection Criteria	Not available.
Methods	Not available.
Success/Failure Criteria	Not available.
Results	<ul style="list-style-type: none"> • <i>Historical Background</i> <ul style="list-style-type: none"> ○ Piezoelectric effect of bone was first demonstrated in the 1950s. ○ When bone is placed under stress, a negative charge occurs at the area under compression and a positive charge occurs at the area under tension. ○ The electrical potential generated by mechanical stress may result in biological activity leading to bone remodeling. ○ Studies on wet bone have demonstrated a streaming potential that is thought to be responsible for the stress-generated potentials under physiologic conditions. ○ Bioelectric potentials have been observed <i>in vivo</i> without applying stress. ○ The discovery of endogenous potentials led to experiments to determine if exogenous sources could stimulate bone growth and healing. • <i>Types of Devices</i> <ul style="list-style-type: none"> ○ Clinical trials in the 1970s led to the U.S. FDA marketing release of three types of devices: <ul style="list-style-type: none"> ▪ Semi-invasive constant direct current with percutaneous cathodes. ▪ Invasive constant direct current with totally implanted electrodes. ▪ Noninvasive inductive coupling system. ○ Semi-invasive device: <ul style="list-style-type: none"> ▪ Developed by Brighton et al. ▪ Requires percutaneous placement of electrodes with the cathode placed directly in the non-union site and the anode placed under the surface of the skin. ▪ Power pack is incorporated into the cast. ▪ Constant current is applied. ▪ Too little current results in no response; whereas, excess current causes necrosis. ▪ Optimum current is from 5-20 μamp.

- Disadvantage of the system is for non-unions of the lower extremity, the patient must be non-weight-bearing or the cathode can break or dislodge.
- Invasive constant direct current system:
 - Developed by Dwyer and Wickham.
 - Device must be surgically implanted.
 - Device is monitored to ensure that a constant direct current of 20 μ amp is being delivered.
 - Requires the least patient cooperation of the three devices.
 - Weight-bearing is allowed when appropriate.
 - Main disadvantage is that two operations are required; one to implant the device and one to remove it.
- Non-invasive inductive coupling system:
 - Developed by Bassett et al.
 - Used externally mounted coils of wire to produce pulsing electromagnetic fields.
 - Induce varying small electric currents in the tissues that are similar to currents generated by bone in response to mechanical deformation.
 - Protocol calls for strict non-weight-bearing during early phases of treatment for fractures of the lower extremities.
- Capacitor plate device:
 - Recently released noninvasive method of electrical stimulation.
 - Electric field is produced by a charge; the field penetrates the tissues and the resulting voltage gradient induces current flow.
- Differences between devices:
 - Capacitor plates produce primarily electric fields, which result in relatively small voltage gradients over large volumes of tissue; no means of direct monitoring of fields and current densities produced inside tissues.
 - PEMF produces magnetic fields also result in small voltage gradients but over relatively small volumes of tissue; no means of direct monitoring of fields and current densities produced inside tissues.
 - Direct current electrodes produce high local voltage gradients; can be measured accurately.
- *Results*
 - Reported success rates range from 70-95% while the reported success rate of bone grafting is 88%.
 - Difficult to compare the results of the various methods due to the following:
 - Differences in the definitions of non-union and delayed union.
 - Type and anatomic site of fracture.
 - Adequacy of reduction of the fracture.

	<ul style="list-style-type: none"> ▪ Age, sex, and nutritional status of the patient. ▪ No double-blind, controlled, randomized clinical studies have been performed to date; issues with patient recruitment. <ul style="list-style-type: none"> • <i>Advantages and Disadvantages</i> <ul style="list-style-type: none"> ○ PEMF requires no surgery; active infection is not a contraindication; protocol requires initial non-weight-bearing; patient must be cooperative; and the equipment is not portable. ○ Capacitor plate method requires no surgery; active infection is not a contraindication; protocol allows for full weight-bearing; and the equipment is portable. ○ Semi-invasive method requires percutaneous placement of the electrodes; system is portable; patient must be cooperative; non-weight-bearing in lower extremities is required; and active infection is a contraindication. ○ Totally-invasive system requires two surgeries; is portable; does not require patient cooperation; weight-bearing in the lower extremities is encouraged; and active infection is not a contraindication. • With all electrical stimulators, the presence of a gap longer than one-half the diameter of the bone at the level of the non-union is a contraindication as is the presence of a synovial pseudoarthrosis unless the synovial lining is removed first. • <i>Recommendations</i> <ul style="list-style-type: none"> ○ Electrical stimulation is probably best used only in select cases of non-unions. ○ It offers a reasonable means of treatment for non-unions that have failed to respond to previous bone grafting over an extended time. ○ It offers an advantage over bone grafting in patients for whom surgery is contraindicated.
Potential Sources of Bias	This review paper focused primarily on the basic science behind the different types of electrical stimulation devices; the clinical data in the literature was not really discussed.
Other Limitations of the Study	None.

23. Ryaby, 1998

Citation	Clinical Effects of Electromagnetic and Electric Fields on Fracture Healing J.T. Ryaby Clin Orthop Relat Res, 355 Suppl: S205 - 15, 1998
Intended Use	<i>Review</i>
Stimulation Type	<input checked="" type="checkbox"/> Capacitive coupling <input checked="" type="checkbox"/> PEMF <input checked="" type="checkbox"/> Combined magnetic field <input checked="" type="checkbox"/> Implanted stimulation device
Commercial Device Name(s)	Not available.
Overall Study Design	<input checked="" type="checkbox"/> Other: <u>Review</u>

# Patients	Not available.
Selection Criteria	Not available.
Methods	Not available.
Success/Failure Criteria	Not available.
Results	<ul style="list-style-type: none"> • <i>Basic Research</i> <ul style="list-style-type: none"> ○ Physical mechanism of electric and magnetic field interaction and the biologic mechanisms of transduction remain to be elucidated. ○ Cellular studies have addressed the effects of electromagnetic fields on both signal transduction pathways and growth factors. ○ <i>In vivo</i> studies have shown the effects of electromagnetic field effects on bone formation and resorption . • <i>Clinical Studies</i> <ul style="list-style-type: none"> ○ Three general types of bone growth stimulation are available: <ul style="list-style-type: none"> ▪ Direct current stimulation using percutaneous or implanted electrodes (invasive). ▪ Electromagnetic stimulation by inductive coupling using time varying magnetic fields (noninvasive). ▪ Capacitive coupling stimulation using electrodes placed on the skin (noninvasive). ○ Majority of published studies on electric and electromagnetic field stimulation are focused on non-union treatment. ○ First system to be developed was the direct current stimulation with electrodes inserted at the fracture site: <ul style="list-style-type: none"> ▪ Constant current of approx. 20 μA and 1.0V ▪ First report indicated an overall success rate of 62.5% (Brighton et al. 1977) ▪ Follow-up study reported a success rate of 78% (Brighton et al. 1981) ▪ Patterson et al. (1984) reported a success rate of 86% ○ The inductive coupling method used pulsed electromagnetic fields in which external coils produce pulse bursts with a repetition rate of 15 Hz producing a current of 20 mV and approximately 10 μA/cm² in the tissue. <ul style="list-style-type: none"> ▪ Bassett et al. (1981) achieved a success rate of 87% ▪ Heckman et al. (1981) demonstrated a success rate of 64% with a mean time to injury of 2.5 yr. ○ Noninvasive capacitive coupling uses disk electrodes coupled to the skin. <ul style="list-style-type: none"> ▪ Developed by Brighton and Pollack (1985). ▪ Device produces 60 kHz symmetric sine wave which produces a 5V peak to peak current with approx. 7 μA root mean square at the skin level. ▪ Used for 24 hr/day. ▪ First non-union series reported a success rate of 77% (Brighton and Pollack 1985).

- Newest technique is combined magnetic fields.
 - Employs an external pair of coils that produce two parallel low energy magnetic fields.
 - Alternative magnetic field is a sinusoidal wave of 76.6 Hz with an amplitude of 400 mG peak to peak and the static field set at 200 mG.
 - Zoltan et al. (1998) reported a 61% union rate.
- *Double- Blind Studies*
 - Several trials have demonstrated the effectiveness of varied electric and electromagnetic stimulation devices
- *Other Studies*
 - Brighton et al. (1995) was the first to show that the rate of healing for tibial non-union with no risk factors is comparable with direct current, capacitively coupled electric fields, and bone graft; re-treatment with the same method showed statistically significant decreases in healing.
 - Adams et al. (1992) used PEMF on scaphoid non-unions and revised their original success rate from 80% to 69%; this study recommended the use of long arm casts for higher efficiency rates and decreased efficacy for proximal pole fractures.
 - Eyres et al. (1996) addressed the effects of electromagnetic fields on limb lengthening; no effect was observed over 12 months, but there was less osteopenia in the cortical bone distal to the distraction site, which indirectly supports animal studies that have shown the effectiveness of electromagnetic fields on osteopenia.
- *Unanswered Questions*
 - When is electrical stimulation indicated?
 - What fracture indications are indicated?
 - What are the contraindications?
 - What are the relative efficacy rates and how do these healing rates compare with those of other treatment methods?
 - Do hypertrophic non-unions respond better than atrophic?
 - Does combining bone grafting and electrical stimulation show higher efficacy rates than either alone?
 - At what time point after injury should electric stimulation be applied?
- *Comparison to Bone Graft*
 - Studies on the outcome of standard surgical treatments for non-unions have been generally retrospective and poorly controlled.
 - Success rates have ranged from 62% to >90%.
- *Future Directions*
 - Determination of the relative efficacy of bone graft compared with electrical stimulation.
 - Need better information on the use of electric stimulation with bone grafts.
 - Double-blind clinical trials on electric stimulation's effect on fresh fracture healing in severe fractures.
 - Outcome studies comparing surgical intervention with electric

	<p>stimulation.</p> <ul style="list-style-type: none"> ○ Need for a patient registry database with strict fracture classification. ○ Further research is needed to optimize clinical indications for these technologies and for their potential limitations.
Other Limitations of the Study	As a review, it does not provide enough details to allow independent assessment of the individual studies cited.

24. Fitzsimmons et al., 1995

Citation	<p>Combined Magnetic Fields Increase Insulin-like Growth Factor-II in TE-85 Human Osteosarcoma Bone Cell Cultures</p> <p>R. Fitzsimmons, J. Ryaby, S. Mohan, F.P. Magee, and D.J. Baylink</p> <p>Endocrinology 136(7): 3100-106 (1995)</p>
Intended Use	Not available.
Stimulation Type	Custom designed combined magnetic fields system with a low amplitude DC field (20 μ T) and a low frequency AC field (15.3 Hz, at 40 μ T amplitude).
Commercial Device Name(s)	Not available.
Overall Study Design	Lab study, with human sarcoma (TE-85) bone cells, and concurrent control cells.
Results	<p>H-thymidine incorporation (indicating DNA increase, hence increased cell division) increased consistently after 10-min stimulation with CMF. A longer exposure of 30 min gave variable results, sometimes as strong as with 10 min, sometimes no effect.</p> <p>The greater the cell density, the less the H-thymidine incorporation (i.e. the less the bone cell division).</p> <p>The greater the H-thymidine incorporation, the greater the IGF-II in the culture medium, and the greater the mitogenic activity (i.e. cell division) in the culture.</p> <p>IGF-I and IGF-II, added to cell cultures, stimulated H-thymidine incorporation. The maximum dose to stimulate thymidine incorporation was comparable to the maximum amount of IGF in cells stimulated with CMF.</p> <p>An inhibitor of IGF-II stimulation of mitogenic action was shown to block thymidine incorporation. Thus the bone cell division appears to be dependent on IGF-II, and not directly on the electromagnetic fields.</p> <p>So: Low-energy electromagnetic fields are known to be produced endogenously in injured bone in response to stress. Fields in the lower part of the same range are produced by the CMF system used here. CMF for 10 min, not for 30 min, consistently stimulates bone cells to produce IGF-II which promotes bone cell division. Reason for the time-dependent response not known.</p> <p>It's believed that cytokines, as well as growth factors, may control bone metabolism. Not tested here.</p> <p>CMF exposure is known to increase Ca uptake in TE-85 cell cultures. Elevated extracellular Ca is known to increase the concentration of IGF-II in culture medium from bone cells.</p>
Other Limitations of the Study	The same mechanisms may not apply to the more complicated in vivo environment.

25. Fitzsimmons et al., 1994

Citation	Combined Magnetic Fields Increased Net Calcium Flux in Bone Cells R.J. Fitzsimmons, and J.T. Ryaby, et al. Calcif. Tissue Int. 55(5): 376-80 (Nov. 1994)
Stimulation Type	Combined magnetic fields, tuned to increase resonance of Ca, then frequency varied. 20 μ tesla amplitude DC field, and 40 μ tesla amplitude for AC field.
Overall Study Design	Human bone cell cultures exposed to varying fields for varying time periods, control cultures
Results	Calcium uptake was increased during CMF exposure, but fell to control levels afterwards. The level continued to rise with longer exposure to CMF, up to 40 minutes. AC field frequency of about 16.3 Hz promoted the most uptake, about 17.5 Hz next, about 15.5 Hz next, and a little above 14 Hz was no better than the control level. Abrupt fall of calcium uptake after CMF exposure ended is similar to abrupt fall in calcium uptake after exposure to PEMFs ended in a Bassett experiment.

26. Fitzsimmons and Baylink, 1993

Citation	EMF-Stimulated Bone-Cell Proliferation R.J. Fitzsimmons and D.J. Baylink In Martin Blank, ed., <i>Electricity and Magnetism in Biology and Medicine</i> , 1993
Stimulation Type	Combined magnetic fields
Results	Extremely low amplitude signal can increase cell proliferation. Simply changing the DC field does not affect bone cell proliferation, but adding an AC component causes the bone cells to divide.