Washington State Health Care Authority

Health Technology Assessment

HTA Final Report
Bone Growth Stimulators

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Bone Growth Stimulators

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BONE GROWTH STIMULATORS

PURPOSE OF THE TECHNOLOGY

Bone growth stimulators use either electrical stimulation or low-intensity pulsed ultrasound to induce osteogenesis, stimulate bone growth, and promote fracture healing. Ultrasound bone growth stimulators apply low-intensity, pulsed, high-frequency acoustic pressure waves to the fracture site, whereas electrical stimulators deliver electrical current. Invasive electrical bone growth stimulators are surgically implanted. Noninvasive electrical bone growth stimulators are worn externally.

EXECUTIVE SUMMARY

Clinical Overview

An estimated 7.9 million bone fractures occur in the United States annually. While the majority of fractures heal without complications following standard nonsurgical or surgical therapy, healing is delayed or impaired in 5% to 10% of cases. Delayed union fractures exhibit clinical or radiological evidence of ongoing healing, but do not achieve union within the expected time frame. A nonunion fracture is characterized by a complete cessation of the biological bone healing process, without any chance of spontaneous healing, after such an interval that it is no longer clinically acceptable to delay further treatment.

Bone union is a concern not only in patients with fractures, but also in patients who undergo joint fusion surgery, or arthrodesis. Arthrodesis involves surgical joining of adjacent bones and is most commonly performed for joints severely damaged by arthritis or in the spine as a treatment for degenerative intervertebral disc disease or other conditions that cause instability of the vertebrae. Many types of surgical techniques involving instrumentation and bone grafts have been developed to improve stability during the postoperative period and to promote solid bony arthrodesis. However, even when surgical and immobilization procedures are employed, complications such as nonunion or pseudarthrosis may arise. Pseudarthrosis, or the formation of a false joint, can occur if a fracture or arthrodesis fails to heal properly.

There is a substantial socioeconomic burden associated with fracture healing, as well as significant morbidity and reduction in quality of life (QOL) for patients, particularly when healing is delayed or impaired. Therefore, technologies intended to promote bone union, such as bone growth stimulators, have been investigated. Bone growth stimulators are devices that use either low-intensity pulsed ultrasound or electrical stimulation to induce osteogenesis, stimulate bone growth, and promote fracture healing. These devices are used in patients with fresh fractures and joint fusions to speed healing and reduce risk of delayed or nonunion, and in patients with slow or nonhealing fractures who have not responded to other forms of fracture management.

Policy Context

Bone growth stimulation is a topic of concern to multiple organizations, including members of the Oregon Health & Science University Medicaid Evidence-based Decision (OHSU MED) collaboration and the Washington State Health Care Authority (HCA). Accordingly, bone growth stimulation is one of seven health technologies selected by the Washington State HCA for review in 2009 (HCA, 2008). Some applications of bone growth stimulation have been in clinical use for over 30 years, but uncertainty remains regarding several important issues.

Scope

This report addresses the use of ultrasound bone growth stimulators, invasive (implanted) electrical bone growth stimulators, and noninvasive electrical bone growth stimulators in the prevention and treatment of delayed union or nonunion of fractures, spinal fusion, and joint arthrodesis. Application to both traumatic fractures and stress fractures will be considered, as will use of this technology in both adult and pediatric populations. Bone growth stimulators have been developed to augment rather than replace standard operative and nonoperative treatments for delayed union or nonunion. Thus, comparisons will be made with standard or usual treatment.

Evidence pertaining to the following key questions will be reviewed:

1. Are bone growth stimulators effective in promoting healing, reducing pain, or improving function when applied to fresh fractures, delayed union or nonunion fractures, or fusion sites?

2. Are bone growth stimulators safe?

3. Does effectiveness vary by type of bone, the presence/absence of comorbidities, or other patient characteristics?

Methods

Evidence for this rapid review was obtained from three sources:

1) Hayes Medical Technology Directory Reports on the topics of *Ultrasound Bone Growth Stimulation* (October 2003); *Electrical Bone Growth Stimulation, Invasive* (February 2004); and *Electrical Bone Growth Stimulation, Noninvasive* (May 2004).
2) A search of the peer-reviewed literature in the MEDLINE and EMBASE databases, spanning 2003 through July 2009.
3) A search of numerous websites for other recently published systematic reviews, using the MED Project primary core sources (November 2008) as a guide.

Systematic reviews were selected if they met these quality criteria: systematic literature search, critical appraisal of selected studies, synthesis of evidence by indication, and explicit conclusions by indication. Primary studies published more recently than the last Hayes Medical Directory Technology reports were selected for detailed review if they were not included in any of the selected systematic reviews and if they met sample size thresholds and/or provided information not available from the systematic reviews. The literature search resulted in the selection of two published systematic reviews and 13 recent primary studies. The systematic reviews (Hayes reports included) analyzed 28 randomized controlled trials (RCTs). The 13 primary studies included three RCTs.

The quality of selected primary studies was assessed with the aid of MED checklists for RCTs and cohort studies and were graded as "good," "fair," or "poor." Overall bodies of evidence by outcome and indication were graded as "high," "moderate," or "low" quality according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

Findings

The key limitations of the available body of evidence were small sample sizes, few studies per indication, no RCTs for some indications, substantial loss to follow-up in some studies, and no assessment of pain or functional outcomes in most studies. The studies of application to fresh fractures and primary surgical fusion procedures were further weakened by the use of radiographic fusion as the only measure of healing (for additional information regarding this point, see ***Conclusion and Discussion***). Many of the RCTs had methodological or reporting flaws.

1. Are bone growth stimulators effective in promoting healing, reducing pain, or improving function when applied to fresh fractures, delayed union or nonunion fractures, or fusion sites?

Bone growth stimulation has been studied in a variety of bones (e.g., clavicle, radius, ulna, scaphoid, tibia, and malleolus), but the bulk of evidence is for long bones, with the tibia being the most commonly treated. Earlier Hayes reviews reported strongly or moderately positive conclusions regarding fresh fractures treated with low-intensity pulsed ultrasonography (LIPUS), nonunion fractures treated with LIPUS, and delayed union or nonunion fractures treated with pulsed electromagnetic field (PEMF) (a form of noninvasive electrical stimulation). The three reviews formed weakly positive or no conclusions regarding other indications due to weak or missing evidence.

Using meta-analysis, a published systematic review showed LIPUS to have a substantial impact on healing in nonoperatively *managed fresh fractures but did not demonstrate an effect on return to function in nonoperatively managed fresh fractures; neither an effect on healing nor an effect on return to function was demonstrated in* operatively *managed fractures. They reported positive evidence of an impact on healing in a small study of LIPUS for nonunion. The authors of a second published review concluded that the use of noninvasive electrical stimulation in long bones remains uncertain.*

Recently published studies do not substantially add to the body of evidence for any form of bone growth stimulation or for any indication. After consideration of the earlier Hayes reports, the two published systematic reviews, and primary studies selected from the recent literature, this rapid review suggests the following conclusions.

Fresh fractures: *Evidence of moderate quality has shown LIPUS to promote healing in* nonoperatively *managed fresh fractures, with a greater quantity of evidence pertaining to long bones than to other types of bone; evidence that LIPUS affects functional outcomes is conflicting and of low quality. Evidence of a benefit in healing and functional recovery for patients treated with LIPUS for* operatively *managed fresh fractures is mixed and of low quality. Evidence that semi-invasive direct current electrical stimulation (DCES) has a beneficial treatment effect on fresh fractures was sparse and of low quality.*

Delayed union or nonunion of fracture: *Evidence of moderate quality has shown noninvasive electrical stimulation to promote healing of delayed and nonunion fractures, with the bulk of evidence pertaining to PEMF stimulation and long bones. Evidence of low quality from older literature indicates that invasive and semi-invasive DCES promotes healing of nonunion and delayed union fractures, with the largest body of evidence related to long bone fractures. Evidence pertaining to pain and functional outcomes in patients with delayed union or nonunion is lacking.*

Primary spinal fusion: Evidence continues to show that invasive DCES, as an adjunct to surgical intervention, may promote healing after spinal fusion in high-risk patients (low-quality evidence); the largest body of evidence pertains to lumbar or lumbosacral spinal fusion. There was positive but low-quality evidence from non-RCTs that DCES may reduce pain, improve function, and enhance QOL. Noninvasive electrical stimulation, particularly PEMF, continues to show promise (low-quality evidence) as a means of promoting healing following spinal fusion. The single study of PEMF cervical fusion in high-risk patients was of somewhat better quality than the studies of PEMF in lumbar fusion (mixed risk profile), but results need to be corroborated by additional studies of PEMF with cervical fusion.

Primary foot and ankle arthrodesis: A very small body of recent evidence indicates that invasive DCES may improve healing when used as an adjunct treatment following foot and ankle arthrodesis (low-quality evidence). There was positive but low-quality evidence from a non-RCT that DCES may enhance QOL. PEMF also shows promise (low-quality evidence) for adjunctive use in promoting healing following foot and ankle arthrodesis.

Salvage treatment for failed spinal fusion or failed foot or ankle arthrodesis: A very small body of evidence has reported conflicting, largely negative results regarding the effectiveness of invasive or noninvasive electrical stimulation as salvage treatment in cases of failed spinal fusion or failed joint arthrodesis (low-quality evidence).

It should be noted that the evidence pertaining to impact on healing in fresh fractures does not necessarily address the question of whether stimulation prevents delayed union or nonunion. Most of the data pertaining to fresh fractures came from studies of LIPUS. The majority of the studies evaluating stimulation for *nonoperatively* managed fresh fractures implemented follow-up periods of varying length (3 months to 4 years), and two studies provided no information on duration of follow-up. The studies did not always report the occurrence of subsequent diagnoses of delayed union or nonunion in patients who had not healed by the end of the study period. Thus, there is insufficient information to determine the extent to which nonunions or delayed unions were prevented in nonoperatively managed fractures. For *operatively* managed fractures, the duration of follow-up periods were sufficiently long (12 to 18 months) that reported healing rates can be equated with prevention of nonunion (incomplete healing after 9 months). However, the results in studies of operatively managed patients were inconsistent.

2. Are bone growth stimulators safe?

No serious device-related complications were reported by any of a large number of studies of LIPUS and the noninvasive forms of electrical stimulation. The quantity of long-term data is only modest since most studies did not follow patients beyond discontinuation of treatment and none included patients who underwent repeated trials of stimulation. However, the literature does not report any suspicion of long-term adverse effects from these noninvasive technologies.

Device-related complications in patients treated with DCES were relatively infrequent and were generally mild and localized in general populations. However, serious complications were reported in a trial of high-risk patients undergoing fusion surgery. Some instances of known device-related complications (e.g., broken wires) were reported. However, the relationship between the implanted stimulator and general surgical complications, such as infection, is not known. The safety and effectiveness of long-term implantation in children and the elderly are unknown.

3. Does effectiveness vary by type of bone, the presence/absence of comorbidities, or other patient characteristics?

No studies were designed to measure an effect differential between different types of bone. Subgroup analyses or multiple regression analyses in small studies suggested that for treatment of delayed union and nonunion fractures, LIPUS is more effective in patients with younger (more recent) fractures than in patients with older fractures (four small studies) and provides greater benefit to patients who have risk factors generally associated with prolonged fracture healing (two studies). Otherwise, evidence of the relative effect of stimulation according to risk factors and demographic characteristics was missing or very sparse. Almost all studies were limited to skeletally mature individuals, and, therefore, no conclusions can be made regarding the use of bone growth stimulation in children. Bone growth stimulators are contraindicated in the presence of implanted electrical devices and have not been studied in patients with

serious systemic disease or who are taking medications such as immunosuppressants that would interfere with bone healing.

Conclusions and Discussion

Synopsis of Evidence

A large body of evidence indicates that in adults, bone growth stimulation is generally safe and that efficacy varies by indication and by type of stimulator device. Although the available evidence includes a large number of RCTs and several meta-analyses, no single indication is supported by a high-quality body of evidence. Only two indications are supported by evidence of moderate quality showing a positive effect on bone healing:

- Fresh fractures treated with by LIPUS as part of a nonoperative management strategy.
- Delayed union or nonunion fractures, with the bulk of evidence pertaining to the use of PEMF in long bones.

Several additional applications merit further study because of low-quality evidence that suggests an effect on bone healing. Evidence of an effect on pain, function, or QOL for any indication is very sparse and conflicting.

The available evidence suggests positive results in high-risk populations, but the overall evidence for these indications is of low quality. Examples of high-risk factors include multiple-level grafting, smoking, and obesity.

Translation of Evidence to Policy and Practice

For fractures and procedures that involve bone fusion, the key outcome is bone healing, which can be assessed radiographically or by a combination of radiographic and clinical criteria. In this rapid review, assessments of the quality of evidence assumed that radiographic fusion was an adequate measure of healing for delayed or nonunion fracture and for failed surgical fusion since these diagnoses are confirmed by imaging. Radiographic plus clinical assessments were considered the most appropriate measure of healing for fresh fractures and primary surgical fusion.

The observed effect on healing in RCTs was clinically meaningful. For example, a systematic review of LIPUS reported pooled relative reductions in radiographic healing times of 17% to 40%, depending on the indication. In the individual studies included in the same review, time to radiographic fusion was 19 to 88 days shorter in LIPUS groups than in control groups. PEMF for treatment of delayed union or nonunion fractures improved the probability of healing success by 20 to 60 percentage points. In RCTs of primary spinal fusion, success rates differed by 13 to 30 percentage points. The only RCT to measure time to healing demonstrated a difference of several weeks between patients receiving PEMF and control patients following primary foot or ankle arthrodesis.

Beyond healing, the available evidence does not provide much guidance on how patients perceive the benefits of bone growth stimulation. The impact of bone growth stimulation on secondary outcomes is still largely unknown. It could be assumed that healing, even when defined only in radiographic terms, will eventually lead to reduction in pain and improvement in function and QOL. However, the few studies that assessed these secondary outcomes reported conflicting results.

Other gaps in the evidence hinder the translation of efficacy and safety data to practice and policy:

- Within the category of noninvasive electrical bone growth stimulation, PEMF has become the preferred technology. The studies using capacitive coupling or combined (electro) magnetic field (CMF) technology were published in 2002 or earlier. However, there were no useful direct comparisons between different forms of bone growth stimulation.
- No recent studies were designed to test for the effect of different treatment parameters, and systematic reviews noted variation across studies.
- Patient compliance may be an issue with LIPUS and noninvasive electrical stimulators: some studies reported substantial dropout rates due to noncompliance, whereas others reported high rates of compliance. The validity of compliance measures is unknown.
- Although there is consensus on the definition of delayed union and nonunion, the reviewed literature did not elucidate the specific factors that would call for bone growth stimulation in patients with fresh fractures.
- The evidence does not clearly identify factors predictive of treatment success for any indication.
- Decision makers will want to know how the use of stimulation translates to avoidance of surgical procedures. Except for one clinical study of poor quality, the literature selected as evidence for this rapid review did not provide such data. See **ECONOMIC EVAULATIONS** for older studies in which reoperation rates were modeled or salvage operation rates assumed for fresh fractures treated with LIPUS.
- No controlled studies compared the use of bone growth stimulation with and without concomitant treatment (e.g., immobilization for delayed union or nonunion fractures, instrumentation or bone grafting for surgical fusion).

Despite these unknowns, bone growth stimulation appears to be a convenient, potentially useful treatment for several indications, and in these situations the benefits are likely to outweigh the harms. LIPUS and noninvasive electrical stimulation are not associated with any known or suspected complications other than minor problems such as skin irritation. The balance of harms and benefits for invasive electrical stimulators is less clear since no studies have assessed whether observed complications are attributable to the surgical procedure or the stimulation device. For patients who have received a diagnosis of nonunion, bone growth stimulation offers the only nonoperative option. Larger randomized trials and large observational studies are necessary to confirm the positive benefits of bone growth stimulation, identify any rare adverse effects, demonstrate effectiveness in typical practice settings, and identify characteristics that can be used to select patients most likely to benefit from stimulation.

BACKGROUND

Clinical Overview

Bones are divided into four major classes, dictated by shape: long, short, flat, and irregular. Long bones, which have greater length than width, function in forming levers, supporting weight, and conveying locomotion. They are primarily found in the extremities and include the femur, tibia, fibula, humerus, radius, ulna, and phalanges. Long bones entail a shaft, or diaphysis, and two ends, which are called epiphyses. They are composed of cancellous bone internally and are surrounded by hard, compact bone. Short bones are somewhat cube-shaped in appearance and are designed for strength and compaction. They include the tarsal bones of the foot and the carpal bones of the hand. Flat bones afford protection and provide areas for muscle attachment. Flat bones include the cranial bones, sternum, ribs, and the scapulae. Irregular bones are a category of bone not included in other classifications and include the vertebrae and some facial bones. Two other types of bones not included in this classification by shape include sutural bones between the joints of certain cranial bones and sesamoid bones in tendons such as the patellas (Tortora & Grabowski, 2000).

Bone fractures are among the most common of musculoskeletal injuries, aside from sprains and strains. An estimated 7.9 million bone fractures occur in the United States annually. The economic burden associated with musculoskeletal injuries, including bone fractures, is high. The cost for treatment of hospitalized musculoskeletal injuries was estimated at $26.6 billion, and the large majority of this cost (88%) was associated with hospitalization for fractures (USBJD, 2008). While the majority of fractures heal without complications following standard nonsurgical or surgical therapy, healing is delayed or impaired in 5% to 10% of cases (Busse et al., 2009; Mollon, da Silva, Busse, Einhorn, & Bhandari, 2008).

Fracture healing differs from healing of other tissues in that bone regeneration occurs instead of scar formation. Fracture healing is a complex process that consists of four overlapping stages: (1) inflammation; (2) soft callus or proliferative stage; (3) hard callus or maturing stage; and (4) remodeling. The inflammatory stage occurs immediately after the fracture, lasts for a few days, and is characterized by pain, swelling, heat, and the formation of a hematoma at the fracture site. The release of fibronectin and growth factors by activated platelets in the blood clot signals inflammatory cells to invade the injured area and initiate lysosomal degradation of necrotic tissue. The subsequent cytokine cascade triggers an influx of fibroblasts, endothelial cells, and osteoblasts into the fracture site. The soft callus stage begins approximately 7 to 10 days after the injury. It is characterized by new capillary formation within the periosteal tissues and the arrival of mesenchymal stem cells, which are able to differentiate into fibroblasts, chondroblasts, and osteoblasts. A fibrocartilaginous bridge then forms across the fracture gap. During the hard callus stage, which typically occurs 3 to 4 months after the

injury, the fibrocartilaginous bridge ossifies and is replaced by woven bone. This phase results in clinical union, although the bone is still mechanically weak. During the final remodeling phase, the woven bone is converted into stronger lamellar bone by the complementary processes of osteoclastic bone resorption and osteoblastic bone formation. This process can take months or even years, depending on various prognostic factors, such as the type and location of the fracture and the kind of bone involved (Bostrom, Yang, & Koutras, 2000; Christian, 1998; Hadjiargyrou, McLeod, Ryaby, & Rubin, 1998; Marsh & Li, 1999; Warden, Bennell, McMeeken, & Wark, 2000).

Two factors are critical for bone healing—blood supply at the site of union and stability (AAOS, 2007a). Successful bone regeneration requires the growth of new blood vessels across the fracture gap since the fracture ends are devascularized and cannot participate in the repair process. While the fracture must be mechanically stable for the new blood vessels to survive, a small amount of micromotion is required to stimulate blood flow at the fracture site (Marsh & Li, 1999). However, if the motion is excessive, capillary formation is disrupted and nonunion can occur (Marsh & Li, 1999). Intramedullary blood vessel bridging, as well as union by endosteal callus occurs when the fracture is stabilized. The fracture ends are further stabilized as the callus stiffens, thereby allowing for capillary and bony bridging in the center of the fracture (AAOS, 2007a; Christian, 1998; Hadjiargyrou et al., 1998; Marsh & Li, 1999).

Delayed and Nonunion Fractures

The term “union” can be used to describe the functional endpoint of fracture treatment, that is, when the fractured bone has regained sufficient strength and stiffness to bear weight without external support (Marsh & Li, 1999). However, the studies analyzed for this rapid review typically used the term “union” to refer to radiologic fusion only (see **METHODS**, ***Definition of Terms***.) In addition to functional or radiographic status, the time it takes to achieve union is also an important outcome measure. Delayed union fractures exhibit clinical or radiological evidence of ongoing healing, but do not achieve union within the expected time frame (Griffin, Warner, & Costa, 2008b). The expected time frame for union may vary greatly, depending on the type of fracture and the bone involved; however, fractures that do not heal within 3 to 9 months are generally considered delayed unions (Hadjiargyrou et al., 1998). A nonunion fracture is characterized by a complete cessation of the biological bone healing process, without any chance of spontaneous healing, after such an interval that it is no longer clinically acceptable to delay further treatment (Griffin et al., 2008b; Rutten, Nolte, Guit, Bouman, & Albers, 2007). There is disagreement in the literature with regard to how much time should lapse from when the injury occurs until a nonunion is declared. The range spans from 15 weeks to 12 months after the injury. However, the Food and Drug Administration (FDA) considers a nonunion to be established “when a minimum of 9 months has elapsed since injury and the fracture site shows no visibly progressive signs of healing for minimum of 3 months” (Dijkman, Sprague, & Bhandari, 2009; Gebauer, Mayr, Orthner, & Ryaby, 2005). Nonunions are diagnosed by imaging techniques such as radiography, computed tomography, and magnetic resonance imaging; however,

clinical outcomes, such as pain at the fracture site, may also be a diagnostic consideration (AAOS, 2007a).

Factors that can increase the risk of delayed union or nonunion fracture include the following (AAOS, 2007a; Einhorn, 1995; Griffin et al., 2008b; Hadjiargyrou et al., 1998):

- Inadequate blood supply.
- Extent of soft tissue damage and its interposition.
- Contamination or infection.
- Inadequate immobilization or fixation, distraction of fracture fragments, or excessive periosteal stripping.
- Inadequate reduction.
- Smoking.
- Older age.
- Severe anemia.
- Diabetes.
- Alcoholism.
- Medications such as anticoagulants, steroids, and certain anti-inflammatory drugs (aspirin, ibuprofen).
- Poor nutrition that leads to mineral and vitamin deficiencies.

A variety of treatment methods are available to orthopedic surgeons in the case of nonunion fractures, ranging from conservative cast immobilization to one or more surgical techniques. However, the reference standard of treatment for nonunion fracture is considered to be open reduction with debridement of the nonunion, often with bone grafting, and external or internal fixation for stabilization. Success rates for surgical treatment of nonunion fracture in the reported literature range from 68% to 96%, depending on fracture location and surgical method (Dijkman et al., 2009; Gebauer et al., 2005).

Arthrodesis (Fusion)

Bone union is a concern not only in patients with fractures, but also in patients who undergo joint fusion surgery, or arthrodesis. During arthrodesis, bones, joints, or vertebrae are surgically joined together. Pain relief or stabilization of an undependable joint is the most common reason for joint fusion surgery. A successful fusion thus removes the joint and eliminates motion (AAOS, 2009). Spinal fusion surgery is used to treat vertebral injuries, herniated disks, scoliosis or kyphosis, and spinal weakness or instability due to infections or tumors (AAOS, 2007b). Arthrodesis of the foot or ankle joint is used to treat severe arthritis (AAOS, 2008).

Many types of surgical techniques involving instrumentation (metal pins, screws, and cages) used alone or in conjunction with bone grafts, have been developed to improve stability during the postoperative period and to promote solid bony arthrodesis. In

addition, external immobilization is often used as an adjunct to increase the likelihood of fusion (Welch, Willis, & Gerszten, 2004). For example, fusion success rates for anterior cervical spine fusion with allograft bone and instrumentation have been reported as 92% to 100% for single-level surgery and 72% to 100% for multilevel surgery (Foley et al., 2008). However, even when surgical and immobilization procedures are employed, complications such as nonunion or pseudarthrosis may arise (Dhawan, Conti, Towers, Abidi, & Vogt, 2004). Pseudarthrosis, or the formation of a false joint, can occur if a fracture or arthrodesis fails to heal properly (AAOS, 2009; Dhawan et al., 2004; Simmons, Mooney, & Thacker, 2004). Previous studies have reported nonunion rates of 0% to 16% following subtalar joint arthrodeses, 0% to 41% after ankle arthrodeses, and up to 50% following lumbar fusion (Saxena, DiDomenico, Widtfeldt, Adams, & Kim, 2005; Welch et al., 2004).

Factors that may increase the likelihood of nonunion of arthrodesis include smoking, immunosuppressant medications, diabetes, alcoholism, as well as previous surgery (Saxena et al., 2005). Additional factors such as the absence of fixation, involvement of multiple levels, use of allograft, and surgical technique may negatively impact the success rate of spinal fusion surgery (Foley et al., 2008; Simmons et al., 2004).

Bone Growth Stimulation

Bone growth stimulators are devices that use either low-intensity pulsed ultrasound (LIPUS) or electrical stimulation to induce osteogenesis, stimulate bone growth, and promote fracture healing (AAOS, 2007a; Davidson, 2002). A recent survey of 450 Canadian orthopedic trauma surgeons found that 45% of respondents used bone stimulators to manage tibial fractures, with use evenly divided between ultrasound (US) bone growth stimulators and electrical bone growth stimulators (Busse, Morton, Lacchetti, Guyatt, & Bhandari, 2008).

US Bone Growth Stimulators: US bone growth stimulators deliver mechanical stimulation to the fracture site through the application of low-intensity, pulsed, high-frequency acoustic pressure waves. Significant progress has been made in determining the specific mechanism(s) through which ultrasound stimulates bone healing. Research suggests that LIPUS accelerates several phases of the fracture healing process (inflammation, soft callus formation, hard callus formation) in vivo (Dijkman et al, 2009; Pounder & Harrison, 2008). As LIPUS appears to exert beneficial effects throughout the fracture healing process, multiple signaling pathways are likely involved. In vitro studies suggest the involvement of integrins (transmembrane cell adhesion molecules) with downstream effects to enhance production of cyclooxygenase 2 (COX-2) and prostaglandin E2, which is associated with mineralization in osteoblast cultures in vitro and enhanced endochondral ossification in vivo (Pounder & Harrison, 2008).

Electrical Bone Growth Stimulators: The use of electrical stimulation for the treatment of delayed and nonunion fractures dates back over 100 years. However, a scientific basis for the use of this technology was not available until the reporting of two key findings in the 1950s. First, new bone formation was observed near the site of electronegative potential (Dhawan et al., 2004; Saxena et al., 2005). Second, investigators learned that

bone produces electrical potential after exposure to mechanical forces (Punt, Den Hoed, & Fontijne, 2008; Welch et al., 2004). Later research found that osteogenesis (bone formation) could be modulated by bioelectric potentials (Mollon et al., 2008; Punt et al., 2008). The different types of electrical bone growth stimulators may be categorized as (Griffin et al., 2008b):

- *Invasive electrical stimulators*, which deliver direct current to the fracture site through a completely implanted system.
- *Semi-invasive electrical stimulators*, which deliver direct current via a percutaneous cathode and an anode placed in contact with the skin.
- *Noninvasive electrical stimulators*, which are located externally and deliver electrical current to the fracture site via pulsed electromagnetic field (PEMF), capacitive coupling, or combined (electro) magnetic field (CMF) technology.

While the precise mechanism of action of electrical stimulation has not been determined, research suggests that it may affect many cellular pathways. Electrical stimulation may facilitate bone healing by increasing gene expression and protein synthesis of growth factors, with the specific growth factors involved depending on the dose and type of electrical stimulation (Mollon et al., 2008; Onibere & Khanna, 2009). Additional cellular processes, including proteoglycan and collagen regulation within the extracellular matrix and cytokine production, may also be impacted; taken together, all of these effects ultimately may stimulate the calcium-calmodulin pathway to promote bone healing (Mollon et al., 2008).

Washington State Data

Data from three Washington State Agencies were provided by the Health Technology Assessment Program. HTA coordinates the collection of any relevant agency utilization data.

Bone Growth Stimulation (BGS) is a selected topic. BGS is a technique of promoting bone growth in difficult to heal fractures or in areas trying to be fused by applying a low electrical current or ultrasound to the fracture. Ultrasound stimulation is a device that generates low intensity pulses of sound and is applied to the skin over the fracture. Each method (electrical and ultrasound) must be used for at least three to six months to be effective.

Estimates for costs and utilization from the Uniform Medical Plan, Washington State's Medicaid Program and Washington State's Department of Labor and Industries are presented below in Table A. They provide an estimate of base costs and may not include all costs for Bone Growth Stimulator procedures and treatments. Information on relevant procedure and diagnostic codes is included after the result tables.

Table A –

Procedure Code by Year

UMP, Medicaid, L&I

PROC CODE (ICD-9, CPT, HCPCS)	2005	2006	2007	2008	Total
78.91 (Invasive electrical,	0	0	0	1	**1**
78.94 (Invasive electrical,	1	0	0	0	**1**
78.95 (Invasive electrical,	0	1	0	0	**1**
78.97 (Invasive electrical,	1	0	0	1	**2**
78.98 (Invasive electrical, tarsals, metatarsals)	1	0	0	2	**3**
78.99 (Invasive electrical, spine, pelvis, phalanges)	4	6	4	1	**15**
20974 (Noninvasive electrical)	14	11	2	7	**34**
20975 (Invasive electrical)	12	7	5	10	**34**
20979 (Noninvasive ultrasound)	3	3	3	6	**15**
E0747 (Noninvasive electrical, other than spine)	130	157	134	138	**559**
E0748 (Noninvasive electrical, spine)	50	28	80	86	**244**
E0749 (Invasive, electrical)	0	0	0	0	**0**
E0760 (Noninvasive ultrasound)	39	45	47	60	**191**
Total	**255**	**258**	**275**	**312**	**1100**

ICD-9, CPT, HCPCS codes are unduplicated counts. HCPCS codes are not available for cases listed by ICD-9 or CPT code. Counts for E0749 are not available due to bundled billing.

Top 5 Diagnoses by Procedure Code

UMP, Medicaid, L&I | 2005-2008

	HCPCS CODE			
Principal ICD-9 Diagnosis	**E0747**	**E0748**	**E0760**	**Total**
Nonunion of fracture	170	1	5	**176**
Arthrodesis status	27	87	0	**114**
Fracture metatarsal-closed	26	0	44	**70**
Back disorder NOS	4	17	0	**21**
Fracture ankle NOS-closed	0	0	13	**13**
Total	**227**	**105**	**62**	**394**

Average* Payments by Procedure

UMP, Medicaid, L&I | 2005-2008

HCPCS CODE	Average Payments
E0747 (Noninvasive electrical, other than spine)	$3,688
E0748 (Noninvasive electrical, spine)	$3,537
E0760 (Noninvasive ultrasound)	$2,820

* Weighted average

Total Payments by Procedure by Year

UMP, Medicaid, L&I | 2005-2008

HCPCS CODE	2005	2006	2007	2008	Total
E0747	$503,083	$573,974	$488,099	$489,267	**$2,054,424**
E0748	$186,835	$89,177	$265,033	$311,419	**$852,464**
E0760	$101,781	$124,291	$130,185	$179,616	**$535,873**
Total	**$791,700**	**$787,442**	**$883,317**	**$980,302**	**$3,442,761**

Distribution of Procedures by Bone Type

UMP, Medicaid, L&I | 2005-2008

	Bone Type			
HCPCS CODE	**Long**	**Spine**	**Other***	**Total**
E0747 (Noninvasive electrical, other than spine)	109	7	443	**559**
E0748 (Noninvasive electrical, spine)	0	203	61	**264**
E0760 (Noninvasive ultrasound)	72	0	121	**193**
Total	**181**	**210**	**625**	**1016**

* Other bones typically include bones of the hand and foot.

Procedure Codes

ICD9 Operation Codes

78.9 – Insertion of bone stimulator (electrical) to aid bone healing osteogenic electrodes for bone growth stimulation totally implanted device (invasive).
78.90 – Unspecified site
78.91 – scapula, clavicle, and thorax (ribs and sternum)
78.92 – Humerus
78.93 – radius and ulna
78.94 – Carpals and metacarpals
78.95 – Femur
78.96 – Patella
78.97 – Tibia and Fibula
78.98 – Tarsals and metatarsals
78.99 – Other

CPT Codes

20974 – Electrical stimulation to aid bone healing; noninvasive (nonoperative)
20975 – Invasive (operative)
20979 – Low intensity ultrasound stimulation to aid bone healing, noninvasive (nonoperative)

HCPCS Codes

E0747 – Osteogenesis stimulator, electrical, noninvasive, other than spinal applications
E0748 – Osteogenesis stimulator, electrical, noninvasive, spinal applications
E0749 – Osteogenesis stimulator, electrical, surgically implanted
E0760 – Osteogenesis stimulator, lower intensity ultrasound, noninvasive

Policy Context

Bone growth stimulation is a topic of interest to members of the Oregon Health & Science University Medicaid Evidence-based Decision (OHSU MED) collaboration and the Washington State Health Care Authority (HCA). Accordingly, bone growth stimulation is one of seven health technologies selected by the Washington State HCA

for review in 2009 (HCA, 2008). Some applications of bone growth stimulation have been in clinical use for over 30 years, but uncertainty remains regarding several important issues, including:

- The efficacy of ultrasound, invasive and semi-invasive electrical, and noninvasive electrical bone growth stimulators relative to standard or usual treatment.
- The long-term safety of different types of bone growth stimulation technologies.
- The impact of bone growth stimulation on healing.
- The clinical relevance of observed treatment effects on bone healing.
- The role of bone growth stimulation in reducing pain, improving function, and enhancing quality of life (QOL) in patients.
- Differential effectiveness, depending on bone or lesion type, patient comorbidities, and other risk factors or patient characteristics.

Given the potential benefits of bone growth stimulation, healthcare decision makers will benefit from a systematic reappraisal of the evidence. This rapid review evaluates previous systematic reviews and recent primary studies of ultrasound bone growth stimulators, invasive (implanted) electrical bone growth stimulators, and noninvasive electrical bone growth stimulators for the prevention and treatment of delayed union or nonunion of fractures, spinal fusion, and joint arthrodesis.

The Food and Drug Administration (FDA) approves bone growth stimulators as Class III devices, meaning that they are deemed to pose the highest level of risk and thus require premarket approval. A search of the Premarket Approval (PMA) database indicates that the agency began approving electrical bone growth stimulators in1980 and ultrasonographic osteogenic stimulators in 1994. No information regarding approved indications is currently available from the FDA database, but approved indications reported by manufacturers are discussed under **DESCRIPTION** (CMS, 2005; FDA, 2009; HCA, 2008).

The Centers for Medicare & Medicaid Services (CMS) has issued a National Coverage Determination (NCD) granting Medicare coverage for invasive and noninvasive electrical stimulation for nonunion long bone fractures, for failed spinal fusion, and as an adjunct to spinal fusion. CMS has also issued an NCD granting coverage for ultrasound stimulation for nonunion fractures (type of bone not specified). Ultrasound stimulation for fresh fractures is specifically not covered by CMS.

Key Questions

1. Are bone growth stimulators effective in promoting healing, reducing pain, or improving function when applied to fresh fractures, delayed union or nonunion fractures, or fusion sites?

2. Are bone growth stimulators safe?

3. Does effectiveness vary by type of bone, the presence/absence of comorbidities, or other patient characteristics?

TECHNOLOGY DESCRIPTION

Ultrasound Bone Growth Stimulators

Low-intensity pulsed ultrasound bone growth stimulators (LIPUS) transmit mechanical pressure waves through skin and soft tissue to the fracture site to accelerate and enhance the fracture repair process. An older device model, the Exogen 2000, was also known as the Sonic Accelerated Fracture Healing System (SAFHS) SAFHS® Model 2000. Exogen Inc., which originally developed the SAFHS, was acquired by Smith & Nephew Inc. (Memphis, TN) in 1999 (Hayes, 2003). The EXOGEN 4000+™ Low-Intensity Ultrasound Bone Healing System is the most recent device model manufactured by Smith & Nephew Inc. This recent model or any other EXOGEN Bone Healing System is indicated for the treatment of established nonunions, excluding the skull and vertebra. In addition, the device is indicated for accelerating the time to healing for fresh, closed, posteriorly displaced distal radius fractures, and fresh, closed, or grade I open tibial diaphysis fractures in skeletally mature individuals that are managed by closed reduction and cast immobilization (Smith & Nephew, 2009). The device generally consists of: (1) a main operating unit, powered by a lithium battery; and (2) a transducer, powered by the main operating unit battery supply, which supplies the ultrasound signal to the skin at the fracture site. The transducer and the main operating unit are connected by permanently attached coiled interconnecting fiberoptic cables. A coupling gel must be applied to the transducer surface at the beginning of each treatment period in order to permit transmission of the ultrasound signal from the transducer surface to the skin over the fracture site (Gebauer et al., 2005; Smith & Nephew, 2009). The device can be applied to the fracture site within a cast, on a cast, or without a cast. For in-cast and on-cast applications, the device is contained in a retaining and alignment fixture that allows the entire device to be attached to the fracture site. For a noncast application, the device is contained in a strap assembly, allowing contact of the transducer surface with the skin. The ultrasound pressure wave signal is characterized by a 200-microsecond (μs) burst of 1.5 megahertz (MHz) acoustic sine waves, with a repetition rate of 1 kilohertz (kHz) and a spatial average-temporal average intensity of 30 milliwatts (mW) per cm^2 (mW/cm^2). Treatment consists of a single 20-minute session per day until the fracture is healed, as determined by the physician (Hayes, 2003).

Invasive and Semi-Invasive Electrical Bone Growth Stimulators

Invasive Direct Current Stimulation

The OsteoGen™ Bone Growth Stimulator is currently marketed by Biomet Inc. It is designed for adjunctive use in the treatment of nonunions when surgery is required or when patient compliance is expected to be inadequate. The device is appropriate for any form (e.g., transverse, segmented, comminuted) of fracture. It is most often used on long bones and the clavicle. Variations of the OsteoGen device are available for high-risk fractures (OsteoGen™ Dual Lead Bone Growth Stimulator) and with mesh cathodes designed to provide scaffolding

(OsteoGen™-M Bone Growth Stimulator). Surgical implantation can involve coiling the electric wire and placing it inside the fracture or drilling holes into the bone and weaving the wire into the bone. Special techniques have been devised for integrating the wires with different bone graft materials and fixation products. The generator is placed subcutaneously 8 to 10 cm from the wire and, if necessary, is sutured to soft tissue (Biomet, 2009a). A study reviewed in detail for this report used the OsteoGen as adjunctive treatment in foot and ankle arthrodesis (Saxena et al., 2005).

Two invasive electrical stimulators for use in spinal fusion are currently marketed by Biomet Inc.: SpF®-XL IIb Spinal Fusion Stimulator; and SpF® PLUS-Mini Spinal Fusion Stimulator. One study described insertion of an electrical stimulator during cervical fusion to consist of the following steps: placement of the electrodes on either facet of the appropriate vertebra, placement of the bone graft against the electrodes, closure of the fascia, and placement of the generator in a subcutaneous pocket created lateral to the incision (Welch et al., 2004).

Product information for OsteoGen, SpinalPak, and related devices recommends that the generator be removed when it is no longer needed since the safety of long-term implantation has not been studied. Explantation (removal) can be performed using local anesthesia. Growth of new bone will require that some of the wire remain implanted (Biomet, 2009a, 2009b).

Semi-invasive Direct Current Stimulation

A search of the literature published since 2003 and a search of the Internet suggests that semi-invasive stimulators are no longer used. Current information is not available on the one system (Quadpak, Zimmer Inc.) identified in the previous report by Hayes (2004a). Information is available from older literature. Under local or general anesthesia, four cathodes are surgically inserted with a hand drill under roentgenographic or fluoroscopic guidance into the cortex on one side of the nonunion site. The cathodes are connected to a lead from the power source. Each cathode constantly delivers 20 microamperes (μA) of direct electrical current to the fracture site. A nonmetallic, self-adherent, disposable anode is attached to the skin, and the power pack is incorporated into a cast. The patient must change the skin anode every other day. The cast and percutaneous cathodes are removed after 12 weeks, at which point a cast is applied for an additional 12 weeks. The entire 24-week treatment may be repeated as often as necessary (Brighton et al., 1981; Haupt, 1984).

Semi-invasive systems have been used for nonunions of the tibia, femur, humerus, radius, ulna, scaphoid, clavicle, metatarsal, fibula, and medial malleolus. Advantages of the semi-invasive system include full portability, compatibility with all metallic fixation devices, and nonsurgical removal of the cathodes (Day, 1981; Haupt, 1984). However, patient compliance is required for changing of the anodes. Another disadvantage is the open communication between the outside environment and the nonunion site along the external wires of the semi-invasive system, which predisposes the patient to infection (Cohen, Roman, & Lovins, 1993).

Noninvasive Electrical Bone Growth Stimulators

Noninvasive bone growth stimulators deliver electrical current to the fracture site via pulsed electromagnetic field (PEMF), capacitive coupling, or combined (electro) magnetic field (CMF) technology. PEMF and CMF stimulators are classified as inductive coupling stimulators, which function by creating a time-varying magnetic field that induces current flow in conducting tissue subjected to the field. In PEMF stimulators, the electromagnetic field can be pulsed on and off, whereas in CMF stimulators, the electromagnetic field is a combination of static and a sinusoidal varying field. In contrast, capacitive coupling stimulators function by creating an electrical field with a voltage gradient between two charged plates, which in turn produces a current flow (Anglen, 2002). Recent literature suggests that PEMF stimulators have become the preferred form of noninvasive electrical bone stimulation. Representative devices in the PEMF, capacitive coupling, and CMF categories are described in the following discussion.

Pulsed Electromagnetic Field (PEMF) Stimulation

The EBI Bone Healing System® (currently marketed by Biomet Inc.) is indicated for nonunion fractures, failed fusions, and congenital pseudarthrosis. The electromagnetic coil is housed in a lightweight, flexible unit that can be worn directly over the fracture site. It is connected to a control unit that can be attached to the patient's belt. Patients may wear the device during any activity or during sleep. Recommended treatment time is 10 hours per day (Biomet, 2009c). The company also offers the SpinalPak® II Spinal Fusion Stimulator (Biomet, 2009b). The Physio-Stim (Orthofix®) is indicated for the treatment of an established nonunion acquired secondary to trauma, excluding vertebrae and all flat bones, where the width of the nonunion defect is less than one half the width of the bone to be treated. It consists of a combined stimulator-control unit that may be worn directly over the fracture site or over a cast or other immobilization device. Manufacturer recommendations indicate that the Physio-Stim should be worn for 3 hours per day (Orthofix, 2009a).

The Spinal-Stim (Orthofix) is indicated for adjunctive use in spinal fusion to increase the probability of fusion success and as a nonoperative salvage treatment in cases of failed spinal fusion, where a minimum of 9 months has elapsed since the last surgery. Models designed for lumbar fusion are buckled around the waist so that there is an electromagnetic coil (inside a frame) both in front of and behind the lumbar spine. In models designed for cervical fusion, a lightweight strap houses the electromagnetic coil and is worn around the neck in necklace fashion. Patients may use cervical devices during any activity or during sleep. The prescribed treatment time with Spinal-Stim is usually a total of two or more hours per day either in a single session or in multiple sessions. The Orthofix Cervical-Stim unit is the only FDA-approved device for adjunctive use in cervical spine fusion in patients who are at high risk for fusion failure. Recommended treatment time with the Cervical-Stim is a total of four hours per day. Both Spinal-Stim and Cervical-Stim have built-in systems to record "on" time for purposes of monitoring patient compliance (Foley et al., 2008; Orthofix, 2009b, 2009c).

Capacitive Coupling: The OrthoPak® 2 Bone Growth Stimulator (currently marketed by Biomet Inc.) applies stimulation through electrodes placed near the fracture site. The rechargeable battery pack can be attached to a soft band worn around the fracture site (Biomet, 2009c).

CMF Stimulation: CMF OL1000 Bone Growth Stimulators (marketed by DJO Inc.) are indicated for use in the noninvasive treatment of an established nonunion fracture acquired secondary to trauma, excluding all vertebrae and flat bones. These devices are portable and consist of a stimulation unit and a control unit. The stimulation unit can be worn directly over a fracture site or over a cast. The CMF SpinaLogic® (DJO Inc.) is indicated as an adjunct electromagnetic treatment to primary lumbar spinal fusion surgery for one or two levels. It consists of a flat stimulator unit to be placed over the fusion area and a control unit. Both types of devices are battery powered and are designed to be used for 30 minutes per day (DJO, 2009).

METHODS

Search Strategy and Study Selection Criteria

Evidence for this rapid review was obtained from three sources:

1) Hayes Medical Technology Directory Reports on the topics of *Ultrasound Bone Growth Stimulation* (October 2003); *Electrical Bone Growth Stimulation, Invasive* (February 2004); and *Electrical Bone Growth Stimulation, Noninvasive* (May 2004).
2) A search of the peer-reviewed literature in the MEDLINE and EMBASE databases, spanning 2003 through June 2009. Searches were restricted to human participants. The search strategy used variations of the terms *ultrasound*, *sonic, electrical stimulation*, *pulsed electromagnetic*, *combined electromagnetic*, and *capacitive* as keywords and subject heading words, in combination with variations of *arthrodesis*, *fracture*, *bone*, *healing*, *fusion*, *spinal fusion, osteoarthritis, and necrosis*. Bibliographies of selected studies, systematic reviews, and meta-analyses were manually searched for additional relevant references (see **Appendix I**).
3) A search of numerous websites for other recently published systematic reviews, using the MED Project primary core sources (November 2008) as a guide. The following sources were searched: Agency for Healthcare Research and Quality (AHRQ), American Academy of Orthopaedic Surgeons (AAOS), Food and Drug Administration (FDA), Centers for Medicare & Medicaid Services (CMS), Cochrane Collaboration, Blue Cross Blue Shield Technology Evaluation Center (BCBS TEC), Institute for Clinical Systems Improvement (ICSI), Canadian Agency for Drugs and Technologies in Health (CADTH), National Library for Health (NLH), Veterans Affairs Department of Defense (VA DOD), Turning Research Into Practice (TRIP), and the Centre for Reviews and Dissemination at York University.

Inclusion Criteria: Clinical studies and systematic reviews selected for inclusion were those that evaluated the safety and efficacy of bone growth stimulators and met these additional criteria:

- Populations: Adults and children being treated for traumatic fracture or diseases requiring fusion of the spine or joints.
- Interventions: Ultrasound (US) bone growth stimulation, invasive electrical bone growth stimulation, and noninvasive bone growth stimulation.
- Comparators: No stimulation or sham stimulation.
- Outcomes: Primary outcome was healing, defined in radiographic or radiographic plus clinical terms; secondary outcomes were time to healing, reduction in pain, return to function, and impact on quality of life (QOL).

Primary studies published more recently than the last Hayes Medical Directory Technology reports were selected for detailed review if they were not included in the selected systematic reviews and if they met sample size thresholds and/or provided information not available from the systematic reviews. Only English-language articles were selected.

Systematic reviews were selected if they met certain quality criteria (Cook, Mulrow, & Haynes, 1997; Rys, Wladysiuk, Skrzekowska-Baran, & Malecki, 2009):

- Systematic literature search
- Critical appraisal of selected studies
- Synthesis of evidence by indication
- Explicit conclusions by indication

See **Appendix I** for additional details regarding the search strategy.

Exclusion Criteria: Studies of bone growth stimulation for treatment of osteoarthritis or necrosis were excluded; case studies; nonclinical studies.

Selected Reviews and Studies

The following systematic reviews and clinical studies were selected.

- *Ultrasound:*
  - One systematic review of randomized controlled trials (RCTs) assessing the use of LIPUS for any type of fracture (Busse et al., 2009). The literature search in the review by Busse and colleagues extended through September 2008. The reviewed studies covered these indications: nonoperatively managed fresh fractures; nonoperatively managed stress fractures; distraction osteogenesis; bone grafting for nonunion; and operatively managed fresh fractures.
  - Five clinical studies (Gebauer & Correll, 2005; Gebauer et al., 2005; Handolin, Kiljunen et al., 2005b; Jingushi, Mizuno, Matsushita, & Itoman, 2007; Rutten et al., 2007). These studies were selected because they had sample sizes ≥ 50 (Gebauer et al., 2005; Rutten et al., 2007) or provided information not available from the studies reviewed by Busse et al. (2009), i.e., use of US for delayed union or nonunion following limb lengthening in children (Gebauer & Correll, 2005), long-term (18 months) follow-up data (Handolin, Kiljunen et al., 2005b), and multivariate analysis of risk factors (Jingushi et al., 2007).

- *Electrical Stimulation, Invasive:* Three clinical studies of electrical stimulation (ES) for cervical fusion (Welch et al., 2004) and delayed union or nonunion of arthrodesis of foot or ankle (Lau, Stamatis, Myerson, & Schon, 2007; Saxena et al., 2005). No systematic reviews of invasive ES were identified.

- *Electrical Stimulation, Noninvasive:*
  - One systematic review of RCTs assessing noninvasive ES for any long bone application (Mollon et al., 2008). The literature search extended through April 2008. The reviewed studies covered these indications: delayed or nonunion fractures; congenital pseudarthrosis; fresh fractures; stress fractures; and osteotomies.
  - Five clinical studies assessing noninvasive ES for any application other than for long bones: an RCT of PEMF as an adjunct to hindfoot arthrodesis (Dhawan et al., 2004); an RCT of PEMF as an adjunct to cervical fusion (Foley et al., 2008); and uncontrolled studies of PEMF for failed foot or ankle arthrodesis (Saltzman, Lightfoot, & Amendola, 2004); failed lumbar fusion (Simmons et al., 2004); and fracture nonunion with long and nonlong bone results reported separately (Punt et al., 2008).

See **Appendix I** for additional details pertaining to selection criteria and **Appendix II** for a listing of reviews and studies that met the initial selection criteria but were subsequently excluded.

Definition of Terms

The following definitions reflect the usage of these terms in the literature reviewed for this rapid review.

- **Radiographic healing, radiographic union, radiographic fusion:** Bone healing or union was generally evaluated radiographically. There is no standard definition of radiographic fusion. Some studies defined radiographic fusion as healing characterized by at least 50% of bridging, or assimilation, between surfaces. Radiographic success and time to healing/union/fusion were common outcome measures. “Healing,” “union,” and “fusion,” when used alone, generally refers to radiographic fusion unless clinical criteria are also defined.

- **Radiographic success rate:** The percentage of fractures (or fusion procedures) that result in radiographic fusion within a given time period.

- **Time to healing:** In studies of adjunctive stimulation, this referred to the mean time between fracture (or fusion procedure) and a determination that radiographic fusion has occurred. In studies of stimulation as a salvage treatment, this referred to the mean time between initiation of stimulation treatment and a determination that radiographic fusion has occurred.

- **Clinical healing:** Clinical measures of healing included such endpoints as discontinuation of immobilization, a specified level of physician-reported motion at the fracture site, success on a test of physical function appropriate for the particular bone being treated, or aversion of repeat surgery. Clinical healing

sometimes encompassed more patient-important outcomes measured by pain scales, anatomy-specific disability scales, or general status scales (e.g., SF-36®; Medical Outcomes Trust).

- **Clinical success rate:** The percentage of fractures (or fusion procedures) that meet a combination of specified clinical healing measures.

- **Fresh fracture:** A fracture that has recently occurred, typically within the past 7 days, that has not had previous treatment, other than emergency splinting prior to evaluation and fixation.

- **Delayed union fracture:** A fracture that does not achieve union within the anticipated time frame for that type of fracture. Fractures that do not heal within 3 to 9 months are generally considered delayed unions (Griffin et al., 2008b; Hadjiargyrou et al., 1998). The studies reviewed in detail and the studies included in the two selected systematic reviews seemed to observe this definition.

- **Nonunion fracture:** A fracture characterized by a complete cessation of the biological bone healing process, without any chance of spontaneous healing to the point that is no longer clinically acceptable to delay further treatment (Griffin et al., 2008b; Rutten et al., 2007). The FDA defines fractures as nonunion when at least 9 months has elapsed since injury and the fracture site shows no visibly progressive signs of healing for at least 3 months. The studies reviewed in detail and the studies included in the two selected systematic reviews seemed to observe this definition and made assessments of nonunion primarily according to radiographic evidence.

In the **FINDINGS** section, "healing," "union," and "fusion" refer to radiographic fusion unless otherwise noted.

Quality Assessment

Systematic Reviews: See ***Search Strategy and Study Selection Criteria*** for information on the quality criteria used to select systematic reviews. [NOTE: The individual studies included in systematic reviews were not reviewed in depth and thus could not be assigned a definitive quality rating. Quality assumptions were made based on study design, sample size, and limitations identified by the systematic review authors.]

Primary Studies: Individual primary studies published since the selected systematic reviews were first rated based on study design:

- Good = randomized controlled trials (RCTs).
- Fair = quasi-RCT, nonrandomized controlled study, or nonrandomized comparative study).

- Poor = studies without concurrent control or comparison groups.

The quality ratings for studies were then modified based on study strengths and limitations, using the MED Project checklists for RCTs (**Appendix III**) and cohort studies (**Appendix IV**). For uncontrolled/noncomparison studies, no formal checklist was used. However, quality factors were detailed in the evidence tables and could potentially upgrade an uncontrolled study to a higher quality rating.

Body of Evidence Evaluation: For each clinically significant outcome, e.g., healing or functional status, the overall quality of the body of evidence was evaluated according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines (Atkins et al., 2004; Guyatt et al., 2008). The following categories were observed:

- High = further research is very unlikely to change our confidence in the estimate of effect.
- Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate, or no estimate of effect can be made at this time.

In the GRADE system, evidence based on RCTs is considered the highest quality evidence. However, a high-quality rating can be downgraded on the basis of the methodological limitations of individual studies and other factors such as inconsistency across studies and the directness of outcome measures. Evidence from study designs not usually considered high quality, i.e., nonrandomized controlled or comparative studies and uncontrolled studies can sometimes be upgraded. For bone growth stimulation as a treatment of delayed union or nonunion fracture, radiographic fusion was considered an adequate measure of healing since the problem being treated is diagnosed on the basis of radiographic findings. This applies to failed spinal fusion and joint arthodesis as well. However, a combination of both radiographic and clinical criteria was considered the most direct measure of healing for fresh fractures and primary procedures involving bone fusion.

Other Considerations: When the quality of the evidence has been graded for each outcome, several additional considerations are important before recommendations can be made. These considerations include the relative importance of the various outcomes, the magnitude (clinical significance) of observed benefits, the benefits of the technology weighed against observed and potential harms, the availability and effectiveness of alternatives, and patient compliance issues. Such issues have been reviewed in the overall conclusion of this rapid review (see **EXECUTIVE SUMMARY**).

FINDINGS

Ultrasound Bone Growth Stimulators (Tables 1 and 2)

Systematic Reviews

Two systematic reviews, a Hayes Medical Technology Directory Report on *Ultrasound Bone Growth Stimulation* (Hayes, 2003), and a systematic review and meta-analysis from the peer-reviewed literature (Busse et al., 2009), were reviewed. These two reviews are summarized in Table 1. The Hayes report included three randomized controlled trials (RCTs) and two retrospective case series studies published in October 2003 or earlier (total across all studies, n=1567 patients; sample size range across individual studies, 32 to 1317). Busse and colleagues selected only RCTs published in September 2008 or earlier. The review by Busse and colleagues included a total of 13 RCTs (total, n=563; range, 8 to 120); nine of these trials were published after 2003, and thus not included in the earlier Hayes report. The Hayes report included a reanalysis of data from two RCTs, and two retrospective case series studies that were excluded by Busse and colleagues. In both systematic reviews, only studies that evaluated low-intensity pulsed ultrasound (LIPUS) were considered for review.

Primary Studies

Five primary studies of LIPUS in patients with fresh, delayed union, or nonunion fractures met the selection criteria for studies published after the last Hayes report and not covered in the systematic review by Busse and colleagues. These five studies consisted of three prospective, uncontrolled studies; one randomized, placebo-controlled study that provided long-term (18-month) follow-up data; and one retrospective study with multiple regression analysis to evaluate prognostic factors. One prospective study included self-paired controls, whereby patients served as their own controls. A single prospective case series evaluated pediatric patients (average age, 7.6 years) who underwent LIPUS following limb-lengthening procedures. Study populations ranged in size from very small (n=16) to moderate (n=85).

Patient Characteristics and Study Protocols

When reported, inclusion criteria generally included skeletal maturity. Some studies excluded children and older patients; patients with alcohol or drug dependency; patients with comorbidities that could interfere with treatment; and concurrent use of some medical treatments that could also interfere with treatment. Neither of the systematic reviews provided information on how patients with fresh fractures were selected to receive bone growth stimulation. Delayed unions were generally defined as no union by 3 months after the fracture occurred or after the most recent surgical treatment. Similarly, nonunions were generally defined by incomplete healing at a minimum of 8 months after the fracture occurred or after the most recent surgical treatment.

Both systematic reviews generally described LIPUS as an adjunct treatment, designed to augment standard operative (intramedullary nail, bone graft) and nonoperative

(closed reduction, cast immobilization) treatments. However, two of the selected primary studies reported that no concomitant treatment was used with LIPUS in patients with delayed union or nonunion fractures. Typical treatment protocol, as reported by the selected primary studies, was a 20-minute daily, LIPUS treatment with an ultrasound pressure wave signal, characterized by a 200-µs burst of 1.5 MHz sine waves, repeating at a frequency of 1 kHz.

1. Are bone growth stimulators effective in promoting healing, reducing pain, or improving function when applied to fresh fractures, delayed union or nonunion fractures, or fusion sites?

The systematic review by Busse et al. (2009) conducted an overall meta-analysis of the effect of LIPUS for a variety of fracture types by pooling the data on radiographic healing measures from six RCTs. The meta-analysis found a statistically significant relative reduction in radiographic healing time of 33.6% associated with LIPUS. As both the Hayes (2003) and Busse et al. (2009) systematic reviews evaluated the efficacy of LIPUS according to the clinical presentation of the patient, the remainder of this section will elaborate on the efficacy of LIPUS therapy by different categories of fractures.

Fresh Fractures (systematic reviews): Positive healing results from 3 RCTs reported for nonoperatively managed fresh fractures; mixed healing results from 4 RCTs for operatively managed fresh fractures; no demonstrated benefit to functional recovery outcomes for either operatively or nonoperatively managed fresh fractures.

- *A meta-analysis of three RCTs resulted in a significant relative reduction in radiographic healing time by 36.9% in patients with* nonoperatively *managed fresh fractures of tibia, distal radius, or scaphoid bones (Busse et al., 2009). Two of these three studies were also reviewed in the Hayes (2003) report. The issue of concomitant treatment (i.e., immobilization and/or non–weight-bearing) was not discussed.*
- The authors of the review by Busse et al. (2009) pooled multiple functional measures in two studies of nonoperatively managed fresh fractures in order to estimate overall return to function. They calculated estimates of a reduction by 1.4 days in return to function (moderate-size RCT, clavicle fractures) and a reduction by 0.4 days in return to active military duty (small RCT, tibial stress fracture). However, the estimates were nonsignificant (confidence intervals included negative values, which represented the possibility of an *increase* in time to functional recovery). They concluded that LIPUS did not provide a functional benefit.
- Results from four small RCTs were mixed with respect to the effectiveness of LIPUS for fresh fractures treated *operatively.* One RCT reported that LIPUS did not significantly reduce radiographic healing time in fresh tibial shaft fractures (Busse et al., 2009; Hayes, 2003). In another small RCT involving tibial fractures, there was a significant reduction in clinical and radiographic healing time. Busse and colleagues reported a pooled (across the two studies) estimate of a relative

reduction in healing time of 16.6%, attributable to LIPUS, but the estimate was nonsignificant. Two other very small RCTs indicated that LIPUS for the treatment of lateral malleolus fractures was not effective for bone healing after 3 to18 months of follow-up (Busse et al., 2009).

- Two RCTs also provided inconsistent evidence of an effect of LIPUS on functional recovery in patients treated with operative management of tibial fresh fractures (Busse et al., 2009). A pooled estimate of the absolute reduction in time to functional recovery was 3.4 weeks, but this was nonsignificant. A third small RCT evaluating operatively managed malleolar fractures reported a small though nonsignificant improvement in functional recovery scores.

Fresh Fractures (RCT): In a randomized, placebo-controlled trial (Handolin, Kiljunen et al., 2005b), LIPUS was used as an adjunctive therapy following screw fixation for malleolar fractures of the ankle. In the placebo control group, a nonoperative sham unit that appeared identical to the LIPUS unit was applied. After long-term follow-up of 18 months, no significant differences between the placebo and control groups were observed with regard to clinical outcomes, including rate of healing, bone morphology, or bone mineral density.

Nonunion/Delayed Bone Fractures (systematic reviews): RCT showed reduced healing time in various bone types; non-RCTs reported high rates of healing.

- One small RCT evaluated LIPUS in patients who underwent bone grafting for nonunion fractures of the scaphoid bone. LIPUS therapy accelerated radiographic healing; there was a mean reduction in healing time of 40.4% (Busse et al., 2009).
- Two retrospective case series evaluated patients who received LIPUS therapy for nonunion fractures or delayed union fractures of different types of bones. Overall healing rates ranged from 84% to 87% for patients with nonunion fractures and from 87% to 98% for patients with delayed union fractures, which represented a significant improvement in patients with prior treatment failure (Hayes, 2003).

Nonunion/Delayed Union Bone Fractures (non-RCT): Relatively high rates of healing in both adults and children.

- *In adult patients with delayed union and nonunion fractures, mostly of the long bones (total, n=221 patients), overall healing rates were good to excellent and ranged from 73% to 100% (Gebauer et al., 2005; Jingushi et al., 2007; Rutten et al., 2007). The time required for healing in these patients ranged from 168 to 219 days. Healing rates were based on either radiographic evidence alone, or radiographic evidence and clinical assessment. Clinical examinations generally incorporated pain level on palpation, degree of weight bearing, if applicable, and degree of motion at fracture site. When reported, average fracture age ranged from 8.6 to 39 months. Two studies indicated that no concomitant treatment (e.g.,*

reinstigation of immobilization) was used during the LIPUS treatment period (Jinguishi et al., 2007; Rutten et al., 2007); this information was not provided by the other study (Gebauer et al., 2005).

- *A single prospective, uncontrolled study demonstrated that children with delayed unions or nonunions resulting from limb-lengthening procedures experienced 100% bone healing based on radiographic assessments following LIPUS therapy, but time to healing varied widely (3 to 12 months) (Gebauer & Correll, 2005).*

Other Indications (systematic reviews): Three RCTs indicated accelerated functional improvement associated with LIPUS treatment after distraction osteogenesis of tibia or mandible (Busse et al., 2009). [NOTE: These indications were excluded in the literature search performed for this rapid review.]

Effectiveness Summary: The Hayes (2003) review reported positive conclusions regarding the safety and effectiveness of LIPUS for nonoperatively managed fresh fractures, noting that the evidence applied primarily to the long bones. In addition, this review reported positive conclusions regarding LIPUS as an adjunct to surgery for operatively treated fresh fractures and as primary treatment for nonunion fractures; these conclusions applied to the tibia and radius. However, subsequent evidence, reflected in this rapid review, has introduced uncertainty regarding the benefit of LIPUS for operatively managed fresh fractures. The Hayes review stated only weakly positive conclusions regarding use of LIPUS for delayed union and negative or no definitive conclusions regarding all other applications and indications. In addition, no studies evaluated direct measures of function or QOL.

Using meta-analysis, Busse and colleagues showed LIPUS to have a substantial impact on healing in nonoperatively *managed fresh fractures but did not demonstrate an effect on return to function in nonoperatively managed fresh fractures; neither an effect on healing nor an effect on return to function was demonstrated in* operatively *managed fractures. They reported positive evidence of an impact on healing in a small study of LIPUS for nonunion but considered this evidence to be of low quality. In their conclusion, they called for large trials of high methodological quality to determine whether patient-important outcomes are improved by the use of LIPUS.*

Additional evidence provided by the primary studies did not encompass all indications evaluated in the two systematic reviews. However, for the indications that did overlap, results from the recently published primary studies did not substantially alter the overall body of evidence. As in earlier studies, positive results from treatment of delayed union or nonunion were reported by four primary studies, but these were of low quality (nonrandomized trials with serious methodological limitations). The fifth study was a single RCT that evaluated application of LIPUS to fresh malleolar fractures. This study was by the same authors as the malleolar fracture trials assessed by Busse and colleagues. It was characterized by serious limitations, including a very small sample size.

Altogether, evidence of moderate quality has shown LIPUS to promote healing in *nonoperatively* managed fresh fractures; evidence of an effect on functional outcomes is conflicting and thus of low quality. Evidence of a benefit in healing and functional recovery for patients with *operatively* managed fresh fractures is mixed and of low quality. Evidence of low quality suggests that LIPUS may accelerate healing of delayed union or nonunion fractures but evidence pertaining to pain and functional outcomes in this indication is lacking. [NOTE: Busse and colleagues (2009) considered the evidence in favor of an effect on healing in nonoperatively managed fresh fractures to be of low quality because healing was assessed by radiographic fusion only and because of study weaknesses, including substantial loss to follow-up in three of the four trials. However, the three trials consistently reported treatment effects of substantial size; hence, the designation "moderate" quality in the context of this rapid review.]

It should be noted that the evidence pertaining to impact on healing in fresh fractures does not necessarily address the question of whether LIPUS prevents delayed union or nonunion. The majority of the studies evaluating nonoperatively managed fresh fractures implemented follow-up periods of varying length (3 months to 4 years), and two studies provided no information on duration of follow-up. Studies did not always report the occurrence of subsequent diagnoses of delayed union or nonunion in patients who had not healed by the end of the study period. Thus, there is insufficient information to determine the extent to which nonunions or delayed unions were prevented in nonoperatively managed fractures. For operatively managed fractures, duration of follow-up periods were sufficiently long enough (12 to 18 months) that reported healing rates can be equated with prevention of nonunion (incomplete healing after 9 months). However, the results in the studies of operatively managed patients were inconsistent.

2. Are bone growth stimulators safe?

Evidence from Systematic Reviews and Technology Assessments: No important complications were reported by any of the studies covered in these two reviews.

Evidence from Primary Studies (RCTs and non-RCTs): There were no device-related complications or associated morbidities reported in the five studies. Gebauer et al. (2005b) reported that children may be susceptible to possible harm to the growth plate following one or more LIPUS treatments, although animal and in vitro studies have demonstrated no effects of ultrasound therapy on growth plates thus far. Additional well-designed, randomized controlled trials are necessary to further investigate the safety of LIPUS in a pediatric population.

Safety Summary: To date, no important safety issues have been identified. No serious device-related complications were reported by any of a large number of studies. However, the quantity of long-term data is only modest. The literature does not report any suspicion of long-term adverse effects from this noninvasive technology.

3. Does effectiveness vary by type of bone, the presence/absence of comorbidities, or other patient characteristics?

Evidence from Systematic Reviews: When patients in two small RCTs (with substantial loss to follow-up) were stratified by various risk factors, the treatment effect of LIPUS was most pronounced in smokers, in older individuals > 50 years of age, and in patients who had other risk factors for poor or prolonged bone healing. Based on tests of interaction, Busse et al. (2009) reported no differences in treatment effects across several fracture types, managed either nonoperatively or operatively. There was no evidence pertaining to the safety and effectiveness of LIPUS treatment in unstable fractures, pathological fractures, fractures related to malignancy, or in fractures with considerable displacement, angulation, or malalignment. Neither review identified studies specifically assessing the use of LIPUS in children or the elderly; the Hayes report provided data suggesting that there were no study participants younger than 16 years of age or older than 75 years of age (Busse et al., 2009; Hayes, 2003).

Evidence from Non-RCTs: Two small studies reported a significant relationship between fracture age (or length of time since fracture) and the rate of healing with the use of LIPUS. Patients with fractures ≤ 5 years demonstrated significantly higher healing rates, ranging from 86% to 95%, compared with a healing rate of 50% in patients with older fractures > 5 years (Gebauer et al., 2005). Similarly, in a retrospective study that conducted a multivariate analysis, young fractures, ranging from 3 to 6 months, achieved significantly higher rates of healing (90%) compared with fractures that were 6 to 12 months old (80%) and ≥ 12 months old (64%) (Jingushi et al., 2007). The multivariate analysis also identified additional factors that influenced outcomes, including time from most recent surgery to LIPUS therapy and the time from start of LIPUS therapy to first sign of radiological improvement.

Summary of Factors Affecting Effectiveness: The evidence indicates that for treatment of delayed union and nonunion fractures, LIPUS is more effective in patients with younger (more recent) fractures than in patients with older fractures and provides greater benefit to patients who have risk factors generally associated with prolonged fracture healing. However, the evidence was of low quality, and no conclusions can be drawn regarding the relative effect of LIPUS according to type of bone, age of fractures, demographic characteristics, or risk factors. Evidence generally applies to adult patients without serious comorbidities who are not dependent on drugs or alcohol and who do not take medications that would interfere with treatment. Except for one study that reported positive data pertaining to limb-lengthening procedures in children, there was no evidence regarding safety and effectiveness in a pediatric population.

Strengths and Limitations of the Evidence

The quality of the body of evidence pertaining to each indication is characterized in the summaries at the end of the description of findings for each key question. The following

sections describe the quality of studies included in the systematic reviews and the selected primary studies from recent literature.

Effectiveness Evidence from Systematic Reviews: The Hayes (2003) review included evidence from RCTs, as well as from retrospective case series studies. This review identified several studies that were supported by the manufacturer, including the four RCTs of LIPUS for fresh fracture (see ***APPENDIX V)****. However, the review did not specifically discuss source of funding as a possible source of bias. The study populations were generally small and there were high rates of attrition following randomization, with intention-to-treat (ITT) analyses performed in only a few studies. Hayes (2003) also noted that retrospectively collected data have the potential for patient selection and observer bias since the patients are selected from criteria developed after patients have already been treated and outcomes assessed.*

In the systematic review conducted by Busse et al. (2009), several sources of heterogeneity affected the quality of meta-analyses. There were considerable differences in the patient populations and some variation in duration of LIPUS, as well as in imaging methods to determine radiographic union studies. Only 5 of 13 studies evaluated functional outcomes. Among the 13 reviewed RCTs, 9 trials did not clearly report whether concealment of treatment allocation took place, or if patients, caregivers, or outcome assessors were blinded. A few studies reported high attrition rates, ranging from 28% to 47%. No studies reported an ITT analysis, but neither was any substantial crossover reported. This review did not discuss source of study funding as a potential factor for reporting bias. A key strength of the meta-analysis performed by Busse and colleagues was that they determined the optimal sample size for each RCT and considered results imprecise if the actual sample size was less than the optimal sample size. Overall, the authors considered the review to be based on very low to moderate-quality evidence, depending on the indication and outcome. They noted that the quality of evidence related to healing was diminished by the use of a surrogate measure (radiographic fusion without consideration of clinical measures).

Effectiveness Evidence from Primary Studies: The individual studies were generally of poor or fair quality, with very small to moderate sample sizes, which prevented meaningful results for certain outcome measures in some studies. The only randomized, placebo-controlled study, which applied LIPUS to malleolar fracture, was very small and was conducted by the same authors who conducted the malleolar fracture trials reviewed by Busse et al. (2009). Only one study was self-paired. No studies compared LIPUS with other forms of stimulation. Funding source information was available in three of the primary studies evaluated for this rapid review.

Evidence Pertaining to Key Questions #2 and #3: Safety data across the available studies appears sufficient to confirm that the use of LIPUS is associated with only minor complications, and that serious complications are unlikely. A very modest quantity of long-term data suggests that there are no complications associated with long-term use of LIPUS. Evidence of effectiveness by patient subgroup was sparse.

- **Table 1. Systematic Reviews of Studies Assessing Ultrasound Bone Growth Stimulators**

Key: BGS, bone growth stimulation; CI, confidence interval; f/u, follow-up; grp(s), group(s); GRADE, Grading of Recommendations Assessment, Development and Evaluation; hx, history; I, I index (statistical measure of heterogeneity); LIPUS, low-intensity pulsed ultrasonography; NOM, non-operative management; no-tx, no treatment; OM, operative management; pt(s), patient(s); RCT, randomized controlled trial; SAFHS, Sonic Accelerated Fracture Healing System; tx, treatment (or therapy); tx'd, treated; US, ultrasound

Authors/Sponsor Review Objective	Study Population	Review Methodology	Findings	Evaluation of Review
Hayes Inc. (2003)[a] Systematic review of studies assessing effectiveness and safety of US BGS used alone or in combination w/ another tx for fresh, delayed union, and nonunion fractures *F/u:* Varied across studies from mean of 111 days to ≥4 yrs *Funding source:* No outside sources for this systematic review; 2 RCTs and 1 case series study supported by manufacturer of SAFHS device; manufacturer provided SAFHS devices for 1 RCT.	*# and type of studies included:* 3 small double-blind RCTs published as 5 separate articles evaluating SAFHS devices in pts w/ fresh bone fractures (Heckman et al., 1994; Cook et al., 1997b; Kristiansen et al., 1997; Emami et al., 1999a; Emami et al., 1999b) 2 retrospective case series evaluating pts w/ delayed unions or nonunions (Mayr et al., 2000a; Nolte et al., 2001) *# pts:*[b] RCTs: n=211 Case series: n=1398 *Comparators/controls:* Placebo and no-tx grps; any medical, mechanical, or surgical intervention designed to tx fractures; different tx regimens w/in the US tx modality *Typical pt inclusion/exclusion criteria:* Included skeletally mature pts w/ fresh fractures,	*Databases searched:* PubMed, PreMEDLINE, MEDLINE, HealthSTAR, The Cochrane Library, EMBASE, and Current Contents *Time span of literature search:* 1966 – October 2003 for all databases but Current Contents database (January 2001 – October 2003) *Inclusion criteria:* Systematic reviews; RCTs; nonrandomized comparative studies; case series w/ ≥10 pts; English-language articles; articles published from 1986 onward; full-length, peer-reviewed articles; measures of fracture healing as outcomes *Exclusion criteria:* Abstracts; studies w/ outcomes unrelated to fracture healing Studies were evaluated for methodological strength and applicability to the key	*Fresh fractures (NOM):* RCTs: Data from 2 RCTs indicate that low-intensity US accelerates healing of fresh tibial shaft and distal radius fractures and decreases incidence of nonunion in tibial fractures in selected pts (Heckman et al., 1994; Kristiansen et al., 1997). Stratification by various risk factors of the data from the above 2 studies found that tx effect of US was largest in smokers and older individuals (Cook et al., 1997b). *Fresh fractures (OM):* RCTs: In a small RCT, US tx did not significantly promote healing of fresh tibial fractures that were 1st tx'd w/ closed reduction and intramedullary nailing; f/u 1 yr from surgery (Emami et al., 1999a; Emami et al., 1999b). *Delayed unions and nonunions (type of fracture not specified):* Non-RCTs: In 2 retrospective case series studies on nonunions (fracture age ≥9 mos) in pts who had failed prior tx, overall healing rates ranged from 84% to 100%. This was significantly higher relative to the self-paired control of failed tx (Mayr et al., 2000a; Nolte et al., 2001). In the same case series studies, healing	*Overall conclusion(s):* Use of SAFHS device accelerates fracture healing when used in conjunction w/ closed reduction and cast immobilization for tx of selected pts w/ fresh fractures of tibia or radius who are tx'd w/in 7 days postfracture. There is insufficient evidence to conclude that US therapy is useful for any other type of fresh fracture. US therapy also promotes fracture healing in pts w/ nonunion fractures of ≥9 mos and in those w/ delayed union fractures of 3-9 mos in whom healing has ceased or is not progressing. *Limitations:* Only English-language publications included; data were limited since only small RCTs and retrospective case series were available for review; study-funding sources may not have been routinely reported.

	delayed unions, or nonunions that were not tumor related Several studies excluded older pts age >75 yrs and children age <16 yrs; comminuted, displaced, angled, or misaligned fractures; pts w/ alcohol or drug dependency; comorbidities (arthritis, neuropathy, malignancy, nutritional deficiency, vascular insufficiency); immunosuppressive, anticoagulant, or biphosphonate tx; pregnancy	questions. *Outcome measures:* Varied by study	rates of delayed unions (fracture age 3-9 mos) were also statistically significant and ranged from 87%-98%. Healing rates for both delayed unions and nonunions peaked for pts aged 30-50 yrs. Stratification of data by fracture and pt characteristics found that older age, vascular or renal insufficiency, smoking, and medications that alter bone metabolism impair fracture healing. Long-term f/u showed that fracture healing following US tx of nonunions was durable (Nolte et al., 2001). *Device/procedure-related complications:* Transient muscle cramping (<1 wk) in pt tx'd w/ US for fresh fracture; no other complications reported.	
Busse et al. (2009) Institute for Work and Health, Toronto, Canada; McMaster University, Hamilton; University of Western Ontario, London, ON; Boston University School of Medicine, Boston, MA; Italian National Cancer Institute Regina Elena, Rome, Italy Systematic review and meta-analysis of RCTs evaluating the efficacy of LIPUS for healing of fractures *F/u:* Duration of study	*# and type of studies:* 13 RCTs published as 15 separate articles NOM fresh fractures: 4 RCTs (Heckman et al., 1994; Kristiansen et al., 1997; Mayr et al., 2000; Lubbert et al., 2008) NOM stress fractures: 1 RCT (Rue et al., 2004) OM fresh fractures: 4 RCTs (Emami et al., 1999a; Emami et al., 1999b; Leung et al., 2004; Handolin, Kiljunen et al., 2005a; Handolin, Kiljunen, Arnala, Parjarinen et al., 2005) Bone grafting for nonunion:	*Databases searched:* CINAHL, EMBASE, MEDLINE, HealthSTAR, and the Cochrane Central Registry of Controlled Trials (no language restrictions) *Time span of literature search:* From inception of databases to September 10, 2008 *Inclusion criteria:* Random allocation of pts w/ any type of fracture to LIPUS or control grp *Exclusion criteria:* Studies that were reanalysis of primary trials; trials investigating high-intensity	NOTE: Evidence quality ratings (e.g., "low" or "moderate") were assigned by the systematic review authors. All reviewed studies were RCTs and are presented by indication. *Overall analyses (pooling across all studies w/ radiographic healing measures):* Reduction in healing time (% reduction): Moderate effect in favor of LIPUS when results were pooled across 7 studies (n=241; pooled mean of 33.6% relative reduction; 95% CI, 21.4%-43.8%) (Heckman et al., 1994; Kristiansen et al., 1997; Emami et al., 1999a; Emami et al., 1999b; Mayr et al., 2000; Leung et al., 2004; Ricardo 2006). (The authors did not explain why the studies of malleolar fracture were not included in the analysis.) However, heterogeneity of the studies was high (I^2=76.9%; heterogeneity *P*<0.01).	*Overall conclusion(s):* Across 6 reviewed studies w/ measures of radiographic healing; LIPUS appears to accelerate healing time by 33.6%. Meta-analyses by type of fracture indicated a significant reduction in healing time w/ LIPUS tx for NOM fresh fractures and bone grafting for nonunions, but not for OM fresh fractures. However, meta-analyses did not find a significant effect of LIPUS tx on functional recovery for any type of fracture, including NOM fresh fractures, NOM stress fractures, or OM fresh fractures. *Limitations:* Possibility of bias

f/u NR for reviewed studies Only duration of LIPUS was reported and this varied (until healed, set time ranging from 13 hrs to 90 days, or maximum of 140 days until fracture healed) *Funding source:* No external funding for this review; however, 3 authors are involved in a multicenter RCT that has received partial funding from Smith & Nephew Inc.	1 RCT (Ricardo 2006) Distraction osteogenesis: 3 RCTs (Tsumaki et al., 2004; El-Mowafi & Mohsen 2005; Schortinghuis et al., 2005) *# pts:* 563 randomized, 488 analyzed *Comparators/controls:* Sham US device; US in addition to usual care vs usual care alone; US on 1 limb and control on the other limb in pts w/ bilateral tibial osteotomy *Typical pt inclusion/exclusion criteria:* Pts had NOM fresh or stress fractures, distraction osteogenesis, bone grafting for nonunion, or OM fresh fractures No additional information or pt characteristics based on inclusion/exclusion criteria was provided.	continuous US; grouping of studies into 5 clinical categories (NOM fresh fractures, NOM stress fractures, distraction osteogenesis, bone grafting for nonunion, OM fresh fractures) Time to bridging of 3 cortices equivalent to time to achieve ≥70% bridging of fracture. Time to bridging of 3 calluses considered equivalent to time to appearance of 3rd callus. GRADE criteria used to evaluate quality of evidence by outcome. Random effects meta-analyses used to determine pooled estimates when appropriate. Optimal information size calculated for meta-analyses. *Outcome measures:* Varied across studies; categorized as either functional improvement or radiographic healing	Tests of interaction did not find a different effect of LIPUS tx across clinical presentations. *Fresh fractures (NOM):* Reduction in healing time (% reduction): Low-quality evidence from 3 trials (tibia, distal radius, and scaphoid fractures) suggests that LIPUS significantly accelerates radiographic healing time (n=158; pooled mean relative reduction of 36.9%; 95% CI, 25.6%-46.0%) (Heckman et al., 1994; Kristiansen et al., 1997; Mayr et al., 2000). Return to function (time to functional recovery): Moderate quality evidence from 1 trial found no effect of LIPUS on functional recovery from conservatively managed fresh clavicle fractures (n=101; mean, 1.40 days; 95% CI, –0.56 to 3.36) (Lubbert et al., 2008). *Fresh tibial stress fracture (NOM):* Return to function (time to active duty): Moderate-quality evidence from 1 trial found no effect of LIPUS on return to function in pts w/ NOM tibial stress fractures (n=26; mean of 0.4 days; 95% CI, –13.1 to 13.9) (Rue et al., 2004). *Fresh tibial fractures (OM):* Reduction in healing time (% reduction): 2 trials provided very low quality, inconsistent evidence regarding accelerated healing tx (n=61; pooled mean relative reduction of16.6%; 95% CI, –76.8% to 60.7%) (Emami et al., 1999a; Emami et al. 1999b; Leung et al., 2004 Return to function (time to full weight bearing): Same 2 trials provided low-quality, inconsistent evidence regarding improvement in functional outcomes (n=61;	since only RCTs, which generally had small sample size, were included in the review; inconsistency in findings across studies may arise from the heterogeneity of pt populations even w/in the 5 clinical categories.

			mean absolute reduction by 3.4 wks; 95% CI –2.1 to 8.9 wks) (Emami et al., 1999a; Emami et al. 1999b; Leung et al., 2004). *Fresh malleolar fracture (OM):* Return to function: Small but NS difference at 18 mos in a single very small trial (Handolin, Kiljunen, Arnala, Parjarinen et al., 2005). Reduction in healing time: NS difference in 2 very small trials (2 reports for 1 trials) Handolin, Kiljunen et al., 2005a; Handolin, Kiljunen, Arnala, Parjarinen et al., 2005). *Nonunions (tx'd by bone grafting w/ LIPUS):* Reduction in healing time (% reduction): Low-quality evidence from 1 trial suggests accelerated radiographic healing time of established nonunions of scaphoid bone managed by bone graft w/ LIPUS tx (n=21; mean relative reduction of 40.4%; 95% CI, 30.8%-48.7%) (Ricardo 2006). *Distraction osteogenesis:* Return to function: 3 trials provided very low quality evidence for accelerated functional improvement after distraction osteogenesis of tibia (Tsumaki et al., 2004; El-Mowafi & Mohsen 2005) or mandible (Schortinghuis et al., 2005). Meta-analyses of these trials not conducted due to heterogeneity of outcome measures. *Complications:* NR	

[a] See Appendix V for detail pertaining to each selected study.
[b] There is some overlap of data and the patient populations between studies as most of the studies involved patients from a prescription use registry and/or were studies supported by the manufacturer of the Sonic Accelerated Fracture Healing System® (SAFHS) device.

Table 2. Primary Studies Assessing Ultrasound Bone Growth Stimulators (ordered by study design)

Key: BMI, body mass index; CI, confidence interval; cm, centimeter; DXA, dual-energy x-ray absorptiometry scans; f/u, follow-up; g, gram; grp(s), group(s); kHz, kilohertz; LIPUS, low-intensity pulsed ultrasound; ITT, intention-to-treat; MDCT, multidetector computed tomography; M/F, male/female; MHz, megahertz; μs, microsecond; mW, milliwatt; NR, not reported; OR, odds ratio; pt(s), patient(s); SAFHS 2A, Sonic Accelerated Fracture Healing System 2A; SD, standard deviation; Se, sensitivity; Sp, specificity; tx, treatment; US, ultrasound

Authors/Study Design	Study Population	Procedures/Outcome Measures	Results/Complications	Conclusions/Limitations/ Quality Ratings
Handolin, Kiljunen, et al. (2005b) Helsinki University Central Hospital, Dextra Medical Center, Helsinki; Kanta-Hämeenlinna, Finland Randomized, double-blind, placebo-controlled trial to assess long-term effects of LIPUS tx on malleolar fractures *F/u:* 18 mos *Time frame:* NR *Funding source:* Study supported by research grants from the Foundation for Orthopaedical and Traumatological Research in Finland, Helsinki University Central Hospital, and the Academy of Finland	n=16 pts w/ lateral malleolar fractures (M/F 7/9) Mean age (yrs) (tx; control): 43.3 (range 28-66); 41.8 (range 22-59) *Inclusion criteria:* NR *Exclusion criteria:* Bimalleolar and trimalleolar ankle fractures	Lateral malleolar fractures fixed w/ poly-L-lactic acid screws in all pts. Tx: Active LIPUS tx (SAFHS 2A, Exogen) for 20 mins daily for 6 wks, beginning 2 wks after the operation (n=8) Control: Sham tx for 20 mins daily for 6 wks (n=8) F/u evaluations were blinded. ITT analysis not performed. *Outcome measures:* Radiological bone morphology (MDCT scans); bone mineral density (DXA scans); clinical outcomes (Olerud-Molander score and clinical exam of the ankle)	*Clinical outcomes:* All fractures healed, and all ankles were stable at 18 mos; 7 pts had mild pain and restriction on movement. Mean Olerud-Molander score preop vs postop at 18 mos (tx; control): 99.4% vs 95.0%; 98.8% vs 96.3% (NS) *Radiological bone morphology:* At 18 mos, NS differences observed between 2 grps in fracture healing on plain radiographs or MDCT scans; NS differences observed between 2 grps in radiological bone morphology at fracture or screw site. *Bone mineral density (tx; control):* Immediate postop: 0.511 g/cm^2; 0.533 g/cm^2 (difference of means –0.022, 95% CI, –0.102 to 0.059; NS) At 3 mos: 0.486 g/cm^2; 0.538 g/cm^2 (difference of means –0.052; 95% CI, –0.138 to 0.033; NS) At 18 mos: 0.529 g/cm^2; 0.571 g/cm^2 (difference of means –0.042; 95% CI, –0.130 to 0.046; NS) No pts lost to f/u. *Complications:* NR	Results suggest that LIPUS tx had no effect on bone morphology, bone mineral density, or clinical outcomes. *Limitations:* Very small sample size; methods of randomization and blinding NR. *Quality:* Fair (downgraded due to very small sample size and lack of transparency regarding randomization and blinding) for effect on healing, functional outcomes, and bone morphology.
Gebauer et al. (2005) Orthopädische Klinik	n=72 eligible pts (average age ± SD,	LIPUS tx: Pts used LIPUS device for 1 continuous 20-	Healing rate for established nonunions: 85% (57/67)	Results suggest that LIPUS tx for established nonunions

Tegernsee; Zentralklinikum Augsburg; Germany; Krankenhaus der Barmherzigen Schwestern vom Heiligen Geist, Unfallchirurgie, Wels, Austria Prospective study w/ self-paired controls to assess LIPUS in pts w/ established nonunion *F/u:* Median 381 days *Time frame:* NR *Funding source:* Exogen, Inc. provided prescription registry data	46±19.9 yrs; M/F 41/26) selected from 85 consecutive pts who met initial inclusion criteria of established nonunion (defined as no healing ≥ 8 mos) 13 pts were excluded because last surgical procedures was < 4 mos before start of LIPUS (all 13 cases healed during tx period) Of 72 eligible pts, 5 excluded due to death (n=1), noncompliance (n=2), and early withdrawal (n=2). Pts w/ nonunions were a subgrp of consecutive pts who had been tx'd w/ LIPUS during July 1995 – April 1997. Mean fracture age ± SD: 39± 6.2 mos (range 8-198) Mean # of mos w/o surgery before LIPUS: 24.2±4.9 (range 4-197) Mean # of failed surgical procedures in study grp: 2.0±0.3 *Inclusion criteria:* Established nonunion	min period per day at home for tx of various fracture types, including tibia, clavicle, femur, metatarsal, ulna, humerus, ankle, fibula, scaphoid, pelvis, calcaneus, rib, knee, or radius/ulna US pressure wave signal was characterized by 200-µs burst of 1.5-MHz acoustic sine waves, repeating at a frequency of 1 kHz (Exogen GmbH). Controls: Pts served as own controls; LIPUS results compared w/ prior outcome of failure to heal At 1- to 2-mo intervals, anterior/posterior radiographs were taken after start of LIPUS. At each f/u visit, pts underwent clinical exam to assess pain level on palpation, extent of weight bearing, and degree of motion at fracture site to determine extent of healing. Nonunions were considered healed when fracture healing was demonstrated on both clinical and radiographic assessments. *Outcome measures:*	Subset A (fully validated subgrp where radiographic data was reviewed before and after US; all additional inclusion criteria confirmed to be met): 48/67 (72%) Subset B (nonvalidated subgrp where radiographic data was not available; clinical records, fx age, and long-term f/u data were used for validation): 19/67 (28%) Healing rate, subset A: 85% (*P*=0.00001 for comparison against prior results of 100% failed cases Healing rate, subset B: 84% (*P*=0.00001 for comparison against prior results of 100% failed cases) Mean healing time (all healed nonunions) (days ± SD): 168±10.2 (range 57-375) Mean fracture age for all healed unions (mos ± SD): 31.2±5.6 (range 8-197) Mean fracture age for all failed cases (mos ± SD): 84.4±22.1 (range 9-194) *Comparison between fracture age ≤5 yrs and >5 yrs:* Healing rates by fracture age (≤1 yr, >1 yr to ≤2 yrs, ≥2 yrs to ≤5 yrs): 95%, 86%, 93% Healing rates of fracture age (>5 yrs): 50%; this value was statistically significant when compared across all age strata (*P*=0.015). Long-term f/u data on all healed nonunions available for 91% (52/57) of pts. *Complications:* NR	resulted in a high percentage of healed nonunions in an acceptable time frame, particularly in pts age ≤5 yrs w/ fractures. *Limitations:* Small sample size; clinical and radiographic assessments not fully reported; long-term f/u data of healed cases did not involve clinical or radiographic assessments; whether concomitant tx was used was NR; use of manufacturer registry data; potentially incorrect use of term, ITT; lack of outcome data regarding 5 eligible pts; some loss of f/u. *Quality:* Poor

	defined as ≥8 mos from fracture date; radiographic assessment before and at start of LIPUS to indicate that fracture healing had not progressed or had stopped ≥3 mos before start of LIPUS; fracture line visible on radiographs; ≥4 mos w/o surgical intervention prior to LIPUS *Exclusion criteria:* Skeletally immature; pregnant or nursing; nonunions that were malaligned, grossly unstable, actively infected, or had extensive bone loss	Healing rate; healing time; effects of fracture age on healing rate		
Rutten et al. (2007) Tergooiziekenhuizen, Hilversum; Spaarne Ziekenhuis Hoofddorp; Kennemer Gasthuis, Haarlem, the Netherlands Prospective noncomparative study to evaluate LIPUS for posttraumatic nonunions of the tibia *F/u:* Ave 2.7 yrs (range 1.1-4.6) *Time frame:* NR *Funding source:*	n=71 eligible pts (M/F, 56/15; mean age, 40 yrs) w/ posttraumatic consecutive nonunions of the tibia selected from 123 pts (52 pts were excluded according to enrollment criteria); pts received no additional cast or surgical tx at start or during US tx Median US tx duration for all pts: 160 days (range 52-739) Modified ITT anlaysis performed. *Initial fracture characteristics and*	Pts underwent LIPUS once daily for 20 continuous mins; US pressure wave signal consisted of 200-µs burst of 1.5 MHz acoustic sine waves, repeating at a modulation frequency of 1 kHz w/ intensity of 30 mW/cm^2 Average duration of LIPUS for all included cases: 188 days (range 52-739; median 160) Nonunions were considered healed when 3of 4 cortices were bridged in 2 orthogonal radiographical views.	Overall rate of healing: 73% (52/71) Of 52 excluded cases, 39 pts were available for long-term f/u (20 pts healed and 19 did not); 13/52 were lost to f/u Modified ITT analysis of n=110 pts showed 65% heal rate (72 healed and 38 not healed); compared w/ nonoperative immobilization alone, heal rate of LIPUS was significantly higher (P<0.0001). Mean healing time (days ± SD): 184±17.8 (range 52-739) Mean fracture age (days): 257 (range 180-781) Average time period between last surgery and start of US tx (days): 195 (range 90-717)	Results suggest that adjunctive LIPUS resulted in a relatively high percentage of healed nonunions of the tibia. *Limitations:* Small sample size; no comparator or controls; lack of randomization; study supported by manufacturer; f/u data reported by questionnaire, which may introduce recall bias; high loss to f/u *Quality:* Poor

Study was supported by Smith & Nephew B.V.	*severity:* Displaced: n=61 (86%) Comminuted: n=53 (75%) Displaced + comminuted: n=48 (67%) *Inclusion criteria:* Nonpathologic trauma; minimal fracture age 6 mos; skeletal maturity; visible fracture line in 2 orthogonal views; radiographs did not demonstrate any healing improvements in 3 mos prior to start of US tx; time interval between last surgery and start of LIPUS ≥3 mos *Exclusion criteria:* Tx <3 mos or a new tx intervention was introduced w/in 3 mos after start w/ US tx	Conservative fracture tx: n=19 Operative tx: n=52 Operative tx, including plate and screw osteosynthesis: n=9; intramedullary osteosynthesis, n=27; external fixation, n=16 Average # of surgical interventions for total study grp: 1.2 *Outcome measures:* Overall healing rate (healed or failed) stratified by various variables; mean healing time	Mean healing rate of LIPUS + preexisting immobilization was significantly higher than nonoperative immobilization alone (P<0.001). Mean healing time (days) was significantly shorter for hypertrophic nonunions (128) vs oligotrophic (218) and atrophic nonunions (183) (P<0.05). NS differences in healing rate for remaining stratified variables, although there were some positive trends: Healing rate (smokers, nonsmokers): 63%, 84% (NS) Healing rate (nonunions middle 3rd of tibia, proximal tibia): 89%, 77% (NS) For all cases of healing, radiologic review demonstrated no difference in healing rates. 55 pts had long-term f/u data (41 healed; 14 not healed); all 55 pts showed no refractures; 16 pts were lost to f/u (11 healed and 5 not healed); 98% of all f/u pts were highly compliant. Of 52 excluded cases, 39 pts were available for long-term f/u (20 pts healed and 19 did not); 13/52 (25%) were lost to f/u. Modified ITT analysis of n=110 pts showed 65% healing rate (72 healed and 38 not healed); compared w/ nonoperative immobilization alone, healing rate of LIPUS was significantly higher (P<0.0001). *Complications:* NR	
Jingushi et al. (2007)	n=72 pts w/ long bone fractures (M/F 52/20)	LIPUS tx was performed using US pressure wave	Overall rate of union: 75% of all long bone fractures	Results suggest that the time from the most recent surgery to

Kyushu University, Fukuoka, Japan Retrospective study evaluating LIPUS for the tx of delayed union or nonunion of long bone fractures *F/u:* NR *Time frame:* NR *Funding source:* NR	Delayed union was defined as no healing or union for >3 mos after most recent surgical procedure; nonunion was defined as additional surgical tx indicated for the fracture case. Mean age at start of LIPUS tx (yrs): 40.4 (range 14-83) Fracture types: Closed, 56%; open, 42% Time since most recent surgery (mos): 11.5 (range 3-68) Upper extremity, long bone fractures: Humerus (n=13), radius (n=1), ulna (n=8) Lower extremity, long bone fractures: Femur (n=22), tibia (n=28) # of surgical operations undergone prior to LIPUS tx: 1 (61%), 2 (22%), ≥3 (17%) *Inclusion criteria:* Fractures of long bones in upper and lower extremities *Exclusion criteria:* Cases not requiring prior operative txs	signal characterized by 200-µs burst of 1.5-MHz acoustic sine waves repeating at a frequency of 1 kHz. No additional concurrent txs were performed during study tx. Effects of LIPUS were assessed clinically and radiographically each mo by an experienced orthopedic physician. Data from an earlier 2003 prospective, multicenter study was analyzed using a logistic regression method to determine factors influencing the healing rate. *Outcome measures:* Rate of healing (healing defined according to both radiographic criteria and physician-reported stability and pain); prognostic factors affecting final outcome (logistic regression analysis); radiological assessments to predict degree of union (sensitivity and specificity)	Fracture age, range (mos) (all long bone fractures; long bone fractures in upper extremities; long bone fractures in lower extremities): 18.9 (3-159); 19.9 (3-159); 18.4 (3-105) Rate of union in upper and lower extremity long bone fractures, 55% and 84%, respectively. Overall mean period until union (days): 219 (range 56-588) Mean period until union in upper and lower extremity long bone fractures (days): 192 (range 118-352) and 226 (range 56-588) Mean period of tx in pts who failed to achieve union (days): 306 (range 108-639) For all bones, relationship between time from most recent surgery to start of LIPUS (mos) and % union: 3-6 mos: 89.7% (*P*=0.006) (OR, 2.78; 95% CI, 1.34-5.80) 6-12 mos: 75.0% ≥12 mos: 52.6% For all bones, relationship between time from fracture to start of LIPUS (mos) and % union: 3-6: 89.5% (*P*=0.039) (OR, 2.22; 95% CI, 1.04-4.75) 6-12: 80.0% ≥12: 63.6% Significant relationship between time from start of LIPUS and 1st sign of radiological improvement (*P*<0.02). For upper extremities, relationship between time from most recent surgery to start of	the beginning of LIPUS tx is an important factor for determining the union rate of long bone fractures and for predicting the effect of LIPUS tx on union as demonstrated by radiography; the highest union rates were achieved at 3 to 6 mos from the most recent surgery to the start of LIPUS. *Limitations:* Retrospective study design; relatively small study design; single-institution study; results not stratified by type of healing failure. *Quality:* Poor

			LIPUS (mos) and % union: 3-6: 83.3% (*P*=0.014; OR, 5.77; 95% CI, 1.44-23.14) 6-12: 25.0% ≥12: 16.7% For lower extremities, relationship between time from fracture to start of LIPUS (mos) and % union: 3-6: 88.9% (*P*=0.016; OR, 4.67; 95% CI, 1.34-16.31) 6-12: 40.0% ≥12: 25.0% In lower extremity fractures, there was a significant relationship between union rate and time when radiological improvement was 1st observed (*P*<0.03). *Performance of radiography to predict union when LIPUS tx began w/in 6 mos of fracture:* For all cases of long bone fractures at 4 mos of tx (sensitivity, specificity): 92%, 100% For upper extremity long bone fractures (sensitivity, specificity): 94%, 100% For lower extremity long bone fractures (sensitivity, specificity): 92%; 100% *Complications:* NR	
Gebauer & Correll (2005) Orthopedic Clinic Tegernsee; University of Munich; Children's Orthopedic Clinic Aschau, Aschau, Germany Prospective case	n=17 children w/ diminished calcification of the generate, which was judged stopped if calcification of newly formed bone failed to improve for ≥3 mos (average age 7.85 yrs; range 6-15; M/F 7/10)	112 pts underwent leg-lengthening procedures w/ and w/o deformity correction performed by external fixation; of these, 19 (16.9%) pts lacked solid bone consolidation, and delayed unions (n=13) or nonunions (n=4) resulted.	17/17 (100%) pts experienced complete union. Time to healing (mos): range 3.0-12.0 Mean time until the start of LIPUS (mos): 6.29 In 7/17 pts, duration of LIPUS ranged from 3-5.5 mos.	Results suggest that LIPUS tx for delayed unions and nonunions following limb-lengthening surgery resulted in a high rate of healing and may be considered a reasonable salvage procedure. *Limitations:* Very small study sample; lack of comparator or

series to assess LIPUS tx for delayed unions and nonunions in children following leg-lengthening surgery *F/u:* Up to 4 yrs *Time frame:* 1998-2001 *Funding source:* NR	No other concurrent txs performed during US tx. Nonunions were defined as 8 mos of no healing; delayed unions were defined as a period of no healing from 3-7.3 mos *Inclusion/exclusion criteria:* NR	Of 19 pts, 17 underwent LIPUS and tx was discontinued when solid bone consolidation was observed by radiography. Pts used LIPUS device (Smith & Nephew Inc.) for 20-min period daily for tx of the lengthened bone, which included the tibia (n=15), femur (n=1), and tibia segment (n=1) until fracture healed. Mean time to start of LIPUS tx following leg lengthening: 6.29 mos, range 3.0-10.2 LIPUS effects were assessed by x-ray imaging every 6 wks. US pressure wave signal was characterized by 200-µs burst of 1.5-MHz acoustic sine waves repeating at a frequency of 1 kHz. *Outcome measures:* Healing rate; healing time	3/17 (18%) pts required ≥10 mos of LIPUS tx to achieve full healing. Based on clinical control of the unilateral cases w/ LIPUS tx, both limbs subsequently grew at the same rate. *Complications:* NR; no effects of US were observed on the growth plates	sham control grp; complete f/u data NR; complete radiographic assessments following LIPUS tx NR; radiographic and clinical definitions of healing NR; clinical control not fully described. *Quality:* Poor

Invasive and Semi-Invasive Electrical Bone Growth Stimulators (Tables 3 and 4)

Systematic Reviews

The Hayes Medical Technology Directory Report on *Electrical Bone Growth Stimulation, Invasive* (Hayes, 2004a) was the only systematic review that evaluated invasive electrical bone growth stimulators. This report included two randomized controlled trials (RCTs), eight nonrandomized comparative studies, and five case series studies published in February 2004 or earlier. A total of 3683 patients were involved across all studies, with sample sizes ranging from 28 to 1686. This review is summarized in Table 3. The Hayes report is divided into three table entries according to type of stimulator (invasive or semi-invasive) and/or indication. Eleven of the 15 studies investigated invasive DCES and four investigated semi-invasive DCES. Invasive DCES was evaluated for nonunion or delayed union fractures and as an adjunct to spinal fusion. Semi-invasive DCES was evaluated for fresh fractures and nonunion or delayed union fractures.

Primary Studies

Three primary studies of invasive DCES bone growth stimulation in patients requiring fusion surgery met the selection criteria for studies published after February 2004 and thus are not covered in the Hayes (2004a) systematic review (Lau et al., 2007; Saxena et al., 2005; Welch et al., 2004). These studies are summarized in Table 4. Two studies evaluated delayed union or nonunion of arthrodesis of the foot or ankle (Lau et al., 2007; Saxena et al., 2005). Lau et al. (2007) included a control group of patients who had not undergone invasive stimulation; historical patient data originated from a previous database with similar demographics. This study evaluated invasive stimulation in patients as an end-stage salvage treatment. A single study evaluated cervical spinal fusion in both children and adults (Welch et al., 2004). All three studies were retrospective in design and evaluated implantable electrical stimulators in combination with surgical intervention. Only patients at high risk of fusion failure were included in each study. Surgical intervention generally included internal fixation and bone grafting with either autograft or allograft bone. Patient populations were very small and ranged from 20 to 38 patients. Follow-up periods ranged from 9 to 27 months. Outcome measures included healing rates, time to healing by radiographic and/or clinical assessment, and pain. One study used formal assessment tools, including the SF-36® Health Survey (Medical Outcomes Trust) and foot and ankle scoring systems, to monitor patient improvement in pain, function, and QOL (Lau et al., 2007).

Patient Characteristics

When reported, inclusion/exclusion criteria typically required that patients be adults, nonsmokers, and free of serious systemic disease that might interfere with treatment. Inclusion criteria for studies that evaluated the impact of DCES on high-risk patients

undergoing spinal fusion or joint arthrodesis selected only patients with one or more high-risk factors, e.g., previous failed spinal fusion, obesity, severe spondylolisthesis, multilevel fusion requiring bone grafting, or smoking. In one study, delayed union of long bones was defined as at least 12 weeks duration following initial injury, and other studies defined established nonunions as at least 9 months duration. The presence of implanted electrical devices, including cardiac pacemakers and defibrillators, was mentioned as an exclusion criterion in one study, and another study excluded patients with pseudarthrosis or nonunions secondary to pathological fractures (Hayes, 2004a).

1. Are bone growth stimulators effective in promoting healing, reducing pain, or improving function when applied to fresh fractures, delayed union or nonunion fractures, or fusion sites?

Fresh Fractures (systematic review): Positive results in non-RCTs.

- Two concurrently controlled trials found that healing of fresh fractures of the jaw or tibia was accelerated by semi-invasive DCES. However, a comparison of the proportion of successful unions achieved in the treatment groups was not reported.
- Two relatively large case series studies evaluated various fracture profiles, including tibial nonunions. The healing rate achieved with semi-invasive electrical stimulation ranged from 84% to 87%.

Nonunion/Delayed Union Bone Fractures (systematic review): Positive results in non-RCTs.

- In a small nonrandomized comparative study, patients with primarily nonunion fractures of long bones who were treated with either invasive or semi-invasive DCES achieved higher rates of bone union than those who underwent pulsed electromagnetic field therapy (pulsed electromagnetic field [PEMF], a noninvasive electrical stimulation modality), although this was not confirmed statistically.
- In a single case series study of invasive DCES, successful union was achieved with electrical stimulation in 86% of delayed or nonunion fractures, the majority of which were tibial.
- In two case series studies, healing rates achieved with semi-invasive DCES for nonunion fractures ranged from 84% (tibial fractures) to 87% (varying types of fractures).
- A logistic regression analysis comparing healing rates of tibial nonunions treated with semi-invasive DCES, capacitive coupling, or bone grafting determined that there were no significant differences among the treatment options when no risk factors were extant, but the presence of risk factors adversely affected healing rate regardless of treatment modality.

Spinal Fusion (lumbar or lumbosacral fusion, systematic review): One RCT showed substantial benefit of invasive DCES relative to control for radiographic spinal fusion; however, in the other

RCT, the control group exhibited greater rates of spinal fusion and clinical success (but these were not statistically significant); positive results in non-RCTs.

- Two RCTs reported conflicting results pertaining to the impact of invasive DCES on spinal fusion success. One small RCT reported successful spinal fusion in 81% of high-risk patients who had DCES, compared with only 54% of patients who underwent surgery alone (*P*=0.026). However, a second small RCT (high-risk and normal-risk patients) that evaluated instrumented spinal fusion alone or in combination with either DCES or PEMF therapy reported no statistical differences between DCES, PEMF therapy, and placebo in achieving radiographic spinal fusion or clinical success.
- Four studies with historical control groups found that invasive DCES improves spinal fusion rates; successful fusion rates ranged from 92% to 96% of stimulated patients and 75% to 85% of unstimulated patients. Two of the four studies had overlapping patient populations. One study was restricted to high-risk patients.
- A retrospective study analyzed data from a large healthcare claims database and reported that patients who underwent spinal fusion in conjunction with invasive DCES required less inpatient care in the 2 years following surgery compared with those who did not receive adjunctive DCES; however, rates of spinal fusion were not reported.
- Spinal fusion was successful in 92% and 93% of stimulated patients in two case series studies with overlapping patient populations.

Cervical Spinal Fusion in High-Risk Patients (non-RCT): A retrospective study found that in patients at high risk for nonunion treated with adjunctive invasive DCES following para-axial cervical arthrodesis, solid arthrodesis occurred in 94% of patients (Welch et al., 2004).

Primary Foot/Ankle Arthrodesis in High-Risk Patients (non-RCT): A retrospective review of high-risk patients treated with invasive DCES for prevention of delayed union/nonunion following foot or ankle arthrodesis used a proxy outcome measure as the study did not specifically report the percentage of patients who achieved successful fusion. In this study, 79% of patients did not require further surgery (Saxena et al. 2005). In addition, radiographic consolidation occurred in 86% of arthrodeses at a mean of 10.3 weeks.

Salvage Foot/Ankle Arthrodesis in High-Risk Patients (non-RCT): The retrospective case-controlled study by Lau et al. (2007) evaluated invasive DCES as an end-stage salvage treatment for foot and ankle arthrodesis. Union was achieved in 65% of the cases, but the study did not compare union rate to the historical control group. Thus, the magnitude of the treatment effect is difficult to determine. At follow-up, 89% of patients reported satisfaction, although < 50% of all patients were available to complete the satisfaction questionnaire.

Pain and Functional Outcomes (systematic review): In one non-RCT, a high percentage of patients had no or mild pain and returned to work.

- One case series study reviewed by the Hayes report (2004a) found that in "difficult-to-treat" patients who underwent spinal fusion, 72% of patients had no posttreatment pain, 23% had mild occasional pain, and 5% had some degree of moderate pain after treatment with bone graft and spinal fusion. Furthermore, 85% of patients returned to work, 10% retired, 4% were not working prior to surgery, and 1% were unable to return to work following treatment.

Pain and Functional Outcomes (non-RCTs): Positive results for pain reduction in one non-RCT and for QOL improvement in a second non-RCT.

- In an uncontrolled study evaluating adjunctive invasive DCES following cervical spinal fusion, all patients experienced either significant reduction in neck pain or completion resolution of pain, although a formal scoring method for pain assessment was not used (Welch et al., 2004).
- Lau et al. (2007) reported significant differences in QOL measures (SF-36® Health Survey) for physical functioning, social functioning, bodily pain, and emotional wellness in patients treated with invasive electrical stimulation compared with controls. However, only 30% of all patients (n=12) provided complete SF-36 data. In addition, the use of historical controls limited accurate and meaningful comparisons. Patients in whom union was not achieved had significantly greater bodily pain at follow-up than did patients in whom union was achieved. Similarly, complications were associated with significantly greater bodily pain at follow-up. These subgroup comparisons were obtained from a very small number of patients, which may have limited the ability of the statistical analyses to detect treatment effects. There were no significant differences between treatment and control groups for outcomes measured by the remaining site-specific, foot and ankle scoring systems.

Effectiveness Summary: The Hayes (2004a) report stated weakly positive conclusions regarding the use of invasive or semi-invasive DCES for spinal fusion and nonunion or fresh fractures of long bones; however, the report stated very weak conclusions for any other applications or indications. More recently published studies do not alter these conclusions. The following paragraph summarizes the combined data from the systematic review and recent primary studies by indication.

Some conclusions can be drawn with respect to impact on healing, but not with respect to other outcomes. Healing was generally assessed in terms of radiographic fusion. Radiographic fusion is considered an appropriate measure in studies of salvage treatment since the diagnosis of delayed union and nonunion is often based on radiographic evidence alone. It is a less direct measure in studies of fresh fractures or primary fusion/arthrodesis. Evidence continues to show that invasive DCES, as an adjunct to surgical intervention, may promote healing after spinal fusion (low-quality

evidence); the largest body of evidence pertains to lumbar or lumbosacral spinal fusion. Evidence of low quality for older literature indicates that invasive and semi-invasive DCES promotes healing of nonunion and delayed union fractures, with the largest body of evidence related to long bone fractures. A very small body of recent evidence indicates that invasive DCES may have promise as an adjunct treatment following foot and ankle arthrodesis in high-risk patients or as an end-stage salvage treatment for foot and ankle arthrodesis (low-quality evidence). Data pertaining to healing in other indications, including fresh fractures, remains sparse (low-quality evidence). The efficacy of invasive and semi-invasive electrical stimulation to reduce pain, improve function, and enhance QOL is not clear as the evidence is generally positive, but sparse and of low quality.

2. Are bone growth stimulators safe?

Evidence from Systematic Reviews: Procedure-related complications were relatively infrequent and were generally mild and localized. They included minor skin irritations and superficial wound infections. However, several serious complications were also reported, including hematomas, deep venous thrombosis (DVT), extruded bone grafts, delayed wound healing, wound infection requiring intervention, broken electrode wires, battery-pack failure, osteomyelitis recurrence, and dislodgement or breakage of the cathode. Some of these complications may have been related to the fusion procedure and not the stimulation device (Hayes, 2004a).

Evidence from Primary Studies (3 non-RCTs): Two studies reported a few cases of mild and superficial wound infections and cable breakage (Welch et al., 2004; Lau et al., 2007). Local discomfort and more serious wound infections warranted the surgical removal of the implantable device in several patients (Lau et al., 2007). There were several patients who experienced more serious device-associated complications, including deep wound infections, DVT, ulcers, postoperative neuroma, excessive bleeding, malunion, and stress fracture (Saxena et al., 2005; Welch et al., 2004). Lau et al. (2007) reported a relatively high rate of serious complications in the overall patient population (40%). The most serious complications were reported in three high-risk patients, who all required amputations as a result of intractable neuritis and deep infection following treatment with implantable electrical stimulation (Lau et al., 2007). However, the extent to which the implanted device was responsible for the complications described previously, except for the instances of discomfort leading to removal, is not known.

Safety Summary: Procedure-related complications were relatively infrequent and were generally mild and localized in general populations. Serious complications, including amputations, were reported in several high-risk patients. Some instances of known device-related complications were reported: broken electrode wires, battery pack failure, and dislodgement or breakage of the cathode. The relationship between the implanted stimulator and reported complications is not known. The safety of long-term implantation of these devices is not known as they are generally removed when treatment is

completed. The safety of invasive and semi-invasive DCES in children and the elderly is unknown.

3. Does effectiveness vary by type of bone, the presence/absence of comorbidities, or other patient characteristics?

Evidence from Systematic Reviews: The Hayes (2004a) review reported results from a retrospective study with historical controls that conducted a logistic regression analysis to identify risk factors predictive of healing success by type of nonunion treatment. The treatment modalities included semi-invasive DCES, capacitively coupled electrical stimulation, or bone grafting. Healing was adversely affected by risk factors. Analyzed risk factors included nonunion duration, prior graft surgery or electrical treatment, open fracture, osteomyelitis, comminuted or oblique fracture, and atrophic nonunion. When no risk factors were extant, there were no differences in healing rates among the three modalities. When risk factors were present, they adversely affected the healing rate, regardless of treatment. Two statistically significant relationships between risk factor and treatment method were found: (1) previous failure with similar treatment was a stronger risk factor for bone graft surgery than for either of the forms of stimulation, and (2) atrophic nonunion was a stronger risk factor for capacitively coupled electrical stimulation than for semi-invasive DCES or bone grafting.

The Hayes (2004a) review also discussed the results of a prospective RCT that compared spinal fusion surgery with adjunct invasive DCES versus surgery alone in high-risk patients. Patients were characterized as high risk if they were grossly obese, with one or more prior failed spinal fusions, grade II or worse spondylolisthesis, or multilevel fusion requiring extensive bone grafting. Despite the presence of these risk factors, a significantly greater number of DCES patients achieved successful spinal fusion compared with surgery alone. Both groups exhibited reduced rates of success in patients who required fusion at two or more levels compared with patients who only required fusion at one level. There was also a limited amount of data regarding the long-term durability of unions achieved in this high-risk population.

Evidence from Primary Studies (non-RCTs): Three studies of invasive DCES bone growth stimulation evaluated a subset of the population at high risk for delayed union or nonunion fractures (Lau et al., 2007; Saxena et al., 2005; Welch et al., 2004). A few of the high-risk factors for these studies included patients with advanced age (> 65 years), diabetes, Charcot neuroarthropathy, prior failed arthrodesis, obesity with a body mass index (BMI) ≥ 28, tobacco use, alcohol abuse, and use of immunosuppressive agents. In the study by Saxena et al. (2005), a statistical analysis using Fisher's exact test demonstrated a significant relationship between the presence of two or more of these risk factors and patients who required additional surgery following invasive electrical stimulation treatment. In contrast, time to healing in patients with diabetes was not significantly different from time to healing in patients without diabetes. The study by Welch et al. (2004) included some children, but the study was too small to permit subgroup analysis.

Summary of Factors Affecting Effectiveness: There was no more than sparse evidence regarding the relationships between the presence of one or more risk factors for nonhealing and treatment success in patients treated with electrical stimulation. No controlled studies evaluated the interaction of risk factors with stimulation. Therefore, no conclusions can be drawn regarding the relative effect of invasive and semi-invasive DCES according to type of bone, demographic characteristics, or risk factors. The available evidence from RCTs generally applies to adults without serious systemic disease, and in the case of primary surgical procedures, patients who have other risk factors for poor healing, such as site-specific disease or smoking. The effectiveness of invasive and semi-invasive DCES in children and the elderly is unknown.

[NOTE: Although no clear predictors of effectiveness have been identified, some considerations are important due to safety issues. In the study conducted by Lau et al. (2007), six patients with deep infections had a mean of 2.3 risk factors (range, 2 to 4 risk factors). Results from a chi-square analysis indicated that no single risk factor significantly affected the rate of healing. However, given the relatively high rate of serious complications in the overall group of patients (40%), the use of implantable electrical stimulation in high-risk patients may not be warranted.]

Other Issues

The relative effectiveness of invasive and semi-invasive electrical stimulation to each other is not known. Invasive electrical stimulation appears to be the current preferred technology as no new evidence was available for semi-invasive electrical stimulation.

Strengths and Limitations of the Evidence

The quality of the body of evidence pertaining to each indication is specified in the effectiveness summary at the end of the description of findings for key question number 1. The following discussion describes the quality of the studies included in the systematic reviews and the selected primary studies from recent literature.

Effectiveness Evidence from Systematic Review: The quality of the evidence regarding implantable electrical bone growth stimulators was generally poor in studies evaluated in the Hayes (2004a) systematic review. Studies consisted primarily of comparative trials with historical controls or case series studies; neither of these study designs is adequate to form definitive conclusions. The majority of the comparative and case series studies had small to moderate sample sizes, and were also weakened by the use of retrospective data collection. In addition, important details, including postoperative treatment regimens, inclusion/exclusion criteria, and follow-up periods were often not reported. In some cases, there was significant post hoc manipulation of data, and reports of high losses to follow-up or failure to report loss to follow-up. Studies with substantial dropout rates generally did not perform intention-to-treat (ITT) analysis or impute values for missing data. This systematic review indicates which, if any studies received external sources of funding and did not discuss this issue as a potential factor for biased reporting of results.

Effectiveness Evidence from Primary Studies: The reviewed primary studies evaluating invasive electrical stimulators were of poor quality. The most notable limitations of the available studies were the retrospective study design and very small sample size. Studies either did not specify the number of patients lost to follow-up (Saxena et al., 2005) or there were high numbers of patients lost to follow-up (Lau et al., 2007; Welch et al., 2004). There were no blinded assessments of radiographs following invasive electrical stimulation treatment, which may have introduced the potential for examiner bias. Only one study provided an age-matched control group, and the results from this comparative study were limited by the historical nature of the controls (Lau et al., 2007). One study included only two children, and, despite the early positive results in these two cases, no meaningful conclusions could be drawn regarding the safety and effectiveness of invasive electrical stimulation in this pediatric population (Welch et al., 2004). One study investigator was a consultant for the manufacturer of the evaluated implantable spinal fusion stimulator (Welch et al., 2004), and this affiliation may have introduced the potential for bias; very positive results were reported in this study. Funding sources were not reported in the other primary studies evaluated for this rapid review.

Evidence Pertaining to Key Questions #2 and #3: Safety data across the available studies indicate that complications associated with invasive and semi-invasive DCES are generally mild and localized, and relatively infrequent. However, additional well-designed trials are necessary to clearly further refine appropriate patient selection criteria as serious complications, including amputations, were reported in several high-risk patients. Evidence related to effectiveness by patient subgroup was too sparse to permit conclusions.

Table 3. Systematic Review of Studies Assessing Invasive or Semi-Invasive Electrical Bone Growth Stimulators

Key: BGS, bone growth stimulator or bone growth stimulation; DCES, direct current electrical stimulation; ES, electrical stimulation; f/u, follow-up; grp(s), group(s); hx, history; inpt, inpatient; posttx, post-treatment; pt(s), patient(s); NR, not reported; NS, not statistically significant; PEMF, pulsed electromagnetic field; RCT(s), randomized controlled trial(s); tx, treatment (or therapy); tx'd, treated

Authors/Sponsor Review Objective	Study Population	Review Methodology	Findings	Evaluation of Review
Hayes Inc. (2004a)[a] Systematic review of studies assessing effectiveness and safety of **semi-invasive DCES** *F/u:* Range across 2 studies was 6 wks to 5 yrs *Funding source:* No outside sources for this systematic review; no commercial support for selected studies reported	*# and type of studies:* 2 nonrandomized comparative studies w/ concurrent controls evaluating semi-invasive DCES for fresh facture of jaw and tibia (Jorgensen, 1977; Masureik and Eriksson, 1977) 2 case series studies evaluating semi-invasive DCES for tibial nonunion or various fracture profiles (Brighton, 1981; Brighton et al., 1981) 1 logistic regression analysis used data derived from 2 prior studies to compare semi-invasive DCES, capacitive coupling, and bone grafting (Brighton et al., 1995) *# pts:* Nonrandomized comparative studies: 422 Case series studies: 395[b] *Comparators/controls:* Placebo and no-tx grps; any medical mechanical or surgical intervention	*Databases searched:* PubMed, PreMEDLINE, MEDLINE, HealthSTAR, CINAHL, Science Citation Index, The Cochrane Library, and EMBASE databases *Time span of literature search:* 1966 – February 2004 *Study inclusion criteria:* Systematic reviews; RCTs; case series studies w/ ≥50 pts; full-length, peer-reviewed articles *Study exclusion criteria:* Abstracts; studies of pts w/ pathological fractures or those undergoing bone-lengthening procedures; systematic reviews that did not provide separate analysis for invasive vs noninvasive BGS Studies were evaluated for methodological strength and applicability to the key questions. *Outcome measures:*	*Fresh fractures:* <u>Non-RCTs:</u> Healing of fresh fractures of the jaw and tibia was accelerated by semi-invasive DCES in 2 nonrandomized comparative studies. However, a comparison of the proportion of successful unions achieved in the tx grps was NR (Jorgensen, 1977; Masureik and Eriksson, 1977). *Nonunion fractures:* <u>Non-RCTs:</u> In 2 case series studies, the healing rate achieved with semi-invasive electrical stimulation for nonunion fractures ranged from 84% (tibial fractures) to 87% (varying types of fractures) (Brighton, 1981; Brighton et al., 1981). A logistic regression analysis comparing healing rates of tibial nonunions tx'd w/ semi-invasive DCES, capacitive coupling, or bone grafting determined that there were NS differences among the tx options when no risk factors were extant. The presence of risk factors adversely affected healing rate regardless of tx method (Brighton et al., 1995). *Device/procedure-related complications:* Skin reaction around screws; heat and pain during tx; electrode dislodgement; broken wire or electrode; superficial pin track irritation; skin irritation under anode;	*Overall conclusion(s):* Data suggests that implantable semi-invasive DCES promotes healing of fresh fractures and nonunion in long bones. Efficacy not demonstrated in well-designed studies w/ adequate controls, pt selection criteria not clearly defined, and long-term f/u data were lacking. *Limitations:* Data were limited since only small RCTs and retrospective case series were available for review.

	designed to tx fractures; different tx regimens w/in DCES modality *Typical pt inclusion/exclusion criteria:* Some studies included pts w/ well established nonunions, defined as at least 9 mos' duration; 1 study excluded pts w/ pseudarthrosis or nonunions secondary to pathological fractures	Varied by study	cathode dislodgement; recurrence of osteomyelitis; infection around cathode; battery pack failure	
Hayes Inc. (2004a)[a] Systematic review of studies assessing effectiveness and safety of implanted **invasive or semi-invasive DCES** for fracture **nonunion** *F/u:* Long-term f/u in 1 study had mean of 10.3 yrs; otherwise, f/u NR *Funding source:* No outside sources for this systematic review; no commercial support for selected studies reported	*# and type of studies:* 1 nonrandomized comparative study of pts w/ nonunion fractures of primarily long bones (Miller 1983) 1 case series study of pts w/ mostly tibial nonunion fractures (Paterson et al., 1980; Cundy and Paterson, 1990) *# pts:* Nonrandomized comparative study: 28 Case series study: 81 *Comparators/controls:* Placebo and no-tx grps; any medical mechanical or surgical intervention designed to tx fractures; different tx regimens w/in DCES modality *Typical pt inclusion/exclusion criteria:* Evidence of delayed union	*Databases searched:* PubMed, PreMEDLINE, MEDLINE, HealthSTAR, CINAHL, Science Citation Index, The Cochrane Library, and EMBASE databases *Time span of literature search:* 1966 – February 2004 *Study inclusion criteria:* Systematic reviews; RCTs; case series studies w/ ≥50 pts; full-length, peer-reviewed articles *Study exclusion criteria:* Abstracts; studies of pts w/ pathological fractures or those undergoing bone-lengthening procedures; systematic reviews that did not provide separate analysis for invasive vs noninvasive BGS Studies were evaluated for	*Nonunion fractures:* Non-RCTs: In a small nonrandomized comparative study, nonunion fractures (primarily of long bones) were tx'd w/ invasive or semi-invasive DCES. Pts tx'd w/ DCES achieved higher rates of bone union than those who underwent PEMF therapy, but this was not confirmed statistically (Miller 1983). In a case series study, successful fracture union was achieved w/ electrical stimulation in 86% of nonunions, the majority of which were tibial (Paterson et al., 1980; Cundy and Paterson, 1990). <50% of pts in the case series study were assessed 10 yrs post-tx. Bone healing was durable in pts who initially achieved union with DCES. *Device/procedure-related complications:* Extrusion of power pack through soft tissue; migration of coiled electrode from bone trough; difficulty removing device at end of tx; superficial cathode pin track infections; skin irritation at anode pads; delayed wound healing; cathode wire protruding through atrophic skin; persistent infection around	*Overall conclusion(s):* Data suggest that implantable electrical BGS can promote healing of nonunion in long bones. Efficacy not demonstrated in well-designed studies w/ adequate controls, pt selection criteria not clearly defined, and long-term f/u data were lacking. *Limitations:* Data were limited since only small RCTs and retrospective case series were available for review.

	of long bones ≥12 wks after initial injury w/ confirmation of lack of union at time of surgery; exclusion criteria NR	methodological strength and applicability to the key questions. *Outcome measures:* Fracture union	generator	
Hayes Inc. (2004a)[a] Systematic review of studies assessing effectiveness and safety of implanted **invasive DCES** as an adjunct to **spinal fusion** *F/u:* Varied across studies from 1 yr to median of 5 yrs *Funding source:* No outside sources for this systematic review; no commercial support for selected studies reported	*# and type of studies:* 2 small RCTs (Kane 1988; Jenis et al., 2000) 5 nonrandomized comparative studies (Kane 1988; Meril, 1994; Kahanovitz and Pashos, 1996; Rogozinski and Rogozinski, 1996; Kucharzyk, 1999) 2 case series studies (Kane 1988; Tejano et al., 1996) *# pts:* RCTs: 120 Nonrandomized comparative studies: 2378 Case series: 259 *Comparators/control:* Placebo and no-tx grps; any medical mechanical or surgical intervention designed to achieve spinal fusion; different tx regimens w/in DCES modality; PEMF stimulation *Typical pt inclusion/exclusion criteria:* Some studies specifically included pts w/ high risk factors to evaluate DCES in this population grp, and included pts w/ 1 or more	*Databases searched:* PubMed, PreMEDLINE, MEDLINE, HealthSTAR, CINAHL, Science Citation Index, The Cochrane Library, and EMBASE databases *Time span of literature search:* 1966 – February 2004 *Study inclusion criteria:* Systematic reviews; RCTs; case series studies w/ ≥50 pts; full-length, peer-reviewed articles *Study exclusion criteria:* Abstracts; studies of pts w/ pathological fractures or those undergoing bone-lengthening procedures; systematic reviews that did not provide separate analysis for invasive vs noninvasive BGS Studies were evaluated for methodological strength and applicability to the key questions. *Outcome measures:* Varied by study	*Spinal (lumbar) fusion:* <u>RCTs:</u> 1 RCT reported successful spinal fusion in 81% of high-risk pts who had DCES as adjunct to noninstrumented spinal fusion, compared w/ only 54% of high-risk pts who underwent surgery alone (63 pts met inclusion criteria, 59 available for f/u [9.4%]) (Kane 1988). A more recent, small RCT that evaluated instrumented spinal fusion alone or in combination w/ DCES or PEMF tx found no discernible difference between DCES, PEMF, and placebo in achieving spinal fusion and clinical success (61 pts met inclusion criteria and are presented in study, dropouts and loss to f/u NR) (Jenis et al., 2000). <u>Non-RCTs:</u> In 4 studies w/ historical control grps, successful fusion rates ranged from 92% to 96% of stimulated pts and 75% to 85% of unstimulated pts (Kane 1988; Meril, 1994; Rogozinski and Rogozinski, 1996; Kucharzyk, 1999), but data from historical controls are insufficient for definitive comparisons. 1 study included only high-risk pts. A retrospective study of DCES pts and controls analyzed data from a large healthcare claims database; pts who underwent spinal fusion combined w/ instrumented DCES required less inpt care in the 2 yrs after surgery than those who did	*Overall conclusion(s):* Data from most studies indicate that invasive electrical BGS can improve rate of successful spinal fusion in pts w/ certain risk factors, but data from 1 study do not show a benefit. Efficacy not demonstrated in well-designed studies w/ adequate controls, pt selection criteria not clearly defined, and long-term f/u data were lacking in several studies. *Limitations:* Data were limited since only small RCTs and retrospective case series were available for review.

	prior failed spinal fusions; grade II or worse spondylolisthesis; multilevel fusion that required bone grafting, or obesity; another study excluded smokers, and required smokers to quit prior to surgery		not receive adjunctive DCES (Kahanovitz and Pashos, 1996). Fusion was successful in 92% and 93% of stimulated pts in the 2 case series studies (Kane 1988; Tejano et al., 1996). *Device/procedure-related complications:* Hematoma; deep venous thrombosis; extruded bone graft; superficial wound infection; deep infection; removal of device due to discomfort	

[a] See Appendix VI for details pertaining to each selected study.
[b] Patient populations overlapped for the 2 case series studies, so the total number of patients across the 2 studies is likely to be less than this number.

Table 4. Primary Studies Assessing Invasive Electrical Bone Growth Stimulators (ordered by study design)

Key: AOFAS, American Orthopaedic Foot and Ankle Society; AOS, Ankle Osteoarthritis Scale; BGS, bone growth stimulation; BMI, body mass index; DC, direct current; DCES, direct current electrical stimulation; DVT, deep vein thrombosis; dx, diagnosis; ES, electrical stimulation; FFI, Foot Function Index; f/u, follow-up; grp(s), group(s); hx, history or historical; LBF, long bone fracture; M/F, male/female; NLBF, nonlong bone fracture; NR, not reported; NS, not statistically significant; PEMF, pulsed electromagnetic field; pt(s), patient(s); QOL, quality of life; RA, rheumatoid arthritis; ROM, range of motion; SD, standard deviation; SE, standard error; SF-36, Short Form Health Survey; subgrp(s), subgroup(s); tx, treatment (or therapy)

Authors/Study Design	Study Population	Procedures/Outcome Measures	Results/Complications	Conclusions/Limitations/ Quality Ratings
Lau et al. (2007) Union Memorial Hospital, Baltimore, MD Retrospective case-controlled study to evaluate implantable DCES for revision foot and ankle surgery *F/u:* Mean 37.4 wks (range 12-90) *Time frame:* 2000-2001 *Funding source:* NR	n=38 pts (40 feet) (M/F 22/16; mean age 51 yrs, range 28-75) *Inclusion criteria:* Pts at high risk of failed tx for whom bone stimulators were used as part of salvage tx *Pt surgeries:* Ankle arthrodesis (n=3); midfoot arthrodesis (n=6); subtalar arthrodesis (n=8); triple arthrodesis (n=6); tibiotalocalcaneal arthrodesis (n=13), tibial osteotomy (n=2); and other fusions (n=2) Risk factors determined for nonunions included worker's compensation (n=6); smoking (n=13); previous nonunion (n=19); medical morbidity (n=5); steroid use (n=4); RA (n=3); diabetes mellitus (n=15); Charcot (diabetic neuroarthropathy; n=14); avascular necrosis of	Tx grp: 40 surgical procedures were performed w/ implantable DCES stimulators All pts received implantable DC bone stimulator; bone stimulator plus autograft (n=17) or allograft (n=14); bone graft not used in 9 pts. Control grp: Data from previous database w/ identical demographics, dx, and tx, but no implantable DCES Pts were evaluated w/ physical exams, and functional and radiographic assessments (n=18) or pt data comprised of charts and x-rays (n=20) was reviewed. Definition of clinical success: Stable, nontender physical exam; stable x-ray w/ trabeculae crossing the fracture, arthrodesis, or osteotomy site; no change	47 pts identified as eligible; 9 excluded (1 died, 2 had f/u <12 wks, 6 not available for f/u and charts or x-rays incomplete) *% union:* 26/40 feet (65%) *QOL:* At f/u, SF-36 scores were significantly lower than those of the control grp for physical function (P<0.001), physical (P=0.0029); bodily pain (P<0.001); social function (P<0.001); emotional (P=0.0357); bodily pain was significantly worse for pts w/ nonunion vs union (P=0.027) and for 8 pts w/ complications vs no complications (P=0.0172) AOS, FFI, and AOFAS score differences were NS for pts w/ union vs pts w/ nonunion fractures, and there were NS differences for pts w/ and w/o complications. *Pt satisfaction:* Of 18 pts who completed questionnaire, 14 (78%) were functionally improved, and 16 (89%) expressed satisfaction. *Device-related complications:* Amputations due to intractable neuritis and deep infection in high-risk pts (n=2); deep infection (n=6); malunions of arthrodesis (n=2); 1 pt had DVT (n=1); superficial wound infection	Although >50% of pts experienced complete union, DC bone stimulators resulted in a high # of adverse events in high-risk pts. *Limitations:* Retrospective study design; small sample size; single-institution study; hx controls; missing data from SF-36 forms; % union for control grp NR; % unions NR to be confirmed by radiographic and/or clinical assessment. *Quality:* Poor (downgraded because of historical controls, % union for controls NR, and missing data from SF-36 forms).

	talus (n=6); tibiotalar cysts (n=1); nondiabetic neuroarthropathy (n=3)	in hardware position *Outcome measures:* % union; QOL (SF-36, n=15); AOFAS; FFI; pt assessment of function and satisfaction	(n=1); ulcer due to cast immobilization (n=1); postop neuroma; excessive bleeding; wound breakdown after rotational flap (n=1); malunions of arthrodesis (n=2), distal tibia stress fracture after distal tibial osteotomy (n=1)	
Welch et al. (2004) University of Pittsburgh School of Medicine, Pittsburgh, PA Retrospective study evaluating DCES for para-axial cervical arthrodesis *F/u:* Mean 19 mos (range 2-60) *Time frame:* NR *Funding source:* Primary author is a consultant for EBI	n=20 pts at high risk for nonunion following cervical fusion (M/F 13/7; age range 11-64 yrs) 4 pts dropped out or were lost to f/u; clinical data not available in 1 pt. Pts were at increased risk for nonunion due to advanced age (>65 yrs), RA, prior failed fusion attempts, infection, immunosuppressive agents, or a combination of these. *Inclusion criteria:* Pts who required posterior cervical arthrodesis from occiput to C3 to correct instability of congenital, traumatic, inflammatory, infectious, postsurgical, or degenerative etiology *Exclusion criteria:* NR	All pts underwent surgical internal fixation to increase stability and promote arthrodesis; placement of transarticular screws were performed for pts who required atlantoaxial fusion only, and when possible, this was supplemented w/ Brooks fusion, using mostly autograft bone or sometimes allograft bone; ES device implanted at time of surgery. *ES device:* SpF-2T® Implantable Spinal Fusion Stimulator (EBI) Radiographs at immediate postop period and 3-mo intervals until solid fusion took place. *Outcome measures:* Time until fusion; radiographic evidence of solid fusion; pain assessment	16 pts available for f/u (1 pt had died from underlying medical illness in early post-op period, 3 pts lost to f/u). Mean time until fusion (mos): 4.6 (range 1.5-13.0) 67% of pts had significant reduction of neck pain, and 33% reported complete resolution of pain. Solid arthrodesis occurred in 15/16 (94%) pts. 1/16 (6%) pts failed to demonstrate radiographic evidence of solid fusion, and, following additional surgery, pseudarthrosis was suspected. *Device-related complications:* 1 pt developed a superficial wound infection; 4 pts experienced enough local discomfort to have the device surgically removed.	Cervical arthrodesis combined w/ implantation of ES device resulted in radiographic consolidation in majority of pts. *Limitations:* Retrospective study design; small sample size; single-institution study; no blinded or independent evaluation; lack of control or comparator grp; no assessment of clinical union or functional outcomes; use of formal pain assessment instrument not reported. *Quality:* Poor
Saxena et al. (2005) Palo Alto Medical Foundation, Palo Alto, CA; Northside Medical Center, Youngstown, OH Retrospective review	n=26 pts (28 arthrodeses) (mean age 56 yrs, range 31-79; 27% men, 2 of whom had bilateral arthrodeses) *Inclusion criteria:* ≥1 yr of f/u data available *and* the	All pts underwent standard arthrodesis; internal screws (n=26), bioabsorbable screws (n=1), or external fixation (n=1). Bone graft also used. ES device implanted at time of surgery.	# of pts eligible for study NR; appears that only # of pts w/ complete data is reported. Arthrodeses included fusions of metatarsal (n=16), talonavicular joint (n=3), tibiocalcaneal joint (n=4), first metatarsophalangeal joint (n=3), ankle (n=1), and subtalar joint (n=1).	Foot and ankle arthrodesis combined w/ implantation of ES device resulted in radiographic consolidation for most pts. *Limitations:* Small sample size; lack of control grp; no blinded

of DCES for prevention of delayed union/nonunion in foot or ankle arthrodesis in high-risk pts *F/u:* Mean 27.2 mos *Time frame:* 1998-2002 *Funding source:* NR	following characteristics: diabetes, BMI >28, hx of previous failed arthrodeses, hx of smoking or alcohol abuse, *or* hx of immunosuppressive medications *Clinical hx/pt characteristics (% pts):* Diabetes (69%), BMI >28 (42%), smokers (23%), alcohol abuse (15%), prior failed first metatarsophalangeal joint implant (12%), prior failed arthrodeses (15%), Charcot foot (62%)	*ES device:* OsteoGen (EBI) Radiographs at 1 mo and approximately every 2 wks thereafter until consolidation; evaluated by an independent but not blinded evaluator. *Outcome measures:* Radiographic consolidation; complete fusion (bony trabeculation across joint, clinical lack of motion, maintenance of hardware/fixation, and no radiographic signs of nonunion or pseudarthrosis); relationship between fusion and risk factors	*Radiographic consolidation*: 86% of arthrodeses at mean 10.3 wks from index surgery *Effect of diabetes on time to consolidation:* Diabetic, 10.5±3.7 wks; nondiabetic, 8.3±3.2 wks (NS) *Effect of gender on rate of consolidation:* Women, 9.95±4.06 wks; men, 11.11±3.89 wks (NS) *Success rate (% pts w/ complete fusion according to study definition):* NR clearly; 79% (19/24) of pts did not require further surgery. *Success predictors:* Presence of ≥2 risk factors associated w/ need for additional surgery (*P*=0.015); time to healing was 2 wks greater in diabetics than in nondiabetics, but difference was NS. *Surgical complications:* 5 pts had postop infection, and, in 2 pts, the device was removed; all had successful arthrodesis. *Device-related complications:* Breakage of cables (n=2); fall at 18 mos (n=1) resulting in hardware failure; repeat surgery required (n=5)* *1/5 pts fell and damaged the joint. It is not clear whether other required repeat surgeries were due to device failure per se or general arthrodesis failure.	evaluation; sample size too small to allow comparison of diabetic vs nondiabetic and men vs women; expressions of variability not defined as SE or SD; no clear reporting of overall success rate; no assessment of clinical union, pain, or functional outcomes. *Quality:* Poor

Noninvasive Electrical Bone Growth Stimulators (Tables 5 and 6)

Systematic Reviews

The Hayes Medical Technology Directory Report on *Electrical Bone Growth Stimulation, Noninvasive* (Hayes, 2004b) and a systematic review from the peer-reviewed literature (Mollon et al., 2008) were reviewed and are summarized in Table 5. The Hayes report, which is presented in three different table entries according to type of stimulator, included prospective studies published in October 2003 or earlier. The report reviewed 15 studies, including 10 RCTs. A total of 2130 patients were involved across studies. Sample sizes ranged from 16 to 201 in most studies, but one study had a sample size of 1098. Eight of the 15 studies investigated pulsed electromagnetic field (PEMF) stimulation, 5 investigated capacitive coupling, and 2 investigated combined magnetic field (CMF) stimulation. The review by Mollon and colleagues selected RCTs investigating electromagnetic stimulation (PEMF or capacitive coupling) for long bone lesions. The review included 11 RCTs (total across studies, n=347). Four selected trials, which were published in 1996 or earlier, were not reviewed in the Hayes report. The Hayes report included some observational studies that were excluded by Mollon and colleagues, as well as three RCTs that were not included by Mollon and colleagues. One of the three RCTs missing from the review by Mollon and colleagues may have been excluded because it evaluated combined (electro)magnetic field (CMF) stimulation.

Primary Studies

Five primary clinical studies were selected: one study applying stimulation to traumatic fractures with results reported separately for long and nonlong bones (Punt et al., 2008); two studies applying stimulation to failed lumbar fusion (Simmons et al., 2004) or adjunctively in high-risk cervical fusion (Foley et al., 2008); and two studies applying adjunctive stimulation to primary foot and ankle arthrodesis (Dhawan et al., 2004) or as adjunctive treatment for failed foot/ankle arthrodesis (Saltzman et al., 2004). The studies by Dhawan et al. and Foley et al. were RCTs. In the before-and-after studies by Simmons et al. and Punt et al., patients (all with diagnoses of nonunion) served as their own controls. The study by Saltzman and colleagues had no control (patients could not be considered self-controls since all had delayed union rather than nonunion). Sample sizes were small to moderate: 64 to 323 in the two RCTs; 19, 93, and 100 in the non-RCTs. Pulsed electromagnetic field (PEMF) devices were used in all studies.

Patient Characteristics

When reported, inclusion/exclusion criteria for the studies in the systematic reviews and the selected primary studies typically required that patients be adults free of serious systemic disease that might interfere with treatment. Use of steroids and the presence of an implanted electrical device were sometimes mentioned as exclusion criteria. In the studies where a definition was provided, nonunion meant lack of complete union at 9 months following injury or surgery. Healing was most often defined by radiographic

fusion, generally assessed by a blinded evaluator. A small number of studies also incorporated clinical criteria when assessing healing or assessed functional outcomes.

1. Are bone growth stimulators effective in promoting healing, reducing pain, or improving function when applied to fresh fractures, delayed union or nonunion fractures, or fusion sites?

Fresh Fractures, Including Stress Fracture (systematic reviews): Results in RCTs varied by fracture location.

- A single small RCT suggested that stimulation provides only short-term acceleration of healing in the treatment of extra-articular Colles fractures and has no effect on redisplacement (Mollon et al., 2008). Only bone densiometry was assessed.
- A single small RCT demonstrated a substantial effect on healing in patients treated with PEMF for fresh fracture of the femoral neck (Mollon et al., 2008).

Nonunion/Delayed Union Bone Fractures (systematic reviews): Substantial benefit shown by four RCTs, but no effect after adjustment for smoking in one of the RCTs; positive results in non-RCTs; inconclusive meta-analysis.

- Two small RCTs and a subgroup analysis of a very large prospective uncontrolled study indicated that *PEMF stimulation* can substantially improve the probability of healing within 3 to 6 months, as determined by radiographic evidence, in patients with delayed union or nonunion of long bone fractures. The two RCTs included tibial fractures only. The treatment effect in the two RCTs was large. However, in one of the RCTs, control patients were more likely to be smokers and the treatment effect was eliminated after adjustment for smoking status. Clinical benefit was suggested by the observational study but was either not measured or not detected by the two RCTs (Hayes, 2004b).
- One small RCT and two uncontrolled studies, all published in 1999 or earlier, provided positive but sparse evidence of radiographic fusion in patients treated with *capacitive coupling* for delayed union or nonunion fractures of different types of bone, mostly long bones. The RCT demonstrated a large treatment effect on both radiographic and clinical success (Hayes, 2004b).
- Meta-analysis based on four small (n=116) RCTs suggested an association between noninvasive electrical stimulation and the success rate for radiographic fusion, but the results were nonsignificant and there was high heterogeneity across studies (Mollon et al., 2008). The authors found in sensitivity analyses that type of bone and type of lesion (delayed union versus nonunion) did not account for the heterogeneity. They did not report a sensitivity analysis based on these other sources of variation: three studies assessed PEMF, while one study evaluated capacitive coupling, and stimulation followed surgical treatment in only one of the four studies. Fractures were immobilized in all studies. The four studies included the two tibial fracture RCTs reviewed by Hayes (2004b).

Nonunion/Delayed Union Bone Fractures (non-RCT): A retrospective review of records for 82 patients showed PEMF for treatment of nonunion in traumatic fractures to have been accompanied by discontinuation of immobilization for most patients (Punt et al., 2008). Because patients had already been diagnosed with nonunion, they served as their own controls. Patients underwent a median 13 weeks of treatment. At 6 months following removal of the device, 63% to 88% of patients, depending on type of bone, had discontinued immobilization. Overall success at 6-month follow-up was 76% to 79%. Overall success was measured in terms of immobilization discontinuation, pain, physician-reported motion at the fracture site, and radiographic fusion. Conclusions regarding a treatment effect are limited by the lack of a true control group.

Primary Lumbar Fusion for Degenerative Disease (systematic reviews): RCTs generally showed substantial benefit of noninvasive electrical stimulation.

- Two randomized trials reported conflicting results pertaining to the impact of *PEMF* on radiographic fusion when used immediately after lumbar fusion. However, the trial reporting strongly positive results was larger than the trial reporting no impact on fusion (Hayes, 2004b).
- One moderate-size RCT demonstrated a substantial improvement in overall (radiographic and clinical) success with the use of *capacitive coupling* immediately following lumbar fusion (Hayes, 2004b).
- A single, moderate-size RCT provided sparse evidence that *combined (electro) magnetic field (CMF)* stimulation improves radiographic healing in patients who have undergone lumbar fusion (Hayes, 2004b).

Primary Cervical Fusion in High-Risk Patients (RCT): A single-blind RCT demonstrated a substantial acceleration of radiographic fusion when PEMF was used for 3 months immediately after cervical fusion in patients at high risk of fusion failure (Foley et al., 2008). At 6 months following surgery, 84% of per-protocol PEMF patients and 69% of per-protocol control patients (P=0.0065) had radiographic fusion. Both treatment arms experienced substantial loss to follow-up resulting in missing data, but analysis based on various assumptions supported a positive interpretation of 6-month results. However, by 1 year after surgery, there was only a small, nonsignificant difference between groups.

Salvage Spinal Fusion (non-RCT): A multicenter series of 100 patients who had not yet experienced complete radiographic fusion at ≥ 9 months following lumbar fusion used PEMF for 3 to 21 months (Simmons et al., 2004). Radiographic success was observed in 67% of patients at a mean of 8 months. When both clinical measures (not defined) and radiographic evidence were considered, 42% of patients experienced excellent or good overall success. This before-and-after study provides some evidence of improvement attributable to PEMF. However, several deficiencies detract from usefulness of this study: the lack of an actual control group, the apparent lack of a common definition of clinical success, and wide variation among patients in the time interval between surgery and initiation of PEMF treatment.

Salvage Arthrodesis, Various Joints (systematic reviews): Positive non-RCT evidence.

- Evidence of radiographic and clinical benefit from *PEMF* stimulation in patients with failed arthrodesis (various joints, single uncontrolled study) was positive but does not permit conclusions (Hayes, 2004b).
- A small, partially randomized trial reported substantially reduced time to healing, attributable to *CMF* stimulation in patients undergoing foot or ankle fusion (Hayes 2004b).

Primary Foot/Ankle Arthrodesis (RCT): The single-blind RCT by Dhawan and colleagues (2004) (n=64) demonstrated that compared with no stimulation, the use of PEMF immediately after surgery accelerated healing time. Time to radiographic fusion ranged from 12 to 13 months in PEMF patients and from 14.5 to 18 months in the control group, depending on the particular joint fused. Differences were statistically significant, except for subtalar joint fusions. Correlation tests suggested that PEMF reduced the healing variability across joint types. No improvement in eventual success rate was noted; all patients experienced complete healing, except for the patients undergoing revision surgery in the control group. Pain and functional outcomes were not assessed, and no measure of compliance with the PEMF regimen was reported.

Salvage Foot/Ankle Arthrodesis (non-RCT): In contrast to the study of primary arthrodesis, an uncontrolled study of PEMF plus immobilization as salvage treatment for foot and ankle arthrodesis reported a low rate of fusion success (5 of 19 patients, 26%) within a 4-month treatment period (Saltzman et al., 2004). The 14 patients who did not experience complete healing during this interval were advised to undergo repeat arthrodesis. In addition to a retrospective uncontrolled study design, the very small sample size and lack of blinded evaluation limit conclusions from this study. PEMF was combined with non–weight-bearing and immobilization in both studies.

Pain and Functional Outcomes (for fresh, delayed, and nonunion fractures) (systematic reviews): Mixed results from RCTs.

- In the studies reviewed by the Hayes report, a few RCTs reported clinical outcomes separately from radiographic fusion. Two RCTs (PEMF for tibial delayed/nonunion, PEMF or invasive electrical stimulation for primary lumbar fusion) were unable to detect improvement in clinical outcomes with the use of stimulation. In another RCT (capacitive coupling for primary lumbar fusion), clinical outcomes substantially favored the stimulation group (Hayes, 2004b).
- Mollon and colleagues noted that only one of four RCTs assessing impact on pain reported a benefit, and this finding applied only to patients who were compliant with the intervention. The study with positive results applied PEMF to fresh femoral neck fracture due to osteonecrosis. The three studies with negative results applied PEMF to delayed union or nonunion tibial fractures (including the one negative study reported by Hayes) or applied capacitive coupling to tibial stress fracture (Mollon et al., 2008). The study of fresh tibial stress fracture (Beck et al., 2008) found no effect on time to healing when healing was defined as complete absence of pain during hopping on the affected limb for 30 seconds to a height of 10 cm off the ground with confirmation by investigator examination.

Pain and Functional Outcomes (primary cervical fusion) (RCT): In the study by Foley et al. (2008), no important differences in pain or physical health status were observed, and neck disability was actually slightly worse in the PEMF group than in the no stimulation control group, at both 6-month and 1-year evaluation. The study did not use a placebo (sham treatment) as control. However, since no treatment effect on these patient-reported outcomes was observed, the lack of placebo control was not an important limitation.

Other Indications (systematic reviews):

- The reviews report a few small controlled studies suggesting that noninvasive electrical stimulation improved radiographic healing or bone mineral density in patients with degenerative disease of the knee or hip (Hayes, 2004b; Mollon et al., 2008).
- No benefit in ultimate clinical outcomes was demonstrated by one small RCT involving adjunctive stimulation after primary distraction osteotomy for limb lengthening (Mollon et al., 2008).
- A small RCT found no benefit on limb-length imbalance or on need for reoperation with the use of adjunctive PEMF after surgical treatment of pseudarthroses (Mollon et al., 2008).

[NOTE: These indications were excluded in the literature search performed for this rapid review.]

Effectiveness Summary: The Hayes (2004b) report stated a moderately strong, positive conclusion regarding the effectiveness of PEMF for long bone nonunions but did not state strong conclusions for any other applications or indications. The other systematic review concluded that the use of electromagnetic stimulation (PEMF or capacitive coupling) in long bones remains uncertain due to low-quality evidence and heterogeneity across studies (Mollon et al., 2008). More recently published studies do not alter these conclusions. The following paragraph summarizes the combined data from systematic reviews and recent primary studies by indication. Contrary to the analysis by Mollon et al., the following analysis considers the three forms of noninvasive stimulation separately.

Some conclusions can be drawn with respect to impact on healing. Although healing was generally assessed in terms of radiographic fusion without consideration of clinical factors, this was not considered to limit bodies of evidence for salvage treatment since the diagnosis of delayed union and nonunion is based on radiographic evidence alone. Evidence of moderate quality has shown noninvasive electrical stimulation to promote healing of delayed and nonunion fractures, with the strongest body of evidence pertaining to PEMF stimulation and long bones. Noninvasive electrical stimulation, particularly PEMF, continues to show promise (low-quality evidence) as a means of promoting healing following spinal fusion. The single study of cervical fusion was of somewhat better quality than the lumbar fusion studies, but the results need to be corroborated by other studies applying stimulation to cervical fusion. PEMF also shows promise (low-quality evidence) for adjunctive use following foot and ankle arthrodesis. A very small body of evidence has reported conflicting, largely negative results regarding the effectiveness of noninvasive electrical stimulation as salvage treatment in cases of failed spinal fusion or failed joint arthrodesis (low-quality evidence). Data pertaining to other indications, including fresh fractures, remains sparse (low-quality evidence).

Two other observations can be made. The ability of noninvasive electrical stimulation to improve pain, accelerate return to function, or enhance QOL remains uncertain (low-quality evidence consisting of generally negative results). Although evidence is lacking pertaining to the relative effectiveness of the three forms of noninvasive electrical stimulation, PEMF has become the preferred technology.

2. Are bone growth stimulators safe?

Evidence from Systematic Reviews: There were some reports that patients found the PEMF device to be bulky or uncomfortable or that patients experienced minor skin rash or pain while using the device (Hayes, 2004b). A few studies followed patients for several months or more after discontinuation of treatment. Safety was not addressed in the published systematic review (Mollon et al., 2008) or in the most recent clinical study (Beck et al., 2008) included in this review.

Evidence from Primary Studies (2 RCTs; 3 non-RCTs): None of the studies reported device-related complications. Two studies observed patients for 6 months (Punt et al., 2008) to 9 months (Foley et al., 2008) after discontinuation of treatment.

Safety Summary: In 27 studies, no safety issues were identified during treatment periods of several weeks to a few months. Only a small number of studies followed patients beyond discontinuation of treatment. None included patients who underwent repeated treatments.

3. Does effectiveness vary by type of bone, the presence/absence of comorbidities, or other patient characteristics?

Evidence from Systematic Reviews: The Hayes report noted that one RCT investigating PEMF reported treatment success to be unaffected by several demographic variables (Hayes, 2004b). The report concluded that long bone versus non-long bone fracture was the only reliable patient selection criterion, but this conclusion was based on the fact that the preponderance of available evidence was for long bone fractures. Effectiveness by patient subgroup was not addressed by the published systematic review (Mollon et al., 2008). However, in the most recent study included in the Mollon et al. review, the treatment effect associated with capacitive coupling stimulation for tibial stress fractures was statistically significant in women, whereas it was nonsignificant in men and in the combined study group (Beck et al., 2008). Neither review found studies specifically assessing the use of stimulation in children or the elderly; the Hayes report provided information suggesting that no study participants were younger than 17 years of age (Hayes, 2004b; Mollon et al., 2008). Evidence from the two reviews generally applies to patients without serious systemic disease who are not taking steroids.

Evidence from RCTs: Subgroup analysis in an RCT of PEMF following cervical fusion suggested that PEMF had a greater effect in men than in women and in patients older than 50 years of age, but there was no direct test for effect modification (Foley et al., 2008).

Evidence from Non-RCTs: Subgroup analysis in an uncontrolled study suggested that PEMF in combination with immobilization could have a greater effect on nonunion when applied to bones other than long bones (Punt et al., 2008). At 6 months following removal of the device, immobilization had been discontinued in 63% of patients with long bone fractures, compared with 88% of patients with fractures of other types of bones. However, overall success at 6-month follow-up was similar (76% to 79%) for both types of fractures. The study was

underpowered to demonstrate a statistically significant difference in results between long bones and nonlong bones. In a series of 100 patients treated with PEMF for failed lumbar fusion, there was no association between radiographic success and fusion technique, single versus multiple levels, smoking status, or workmen's compensation status (Simmons et al., 2004). For a series of 19 patients treated with PEMF for delayed union of foot and ankle arthrodesis, smoking status did not affect the success rate (Saltzman et al., 2004). All of the patients in this study were at risk of fusion failure by virtue of smoking status or the number of levels requiring fusion.

No studies assessed the use of stimulation in children or the elderly.

Summary of Factors Affecting Effectiveness: There was no more than sparse evidence for any one factor. Therefore, no conclusions can be drawn regarding the relative effect of noninvasive electrical stimulation according to type of bone, demographic characteristics, or risk factors. The available effectiveness evidence generally applies to adults without serious systemic disease who are not taking steroids or other immunosuppressants. The safety and effectiveness of noninvasive electrical stimulation in children and the elderly is unknown.

Other Issues

The Hayes report noted that a dose-setting study determined that a threshold ≥ 3 hours per day was necessary for treatment effect on a variety of fracture nonunions (Hayes, 2004b). One study reported successful healing of long bones only when the distance between plates in a capacitive coupling device was not excessive (Hayes, 2004b).

Strengths and Limitations of the Evidence

The quality of the body of evidence pertaining to each indication is characterized in the summaries at the end of the description of findings for each key question. The following discussion describes the quality of the studies included in the systematic reviews and the selected primary studies from recent literature.

Effectiveness Evidence from Systematic Reviews: The two systematic reviews included a high number of RCTs, but study weaknesses and limitations in overall bodies of evidence were noted. The Hayes report was based on 10 RCTs, one partially randomized trial, and four nonrandomized studies (Hayes, 2004b). Most of the RCTs were double-blind. The authors noted that the quality of available evidence was compromised by small study groups with varying levels of baseline risk. There were numerous sources of heterogeneity across studies, such as variation in whether stimulation was used in conjunction with prior surgery. The number of studies available for each indication was small, which limits the precision of possible conclusions. Some studies were hindered by substantial dropout rates and/or noncompliance and generally did not perform intention-to-treat (ITT) analysis or impute values for missing data. Evidence tables noted manufacturer support for a few studies but this was not discussed as a limitation and does not appear to characterize the body of evidence for any indication.

The authors of the published systematic review likewise determined that although the selected RCTs generally used single to triple blinding, they were sometimes lacking in other ways (Mollon et al., 2008). Among the 11 reviewed RCTs, three studies did not describe the randomization method, eight studies did not observe allocation concealment or did not report the method, no studies provided intention-to-treat analysis, and three studies reported a loss to

follow-up greater than 10%. Several studies in this review had additional limitations that compromised the internal validity or distorted the results. Few of the studies included in either review assessed pain, functional, or QOL outcomes. Overall, the two systematic reviews were judged to be based on low quality to moderate-quality evidence. The review did not mention manufacturer support in its discussion of the quality of the evidence.

Effectiveness Evidence from Primary Studies: The primary studies published after the systematic reviews were not of sufficient quality to allow new conclusions. Two RCTs provided the first published evidence suggesting that adjunctive PEMF promotes healing following high-risk cervical fusion (fair-quality study by Foley et al., 2008) and foot/ankle arthrodesis (good-quality study by Dhawan et al., 2004). However, results need to be corroborated by additional studies. The other three studies did not have true control groups, but the study by Punt et al. (2008) (salvage treatment of nonunions) was upgraded to fair quality. Two studies assessed outcomes at the end of treatment only, i.e., there was no follow-up. However, this deficiency is probably immaterial with respect to effectiveness conclusions since treatment periods of 3 to 4 months suggest that further improvement was unlikely. All studies were limited by small sample sizes, which prevented meaningful results for certain outcome measures in some studies. All but one of the poor quality studies reported blinded evaluation.

Evidence Pertaining to Key Questions #2 and #3: The quantity of safety data across studies seems adequate to confirm that serious complications are unlikely. A modest quantity of long-term data suggests that there are no long-term complications. The literature does not indicate any suspected long-term adverse effects from this noninvasive technology.
Evidence related to effectiveness by patient subgroup was too sparse to permit conclusions.

Table 5. Systematic Reviews of Studies Assessing Noninvasive Electrical Bone Growth Stimulators

Key: AVN, avascular necrosis; BGS, bone growth stimulation or stimulator; BMD, bone mineral density; CI, confidence interval; CMF, combined (electro)magnetic field; DC, direct current; EMS, electromagnetic stimulation; ES, electrical stimulation; f/u, follow-up; grp(s), group(s); I, I index (statistical measure of heterogeneity); NR, not reported; PEMF, pulsed electromagnetic field; pt(s), patient(s); RCT, randomized controlled trial; RR, relative risk; tx, treatment (or therapy); tx'd, treated

Authors/Sponsor Review Objective	Study Population	Review Methodology	Findings	Evaluation of Review
Hayes Inc. (2004b)[a] Systematic review of studies assessing effectiveness and safety of **PEMF** *F/u:* Varied across studies from 60 days to mean of 4.1 yrs *Funding source:* No outside sources for this systematic review; no commercial support for selected studies reported	*# and type of studies:* 6 RCTs (Borsalino et al., 1988; Mooney, 1990; Sharrard 1990; Mammi et al., 1993; Jenis et al., 2000; Simonis et al., 2003) 2 uncontrolled prospective studies (Bassett et al., 1982; Garland et al., 1991) *# pts:* RCTs: 407 Uncontrolled prospective studies: 1217 *Comparators/controls:* Placebo or dummy stimulator; DC implanted stimulator; no PEMF tx grp *Typical pt inclusion/exclusion criteria:* Some studies specifically excluded elderly and/or children; none reported participants age <17 yrs; pts w/ systemic disease (e.g., rheumatoid arthritis, Paget's disease, cancer, renal failure) that could interfere w/ tx often excluded; 3 studies excluded pts using steroids	*Databases searched:* MEDLINE and EMBASE *Time span of literature search:* July 2001 – May 2004 (MEDLINE); July 2001 – October 2003 (EMBASE) *Study inclusion criteria:* RCTs; uncontrolled prospective studies; English-language articles w/ human participants *Study exclusion criteria:* Retrospective studies Studies were evaluated for methodological strength and applicability to the key questions *Outcome measures:* Varied by study	*Nonunion or delayed union fractures (tibial fractures):* <u>RCTs:</u> (1) In 1 small RCT of strictly selected pts w/ delayed union or nonunion tibial fractures, radiographic assessment found significant differences in healing in favor of PEMF grp (50% of pts w/ some radiographic evidence of healing, PEMF; 8%, control). However, no significant differences between grps on clinician assessment of pain or movement (Sharrard 1990). (2) In 1 RCT of PEMF stimulation for established tibial nonunions, radiographic and clinical evaluation showed that 89% of the PEMF grp fractures united vs only 50% of placebo grp. PEMF stimulation was associated with significant increase in rate of union, but only before adjustment for smoking (Simonis et al., 2003). *Nonunions, delayed unions, or failed arthrodeses (long bones or other appendicular bones):* <u>Non-RCTs:</u> (1) 1 moderate-size, uncontrolled, prospective study of PEMF tx for fracture nonunions and failed arthrodeses reported a threshold dosage ≥3 hours/day to effect union. Healing rates in pts receiving this dosage were 80%. Tx success unaffected by several demographic variables (Garland et al., 1991). (2) 1 large (n=1078) uncontrolled,	*Overall conclusion(s):* Available evidence from relatively small, randomized, placebo-controlled trials and uncontrolled studies suggests that PEMF can stimulate healing of delayed union or nonunion long bone fractures. However, due to lack of sufficient data, no definitive conclusions can be drawn regarding the efficacy PEMF stimulation for nonunions of appendicular bones other than long bones. There also was some evidence to support the efficacy of PEMF as an adjunct to surgery for spinal fusion, but the evidence was inconsistent. *Limitations:* Only English-language publications included; time span of EMBASE literature search shortened relative to MEDLINE search, which could have resulted in missing studies relevant to the review.

	or w/ depressed immune system; if defined, nonunion = no union after 9 mos or 1 yr; 1 study excluded pts w/ implanted electrical devices; pts w/ trauma or inflammatory disease excluded from lumbar fusion studies		prospective study evaluated PEMF stimulation in pts w/ delayed union or nonunion fractures (tibia, femur, humerus, radius/ulna, scapula, clavicle, or metatarsals) or failed arthrodesis (hip, knee, ankle, shoulder, or wrist). Overall success rate, by radiographic and clinical evaluation, was 77%, w/ 82% success rates both for nonunions of tibia and failed arthrodeses (Bassett et al., 1982). *Lumbar spinal fusion:* RCTs: (1) In a moderate-size, multicenter, randomized trial, consistent users of PEMF (≥8 hrs/day, later set to 2 hrs/day) had significantly higher success rate of interbody spinal fusion than pts in placebo grp (92% and 67%, respectively). Inconsistent PEMF users achieved success rate similar to pts in placebo grp (Mooney 1990). (2) A small, randomized trial compared the effect of adjunctive noninvasive PEMF and invasive DC stimulation on augmentation of instrumented lumbar spinal fusion. Neither form of ES resulted in improved fusion rates or clinical outcome (pain, function) in instrumented lumbar arthrodesis. However, there was an insignificant trend toward increased fusion mass BMD in both ES grps relative to surgery-only grp (Jenis et al., 2000). *Other indications (degenerative joint disease):* RCTs: 2 small RCTs in homogeneous populations (1) In 1 small RCT in homogeneous populations, PEMF stimulation favored osteotomy healing, w/ statistically significant differences between PEMF and placebo grps at 40 and 90 days in pts tx'd w/	

			femoral intertrochanteric osteotomy for hip degenerative arthritis (Borsalino et al., 1988). (2) In another small RCT in homogeneous populations, radiographic evaluation at 60 days showed complete or almost complete healing in 72% of PEMF grp vs 26% of controls (statistically significant difference) in pts tx'd w/ valgus tibial osteotomy for degenerative arthrosis of knee (Mammi et al., 1993). *Device/procedure-related complications:* Device bulky or uncomfortable; minor skin rash; pain while using device	
Hayes Inc. (2004b)[a] Systematic review of studies assessing effectiveness and safety of **capacitive coupling** *F/u:* Varied across studies from range of 8-42 wks on low end to mean of 31 mos on high end *Funding source:* No outside sources; for this systematic review; no commercial support for selected studies reported	*# and type of studies:* 3 RCTs (Steinberg et al., 1990; Scott & King, 1994; Goodwin et al., 1999) 2 uncontrolled prospective studies (Zamora-Navas et al., 1995; Abeed et al., 1998) *# pts:* RCTs: 236 Uncontrolled prospective studies: 38 *Comparators/controls:* No tx; placebo stimulation *Typical pt inclusion/exclusion criteria:* Some studies specifically excluded elderly and/or children; none reported participants age <17 yrs; pts w/ systemic disease (e.g., bone metabolic disease, diabetes, severe osteoporosis) that could	*Databases searched:* MEDLINE and EMBASE *Time span of literature search:* July 2001 – May 2004 (MEDLINE); July 2001 – October 2003 (EMBASE) *Study inclusion criteria:* RCTs; uncontrolled prospective studies; English-language articles w/ human participants *Study exclusion criteria:* Retrospective studies Studies were evaluated for methodological strength and applicability to the key questions. *Outcome measures:* Varied by study	*Nonunion fractures (long bones or other appendicular bones):* <u>RCTs:</u> (1) In a small RCT of pts w/ established nonunions of the tibia, ulnar, or femur, 60% of actively managed pts and no controls achieved union by radiographic and clinical criteria, a statistically significant difference (Scott and King, 1994). <u>Non-RCTs:</u> (1) A small, uncontrolled study reported successful healing in 69% of nonunions of the radius, tibia, femur, or ulna after tx. However, healing took place only if the distance between the plates was not excessive (Abeed et al., 1998). (2) A small, uncontrolled heterogeneous study of pts w/ established nonunions of the tibia, humerus, radius, clavicle, carpal scaphoid, or ulna, found that solid bony union occurred in 73% of pts. The success rate in gaps >0.5 cm did not differ from the rate in gaps that were narrower, and the authors suggested that tissue type w/in gap (not distance) may affect tx effect (Zamora-Navas et al., 1995).	*Overall conclusion(s):* Evidence from studies involving capacitive coupling is not as strong as for PEMF, as there were fewer studies and, thus, a lower total # of pts enrolled in capacitive coupling trials, and none of the studies had been published more recently than 1999. Evidence pertaining to long bone fracture and lumbar fusion was positive, while evidence pertaining to tx of AVN was negative. *Limitations:* Only English-language publications included; time span of EMBASE literature search shortened relative to MEDLINE search, which could have resulted in missing studies relevant to the review.

	interfere w/ tx often excluded; if defined, nonunion = no union after 9 mos; pts undergoing lumbar fusion for reasons other than degenerative disease excluded		*Lumbar spinal fusion:* RCTs: In 1 moderate-size RCT, capacitive coupling was used adjunctively to primary lumbar spine fusion. The overall success rate (both clinical and radiographic) was 85% for the active grp compared w/ 65% for the placebo grp, a statistically significant difference. When clinical outcomes were assessed separately, between-grp difference favored stimulation. Capacitive coupling was effective, especially for pts w/ posterolateral fusion and internal fixation (Goodwin et al., 1999). *Other indications (AVN):* 1 small RCT found that capacitive coupling used as an adjunct tx to decompression and grafting of AVN of femoral head did not have any added benefit relative to the main tx alone on clinical (function, need for surgery) or radiographic parameters (Steinberg et al., 1990). *Device/procedure-related complications:* Occasional skin irritation under electrodes; allergic reaction to electrode disks on skin	
Hayes Inc. (2004b)[a] Systematic review of studies assessing effectiveness and safety of adjunctive **CMF** *F/u:* NR in 1 study, 9 mos to study endpoint + 3 additional mos in other study *Funding source:* No outside sources for this systematic review;	*# and type of studies:* 1 RCT in pts who had undergone primary noninstrumented posterolateral lumbar spinal fusion (Linovitz et al., 2002) 1 partially randomized controlled expanded pilot study in pts w/ acute, phase 1 Charcot neuroarthropathy (Hanft et al., 1998) *# pts:* 232 pts (total of both studies)	*Databases searched:* MEDLINE and EMBASE databases *Time span of literature search:* July 2001 – May 2004 (MEDLINE); July 2001 – October 2003 (EMBASE) *Study inclusion criteria:* RCTs; uncontrolled prospective studies; English-language articles w/ human participants	*Lumbar spinal fusion:* RCTs: In 1 RCT (n=201), pts w/ noninstrumented posterolateral fusions, adjunctive use of CMF ES significantly increased the 9-mo radiographic fusion success rates in the overall (64% vs 43%) and female (67% vs 35%) study populations but not the male population (58.5% vs 55%). In addition, there was an acceleration of the healing process (Linovitz et al., 2002). *Foot/ankle arthrodesis:* Non-RCTs: In a partially randomized trial (n=31), pts who had peripheral neuropathy	*Overall conclusion(s):* The evidence was quite sparse for CMF, consisting of only 2 studies. However, both studies reported positive findings and 1 was a moderate-size multicenter RCT. *Limitations:* Only English-language publications included; time span of EMBASE literature search shortened relative to MEDLINE search, which could have resulted in

no commercial support for selected studies reported	*Comparators/controls:* No tx grp; placebo grp (dummy stimulators) *Typical pt inclusion/exclusion criteria:* Neither study reported participants age <36 yrs; pts w/ systemic disease (e.g., diabetes) that could interfere w/ tx excluded (lumbar fusion); open wound excluded (Charcot neuropathy)	*Study exclusion criteria:* Retrospective studies Studies were evaluated for methodological strength and applicability to the key questions. *Outcome measures:* Varied by study	secondary to diabetes mellitus and Charcot joint (w/ degenerative joint destruction of the foot or ankle), CMF stimulation significantly accelerated consolidation (11 wks for CMF grp vs 23.8 wks for control no-tx grp) and decreased the amount of residual deformity (Hanft et al., 1998). *Device/procedure-related complications:* NR in both studies	missing studies relevant to the review.
Mollon et al. (2008) The University of Western Ontario, London, Ontario; McMaster University, Hamilton, Ontario; Boston University, Boston, MA Systematic review of RCTs to evaluate whether EMS **(PEMF or capacitive coupling)** would improve union rates of long bone fractures *F/u:* Duration of study f/u NR EMS administered 4-24 hrs/day over tx period of 4-76 wks *Funding source:* No outside funding or grants in support of research for or	*# and type of studies:* 11 RCTs Osteotomies for degenerative disease: 2 RCTs (Borsalino et al., 1988; Mammi et al., 1993) Fresh fractures: 2 RCTs (Wahlstrom 1984; Betti et al., 1999) Long bone fracture nonunions: 3 RCTs (Barker et al., 1984; Scott & King, 1994; Simonis et al., 2003) Delayed long bone fracture unions: 1 RCT (Sharrard 1990) Tibial stress fractures: 1 RCT (Beck et al., 2008) Primary distraction osteotomy (limb lengthening): 1 RCT (Eyres et al., 1996) Pseudarthrosis resulting from limb lengthening: 1 RCT (Poli et al., 1985) *# pts:* 347	*Databases searched:* MEDLINE, EMBASE, CINAHL, and all evidence-based medicine reviews (no language restrictions); manual search of 7 key journals. RRs calculated where possible and pooled where feasible *Time span of literature search:* From inception of databases to April 16, 2008; from 1980 to April 16, 2008 for key journal search *Study inclusion criteria:* Random allocation of pts to tx assignment; pts w/ long bone lesions; inclusion of tx arm receiving electromagnetism of any waveform to impact bone healing; report of the effect of EMS on direct bone healing	All reviewed studies were RCTs and are presented by indication. *Fresh fractures:* (1) For radiographic outcomes (i.e., bone union), 1 small RCT favored EMS in pts w/ fresh femoral neck fracture, but nonsignificant (n=65; estimated RR,1.26; 95% CI, 0.99-1.60) (Betti et al., 1999) (2) 1 RCT found EMS produced significant increases in the short term (≤2 wks), but not long term (≥4 wks) for scintimetric healing activity in nonoperatively tx'd fresh Colles fractures in women; no impact in redisplacement rates (Wahlstrom 1984). (3) See *Clinical outcomes.* *Nonunion and delayed union fractures:* 4 studies that favored EMS on radiographic outcomes (i.e., bone union), but nonsignificant (n=116; pooled estimated RR, 1.76; 95% CI, 0.81-3.80) (Barker et al., 1984; Sharrard 1990; Scott and King, 1994; Simonis et al., 2003). High heterogeneity (I^2=60%); sensitivity analyses by type of bone and lesion did not explain the heterogeneity; sensitivity analysis by technical parameters not	*Overall conclusion(s):* Meta-analyses did not find any statistically significant tx effect of EMS for improving radiographic outcomes for nonunion or delayed union fractures, fresh fractures, or tibial osteotomy. EMS tx generally did not improve clinical outcomes, although 1 of 4 studies noted reduction of pain in a subgrp of pts. Evidence regarding the effect of EMS on bone densitometry measures varied both across and w/in studies. *Limitations:* Selection of only RCTs provided a limited evidence base, consisting of articles w/ generally small sample size; sensitivity analyses did not explain high heterogeneity in meta-analyses; inconsistency in results across studies may arise from type of electromagnetic stimulation

preparation of this study; no commercial support of selected studies reported	*Type of ES:* PEMF in most (8 studies); also capacitive and extremely low frequency electromagnetic tx *Comparators/controls:* Sham EMS device; inactive device, coil, or pulse generator; usual care only *Typical pt inclusion/exclusion:* NR	*Study exclusion criteria:* Outcomes not directly related to bone healing; active tx intervention did not involve some form of EMS GRADE criteria used to evaluate quality of evidence by outcome. RR calculated for each study describing bone union results. *Outcome measures:* Radiographic outcomes (bone union); clinical outcomes; bone densitometry	feasible because of small # of studies; differences according to whether ES was combined w/ surgery not considered. According to GRADE assessment, these trials were of very low quality and had serious limitations in consistency. *Pain, fractures:* 3 RCTs of delayed union or nonunion tibial fracture found no impact of EMS on pain (Barket et al., 1984; Sharrard 1990) or fresh tibial stress fracture (Beck et al., 2008); 1 study of tx for femoral neck fracture noted reduction in pain w/ EMS, but this was based on subgrp analysis of pts who were compliant w/ intervention (Betti et al., 1999). *Other indications (degenerative disease, limb lengthening):* (1) 1 small RCT that favored EMS tx in pts undergoing tibial osteotomy, but nonsignificant (n=37; estimated RR, 2.81; 95% CI, 0.88-8.98) (Mammi et al., 1993) (2) EMS improved bone density in pts undergoing femoral intertrochanteric osteotomy (Borsalino et al., 1988). (3) No effect on ultimate clinical outcome in pts undergoing primary limb-lengthening procedures (Eyres et al., 1996). (4) No effect on limb-length imbalance or on need for reoperation of adjunctive EMS for surgically managed pseudarthroses (Poli et al., 1985). *Complications:* NR	and/or heterogeneity of pt populations; no review of safety issues; fusion results reported by Beck et al. (2008) NR.

[a] See Appendix VII for detail pertaining to each selected primary study.

Table 6. Primary Studies Assessing Noninvasive Electrical Bone Growth Stimulators (ordered by study design)

Key: BGS, bone growth stimulation; CT, computed tomography; DC, direct current; dx, diagnosis; FDA, Food and Drug Administration; f/u, follow-up; grp(s), group(s); hx, history; IDE, Investigative Device Exemption; ITT, intention-to-treat; LBF, long bone fracture; MRI, magnetic resonance imaging; NDI, neck disability index; NLBF, nonlong bone fracture; NR, not reported; NS, not statistically significant; NWB, non–weight-bearing; PEMF, pulsed electromagnetic field; postop, postoperative(ly); preop, preoperative(ly); pt(s), patient(s); *r*, correlation coefficient; ROM, range of motion; SF-12, Short Form-12 health survey; subgrp(s), subgroup(s); tx, treatment (or therapy); VAS, visual analog scale

Authors/Study Design	Study Population	Procedures/Outcome Measures	Results/Complications*	Conclusions/Limitations/ Quality Ratings
Foley et al. (2008) Multiple sites in the U.S. Multicenter single-blind RCT to assess PEMF as adjunct to cervical fusion in pts at risk for fusion failure (FDA-sponsored IDE study for Cervical-Stim, Orthofix Inc.) *F/u:* 1 yr *Time frame:* NR *Funding source:* NR	n=323 pts (mean age 47 yrs; 54% men) undergoing cervical fusion w/ allograft and instrumentation *Inclusion criteria:* Age 18-75 yrs; evidence of nerve root compression according to CT-myelogram or MRI and correlative symptoms; VAS pain score≥5 and/or upper extremity weakness correlative to level of radiographic findings; smokers (>1 pack/day) or requiring multilevel fusion *Exclusion criteria:* Pertinent hx of trauma, previous posterior cervical approach or revision surgery; potentially interfering systemic conditions; regional condition (i.e., Paget's disease or spondylitis); hx of systemic or local infection w/in 2 wks of surgery; migraine headaches;	All pts underwent anterior cervical discectomy and fusion w/ allograft bone grafting and instrumentation and were randomized to postop tx grp. Both tx grps wore soft cervical collar for 1 wk. *PEMF grp (n=163):* Cervical-Stim (Orthofix Inc.), started w/in 7 days of surgery, 4 hrs/day for 3 mos; compliance assessed at each f/u visit by means of device-recorded "on" time *Control grp (n=160):* No stimulation. F/u visits at 1, 2, 3, 6, and 12 mos. Radiographic exam at 3, 6, and 12 mos w/ blinded reading by 2 independent orthopedic surgeons and resolution of disagreement by blinded radiologist; included computerized assessment of motion. Evaluation of other outcomes at 6 and 12 mos.	No important between-grp differences in age, sex, race, workmen's compensation claims, litigation, smoking status, or preop dx. PEMF grp was somewhat more likely to report other medical problems (31% vs 26%). *Type of surgery (PEMF, control) (% pts):* Single level: 23.3%, 20.0% 2 levels: 56.4%, 62.5% 3 levels: 16.6%, 16.2% Differences NS; *P* values NR. *Loss to f/u at 6 mos (% pts) (PEMF, control):* 25.1%, 26.2%. Reasons included voluntary withdrawal, violation of study protocol (7 in PEMF grp vs 1 in control grp), or radiographs deemed not evaluable. *Fusion success at 6 mos (PEMF, control) (% pts):* Assume fusion success in missing pts: 85.9%, 76.3% (*P*=0.0269) Impute results from last visit in missing pts: 78.2%, 64.8% (*P*=0.0127) Assume fusion failure in missing pts: 65.6%, 56.3% (*P*=0.0835) Actual: 83.6%, 68.6% (*P*=0.0065). (actual at 12 mos, 92.8% PEMF grp and 86.7% control grp; *P*=0.1129) *Differences in 6-mo fusion rates w/in risk factor subgrps (PEMF, control) (% pts w/*	PEMF was effective in promoting earlier healing of cervical fusion in pts at high risk of fusion failure. PEMF may have had greater effect in men than in women and in pts <50 yrs of age. PEMF did not improve pain, health status, or functional outcome. PEMF was apparently safe. *Limitations:* Methods of randomization and allocation concealment NR; high loss to 6-mo f/u; loss to f/u at 12 mos NR; unclear whether compliance measure actually indicated that the device was worn; compliance rates NR; significance level for statistical testing NR; no direct test for interaction between tx and risk factors; men vs women rates w/in control grp NR. Website for manufacturer of PEMF device features a slide presentation by the principal author; suggests a relationship (Orthofix, 2009b). *Quality:* Fair (downgraded because of loss to f/u) for

	seizure disorder; neurological disease or injury; incompetent immune system; cardiac pacemaker, defibrillator, DC stimulator implant, cochlear implant, or cranial stimulator; or pregnancy or planning pregnancy or nursing *Clinical hx/pt characteristics (% pts):* Workmen's compensation (24%), litigation (5%), smokers (49%)	*Outcome measures:* Radiographic fusion (≥50% bony bridging through both surfaces of graft-vertebra interface, no radiolucency, and ≤4° motion between adjacent fused vertebrae for *all* fusion levels); pain (10-point VAS), physical health status (SF-12), and functional status (NDI); safety (anticipated and unanticipated adverse events). ITT analysis	*success):* Men (80.9%, 64.4%) vs women (87.0%, 72.9%): Global *P*=0.0053 Age <50 yrs (85.3%, 74.4%) vs ≥50 (80.9%, 55.6%): Global *P*=0.0040 Smoker (86.9%, 69.2%) vs nonsmoker (80.3%, 67.9%): Global *P*=0.0172 Single-fusion level (92.3%, 84.0%) vs multiple (81.3%, 64.5%): Global *P*=0.0062 (NS differences at 12 mos) *Effect of risk factors on fusion rates w/in control grp:* Age: Much higher rates in pts age <50 yrs at 6 and 12 mos (*P* values <0.05) Smoking status: Slight differences (high *P* values) # of levels: Somewhat higher rates when surgery involved a single level (*P*=0.0623 at 6 mos, 0.2711 at 12 mos) *Pain (10-point VAS) and SF-12 physical health status:* No important between-grp differences at rest or w/ activity preop, at 6 mos, or at 12 mos. Both grps improved on both measures, particularly during 1st 6 mos. *NDI (PEMF, control):* Preop: 48.0, 45.6 6 mos: 31.0, 23.0 12 mos: 25.6, 22.8 All differences reported to be NS (*P* values NR) *Device-related complications:* Authors assumed none since there were no between-grp differences in anticipated or unanticipated adverse events.	effect on healing, function, and QOL; for safety; and for effectiveness by subgrp.
Dhawan et al. (2004) Allegheny General Hospital, Pittsburgh, PA	n=64 consecutive pts (70 feet) undergoing elective triple arthrodesis or subtalar arthrodesis	All pts underwent triple or isolated subtalar joint arthrodesis by standard technique and wore short-	No difference between tx grps in % of pts w/ osteopenia. No loss to f/u evaluation and no dropouts reported. 6 of original 70 pts excluded due to incomplete series of	PEMF was effective in accelerating radiographic healing time following hindfoot arthrodesis and reduced the

RCT w/ blinding, comparing routine PEMF vs no stimulation following elective hindfoot arthrodesis *F/u:* 27 wks *Time frame:* March 1993 – March 1996 *Funding source:* NR	(mean age 46 yrs; 56% men) w/ complete data (out of 70 pts originally enrolled) *Joints fused (PEMF, control) (# joints):* Subtalar: Primary (22, 33); revision (5, 4) Talonavicular: Primary (20, 19); revision (3, 0) Calcaneocuboid: Primary (17, 21); revision (2, 0) *Clinical hx (# feet):* Normal bone density (n=63), osteopenia (n=7)	leg cast until evidence of radiographic consolidation. Pts randomized to PEMF or control. *PEMF grp (n=38 feet):* External device (EBI Medical) applied over cast ~10 days after surgery, 12 hrs/day, until complete radiographic union. *Control grp (n=32 feet):* No stimulation Radiographs preop; postop; at 2, 6, and 12 wks; and at every 3 wks thereafter up to 27 wks or until radiographic union. Blinded evaluation. *Main outcome measures:* Radiographic joint fusion; time to radiographic fusion	radiographs. *Success rate (% pts w/ radiographic union):* PEMF, 100%, including revisions; control, 100% of primary revisions and 0 of the 4 subtalar revisions *Time to radiographic union in primary fusions (PEMF, control) (wks):* Subtalar: 12.9, 14.5 (NS) Talonavicular: 12.2, 17.6 (*P*=0.003) Calcaneocuboid: 13.1, 17.7 (*P*=0.010) *Correlation of joint-specific fusion times:* W/in PEMF grp, fusion times between different types of joint were highly correlated (*r*=0.87-0.96; *P*=0.001 for each relationship). W/in control grp, correlation was moderate (*r*=0.36-0.42) and NS. *Device-related complications:* None reported.	variability in healing times among joints. No effect on success rate was detected. *Limitations:* Small sample size; reason for arthrodesis NR; methods of randomization and allocation concealment NR; infrequent f/u intervals prevented more than approximate estimate of healing time; perfect success rate for primary fusion in both grps and very small # of revision procedures preclude assessment of effect on success rate; no assessment of clinical union, pain, or functional outcomes. *Quality:* Good
Simmons et al. (2004) Multiple sites in the U.S. Multicenter, open prospective study to assess PEMF as salvage tx of pseudarthrosis after lumbar fusion *F/u:* None; outcomes assessed at end of tx (≤21 mos) *Time frame:* NR	n=100 pts (mean age 43.3 yrs; 64% men) *Inclusion criteria:* Radiographic documentation of pseudarthrosis and clinical symptoms, e.g., motion, indicative of pseudarthrosis at ≥9 mos after last arthrodesis attempt; no radiographic evidence of progression of healing for 3 mos. Radiographic evaluation by CT, MRI, or plain x-ray.	Pts underwent lumbar fusion; interbody (36%), posterolateral (64%). Pts used PEMF device ≥2 hrs/day for ≥90 days. *PEMF device:* Spinal-Stim (Orthofix® Inc.) Radiographic success judged by clinician investigators and by radiologist blinded to clinical information. Differences between radiographic and clinical judgment of radiographic healing resolved by	Good compliance, confirmed by internal computer chip, Duration of PEMF tx, 8.3 mos, range 3-21. *Factors prognostic of radiographic healing:* Important differences were observed for age >50 yrs vs age <50 yrs (73% vs 65%), women vs men (72% vs 64%), and allograft/mixed vs autograft (78%/75% vs 61%). No important differences according to fusion technique, single/multiple levels, smoking status, or workmen's compensation status. NS multiple regression predictors revealed after controlling for other factors. *Overall success rate (clinical/radiographic):* Excellent/success, 12%; good/success, 30%; fair/success, 15%; poor/success, 10%.	Very substantial proportion but not a majority of pts experienced radiographic healing and excellent or good clinical outcome following PEMF for failed lumbar fusion. Presence of risk factors for failed fusion, e.g., smoking, did not affect success of PEMF. *Limitations:* Lack of control grp; definition of clinical success NR, which may represent heterogeneity across sites; wide variation in time of PEMF placement since surgery and no assessment of impact of this factor on healing rate;

Funding source: NR	*Exclusion criteria:* Cardiac pacemakers, spinal trauma, spondylitis, Paget's disease, severe osteoporosis, metastatic cancer, uncontrolled diabetes mellitus, or renal dysfunction. *Clinical hx/pt characteristics (% pts or mean):* Primary fusion (72%), revision (28%), single level involved (53%), autograft/allograft/mixed (62%/18%/20%), smoker (33%), fixation (81%), workmen's compensation (68%), time of PEMF placement (mean 18.7 mos, range 9 mos – 12.5 yrs)	independent third surgeon, except in cases of investigator's determination of failure, which was never allowed to be overturned. *Outcome measures:* Radiographic success (≥50% assimilation), clinical success (definition NR), prognostic factors assessed by stratified analysis and by multivariate analysis (logistic regression; age, sex, and other factors listed as *Clinical hx/pt characteristics,* except for time to PEMF placement)	(67% of pts experienced radiographic success). Excellent/failure, 4%; good/failure, 6%; fair/failure, 14%; poor/failure 9%.	incomplete description of mechanism for confirming compliance; f/u interval NR. *Quality:* Poor
Punt et al. (2008) 10 hospitals in the Netherlands Retrospective, before-and-after, blinded analysis of PEMF for salvage tx of nonunion of traumatic fractures *F/u:* 6 mos *Time frame:* January 1996 – January 2000 *Funding source:* NR	n=93 fully eligible pts selected from 415 consecutive pts (median 38 yrs, range 16-83) tx'd w/ PEMF for nonunion of fracture *Inclusion criteria:* Skeletally mature; dx of nonunion (defined as incomplete healing by 8 mos after injury and no evidence of healing activity w/in previous 3 mos) *Exclusion criteria:* Surgical intervention at nonunion site w/in 3 mos	Information collected w/ use of case report forms designed for the study. No tx other than stimulation was reported. *PEMF device:* Orthopulse® I and Orthopulse® II; tx parameters NR Radiographic and clinical evaluation at 3 mos prior to stimulation, at time of stimulation, at 6 and 12 wks after start of stimulation, and at 6 mos after removal of stimulation. Each investigator evaluated own pts. In addition, an	Pts were tx'd for a median of 12.9 wks (range 4.9-36.6). *Loss to f/u at 6 mos after BGS removal:* LBF, 8%; NLBF, 17% *Discontinuation of immobilization at 6 mos after BGS removal (LBF, NLBF) (% pts):* 65%, 91% *% motion (BGS application, 6 wks, 12 wks, 6 mos after removal):* LBF: 38%, 26%, 8%, 2% ($P \leq 0.002$ at each f/u interval for comparison w/ BGS application) NLBF: 18%, 7%, 4%, 0 (trend toward significance in change at 6 mos after removal)	Compared w/ clinical conditions at the time of initiation of BGS stimulation, pts w/ a dx of nonunion experienced substantial clinical improvement and radiographic evidence of healing. Overall clinical and radiographic success was similar for LBFs and NLBFs. *Limitations:* Sample size too small to allow comparison between LBF and NLBF; some loss to f/u; tx parameters NR; unclear whether radiographic outcomes reflect investigator evaluation, independent evaluation, or a consensus

	prior to PEMF, nontraumatic fracture, synovial or congential nonunion, active osteomyelitis, fracture gap >10 mm, pregnancy, pacemaker *Clinical hx/pt characteristics:* LBF (69% of pts), NLBF (31% of pts), time since injury (median 14 mos, range 8-461), most common LBF (tibia), internal or external fixation (78% LBFs, 31% NLBFs), bone graft (9% LBFs, 31% NLBFs) cast/brace at time of injury (slightly <50% of pts), duration of immobilization (median 8 wks, LBF; 12 wks, NLBF; range 2-56)	independent surgeon blinded to pt, surgeon, and facility evaluated x-rays. *Outcome measures:* Discontinuation of immobilization; pt-reported pain (VAS, 1=no pain, 5=extreme pain); physician-reported % motion at fracture site based on manual exam; clinical success (pain 1-2 and 0 motion at time of BGS removal); radiographic success (fuzzy appearance, 2 cortices bridged by dense bone, and no visible fracture line at time of BGS removal) Differences between LBF and NLBF were not tested for significance because of small size of these 2 subgrps.	*Pain (BGS application, 6 wks, 12 wks, 6 mos after removal) (mean on 1-5 scale):* LBF: 2.4, 1.7, 1.4, 1.3 NLBF: 2.8, 2.0, 1.5, 1.4 For both types fractures, *P*<0.001 at each f/u interval for comparison w/ BGS application. *Clinical + radiographic success at time of BGS removal (% pts):* LBF, 76%; NLBF, 79% *Device-related complications:* None reported	*Quality:* Fair for effect of BGS (upgraded because of before-and-after comparison, well-defined selection process and inclusion/exclusion criteria, and consideration of clinical factors and pain; some concern regarding whether a substantial # of pts were excluded due to missing chart data). Poor for comparison of LBF vs NLBF.
Saltzman et al. (2004) University of Iowa Hospitals and Clinics, Iowa City, Iowa Retrospective evaluation of the adjunctive use of PEMF as salvage tx for delayed unions of foot/ankle arthrodesis *F/u:* None; outcomes assessed at end of tx (4 mos)	n=19 pts w/ delayed union of foot or ankle arthrodesis (median age 57 yrs, range 27-82) *Inclusion criteria:* Delayed union (failure to heal at ≥4 mos postop) of ankle, hindfoot, or midfoot arthrodesis *Clinical hx/pt characteristics:* Smokers (n=5), previous nonunions (n=8), previously attempted arthrodeses (median 1,	Pts continued to use PEMF, were NWB, and wore short-leg cast for ≥6 wks; weight bearing gradually increased based on radiographic evidence of healing. PEMF use continued until fusion. If no fusion after 4 mos of tx, repeat arthrodesis recommended. *Outcome measures:* Complete healing (radiographic fusion)	*% of pts w/ radiographic fusion:* 26.3% (n=5) *Median time to radiographic fusion (n=5) (mos):* 8 (range 8-15) *Use of PEMF after repeat arthrodesis:* 9/14 pts w/ failed PEMF tx underwent repeat arthrodesis w/ bone autograft and were tx'd postop in same manner as initially. Of these, 77.8% (7/9) pts had complete fusion at median 5.5 mos. No pattern showing a relationship between age or smoking status and tx success could be detected. *Device-related complications:* None	Use of PEMF as an adjunct to a NWB regimen and immobilization for tx of delayed union of foot or ankle arthrodesis resulted in fusion for a relatively small proportion of pts. In pts who underwent repeat arthrodesis due to failed PEMF tx, bone grafting and repeat postop use of PEMF resulted in fusion for most pts. *Limitations:* Small sample size; retrospective design; lack of control grp; PEMF device and PEMF tx parameters NR; blinded evaluation NR; clinical

Time frame: December 1995 – February 2000 *Funding source:* NR	range 0-6), tibiocalcaneal joint (n=1), tibiotalocalcaneal joint (n=1), ankle joint (n=7), subtalar joint (n=3), talonavicular joint (n=2), calcaneocuboid joint (n=1), naviculocuneiform joint (n=3), tarsometatarsal joint (n=1), time from initial attempted arthrodesis (median 7 mos, range 5-27)		reported	outcomes NR; unknown whether NWB + immobilization or PEMF caused healing in 5 pts w/ success; unknown whether bone grafting and PEMF had separate effects in pts who underwent repeat arthrodesis; no f/u. *Quality:* Poor

*Significance level of 0.05.

Guidelines

Guidelines and health technology assessments (HTAs) published in 2004 or later were identified by consulting all sources included in the three sections of the MED core source list (November 2008) and by searching the website for the American Academy of Neurological Surgeons (AANS) and the American Association of Orthopaedic Surgeons (AAOS).

American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS): The AANS/CNS Joint Section of Disorder of the Spine and Peripheral Nerves selected a group of orthopedic and neurosurgical spine surgeons to conduct an evidence-based review of the literature on lumbar fusion procedures for degenerative disease of the lumbar spine. The group (with input from the Guidelines Committee of AANS/CNS and the Clinical Guidelines Committee of North American Spine Society) then developed a comprehensive set of evidence-based guidelines to clarify patient care and best-practice standards for this patient population. The guidelines used Class I evidence (well-designed randomized controlled trials, and reviews and/or meta-analyses of RCTs) to support *treatment standards*, the strongest type of recommendations that reflect a high degree of clinical certainty. Class II evidence (well-designed comparative clinical studies, such as nonrandomized cohort studies, case-control studies, and other comparable studies, including less well-designed randomized controlled trials) was used to support *treatment guidelines*, recommendations that reflect a moderate degree of clinical certainty (Resnick et al., 2005a).

One of these guidelines addressed the use of bone growth stimulators for lumbar fusion in patients with degenerative disease of the lumbar spine. The authors conducted a search of the National Library of Medicine database from 1966 through May 2003. A total of 10 studies were identified that evaluated bone growth electrical stimulation in patients undergoing spinal fusion. This guideline reviewed only studies published in 2003 or earlier, and thus does not include any new evidence published subsequent to the Hayes Medical Technology Directory Reports on bone growth stimulators (Hayes, 2004a, 2004b). Two low-quality studies were included during the development of this guideline, but were not reviewed in the Hayes reports.

The guideline development team concluded that there was insufficient evidence to recommend a treatment standard (Resnick et al., 2005b). However, the following treatment guidelines were presented:

- Direct current electrical stimulation (DCES) or capacitive coupled stimulation were recommended as an adjunct to spinal fusion to increase fusion rates in patients who are high risk for arthrodesis failure after lumbar posterolateral fusion. This recommendation was based on eight studies, of which only one very low-quality study was not evaluated in the Hayes reports.

- PEMF stimulation was recommended as an adjunct to increase fusion rates in similar patients who were treated with lumbar interbody fusion procedures.

The recommendations set forth in this guideline are similar to those reached in the Hayes reports.

Agency for Healthcare Research and Quality (AHRQ): In 2005, AHRQ commissioned an evidence report with a systematic review on the role of bone growth stimulating devices and orthobiologics in healing of nonunion fractures. The report was prepared by ECRI Evidence-based Practice Center and was used to assist Centers for Medicare & Medicaid Services (CMS) and the Medicare Coverage Advisory Committee in considering management options for nonunion fractures in the Medicare population. Bone growth stimulators evaluated in the systematic review included ultrasound (US), direct current (invasive ES), PEMF (noninvasive ES), and capacitive coupling (noninvasive ES) treatment. This review was not considered as an evidence source (see **FINDINGS**) since it only reviewed studies published in 2003 or earlier. The report concluded that the overall quality of evidence for each intervention is generally low. Furthermore, in many of the reviewed studies, the treatment effect of the device could not be distinguished from possible therapeutic effects of concurrent treatments. Generalizability of the reviewed studies to the Medicare population was poor; few studies reported results separately for participants aged 65 years or older or provided analysis by age groups (AHRQ, 2005).

ECONOMIC EVALUATIONS

Ultrasound Bone Growth Stimulation for Fresh Fractures

[NOTE: This rapid review concluded that moderate-quality evidence suggests that LIPUS is effective in accelerating bone healing in fresh fractures.]

The Hayes (2003) review included an economic study published in 1997 that constructed three models based on a pool of 1000 patients with closed and open grade I tibial diaphysis fractures. The first model assumed standard conservative or operative orthopedic management without the use of ultrasound (US); the second assumed low-intensity ultrasound (LIPUS) treatment in nonoperatively managed patients; and the third assumed LIPUS treatment in both nonoperative and operatively managed patients. Investigators hypothesized that adjunctive treatment with LIPUS would reduce the surgical costs associated with reoperation due to delayed fracture healing; reduce the workers' compensation costs due to reduced healing time; and reduce the amount of outpatient care required in the second phase of fracture healing. The models predicted that LIPUS would provide cost savings, whether used as part of nonoperative treatment or immediately following surgical treatment. However, the study did not calculate lost productivity or the effects on quality of life (QOL). The economic analysis was further weakened by the potential for publication bias since one of the authors was the primary author of a previously published randomized controlled trial supported by the manufacturer of the US device.

The Hayes (2003) review also included a 2001 systematic review that evaluated the cost-effectiveness of LIPUS to treat fresh tibia, radius, and scaphoid fractures. The perspective was the Australian healthcare system. Estimates of the proportion of patients with and without US treatment who would subsequently require an operation for delayed or nonunion fracture were derived from the literature. The analysis indicated that the total cost of treatment per patient, incorporating both direct and indirect costs, was higher for US treatment than for standard nonoperative treatment for all three fractures types. Treating fresh fractures with US was far less cost effective than interventions for other common health problems, including mammography screening and cochlear implants for children. At the time of the review, there was insufficient evidence regarding the effectiveness of US treatment for delayed and nonunion fractures to permit a cost-effectiveness analysis for these indications. The authors surmised that the use of US treatment instead of surgical intervention for delayed union or nonunion would result in higher indirect and direct healthcare costs.

The literature search for this rapid review yielded one more recent economic evaluation (Busse, Bhandari, Sprague, Johnson-Masotti, & Gafni, 2005). Investigators conducted a burden of illness (BOI) study from the perspective of both local government (the Ontario Ministry of Health and Long-Term Care) and society. The four different treatment strategies included casting, casting with therapeutic US, operative treatment with nonreamed intramedullary nailing, and operative treatment with reamed intramedullary nailing. Loss of productivity was calculated as the amount of time taken off from work

associated with each treatment strategy based on the time required to achieve fracture healing. Loss of productivity also included out-of-pocket expenses and lost productivity for family members and other caregivers. Unit costs were described in detail. Hospital costs and fees associated with healthcare use were provided by the Ontario Physician's Schedule of Benefits. The costs of prescribed medications were provided by hospital pharmacy records. Fees associated with hospital stays were calculated by estimating the weighted average orthopedic ward fee per day from a local hospital. A review of the literature provided resource utilization costs for patients undergoing treatment for tibial fractures. Investigators used a decision tree to perform all cost analyses, with probabilities derived from published RCT data. A sensitivity analysis was conducted through Monte Carlo simulations for models developed from both societal and governmental perspectives. All cost estimates were described in United States dollars (2004). From a governmental perspective, the mean associated costs of treatment of closed or open tibial fractures were as follows: (1) $3365 ± 1425 for reamed intramedullary nailing; (2) $5041 ± 1363 for nonreamed intramedullary nailing; (3) $5017 ± 1370 for casting; and (4) $5312 ±1474 for casting with therapeutic US. From a societal perspective that incorporated loss of work productivity, the sensitivity analysis favored reamed intramedullary nailing ($12449 ± 4894) and casting with therapeutic US ($13266 ± 3692) over nonreamed intramedullary nailing (15571 ± 4293) and casting alone ($17343 ± 4784). From both a societal and governmental perspective, investigators judged that operative management with reamed intramedullary nailing was the most economical choice for treatment of closed and open grade I tibial fractures. Investigators also reported that therapeutic US in combination with casting may also be an economical choice, but additional data are required to define the clinical effectiveness of this treatment, as well as confirm its true associated costs.

A descriptive review summarized the results from several economic analyses, one of which evaluated US for the treatment of tibial bone fractures (Kanakaris & Giannoudis, 2007). This article was excluded from detailed evaluation for this rapid review since it was already included in the Hayes (2003) systematic review, discussed previously.

Electrical Stimulation, Invasive and Noninvasive

No economic evaluations for electrical stimulation for the treatment of bone fractures were identified in the literature search.

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APPENDIX I

SEARCH STRATEGY AND SELECTION CRITERIA

The following strategy and selection criteria apply to systematic reviews and clinical studies selected to augment Hayes Medical Technology Directory Reports published in 2003 and 2004.

Search Strategy, Peer-Reviewed Literature

Databases:

- MEDLINE: 2003 through June 2009
- EMBASE: 2003 through June 2009

Limits: Human subjects, English

Search terms:

Technology-related terms:

> *(ultrasound or ultrason* or sonic or "Electric Stimulation" or (electric* or stmulat*) or "pulsed electromagnetic" or "combined electromagnetic" or "combined magnetic" or capacitive or bone growth stimulat*).hw,sh,kf.*

combined (AND) with terms related to health problem

> *(fracture* or "Fractures, Bone" or fracture healing or fusion or spinal fusion or arthrodesis osteonecrosis or osteoarthritis or necrosis or AVN).hw,sh,kf.*

The wild character "*" allowed all terms that start with the preceding letters.

Inclusion Criteria

- Clinical studies evaluating the safety and efficacy of ultrasound bone growth stimulators, invasive electrical bone growth stimulators, or noninvasive bone growth stimulators for the treatment of any type of bone fracture or as an aid to surgical fusion in adults and children.
- Systematic reviews and meta-analyses of clinical studies meeting these criteria.

Initial Exclusion Criteria

- Case reports
- Nonclinical studies
- Bone growth stimulation for degenerative lesions

Final Selection of Systematic Reviews

For each of the three major forms of bone growth stimulation, the best systematic review(s) were selected based on these quality criteria:

- Systematic literature search
- Critical appraisal of selected studies
- Synthesis of evidence by indication
- Explicit conclusions by indication

These criteria are derived from a well-accepted definition of systematic review proposed by Cook et al. (1997) and recently explicated by Rys et al. (2009).

Final Selection of Clinical Studies

Selected studies met *all* of these criteria:

- Were not included in selected systematic reviews.
- Provided information with respect to indications, populations, or risk factors not available in the selected systematic reviews.
- Presented results separately for general indications, e.g., long bones, nonlong bones, spinal fusion, joint arthrodesis.
- *Ultrasound only:* Sample size ≥ 50.
- *Electrical stimulation, invasive, only:* Sample size ≥ 20.

APPENDIX II

EXCLUDED CLINICAL STUDIES AND SYSTEMATIC REVIEWS

These studies and systematic reviews met initial selection criteria but were subsequently excluded.

Study/Review	Reason for Exclusion	Comments
Ultrasound		
Esenwein et al. (2004)	n<50	Uncontrolled, n=20, delayed callotasis
Lerner, Stein, & Soudry (2004)	n<50	Uncontrolled, n=17, delayed union, long bones
Leung, Lee, Tsui, Liu, & Cheung (2004)	Included in selected systematic review (Busse et al., 2009)	
Pigozzi et al. (2004)	n<50	Uncontrolled, fractures in amateur athletes
Tsumaki, Kakiuchi, Sasaki, Ochi, & Yoshikawa (2004)	Included in Busse et al. (2009)	Excluded indication (osteoarthritis)
AHRQ (2005)	Systematic review covering no studies published later than 2003	
El-Mowafi & Mohsen (2005)	Included in Busse et al. (2009)	
Handolin, Kiljunen et al. (2005a)	Included in Busse et al. (2009)	
Handolin, Kiljunen, Arnala, Pajarinen et al. (2005)	Included in Busse et al. (2009)	
Schortinghuis, Bronckers, Stegenga, Raghoebar, & de Bont (2005)	Included in Busse et al. (2009)	Excluded indication (mandible distraction gap)
Ricardo (2006)	Included in Busse et al. (2009)	
Schmelz, Friedrich, Kinzl, & Einsiedel (2006)	n<50	Prospective controlled, n=21, bony defects following tibia fracture
Walker, Denegar, & Preische (2007)	Systematic review overlapping w/ Busse et al. (2009); literature not as up to date; no conclusions or critical appraisal	Searched through 2004
Griffin, Costello, & Costa (2008a)	Systematic review overlapping w/ Busse et al. (2009); literature search not as up to date; no synthesis in literature review	Searched through July 2007
Lubbert, van der Rijt, Hoorntje, & van der Werken (2008)	Included in Busse et al. (2009)	
Electrical Stimulation, Invasive		
Hockenbury, Gruttadauria, & McKinney (2007)	n<20	Uncontrolled, n=10, Charcot ankle arthrodesis
Electrical Stimulation, Noninvasive		
Simonis, Parnell, Ray, & Peacock (2003)	Included in selected systematic review (Mollon et al., 2008)	
AHRQ (2005)	Systematic review covering no studies published later than 2003, except 1 included in review by Mollon et al. (2008)	
Impagliazzo, Mattei, Spurio Pompili, Setti, & Cadossi (2006)	Same indication (long bones) addressed by Mollon et al. (2008)	Uncontrolled, n=30
Lopez-Oliva Munoz, Madronero de la Cal, Garcia de las Heras, Martin Buenadicha, & Forriol Campos (2006)	Mixed indications w/o separate presentation of results	Uncontrolled, n=146, no long-term follow-up or complications data
Walker et al. (2007)	Systematic review overlapping w/ Mollon et al. (2008); literature not as up to date;	Searched through 2004

	no conclusions or critical appraisal	
Beck et al. (2008)	Included in selected systematic review (Mollon et al., 2008)	
Griffin, Warner, & Costa (2008b)	Systematic review overlapping with Mollon et al. (2008); literature review not as up to date	Searched through May 2007

APPENDIX III

MED PROJECT	Methodology Checklist: Randomized Controlled Trials
Study identification (*Include author, title, year of publication, journal title, pages*)	
MED topic:	Key Question No(s):
Checklist completed by:	Date:

Section 1: Internal validity

	In a well conducted RCT study…	In this study this criterion is:			
RANDOM ALLOCATION OF SUBJECTS					
1.1	An appropriate method of randomization was used to allocate participants to intervention groups.	YES	NO	UNCLEAR	N/A
1.2	***An adequate concealment method was used such that investigators, clinicians, and participants could not influence enrolment or intervention allocation.***	YES	NO	UNCLEAR	N/A
1.3	The intervention and control groups are similar at the start of the trial. (The only difference between groups is the treatment under investigation.)	YES	NO	UNCLEAR	N/A
ASSESSMENT AND FOLLOW-UP					
1.4	Investigators, participants, and clinicians were kept 'blind' about treatment allocation and other important confounding/prognostic factors. If the answer is no, describe any bias that might have occurred.	YES	NO	UNCLEAR	N/A
1.5	The intervention and control groups received the same care apart from the intervention(s) studied.	YES	NO	UNCLEAR	N/A
1.11	The study had an appropriate length of follow-up.	YES	NO	UNCLEAR	N/A
1.12	All groups were followed up for an equal length of time (or the analysis was adjusted to allow for differences in length of follow-up).	YES	NO	UNCLEAR	N/A
1.14	What percentage of the individuals or clusters recruited into				

	each group of the study dropped out before the study was completed? What percentage did not complete the intervention(s)?	
1.15	*All the subjects were analyzed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)*	YES NO UNCLEAR N/A

ASSESSMENT AND FOLLOW-UP, Cont.		
1.16	All relevant outcomes are measured in a standard, valid and reliable way.	YES NO UNCLEAR N/A
1.17	The study reported only on surrogate outcomes. (If so, please comment on the strength of the evidence associating the surrogate with the important clinical outcome for this topic.)	YES NO UNCLEAR N/A
1.18	The study uses a composite (vs. single) outcome as the primary outcome. If so, please comment on the appropriateness of the composite and whether any single outcome strongly influenced the composite.	YES NO UNCLEAR N/A
CONFLICT OF INTEREST		
1.19	There is a conflict of interest statement.	YES NO UNCLEAR N/A
1.20	There is a description of source(s) of funding.	YES NO UNCLEAR N/A
Section 2: Overall Study Assessment		
2.1	***How well was the study done to minimize bias?*** **Code Good, Fair, or Poor**	GOOD FAIR POOR
2.2	If coded as Fair or Poor what is the likely direction in which bias might affect the study results?	
2.3	Are the results of this study directly applicable to the patient group targeted by this topic?	YES NO UNCLEAR N/A
2.7	Other reviewer comments:	

APPENDIX IV

MED PROJECT	Methodology Checklist: Cohort Studies

Study identification (*Include author, title, year of publication, journal title, pages*)

Review topic:	Key Question No.(s), if applicable:
Checklist completed by:	Date:

Section 1: Internal validity

	In a well conducted cohort study:	In this study the criterion is:
1.1	The study addresses an appropriate and clearly focused question.	YES NO UNCLEAR N/A
	SELECTION OF SUBJECTS	
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	YES NO UNCLEAR N/A
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	YES NO UNCLEAR N/A
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrollment is assessed and taken into account in the analysis.	YES NO UNCLEAR N/A
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed?	
1.6	**Comparison is made between full participants and those who dropped out or were lost to follow up, by exposure status.**	YES NO UNCLEAR N/A
	ASSESSMENT AND FOLLOW-UP	
1.7	The study employed a precise definition of outcome(s) appropriate to the key question(s).	YES NO UNCLEAR N/A
1.8	The assessment of outcome(s) is made blind to exposure status.	YES NO UNCLEAR N/A
1.9	Where outcome assessment blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	YES NO UNCLEAR N/A
1.10	The measure of assessment of exposure is reliable.	YES NO UNCLEAR N/A
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	YES NO UNCLEAR N/A

1.12	Exposure level or prognostic factor is assessed more than once.	YES NO UNCLEAR N/A
1.13	The study had an appropriate length of follow-up.	YES NO UNCLEAR N/A
1.14	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	YES NO UNCLEAR N/A
CONFOUNDING		
1.15	The main potential confounders are identified and taken into account in the design and analysis.	YES NO UNCLEAR N/A
STATISTICAL ANALYSIS		
1.16	Have confidence intervals been provided?	YES NO UNCLEAR N/A
CONFLICT OF INTEREST		
1.17	There is a conflict of interest statement.	YES NO UNCLEAR N/A
1.18	There is a description of source(s) of funding.	YES NO UNCLEAR N/A
SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	How well was the study done to minimize the risk of bias or confounding, and to establish a causal relationship between exposure and effect? *Code Good, Fair, or Poor*	GOOD FAIR POOR
2.2	If coded as Fair, or Poor what is the likely direction in which bias might affect the study results?	
2.3	Are the results of this study directly applicable to the patient group targeted by this topic?	YES NO UNCLEAR N/A
2.4	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the exposure being investigated?	YES NO UNCLEAR N/A
2.5	Other reviewer comments:	

APPENDIX V

STUDIES EVALUATING EFFICACY AND SAFETY OF US BONE GROWTH STIMULATION
From Hayes Medical Technology Directory Report on *Ultrasound Bone Growth Stimulation* (Hayes, 2003)

Table A. Randomized Controlled Trials Evaluating the Efficacy and Safety of US Bone Growth Stimulation for Fresh Bone Fractures

Key: cm, centimeter; f/u, follow-up; grp(s), group(s); hx, history; IM, intramedullary; mW, milliwatts; NSAID, nonsteroidal anti-inflammatory drug; pt(s), patient(s); SAFHS, Sonic Accelerated Fracture Healing System; SATA, spatial average-temporal average; tx, treatment; US, ultrasound

Authors/Study Design	Study Population	Treatment Protocol and Outcome Measures	Results	Conclusions/Comments/ Limitations
Heckman et al. (1994) University of Texas Health Science Center, San Antonio, TX Multicenter, randomized, double-blind, placebo-controlled trial conducted in the United States (16 sites) and Israel (1 site) to evaluate the efficacy and safety of US for healing fractures of the tibial diaphysis *F/u*: Up to ≥4 yrs *Time frame:* September 1986 – December 1990 Study supported by Exogen, Inc.	n=96 pts (97 fractures) Open grade I (n=3) Mean age: US grp, 36.0±2.3 yrs; placebo grp, 31.0±1.8 yrs No statistically significant difference between US and placebo grp in 17 baseline patient and fracture parameters (*P*>0.05) *Inclusion criteria:* Closed or grade I open tibial diaphyseal fracture that was primarily transverse short oblique or short spiral and amenable to tx w/ closed reduction and cast immobilization; age ≤75 yrs; skeletally mature *Exclusion criteria:* Postreduction displacement >50% of shaft width; fracture gap >0.5 cm; open fracture (except grade I); long spiral or long oblique fracture; pathological or tibial metaphysis fracture; fractures with persistent post-reduction	Closed fractures were treated w/ closed reduction and immobilization in an above-the-knee cast. Open grade fractures were treated w/ initial debridement prior to immobilization. Randomized to US plus cast immobilization (n=48) or placebo US plus cast immobilization (n=49). US w/ SAFHS (SATA intensity 30 mW/cm^2) beginning w/in 7 days after fracture at 20 mins/day for 20 wks or until fracture healed. *Outcome measures:* Primary measure was fracture healing (3/4 cortices bridged). Secondary measures were times to intermediate indices of clinical and radiological healing; endosteal healing; pt compliance, and complications. F/u by clinical examination at cast changes and by radiological examination at 4, 6, 8, 10, 12, 14, 20, 33, and 52 wks after	13 pts (13 fractures) lost to f/u and 17 pts (17 fractures) excluded due to deviations from the protocol. Core study grp comprised the remaining 67 fractures (33 US grp and 34* placebo grp). Mean f/u (days): US grp, 250±18.1; placebo grp, 284±19.2 (*P*=0.21). Pt compliance w/ f/u protocol: US grp, 89%; placebo grp, 90%. Use of SAFHS device comparable between US and placebo grp. Mean time to clinical and radiological healing (3/4 cortices bridged): US grp, 96±4.9 days; placebo grp, 154±13.7 days (*P*<0.0001). Mean time to radiological healing (3/4 cortices bridged): US grp, 89±3.7 days; placebo grp, 148±13.2 days (*P*=0.0001). Mean time to clinical healing: US grp, 86±5.8 days; placebo grp, 114±10.4 days (*P*=0.01). Healed fracture at 150 days: US grp, 94%; placebo grp, 62%. Mean time to discontinuation of cast: US grp, 94±5.5 days; placebo grp, 120±9.1 days (*P*=0.008). By regression analysis, age, gender, and grade, type, and	US had no discernible effect on time to fracture healing in pts w/ tibial fractures fixed w/ a reamed locked IM nail. More US treated pts had delayed union than placebo pts, but the difference was not statistically significant. Since serum levels of cross-linked telopeptide were lower in the US grp at 1 wk, US may have reduced early bone resorption. However, US had no discernible effect on markers of bone formation. *Limitations:* Small sample size; method of allocation concealment not reported.

Authors/Study Design	Study Population	Treatment Protocol and Outcome Measures	Results	Conclusions/Comments/ Limitations
	shortening >1 cm, persistent angulation ≥10° or butterfly fragment >2 times the diameter of shaft; most comminuted fractures; steroid, anticoagulant, prescription NSAID, calcium channel blocker, or diphosphonate tx; pregnancy; hx of thrombophlebitis, vascular insufficiency, alcoholism, or nutritional deficiency	fracture or when indicated w/ blinded evaluation by 2 independent observers (principal investigator and radiologist).	site of fracture had no statistically significant effect on healing. By an intention-to-treat analysis, the time to fracture healing was significantly shorter for the US grp (*P*=0.005). Among 55 pts (56 fractures) who were followed for up to 2-4 yrs or more, all fractures (100%) remained healed. *Complications:* US grp, muscle cramping <1 wk duration (3%); placebo grp, temporary swelling in the cast (3%).	
Kristiansen et al. (1997) Centers in the United States (9) and Israel (1) Multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of US for healing fractures of the distal radius (Colles' fracture) *F/u:* Mean 111 days *Time frame:* 1987-1990 Study supported by Exogen, Inc.	n=83 pts (85 fractures) Mean age: US grp, 54.0±3.0 yrs; placebo grp, 58.0±2.0 yrs No statistically significant difference between US and placebo grp in 14 baseline pt and fracture parameters (*P*>0.05). *Inclusion criteria:* Age ≥20 yrs; closed, dorsally angulated, metaphyseal fracture of distal radius (Colles') <4 cm from tip; fracture amenable to tx w/ closed reduction and below elbow cast immobilization; skeletally mature. *Exclusion criteria:* Other types of distal radial fracture; fractures requiring surgery or additional reduction after tx initiation; steroid or anticoagulant tx; pregnancy; hx of thrombophlebitis, vascular insufficiency in the arm, alcoholism, or nutritional deficiency	Fractures were treated w/ closed reduction and immobilization in short arm cast. Randomized to active US plus cast immobilization (n=40 fractures) or placebo plus cast immobilization (n=45 fractures). US w/ SAFHS (SATA intensity 30 mW/cm^2) w/in 7 days after fracture at 20 mins/day for 10 wks or until fracture healed. *Outcome measures:* Primary measure was time to fracture healing defined as radiographic evidence of complete bridging of the dorsal, volar, radial, and ulnar cortices, and lack of pain on clinical examination. Secondary measures were times to intermediate indices of clinical and radiological healing, loss of reduction, and pt compliance. F/u by clinical examination at cast changes and radiological examination at 1, 2, 3, 4, 5, 6, 8, 10, 12, and 16 wks after fracture or when indicated w/ blinded	3 pts lost to f/u and 21 fractures (10 US and 11 placebo) excluded due to deviations from the protocol. Core study grp comprised the remaining 61 fractures (30 US grp and 31 placebo grp). Use of SAFHS device comparable between US and placebo grp. Mean time to clinical and radiological healing: US grp, 61±3.4 days; placebo grp, 98±5.2 days (*P*<0.0001). Healed fracture at 84 days: US grp, 90%; placebo grp, 32% (*P*<0.0001). Loss of reduction in a subset of 32 fractures: US grp (15 fractures), 20%; placebo grp (17 fractures), 43% (*P*<0.01). Analyses of the efficacy of US w/in strata showed that US significantly accelerated healing for each stratum w/ an expected prolongation of healing time. These included age ≥50 yrs (*P*<0.0001), articular involvement (*P*<0.0001), >10º of negative volar angulation (*P*<0.0001), and displacement at time of injury (*P*<0.0002). By an intention-to-treat analysis, the time to fracture healing was significantly shorter for the US grp (*P*<0.0001). Among 77 pts who were followed for up for a mean of 72 mos, all fractures (100%) remained healed.	In this study of pts w/ closed or grade I open tibial fractures, US decreased the mean time to clinical and radiological healing and increased the likelihood of fracture healing compared w/ placebo tx. No serious complications reported. Pt compliance was excellent and pts reported ease of use of the device. Fracture healing was durable since 100% of healed fractures in evaluated pts remained healed at 2-4 yrs or more after tx. *Limitations:* Small sample size; method of allocation concealment not reported; block randomization; 30 of the randomized pts not evaluated (31%); unequal intervals between radiological examination of healing, which may result in clumping of healing times; lack of data on functional outcomes; inconsistent

Authors/Study Design	Study Population	Treatment Protocol and Outcome Measures	Results	Conclusions/Comments/ Limitations
		evaluation by 2 independent observers (principal investigator and radiologist).	*Complications:* None attributable to the device.	instructions given to pts on the initiation of weight bearing, but Cox regression analysis established that the start of weight bearing did not significantly affect time to fracture healing.
Emami et al. (1999a); Emami et al. (1999b) Uppsala University Hospital, Uppsala, Sweden Single-center, randomized, double-blind, placebo-controlled trial to evaluate effect of US on fracture healing and serum levels of markers of bone regeneration after surgery for tibial fracture *F/u:* 1 yr *Time frame:* May 1995 – January 1997 SAFHS devices provided by Exogen, Inc.	n=32 pts Open grade I (3 US grp and 1 placebo grp); isolated tibial fracture (n=7) or tibia and fibula fracture (n=23) Mean age: US grp, 40±4.2 yrs; placebo grp, 34±3.4 yrs 3.4 No statistically significant difference between US and placebo grp in 7 baseline pt and fracture parameters or in serum bone marker levels at admission (*P*>0.05) *Inclusion criteria:* Age ≥16 yrs; closed or grade I open tibial fracture treated w/ closed reduction and a reamed and locked IM nail *Exclusion criteria:* Severely comminuted fractures or open physes; Gustilo-type Grade II	Fractures treated w/ closed reduction and locked IM nail. Randomized to active US plus IM nail (n=15) or placebo plus IM nail (n=17). US w/ SAFHS (SATA intensity 30 mW/cm^2) beginning w/in 3 days after surgery for 20 mins/day for 75 days. *Outcome measures:* Primary measure was time to fracture healing (3/4 cortices bridged). Secondary measures were time until first visible callus identified on the radiographs; serum levels of cross-linked telopeptide† (bone resorption), and bone-specific alkaline phosphatase and osteocalcin‡ (bone formation); patient compliance. Delayed union was defined as fracture healing at ≥6 mos. F/u by clinical and radiographic examination every 3rd wk until	Use of SAFHS device comparable between US and placebo grp. Mean healing time: US grp, 155±22.0 days; placebo grp, 125±11.0 days (*P*=0.76). Median healing time: US grp, 113 days; placebo grp, 112 days (*P*=0.76). Fractures healed at <6 mos in 10/15 (67%) in US grp and 13/15 (87%) in placebo grp. Healing time was ≥6 mos in 5 (33%) in US grp and 2 (13%) in placebo grp. Serum levels of markers of bone regeneration were measured in 30 pts (15 US grp and 15 placebo grp). Mean level of cross-linked telopeptide at 1 wk was lower in US grp compared w/ placebo grp (*P*<0.007). US grp had lower mean levels throughout study, but the difference was not statistically significant. There were no differences in this marker between pts w/ normal healing and those w/ delayed healing at any time. There were no differences in mean level of bone-specific alkaline phosphatase between US and placebo grps at any time. At 4 wks, pts w/ normal healing had higher levels	US accelerated the healing of fresh closed fractures of the distal radius, decreased the loss of reduction, and increased the likelihood of fracture healing, compared w/ placebo tx. US mitigated the effect of factors, such as older age, that can prolong healing time. Pts reported ease of use of the device. No serious complications reported. *Limitations:* Small sample size; 24 of the randomized pts not evaluated (29%); unequal intervals between examination of healing, which may result in clumping of healing times; incomplete data on clinical outcomes due to differences in carrying out the study protocol (i.e., not all investigators elected to change casts at same time); lack of data on

Authors/Study Design	Study Population	Treatment Protocol and Outcome Measures	Results	Conclusions/Comments/ Limitations
	or III open fracture; multiple fractures; injuries other than tibial fracture; alcoholism; drug abuse; neuropathy; arthritis; malignant disease; steroid, anticoagulant, NSAID, or biphosphonate tx	healing, and at 26 and 52 wks w/ blinded evaluation by 2 independent observers (orthopedic trauma surgeon and radiologist). Blood sampled at 1, 4, 7, 10, 13, 16, 26, and 52 wks after fracture event.	(*P*<0.03) than those w/ delayed healing, but the difference was not significant at 7 wks (*P*=0.06). There were no differences in mean level of osteocalcin between US and placebo grps at any time. The levels were similar between pts w/ normal healing and those w/ delayed healing at all times.	functional outcomes; pt smoking status documented retrospectively 5-8 yrs later.

***** Data were missing for 1 fracture in placebo group.
† > 90% of the bone matrix is composed of type I collagen. During bone resorption, collagen is digested and its breakdown product, cross-linked telopeptide, is released into the blood.
‡ The noncollagenous protein, osteocalcin, and bone-specific alkaline phosphatase demonstrate osteoblastic activity during bone formation and are released into the blood.

Table B. Case Series Studies on the Efficacy and Safety of US Bone Growth Stimulation for Nonunions

Key: FDA, Food and Drug Administration; f/u, follow-up; grp(s), group(s); IM, intramedullary; NR, not reported; NSAIDs, nonsteroidal anti-inflammatory drugs; ORIF, open reduction and internal fixation; PMA, Premarket Approval; pt(s), patient(s); SAFHS, Sonic Accelerated Fracture Healing System; SATA, spatial average-temporal average; tx, treatment; US, ultrasound

Authors/Study Design	Study Population	Treatment Protocol and Outcome Measures	Results	Conclusions/Comments/ Limitations
Mayr et al. (2000a) Klinik für Unfall- und Wiederherstellungschirurgie, Zentralklinikum Augsburg, Germany Retrospective case series w/ self-paired controls to compare efficacy of US for healing delayed unions and nonunions in subgrp of Exogen registry pts and registry pts as a whole *F/u:* NR *Time frame:* October 1994 – July 1997	n=42 pts (26 delayed unions and 16 nonunions) Mean fracture age: 1.3 yrs n=1317 pts from Exogen registry (951 delayed unions and 366 nonunions) served as historical controls *Inclusion criteria:* Consecutive pts w/ delayed union* (n=26) or nonunion† (n=16); last tx change 2 mos prior to study; no other tx changes during US tx	SAFHS (SATA intensity 30 mW/cm^2) tx 20 mins/day until fracture healed (no further details provided). Pts served as own controls. US results compared w/ prior outcome of failure to heal. *Outcome measures:* Healing defined as 3/4 cortices bridged in 2 x-ray planes or 80% trabecular bridging of cancellous fractures. Healing rates, mean fracture age, and mean healing time were compared between study grp and registry pts for delayed union and nonunions combined, and separately for delayed tibial unions and nonunions with fracture age ≥270 days.	Healing rates (all fractures): Study grp, 37/42 (88%); registry, 1176/1317 (89%) (*P*=NR). Mean healing time (all fractures): Study grp, 139±12.3 days; registry, 131±2.4 days (*P*=0.48). Mean fracture age (all fractures): Study grp, 482±162.7 days; registry, 312±18.5 days (*P*=0.31). Healing rates (delayed unions): Study grp, 22/26 (85%); registry, 862/951 (91%) (*P*=NR). Mean healing time (delayed unions): Study grp, 135±12.8 days; registry, 124±2.6 days (*P*=0.33). Mean fracture age (delayed unions): Study grp, 158±11.3 days; registry, 151±1.6 days (*P*=0.52). Healing rates (nonunions): Study grp, 15/16 (94%); registry, 314/366 (86%) (*P*=NR). Mean healing time (nonunions): Study grp, 145±26.0 days; registry, 152±5.3 days (*P*=0.83). Mean fracture age (nonunions): Study grp, 1060±418.3 days; registry, 755±62.8 days (*P*=0.48). Mean healing time for delayed union of tibial fractures: Study grp, 130±9.8 days; registry, 138±4.5 days (*P*=0.60).	High percentage of delayed unions and nonunions healed in both the study grp and registry pts w/ no significant differences in healing rates, mean healing times, or mean fracture age between the 2 grps. Thus, the data on US tx of nonunions are relatively consistent between studies. *Limitations:* Retrospective analysis; lack of details on tx protocol; length of f/u not reported.

Authors/Study Design	Study Population	Treatment Protocol and Outcome Measures	Results	Conclusions/Comments/ Limitations
Mayr et al. (2000a) Klinik für Unfall- und Wiederherstellungschirurgie, Zentralklinikum Augsburg, Germany Retrospective case series to evaluate efficacy of US for healing delayed unions and nonunions in Exogen registry pts *F/u:* NR *Time frame:* October 1994 – July 1997	n=1317 pts (951 delayed unions and 366 nonunions) Mean fracture age: Delayed union, 150 days; nonunion, 755 days *Inclusion criteria:* Consecutive pts in Exogen registry; delayed union* or nonunion†	SAFHS (SATA intensity 30 mW/cm^2) 20 mins/day until fracture healed (no details provided). *Outcome measures:* Healing rate, healing time, and mean fracture age. Data stratified based on fracture site, prior tx, comorbidities, medication use, and smoking status. Definition of healed fracture not clearly stated for registry pts.	Healing rates: Nonunion, 314/366 (86%); delayed union, 865/951 (91%). Healing time: Nonunion, 152±5.3 days; delayed union, 129±2.7 days. Healing rate was lowest for humerus fractures in both grps, 69% for nonunions and 76% for delayed unions. Among nonunions, the highest rate of healing was for scaphoid fractures. For delayed unions, the highest rate of healing was for fibula and metatarsal fractures. The percentages of nonunions and delayed unions that healed peaked between the ages of 30 and 50 (86%-88% and 90%-92%, respectively). For nonunions, healing rates decreased from 97% at 21 yrs to 71% at 70 yrs. For nonunions, healing rates ranged from 84% to 100%, depending on fracture type, and for delayed unions, healing rates ranged from 87% to 98%. The healing time was shorter for nonunions w/ no surgical intervention (132/153 [86%] in mean of 140 days) compared w/ those treated surgically (182/213 [85%] in mean of 169 days). The healing rate was comparable for delayed unions w/ no surgical intervention (457/507, 90%) compared w/ those treated surgically (405/442, 92%). For surgically treated nonunions, healing rates ranged from 77% for IM nail fixation to 90% for bone grafting. For surgically treated delayed unions, healing rates ranged from 89% for external fixation to 94% for IM nail fixation. Variables that had negative effects upon fracture healing were vascular (70%) or renal (76%) insufficiency. For nonunions, use of calcium channel blockers (63%), NSAIDs (75%), and steroids (73%) decreased healing rates. Smokers had lower healing rates compared w/ nonsmokers in both the nonunion (79% vs 87%, respectively) and the delayed union (87% vs 93%, respectively) grps.	The majority of pts treated w/ US had fracture healing of both delayed unions and nonunions. Increasing pt age decreased the likelihood of healing. Use of calcium channel blockers, NSAIDs, and steroids decreased the likelihood of healing for nonunions. Smoking decreased the likelihood of healing for both nonunions and delayed unions. Due to the lack of statistical analyses of the results, it is unclear whether US itself is responsible for healing and how the various prognostic variables ultimately affected tx outcomes. *Limitations:* Inherent biases of registry data; lack of randomization, blinding, and statistical analysis of results; length of f/u not reported; delayed unions comprised majority of pt population, although study focus was on nonunions. *(Continued)*

Authors/Study Design	Study Population	Treatment Protocol and Outcome Measures	Results	Conclusions/Comments/ Limitations
Nolte et al. (2001) 19 hospitals in the Netherlands Multicenter, retrospective case series to evaluate the safety and efficacy/effectiveness of SAFHS for nonunions *F/u:* 1 yr *Time frame:* November 1995 – May 1997 Study supported by Exogen, Inc. Incorporates data submitted by Exogen, Inc. to the FDA in PMA supplement application.	n=39 pts (mean age 47.0±3.4 yrs) (41 nonunions) Core grp (n=29): Established nonunion ≥9 mos from fracture and no surgery w/in 3 mos of US tx; completed tx *Inclusion criteria:* Established nonunions‡ ≥6 mos from fracture and radiographic healing had not progressed or had stopped ≥3 mos prior to US tx	US w/ SAFHS (SATA intensity 30 mW/cm^2) 20 mins/day until fracture healed. Pts served as own controls. US results compared w/ prior outcome of failure to heal. *Outcome measures:* Healing rate, time to healing, mean fracture age, and pt compliance. Clinical healing defined as absence of pain upon stress or weight bearing (long bones only). Radiological healing defined as 3/4 cortices bridged (long bones) or callus bridging the nonunion site. Outcomes assessed by radiographic and clinical exam at regular 6- to 8-wk intervals. Data stratified based on gender, age, fracture age, prior interval w/o surgery, bone, smoking status, nonunion type, and fixation.	11 pts (12 fractures) not available for f/u (4 noncompliant, 7 had surgery w/in 3 mos of US tx). Core study grp comprised the remaining 29 fractures. Pt compliance with device use: 19/25 (76%) healed cases and 2/4 (50%) of failed cases had good compliance. Healing rate: 25/29 (86%) nonunions who completed SAFHS tx healed (*P*<0.0001 compared w/ self-paired control). Healing time: Mean, 152±15.5 days; median, 119 days (range 52-398). Fracture age (for healed fractures): Mean, 429±38.9 days; median, 448 days (range 178-957). By intention-to-treat analysis, 33/41 (80%) healed (*P*=NR). Age, gender, fracture age, prior interval w/o surgery, fracture site, nonunion type, and fixation not significantly related to healing. Smokers and ex-smokers had lower healing rates (82% and 60%, respectively) compared w/ nonsmokers (100%) (*P*=0.05). At long-term f/u (mean, 62 wks; range 30-110), 100% of healed cases remained healed. *Complications:* None attributable to the device.	Results suggest that SAFHS is safe and efficacious for healing nonunions. *Limitations:* Retrospective analysis; no control group; small sample size makes conclusions based on statistical analysis of strata within the sample doubtful.

***** Unhealed at 3 to 9 months postfracture.
† Failure of healing process at > 9 months postfracture.
‡ Definition of nonunion required that the healing process had stopped, and the nonunion line was visible on two radiographic views.

APPENDIX VI

STUDIES EVALUATING EFFICACY AND SAFETY OF INVASIVE ELECTRICAL BONE GROWTH STIMULATION
From Hayes Medical Technology Directory Report on *Electrical Bone Growth Stimulation, Invasive* (Hayes, 2004a)

Table C. Studies Assessing Invasive Direct Current Electrical Bone Stimulation Used Adjunctively With Spinal Fusion

Key: DC, direct current; DCES, direct current electrical stimulation; f/u, follow-up; grp(s), group(s); NR, not reported; NS, not statistically significant; PEMF, pulsed electromagnetic field; pt(s), patient(s); RCT, randomized controlled trial; tx, treatment(s); μA, microamperes

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Comments/ Limitations
Kane (1988) Multiple centers in the U.S. Prospective RCT to evaluate the efficacy of an implanted DC bone growth stimulator to augment spinal fusion in "difficult to treat" pts *F/u:* 18 mos *Time frame:* NR	n=59 Age distribution: DCES grp: <20 yrs (3.2%), 21-60 yrs (90.3%), >60 yrs (6.5%) Placebo grp: <20 yrs (0%), 21-60 yrs (96.4%), >60 yrs (3.6%) Gender mix: NR No statistically significant difference between DCES and control grp w/ respect to age, entry criteria, or number of levels fused (*P*=NR) *Inclusion criteria:* One or more prior failed spinal fusions; Grade II or worse spondylolisthesis; multilevel fusion requiring extensive bone grafting; other high-risk factors for fusion failure, such as gross obesity *Exclusion criteria:* NR	Pts randomly assigned to tx w/ implantable DCES used in conjunction with noninstrumented spinal fusion and autogenous bone graft (n=31) or surgery alone (n=28). DCES was achieved w/ the Osteostim HS11 (BGS Medical Corporation), which consists of a hermetically sealed generator providing 20 μA of DC divided equally between 4 titanium cathodes. Tx was continued for ~22 wks. *Outcome measures:* Radiographically documented spinal fusion assessed by operating surgeon and independent radiologist (detailed definition of success NR).	Randomization was in blocks of 4 pts so each investigator had to enter at least 4 pts to participate; 99 pts were entered into the trial, of which 63 were from investigators that met this criterion. The core study grp comprised 59 pts from 7 investigators (31 DCES grp and 28 control grp). Successful spinal fusion: DCES grp, 25/31 (80.6%); control grp 15/28 (53.6%) (*P*=0.026). No difference observed in fusion success rates between males and females w/in either DCES or control grp. For both tx grps, fusion was less successful in pts requiring fusion at 2 or more levels than in those requiring fusion at only 1 level. Fusion rates appeared to be higher for multilevel fusion pts tx'd w/ DCES, compared w/ control grp, but this was not confirmed statistically.	Successful spinal fusion rate was higher for "difficult to treat" pts after combined DCES and surgery, compared w/ surgery alone. *Limitations:* Small sample size limits statistical significance; no details of postoperative management provided, which hampers interstudy comparison and undermines comparisons between grps; method of block randomization NR.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Comments/ Limitations
Kane (1988) 18 centers in the U.S. Nonrandomized comparative study w/ historical controls to evaluate the effectiveness of implanted DC bone growth stimulator to augment spinal fusion (unclear if data collection was prospective or retrospective) *F/u:* NR *Time frame:* DCES grp, 1978 – February 1980; control grp, NR	n=243 (age and gender NR) Previous surgery: DCES grp, 80%; control grp, 28% Pseudarthrosis: DCES grp, 55%; control grp, 20% No statistically significant difference between DCES and control grp w/ respect to age or gender distribution. *Inclusion criteria:* NR *Exclusion criteria:* NR	Tx w/ implantable DCES used in conjunction w/ noninstrumented spinal fusion and autogenous bone graft (n=82) compared w/ historical data on surgery alone (n=159). DCES was achieved w/ the Osteostim HS11 (BGS Medical Corporation), which consists of a hermetically sealed generator providing 20 µA of DC divided equally between four titanium cathodes, and was continued for ~22 wks. *Outcome measures:* Radiographically documented spinal fusion (detailed definition of success NR)	One pt in the DCES grp was lost to f/u and another pt had the implant removed shortly after surgery because of unexplained pain. The core study grp included 241 pts (82 DCES grp and 159 control grp). Successful spinal fusion: DCES grp, 75/82 (91.5%); control grp 128/159 (80.5%) (*P*=0.02). Fusion was achieved in 42/46 (91.3%) DCES pts w/ pseudarthrosis.	A statistically significant increase in the fusion success rate was observed in the DCES grp, compared w/ the control grp, even though more of the DCES pts were at risk of fusion failure because of previous failed surgery or pseudarthrosis. *Limitations:* Nonrandomized study; comparisons w/ retrospective controls insufficient to draw accurate conclusions; unclear if DCES pts were consecutive or selected by the investigators; length of f/u NR; unclear if data collection was prospective or retrospective; no details of postop management provided, which hampers interstudy comparison and undermines comparisons between the grps.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Comments/ Limitations
Kane (1988) Multiple centers in the U.S. Case series to assess the safety and effectiveness implanted DC bone growth stimulator to augment spinal fusion (unclear if data collection was prospective or retrospective) *F/u:* NR *Time frame:* NR	n=116 Gender mix and age: 62 males, mean age 42 yrs; 54 females, mean age 47 yrs 30/116 (25.8%) w/ previously failed fusion; 6/30 w/ >1 prior failed surgery *Inclusion criteria:* NR *Exclusion criteria:* NR	Tx w/ implantable DCES used in conjunction w/ noninstrumented spinal fusion and autogenous bone graft. DCES w/ the Osteostim HS11 (BGS Medical Corporation), consisting of a hermetically sealed generator providing 20 µA of DC divided equally between four titanium cathodes. Tx was continued for ~22 wks. *Outcome measures:* Radiographically documented spinal fusion (detailed definition NR).	Successful spinal fusion: 108/116 (93.1%) Successful fusion in 59/62 (95.2%) males versus 49/54 (90.7%) females. Successful fusion in 43/43 (100%) pts over 50 yrs of age. Successful fusion in 26/30 (86.7%) w/ previously failed fusion. *Complications:* NR	DCES appears to be an effective supplement to standard lumbosacral fusion. *Limitations:* Uncontrolled study design; unclear if data collection was prospective or retrospective; length of f/u NR; safety data NR and no details of postop management, which hampers interstudy comparison.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Comments/ Limitations
Meril (1994) Garland Orthopedic Clinic, Garland, TX Prospective, nonrandomized, comparative study w/ historical controls to evaluate the effectiveness of implanted DC bone growth stimulator to augment spinal fusion *F/u:* DCES grp, median 19 mos (range 6-45); control grp, median 21 mos (range 1-72) *Time frame:* DCES grp, NR; control grp, 1986-1988	n=225 Age distribution: DCES grp, 39 yrs (range 21-61); control grp, 47.1 yrs Gender mix: DCES grp, M/F = 71 (58.2%)/51 (41.8%); control grp, M/F = 57 (55.3%)/46 (44.7%) No statistically significant difference between grps in type of procedure (single or multilevel), smoking status, or prior fusion attempts (*P*=NR); more DCES pts underwent anterior fusion, whereas more control pts had internal fixation and posterior fusion (*P*=NR) *Inclusion criteria:* Pts who underwent either an anterior or posterior lumbar interbody fusion; postop f/u ≥6 mos in DCES pts *Exclusion criteria:* 2-level fusions in which only 1 level successfully fused	Tx w/ implantable DCES used in conjunction w/ lumbar interbody fusion (w/ or w/o instrumentation) and autogenous bone graft (n=122) compared w/ historical data on surgery alone (w/ or w/o instrumentation) (n=103). Electrical stimulator (EBI) consisted of a hermetically sealed generator providing 20 µA of DC continuously through 2 titanium cathodes for a minimum of 24 wks. For anterior fusions, the generator was placed on the psoas muscle; for posterior fusions, it was placed in a soft tissue pocket lateral to the spinous process. F/u performed 3, 6, 12, and 24 mos. *Outcome measures:* *DCES grp:* Spinal fusion, documented on multiplanar CT (more than half of curved coronal views showed unequivocal incorporation of graft into adjacent vertebral endplates), was assessed by the surgeon and an independent radiologist. Pt satisfaction was assessed by individual interview. *Control grp:* Spinal fusion documented by radiographs and linear tomograms (detailed definition NR). A subgrp of pts (n=46) were also assessed w/ multiplanar CT.	Successful fusion: DCES grp, 93%; control grp, 75% (*P*=0.0003) Fusion rates were much higher in high-risk grps such as smokers (92% versus 71%, *P*=0.001), those w/ no internal fixation (91% versus 65%, *P*=0.0006), and L4-L5 fusions (91% versus 59%, *P*=0.003). *Complications:* DCES grp: Hematoma (2.5%), deep venous thrombosis (1.6%), extruded bone graft (0.8%), minor superficial wound infection (2.5%), deep infection (0.8%), removal of device due to discomfort (3.3%).	Fusion rate statistically higher in stimulated pts compared w/ nonstimulated pts. Fusion rates also statistically higher in high-risk stimulated pts such as smokers, pts w/ no internal fixation, and pts w/ L4-L5 fusions. *Limitations:* Nonrandomized study; comparisons w/ retrospective controls insufficient to draw accurate conclusions; significant selection bias since pts w/ 2-level fusions in which only 1 level fused successfully were excluded from analysis; no details of postop management provided, which hampers interstudy comparison and undermines comparisons between the grps.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Comments/ Limitations
Kahanovitz and Pashos (1996) Anderson Orthopaedic Institute, Arlington, VA; Harvard Medical School, Cambridge, MA Retrospective, nonrandomized comparative study w/ concurrent controls evaluating the postoperative medical resource utilization of pts undergoing spinal fusion in conjunction w/ DCES. Pt data were drawn from a healthcare claims database of more than 7 million people. *F/u*: 2 yrs *Time frame:* 1989-1992	n=1686 Mean age: NR Gender mix: NR Statistical comparison of preoperative parameters for tx grps: NR *Inclusion criteria:* Pts who underwent spinal fusion w/ or w/o adjunctive implantable DCES *Exclusion criteria:* NR	Tx w/ implantable DCES (no details provided) used in conjunction w/ instrumented spinal fusion (n=33) compared w/ instrumented spinal fusion alone (n=580); DCES w/o instrumentation (n=53) compared w/ noninstrumented spinal fusion alone (n=1020). Outcomes analyzed at 6, 12, and 24 mos postoperatively. *Outcome measures:* Postdischarge inpt day counts and costs.	Mean postdischarge inpt days: DCES w/ instrumentation grp, 0.73; instrumented spinal fusion grp, 3.08; DCES w/o instrumentation, 1.79; noninstrumented spinal fusion grp, 3.02. Mean postdischarge inpt day charges: DCES w/ instrumentation grp, $796; instrumented spinal fusion grp, $6735; DCES w/o instrumentation, $3637; noninstrumented spinal fusion grp, $6110. *Complications:* NR	Pts who underwent DCES in conjunction w/ instrumented spinal fusion had the lowest postdischarge utilization of hospital resources 2 yrs after surgery compared w/ those who did not have DCES. *Limitations:* Nonrandomized study; widely disparate sample sizes for the different tx grps; results confounded by inherent biases of epidemiological surveillance data and lack of statistical analysis of results; lack of details on DCES tx and postoperative management limits intra- and interstudy comparisons; no baseline pt information provided so it is likely that confounding prognostic factors were unevenly distributed between tx grps.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Comments/ Limitations
Rogozinski and Rogozinski (1996) Rogozinski Orthopedic Clinic, Jacksonville, FL Prospective, nonrandomized, comparative study w/ mixed concurrent and historical controls to evaluate the efficacy of implanted DC bone growth stimulator to augment spinal fusion *F/u:* DCES grp, mean 19 mos; control grp, mean 22.5 mos *Time frame:* DCES grp, May 1991 – December 1992; control grp, May 1990 – December 1992	n=94 Mean age: DCES grp, 41 yrs; control grp, 38 yrs Gender mix: DCES grp, M/F = 32 (60.4%)/21 (39.6%); control grp, M/F = 26 (63.4%)/15 (36.6%) *Inclusion criteria:* Instrumented lumbosacral arthrodesis. Smokers were required to quit before surgery and this was confirmed by serial measurement of carboxyhemoglobin levels. *Exclusion criteria:* Pts receiving simultaneous combined anterior-posterior fixations or posterior lumbar interbody fusion	Electrical stimulation in conjunction w/ instrumented (Rogozinski System) posterolateral spinal fusion and autogenous bone graft (n=53) compared w/ surgery alone (n=41). Consecutive pts were selected for tx; later pts were randomly assigned to tx (DCES grp, n=11; control grp, n=15). An implantable SpF-2T DCES device (EBI) was used to provide 20 µA of DC to the fusion site. Postop management was the same for both grps and involved ambulation on the first postop day and a rehabilitation program. No immobilization devices were used. If fusion was solid at 8-12 wks, pts were entered into a reconditioning program for a further 8-12 wks. F/u performed at 10 days, 6 wks, 3 mos, 6 mos, and 1 yr. *Outcome measures:* Radiographically documented spinal fusion (presence of mature trabeculated bone mass across instrumented levels w/ no movement on stress views and no loss of fixation) assessed by 2 operating surgeons. Pts also completed questionnaires on levels of pain and function.	One pt from the DCES grp was lost to f/u after 3 mos, but the data on this pt was included in the clinical results. Successful fusion: DCES grp, 51/53 (96.2%); control grp, 35/41 (85.4%) (*P*=0.02). No comparisons drawn for subgrp of randomized pts. Successful fusion among the subgrp of pts w/ previous back surgery: DCES grp, 19/19 (100%); control grp, 11/14 (78.6%) (*P*=0.02). Successful fusion among the subgrp of pts requiring fusion at 2 or more levels: DCES grp, 35/37 (94.6%); control grp, 17/21 (80.9%) (*P*=0.04). Successful fusion among subgrp of pts that resumed smoking after surgery: DCES grp, 5/6 (83.3%); control grp, 4/6 (66.7%) (*P*=0.25). *Complications:* NR	A higher rate of spinal fusion was achieved in pts after combined DCES and instrumented spinal fusion, compared w/ surgery alone, across all high-risk categories. *Limitations:* Small sample size limits statistical significance; nonrandomized study; comparisons w/ mixed concurrent and historical data not adequate to draw definitive conclusions; lack of details on duration of DCES tx limits interstudy comparison; chronological arrangement of study, so results may be confounded by a learning curve effect.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Comments/ Limitations
Tejano et al. (1996)* Hertzler Clinic, Halstead, KS; University of Louisville, Louisville, KY; University of the Philippines/Philippine General Hospital, Manila, Philippines Prospective case series to assess safety and effectiveness of an implanted DC bone growth stimulator to augment spinal fusion in "difficult to treat" pts *F/u:* Median 5 yrs (range 2-9) *Time frame:* NR	n=143 Mean age: 49 yrs (range 20 to 66) Gender mix: M/F = 72 (50.3%)/71 (49.7%) *Inclusion criteria:* One or more prior failed spinal fusions; Grade II or worse spondylolisthesis; multilevel fusion requiring extensive bone grafting *Exclusion criteria:* NR	Tx w/ implantable DCES used in conjunction w/ autogenous bone graft and noninstrumented posterior facet or posterolateral spinal fusion. DCES was achieved w/ a hermetically sealed DC generator (EBI) that provides 20 µA of DC, divided equally between 4 titanium cathodes, to the fusion site for a minimum of 24 wks. Postop management included immobilization for 6 mos w/ a body cast, lumbosacral chair back brace, or lumbar corset (fusion rates were not affected by the type of immobilization used, *P*>0.05). F/u examinations were performed at 3, 6, 12, 18, and ≥24 mos. *Outcome measures:* Radiographically documented spinal fusion (evidence of bony fusion and 0° of motion between vertebrae); neurologic tests, pain, and employment status.	25/143 (17.5%) unavailable for f/u (19 pts lost to f/u, 5 refused to return for f/u, 1 pt died of causes unrelated to the spine surgery). Core study grp was comprised of the remaining 118 pts. Successful spinal fusion at long-term f/u: 109/118 (92%). No statistically significant difference between fusion rates at a median of 12 mos and 5 yrs postsurgery (*P*>0.05). Successful spinal fusion for multilevel procedures: 2-level (n=90) 93%; 3-level procedures (n=22) 91%. Fusion rates were not affected by the type of operation performed (posterolateral fusions versus facet fusions, *P*>0.05). 72% of pts had no post-tx pain, 23% had mild occasional pain, 5% had some degree of moderate pain; 85% returned to work post-tx, 10% retired, 4% were not working prior to surgery, and 1% were unable to return to work. *Complications:* None attributable to the surgery.	DCES is an effective adjunct to noninstrumented spinal fusion and may obviate the need for instrumentation in select pt grps. *Limitations:* Uncontrolled study design; 13.2% of pts lost to f/u.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Comments/ Limitations
Kucharzyk (1999) St. Anthony's Medical Center, Crown Point, IN Nonrandomized comparative study w/ historical controls to evaluate use of implanted DC bone growth stimulator to augment spinal fusion (unclear if data collection was prospective or retrospective) *F/u:* Mean 3.8 yrs for the combined pt pool of n=130 *Time frame:* May 1993 – September 1994.	n=130 Mean age: DCES grp, 56.2 yrs; control grp, 54.1 yrs Gender mix: DCES grp, M/F = 30 (46.2%)/ 35 (53.8%); control grp, M/F = 32 (49.2%)/ 33 (50.8%) DCES and control grp appeared to have similar distributions of diagnostic categories *Inclusion criteria:* High-risk lumbar fusion *Exclusion criteria:* NR	Tx w/ implantable DCES (no details provided) used in conjunction w/ instrumented (Rogozinski System) posterolateral spinal fusion and autogenous bone graft (n=65) compared w/ historical data on surgery alone (n=65). Postop management was the same for both grps and involved ambulation on first postop day and use of a thoracolumbosacral brace. Pts began a rehabilitation program after discharge and entered a structured outpt physical therapy program on postop day 7. F/u performed at 10 days, 6 wks, 12 wks, 6 mos, 1 yr, 2 yrs, and 3 yrs. *Outcome measures:* Radiographically documented spinal fusion (bridging trabeculae, bone graft consolidation, intact instrumentation, no pseudarthrosis lines), classified according to Dawson's criteria (A0 to A4), was assessed by operating surgeon and independent radiologist. Clinical success, defined as excellent or good rating on Modified Smiley-Webster Surgical scale, was assessed by operating surgeon and second orthopedic surgeon.	Successful spinal fusion: DCES grp, 95.6%; control grp 87% (*P*=0.05). Clinical success rate: DCES grp, 95%; control grp 79% (*P*=0.02). Assessment of pts w/ nonunions from both DCES and control grps showed an equal distribution of smokers versus nonsmokers, multiple previous surgeries versus no previous surgery, and multilevel versus single-level fusions between grps (not confirmed statistically). More DCES pts achieved an A4 category (solid fusion w/ graft hypertrophy) according to Dawson's criteria, compared w/ control pts (64.6% versus 47.7%, respectively; *P*=0.04).	Higher rates of spinal fusion and clinical success were achieved in pts after combined DCES and surgery compared w/ surgery alone. *Limitations:* Small sample size limits statistical significance; nonrandomized study; comparisons w/ retrospective data not adequate to draw definitive conclusions; unclear if DCES pts were consecutive or selected by investigators, or whether data collection was prospective or retrospective; lack of details on duration and type of DCES tx limits interstudy comparison.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Comments/ Limitations
Jenis et al. (2000) New England Baptist Spine Center, Boston, MA; Rush-Presbyterian-St Luke's Medical Center, Chicago, IL Prospective RCT to evaluate the effectiveness of adjunctive electrical stimulation in augmenting instrumented lumbar fusion *F/u:* 1 yr *Time frame:* 1995-1997	n=61 Mean age: DCES grp, 51.0 yrs; PEMF grp, 53.0 yrs; control grp, 47.1 yrs Gender mix: DCES grp, M/F = 10 (58.8%)/7 (41.2%); PEMF grp, M/F = 11 (50%)/11 (50%); control grp, M/F = 14 (63.6%)/8 (36.4%) Statistical comparison of preoperative parameters for tx grps: NR *Inclusion criteria:* Pts 18-75 yrs of age requiring either primary or revision lumbar or lumbosacral posterolateral fusion w/ instrumentation and autogenous iliac bone graft *Exclusion criteria:* Requiring a fusion technique other than posterolateral fusion; preoperative infection; depressed immune system; cardiac pacemaker, defibrillator, and/or dorsal column stimulator; regional conditions that would affect bone metabolism; systemic conditions including renal failure, metastatic carcinoma, or uncontrolled diabetes	All pts underwent posterior lumbar fusion w/ pedicle screw rod instrumentation and autogenous bone graft. Pts were randomly assigned to tx w/ implantable DCES (n=17), PEMF tx (n=22), or no bone stimulation (n=22). Pts were fitted w/ a rigid lumbosacral brace for 10 to 12 wks postoperatively. SpF-2T DCES (EBI) was implanted into a subfascial location distant from the fusion site w/ the coiled leads being placed superficial to the decorticated transverse processes and deep to the bone graft. PEMF pts wore the SpinalStim model 8212 (Orthofix Inc./AME), which was fitted w/in 30 days of surgery, for a minimum of 2 hrs/day on at least 90% of the 150 consecutive tx days following surgery. F/u examinations were performed 3 mos and 1 yr postoperatively. *Outcome measures:* Radiographically documented spinal fusion (bridging trabeculae and solid arthrodesis) was assessed by an independent observer. Bone density of the fusion mass was measured w/ radiographic microdensitometry. Clinical success, based on subjective analysis of pain and function levels, was assessed w/ a questionnaire.	Successful spinal fusion: DCES grp, 61%; PEMF grp, 65%; control grp 81% (differences between tx grps NS, *P*>0.05). Change in mean fusion mass bone density: DCES grp, ↑5.0%; PEMF grp, ↑7.8%; control grp ↓1.9% (changes w/in tx grps w/ respect to baseline and differences between tx grps NS, *P*>0.05). Clinical success (return to full preoperative activities, absence of significant subjective pain, no analgesic requirement): DCES grp, 32%; PEMF grp, 35%; control grp 43% (differences between tx grps NS, *P*>0.05). Pt compliance w/ PEMF postoperative protocol was 77.3%. Trends in the data suggested that pts who required multilevel fusion, had >2 risk factors for pseudarthrosis, or who smoked had diminished fusion density over time, compared w/ pts w/o such risk factors, regardless of whether they received electrical stimulation or not. In pts w/ >2 risk factors, those who received either DCES or PEMF tx had average fusion bone density values that were 24% and 36% greater than control pts. However, no significant effect on fusion rate was detected. *Complications:* DCES grp: Wound infection requiring irrigation and debridement (11.8%) PEMF grp: Wound infection requiring irrigation and debridement (9.1%) Control grp: Postop epidural hematoma (4.5%).	Results suggested that neither DCES nor PEMF significantly enhances fusion in pts undergoing instrumented lumbar arthrodesis, compared w/ surgery alone. There was no discernible difference in tx effect between DCES and PEMF. There was a trend towards increased bone density of the fusion mass after 1 yr postsurgery in pts tx'd w/ DCES or PEMF, compared w/ control pts, but this was not statistically significant. *Limitations:* Small sample size limits statistical significance; very limited baseline pt information provided, so unclear if randomization was successful in evenly distributing confounding prognostic factors between tx grps; method of randomization NR.

***** Patient population overlaps with Kane (1988).

Table D. Studies Assessing Invasive Direct Current Electrical Bone Stimulation

Key: DC, direct current; DCES, direct current electrical stimulation; f/u, follow-up; grp(s), group(s); NR, not reported; PEMF, pulsed electromagnetic field; pt(s), patient(s); tx, treatment (or therapy); μA, microamperes

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Comments/ Limitations
Paterson et al. (1980); Cundy and Paterson (1990) Multiple centers in Australia Prospective case series to assess the effectiveness of electrical stimulation in healing delayed union and nonunion *F/u:* Short-term, NR; long-term, mean 10.3 yrs (range 9.5-11.9) *Time frame:* NR	n=81 (84 fractures: 47 delayed union, 37 nonunion; 72 tibial fractures) Mean age: 30 yrs, range 5-81 Gender mix: M/F = 64 (76.2%)/20 (23.8%) Mean duration of nonunion: 10 mos (range 3 mos to 7.5 yrs) Statistical comparison of preop parameters for tx grps NR. However, at 10-yr f/u, there were no statistically significant difference between the pts available for f/u and those who were unavailable w/ respect to preop characteristics of age, number of prior surgeries, duration of nonunion, prior infection, fracture site, or initial outcome compared w/ follow-up result (P>0.05). However, there more males were available for f/u than females (P<0.03). *Inclusion criteria:* Clinical, radiologic, and nuclear scan evidence of delayed union of long bones at least 12 wks after initial injury together w/ confirmation of lack of union at the time of surgery *Exclusion criteria:* NR	Tx consisted of immobilization and electrical stimulation w/ an implanted Osteostim S12 (Telectronics P/L, NSW, Australia) device that uses a single titanium cathode to deliver 20 μA of DC to the fracture site. Tx duration was 3 mos for pts tx'd early in the study period and 6 mos in later cases. *Outcome measures:* Fracture union, defined as the time when it is either radiologically or clinically safe, or both, to remove the cast and allow full weight bearing.	Successful union: 72/84 (85.7%) Mean time to union: 16 wks (range 12 to 36) Union achieved in 7/10 pts who underwent ≥3 previous operations. Successful union achieved in 10/12 pts (83.3%) who underwent cancellous bone grafts and 13/15 pts (86.7%) who presented w/ infected fractures. Tx failures were ascribed to incorrect cathode placement, inadequate duration of DCES in pts tx'd early in the study period, and premature removal of plaster immobilization. At 10-yr f/u: Clinical and radiographic assessment was available for 37/81 pts (54.3%) (38 fractures; 32 men and 5 women; 7 had died from unrelated causes). 32/38 (84.2%) fractures that originally healed w/ DCES remained healed, and no refractures were reported. The 6 tx failures healed through other interventions over the 10-yr period. *Complications:* Short-term; delayed wound healing (5.9%), cathode wire protruding through atrophic skin (2.4%), persistent infection around generator (1.2%). None reported at long-term f/u.	Continuous invasive and semi-invasive DCES were more effective in treating nonunions than PEMF tx, but this was not confirmed statistically. The latter modality should be reserved for pts w/ infected nonunions who are likely to be very compliant w/ tx protocol. *Limitations:* Small sample size; nonrandomized study; unclear if controls were concurrent or historical; length of f/u NR; only very limited baseline pt information provided, and it is likely that confounding prognostic factors were unevenly distributed between tx grps; no details of postop management, which hampers interstudy comparison and undermines comparisons between tx grps.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Comments/ Limitations
Miller (1983) University of Florida College of Medicine, Gainesville, FL Retrospective nonrandomized comparative study to evaluate the effectiveness of electrical stimulation in healing fracture nonunions (unclear if controls were concurrent or historical) *F/u:* NR *Time frame:* NR	n=28 Mean age: Invasive DCES, 43 yrs; semi-invasive DCES, 32 yrs; PEMF, NR for the subgrp w/ non-pathological fractures Gender mix: Invasive DCES, M/F = 4 (40%)/6 (60%); semi-invasive DCES, M/F = 8 (66.7%)/4 (33.3%); PEMF NR for the subgrp w/ non-pathological fractures Statistical comparison of preoperative parameters for tx grps: NR Mean duration of nonunion: Invasive DCES, 22 mos; semi-invasive DCES, 16 mos; PEMF, NR for the subgrp w/ non-pathological fractures *Inclusion criteria:* NR *Exclusion criteria:* NR	Tx w/ invasive DCES (n=10), semi-invasive DCES (n=12), or PEMF therapy (n=6). Pts undergoing invasive DCES received bone grafting and 4 to 6 mos of stimulation w/ an implanted Osteostim (EBI) device. Semi-invasive DCES was performed for 11 to 13 wks w/ a Quadpak system (Zimmer, Inc., Warsaw, IN) that uses 4 Teflon-coated stainless steel electrodes placed at the nonunion site. PEMF pts were tx'd w/ the Biosteogen (EBI) device for an average of 7.5 mos. *Outcome measures:* Fracture union (detailed definition NR).	Successful union: Invasive DCES, 80%; semi-invasive DCES, 91.7%; PEMF, 66.7% (difference NS). *Complications:* Invasive DCES: Extrusion of power pack through soft tissue (10%), other problems included migration of the coiled electrode from the bone trough and difficulty removing the DCES device at the end of tx. Semi-invasive DCES: Superficial cathode pin track infections (50%) and reports of minor skin irritation at the anode pads. PEMF grp: Problems w/ compliance were noted, and some pts reported minor aches and pains during tx.	Invasive DCES is an effective tx for ununited fractures of long bones. *Limitations:* Uncontrolled study design; dropout rate too great to determine definitive long-term results; no details of postop management provided, which hampers interstudy comparison.

Table E. Studies Assessing Semi-Invasive Direct Current Bone Stimulation

Key: CC, capacitive coupling; DC, direct current; DCES, direct current electrical stimulation; f/u, follow-up; grp(s), group(s); hx, history; NR, not reported; NS, not significant; pt(s), patient(s); tx, treatment; μA, microamperes

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Comments/ Limitations
Jorgensen (1977) Randers, Denmark Nonrandomized comparative study w/ concurrent controls to evaluate the effect of electrical stimulation on fresh tibial fractures tx'd w/ external fixation (unclear if data collection was prospective or retrospective) *F/u:* 5 yrs *Time frame:* NR	n=71 (age and gender NR) As far as possible, consecutive pts were alternately assigned to DCES or control tx. Pt selection was manipulated to achieve a homogeneous distribution of age and fracture type between the two tx grps, but a statistical comparison of preoperative parameters for the DCES and control grps was NR. *Inclusion criteria:* Primary wound healing for open fractures *Exclusion criteria:* NR	Fractures tx'd w/ reduction and external fixation via a Hoffman apparatus. Pts were tx'd w/ a custom-built semi-invasive DCES device that delivered 40 μA to the fracture site through 2 bone screws of the Hoffman apparatus (n=28) until a clinically stable union was achieved or no bone stimulation (n=43). Radiographic f/u examinations were performed monthly. *Outcome measures:* Clinically stable union as determined by a mechanical measuring bridge mounted on the Hoffmann apparatus, which stressed the fracture w/ a spring balance.	4/28 (14.3%) DCES pts were excluded from f/u (2 had infection around the electrodes, 1 overloaded the fracture, 1 refused to continue DCES because of heat and pain). Core DCES grp was comprised of the remaining 24 pts. 10/43 (23.3%) of control pts were excluded from f/u (3 pts had infection around the electrodes, 4 pts overloaded the fracture, 3 pts had inadequate fracture fixation). Core control grp was comprised of the remaining 33 pts. Mean time to clinical healing: DCES grp, 2.4 mos; control grp, 3.6 mos (P<0.001). 5-yr f/u was available for 65% of the DCES pts (50% were clinically examined and 15% were contacted indirectly): No destructive processes were evident on radiographs; some tibial bones developed thickened cortices and some of the comminuted fractures showed a bony prominence at the fracture site; some screw canals in the bone had filled w/ tiny osteomas. *Complications:* Twice as many DCES pts experienced skin reaction around the screws, compared w/ control grp. DCES pts also complained of heat and pain during tx. These complications were largely eliminated by reversing the polarity of the electrodes daily.	The repair of externally fixed tibial fractures was accelerated by 30% in pts tx'd w/ semi-invasive DCES, compared w/ pts who did not receive electrical stimulation. *Limitations:* Small sample size limits statistical significance; unclear if data collection was prospective or retrospective; pt selection was manipulated by the investigator and lack of details on baseline pt information made it impossible to discern whether there was an uneven distribution of possible confounding prognostic factors between pt grps; long-term f/u was anecdotal and poorly documented.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Comments/ Limitations
Masureik and Eriksson (1977) University of Pretoria, Pretoria, Republic of South Africa Nonrandomized comparative study w/ concurrent controls to evaluate the effect of electrical stimulation on the healing of fresh jaw fractures (unclear if data collection was prospective or retrospective) *F/u:* 6 wks *Time frame:* NR	n=80 (age and gender NR) Pts divided into 2 similar fracture grps, but statistical comparison of preop parameters for DCES and control grps NR *Inclusion criteria:* Fractures anterior to the mental foramen *Exclusion criteria:* NR	Fractures tx'd w/ reduction via intermaxillary cross and vertical wires and immobilized for 6 wks. Pts were tx'd w/ a custom-built semi-invasive DCES device that delivered 10-20 µA to the fracture site (n=40) for 10-14 days or no bone stimulation (n=40). F/u examinations were performed at 7 days, 14 days, and 6 wks. *Outcome measures:* Fracture mobility measured by clinical examination or w/ a Mühlemann macroperiodontometer; serum levels of alkaline phosphatase and calcium were sampled at time of fracture reduction and on day 7, day 14, and up to 8 wks postreduction.	Good/excellent fracture mobility 2 wks postreduction: DCES grp, 90%; control grp, 12.5%. Differences in fracture mobility between grps were not as marked at 6 wks postreduction (not confirmed statistically). Serum alkaline phosphatase activity appeared to be higher in the DCES grp than in the control grp. *Complications:* DCES grp, electrode dislodgement after 4 or 5 days (5%)	The repair of fresh jaw fractures was enhanced by semi-invasive DCES in the first 10-14 days after reduction. *Limitations:* Small sample size limits statistical significance; short-term f/u; unclear if data collection was prospective or retrospective; unclear whether DCES pts were consecutive or selected by investigators; lack of details on baseline pt information made it impossible to discern whether there was an uneven distribution of possible confounding prognostic factors between pt grps.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Comments/ Limitations
Brighton et al. (1981) University of Pennsylvania (U of P) School of Medicine, Philadelphia, PA, and 12 tx centers in the U.S. Case series to assess the safety and effectiveness of using a semi-invasive DC bone growth stimulator to treat fracture nonunion (unclear if data collection was prospective or retrospective) *F/u:* NR *Time frame:* 1970; end date NR	n=265 (269 nonunions) U of P (186 pts w/ 189 nonunions): Mean age 38.9 yrs; 122 males, 64 females; mean duration of nonunion, 2.7 yrs; fractures of tibial shaft (90), femoral shaft (31), ulnar shaft (16), clavicle (15), humeral shaft (13), medial malleolus (11), radial shaft (7), carpal navicular (5), fibula (1) Tx centers (79 pts w/ 80 nonunions): Mean age 41 yrs; 52 males, 27 females; mean duration of nonunion, 3.3 yrs; fractures of tibial shaft (46), femoral shaft (17), ulnar shaft (3), humeral shaft (8), metatarsal shaft (2), clavicle (1), olecranon (1), carpal navicular (2) *Inclusion criteria:* Well-established nonunion; willingness and ability to return for periodic f/u examinations *Exclusion criteria:* Congenital pseudarthroses or nonunions secondary to pathological fractures	Tx consisted of cast immobilization and electrical stimulation w/ a Quadpak system (Zimmer, Inc.) that uses 4 Teflon-coated stainless steel electrodes to deliver 20 µA of DC to the nonunion site (11 U of P pts received 10 µA) for 12 wks. Current was monitored monthly by a physician. After 12 wks of stimulation, the electrodes were removed and immobilization was continued for a further 12 wks. F/u examinations were performed at 12 and 24 wks. *Outcome measures:* Radiographically documented union (detailed definition NR)	U of P: 149/189 (78.8%) achieved union. 11 early failures were due to inadequate electrical current (10 µA cathode). Of the later pts adequately tx'd w/ electricity, 149/178 (83.7%) achieved union. Overall, 14/18 (77.8%) healed after 2nd tx, 4/6 (66.7%) healed after 3rd tx, 2/4 (50%) after 4th tx, 0/1 after 5th tx. There was no correlation between duration and tx result for nonunions of <40 mos' duration. Tx centers: 58/80 (72.5%) achieved fusion in 1 tx session. There was no correlation between nonunion duration and tx result. Tx failures were ascribed to inadequate DC or immobilization, presence of synovial pseudarthrosis or osteomyelitis, gap of more than one half the diameter of the bone at the nonunion site, or dislodgement of the electrodes. No statistically significant difference in healing rates between the U of P and Tx centers grps (*P*=NR). Presence of previously inserted metallic fixation devices did not affect healing rate (*P*=NR). *Complications:* U of P: Broken wire or electrode (10.6%), superficial pin track irritation (11.1%), skin irritation under anode (3.8%), cathode dislodgement (1.6%), recurrence of osteomyelitis (1.1%). Tx centers: Irritation or superficial infection around a cathode (10.1%), pressure sore due to tight-fitting cast (1.3%).	The semi-invasive application of DCES in the tx of nonunion is effective. The technique can be used successfully by orthopedic surgeons who have no prior experience w/ DCES tx. *Limitations:* Uncontrolled study design; unclear if data collection was prospective or retrospective; length of f/u not clearly stated.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Comments/ Limitations
Brighton (1981)* University of Pennsylvania School of Medicine, Philadelphia, PA Case series to assess the safety and effectiveness of using an implanted DC bone growth stimulator to treat tibial nonunion (unclear if data collection was prospective or retrospective) *F/u:* NR *Time frame:* 1970; end NR	n=130 (mean age 36.6 yrs; 101 males, 29 females) (131 tibial nonunions; mean duration 2.6 yrs) *Inclusion criteria:* Well-established nonunion; willingness and ability to return for periodic f/u examinations. *Exclusion criteria:* Congenital pseudarthroses or nonunions secondary to pathological fractures	Tx consisted of cast immobilization and electrical stimulation w/ a Quadpak system (Zimmer, Inc.) that uses 4 Teflon-coated stainless steel electrodes to deliver 20 µA of DC to the nonunion site (8 pts received 10 µA) for 12 wks. The current was monitored monthly by a physician. After 12 wks of stimulation, the electrodes and cast were removed and immobilization in a weight-bearing cast was continued for a further 12 wks. F/u examinations were performed at 12 and 24 wks. *Outcome measures:* Radiographically documented union (detailed definition NR)	107/131 (81.7%) achieved union; 8 early failures were due to inadequate electrical current (10 µA cathode). Of the later pts adequately tx'd w/ electricity, 107/123 (87%) achieved union. Overall, 93/111 pts (83.8%) healed after 1 tx, 12/15 (80%) healed after 2nd tx, 1/3 (33.3%) healed after 3rd tx, 1/2 (50%) healed after 4th tx. The presence of previously inserted metallic fixation devices or a hx of osteomyelitis at the fracture site did not affect healing rate (*P*=NR). Tx failures were ascribed to inadequate DC (6.1%), chronic osteomyelitis (4.6%), synovial pseudarthrosis (1.5%), and electrode dislodgement (0.8%). In 7 pts, there was no apparent cause of failure. *Complications:* Superficial pin track irritation (9.2%), broken wire (6.9%), osteomyelitis recurrence (6.2%), irritation under anode pad (1.5%), cathode dislodgement (1.5%), battery pack failure (1.5%).	The semi-invasive application of DCES in the tx of tibial nonunion is safe and effective. *Limitations:* Uncontrolled study design; unclear if data collection was prospective or retrospective; length of f/u not clearly stated.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Comments/ Limitations
Brighton et al. (1995)† University of Pennsylvania, Philadelphia, PA Retrospective, nonrandomized comparative study w/ mixed concurrent and historical controls to evaluate the effect of electrical stimulation on the healing of tibial nonunions *F/u:* NR *Time frame:* DCES grp, 1971-1982; CC grp, 1982-1994; bone graft surgery, 1971-1994	n=271 11 DCES and 8 CC pts withdrew to have bone graft surgery, 7 bone graft surgery pts were unavailable for f/u; 21 nonunions of >70 mos' duration were excluded because sample was too small to provide a reliable estimate of healing rate for this subgrp. Data from these pts was not included in the final analysis. Mean age: DCES, 35.8 yrs; CC, 35.9 yrs; bone graft surgery, 33.3 yrs. Gender mix: DCES, M/F = 126 (75.5%)/41 (24.5%); CC, M/F = 44 (78.6%)/12 (21.4%); bone graft surgery, M/F = 32 (66.7%)/16 (33.3%) There were no statistically significant differences between the tx grps w/ respect to age, gender distribution, duration of nonunion, and fracture condition (open or closed). There were differences according to type of fracture and nonunion; hx of osteomyelitis, electrical tx, and bone graft surgery; location of fracture; and presence of metal. Mean duration of nonunion: DCES, 24.3 mos (range 9-69); CC, 22.1 mos (range 9-61); bone graft surgery, 22.4 mos (range 9-64). *Inclusion criteria:* Well-established nonunion of at least 9 mos' duration; willingness and ability to return for periodic f/u examinations. *Exclusion criteria:* Pts w/ draining osteomyelitis of the nonunion excluded from DCES or bone graft surgery	Fractures tx'd w/ DCES (n=167), CC (n=56), or bone graft surgery (n=48). DCES tx consisted of cast immobilization and electrical stimulation w/ a Quadpak system (Zimmer, Inc.) that uses 4 Teflon-coated stainless steel electrodes to deliver 20 µA of continuous DC to the nonunion site for 12 wks. CC tx consisted of cast immobilization and electrical stimulation via electrode plates placed on the skin. A 60-kHz, 5-volt symmetrical sine wave was applied continuously to the nonunion site for 12-24 wks. Anterolateral or posterolateral autogenous bone graft surgery was performed in conjunction w/ internal fixation (15 pts), external fixation (4 pts), and cast alone (29 pts who already had internal fixation in place). *Outcome measures:* Radiographically documented union (when all 4 radiographic views showed bony trabeculae spanning the full width of the nonunion gap) or nonunion (all 4 radiographic views taken serially during a 3-mo period demonstrate no progressive change in the callus).	Successful union: DCES, raw data NR; CC, raw data NR; bone graft surgery, 28/48 (58.3%). The results were analyzed using logistic regression. There were no significant differences among the tx options when no risk factors were present, but healing rate was inversely related to the number of risk factors present, regardless of tx method. Healing rates for bone graft surgery were lower than for DCES or CC tx when there was a previous bone graft failure. CC tx was less effective than DCES or bone graft surgery when an atrophic nonunion was present.	There were no significant differences between the 3 tx options when no risk factors were present. However, the presence of risk factors adversely affected healing rate regardless of tx method. Bone graft surgery was less effective in pts w/ previous bone graft failure, and CC tx had a lower healing rate when an atrophic nonunion was present. *Limitations:* Post hoc analyses are highly susceptible to bias, which raises concerns about the veracity of the study conclusions; length of f/u NR; no details of postop management provided, which hampers interstudy comparison; chronological arrangement of study means that the results may be confounded by a learning curve effect.

***** Patient population overlaps with Brighton et al. (1981).
† Patient population overlaps with Brighton (1981) and Brighton et al. (1981).

APPENDIX VII

STUDIES EVALUATING EFFICACY AND SAFETY OF NONINVASIVE ELECTRICAL BONE GROWTH STIMULATION
From Hayes Medical Technology Directory Report on *Electrical Bone Growth Stimulation, NonInvasive* (Hayes, 2004b)

Table F. Studies Evaluating Noninvasive Electrical Stimulation Using Capacitive Coupling, PEMF, or CMF

Key: ↑, increase(d); ↓, decrease(d); AVN, avascular necrosis; BMD, bone mineral density; CI, confidence interval; CMF, combined magnetic field; DC, direct current; dx, diagnosis; f/u, follow-up; grp(s), group(s); hx, history; NR, not reported; OR, odds ratio; PEMF, pulsed electromagnetic field; preop, preoperative; postop, postoperative; pt(s), patient(s); THA, total hip arthroplasty; tx, treatment (or therapy)

Authors/Study Design	Study Population/Treatment	Results/Complications	Conclusions/Limitations
Capacitive Coupling			
Steinberg et al. (1990)[1] University of Pennsylvania School of Medicine, Philadelphia, PA Randomized, double-blind, placebo-controlled trial to determine effectiveness of capacitive coupling as adjunctive tx to decompression and grafting of AVN of femoral head *F/u:* Mean 31 mos, range 2-4 yrs *Time frame:* NR	n=40 pts Stimulated grp: n=20 (units active) Nonstimulated grp: n=20 (units inactive) Both grps well matched w/ respect to gender, etiology, and roentgenographic stages of AVN at start of tx. *Inclusion criteria:* Pts w/ stages I-III AVN of femoral head tx'd w/ core decompression and grafting *Tx:* Continuous for 6 mos; capacitive coupling units w/ electrodes placed over femoral heads (1/2 of units active and 1/2 inactive)	Clinical evaluation (using preop and postop Harris ratings): 42% of hips in stimulated grp improved or unchanged vs 50% in nonstimulated grp. Radiographic evaluation: Improvement or no evidence of progression in 42% of stimulated hips and 50% of nonstimulated hips. Number of hips requiring THA: 25% of stimulated grp and 20% of nonstimulated grp. *Complications:* Occasional skin irritation under electrodes.	There were no significant differences by any evaluation parameters (clinical or radiographic) between stimulated and nonstimulated grps. Therefore, capacitive coupling did not provide added benefit to decompression and grafting in tx of AVN of femoral head. *Limitations:* Very small sample size; size may limit power to detect tx effect and generalizability of results; study did not attempt to evaluate capacitive coupling alone in tx of AVN.

Authors/Study Design	Study Population/Treatment	Results/Complications	Conclusions/Limitations
Scott and King (1994) Royal London Hospital, London, UK Randomized, double-blind, placebo-controlled trial to evaluate effectiveness of capacitive coupling in tx of established nonunion of long bones *F/u:* 12-mo minimum *Time frame:* 1988-1989	n=21 pts evaluable pts of 23 initially enrolled Actively managed grp: n=10 (mean age 40 yrs, range 27-55; 8 men, 2 women) Placebo grp: n=11 (mean age 46 yrs, range 23-87; 8 men, 3 women) *Inclusion criteria:* Established nonunion of tibia, ulnar, or femur; pt entered at 9 mos after injury: continuous immobilization w/ no other form of tx; pt entered after >9 mos: immobilization continuous for 3 mos preceding start of tx and no other form of tx during 3-mo period; skeletal maturity *Exclusion criteria:* Synovial pseudarthrosis; gap or bone defect > half width of bone at fracture location; generalized disorders of bone metabolism *Tx:* Continuous for 6 mos; OrthoPak bone growth stimulators modified to accomplish double-blinding (~1/2 placebo)	Radiographic and clinical evaluation: 6/10 actively managed pts (60%) and none of 11 controls (0%) achieved union (*P*=0.004). Among 6 pts in placebo grp who subsequently received electrical stimulation, 2 achieved unions, 2 showed improvement (but fractures failed to unite completely), and 2 showed no change. *Complications:* Allergic reaction to electrode disks on skin (2), which resolved after hydrocortisone tx and adjustment of position of disks.	Results suggest electrical stimulation can promote healing of established nonunions. *Limitations:* Very small sample size; size may limit power to detect magnitude of tx effect and generalizability of results; heterogeneous study population in terms of fracture site (and all femoral fractures assigned to actively managed grp); 2/23 (8.6%) original enrollees did not follow study protocol and were excluded from analysis (thus, not intention-to-treat analysis); 2 oldest pts may have confounded results.
Zamora-Navas et al. (1995) Multiple centers in Spain Uncontrolled prospective study to evaluate capacitive coupling for tx of nonunions w/ gap >0.5 cm *F/u:* Range 8-42 wks *Time frame:* 1990-1993	n=22 pts (mean age 35 yrs, range 17-70; 16 men, 6 women) w/ nonunion gaps ranging from <0.5-1.8 cm *Inclusion criteria:* Established nonunion of tibia (10), humerus (8), radius (2), clavicle (1), carpal scaphoid (1), ulna (1) *Tx:* Mean 26 wks, range 8-42	Radiography: Solid bony union in 16/22 (72.7 %) pts; no healing in 2/10 tibial fractures, 2/6 humeral fractures, 1/1 clavicle, and 1/1 carpal scaphoid; better results when fracture site was metaphyseal; results not affected by presence of infection. *Complications:* Osteomyelitis in 8 pts, but nonunion healed in all cases.	Successful healing w/ electrical stimulation in majority of long bone nonunions; scaphoid and clavicle did not heal. Success rate in gap wider than 0.5 cm was not different from success rate obtained in cases in which the gap was narrower. The tissue type occupying the gap, rather than the distance, may affect tx success. *Limitations:* Uncontrolled study design; very small sample size, heterogeneous in regard to fracture site.

Authors/Study Design	Study Population/Treatment	Results/Complications	Conclusions/Limitations
Abeed et al. (1998) General hospital setting, Lahore, Pakistan Uncontrolled prospective study to evaluate capacitive coupling for tx of nonunion of long bone fractures *F/u:* Until healed, but maximum of 30 wks *Time frame:* NR	n=16 pts (mean age 37 yrs, range 17-63; 11 men, 5 women) w/ nonunited fractures of 9-76 mos *Inclusion criteria:* Long bone nonunion (radius, tibia, femur, ulna) ≥9 mos *Tx:* 8 hrs/day for ≤30 wks	11/16 (68.7%) nonunions healed at average of 15 wks. Only significant factor affecting success of healing was distance between plates: Distance <80 mm resulted in healing in all cases (*P*<0.01); healing not affected significantly by surgical tx prior to electrical stimulation, infection, weight bearing after tx, or presence of metal at fracture site from previous surgery. *Complications*: NR	Successful healing w/ capacitive coupling electrical stimulation occurred in ~69% of pts, confirming findings of other studies that this technology promotes bone healing of fracture nonunions. But healing took place only if distance between plates was not excessive, suggesting that maintaining sufficient current across plates is necessary to allow healing. *Limitations:* Uncontrolled study design; very small sample size; heterogeneous population in regard to fracture site, although all were long bone nonunions.
Goodwin et al. (1999)[1] Multiple centers in U.S. Randomized, double-blind, placebo-controlled trial to evaluate effectiveness of capacitive coupling as an adjunct to lumbar spinal fusions *F/u:* Until healed, but maximum of 9 mos *Time frame:* 1992-1997	n=179 evaluable pts of 337 pts initially enrolled (study is ongoing) Active stimulation grp: n=85 (mean age 45 yrs, range 21-76; 48 men, 37 women) Placebo stimulation grp: n=94 (mean age 40 yrs, range 22-73; 49 men, 45 women) *Inclusion criteria:* Primary dx of degenerative disc disease w/ or w/o degenerative changes; adult; 1- or 2-level primary lumbar fusion; posterior lumbar interbody, anterior lumbar interbody, or posterolateral fusion; allograft, autograft, or mixture of graft materials; any type of internal fixation except interbody fusion cages *Exclusion criteria:* Spinal pathologic processes including tumors or infection, spinal fracture, or systemic disease, such as diabetes or osteoporosis that might affect fusion *Tx:* 24 hrs/day until healing occurred, or 9 mos if healing delayed	179 pts completed final status documents and radiographic analysis. Clinical success (good to excellent outcome): 88.2% for active grp and 75.5% for placebo grp (*P*=0.046). Radiographic success: 90.6% of active grp and 81.9% of placebo grp (*P*=0.1454). Overall success (both clinical and radiographic): 84.7% for active grp and 64.9% for placebo grp (*P*=0.0043); best results (20% or greater success rate) occurred when active stimulation used in conjunction w/ posterolateral fusion (89.1% vs 64.9%, *P*=0.006) or internal fixation (81.5% vs 61.0%, *P*=0.013). Significantly better outcomes in pts w/ degenerative disc disease (87.5% vs 59.7%, *P*=0.002) and in nonsmokers (84.7% vs 69.4%, *P*=0.006). *Complications:* Skin irritation (9), wound infection (1); no serious complications.	Capacitive coupling electrical stimulation is an effective adjunct to primary spine fusion, especially for pts w/ posterolateral fusion and those w/ internal fixation. *Limitations:* Relatively small sample size; size may limit power to detect tx effect and generalizability of results; heterogeneous pt population in regard to fixation, fusion level, grafting, and fusion site; some strata had insufficient numbers of pts to determine statistical significance; did not use intention-to-treat analysis; some pts lost to f/u (high dropout rate), others still wearing device (this is an ongoing study and analysis is preliminary).

Authors/Study Design	Study Population/Treatment	Results/Complications	Conclusions/Limitations
PEMF			
Bassett et al. (1982) Columbia-Presbyterian Medical Center, New York, NY; secondary centers in U.S. and academic orthopedic centers abroad Uncontrolled prospective study of PEMF tx in ununited fractures and failed arthrodeses *F/u:* Mean 5.5 mos *Time frame:* Since 1974, majority of pts since 1979	n=1078 pts w/ ununited fractures or failed arthrodeses *Inclusion criteria:* Nonunion or delayed union of fracture of tibia, femur, humerus, radius/ulna, scapula, clavicle, metatarsals or failed arthrodesis of hip, knee, ankle, shoulder, or wrist; achievement of definable endpoint in tx (either healing or failure) *Exclusion criteria:* Synovial pseudoarthrosis or gaps >1 cm *Tx:* 10-12 hrs/day for mean 5.5 mos	Overall success rate, by radiographic and clinical evaluation: 77.4% (834/1078) Columbia pts: 80.9% (178/220) International pts: 78.5% (183/233) U.S. pts: 75.7% (473/625) Success rate for nonunions of tibia: 82.0% (identical for all 3 geographic locations) Success rate in subgrp of 332 difficult cases (average 4.7 yr disability duration, average 3.4 previous operations, 35% rate of infection): 75.0% Success rates for failed arthrodeses: 81.7% (58/71) Columbia pts: 87.0% (20/23) International pts: 83.3% (5/6) U.S. pts: 78.6% (33/42) *Complications:* None	Results suggest that PEMF may be effective for tx of nonhealing fractures. Success more likely in tibial lesions than femoral lesions, while both were greater than success in lesions of upper extremity, w/ exception of carpal navicular bone. *Limitations:* Uncontrolled study design; sample heterogeneous w/ respect to infection, bone type, duration of disability, and previous operations.
Borsalino et al. (1988) Multiple centers in Italy Randomized, double-blind, placebo-controlled trial to evaluate PEMF for osseous repair in pts tx'd w/ femoral intertrochanteric osteotomy for hip degenerative arthritis *F/u:* 3 mos *Time frame:* 1985-1987	n=32 consecutive pts tx'd w/ femoral intertrochanteric osteotomy for hip osteoarthritis Active stimulation grp: n=16 (mean age 56 yrs, range 36-70; 5 men, 11 women) Placebo stimulation grp: n=16 (mean age 55 yrs, range 38-69; 4 men, 2 women) *Inclusion criteria:* Age <70, degenerative osteoarthritis of hip, tx'd w/ femoral osteotomy *Exclusion criteria:* Rheumatoid arthritis *Tx:* 8 hrs/day for 3 mos beginning 3 days after osteotomy	1 active grp pt lost to f/u; analysis based on 15 active-grp and 16 placebo-grp pts. Radiographic evaluation at day 40: Active grp showed more pronounced bone callus presence and trabecular bridging in lateral cortex and medial cortex (P<0.02 for each). Radiographic evaluation and callus density measurements performed w/ image analyzer at day 90: Active grp showed greater formation in periosteal bone callus on medial cortex (P<0.05), greater calcification (P<0.05), and more pronounced trabecular bridging at lateral cortex (P<0.001) and medial cortex (P<0.001). *Complications:* NR	In this extremely homogeneous pt population, PEMF stimulation favored osteotomy healing, increasing callus formation and trabecular bone bridging. Statistically significant differences between actively tx'd grp and placebo grp were observed at 40 and 90 days. *Limitations:* Very small sample size; size may limit power to detect magnitude of tx effect and generalizability of results; data do not apply to fresh fractures nor to nonunions; attempts to quantify bone healing by callus patterns and trabecular bridging are more subjective than densitometric methods; lack of intention-to-treat analysis.

Authors/Study Design	Study Population/Treatment	Results/Complications	Conclusions/Limitations
Mooney (1990)[2] Multiple centers in U.S. Randomized, double-blind, placebo-controlled trial of PEMF for lumbar interbody fusions *F/u:* ≥12 mos *Time frame:* NR	n=195 pts Active grp (brace w/ PEMF equipment): n=98 (mean age 38 yrs) Placebo grp (sham brace): n=97 (mean age 37.6 yrs) *Inclusion criteria:* Adults undergoing initial attempts at interbody spinal fusion either from anterior or posterior approach *Exclusion criteria:* Trauma, inflammatory disease of spine, severe osteoporosis, or metabolic conditions (diabetes, renal dysfunction, or metastatic cancer) *Tx:* ≥8 hrs/day for 40-90 days	Success rate (radiographic proof of solid fusion defined as >50% assimilated): Consistent-use* active grp: 92.2% (59/64) Inconsistent-use* active grp: 64.7% (22/34) Total active grp: 82.7% (81/98) Consistent-use placebo grp: 67.9% (36/53) Inconsistent-use placebo grp: 61.4% (27/44) Total placebo grp: 64.9% (63/97) Significant difference between consistent-use active grp and total placebo grp (P<0.05)†. Inconsistent PEMF users and all categories of placebo grp achieved similar success rates. *Complications:* Device bulky or uncomfortable (both grps, 13%); minor skin rash (active, 2%; placebo, 0%); pain while using device (both grps).	Results suggest that consistent use of PEMF promotes healing of interbody spinal fusion w/ no significant adverse effects. *Limitations:* Inconsistent device use among 35% of active pts and 45% of placebo pts; analysis not intention-to-treat (originally 107 pts in active grp and 99 in placebo grp, but 9 and 2, respectively, lost to f/u, and analysis based on 98 and 97 pts, respectively, who completed trial); relatively small sample size; size may limit power to detect magnitude of tx effect and generalizability of results.

Authors/Study Design	Study Population/Treatment	Results/Complications	Conclusions/Limitations
Sharrard (1990) Multiple centers in UK Randomized, double-blind, placebo-controlled trial in pts w/ ununited tibial fractures to compare tx by immobilization and active PEMF stimulation w/ similar immobilization and a dummy stimulator *F/u:* 12 wks *Time frame:* 1981-1987	n=45 pts Active grp: n=20 (mean age 34.7 yrs, range 18-84; 14 men, 6 women) Placebo grp: n=25 (mean age 45.4 yrs, range 18-76; 18 men, 7 women) *Inclusion criteria:* Age >18; fracture of tibial shaft ≥5 cm from ankle or knee; ≥16 wks nonunion; ≤32 wks conservative tx; tx by immobilization in long-leg plaster cast; ≥2 of factors of moderate or severe displacement or angulation, moderate or severe comminution, or moderate or severe wound *Exclusion criteria:* Surgery other than required for initial management of wound and open reduction of initial fracture, tx by internal or external fixation, gap between bone ends >0.5 cm, severe generalized disease, receiving systemic steroid tx, bone disease such as Paget's disease, severely atrophic bone w/ spindle-shaped bone ends, fractures w/ marked hypertrophy *Tx:* 12 hrs/day for 12 wks	Radiographic assessment by radiologist: Active grp: 3 (15%) full unions, 2 (10%) probable unions, 5 (25%) progress to union, 10 (50%) no progress Placebo grp: 1 (4%) probable union, 1 (4%) progress to union, and 23 (92%) no progress Significant difference in favor of active grp (*P*=0.002). Radiographic assessment by orthopedic surgeon: Active grp: 9 (45%) unions, 2 (10%) improved but not united, 9 (45%) no progress Placebo grp: 3 (12%) unions, 5 (20%) improved but not united, 17 (68%) no progress Significant difference in favor of active grp (*P*=0.02). Clinical assessment: No significant differences between 2 grps in any of clinical criteria, such as movement, pain, or tenderness. *Complications:* NR	This study used strict selection criteria to identify tibial fractures w/ a tendency to delayed-union or nonunion. These were fractures that initially had been moderately or severely displaced, or angulated, comminuted, or associated w/ soft tissue injury, and were making no or minimal progress to union. In this select pt population, results suggest that PEMF promotes healing of tibial fractures w/ delayed union or nonunion. *Limitations:* Very small sample size; size may limit power to detect magnitude of tx effect and generalizability of results; significant difference in age distribution between grps; analysis not intention-to-treat (originally 51 pts enrolled in trial, but analysis based on 45 who completed trial).

Authors/Study Design	Study Population/Treatment	Results/Complications	Conclusions/Limitations
Garland et al. (1991) University of Southern California School of Medicine, Los Angeles, CA Uncontrolled prospective study to evaluate long-term safety and effectiveness of PEMF tx for fracture nonunions and failed arthrodeses and to determine effective tx dosage range to achieve union *F/u:* Mean 4.1 yrs (range 3.6-5.4) in 90 pts *Time frame:* 1983-1984	n=139 pts (mean age 42 yrs) w/ 149 fractures *Inclusion criteria:* Established fracture nonunion of ≥9 mos, or established nonunion that underwent bone grafting or internal fixation and no evidence of healing radiographically by 3 mos after procedure *Tx:* Minimum 8 hrs/day for 6 mos or until union	Success rate, by radiographic and clinical evaluation, according to daily usage of PEMF: <3 hrs/day (n=13 pts): 35.7% (5/14 fractures) >3 hrs/day (n=126 pts): 80.0% (108/135 fractures) Difference significant (*P*<0.05). Tx success unaffected by long vs short bone, open vs closed fracture, nonunion of 9-12 mos vs 1-10 yrs, age <60 yrs vs >60 yrs, gender, recalcitrant vs 1st time tx, infected vs noninfected nonunion, fracture gap ≤1 cm, or weight-bearing vs non–weight-bearing. 97 fractures in 90 pts who used PEMF >3 hrs/day showed 92% (89/97) maintenance of fusion at mean 4.1 yrs f/u. *Complications:* None long-term	Results validate long-term safety and efficacy of PEMF for tx of fracture nonunions and failed arthrodeses. There is a threshold dosage of ≥3 hrs/day and not 10-12 hrs/daily to effect union, as previously thought. *Limitations:* Uncontrolled study design; relatively small sample size; sample heterogeneous for location of fraction, size of fraction, and presence of infection.
Mammi et al. (1993) Multiple centers in Italy Randomized, double-blind, placebo-controlled trial to evaluate PEMF stimulation in pts tx'd w/ valgus tibial osteotomy for degenerative arthrosis of knee *F/u:* 60 days *Time frame:* NR	n=40 consecutive pts Active stimulation grp: n=20 (mean age 62 yrs, range 49-77; 15 women, 5 men) Placebo grp (dummy stimulators): n=20 (mean age 61 yrs, range 33-78; 16 women, 4 men) *Inclusion criteria:* Degenerative arthrosis of knee, tx'd w/ tibial osteotomy; ≤80 yrs; good health consistent w/ age *Exclusion criteria:* Autoimmune disorder, metabolic or neoplastic disease, concurrent use of steroids *Tx:* 8 hrs/day for 60 days	Radiographic results quantified into score of 1-4, w/ 1 showing little healing and 4 showing complete healing. Radiographic evaluation at 60 days postop: Scores 1 or 2: 14/19 (73.7%) controls vs 5/18 (27.8%) actives (*P*<0.04) Scores 3 or 4: 5/19 (26.3%) controls vs 13/18 (72.2%) actives (*P*<0.006) Average score: 2.1 for controls vs 3 for actives *Complications:* Thrombophlebitis (5 controls, 3 active pts).	This was a homogeneous pt population w/ regard to surgical procedure, use of osteosynthesis device to stabilize osteotomy, and postop rehabilitation program. Results confirm those of other studies that PEMF stimulation enhances rate of union of a tibial osteotomy. *Limitations:* Very small sample size; size may limit power to detect magnitude of tx effect and generalizability of results; analysis based on 18 pts in active grp and 19 pts in placebo grp, thus, not intention-to-treat analysis.

Authors/Study Design	Study Population/Treatment	Results/Complications	Conclusions/Limitations
Jenis et al. (2000) New England Baptist Spine Center, Boston, MA Randomized controlled trial to compare effect of adjunctive DC electrical stimulation or PEMF on augmentation of instrumented lumbar spine fusion *F/u:* 1 yr *Time frame:* 1995-1997	n=61 pts PEMF stimulation grp: n=22 (mean age 53.0 yrs; 11 women, 11 men) DC stimulation grp (implanted stimulator): n=17 (mean age 51.0 yrs; 10 women, 7 men) Nonstimulated grp (surgery alone): n=22 (mean age 47.1 yrs; 8 women, 14 men) *Inclusion criteria:* Pts undergoing primary or revision lumbar or lumbosacral posterolateral fusion surgery w/ instrumentation and autogenous iliac crest bone grafting; age 18-75 yrs *Exclusion criteria:* Lumbar fusion technique other than posterolateral fusion (i.e., interbody fusion); depressed immune system; regional conditions that would affect bone metabolism (Paget's disease); systemic conditions, including renal failure, metastatic carcinoma, or uncontrolled diabetes; cardiac pacemakers, defibrillators, and/or dorsal column stimulators *Tx:* PEMF (≥2 hrs/day ≥90% of 150 tx days after surgery) w/in 30 days of surgery or DC stimulator implanted at time of surgery	Radiographic fusion evaluation at 1 yr (grade 3 indicates solid fusion): PEMF grp: 5.0%, 30.0%, 65.0% for grades 1, 2, 3, respectively DC grp: 0%, 38.9%, 61.1% for grades 1, 2, 3, respectively Nonstimulated grp: 4.7%. 14.3%, 81.0% for grades 1, 2, 3, respectively No significant differences among grps. BMD measurement at 3 and 12 mos: PEMF grp: ↑ from 116.6% to 125,2% DC grp: ↑ from 120.1% to 126.4% Nonstimulated grp: ↓ from 108% to 106% No significant differences among grps. Clinical outcome evaluation at 1 yr (subjective analysis of pain and function levels): PEMF grp: 35% excellent results, 50% good, 10% fair, 5% poor DC grp: 32% excellent, 37% good, 31% fair Nonstimulated grp: 43% excellent, 43% good, 14% fair *Complications:* 2 wound infections in each tx grp; 1 postop epidural hematoma in control grp; no complications directly attributed to use of instrumentation or stimulation device.	Results suggest that electrical stimulation, either w/ PEMF or DC does not result in improved fusion rates or clinical outcome in instrumented lumbar arthrodesis, although an insignificant trend toward increased fusion mass BMD in electrically stimulated grps was observed. Significance of increased BMD is unknown. *Limitations:* Very small sample size; size may limit power to detect tx effect and generalizability of results; fusion rate in control grp relatively high compared w/ other series in literature.

Authors/Study Design	Study Population/Treatment	Results/Complications	Conclusions/Limitations
Simonis et al. (2003) Ashford and St. Peter's Hospitals NHS Trust, Surrey and St. George's Hospital Medical School, London, UK Randomized, double-blind, placebo-controlled trial of PEMF stimulation for tx of established tibial nonunion *F/u:* 6 mos *Time frame:* 5-yr period (not specified)	n=34 pts w/ tibial fractures (mean age 32 yrs; 30 men, 4 women) Active stimulation grp: n=18 (mean age 31.7 yrs) Placebo grp (dummy stimulators): n=16 (mean age 32.3 yrs) *Inclusion criteria:* Tibial shaft fracture ununited ≥1 yr after initial fracture, no metal implant bridging nonunion gap, no radiological progression of fracture union in 3 mos prior to electrical stimulation tx, tx'd surgically w/ oblique fibular osteotomy followed by unilateral external fixator w/ compression *Tx:* ≥14 hrs/day for 6 mos	Radiographic and clinical evaluation for bony fusion: Active grp: 16/18 (88.9%) united Placebo grp: 8/16 (50.0%) united Significant positive association between tibial union and electrical stimulation (unadjusted OR 8, 95% CI 1.5-41, *P*=0.02). However, when rate adjusted for smoking, association was weaker and not significant (adjusted OR 5.4, 95% CI 0.85-34, *P*=0.07). Union rate in smokers and nonsmokers: Smokers: 75% (6/8) in active grp vs 46.2% (6/13) in placebo grp Nonsmokers: 100% (10/10) in active grp vs 66.7% (2/3) in placebo grp	In pts w/ established nonunion of tibial fractures, PEMF stimulation was associated w/ a significant increase in rate of union, but only before adjustment for smoking. The adjusted OR was not significant due to low power. The implication is that nonunions in smokers have a worse prognosis than in nonsmokers and that smoking is detrimental to nonunions healing. PEMF stimulation in both smokers and nonsmokers produced a higher rate of union than in the control grp. *Limitations:* Very small sample size; size may limit power to detect tx effect and generalizability of results; imbalance in smoking habit between 2 grps (44% vs 81% smokers in active vs placebo grps).

Authors/Study Design	Study Population/Treatment	Results/Complications	Conclusions/Limitations
CMF			
Hanft et al. (1998) South Miami Hospital Diabetes Care Center Foot Clinic, Miami, FL Partially randomized, controlled, expanded pilot study to assess role of CMF bone growth stimulation as an adjunct in tx of acute, phase 1, Charcot neuroarthropathy *F/u:* NR *Time frame:* NR	n=31 pts Study grp (adjunctive CMF): n=21 (initial 11 randomized pts and additional 10 nonrandomized pts [assigned after initial results analyzed]; mean age 55.9 yrs, range 36-71) Control grp (no CMF): n=10 (mean age 57.7 yrs, range 31-70) *Inclusion criteria:* Peripheral neuropathy secondary to diabetes mellitus; clinical, thermographic, and radiographic evidence of acute (stage 1) Charcot joint; foot or ankle location *Exclusion criteria:* Open ulceration or wound on limb being studied, active skin or bone infection, previous hx of Charcot episode on limb being studied, dx'd renal failure, o inability to comply w/ prescribed tx *Tx:* 1/2 hr/day for ≥75% of allotted time	Significant reduction in time to consolidation for study grp compared w/ control grp: 11 wks vs 23.8 wks (*P*=0.001) Study grp had less deformity at completion of study than control grp.	In this expanded pilot study in pts w/ acute, phase 1, Charcot joint, use of CMF stimulation as an adjunct to standard tx modalities significantly accelerated the consolidation process and decreased the amount of residual deformity. *Limitations:* Very small sample size; size may limit power to detect tx effect and generalizability of results; pilot study, thus no placebo control and no blinding; tx length and f/u not specified.

Authors/Study Design	Study Population/Treatment	Results/Complications	Conclusions/Limitations
Linovitz et al. (2002)[1,3] 10 clinical sites in U.S. Randomized, double-blind, placebo-controlled trial to evaluate effect of noninvasive adjunctive tx w/ CMF on healing of primary noninstrumented posterolateral lumbar spine fusion Stratification by site and number of levels fused. *F/u:* 9 mos (study endpoint) + additional 3 mos *Time frame:* 1993-1998	n=201 evaluable pts (120 women, mean age 57 yrs; 81 men, mean age 56 yrs) of 243 enrolled Active stimulation grp: n=104 evaluable (41 men, 63 women); n=125 enrolled (mean age 56.8 yrs; 51 men, 74 women) Placebo grp (dummy stimulators): n=97 evaluable (40 men, 57 women); n=118 enrolled (mean age 56.6 yrs; 43 men, 75 women) *Inclusion criteria:* 1-level or 2-level primary intertransverse fusion (between L3 and S1) w/o instrumentation/internal fixation, either w/ autograft alone or in combination w/ allograft; ≥18 yrs of age; device application w/in 30 days postsurgery *Exclusion criteria:* Use of instrumentation/ internal fixation, prior fusion surgery, malignancy, metabolic bone disease, vertebral trauma or scoliosis, moderate to severe osteoporosis, spondylitis, Paget's disease, renal dysfunction, uncontrolled diabetes mellitus, implanted cardiac pacemaker, pregnancy, skeletal immaturity (<18 yrs) *Tx:* 30 mins/day for 9 mos	Fusion status graded from no fusion (0) to solid fusion (3): grades 0 and 1 defined as failure and grades 2 and 3 defined as success. Fusion success rate at 9 mos (201 evaluable pts): Active grp: All pts: 64.4% (67/104) Men: 58.5% (24/41) Women: 66.7% (42/63) Placebo grp: All pts: 43.2% (42/97) Men: 55.0% (22/40) Women: 35.1% (20/57) Significant differences between active and placebo grps in overall and female pt populations (P=0.003 and P=0.001, respectively), but not in male population. In overall population of 201 evaluable pts, repeated measures analyses of fusion outcomes (by generalized estimating equations) showed main effect of tx, favoring active tx (P=0.03) and, in separate model, there was a significant time by tx interaction (P=0.024), indicating acceleration of healing. 1-level fusions significantly improved in active grp (68.7% vs 45.5%, P=0.009). Intention-to-treat analysis performed in full sample of 243 pts gave results qualitatively the same as in evaluable sample of 201 pts. *Complications:* NR	In pts w/ noninstrumented posterolateral fusions, adjunctive use of CMF bone growth stimulation significantly increased 9-mos success of radiographic spinal fusion in overall and female study populations but not in male population. In addition, there was an acceleration of the healing process. *Limitations:* Dropout rate of 17% (21 pts from active grp and 21 pts from placebo grp), but intent-to-treat analysis considered w/drawn pts to represent failure.

***** Consistent use defined as ≥ 8 hrs/day; inconsistent use defined as < 4 hrs/day.
† Typographical error in original study reports P>0.005; subsequent review states correct value is P<0.05 (Bush and Vaccaro, 2000).
[1] Financial support from device manufacturer.
[2] Equipment donated by manufacturer.

[3] One or more authors received benefits for personal or professional use from manufacturer, such as honoraria, gifts, consultancies, royalties, stocks, stock options, decision-making position.