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Optimizing Outcomes with Fresh and Nonunion Fractures Using Low-Intensity Pulsed Ultrasound

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4435 Waterfront Drive, Suite 101
Glen Allen, VA 23060
(804) 527-1905
fax (804) 747-5316

EDITOR-IN-CHIEF
J. Ronald Hunt, MD

PUBLISHER
Jack F. Klose

JOURNAL MANAGEMENT
Douglas Murphy
Communications Inc.
8730 Stony Point Parkway, Suite 250
Richmond, VA 23235
(804) 272-9100
fax (804) 272-1694

MANAGING EDITOR
Bill Edwards
bill.edwards@douglasmurphy.com

ASSOCIATE EDITOR
Kari Jones

ART DIRECTOR
David Balch

DESIGN/PRODUCTION ASSISTANT
Andrea Owens

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Optimizing Outcomes with Fresh and Nonunion Fractures Using Low-Intensity Pulsed Ultrasound

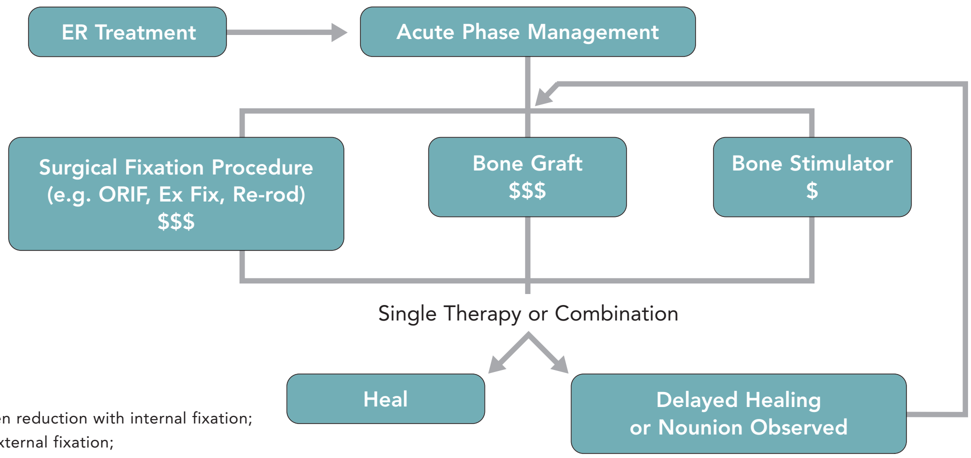
THIS SPECIAL EDITION OF the *Journal of Managed Care Medicine* is based on presentation and discussions at a consensus meeting held November 15, 2006 in Las Vegas, Nevada and sponsored by the National Association of Managed Care Physicians and Smith & Nephew, Inc.

A focus group composed of medical directors from various managed care organizations recently met to discuss issues with ultrasound bone healing and, from a managed care perspective, how to determine appropriate use and coverage. The content of this monograph was developed from presentations given and consensus guidelines developed at that meeting.

There are an estimated 6.3 million fractures that occur annually in the United States.[1] Fractures occur at an annual rate of 3.6 per 100 people.[1] Although fractures occur in many ways, sports, automobile accidents, and falls are three primary causes. During acute phase management, fractures can be stabilized with casts, braces, and surgical implantation of metal plates, metal screws, external fixation devices, or intermedullary fixation (IM) nails (Exhibit 1).

Despite good fracture fixation, 5 to 10 percent of fractures will show delayed or impaired healing.[2] There is no universally accepted definition of delayed healing or nonunion. Most textbooks and orthopedic surgeons define a nonunion as a fracture that, in the opinion of the treating physician, has no possibility of healing without further intervention. A delayed union is widely defined as a fracture that, in the opinion of the treating physician, shows slower progression to healing than was anticipated and is at a substantial risk for becoming a nonunion without further intervention. As defined by the Centers for Medicare & Medicaid Services (CMS), a nonunion fracture is one that has not healed in 90 days or longer or has three consecutive x-

Exhibit 1: Typical Bone Healing Algorithm



ORIF, open reduction with internal fixation;
EX FIX, external fixation;
RE-rod, reinforcement rod

rays showing no evidence of healing.[3] A delayed union is a slow healing fracture that has not gotten to the 90 day window.[3] These last two are the definitions used for the purpose of this discussion.

The two principal reasons for fractures failing to unite are believed to be inadequate stabilization and failure of the biologic processes necessary for new bone formation. Both local and systemic factors may contribute to this breakdown in normal healing. Of the systemic risk factors, smoking, obesity, alcoholism, diabetes, peripheral vascular disease, advanced age, and osteoporosis are all risk factors for poor bone healing and nonunion.[4-8] Those over 65 are 36 percent of the total patient population treated as inpatients for nonunion fractures.[8] Certain medications including corticosteroids and nonsteroidal anti-inflammatories (NSAIDs) are also thought to increase risk for nonunion or infection, which in turn increases the risk for nonunion.[8,9]

Certain characteristics of the fracture and the injury also predispose to nonunion. These include high-energy trauma, higher grade and open fractures, comminution of the fracture, vertical or oblique fracture pattern, infection, and fracture displacement.[2] Soft tissue imbedded between bone fragments impedes healing, and severe soft tissue trauma may interrupt vascular supply and may predispose to infection.[2] Specific bones have higher rates of nonunion than others because of normal limited blood supply or propensity to more severe fractures. Problem bones include the tibia, talus, fifth metatarsal (foot), scaphoid (wrist), and clavicle.[10,11] About 62 percent of all nonunion fractures are in the tibia.[8]

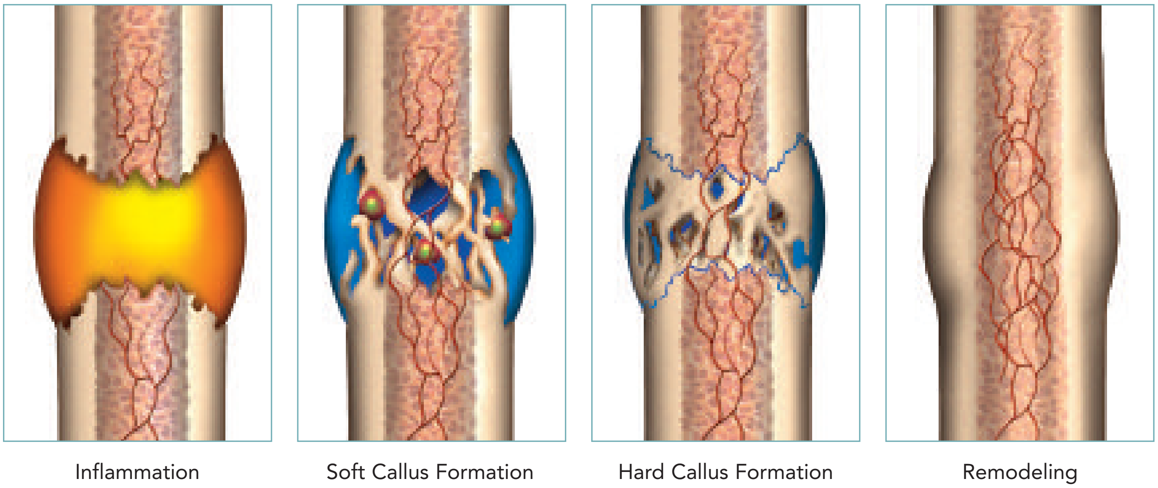
Fracture Costs

There are significant costs to treating fractures – these include hospital and emergency room stays, surgical procedures, casting, bone grafts, adjunctive treatments, pain medications, and rehabilitation. The direct cost for a tibial fracture has been estimated at $3,400 – $15,060, depending on the choice of treatment and the method of determining cost.[12,13] With respect to the financial burden to society, the indirect costs (i.e., lost wages, lost productivity, workman's compensation payments) have been estimated to be between $14,675 and $21,648.[12,13]

Fractures that do not heal in a timely manner are significantly more costly than those that heal promptly. The patient is unable to return to work and requires additional physician visits, X-rays, physical therapy, and occupational therapy generating ultimately higher costs to the health plan. Often, the patient with a nonunion fracture will need additional surgery, which further increases the costs. The average direct cost to heal a nonunion tibial fracture has been estimated at $36,000 ($25,717 not requiring reoperation - $46,292 requiring reoperation).[13,14] In addition to

Fractures that do not heal in a timely manner are significantly more costly than those that heal promptly.

Exhibit 2: Stages of Bone Healing



being costly to treat, nonunion fractures delay returning an employee to work, which is an issue for employers and workman's compensation payers.

Fracture Healing

Fracture healing relies on a coordinated series of phases in which damaged nonfunctional tissue is replaced by tissue that restores the original structure and function of the bone. Each phase in the healing sequence relies on specific growth factors to ensure complete healing and bone restoration. Successful fracture healing is a complex process, which requires the effective functioning of multiple cell types. Along the way, various processes overlap to accomplish the rebuilding of bone tissue.

In the early stages of fracture healing a blood clot forms in the fracture space (Exhibit 2).[15] Macrophages, leukocytes and other inflammatory cells then invade the area. The damage also sensitizes the surviving local cells to respond better to local and systemic messages. The next stage of healing is the formation of a soft callus (a mass of exudate and connective tissue that forms around a break in a bone and is converted into bone in the healing of the break). The earliest callus formation arises from the periosteum. Precursor cells in the periosteum give rise to osteoblasts. The cells that are stimulated and sensitized during the inflammatory stage begin producing new blood vessels, fibroblasts, intra-cellular material, and supporting cells. The hematoma is then replaced with fibrovascular tissue. Fibrocartilage

Exhibit 3: Fracture Healing Over Time

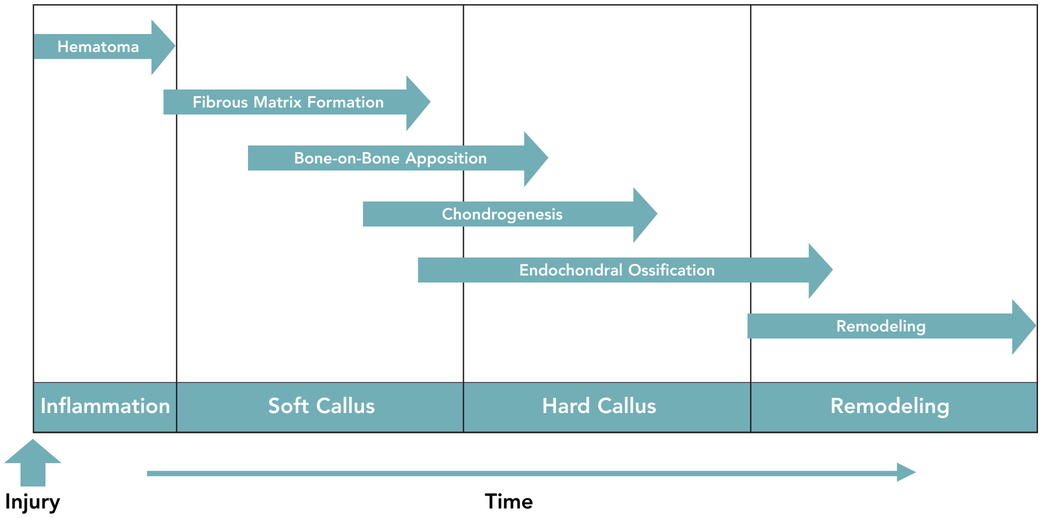


Exhibit 4

then develops and stabilizes the bone ends. After the soft callus forms, mineralization of the cartilage and fibrovascular tissue occurs via endochondral ossification (hard callus). In addition, bone-on-bone apposition also occurs, contributing to formation of the hard callus. In this last stage of fracture repair, woven bone is gradually replaced by lamellar bone. Woven bone is weak, with a small number of randomly oriented collagen fibers, but forms quickly and without a preexisting structure during periods of repair or growth. Lamellar bone is stronger, formed of numerous stacked layers and filled with many collagen fibers parallel to other fibers in the same layer. The fibers run in opposite directions in alternating layers, assisting in the bone's ability to resist torsion forces.

Exhibit 3 presents an overview of this healing process over time. When a nonunion fracture occurs, it appears that the healing process has either halted at some point in the process or is moving very slowly.

Bone Growth Stimulation

Another element in the repair process is the type of stress applied to the bone during healing. Biophysical stimulation has been proposed as a key element in repairing, maintaining, and remodeling bone to meet its functional demands. The biophysical stimulation needed to enhance fracture healing may be supplied through external energy sources such as low-intensity pulsed ultrasound, pulsed electromagnetic field, low power direct current, and extracorporeal shock wave stimulation (not approved for use in U.S.). Although these are all forms of biophysical stimulation, whether these modalities produce different cellular responses is unknown. Cellular response studies have been conducted with ultrasound biophysical stimulation and will be discussed later.[16]

In an effort to reduce the substantial disability and socioeconomic costs associated with healing fractures, a variety of bone growth stimulating interventions are available. In general, the bone stimulation market in the U.S. is about two hundred million dollars. The market for these products is increasing about six to eight percent per year and it is primarily driven by further adoption by orthopedic surgeons. About 25 percent of nonunion fractures are treated with bone simulation devices as an alternative or adjunctive to surgical treatment to help ensure healing or prevent the need for additional surgery. Currently, the majority of bone stimulator use is in nonunion fractures but the use of approved devices for fresh fractures has been growing.

The various technologies approved for use in the U.S. include low-intensity pulsed ultrasound, capacitative coupling, pulsed electromagnetic field, combined magnetic field, and direct electrical current. Each of the bone stimulating devices is a Class 3 medical device. There are three classes of medical devices, which follow a risk-based model for safety and effectiveness. The three classes are class 1 (general regulatory controls/lowest risk), class 2 (special regulatory controls/moderate risk), and class 3 (premarket approval/highest risk).[17] Class 3 devices include devices for which insufficient information exists to determine whether general and special controls are sufficient to provide reasonable assurance of their safety and effectiveness. These devices are life sustaining, life supporting, or substantially important in preventing the impairment of human health, or they present unreasonable risk of illness or injury.[17] To be approved by the FDA, Class 3 medical devices require valid scientific evidence to establish the safety and effectiveness of the device. Valid scientific evidence according to the FDA includes well-controlled investigations, partially controlled studies, uncontrolled studies, well-documented case histories, and reports of significant human experience.[17]

Exhibit 5 provides a comparison of the various devices that are currently available.[18-24] The Exogen Bone Healing System, which uses low-intensity pulsed ultrasound, is the only bone stimulator approved for treating fresh fractures (Exhibit 4). All of the other stimulators are only approved for treating nonunion fractures. The Exogen device requires the shortest treatment time, which may increase compliance compared to the majority of the other non-

Exhibit 5: Comparison of Bone Stimulating Devices [18-24]

Device/ Manufacturer	Daily Treatment Times	Technology	Indications	FDA Approval Wording	Healing Rates	
					Fresh Fracture	Nonunion Fracture
Exogen/Smith & Nephew	20 minutes	Low-intensity pulsed ultrasound	Fresh fractures and nonunion fractures	Indicated for the non-invasive treatment of established nonunions excluding skull and vertebra and for accelerating the time to a healed fracture for fresh, closed, posteriorly displaced distal radius fractures and fresh, closed or Grade I open tibial diaphysis fractures in skeletally mature individuals when these fractures are orthopaedically managed by closed reduction and cast immobilization.	38% acceleration	86%
Orthopak2/ EBI-Biomet	24 hours	Capacitative coupling	Nonunion fractures	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.	Not applicable	72.5%
EBI Bone Healing System/ EBI-Biomet	10 hours	Pulsed electromagnetic field	Nonunion fractures	Indicated for the treatment of fracture nonunions, failed fusions, and congenital pseudoarthroses in the appendicular system.	Not applicable	63.5%
Physio-Stim/ Orthofix	3 - 8 hours	Pulsed electromagnetic field	Nonunion fractures	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.	Not applicable	35.7 – 80%[a]
OL1000/ DJ Ortho	30 minutes	Combined magnetic field	Nonunion fractures	Indicated for the treatment of an established nonunion acquired secondary to trauma, excluding vertebrae and all flat bones.	Not applicable	60.7%
OsteoGen/ EBI-Biomet	24 hours	Direct electrical current (implanted)	Nonunion fractures	Indicated in the treatment of long bone nonunion.	Not applicable	66.7%

Does not include devices indicated for spine bone stimulation.
[a] Lower rate is for inconsistent users (average 1.1 hrs/day). Higher rate is for consistent users (average 7.1 hrs/day).

implanted devices, which require a significant time commitment on the part of the patient. With the electrical stimulation products, there is a dose response. The longer they are used during a day, the better the response so patient compliance directly affects efficacy.

Each of the devices has a similar Medicare reimbursement with an average of $3190 for ultrasound stimulation, $3794 for external electrical stimulation devices, and $3839 for implanted electrical stimulation devices.[25] The one surgically implanted device (OsteoGen) does have a higher cost because of the implantation procedure.

When comparing devices, in addition to considering indications, potential compliance, and costs, possible adverse effects from the devices must also be considered. The only adverse effects reported with low-intensity pulsed ultrasound are minor skin irritations from the conducting gel, which is used with the device.[26] Electrical shock, skin irritation from conducting gel, and thermal burns have been reported with the electrical stimulation devices.[26]

For all the bone stimulating

devices, there is the possibility of an interaction between electrical implants (such as cardiac pacemakers, cardiac defibrillators and neuron-stimulators). [18-23] No adverse interactions between these implants and the devices have been reported.[26] With the electrical stimulators, there is also a potential for interference with the treatment field through magnetic field interaction and/or electrical inductance within metallic fixation devices. Currently, almost all implanted fixation devices are made of non-magnetic materials. The scientific literature is inconclusive regarding adverse device performance associated with non-magnetic, metallic fixation for either capacitative coupling or pulsed electromagnetic field devices. However, evidence of potential decreased device performance in the presence of magnetic, metallic fixation for pulsed electromagnetic field devices does exist.[27]

Ultrasound Bone Stimulation Mechanism of Action

Historically, fracture sites have been considered an absolute contraindication for the use of therapeutic ultrasonography.[28] Some early animal studies found that ultrasound treatment delayed, or even damaged, healing bone. However, more recent work has shown that the effect of therapeutic ultrasonography on healing bone is dictated by the intensity used. A high-intensity (1.0 W/cm^2) continuous-wave ultrasound signal, as was applied in earlier animal studies, appears to be harmful; however, a low-intensity (30 mW/cm^2) pulsed ultrasound signal appears to promote accelerated healing.[28]

Ultrasound is acoustic (sound) energy in the form of waves having a frequency above the human hearing range. The highest frequency that the human ear can detect is approximately 20 thousand cycles per second (20,000 Hz). This is where the sonic range ends, and where the ultrasonic range begins. In ultrasonic medical applications, high-frequency acoustic energy is transmitted into the human body using transducers attached to the skin. In the case of the Exogen device, applying an alternating voltage at a given frequency to an episioelectric crystal generates the ultrasound waves. The crystal expands and contracts at the same frequency as the voltage. The signal from the Exogen device is a low-intensity pulsed ultrasound signal, which is patented. The signal is delivered at 1.5 megahertz, a one-and-a-half million cycle per second, which is pulsed at one kilohertz. The intensity is similar to a fetal ultrasound and is different from a physical therapy ultrasound machine, which needs to be moved because it can cause skin necrosis.

The patient uses the Exogen device at home for 20 minutes each day. If the patient who is to use the device has a cast, then a window is made in the cast to allow the device transducer to touch the skin. Because ultrasound does not pass easily through air, a conducting gel is used to transmit the signal to the skin. Because determining the appropriate location is the key to achieving healing, the application spot for the device is based on x-ray. The unit has a computer chip to record the actual time of day and length of time the device is used so the patient's compliance can be assessed.

Although the device transducer is applied on one side of the bone to be healed, the ultrasound waves are transmitted through and completely around the bone. Thus, a circular, three-dimensional bone can be treated from a single side of the bone. After Exogen treatment, bone density testing on the opposite side of the bone, from the treatment site, finds the same density values.

Over 30 peer-reviewed papers investigating the action mechanism of low-intensity pulsed ultrasound have been published in the last five years. The Exogen Bone Healing System uses a mechanical force to stimulate mechanical receptors, producing a biological response. During use, mechanical pressure waves transmit through skin and soft tissue. When the signal reaches the injury site, these waves have a direct effect on the cells. Ultrasound causes movement in the extra-cellular matrix and the signal is detected by mechanical cell surface receptors, which are called integrins. Integrins are found on a wide range of cells, which are crucial to the healing process of fractures. Under normal static conditions, mechanosensitive integrins are in an inactive state. When stimulated by a mechanical force such as the low-intensity pulsed ultrasound signal, integrins are activated. Integrin related signaling initiates an intra-cellular cascade during which, molecules that regulate gene expression are stimulated and move into the nucleus to perform their function. Normal intra-cellular signaling, protein expression and cellular behavior are enhanced.[29,30] Essentially this is accelerating the natural fracture-healing process.

During the hematoma stage, Exogen up-regulates macrophages, which engulf bacteria and other foreign bodies.[31] During the formation of fibrovascular tissue, Exogen accelerates the process of mesenchymal cells, within the fracture gap, differentiating into chondrocytes and osteoblasts.[32,33] Low-intensity pulsed ultrasound stimulates periosteal cells to differentiate and accelerates mineralization. [34] As cartilage replaces the fibrovascular tissue to form the soft callus, Exogen stimulates chondrocytes to accelerate the formation of the extra-cellular matrix.[35-38] As cartilage is replaced by woven bone, Exogen treatment up-regu-

Exhibit 6: Low-intensity Pulsed Ultrasound for Healing Fresh Fractures [46-55]

Study	Bone Investigated	Fracture Management	Co-morbidities /Risk Factors	Outcome Measures	Patient Numbers	Fracture Healing Acceleration
Kristiansen et al (1997)	Distal radius	Conservative	Smoking	Clinical & radiographic healing	N=61 (30 active, 31 placebo)	38% (p<0.0001)
Leung et al (2004)	Tibia	External fixator or intramedullay rod	Open, comminuted, segmental, high energy trauma	Clinical & radiographic healing, bone mineral content	N=30 (16 active, 14 placebo)	42% (p<0.05)
Heckman et al (1994)	Mid-shaft tibia	Conservative	Smoking	Clinical & radiographic healing, not healed at 20 weeks	N=67 (33 active, 34 placebo)	38% (p<0.0001)
Tsumaki et al (2004)	Tibia	External fixator	Osteoarthritis, open repair	Bone mineral density	N=21 (21 active, 21 control)	54% (p=0.02)
Rue et al (2004)	Tibia	Conservative	None	Pain, cortical thickening by radiograph	N=26	13% (not signif.)
Emami et al (1999)	Tibia	Reamed, locked intramedullay nail	None	Radiographic healing	N=32 (15 active, 17 placebo)	0%
Gold et al (2005)	Tibia	Bone transport by Ilizarov external frame	Large fracture gap	External fixation time, external fixation index	N=20 (8 active, 12 control)	17% (not signif.)
Mayr et al (2000)	Scaphoid	Conservative	None	Healing by CT scan	N=30 (15 active, 15 placebo)	31% (p=0.0055)
Strauss et al (1999)	5th metatarsal	Conservative	None	Clinical & radiographic healing, not healed at 20 weeks	N=20 (10 active, 10 placebo)	45%

lates gene and protein expression of key growth factors involved in angiogenesis and endochondral bone formation.[39,40] It has also been shown to elevate the expression of bone differentiation markers osteonectin and osteopontin.[40] In addition, osteocalcin levels are increased in both human periosteal cells and osteoblasts.[34,41,42] Alkaline phosphatase, an enzyme associated with osteoblast differentiation, has also shown increased activity and expression following low-intensity pulsed ultrasound treatment.[43,44] Elevated levels of vascular endothelial growth factor (VEGF), a key growth factor and a crucial regulator of angiogenesis and endochondral bone formation, have been observed in human osteoblasts and periosteal cells following ultrasound stimulation.[34,43] Moreover, increased levels of IGF-1 in osteoblasts and bone marrow stromal cells have been reported following stimulation with the Exogen Bone Healing System.[41]

Efficacy of Low-intensity Pulsed Ultrasound

Non-invasive, low-intensity ultrasound-based technology is proven to accelerate the natural healing process of indicated fresh fractures and resolve nonunions. While the Exogen Bone Healing System has been shown to increase the rate of healing for fresh fractures at each stage of the fracture healing process, the biggest impact occurs when used throughout all of the stages.[27,45] For nonunion fractures, Exogen treatment appears to restart the stalled healing process.

Fresh Fractures

There are no published studies of using electrical stimulation to heal fresh fractures of the bones prone to nonunion. Low-intensity pulsed ultrasound using the Exogen device is the only bone-stimulating device FDA approved for use in some fresh fractures (see Exhibit 5 for specifics).

Several studies of the use of ultrasound in fresh fractures have been published. Selected studies are summarized in Exhibit 6.[46-54] In general, studies have found faster time to heal in the ultrasound group versus the placebo group, a reduction in the number of days to healing, and a reduction in the incidence of delayed unions. For example in a study of conservative management of mid-shaft tibial fractures, ultrasound treatment resulted in a 38 percent acceleration of fracture healing versus placebo.[48] The patients treated with ultrasound healed in 94 days versus 154 days in the placebo group ($p<0.002$).[48] There was an 83 percent reduction in the incidence of delayed unions when the ultrasound group was compared to the placebo group.[48] Subgroup analyses of this study found that use of the Exogen stimulator helped older patients heal as quickly as younger patients and smokers heal like nonsmokers.[48]

From a payer and employer perspective, an intervention such as ultrasound bone growth stimulation that enhances the likelihood of timely healing is an important clinical and economic contribution. In a study of healing radius fractures, the Exogen treated group had a reduced loss of fracture alignment; in other words, the bones healed faster and did not lose reduction.[46] In the placebo group, half of the patients failed the reduction.[46] When a reduction of a fracture fails, there is a risk of permanent deformity of the healed bone, which in this study would be a wrist deformity, which may affect function and ability to return to work.

A systematic review and meta-analysis of randomized controlled trials, to determine whether low-intensity pulsed ultrasonography affects the time to fracture healing, was conducted and published in 2002.[55] Pooled results from three studies, representing 158 fractures, that met strict inclusion criteria, showed that time to fracture healing was significantly shorter in the groups receiving low-intensity pulsed ultrasound therapy than in the control groups. The weighted average effect size was 6.41 (95 percent confidence interval 1.01–11.81), which converts to a mean difference in healing time of 64 days between the treatment and control groups.[55] The authors concluded that there is evidence from randomized trials that low-intensity pulsed ultrasound treatment may significantly reduce the time of fracture healing for fractures treated nonoperatively.[55]

There is some controversy regarding the benefits of ultrasound in patients with tibial fractures who have been treated with IM nailing. The meta-analysis discussed above concluded based on two studies, that there does not appear to be any additional benefit to ultrasound treatment following intramedullary nailing with prior reaming.[28] The two studies that evaluated ultrasound therapy following reamed IM nailing of tibial shaft fractures were limited in size, appear to report results from some of the same patients, and showed no difference in the mean time of healing between the treatment and control groups: 155 (SD=22) days versus 125 (SD=11) days ($p=0.76$) in one study, and 155 (SD=22) days versus 129 (SD=12) days ($p>0.05$) in the other.[51,56] Reaming of fractures is known to have an osteoblastic effect and may explain their negative results.[57] Additionally, these patients had relatively straightforward fractures and few risk factors or complications so their fractures would likely have healed with or without ultrasound intervention.[51,56]

An additional IM nailing tibia fracture study has been published since the Busse meta-analysis. Leung and colleagues evaluated ultrasound treatment of complex (communicated and segmented) tibial fractures resulting from high energy trauma.[47] This study compared ultrasound in patients treated with external fixation or reamed intramedullary nails and found a 42 percent acceleration in the healing of complex tibial fractures and a 40 percent faster time to full weight bearing.[47] The subjects in this study had much more complicated fractures than those in the Emani trials and had high risk for nonunion.[47,51,56] A difference in the length of ultrasound treatment (75 days versus 90 days) may also account for the difference in results.[47,51,56]

Nonunion Fractures

As illustrated in Exhibit 5, there are many different noninvasive treatment options for resolving a nonunion fracture. Both electrical and ultrasound bone stimulators are indicated for noninvasive treatment of nonunion fractures. Based on FDA approved labeling, low-intensity pulsed ultrasound provides a higher healing rate than electrical stimulation (Exhibit 5). The various bone stimulators have not been compared in head-to-head trials.

In a prospective series of 100 nonunion cases, 20 minutes of ultrasound treatment per day healed 83 percent of the atrophic and 100 percent of the hypertrophic fractures.[58] These patients had stable bone fragments, no infections, and were more than 90 days out from any surgery or treatment and more than 120 days out since their fracture. The healing time was 152 days. The hypertrophic nonunion fractures likely responded better to ultrasound because the patient's healing system was already working.

Another prospective series of 29 nonunion fractures examined the effects of ultrasound on the healing of fractures that were more than one year old and had been treated with a mean of 1.4 surgeries.[59] Eighty-six percent of the fractures healed with 20 minutes of ultrasound treatment daily. Interestingly, it appeared in this series that ultrasound normalized the effects of smoking. Seventy five percent of the smokers' fractures healed, despite their continued use of cigarette and tobacco usage.

Gebauer in 2005 published a case series on ultrasound in 67 patients with nonunion.[60] These were fractures that were at least eight months old, had been treated with surgery on an average of two times, and it had been more than four months since the last intervention. Eighty five percent of the fractures healed with an average healing time of 168 days. [60]

Safety of Low-intensity Pulsed Ultrasound

According to the FDA approved labeling, the safety and effectiveness of the use of this device have not been established in nonunions fractures of the vertebra and the skull, in fresh fractures for any locations other than the distal radius or tibial diaphysis, in pregnant or nursing women, or in individuals lacking skeletal maturity.[18] The device will not correct or alter displacement, angulation or other malalignment. Malalignment issues must be corrected with surgery before use of this device. With active, implantable devices, such as cardiac pacemakers, operation may be adversely affected by close exposure to the Exogen device. Interestingly, cell phones may cause interference and patients should avoid cell phone use during treatments. Ultrasound treatment at the frequency delivered by the Exogen device does not produce heat within the tissue or the bone, or heat metal.

> Patients who smoke or have diabetes are at a significant risk for nonunion fractures.

No device-related adverse reactions or medical complications related to the use of this device were reported during the clinical studies. Two patients in a post-market registry reported mild skin irritation caused by skin sensitivity to the conducting gel.[25] Both were resolved by a change to mineral oil or glycerin. Animal studies conducted to date do not suggest any long-term adverse effects from the use of this device.[18] Clinical studies in humans with long-term patient follow-up for up to 78 months do not suggest any long-term adverse side effects from the use of this device. However, possible longer-term adverse effects in humans are unknown.

Managed Care Perspective

In making coverage decisions, managed care payers must evaluate the appropriate use of bone stimulators within their plan. Two components to evaluating a technology are literature reviews for safety and efficacy and economic evaluation for potential costs or possible cost savings.

For safety and efficacy, many managed care companies perform their own technology assessments, contract with outside companies for this service, or utilize published evidence based reviews to determine, based on the available evidence, whether to cover a particular technology. An example group that publishes technology reviews is the Cochrane Group. They have a review of ultrasound bone stimulators in process but it has not been published yet. In 2005, the Agency for Healthcare Research and Quality (AHRQ) published a technology review of the role of bone growth stimulating devices and orthobiologics in healing nonunion fractures with a focus on the Medicare population.[8] According to this review, the place in nonunion therapy for bone growth stimulators is as an alternative to surgery.[8] Based on the published efficacy data, the most appropriate use of ultrasound for fresh fractures would be in patients with risk factors for nonunion.

The other aspect of evaluating coverage decisions is to assess potential cost savings. Four cost effectiveness evaluations of the use of low-intensity pulsed ultrasound have been conducted. Three were for treating fresh tibial fractures and one compared various bone stimulators for treating nonunion fractures. Busse and colleagues evaluated the costs from a Canadian government perspective of treating closed and open grade I (low energy) tibial fractures using a decision tree. The mean associated costs were $3,400 (U.S. dollars) for operative management by reamed IM nailing, $5,000 for operative

Exhibit 7: Managed Care Coverage Guidelines for Bone Growth Stimulators

To prevent and treat nonunions, the following would be covered indications:

- Ultrasound device for fresh fractures at high risk* for nonunion
- Ultrasound device for nonunion of all fractures except skull and vertebrae
- Electrical device for nonunion of skull and vertebrae or ultrasound failure

*High risk is defined by fracture location (fifth metatarsal, talus, tibia, scaphoid, or clavicle fracture) or patient comorbidities (diabetes, smoking, obesity, open fracture, high energy trauma, steroid use, or osteoporosis)

management by non-reamed IM nailing, $5,000 for casting, and $5,300 for casting with therapeutic ultrasound.[12] With respect to the financial burden to society, the mean associated costs were $12,500 for reamed IM nailing, $13,300 for casting with therapeutic ultrasound, $15,600 for operative management by non-reamed IM nailing, and $17,300 for casting alone.[12] They concluded that from an economic standpoint, reamed IM nailing was the treatment of choice for closed and open grade I tibial shaft fractures.[12] When the financial burden to society was also considered, they concluded that treatment with ultrasound and casting also is an economically sound intervention.[12]

Another economic analysis of tibia fractures was published by Heckman and Sarasohn-Kahn.[14] They developed economic models with total costs of treating a pool of 1,000 patients with tibial shaft fractures based on two treatment paths – operative and conservative (casting) – with and without adjunctive ultrasound. The costs accounted for included emergency room visits, surgery and recovery, ultrasound device, outpatient visits, therapy, workman's compensation for both primary and secondary procedures resulting from nonunions, and disability costs. Based on this analysis, a cost savings of over $15,000 per case would be realized by using ultrasound adjunctively with conservative treatment.[14] A similar savings of over $13,000 per case results from the use of ultrasound in the operative path.[14] Because ultrasound appears to normalize healing in smokers, these authors estimated that using ultrasound treatment in a smoker would result in a $20,000 to $30,000 savings.[14]

Taylor and colleagues conducted a cost-effectiveness evaluation of using ultrasound in patients with fresh fractures at risk for nonunion from a Medicare perspective.[13] They examined costs of ultrasound added to conservative treatment or surgical treatment (non reamed IM nailing) in patients who smoked or had diabetes. Their analysis found that adding ultrasound to casting reduced cost per patient by $744 and increased the number of fractures healed by 7.6 percent.[13] Adding ultrasound to surgery reduced cost per patient by $130 and increased the number of fractures healed by 6.4 percent.[13] Overall, they concluded that for a population at risk for nonunion whose probability of healing was 80 percent or less of the general population low-intensity pulsed ultrasound was cost effective.[13] Patients who have an 80 percent or less probability of healing are those who have significant risk factors for nonunion including diabetes, osteoporosis, smoking, steroid therapy and complicated fractures.

Based on published efficacy rates for treating nonunion fractures, a cost effectiveness analysis by Schultz and colleagues demonstrated that the Exogen bone healing system was the most cost-effective bone stimulator compared with other bone stimulators.[61] While prices for the stimulators are similar, the higher probability of treatment success with Exogen makes treatment failure and follow-up surgery less likely, cutting overall cost. Using a Monte Carlo simulation, the authors of this paper determined that Exogen would be the most cost effective bone treatment system for 85 percent of a hypothetical cohort of 10,000 patients compared to the other stimulators.[61]

If the data are available, a managed care organization can develop their own economic model comparing various interventions for either fresh or nonunion fractures. Based on the published economic models, it appears that a healthy person with a fresh fracture, who does not have a high risk fracture or other risk factors for nonunion, may not need an ultrasound bone stimulator unless lost wages and returning to full function as quickly as possible are important to that patient. Many employers would be interested in getting even their low risk employees with fractures back to work as quickly as possible. The most cost effective use of an ultrasound bone stimulator in fresh fractures is to use it in patients with high risk fractures and other risk factors for nonunion. The Exogen Bone Healing System appears to be cost effective and more efficacious compared to other stimulators for treating nonunion fractures.

Employer Perspective

Many employers are getting more sophisticated in trying to reduce absenteeism. Use of the Exogen device should get workers, who have had a fracture, back to work sooner. This will not only reduce lost wages for the worker but will reduce workman's compensation costs for the employer. In addition, by accelerating the healing rate of fresh fractures in workers at risk for nonunion, permanent disabilities from dysfunctionally healed bones should be reduced.

Expert Panel Recommendations

Coverage policies for bone growth stimulators vary widely across the country and even regionally within a given managed care plan. In order to provide some consistency, managed care coverage guidelines based on efficacy and cost effectiveness data were developed by a panel of medical directors. These are presented in Exhibit 7.

Conclusion

Compared with data on electrical stimulators, low-intensity pulsed ultrasound produces the highest heal rates for nonunions of all bone growth stimulators. Especially important for treating nonunion fractures are the efficacy data in tibial fractures, which account for 62 percent of all nonunions. The Exogen ultrasound device is the only bone stimulator approved for treating fresh fractures and the only device with efficacy data for this indication. There is little risk to the use of this type of ultrasound device. It is also very easy for patients to use, which should result in good compliance. Using this device appears to be cost effective and reaps additional benefits for patients, managed care plans, and employers.

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Comments from Ad Board Participants

"Clearly we know that there are some comorbidities and there are some locations that predispose themselves to nonunion."

"The convenience factor of 20 minutes per day, which leads to compliance, is so important. I can't imagine a patient not wanting this over something that was even three hours or eight hours."

"We think you have a very compelling story and compelling studies which are evidence-based as compared to your competitors."

"You've got a better product that's no more expensive."

"You have a clinical story that the competitors don't have."

"It has a unique approval status, which is for fresh fractures and for several bones that the competitor doesn't have."

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