Low-intensity ultrasound (Exogen™) for the treatment of fractures

AGENCE D'ÉVALUATION DES TECHNOLOGIES
ET DES MODES D'INTERVENTION EN SANTÉ

Québec

Low-intensity ultrasound (Exogen™) for the treatment of fractures

Technology brief prepared for AETMIS
by Reiner Banken

Original French version: January 2004
English translation: March 2004

Agence d'évaluation
des technologies
et des modes
d'intervention en santé
Québec

This report was translated from an official French publication of the Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS). Both the original report, entitled *Les ultrasons à faible intensité (Exogen™) pour le traitement des fractures*, and its English version are available in PDF format on AETMIS's Web site.

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How to cite this publication:

Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS). Low-intensity ultrasound (Exogen™) for the treatment of fractures. Technology brief prepared by Reiner Banken. (AETMIS 03-05). Montréal: AETMIS, 2004, x-15 p.

Legal deposit
Bibliothèque nationale du Québec, 2004
National Library of Canada, 2004
ISBN 2-550-41956-1 (original edition ISBN 2-550-41721-6)

MISSION

The mission of the Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS) is to contribute to improving the Québec health-care system and to participate in the implementation of the Québec government's scientific policy. To accomplish this, the Agency advises and supports the Minister of Health and Social Services as well as the decision-makers in the health-care system, in matters concerning the assessment of health services and technologies. The Agency makes recommendations based on scientific reports assessing the introduction, diffusion and use of health technologies, including technical aids for disabled persons, as well as the modes of providing and organizing services. The assessments take into account many factors, such as efficacy, safety and efficiency, as well as ethical, social, organizational and economic implications.

FOREWORD

LOW-INTENSITY ULTRASOUND (EXOGEN™) FOR THE TREATMENT OF FRACTURES

Low-intensity ultrasound (Exogen™) is a home-based treatment for certain fractures and fracture complications. The Société de l'assurance automobile du Québec (SAAQ) asked the Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS) to assess the efficacy and safety of this approach to fracture healing. This technology brief is an adaptation of an advice submitted to the SAAQ.

From the standpoint of safety, according to AETMIS's assessment, the available studies do not report any adverse effects associated with the use of low-intensity ultrasound. As regards efficacy, the report examines the use of the device for three different indications: the acceleration of fracture healing, the prevention of fracture nonunion, and treatment. For these three indications, the efficacy evidence is weak.

As for the acceleration of fracture healing and the prevention of fracture nonunion, the level of evidence is insufficient to recommend the use of low-intensity ultrasound. However, in the case of nonunion of tibial fractures, the prognosis is so grim that it seems reasonable to consider the use of low-intensity ultrasound after failed surgical intervention.

AETMIS therefore considers that low-intensity ultrasound might be an exceptional treatment option for a very limited number of patients. In submitting this report, AETMIS wishes to contribute to the advancement of an evidence-based medicine approach in orthopedics and to provide orthopedic surgeons and managers in Québec's health-care system the necessary information on this technology.

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ACKNOWLEDGMENTS

This report was prepared by **Reiner Banken**, M.D., M.Sc., consulting researcher, at the request of the Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS).

The Agency wishes to thank the external reviewers for their numerous comments, which helped improve the quality and contents of this report:

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SUMMARY

Low-intensity ultrasound (Exogen™) is a home-based treatment for certain fractures and fracture complications. The Société de l'assurance automobile du Québec (SAAQ) asked the Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS) to assess the efficacy and safety of this approach to fracture healing. This technology brief is an adaptation of an advice submitted to the SAAQ, which included information specific to this organization's decision-making context. This report is intended for a wider audience that includes, among others, professionals who treat patients with fracture complications.

Fracture healing depends on a cascade of complex events. If the healing process is slower than expected, one speaks of *delayed union*, or, if the healing process stops, of *nonunion*. Severe fractures, especially of long bones, such as the tibia, are particularly susceptible to bone union problems. The definition of *nonunion* often specifies absence of healing 6 to 12 months after the fracture. The arrest of healing for more than three months, as documented by serial radiographs including multiple views, is also used to define *nonunion*.

The treatment of fractures includes a growing number of various approaches and techniques, one of which is low-intensity ultrasound. This assessment comes at a time when the broadening of the range of therapeutic options for different fractures has not been accompanied by a comparative assessment of the different approaches. The assessments are therefore insufficient and often of relatively poor methodological quality. Also, for many fractures, the optimal treatment is the subject of clinical debate. Furthermore, despite the criteria often used to define nonunion, a fair proportion of these fractures will heal, even after a period of 12 months, if immobilization is maintained long enough.

Presently, Exogen, a technology from the Smith and Nephew Corporation, seems to be the only technology marketed worldwide that uses low-intensity ultrasound to influence the fracture healing process. In Canada, as in the United States, this technology has been approved for the acceleration of the healing of certain fresh fractures with cast immobilization and for the treatment of nonunion. The prevention of nonunion in certain higher-risk patient populations is also promoted as another indication.

Upon an exhaustive analysis of the scientific literature, it was found that the quality of the evidence varies for the three indications mentioned above:

- There is no evidence that low-intensity ultrasound can prevent nonunion in higher-risk patient populations.

- According to a meta-analysis of three randomized trials with a small total number of patients, ultrasound may be effective in accelerating the healing of fractures treated without surgical intervention. Because of the exclusion from this meta-analysis, with no justification given, of one study in which the patients had undergone surgical stabilization and the small total number of patients in the meta-analysis, the efficacy evidence for the acceleration of healing should be considered weak.

- The only studies that have examined the efficacy of Exogen in the treatment of nonunion are retrospective case series with a self-paired study design. This type of analysis seems questionable in cases of nonunion because of the natural course of this healing problem.

According to AETMIS's assessment, the available studies do not mention any adverse effects associated with this treatment modality. Given the efficacy and safety evidence, AETMIS considers that, with regard to the acceleration of healing and the prevention of nonunion, the level of evidence is insufficient to recommend the use of low-intensity ultrasound. However, in the case of nonunion of tibial fractures, the prognosis is so grim that it seems reasonable to consider the use of low-intensity ultrasound after failed surgical intervention and after the consolidation process, as measured by serial radiographs including multiple views, has ceased for several months. As for fracture sites other than the tibia, the uncertainties concerning the efficacy of Exogen in the treatment of nonunion should be assessed in light of the prognosis specific to these fractures and of the clinical context.

Based on the available data, AETMIS therefore considers that low-intensity ultrasound might be an exceptional treatment option for a very limited number of patients.

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TABLES

1 INTRODUCTION

This report briefly assesses the efficacy and safety of an approach to healing certain fractures and fracture complications using low-intensity ultrasound treatment (Exogen™). This technology brief is an adaptation of an advice submitted to the Société de l'assurance automobile du Québec (SAAQ) in the spring of 2003. While the advice contained information specific to the SAAQ's decision-making context, this brief is intended for a wider audience, including, among others, professionals who treat patients with fracture complications. The scientific literature was reviewed up to April 2003 for the advice and up to September 2003 for this technology brief.

2 DESCRIPTION OF THE TECHNOLOGY

The Exogen bone growth stimulator uses low-intensity ultrasound (LIUS), i.e., a spatial-averaged temporal-averaged intensity of 30 mW/cm^2, while the ultrasound used to treat soft-tissue injuries can achieve an intensity of up to 3,000 mW/cm^2 [Medical Services Advisory Committee, 2002, p. 3]. The energy level of this device is close to that of diagnostic ultrasound machines. The treatment is administered at home 20 minutes per day for several months for the purpose of accelerating the healing of certain fractures. The device is rented, or purchased and discarded after use. The total cost of treatment is approximately $3,000[1]. Clinically, the Smith & Nephew Corporation hold the worldwide monopoly on this technology.

The U.S. Food and Drug Administration (FDA) authorized the use of the device for the first time in 1994, for the following indications:

- The acceleration of the healing of fresh fractures of the distal radius with posterior displacement (Colles' fractures); and
- The acceleration of the healing of fresh closed or grade I open fractures of the tibia,

provided such fractures are immobilized with a cast after closed reduction, if appropriate. For the indication of accelerating the healing of certain fractures, Exogen is therefore used as an adjunct to conventional treatment. In 2000, the FDA added the indication of fracture nonunion to its authorization [Center for Devices and Radiological Health, 2000]. For this indication, Exogen is used either to treat patients after other modalities have failed to unite the fracture, or to avoid further surgery. The Canadian authorization includes the same indications as in that of the FDA[2].

1. According to a letter dated February 20, 2002 from Christina Woodside, chief executive officer of Smith & Nephew Canada, to Jacques Privé, vice-president of the SAAQ.

2. Personal e-mail communication with Dorothy Corbett, Health Canada, July 14, 2003.

3 MECHANISMS OF ACTION

The positive effect of ultrasound on the healing process has been researched for several decades. A number of mechanisms of action have been proposed to explain this effect [Hadjiargyrou et al., 1998, Table 1]. The micromovement theory is the one most widely accepted [Pilla, 2002]. It has been established that mechanical stresses, with no macroscopic movement, accelerate fracture healing. This micromovement appears to be the main mechanism of action of ultrasound [Medical Services Advisory Committee, 2002; Pilla, 2002; Sun et al., 2001; Warden et al., 2001a], although it is not known exactly how it works.

There seems to be no information on the link between the stimulation parameters (frequency, intensity, interval between applications) and the therapeutic effect. Research based on an animal model indicates that diagnostic ultrasound, too, has a therapeutic effect in that it increases the fracture healing rate [Heybeli et al., 2002].

4 EPIDEMIOLOGY AND PATHOPHYSIOLOGY OF FRACTURES

An estimated 5.6 million fractures occur in the United States annually, and the healing of 5 to 10% of them is reportedly delayed or impaired [Einhorn, 1995]. As for the situation in Québec and the rest of Canada, it seems that there are no published studies of this type. In 2001, the SAAQ received seven reimbursement requests. Certain fractures, such as those of the tibia and scaphoid, are especially susceptible to healing problems.

Fracture classification systems differentiate between closed fractures and open fractures. An open fracture is defined as one in which there is communication with a break in the integument, usually near the fracture site [Cole and McNally, 2002]. Open fractures are usually classified according to the Gustilo-Anderson system, which includes three levels of severity. Grade I is a fracture with a clean wound less than 1 cm in length, grade II a fracture with a wound more than 1 cm in length without extensive soft-tissue damage. Grade III, fractures caused by high-energy trauma, includes three subtypes (IIIa, IIIb and IIIc) [Cole and McNally, 2002].

Fractures of long bones, such as the tibia, are frequently associated with multiple trauma. Fractures resulting from traffic accidents are usually quite severe, i.e., grade II or III, and are prone to healing problems [Karladani et al., 2001].

Fracture healing depends on a cascade of complex events. The induction of osteogenic cells, inflammatory reaction, fibrocartilaginous callus formation, bony callus formation and remodeling occur in succession over a period of several months [Mandracchia et al., 2001]. If the healing process is slower than expected, one speaks of *delayed union*, or, if the healing process stops, of *nonunion.*

Certain factors, such as advanced age and smoking, slow the healing process, but we do not have any solid data regarding their effect on nonunion. Smoking slows the healing process in closed and grade I open tibial fractures but does not seem to increase the risk of nonunion [Schmitz et al., 1999]. As for more severe tibial fractures, smoking seems to increase the risk of nonunion [Adams et al., 2001]. Furthermore, smoking is a risk factor for tibial fractures, possibly because of its decalcifying effect [Kyro et al., 1993]. Some authors consider that diabetes is also a risk factor for complications [Loder, 1988], but the studies are contradictory in this regard [Herskind et al., 1992].

Given the wide range of fracture types and severity, it is very difficult to establish general criteria for delayed union or nonunion. Examples of definitions of nonunion are provided in Table 1.

A fair proportion of nonunions (as defined in Table 1) will heal if immobilization is maintained long enough. This is because bone regeneration that occurs endosteally can slowly lead to healing, even if the usual route of regeneration with bony callus formation fails [Marsh, 1998].

For the purposes of a reimbursement decision regarding the treatment of nonunion by electromagnetic means, Medicare, based on expert consultation, established a criterion of healing having ceased for at least three months, based specifically on the results of serial radiographs including multiple views [Centers for Medicare & Medicaid Services, 1999].

TABLE 1

Examples of definitions of nonunion

TYPE OF FRACTURE	DEFINITION	REFERENCE
All fractures	Failure of the fracture to unite after more than eight months of its occurrence.	Danis, 1949, cited in Randolph and Vogler, 1985
All fractures	Failure of the fracture to unite after more than six months of its occurrence.	Crenshaw, 1971, cited in Randolph and Vogler, 1985
All fractures	Cessation of healing for more than three months, as documented by serial radiographs including multiple views.	Centers for Medicare & Medicaid Services, 1999
Scaphoid	Failure of the fracture to unite after more than 240 days of its occurrence.	Mayr et al., 2002
Tibial	Failure of the fracture to unite after more than two months to more than 12 months, according to practitioners' opinions.	Opinions of orthopedists expressed in an international survey [Bhandari et al., 2002b]

5 TREATMENT OF FRACTURES AND EVIDENCE-BASED MEDICINE

The aim of treating fractures is to create an environment favourable to healing [Marsh and Li, 1999]. Understanding these processes has led to substantial developments in the techniques and treatment outcomes. During the American Civil War, an open tibial fracture almost always resulted in amputation. For the past few decades, such fractures have required amputation only in very serious cases [Rosenberg and Patterson, 1998]. For type IIIc open tibial fractures, the overall amputation rate varies from 42 to 88%, depending on the study [Rosenberg and Patterson, 1998, Table 1]. The author of the study (Giorgiadis, 1993) with the highest amputation rate in Rosenberg and Patterson's table (88%, or 15/17) reported, nine years later, an amputation rate of 7% (1/14) [Georgiadis, 2002].

The treatment of fractures includes a growing number of various approaches and techniques. Therapies based on the enhancement of natural biological healing phenomena by electromagnetic means, ultrasound or osteogenic proteins are part of these technological developments [Einhorn, 1996; Niyibizi and Kim, 2000].

The broadening of the range of therapeutic options for the different fractures has, however, not been accompanied by a comparative assessment of these different approaches. The assessments are therefore insufficient and often of relatively poor methodological quality [Bhandari et al., 2002a; Bhandari et al., 2001]. For several fractures, the optimal treatment is the subject of clinical debate. In one reference textbook of orthopedics [Rockwood et al., 2001], each description of a clinical problem and its treatment ends with a section entitled "Author's preferred method of treatment". This subjective conclusion to the discussions of therapeutic approaches can probably be explained by the relative lack of an evidence-based approach in orthopedics and by the fact that it is insufficiently used to support clinical practice.

Assessing the efficacy of Exogen falls within this context, where there is little standardization of the practice for a given clinical problem. For example, how should one assess the value of a new technology like Exogen for the treatment of tibial fractures when there is no consensus among orthopedists as to the approaches to be preferred for treating such fractures? There is evidence to guide the treatment choices for certain types of tibial fractures, but practitioners do not always take it into consideration [Bhandari et al., 2001; Bhandari et al., 2002]. As for the treatment of other types of tibial fractures, there is still not enough scientific literature to guide practitioners in their choices [Littenberg et al., 1998].

The lack of standards in measuring treatment outcomes is a major problem when assessing the different therapeutic approaches to a given clinical problem. For instance, an audit of treatment outcomes for closed tibial fractures at a Scottish hospital concludes that there is no validated grading scale. Based on two grading scales containing different criteria, the percentage of treated patients who had a suboptimal outcome was either 4% or 42% [Bridgman and Baird, 1993]. The radiological assessment of healing, which should be more objective, also reflects this lack of standards. Thus, one study of interobserver and intraobserver agreement in the radiological assessment of tibial fracture healing following intermedullary nailing concludes that with a kappa coefficient of 0.82, cortical continuity in multiple views is the best criterion, but that there is no validated assessment scale [Whelan et al., 2002].

6 EFFICACY OF EXOGEN

The efficacy of a given technology or procedure depends on its ability to yield the desired benefit for a given health problem in defined conditions in patients in a specific population. One must therefore define the benefit anticipated with the use of Exogen, its ability to yield this benefit, the health problem of interest, the type of patients targeted and the conditions of utilization for this treatment modality. In the case of fractures, Exogen can be used for three different indications:

- The acceleration of healing, including delayed union;
- The prevention of nonunion; and
- The treatment of nonunion.

We shall now examine the efficacy of Exogen for each of these indications.

6.1 ACCELERATION OF HEALING

As mentioned earlier, in 1994, the FDA authorized the use of Exogen in the United States as an adjunct to the conventional treatment of fresh fractures of the distal radius with posterior displacement (Colles' fractures) and of fresh closed or Gustilo-Anderson grade I open fractures of the tibia (see Section 4).

In 1996 and in 1998, Medicare turned down the manufacturer's requests to cover the cost of using Exogen to accelerate fracture healing. The reasons given in the 1996 refusal were the weak evidence from efficacy studies and the fact that the population insured by Medicare did not fit the profile of the study populations in question. Medicare basically ensures people aged 65 and older, who often have co-morbidities. However, the efficacy studies submitted by the company in support of its request excluded patients receiving anticoagulants, anti-inflammatory medications or calcium channel blockers. Patients with vascular insufficiency or a history of thrombophlebitis, nutritional deficiency or alcoholism were excluded from the treatment efficacy studies as well. As for the 1998 decision, it was based on the lack of studies:

- examining the functional benefits;
- of the efficacy of low-intensity ultrasound therapy in the elderly; and
- of the prevention of delayed union and nonunion [Centers for Medicare & Medicaid Services, 2000].

The Australian technology assessment agency, the Medical Services Advisory Committee, identified four randomized studies on the efficacy of Exogen in accelerating fracture healing [Emami et al., 1999; Heckman et al., 1994; Kristiansen et al., 1997; Mayr et al., 2000b]. Details of these studies are provided in the appendix. Two of these studies, which were considered to be of excellent quality, assessed the efficacy of Exogen in accelerating the healing of closed or grade I open tibial fractures. The study that compared the efficacy of Exogen in combination with cast immobilization concludes that this treatment modality is effective [Heckman et al., 1994]. The other study, which compared the efficacy of Exogen in combination with intramedullary nailing, concludes that this treatment is not effective [Emami et al., 1999]. In light of these contradictory findings, the Australian assessment agency recommends not to cover the cost of using Exogen for the indication of acceleration of fracture healing [Medical Services Advisory Committee, 2002].

The only meta-analysis that has examined the efficacy of ultrasound in accelerating the healing process [Busse et al., 2002] identified the same four randomized studies as the Australian agency did [Medical Services Advisory Committee, 2002]. However, it did not include the studies that compared the efficacy of Exogen in combination with cast immobilization [Heckman et al., 1994; Kristiansen et al., 1997; Mayr et al., 2000b], thereby excluding the study that obtained negative results [Emami et al., 1999]. The authors do not justify the criterion for excluding studies involving surgical stabilization.

According to this meta-analysis, Exogen is effective in accelerating the healing process. Given the various weaknesses of the primary studies and of the meta-analysis, the authors limit themselves to concluding that ultrasound *may be* effective (rather than state that it *is* effective) in this indication. The Bandolier review, an electronic publication in the field of evidence-based medicine, congratulates the authors of this meta-analysis for their prudence when interpreting the data. The review also points out that the studies included in the meta-analysis involved small populations and that unpublished studies with negative results could easily invalidate the conclusions:

> The authors are justifiably cautious in their conclusions. They say that pulsed ultrasound **may** reduce time to fracture healing for fractures treated nonoperatively. They imply that we should beware because of the small amount of data. And the trials are good, with high quality scores, so this isn't like some reviews with small amounts of poor information that ladle on heaps of weasel word sauce.
>
> What we frequently lack in systematic reviews is some idea of **how much** information we need to be sure of the result. If there is little information, as here, then unpublished negative trials could be very important. Someone will be selling this to you soon on the basis that it is "evidence-based"! [Pulsed ultrasound for fracture healing, 2002]

Despite the fact that the studies which have compared the use of Exogen in combination with cast immobilization are of good methodological quality and despite the result of the meta-analysis of these studies, we do note some significant shortcomings in terms of the strength of this evidence because of the small population covered by the meta-analysis and the exclusion of the study involving surgical stabilization, which the authors do not justify.

In animal models, the presence of metal implants does not affect the efficacy of ultrasound [Center for Devices and Radiological Health, 2000]. It would therefore be surprising if the results of the study in which the subjects had been stabilized surgically were negative because of the metal implants. The differences in the results could, perhaps, be explained by the type of patients included in the two studies. If one wishes to study the adjunctive effect of ultrasound in the treatment of cast-immobilized fractures, the fractures have to be stable, since unstable fractures have to be treated by surgical stabilization. The study patients who used ultrasound as therapeutic adjunct in combination with surgical stabilization probably had unstable fractures. Consequently, there was a difference in the type of fractures included in the two studies which arrive at contradictory conclusions.

In addition, in the study involving cast immobilization, 64 of the 67 subjects presented with a closed fracture [Heckman et al., 1994]. One should therefore question the efficacy of Exogen in accelerating the healing of open fractures in general, even grade I open fractures.

None of the three studies measured the effect of the treatment on the functioning of the affected limb. One of the studies used healed fracture assessed radiographically and clinically as an outcome measure [Heckman et al., 1994]. The other two used healed fracture assessed radiographically only [Kristiansen et al., 1997; Mayr et al., 2000b].

6.2 PREVENTION OF NONUNION

It seems that no study has attempted to examine the efficacy of Exogen in preventing nonunion. Based on studies on the acceleration of healing time, some authors state that this treatment modality may prevent nonunion. For instance, the authors of the meta-analysis conclude that ultrasound may not only be effective in accelerating healing, but that it may also reduce the disability associated with delayed union and nonunion [Busse et al., 2002]. In a letter to the editor, a comment on this article states that the assertion concerning nonunion is not supported by scientific evidence [McAlinden, 2002].

Indeed, a treatment that accelerates the healing process will diminish delayed union, which, by definition, is slower-than-expected healing. This does, in no way, mean that it will automatically have an effect on nonunion, which is an arrest of the healing process. To date, there is therefore no evidence that Exogen is effective in preventing nonunion.

At least one U.S. insurance company has nonetheless agreed to cover the cost of using Exogen to treat fractures in smoking or diabetic patients, based on the principle that they are more susceptible to delayed union and nonunion [The Regence Group, 2002].

6.3 TREATMENT OF NONUNION

The only studies that have examined the efficacy of Exogen in treating nonunion are retrospective case series [Frankel and Mizuho, 2002; Mayr et al., 2000a; Mayr et al., 2002; Nolte et al., 2001][4]. The Australian assessment agency considers the evidence from such studies to be too weak to justify covering the cost of using this technology [Medical Services Advisory Committee, 2002]. However, the assessment performed for Medicare in the United States considers that the method used in retrospective case series may be acceptable for this indication, even if randomized studies would have been preferable.

These case series had a self-paired design. They were based on the postulate that the odds of spontaneous healing of nonunion are approximately zero. According to an intent-to-treat analysis, the healing rate is 64 to 82% and therefore sufficient for this treatment modality to be considered effective[5]. The U.S. assessment accepts this analysis, and Medicare covers the cost of using Exogen to treat nonunion, defined as the healing process having ceased for at least three months, based on the results of serial radiographs including multiple views [Centers for Medicare & Medicaid Services, 1999]. In addition, at least one surgical intervention must have been performed to treat the nonunion.

This latter criterion is based on the fact that 80% of the patients included in the studies, which had not yet been published at the time of the Medicare assessment, had undergone at least one surgical intervention before starting treatment with Exogen. Since that assessment, one of these studies has been published [Nolte et al., 2001]. In that study, 21 of the 29 patients (72%) had undergone one surgical intervention to treat the nonunion of fractures of different bones prior to receiving ultrasound treatment.

Since the Medicare assessment, another study has been published. It involved 36 patients with scaphoid fracture nonunion and achieved a success rate of 86.1%. The definition of nonunion used in this study was failure of the fracture to unite after more than 240 days of its occurrence [Mayr et al., 2002]. It is not totally clear from the article how many patients had undergone surgical intervention before starting ultrasound treatment.

The discrepancy between the Australian assessment agency's verdict and that of the U.S. assessment agency concerning the treatment of nonunion illustrates how important the frame of reference is when determining the strength of evidence. As for accepting a case series design where each patient is his/her own control (self-pairing), we question the assertion that the chances of late healing of nonunion are approximately 0%. The interim results of a randomized study of the efficacy of electromagnetic fields in treating tibial fracture nonunion showed similar efficacy in the group treated with electromagnetic fields (5/9) and in the control group, which was treated by prolonged immobilization (5/7) over a 24-week period. These results are surprising, given that the inclusion criteria in this study required that at least one year had elapsed since the fracture's occurrence and that the healing process had ceased for at least three months [Barker et al., 1984]. Unfortunately, we were unable to find other publications concerning this study. These results nonetheless seem to indicate that nonsurgical treatment of nonunion can yield high healing rates, even if the healing process has stopped for three months. These results can probably be explained by bone regeneration via the endosteal route, which can slowly lead to healing, even if the usual route of bone regeneration with bony callus formation fails [Marsh, 1998]. Furthermore, the fact that there are no radiological assessment scales and the variability in interobserver and intraobserver agreement in this assessment [Whelan et al., 2002] can lead to errors in judgment regarding the arrest of the healing process.

4. The Australian agency's assessment and that performed for Medicare also refer to a certain number of studies that were submitted by the manufacturer as unpublished studies.
5. The authors of this analysis conservatively chose a 5% rather than a 0% healing rate [Centers for Medicare & Medicaid Services, 2000].

The study of the treatment of scaphoid fracture nonunion used, as a criterion for nonunion, failure of the fracture to unite after more than 240 days of its occurrence [Mayr et al., 2002]. From this article, one cannot conclude that Exogen is effective according to Medicare's criterion, i.e., healing having stopped for at least three months, based on the results of serial radiographs including multiple views. The other study used the criterion of healing having ceased for at least three months in assessing the efficacy of Exogen (in 29 patients) in the treatment of fractures of different types and at different sites. However, the authors do not explain the method of radiological follow-up [Nolte et al., 2001].

In some European countries, very widespread use is made of extracorporeal shock waves to treat nonunion. A recent assessment indicates that the efficacy evidence based on case series disappears when the clinical improvement is compared with the natural course of this healing problem [Biedermann et al., 2003].

The strength of the efficacy evidence for Exogen in the treatment of nonunion is therefore greatly weakened by the fact that there are no randomized studies and by indications that the method of analysis based on self-pairing used in case series is questionable because of the natural course of this healing problem.

6.4 OTHER INDICATIONS

The potential effect of bone growth stimulation by ultrasound could prove useful in anchoring certain types of prostheses and in treating osteoporosis. One animal study indicates that Exogen enhances bone growth into porous metal implants [Tanzer et al., 2001]. It seems that this use has not been investigated in human studies. Ultrasound does not seem to be effective in influencing the osteoporotic process, probably because the energy level of ultrasound is insufficient to effectively penetrate the cortex of intact bone [Warden et al., 2001b].

7 SAFETY OF EXOGEN

The therapeutic use of ultrasound for soft tissues produces thermal effects. When applied at the maximum power level (mean intensity of 3,000 mW/cm^2), it can damage bone tissue, especially in growing bones [Nussbaum, 1998]. The Exogen bone growth stimulator uses low-intensity ultrasound whose energy level is similar to that of diagnostic ultrasound (mean intensity of 30 mW/cm^2). At this energy level, ultrasound does not have any apparent thermal or harmful effects [Nussbaum, 1998]. The studies submitted in support of expanding the FDA-recognized indications to include nonunion also show that the presence of a metal implant does not cause any thermal effects and that ultrasound does not interact with such implants [Center for Devices and Radiological Health, 2000].

The meta-analysis concerning the efficacy of Exogen in accelerating fracture healing mentions studies showing that ultrasound devices used to treat soft tissues are often insufficiently calibrated. The authors state that Exogen-type devices do not seem to be prone to calibration problems [Busse et al., 2002].

In conclusion, the available studies do not report any harmful effects associated with the use of Exogen technology.

8 CONCLUSIONS

Ultrasound plays a marginal role in the treatment of fracture healing. For instance, a recent orthopedics textbook makes no mention of this treatment modality [Bulstrode, 2002]. Another textbook recommends ultrasound for tibial fracture nonunion when surgical intervention is contraindicated. It is, nonetheless, an exceptional treatment option [Goulet and Hak, 2001].

The efficacy evidence that we analyzed was found to be weak (Table 2).

TABLE 2

Efficacy evidence

INDICATION	EFFICACY EVIDENCE
Acceleration of healing	Effective for fractures treated without surgical intervention, according to a meta-analysis of three randomized studies with a small total number of patients, which considerably weakens the evidence.
Prevention of nonunion	No evidence of clinical efficacy.
Treatment of nonunion	Effective, according to case series. No randomized studies.
Other indications	No evidence of clinical efficacy.

The efficacy evidence for Exogen as regards the acceleration of healing is weakened by the small number of patients included in the studies and the meta-analysis and by the fact that the study of fractures treated by surgical stabilization was excluded from the meta-analysis. As explained in Section 6.1, in the case of tibial fractures, ultrasound only seems effective in accelerating the healing of closed fractures that are sufficiently stable to be cast-immobilized. As for the treatment of nonunion, the efficacy evidence is greatly weakened by the fact that there are no randomized studies and by indications that the method of analysis based on self-pairing used in case series is questionable because of the natural course of this healing problem.

Given this weak evidence, we cannot recommend the use of ultrasound to treat fractures. Nonunion is, however, one exception. As for tibial fracture nonunion, the prognosis is so grim that it seems reasonable to consider the use of low-intensity ultrasound after failure of at least one surgical intervention and after the healing process has ceased for several months, as measured by serial radiographs including multiple views. For fracture sites other than the tibia, the uncertainties concerning the efficacy of Exogen for the treatment of nonunion should be evaluated on the basis of the prognosis specific to these fractures and in light of the clinical context.

Based on the available data, AETMIS therefore considers that low-intensity ultrasound might be an exceptional treatment option for a very limited number of patients.

APPENDIX

Randomized studies of the acceleration of healing

STUDY	FRACTURE SITE	TREATMENT	NUMBER OF FRACTURES		TYPE OF FRACTURE		EFFECT
			Experimental group	**Control group**	**Closed**	**Open**	
Mayr et al., 2000b	Scaphoid	Cast immobilization	15	15	30	0	Average time to healing, as documented radiographically, of 43 vs. 62 days. Difference statistically significant.
Emami et al., 1999	Tibial shaft	Intramedullary nailing	15	17	28	4 (Grade I)	Average time to healing of 155 vs. 125 days. Difference not significant.
Kristiansen et al., 1997	Distal radius	Cast immobilization	30	31	61	0	Average time to healing, as documented radiographically, of 64 vs. 87 days.* Difference statistically significant.
Heckman et al., 1994	Tibial shaft	Cast immobilization	33	34	64	3 (Grade I)	Average time to healing, as documented radiographically, of 102 vs. 190 days.* Difference statistically significant.

* Based on the analysis of this study by the Medical Services Advisory Committee, which used, as a criterion, the bridging of three of four cortices, according to the independent radiologist rather than according to the principal investigator [Medical Services Advisory Committee, 2002].

REFERENCES

Pulsed ultrasound for fracture healing, 2002. Available: http://www.jr2.ox.ac.uk/bandolier/band99/b99-5.html. (January 12, 2004.)

Adams CI, Keating JF, Court-Brown CM. Cigarette smoking and open tibial fractures. Injury 2001;32(1):61-5.

Barker AT, Dixon RA, Sharrard WJ, Sutcliffe ML. Pulsed magnetic field therapy for tibial non-union. Interim results of a double-blind trial. Lancet 1984;1(8384):994-6.

Bhandari M, Guyatt GH, Montori V, Devereaux PJ, Swiontkowski MF. User's guide to the orthopaedic literature: how to use a systematic literature review. J Bone Joint Surg Am 2002a;84-A(9):1672-82.

Bhandari M, Guyatt GH, Swiontkowski MF, Tornetta P 3rd, Sprague S, Schemitsch EH. A lack of consensus in the assessment of fracture healing among orthopaedic surgeons. J Orthop Trauma 2002b;16(8):562-6.

Bhandari M, Guyatt GH, Swiontkowski MF, et al. Surgeons' preferences for the operative treatment of fractures of the tibial shaft. An international survey. J Bone Joint Surg Am 2001;83-A(11):1746-52.

Bhandari M, Guyatt GH, Tornetta P 3rd, et al. Current practice in the intramedullary nailing of tibial shaft fractures: an international survey. J Trauma 2002;53(4):725-32.

Bhandari M, Morrow F, Kulkarni AV, Tornetta P 3rd. Meta-analyses in orthopaedic surgery. A systematic review of their methodologies. J Bone Joint Surg Am 2001;83-A(1):15-24.

Biedermann R, Martin A, Handle G, Auckenthaler T, Bach C, Krismer M. Extracorporeal shock waves in the treatment of nonunions. J Trauma 2003;54(5):936-42.

Bridgman SA, Baird K. Audit of closed tibial fractures: what is a satisfactory outcome? Injury 1993; 24(2):85-9.

Bulstrode CJ. Oxford Textbook of Orthopedics and Trauma. Oxford: Oxford University Press; 2002.

Busse JW, Bhandari M, Kulkarni AV, Tunks E. The effect of low-intensity pulsed ultrasound therapy on time to fracture healing: a meta-analysis. CMAJ 2002;166(4):437-41. Available: http://www.pubmedcentral.gov/articlerender.fcgi?tool=pubmed&pubmedid=11873920. (January 12, 2004.)

Center for Devices and Radiological Health. P900009-Exogen 2000® Summary of Safety and Effectiveness. Rockville, Maryland: Food and Drug Administration, 2000. Available: http://www.fda.gov/cdrh/pdf/p900009s006.html. (January 12, 2004.)

Centers for Medicare & Medicaid Services. Electrical Stimulation for Fracture Healing (#CAG-00043). Baltimore: Centers for Medicare & Medicaid Services, 1999. Medicare Coverage Policy. Available: http://cms.hhs.gov/ncdr/searchdisplay.asp?id=24. (January 12, 2004.)

Centers for Medicare & Medicaid Services. Ultrasound Stimulation for Nonunion Fracture Healing (#CAG-00022N). Baltimore: Centers for Medicare & Medicaid Services, 2000. Medicare Coverage Policy. Available: http://www.cms.hhs.gov/ncdr/memoasp?id=76. (January 12, 2004.)

Cole AS, McNally MA. The management of open fractures. In: Bulstrode CJ. Oxford Textbook of Orthopedics and Trauma. Oxford: Oxford University Press; 2002: 1636-51.

Crenshaw AH. Campbell's Operative Orthopaedics. 5th ed. St. Louis; Mosby, 1971.

Danis R. Théorie et pratique de l'ostéosynthèse. Paris: Masson; 1949.

Einhorn TA. Enhancement of fracture-healing. J Bone Joint Surg Am 1995;77(6):940-56.

Einhorn TA. Enhancement of fracture healing. Instr Course Lect 1996;45:401-16.

Emami A, Petren-Mallmin M, Larsson S. No effect of low-intensity ultrasound on healing time of intramedullary fixed tibial fractures. J Orthop Trauma 1999;13(4):252-7.

Frankel VH, Mizuho K. Management of non-union with pulsed low-intensity ultrasound therapy—international results. Surg Technol Int 2002;10:195-200.

Georgiadis GM. Limb salvage versus amputation. In: Bulstrode CJ. Oxford Textbook of Orthopedics and Trauma. Oxford: Oxford University Press; 2002: 1681-90.

Goulet JA, Hak DJ. Tibial malunion and nonunion. In: Chapman MW, Campbell WC. Chapman's orthopaedic surgery. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001.

Hadjiargyrou M, McLeod K, Ryaby JP, Rubin C. Enhancement of fracture healing by low intensity ultrasound. Clin Orthop 1998(355 Suppl):S216-29.

Heckman JD, Ryaby JP, McCabe J, Frey JJ, Kilcoyne RF. Acceleration of tibial fracture-healing by non-invasive, low-intensity pulsed ultrasound. J Bone Joint Surg Am 1994;76(1):26-34.

Herskind AM, Christensen K, Norgaard-Andersen K, Andersen JF. Diabetes mellitus and healing of closed fractures. Diabete Metab 1992;18(1):63-4.

Heybeli N, Yesildag A, Oyar O, Gulsoy UK, Tekinsoy MA, Mumcu EF. Diagnostic ultrasound treatment increases the bone fracture-healing rate in an internally fixed rat femoral osteotomy model. J Ultrasound Med 2002;21(12):1357-63.

Karladani AH, Granhed H, Karrholm J, Styf J. The influence of fracture etiology and type on fracture healing: a review of 104 consecutive tibial shaft fractures. Arch Orthop Trauma Surg 2001; 121(6):325-8.

Kristiansen TK, Ryaby JP, McCabe J, Frey JJ, Roe LR. Accelerated healing of distal radial fractures with the use of specific, low-intensity ultrasound. A multicenter, prospective, randomized, double-blind, placebo-controlled study. J Bone Joint Surg Am 1997;79(7):961-73.

Kyro A, Usenius JP, Aarnio M, Kunnamo I, Avikainen V. Are smokers a risk group for delayed healing of tibial shaft fractures? Ann Chir Gynaecol 1993;82(4):254-62.

Littenberg B, Weinstein LP, McCarren M, et al. Closed fractures of the tibial shaft. A meta-analysis of three methods of treatment. J Bone Joint Surg Am 1998;80(2):174-83.

Loder RT. The influence of diabetes mellitus on the healing of closed fractures. Clin Orthop 1988;232: 210-6.

Mandracchia VJ, Nelson SC, Barp EA. Current concepts of bone healing. Clin Podiatr Med Surg 2001; 18(1):55-77.

Marsh D. Concepts of fracture union, delayed union, and nonunion. Clin Orthop 1998(355 Suppl):S22-30.

Marsh DR, Li G. The biology of fracture healing: optimising outcome. Br Med Bull 1999;55(4):856-69.

Mayr E, Frankel V, Ruter A. Ultrasound—an alternative healing method for nonunions? Arch Orthop Trauma Surg 2000a;120(1-2):1-8.

Mayr E, Mockl C, Lenich A, Ecker M, Ruter A. Ist niedrig-intensiver Ultraschall bei der Behandlung von Frakturheilungsstörungen wirksam? Unfallchirurg 2002;105(2):108-15.

Mayr E, Rudzki MM, Rudzki M, Borchardt B, Hausser H, Ruter A. Beschleunigt niedrig intensiver, gepulster Ultraschall die Heilung von Skaphoidfrakturen? Handchir Mikrochir Plast Chir 2000b;32(2): 115-22.

McAlinden MM. Fracture healing using low-intensity pulsed ultrasound. CMAJ 2002;167(2):128-a. Available: http://www.cmaj.ca/cgi/content/full/167/2/128-a. (January 12, 2004.)

Medical Services Advisory Committee. Low intensity ultrasound treatment for acceleration of bone fracture healing—Exogen™ bone growth stimulator. Canberra, Australia: Commonwealth of Australia, 2002. Available: http://www.msac.gov.au/pdfs/msac1030.pdf. (January 12, 2004.)

Niyibizi C, Kim M. Novel approaches to fracture healing. Expert Opin Investig Drugs 2000;9(7):1573-80.

Nolte PA, van der Krans A, Patka P, Janssen IM, Ryaby JP, Albers GH. Low-intensity pulsed ultrasound in the treatment of nonunions. J Trauma 2001;51(4):693-702; discussion 702-3.

Nussbaum E. The influence of ultrasound on healing tissues. J Hand Ther 1998;11(2):140-7.

Pilla AA. Low-intensity electromagnetic and mechanical modulation of bone growth and repair: are they equivalent? J Orthop Sci 2002;7(3):420-8.

Randolph TJ, Vogler H. Nonunions and delayed unions. J Foot Surg 1985;24(1):62-7.

Regence Group. Ultrasound Accelerated Fracture Healing (March 5, 2002). Available: http://www.regence.com/trgmedpol/dme/dme40.html. (January 12, 2004.)

Rockwood CA, Green DP, Bucholz RW, Heckman JD. Rockwood and Green's fractures in adults. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2001.

Rosenberg GA, Patterson BM. Limb salvage versus amputation for severe open fractures of the tibia. Orthopedics 1998;21(3):343-9; quiz 350-1.

Schmitz MA, Finnegan M, Natarajan R, Champine J. Effect of smoking on tibial shaft fracture healing. Clin Orthop 1999;(365):184-200.

Sun JS, Hong RC, Chang WH, Chen LT, Lin FH, Liu HC. In vitro effects of low-intensity ultrasound stimulation on the bone cells. J Biomed Mater Res 2001;57(3):449-56.

Tanzer M, Kantor S, Bobyn JD. Enhancement of bone growth into porous intramedullary implants using non-invasive low intensity ultrasound. J Orthop Res 2001;19(2):195-9.

Warden SJ, Bennell KL, Forwood MR, McMeeken JM, Wark JD. Skeletal effects of low-intensity pulsed ultrasound on the ovariectomized rodent. Ultrasound Med Biol 2001a;27(7):989-98.

Warden SJ, Bennell KL, Matthews B, Brown DJ, McMeeken JM, Wark JD. Efficacy of low-intensity pulsed ultrasound in the prevention of osteoporosis following spinal cord injury. Bone 2001b; 29(5):431-6.

Whelan DB, Bhandari M, McKee MD, et al. Interobserver and intraobserver variation in the assessment of the healing of tibial fractures after intramedullary fixation. J Bone Joint Surg Br 2002;84(1):15-8.

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