# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## INTERVENTIONAL PROCEDURES PROGRAMME

## Interventional procedure overview of low-intensity pulsed ultrasound to promote healing of delayed-union and non-union fractures

Broken bones are common and can take many months to heal. This procedure involves a short daily treatment using an ultrasound probe that is placed on the skin at the site of the fracture. The aim is to speed up fracture healing by stimulating bone cells to grow and repair.

## Contents



## Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

### *Date prepared*

This overview was prepared in November 2017.

### *Procedure name*

- low-intensity pulsed ultrasound to promote healing of delayed-union and non-union fractures

### *Specialist societies*

- British Orthopaedic Association
- British Limb Reconstruction Society
- British Trauma Society.

## Description of the procedure

### *Indications and current treatment*

Fractures are a common result of trauma, and are usually described as either closed (skin over the fracture site is intact) or open (involves an open wound). They may vary in complexity from a single break (transverse or oblique) to comminuted, in which the bone has broken into several pieces.

Fractures usually heal within a few weeks after treatment by closed or open reduction and immobilisation using a cast or internal fixation. Sometimes healing may be delayed or not occur at all (non-union). There is no agreed precise definition of a fracture non-union but, typically, it is considered to be when there is failure of bony union 6 to 9 months after the fracture. Risk factors for non-union of fractures include: systemic medical conditions (for example, diabetes, malnutrition, osteoporosis); smoking; use of non-steroidal anti-inflammatory drugs; local factors such as infection; vascular problems; magnitude of injury (for example, fracture location and gap, traumatic fractures); advanced age; and other iatrogenic factors. Treatment of non-union may need complex and prolonged management with implications for the patient's quality of life and functional capacity.

### *What the procedure involves*

The aim of low-intensity pulsed ultrasound (LIPUS) is to stimulate bone healing by delivering micro-mechanical stress to the bone. This procedure is used to treat fractures that are slower to heal than expected (delayed healing) and fractures that have failed to unite (non-union). There is no agreed definition of fracture non-union but typically it is considered to be failure of bony union 6 to 9 months after the fracture.

An ultrasound probe is positioned on the skin over the fracture and patients self-administer LIPUS daily, usually for 20 minutes. If a patient's limb is immobilised in a cast, a hole is cut into the cast for the ultrasound probe. The probe delivers acoustic radiation and coupling gel is used on the skin to aid conduction of the ultrasound signal. An operating frequency of 1.5 MHz, pulse width of 200 microseconds, repetition rate of 1 kHz, and a temporal average power of 30 milliwatts per $cm^2$ is typically used. The exact treatment protocol and duration of treatment may vary.

Progress towards fracture healing is usually assessed radiographically. Treatment duration ranges from a few weeks to several months.

## Efficacy summary

## Fracture non-unions

In a meta-analysis of 13 studies (1,441 non-unions), overall pooled estimate of effect size for heal rate was 82% (95% confidence interval [CI] 77 to 87) for any anatomical site and fracture age of at least 3 months. Significant statistical heterogeneity was detected across primary studies (Q=41.2 [df=12], p<0.001, $Tau^2$=0.006, $I^2$=71). When non-union was defined as fracture age of at least 8 months duration, the pooled estimate of effect size was 84% (95% CI 77 to 91.6; significant statistical heterogeneity : Q=21 (df=8), p<0.001, $Tau^2$=0.007, $I^2$=62)[4]. Factors that affected the results of treatment included type of non-union and prior without-surgery interval (PWSI). Hypertrophic non-unions benefitted more than biologically inactive atrophic non-unions (odds ratio [OR] 2.11, 95% CI 1.26 to 3.54]). An interval without surgery of less than 6 months before LIPUS was associated with a more favourable result (OR 5.72, 95% CI 1.62 to 20.22). Stratification of non-unions by anatomical site showed no statistically significant differences between upper and lower extremity long bone non-unions[1].

In a cohort study of 60 patients with long-bone non-unions (n=61) treated with LIPUS, 33% (20/60) of patients showed successful bone healing at an average time of 5.3 months and 67% (41/61) of patients reported unsuccessful healing.

The time to full weight bearing was significantly different in the successful and unsuccessful groups (5.4 months compared with 9.1 months, p=0.037) and also the length of time out of work (12.2 months compared with 19 months, p=0.017). A total of 70% of patients reported no improvement in pain[4].

**Non-operative treatment of scaphoid non-unions**

In a meta-analysis of 5 observational studies (166 scaphoid fracture non-unions), mean healing rate was 78.6% (95% CI 62.8 to 90.9). The average time to confirmed union was 4.2 months after LIPUS. Four studies reported a union rate after LIPUS of 77% for fractures initially treated conservatively using casting and 83% after unsuccessful surgical correction (5/6)[2].

An RCT of 21 patients with non-union fractures of the scaphoid treated with pedicle bone graft (10 low-intensity pulsed ultrasound compared with 11 sham) reported an average time to healing (defined as clinical healing [solid and not causing tenderness or pain] and radiographic healing [complete bridging cortices]) of 56 days in the ultrasound group and 94 days in the sham group (p <0.001)[3]

## All types of fractures (including fresh conservatively or operatively managed fractures, stress fractures, osteotomies, delayed-unions or non-unions)

***Functional recovery: Time to return to work or active duty (number of days)***

In a meta-analysis of 24 RCTs, (of adult patients with operatively and non-operatively managed fresh fractures and osteotomies, delayed unions and non-unions), results from pooled data (n=3 moderate quality studies, 197 patients) showed that LIPUS did not lead to a reduction in time to functional recovery (mean difference −0.74, 95% CI −5.72 to 4.24; p=0.77, $I^2$=26%).[6]

***Time to radiographic healing/fracture union (days)***

In the meta-analysis of 26 RCTs, radiographic healing effect varied substantially among studies. Fifteen trials reported number of days to radiographic healing. Overall results suggested accelerated healing with LIPUS compared with control (sham device or no device; percentage difference in days to radiographic healing 26%, 95% CI 33.6 to 17.8%, $I^2$=85%). The effect differed statistically significantly between the 12 trials at high risk of bias (percentage difference 32.8%, 95% CI 39.5 to 25.3%; $I^2$=78%; 446 patients) and the 3 trials at low risk of bias (percentage difference 1.7%, 95% CI 11.2 to 8.8%, $I^2$=10%; 483 patients; interaction p<0.001).The effect of LIPUS on days to radiographic healing did not differ across clinical subgroups (interaction p=0.13) or between high and moderate compliance with treatment (interaction p=0.99).[1]

In the meta-analysis of 24 RCTs, results from pooled data (10 low-quality studies, n=429) showed that LIPUS resulted in a mean reduction in healing time of 40 days (95% CI, 17.7 to 62.0 days; $I^2$=94%; heterogeneity p<0.00001). The most reduction in time to radiographic union by LIPUS was seen in fractures with a prolonged natural healing tendency (that is, unfixed fibular osteotomies and complex fractures of the tibia). Subgroup analysis showed that in patients with operatively treated fresh fractures or osteotomies LIPUS did not accelerate fracture union (p=0.07) compared with those with non-operatively managed fresh fractures (p=0.01) or delayed fractured union or non-union (p<0.00001).[6]

***Time to clinical healing/fracture union (days)***

In the meta-analysis of 24 studies, delayed unions and non-unions results from pooled data (n=6 low quality studies, 360 patients) showed that LIPUS resulted in a statistically significant mean reduction of 14.2 days in time to clinical healing (95% CI 1.9 to 26.5 days; $I^2$=96%; heterogeneity, p<0.00001).[6]

***Increase in bone formation***

In the meta-analysis of 24 RCTs**,** evidence from 2 high-moderate quality trials (Rutten 2012, Schofer 2010) showed that LIPUS enhances fracture healing through increased bone formation and accelerating callus maturation in patients with delayed fracture union and/or non-union[6].

## Safety summary

## All types of fractures (including fresh conservatively or operatively managed fractures, stress fractures, osteotomies, delayed unions or non-unions)

### Adverse effects related to the device

In the meta-analysis of 26 RCTs, the pooled risk difference based on 9 trials (0%, 95% CI 1 to 1%; $I^2$=0%; 839 patients) was not statistically significant nor was the pooled risk ratio (RR) of 2 studies reporting mild transient skin irritations in 6 patients (RR 2.65 in favour of control, 95% CI 0.32 to 22.21; 129 patients). There was no significant interaction with risk of bias on the risk difference scale (p=0.75)[5].

In the cohort study of 60 patients with long bone non-unions, an abscess was reported in 1 patient with a history of osteitis in the fourth week of LIPUS. This was treated surgically[4].

### *Anecdotal and theoretical adverse events*

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, specialist advisers listed 1 anecdotal adverse event: irritation of skin from ultrasound gel needing prolonged use of corticosteroid cream.

## The evidence assessed

### *Rapid review of literature*

The medical literature was searched to identify studies and reviews relevant to low-intensity pulsed ultrasound to promote healing of delayed-union and non-union fractures. The following databases were searched, covering the period from their start to 03-10-2017: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

**Table 1 Inclusion criteria for identification of relevant studies**

| Characteristic | Criteria |
|---|---|
| Publication type | Clinical studies were included. Emphasis was placed on identifying good quality studies.<br>Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study.<br>Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature. |
| Patient | Patients with delayed-union and non-union fractures. |
| Intervention/test | Low-intensity pulsed ultrasound. |
| Outcome | Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy. |
| Language | Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base. |

## *List of studies included in the IP overview*

This IP overview is based on 3,283 patients from 4 systematic reviews[1, 2, 5, 6], 1 randomised controlled trial[3] and 1 cohort study[4]. There is an overlap of studies in the systematic reviews. Some of the studies included patients in whom LIPUS had been used for other indications, including patients with primary non-union and those at high risk of primary non-union.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in the appendix.

## Table 2 Summary of key efficacy and safety findings on low-intensity pulsed ultrasound to promote healing of delayed-union and non-union fractures

## Study 1 Leighton R (2017)[1]

### Details

| | |
|---|---|
| Study type | **Systematic review (including meta-analysis)** |
| Country | International |
| Recruitment period | 13 studies from 2001 to 2015 |
| Study population and number | n=**13 observational studies (1441 non unions)**<br>Study type: 7 prospective and 6 retrospective studies.<br>Studies included: (Nolte 2001, Mayr 2002, Lerner 2004, Pigozzi 2004, Gebauer 2005, Jingushi 2007, Rutten 2007, Hemery 2010, Schofer 2010, Roussignol 2012, Watanabe 2013, Farkash 2015, Zura 2015).<br>Fracture location: mix of bones in 9 studies, scaphoid in 1, tibia in 2, tibia/femur in1 study.<br>Non-union status: varied across studies (3 months in 3 studies, 4 months in 1, 6 months in 4, 8 months in 2, 9 months in 1, and 12 months in 1).<br>Fracture age: varied across studies (average age ranged from 6 to 39 months). |
| Age and sex | Varied across studies; mean age 32–47 years; women 0% (0/29) to 47% (359/767) |
| Study selection criteria | **Study selection:** Studies were included if LIPUS was used as an alternative to surgery for non-healing fractures, with >12 patients, LIPUS applied at least 3 months after the last surgical procedure, reported 1 fracture (heal/fail) and a clear definition of delayed union or non-union was included.<br>Studies dealing with fresh fractures (less than 3 months old), <12 patients, reviews, case reports and experimental and animal studies excluded.<br>Data sources: PubMed, Ovid MEDLINE, CINAHL, AMED, EMBASE, Cochrane Library, and Scopus databases were searched, no language restrictions, and manual searches of references in reviews were done. |
| Study characteristics and technique | LIPUS treatment of delayed unions and non-unions. |
| Follow-up | **Varied across some studies (4 months to 52 months), and not reported in some studies.** |
| Conflict of interest/source of funding | 2 authors were paid consultants to Bioventus, and 2 authors were employees of Bioventus. All funding was provided by Bioventus LLC. |

### Analysis

**Study design issues**: this study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Two independent reviewers identified studies, extracted data and disagreements were resolved by discussion. The methodological quality of studies was evaluated using the Methodological Index for Non-Randomized Studies (MINORS), with a level of evidence rating by 2 reviewers independently (level II, scores ranged from 5 to 12, mean 8.7). The moderate quality of studies was as a result of retrospective study design, inadequate description of methodology, losses to follow-up, or lack of power and sample size calculations. Study free of publication bias.

The main outcomes of interest were heal rate and factors that could affect the results of LIPUS treatment of delayed unions and non-unions.

Limitations: a range of different definitions of fracture non-union were used by authors of primary studies. All definitions were similar in that non-union was defined as diagnosable at no less than 3 months post-fracture, and all definitions required radiological confirmation. Studies included were mainly observational, and LIPUS was used as an adjunct in some studies (Nolte 2001, Lerner 2004). This could bias the results of LIPUS treatment.

### Key efficacy and safety findings

| Efficacy |
|---|
| Number of patients analysed: **13 studies (1,441 non unions)**<br>**Overall heal rate across all included studies (all anatomical sites, 13 studies, 1441 non-unions)**<br>**Fracture age [time interval from fracture occurrence to commencement of LIPUS treatment) was 3 months**<br>The pooled estimate of effect size for the heal rate in any anatomical site for non-union and fracture age of at least 3 months was 82% (95% CI 77 to 87%). Significant statistical heterogeneity was detected across primary studies (Q = 41.2 [df = 12], p<0.001, Tau2 = 0.006, I2 = 71).<br><br>**Heal rate across primary studies where non-union was defined at 8 months (9 studies, n=239)**<br>The pooled estimate of effect size for the heal rate was 84% (95% CI 77% to 91.6%) and significant statistical heterogeneity was present (Q = 21 [df = 8], p < 0.001, Tau2 = 0.007, I2 = 62).<br><br>**Subgroup analysis**<br>**Comparison of hypertrophic versus inactive atrophic non-unions in terms of heal rate (8 studies, n=542).**<br>The odds of healing were twice as large in hypertrophic non-unions compared with atrophic non-unions (OR 2.11; 95% CI 1.26 to 3.54; $I^2$=6%, overall effect p=0.005).<br><br>**Heal rate according to prior without surgery interval (PWSI<6 months, 5 studies, n=208).**<br>A PWSI of less than 6 months was associated with a more favourable result compared with PWSI of more than 12 months (OR 5.72; 95% CI 1.62 to 20.22; $I^2$=0%, overall effect p=0.007). |

**Non-unions by anatomical site and heal rate**

| Fracture site | No of references | N | Heal rate (weighted mean) | 95% CI | Heterogeneity |
|---|---|---|---|---|---|
| Tibia | 10 | 354 | 86% | 79-93% | Q = 47, df = 9, p < 0.001, $I^2$ = 81 |
| Femur | 9 | 110 | 80.4% | 70.6-90.3% | Q = 14, df = 8, p = 0.08, $I^2$ = 42.6 |
| Scaphoid | 6 | 61 | 78% | 62.6-93.55 | Q = 16, df = 5, p = 0.007, $I^2$ = 68.5 |
| Humerus | 6 | 44 | 74% | 61.4-86% | Q = 4, df = 5, p = 0.54, $I^2$ = 0 |
| Radius+Ulna | 5 | 18 | 77.5% | 60-95% | Q = 0.096, df = 4, p = 0.99, $I^2$ = 0 |

**Heal rate in upper and lower extremity long bone non-unions**

| Fracture site | N | HR (95%CI) | Median | P |
|---|---|---|---|---|
| Tibia | 354 | 86% (79 to 93%) | 87% | Tibia versus humerus: p=0.3 |
| Humerus | 44 | 745 (61 to 86%) | 75% | Humerus versus femur p=0.3 |
| Radius +Ulna | 18 | 77.5% (60 to 95%) | 100% | Tibia versus radius+ulna p=0.9 |
| Femur | 110 | 80.4% (70.6 to 90.3%) | 92% | Femur versus radius+ulna: p=0.19 |

**Sensitivity analysis**

| Fracture site | No of studies | N | HR 995%CI) | Median | P |
|---|---|---|---|---|---|
| All studies | 13 | 753 | 82% (77 to 87%) | 85% | |
| Exclusion of low quality studies** | 9 | 615 | 81.5% (75 to 88%) | 85% | 0.97 |
| Additional exclusion of study with dubious eligibility* | 8 | 600 | 80% (74 to 85%) | 80% | 0.74 |

*Pigozzi 2004; ** Lerner 2004, Hemery 2010, Farkash 2015, Zura 2015

Abbreviations used: CI, confidence interval; LIPUS, low-intensity pulsed ultrasound; HR, hazard ratio.

## Study 2 Seger EW (2017)[2]

### Details

| | |
|---|---|
| Study type | **Systematic review (including meta-analysis)** |
| Country | US |
| Recruitment period | 5 studies from 2001 to 2015 |
| Study population and number | n=**5 observational studies (166 non-operative treatment of scaphoid fracture non-unions)**<br>Studies included: (Nolte 2001, Pigozzi 2004, Gebauer 2005, Farkash 2015, Rubin 2001)<br>Average fracture age: 20.1 months (range 3 to 169.8 months). |
| Age and sex | mean age 31 years (range 18 to 49 years); 80 to 100% males |
| Study selection criteria | **Study selection:** full-text reports, randomised controlled trials (RCTs), cohort studies, and randomised crossover studies evaluating LIPUS non-operative treatment of scaphoid non- union fractures, non-union scaphoid fracture persisting 3 months after the most recent treatment attempt and reporting union rates as an outcome measure were included.<br>Studies reporting fewer than 5 cases, those not published in English, those not related to LIPUS non-operative scaphoid non- union treatment, those without sufficient data and scaphoid non-unions with associated advanced carpal collapse were excluded.<br>Data sources: PubMed, Embase, and Ovid databases were searched (from 1966 to June 2015), no language restrictions, and manual searches of references in reviews were done. |
| Study characteristics and technique | LIPUS for non-operative treatment of scaphoid fractures non-union- 20-min dose, 30 $mW/cm^2$, and 1.5 mHz frequency daily home treatment. |
| Follow-up | **Varied across studies** |
| Conflict of interest/source of funding | None, authors received no financial support. |

### Analysis

**Study design issues**: this study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Two independent reviewers identified studies and extracted data. The main outcome of interest was total success of LIPUS treatment. Success was defined as definitive healing confirmed by imaging. Within all cohorts, healing rate was defined as the percentage of cases that achieved bony union following each specific intervention. Confirmation of union was made using radiographs.

Limitations: Studies included were small and mainly observational, methodological quality of studies not assessed, and a range of different definitions of fracture non-union were used by authors of primary studies. Only Forest plot was presented in paper and further details were not provided.

**Study population issues**: The average fracture age in the studies included was significantly higher than the 3 month cut off.

## Key efficacy and safety findings

Efficacy

Number of patients analysed: **5 studies included in meta-analysis n=166**

| Study | Fracture heal rate | Treatment months to union (range) |
|---|---|---|
| Farkash 2015 | 22/29 | 2.3 ± NR (1-4) |
| Gebauer 2005 | 2/6 | 5.6 ± 16.3 (5.2-6.0) |
| Pigozzi 2004 | 8/8 | 3.0 ± 1.5 (1.6-4.7) |
| Nolte 2001 | 4/5 | 4.75 ± 2.1 (3.0-7.1) |
| Rubin 2001 | 101/118 | 4.6 ± NR |

**Union rates**

LIPUS-treated scaphoid non-unions reported a mean healing rate of 78.6% (95% CI 62.8% to 90.9%) and an average time to confirmed healing of 4.2 months

Union rate following LIPUS in cases initially treated conservatively using casting 77% (33/43)

Union rate following LIPUS after unsuccessful surgical correction 83% (5/6)

Abbreviations used: CI, confidence interval; LIPUS, low-intensity pulsed ultrasound; NR, not reported.

## Study 3 Ricardo M (2006)[3]

### Details

| | |
|---|---|
| Study type | **Randomised controlled trial** |
| Country | Cuba |
| Recruitment period | 1999-2004 |
| Study population and number | n=**21 patients with fractures of the scaphoid treated with vascular pedicle bone graft for non-union.** (LIPUS n=10 versus sham n=11) |
| Age and sex | Age: 26.7 years (mean); Sex: 100% (21/21) male |
| Patient selection criteria | As stated above |
| Technique | Low-intensity pulsed ultrasound immediately after surgery (daily 20 minute session with signal intensity 30 $mW/cm^2$) versus sham control. |
| Follow-up | **2.3 years (mean)** |
| Conflict of interest/source of funding | not reported |

### Analysis

**Follow-up issues**: Loss to follow up: 0%

**Study design issues**: Method used for randomisation is not reported. Unclear if clinician judging clinical and radiographic healing was independent and blinded to treatment allocation.

**Study population issues**: Average interval between injury and surgery: 38.4 months.

### Key efficacy and safety findings

Efficacy

Number of patients analysed: 21 (10 vs 11)

**Clinical outcomes**

| | LIPUS group (n = 10) | Sham group (n = 11) | p value |
|---|---|---|---|
| Time to healing (defined clinically as solid and not causing tenderness or pain) and radiographically (complete bridging of cortices) | 56±3.2 days | 94±4.8 days | p <0.001 |

66.7% (14/21) patients were very satisfied with the results of surgery.

71.4% (15/21) had occasional; pain or discomfort with strenuous activity.

52.4% (11/21) returned to their previous occupation and leisure activity with mild limitation.

Abbreviations used: LIPUS, low-intensity pulsed ultrasound.

## Study 4 Biglari B M (2016)[4]

### Details

| | |
|---|---|
| Study type | **Prospective observational cohort study** |
| Country | Germany |
| Recruitment period | 2010–13 |
| Study population and number | n=**60 patients with long bone non-unions (n=61)**<br>Treated bones: tibia 57.4% (35/61), femur 18% (11/61), humerus 11% (7/61), radius 5% (3/61) and others 8% (5/61).<br>Age of fracture: average 10.4 months.<br>Number of previous surgeries: average 3.02 operations<br>Average NUSS risk score: average 38.9±10.8. |
| Age and sex | Age: 45.4 years (mean); Sex: 92% male; BMI 28.9. |
| Patient selection criteria | Patients with chronic non-unions who received LIPUS treatment >90 days after their last surgery were included. Patients treated with surgery before the end of therapy, pregnant women, and aged less than 18 years were excluded. |
| Technique | Low-intensity pulsed ultrasound treatment given according to EXOGEN guidelines (fracture has to have sufficient clinical stability and there must be no signs of infection) for 20 minutes daily (frequency was 1.5 MHz, power was 30mW/cm2, pulse duration was 200µs, and signal repetition was 1kWz). |
| Follow-up | **1 year** |
| Conflict of interest/source of funding | None, no external funding. |

### Analysis

**Follow-up issues**: 100% regular follow-up. Patients received follow-up at 6 and 12 weeks, and after 4, 5, 6 and 12 months or after bone consolidation.

**Study design issues**: prospective study in a single centre done as part of a thesis work, patients were selected by a surgeon and rehabilitation physician. Another orthopaedic team examined the patients after 1 year and analysed data. Rate of healing, functional and subjective results were evaluated. Non-unions were classified according to the non-union scoring system (NUSS). Based on clinical and radiological evaluations patients were retrospectively divided into 2 groups to identify factors influencing treatment: G1 (successful treatment) and G2 (unsuccessful treatment). Successful treatment was defined as radiological consolidation and no further surgical revision for the next year. Unsuccessful treatment was defined as non-union not healed and a new surgical intervention was necessary.

**Study population issues**: all patients had difficult non-unions with a high NUSS score. Many patients also had at least 3 unsuccessful surgeries before LIPUS treatment. One patient received LIPUS treatment on 2 different long bones. Twenty-six patients were smokers. 14 patients has osteitis before therapy. There were no significant differences in patient characteristics between the G1 and G2 groups.

**Other issues:** authors state that a possible influence of the last surgery has been excluded by including only patients who did not receive any intervention for 90 days.

### Key efficacy and safety findings

Efficacy

Number of patients analysed: **60 patients (61 non-unions)**

**Pre-therapeutic and clinical outcomes**

| | Total n=61 | G1 Successful treatment % (n)* | G2 Unsuccessful treatment % (n) | P value |
|---|---|---|---|---|
| | | 32.8 (20/61) | 67.2 (41/61) | |
| Age of fracture (months) | | 7.2±3.8 | 11.9±10.3 | 0.011 |
| Defect gap (cm) | 0.67±0.55 | 0.46±0.29 | 0.77±0.62 | 0.01 |
| NUSS score | | 34.7±8.9 | 41±11 | 0.034 |
| Time to healing (months) | | 5.3±1.9 | 5.6±1.8 | NS |
| Full weight bearing (months) | 7.5±5.6 | 5.4±3.9 | 9.1±6.1 | 0.037 |
| Full weight bearing not achieved at end of study, n | 15 | 2 | 13 | 0.065 |
| Time out of work (months) | 16.2±8.3 | 12.2±8.1 | 19.0±7.3 | 0.017 |
| Disability at end of treatment, n | 24 | 5 | 19 | 0.122 |
| **Pain(subjective evaluation)** | | | | 0.004 |
| Improvement | 5 | 5 | 0 | |
| Minimal improvement | 13 | 5 | 8 | |
| No change | 37 | 8 | 29 | |
| Worsening | 1 | 0 | 1 | |
| No pain | 5 | 2 | 3 | |

*In the healed patients the average duration of LIPUS treatment was 5.5±1.8 months.

**Complications**

1 patient with a history of osteitis developed an abscess in the 4th week of LIPUS treatment that was surgically treated.

Abbreviations used: LIPUS, low-intensity pulsed ultrasound; NUSS, non-union scoring system.

## All types of fractures (including fresh conservatively or operatively managed fractures, stress fractures, osteotomies, delayed unions or non-unions)

## Study 5 Schandelmaier S (2017)[5]

### Details

| | |
|---|---|
| Study type | **Systematic review (including meta-analysis)** |
| Country | Canada |
| Recruitment period | 26 RCTs from 1994 to 2016 |
| Study population and number | n=**26 RCTs (with a median sample size of 30 [range 8-501])** of patients with any type of fracture or osteotomy<br>Studies included:<br>**Operatively managed fresh fractures** (n=7)<br>(Busse 2016, 2014, Kamath 2015, Leung 2004, Emami 1999, Handolin 2005a, 2005b)<br>**Non operatively managed fresh fractures** (n=6)<br>(Heckman 1994, Kristiansen 1997, Liu 2014, Lubbert 2008, Mayr 2000,Patel 2014)<br>**Non operatively managed stress fractures** (n=2)<br>(Gan 2014, Rue 2004)<br>**Operatively managed non-unions** (n=3)<br>(Schofer 2010, Ricardio 2006, Rutten 2012)<br>**Distraction osteogenesis** (n=5)<br>(Tsumaki 2004, Schortinghuis 2008, 2005, Salem 2014, Dudda 2011, El-Mowafi 2005)<br>**Osteotomy** (n=2)<br>(Urita 2013-shortening, Zacherl 2009 –deformity correction) |
| Age and sex | Varied across studies; mean age 30–68 years; women 0% to 85% |
| Study selection criteria | **Study selection:** Randomised controlled trials of low-intensity pulsed ultrasound (LIPUS) compared with sham device or no device in patients with any kind of fracture regardless of location (long bone or other bone), type (fresh fracture, delayed union, non-union or stress fracture) or clinical management (operative or non-operative) or any type of osteotomy trials including distraction osteogenesis.<br>Data sources: Medline, Embase, CINAHL, Cochrane Central Register of Controlled Trials and trial registries from inception to November 2016. |
| Study characteristics and technique | Most trials included patients with tibia fractures or osteotomies (n=14).<br>All but 2 trials applied LIPUS for 20 minutes every day, either for a fixed period or until radiographic healing. Otherwise, one trial (Liu 2014) applied LIPUS for 15 minutes a day, and another trial for five minutes every second day (Patel 2015). Fifteen trials (60%) provided their control group with an inactive device that was indistinguishable from the active LIPUS. Only three trials (12%) were explicitly free from industry funding (El Mowafi 2005, Rue 2004, and Tsumaki 2004). |
| Follow-up | **Varied across studies (maximum 5 weeks to 5 years)** |
| Conflict of interest/source of funding | None, no specific grant from any funding agency. Medical journal –sponsored research group with diverse input. One or more co-authors of this study are co-authors of the TRUST trial (Busse 2016) supported by Smith & Nephew 9manufacturer of LIPUS devices). |

### Analysis

**Follow-up issues**: loss to follow-up (%) for radiographic healing outcome varied across studies (from 2% to 45% where reported) and in most studies it was unclear.

**Study design issues**:

Two independent reviewers identified studies, extracted data and assessed risk of bias (using a modified Cochrane risk of bias instrument, comparing publication with published protocol). Disagreements were resolved by discussion with a third reviewer. The systematic review is part of the BMJ Rapid Recommendations project and a parallel guideline committee/panel (with 6 clinical experts, 6 methodologists and 4 patients) provided input on the design and interpretation of the systematic review, including patient selection, outcomes important to patients and radiographic healing and subgroup analyses. Patients considered functional recovery, pain reduction, and operations as critical outcomes, while expressing little interest in the commonly reported surrogate outcome of radiographic healing.

Quality of the evidence was assessed using the GRADE system. Optimal statistical approaches and measures were used. Results on subgroup analysis were based on risk of bias: when effects differed significantly between high and low quality trials, conclusions were based on trials at low risk of bias. Rating of risk of bias were consistent with those of a previous Cochrane review (Griffin 2014).

Limitations: concealment of treatment allocation was not reported in 15 trials, patients were not blinded to treatment in 10 trials, outcome assessors/caregivers were not blinded to treatment in 10 trials and high or unclear number of patients excluded from the analysis (12 trials). 6 trials were considered to be at low risk of bias and remaining 20 to be at high risk of bias.

Most trials did not measure outcomes important to patients. Only 11 trials reported outcomes that patient considered important and were included in the meta-analysis. 4 trials (with operatively managed fresh tibia fracture [Busse 2016, Busse 2014, Emami 1999] or conservatively managed clavicle fracture [Lubbert 2008]) contributed substantial data. Subgroup analysis and meta-regression for radiographic healing found no effect modification based on clinical subgroups.

**Study population issues**: all types of fractures were included. The largest RCT on LIPUS for fracture healing has been included in this review (Busse 2016)

**Other issues**: authors note that subgroup analysis and meta-regression for radiographic healing found no effect modification based on clinical subgroups. Therefore authors suggest that it might be reasonable to apply the results to patients not included at all (children) and underrepresented populations such as those with stress fractures, non-union and osteotomies.

Authors also state that several systematic reviews provided no definitive conclusions. Studies included have been small, had high risk of bias, and have not reported outcomes important to patients.

## Key efficacy and safety findings

Efficacy

Number of patients analysed: **RCTs included in meta-analysis n=23**

**Proportion of healed fractures with LIPUS compared with control**

A randomised controlled trial in patients with delayed union of tibia fracture (Schofer 2010) reported only the proportion of healed fractures at 16 weeks and did not find a statistically significant difference (65% in the LIPUS and 46% in the control arm, P=0.07; high risk of bias towards LIPUS because of serious imbalance in age of fracture at baseline).

**Adverse effects related to device**

**Risk difference in adverse effects related to ultrasound device**

Pooled risk difference based on 9 trials (5/426 compared with 1/413, RD 0.01%, 95% CI 0.01 to 0.01%; $I^2$=4%; p=0.40, 839 patients) was not statistically significant nor was the pooled risk ratio (RR) of 2 studies reporting mild transient skin irritations in 6 patients (RR 2.65 in favour of control, 95% CI 0.32 to 22.21; 129 patients.

**GRADE summary of findings of all outcomes on LIPUS for bone healing after fracture**

| | | **Absolute effect estimates** | | | | |
|---|---|---|---|---|---|---|
| **Outcome** | **Study results (95% CI) and measurements** | **No ultrasound** | **LIPUS** | **Difference (95% CI)** | **Quality of evidence** | **Narrative summary** |
| Days to return to work | % difference: 2.7% (−7.7% to 14.3%) in days, lower better. Based on data from 392 patients in 3 studies | Mean 200 days | Mean 205 days | 5 days later (15 earlier to 20 later) | Moderate* | LIPUS probably has little or no impact on time to return to work |
| Days to full weight bearing | % Difference: 4.8% (−4.0% to 14.4%) in days, lower better. Based on data from 483 patients in 2 trials at low risk of bias | Mean 70 days | Mean 73 days | 3 days earlier (3 earlier to 10 later) | High | LIPUS has no impact on time to full weight bearing |
| Pain reduction. Follow-up 4-6 weeks | Mean difference: −0.93 (−2.51 to 0.64) 0 to 100 visual analogue scale, lower better, minimal important difference: 10-15. Based on data from 626 patients in 3 trials at low risk of bias | Mean 40 | Mean 39 | 1 lower (3 lower to 1 higher) | High | LIPUS has no impact on pain reduction |
| Subsequent operations. Follow-up 8 weeks-44 months | Risk ratio: 0.80 (0.55 to 1.16). Based on data from 740 patients in 7 studies | 160/1000 | 128/1000 | 32 fewer (72 fewer to 26 more) | Moderate* | LIPUS probably has little or no impact on subsequent operation |
| Days to radiographic healing | % Difference: −1.7% (−11.2% to 8.8%) in days, lower better. Based on data from 483 patients in 3 trials at low risk of bias | Mean 150 days | Mean 147 days | 3 days earlier (17 earlier to 13 later) | Moderate* | LIPUS probably has little or no impact on time to radiographic healing |
| Adverse effects related to device. Follow-up 5-52 weeks | Risk difference: 0% (−1% to 1%). Based on data from 839 patients in 9 studies | 0/1000 | 0/1000 | 0 fewer (10 fewer to 10 more) | High | LIPUS has no impact on adverse effects related to device |

*Because of serious imprecision.

Abbreviations used: LIPUS, low-intensity pulsed ultrasound.

## Study 6 Rutten S (2016)[6]

### Details

| | |
|---|---|
| Study type | **Systematic review (including meta-analysis) of RCTs** |
| Country | The Netherlands |
| Recruitment period | 26 RCTs from 1994 to 2016 |
| Study population and number | n=**24 RCTs (with a median sample size of 30 [range 8 to 501])** of patients with any type of fracture or osteotomies, delayed union or non-union.<br>Studies included:<br>**Operative management of fresh fractures (n=7)**<br>(Emami 1999,Nolte 2002b, Leung 2004, Handolin 2005a, 2005b, Zacherl 2009-deformity correction, Urita 2013-shortening)<br>**Non operative management of fresh fractures** (n=6)<br>(Heckman 1994, Kristiansen 1997, Liu 2014, Lubbert 2008, Mayr 2000,Stauss 1998)<br>**Non operative stress fractures** (n=2)<br>(Gan 2014, Rue 2004)<br>**Osteotomy (n=1):** Nolte 2002a<br>**Operative management of delayed union or non-unions** (n=1)<br>(Ricardio 2006,)<br>**Non-operative management of delated union or non-union (n=2)**<br>(Schofer 2010, Rutten 2012, 2008, 2009)<br>**Distraction osteogenesis** (n=5)<br>(Tsumaki 2004, Schortinghuis 2008, 2005, El-Mowafi 2005, Salem 2014, Dudda 2011) |
| Age and sex | Varied across studies |
| Study selection criteria | **Study selection:** Randomised or quasi randomised controlled trials of low-intensity pulsed ultrasound (LIPUS) for adult patients with all types of fractures, delayed unions, non-unions and osteotomies/distraction osteogenesis, randomly assigned to LIPUS treatment or a control group.<br>Patients with metabolic or pathologic bone disease, systematic reviews and narrative reviews were excluded.<br>Data sources: PubMed/Medline, Embase, CINAHL, Cochrane Central Register of Controlled Trials and Web of Science were searched from inception to January 2015 for published studies in any language. Bibliographies of relevant publications, Clinical Trials.gov and WHO trail registers were also searched. |
| Study characteristics and technique | LIPUS treatment compared with either a sham or untreated control.<br>All trails used LIPUS at a peak pressure of 30mW/cm2. LIPUS was applied for 20 minutes every day on an outpatient basis, 1 trail applied twice daily and 1 trial used only for 15 minutes.<br>Duration of treatment varied among the trails and was determined on the basis of radiographic healed fracture, until external fixator or cast removal, or a timeframe which ranged from 4 weeks to 5 months. |
| Follow-up | **Varied across studies** |
| Conflict of interest/source of funding | None, no external grant from any funding agency. |

### Analysis

**Study design issues**: Systematic review was performed according to, the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Two independent reviewers identified studies, extracted data and assessed methodological quality. Disagreements were resolved by consensus with a third reviewer. Quality of the evidence for each outcome was assessed using the GRADE system. All outcomes were pooled and a meta-analysis was performed using a random or fixed effects model. Subgroup analysis was done for each clinical category. Sensitivity analyses was done and heterogeneity was examined using the $I^2$ statistic (>50% considered to represent substantial heterogeneity).

Time tor radiographic fracture union (bridging of at least 3 cortices) was the most common primary outcome evaluated. Delayed union was defined as no union for 3 months and non-union was defined as no union for a period of 9 months or no progression of healing at 6 months following the fracture.

2 of the included trials were thesis chapters by 2 of the systematic review authors. One trial was published as an abstract only. Risk of bias: patients were randomly allocated in 8 trials and no sham treatment was given to control group. Placebo devices were used in all other trials with sham treatment. No crossover was reported. 8 trials included patients who were lost to follow-up and the lost patients were excluded from the analysis.

Limitations: quality of studies varied (mainly low) and some had methodological problems, Substantial heterogeneity in studies (varied outcomes, fracture location and type) noted, publication bias was present (as some studies were not incorporated).

**Study population issues**: all types of fractures were included.

### Key efficacy and safety findings

| Efficacy |
|---|
| Number of patients analysed: **RCTs included in meta-analysis n=24**<br>**Radiographic outcomes**<br><br>**Time to radiographic healing/ fracture union (days) of operative and non-operatively managed fresh fractures**<br>Results from pooled data (n=429 patients from 4 studies with non-operative management of fresh fractures, 4 studies with operative management of fresh fractures and 2 studies with delayed/non-union) showed that LIPUS resulted in a mean reduction in healing time of -39.8 days (95% CI -17.7 to -61.95 days; $I^2$=94%; heterogeneity p<0.00001, overall effect p=0.0004)).<br>Subgroup analysis showed that in patients with operatively treated fresh fractures and/or osteotomies (4 studies), LIPUS did not accelerate fracture union (mean difference -26.34; 95% CI 2.06 to -54.73; I2=82%; overall effect p=0.07) compared with non-operatively managed fresh fractures and/or impaired fractured healing (4 studies) (mean difference -56.51; 95% CI -11.23 to -101.78; I2=98%, overall effect p=0.01).<br><br>The most reduction in time to radiographic union by LIPUS treatment was seen in fractures with a prolonged natural healing tendency (i.e., unfixed fibular osteotomies and complex fractures of the tibia).<br><br>**Time to radiographic union after tibial distraction osteogenesis and bone transportation of the tibia ( 3 low quality studies, 76 patients)**<br>Results from pooled data on the distraction consolidation index (reduction on time to union [days] divided by the length of the distraction gap [cm]) showed a mean decrease of -16.52 days/cm (95% CI 10.6 to 22.4 days/cm; p<0.001); $I^2$=0%, heterogeneity p=0.68) as a result of LIPUS treatment.<br><br>**Time to clinical healing/fracture union (days) of operatively and non-operatively managed fresh fractures ,delayed unions and non-unions (n=6 low quality studies, 360 patients)**<br>Results from pooled data showed that LIPUS treatment resulted in a significant mean reduction of 14.2 days in time to clinical healing (95% CI 1.9 to 26.5 days; $I^2$=96%; heterogeneity, p<0.00001, overall effect p=0.02).<br><br>**Functional recovery: time to return to work/active duty (n=3 moderate quality studies, 197 patients)**<br>Results from pooled data showed that LIPUS treatment did not lead to a reduction in time to functional recovery (mean difference -0.74; 95% CI 4.24 to -5.72; I2=26%; heterogeneity p=0.26; overall effect p=0.77).<br><br>**Prevention of delayed union or non-union associated with LIPUS treatment (7 studies)**<br>Results from pooled data did not show a statistically significant risk reduction for impaired healing by LIPUS (RR 0.70, 95%CI 0.31 to 1.58; $I^2$=14%, heterogeneity p=0.33).<br><br>**Safety:** no adverse events or complications were attributed to LIPUS treatment. |
| Abbreviations used: CI, confidence interval; LIPUS, low-intensity pulsed ultrasound; RR, risk ratio. |

## Validity and generalisability of the studies

- LIPUS is used as an adjunctive therapy to accelerate bone healing along with surgery in some studies and it is difficult to determine the clinical role of LIPUS.
- Studies have evaluated effectiveness of LIPUS on the process of fracture healing/union (bone formation) and functional recovery. Evidence is mainly for adult and skeletally mature patients.
- The duration of exposure to low-intensity pulsed ultrasound varied across the trials, which may impact on outcomes.
- Four systematic reviews have assessed the effectiveness of LIPUS on delayed union and non-union fractures and found the treatment may be beneficial. Reviews had different inclusion criteria, evaluation techniques, and focused on different outcomes and indications.
- Studies included were mainly observational and LIPUS was used as an adjunct in some studies.
- A range of different definitions of fracture non-union were used by authors of primary studies.
- Evidence shows that LIPUS treatment may be beneficial for delayed unions and non-unions and has the potential to accelerate healing. Existing assessments of this procedure.

The Medical Services Advisory Committee (MSAC) in Australia published an assessment report on Exogen™ bone growth stimulator in November 2001. The Committee found that the procedure was safe but should not be used prior to skeletal maturation and that the efficacy data was contradictory. The Committee recommended that public funding should not be supported for this procedure[8].

## Related NICE guidance

Below is a list of NICE guidance related to this procedure.

**Interventional procedures**

- Low-intensity pulsed ultrasound to promote fracture healing. NICE interventional procedures guidance 374 (2010). Available from https://www.nice.org.uk/guidance/IPG374 (currently being updated)
- Percutaneous insertion of craniocaudal expandable implants for vertebral compression fracture. NICE interventional procedures guidance 568 (2016). Available from https://www.nice.org.uk/guidance/IPG568

**Technology appraisals**

- Percutaneous vertebroplasty and percutaneous balloon kyphoplasty for treating osteoporotic vertebral compression fractures. NICE technology appraisal guidance 279 (2013). Available from http://www.nice.org.uk/guidance/TA279

**NICE guidelines**

- Fractures (non-complex): assessment and management. NICE guideline 38 (2016). Available from http://www.nice.org.uk/guidance/NG38
- Fractures (complex): assessment and management. NICE clinical guideline 37 (2016). Available from http://www.nice.org.uk/guidance/CG37
- Hip fracture: management. NICE clinical guideline 124 (2011). Available from http://www.nice.org.uk/guidance/CG124

**Medical technologies guidance**

- EXOGEN ultrasound bone healing system for long bone fractures with non-union or delayed healing. NICE medical technologies guidance 12 (2013). Available from http://www.nice.org.uk/guidance/mtg12

# Additional information considered by IPAC

## *Specialist advisers' opinions*

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Four Specialist Advisor Questionnaires for low-intensity pulsed ultrasound to promote healing of delayed-union and non-union fractures were submitted and can be found on the NICE website.

## *Patient commentators' opinions*

NICE's Public Involvement Programme sent questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). Three commentaries from patients who had experience of this procedure were received, which were discussed by the committee.

## *Company engagement*

A structured information request was sent to 1 company who manufacture a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

## *Issues for consideration by IPAC*

- Some recent meta-analyses (with moderate to very low quality evidence) did not demonstrate a beneficial clinical effect of LIPUS on fracture repair and suggested that future trials should focus on important patient related outcomes.
- Ongoing studies:
  - NCT02383160 A randomised controlled trial comparing low-intensity, pulsed ultrasound to placebo (sham) in the treatment of operatively

managed scaphoid non-unions; n=154, completion date: December 2018; location: Canada; status: currently recruiting participants.

  - NCT00744861 EXO-SPINE: A prospective, multi-centre, double-blind, randomised, placebo controlled pivotal study of ultrasound as adjunctive therapy for increasing posterolateral fusion success following single level posterior instrumented lumbar surgery; n=310; study completion June 2012; location: USA; this study has been terminated.

- JPRN-UMIN000017303: effects of LIPUS treatment in post-operative scaphoid delayed unions or non-unions (further details not available).
- JPRN-UMIN000002005- (further details not available).

## References


1. Leighton R, Tracy WJ et al (2017).Healing of fracture nonunions treated with low-intensity pulsed ultrasound (LIPUS): a systematic review and meta-analysis. Injury; 48 (7), 1339-1347.
2. Seger EW, Jauregui JJ et al (2017). Low-intensity pulsed ultrasound for nonoperative treatment of scaphoid nonunions: A meta-analysis. HAND 1–6 American Association for Hand Surgery DOI: 10.1177/15589
3. Ricardo M. (2006).The effect of ultrasound on the healing of muscle-pediculated bone graft in scaphoid non-union. International Orthopaedics 30:123-127.
4. Biglari B, Yildirim TM et al (2016). Failed treatment of long bone nonunions with low intensity pulsed ultrasound. Archives of Orthopaedic and Trauma Surgery. 136 (8), 1121-1134.
5. Schandelmaier S, Kushal A et al (2017). Low intensity pulsed ultrasound for bone healing: systematic review of randomised controlled trials. BMJ, 356:J656 doi: https://doi.org/10.1136/bmj.j656
6. Rutten S, van devn Bekerom MP et al (2016). Enhancement of bone-healing by low-intensity pulsed ultrasound: A systematic review. Journal of Bone and Joint Surgery, 4 (3):e6

# Literature search strategy

| Databases | Date searched | Version/files |
|---|---|---|
| Cochrane Database of Systematic Reviews – CDSR (Cochrane Library) | 23/03/2018 | Manually searched issues 2017 10 – 2018 03 |
| Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library) | 23/03/2018 | Issue 2 of 12, February 2018 |
| HTA database (Cochrane Library) | 23/03/2018 | Issue 4 of 4, October 2016 |
| MEDLINE (Ovid) | 23/03/2018 | 1946 to Present with Daily Update |
| MEDLINE In-Process (Ovid) & | 23/03/2018 | March 22, 2018 |
| Medline ePub ahead (Ovid) | 23/03/2018 | March 22, 2018 |
| EMBASE (Ovid) | 23/03/2018 | 1974 to 2018 March 22 |

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 ultrasonography, doppler, pulsed/
2 ultrasonic therapy/
3 ultrasound*.tw.
4 (ultrasonic* adj4 therap*).tw.
5 ultra-sound.tw.
6 or/2-5
7 (low adj4 intensit*).tw.
8 6 and 7
9 LIPUS.tw.
10 exogen.tw.
11 (doppler* adj4 echograph*).tw.
12 pulse*.tw.
13 6 and 12
14 1 or 8 or 9 or 10 or 11 or 13
15 exp Fractures, Bone/
16 Fracture Healing/
17 osteogenesis, Distraction/
18 fracture*.tw.

19 (bone* adj4 (heal* or mend* or fuse* or fusion* or break* or broke*)).tw.
20 (distract* adj4 osteogenes*).tw.
21 callotas*.tw.
22 (bone* adj4 graft* adj4 (non-union* or union*)).tw.
23 or/15-22
24 23 and 14
25 animals/ not humans/
26 24 not 25
27 (201008* or 201009* or 201010* or 201011* or 201012* or 2011* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017*).ed.
28 26 and 27
29 limit 26 to ed=20171003-20181231 (10)

## Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

| Article | Number of patients/follow-up | Direction of conclusions | Reasons for non-inclusion in table 2 |
|---|---|---|---|
| Arakawa S, Saito M et al (2015). Applying low-intensity pulsed ultrasounds (LIPUS) to a zoledronate-associated atypical femoral shaft fracture without cessation of zoledronate therapy for 3 years follow up: a case report. Clinical Cases in Mineral and Bone Metabolism; 12(3): 269-272. | Case report<br>N=1 Atypical femoral shaft fracture treated with an intramedullary nail in a patient treated for five years with zoledronate who had breast cancer with metastases to bone. | Bone union was achieved by 3 years following the fracture without cessation of zoledronate therapy by applying low-intensity pulsed ultrasounds (LIPUS), the remodelling phase of the fracture healing process was delayed. | Larger studies included in table 2. |
| Brand JC, Jr., Brindle T, Nyland J et al. (1999) Does pulsed low intensity ultrasound allow early return to normal activities when treating stress fractures? A review of one tarsal navicular and eight tibial stress fractures. Iowa Orthopaedic Journal 19:26-30. | Case series<br>n = 8<br>FU = 8 weeks | All patients resumed or maintained sporting activity at same level of time of diagnosis. | Larger studies included in Table 2. |
| Busse JW, Kaur J et al (2002). The effect of low-intensity pulsed ultrasound therapy on time to fracture healing: a meta-analysis. Can Med Assoc J, 166; 437-41. | Systematic review and meta-analysis of randomised controlled trials of low-intensity pulsed ultrasound therapy for healing of fractures. | 6 trials were included.<br>The pooled results (of 3 trials, 158 fractures) showed that time to fracture healing was significantly shorter in the groups receiving low-intensity ultrasound therapy than in the control groups. The weighted average effect size was 6.41 (95% confidence interval 1.01–11.81), which converts to a mean difference in healing time of 64 days between the treatment and control groups. | More up to date reviews included in table 2. |

| | | | |
|---|---|---|---|
| Busse JW, Kaur J, Mollon B et al. (2009) Low intensity pulsed ultrasonography for fractures: systematic review of randomised controlled trials. [Review] [27 refs]. BMJ 338:b351- | Systematic review of RCTs comparing low intensity pulsed ultrasonography with a control group in patients presenting with any form of fracture. | Thirteen RCTs were included in the review (n=563). Pooled analysis suggested an overall benefit of LIPUS in mean reduction in healing time (33.6%, 95% CI: 21.4, 43.8); evidence of substantial heterogeneity was found ($I^2$=76.9%). Tests of interaction did not indicate a different treatment effect across clinical presentations. Of the 5 trials reporting patient important outcomes, only 1 trial found a positive effect of LIPUS (time to full weight bearing, $p<0.05$). Evidence from 3 trials suggested a benefit of LIPUS in non-operatively managed fractures (faster radiographic mean healing time 36.9%, 95% CI: 25.6, 46.0%; $I^2$=41.6%). Evidence from 1 trial found a benefit of LIPUS in accelerating healing of established non-unions managed by bone graft (38 days, 95% CI: 26.3, 49.7), representing a 40.4% (95% CI: 30.8, 48.7) reduction in healing time. 4 trials provided evidence for acceleration of healing of operatively managed fresh fractures. Results from a pooled analysis (based on two trials) found no statistically significant difference in radiographic healing time between LIPUS and controls on operatively managed tibial shaft fractures (16.6%, 95% CI: -76.8, 60.7; $I^2$=90.0).1 trial found no effect of LIPUS on return to function in non-operatively managed stress fractures. Also, evidence from 3 trials suggested accelerated functional improvement after distraction osteogenesis. | More up to date reviews included in table 2. |

| | | | |
|---|---|---|---|
| Bayat M, Virdi A et al (2017). Comparison of effects of LLLT and LIPUS on fracture healing in animal models and patients: A systematic review. Progress in Biophysics and Molecular Biology<br>Available online 6 July 2017 | Systematic review of LLT and LIPUS alone.<br>(Medline and PubMed searched)<br>Quality of studies not assessed. Narrative synthesis. | Our analysis also suggests that both LIPUS and LLLT may be beneficial to fracture healing in patients, and that LIPUS is more effective. These finding are of considerable importance in those treatments with a LIPUS, as a laser device may reduce healing time. The most clinically relevant impact of the LIPUS treatment could be a significant reduction in the proportion of patients who go on to develop a nonunion. If it is confirmed that the therapeutic influence is true and reliable, patients will obtain benefits from LIPUS and LLLT. Further clinical trials of high methodological quality are needed in order to determine the optimal role of LIPUS and LLLT in fracture healing in patients. | Evidence on animal models also presented. |
| Carlson EJ, Save AV et al (2015). Low-intensity pulsed ultrasound treatment for scaphoid fracture nonunions in adolescents. Journal of Wrist Surgery. 4 (2); 115-120. | Retrospective review<br>N=14 patients with scaphoid nonunion treated surgically followed by adjunctive low-intensity pulsed ultrasound therapy | Thirteen of fourteen (93%) patients healed at a mean interval of 113 days (range 61–217 days). There were no surgical or postoperative complications. One patient developed heterotopic bone formation about the scaphoid. Study suggests that LIPUS can safely be utilized as an adjunctive modality in adolescents to augment scaphoid healing following surgical intervention. | Small retrospective uncontrolled study. No statistical analyses performed. |

| | | | |
|---|---|---|---|
| Korstjens, Clara M., Rutten, S, Nolte, PA et al (2018). Low-intensity pulsed ultrasound increases blood vessel size during fracture healing in patients with a delayed-union of the osteotomized fibula. Histology and histopathology 11972 2018. | Fibular biopsies of 13 patients with a delayed-union of the osteotomized fibula treated for 2-4 months with or without LIPUS originating from a randomised prospective double-blind placebo-controlled clinical trial were investigated to see whether LIPUS increases blood supply in delayed-unions of the osteotomized fibula, and if LIPUS-increased bone formation is correlated to increased blood supply. | Blood vessel parameters were analysed using histology, immunohistochemistry, and histomorphometric analysis as well as their correlation with bone formation and resorption parameters. In histological sections of the fibular biopsies parameters of blood vessel formation were measured and were related to histomorphometric bone characteristics of newly formed bone of the same samples analysed in our previously published study on the effects of LIPUS on bone healing at the tissue level in delayed-unions. LIPUS-treated delayed-unions and sham-treated delayed-unions as well as healed delayed-unions and failed-to-heal delayed-unions were compared. The volume density of blood vessels was increased in LIPUS-treated delayed-unions compared to sham-treated controls. LIPUS did not change blood vessel number, but significantly increased blood vessel size. Healed delayed-unions as well as LIPUS-treated and sham-treated delayed-unions showed significant correlations between blood vessel size and osteoid volume. LIPUS increases blood vessel size, essential for fracture healing, in bone from patients with a delayed-union of the osteotomized fibula. The increased osteoid volume in delayed-unions can largely be explained by increased blood supply and perfusion. | Histopathology results |
| Cook SD, Ryaby JP, McCabe J et al. (1997) Acceleration of tibia and distal radius fracture healing in patients who smoke. Clinical Orthopaedics & Related Research 198-207. | Non randomised comparative study<br><br>n = 127 (63 ultrasound vs 64 sham)<br><br>FU = not reported | Healing time for tibial fractures was reduced 41% in smokers and 26% in non-smokers when ultrasound used. Healing time for distal radius fractures reduced by 51% in smokers and 34% in non-smokers when ultrasound used. | Secondary analysis of patients in Heckman 1994 and Kristiansen 1990. Both are included in systematic review in Table 2. |

| | | | |
|---|---|---|---|
| Coughlin MJ, Smith BW, and Traughber P. (2008) The evaluation of the healing rate of subtalar arthrodeses, part 2: the effect of low-intensity ultrasound stimulation. Foot & Ankle International 29:970-977. | Non randomised comparative study<br>n = **30** (15 vs 15) patients undergoing subtalar arthrodesis procedure<br>2 days after surgery low-intensity pulsed ultrasound (daily 20 minute session for 12 weeks, width 200µs [SD: 10%], 1.5MHz sine waves [SD: 5%], repetition rate 1 kHz [SD: 10%] and intensity 30 mW/cm$^2$ [SD: 30%]) vs no ultrasound following surgery.<br><br>Follow-up: **52 weeks** | The patients who received ultrasound bone stimulation showed a statistically significant faster healing rate on plain radiographs at 9 weeks ($p$ = 0.034) and CT scan at 12 weeks ($p$ = 0.017). A 100% fusion rate was noted. The American Orthopaedic Foot and Ankle Society (AOFAS) ankle and hind foot score was also improved at 12 months postoperatively, a finding that was statistically significant ($p$ = 0.026). | Larger studies included in table 2. |
| Deepak M, Mathivanan N et al (2015). Experience on the Use of Ultrasound in Treatment of Non Union / Delayed Union of Fractures.<br>Research Journal of Pharmaceutical, Biological and Chemical Sciences. 6(2), 964-970 | Case series<br>N= 18 cases with fractures located in Tibia, femur, both bones, clavicle and metatarsal<br>subjects with an elapsed time period of 3 months after their last surgical procedure/or injury with no evidence of fracture healing<br>LIPUS treatment for 20 minutes daily. | Average healing time was 21.3 weeks. There was a success rate of 88.89%. | Larger studies included in table 2. |
| Dijkman BG, Sprague S et al (2009). Low-intensity pulsed ultrasound: Nonunions. Indian Journal of Orthopaedics.43 92):141-148 | Systematic review<br>Articles published up to 2008<br>1RCT, 7 case series (5 prospective and 2 retrospective) were included. | We found 79 potentially eligible publications, of which 14 met our inclusion criteria. Of these, eight studies were used for data abstraction. Healing rates averaged 87%, (range 65.6%-100%) among eight trials. Mean time to healing was 146.5 days, (range 56-219 days). There is evidence from trials that low-intensity pulsed ultrasound may be an effective treatment for healing of nonunions. More homogeneous and larger controlled series are needed to further investigate its efficacy. | Most up to date systematic reviews included in table 2. |

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| Farkash U, Bain O et al (2015). Low-intensity pulsed ultrasound for treating delayed union scaphoid fractures: case series. Journal of Orthopaedic Surgery and Research, 10:72 | Case series<br>N=29 scaphoid nonunions<br>LIPUS treatment<br>(2 subgroups: late diagnosed n=16, early diagnosed n=13) | Overall, 22 of 29 (76 %) fractures healed, 12 of 13 (92 %) of the early diagnosed group, and 10 of 16 (63 %) of the late diagnosed group. Difference in healing rate between proximal pole, waist, and distal pole fractures was not statistically significant. | Included in systematic review (Seger EW 2017) added to table 2. Study included in systematic review (Leighton R 2017) added to table 2. |
| Fujioka H, Tsunoda M, Noda M et al. (2000) Treatment of ununited fracture of the hook of hamate by low-intensity pulsed ultrasound: a case report. [Review] [12 refs]. Journal of Hand Surgery - American Volume 25:77-79. | Case report<br>n = 1<br>FU = 6 months | Patient sought treatment 4 months after injury. Union confirmed with x-ray and CT after 4.5 months of treatment. Patient asymptomatic at 6 months. | Larger studies included in Table 2. |
| Fujioka H, Kokubu T et al (2009). Stress Fracture of the Fifth Metatarsal Bone as a Late Complication of Total Knee Arthroplasty. Kobe J. Med. Sci., Vol. 55, No. 4, pp. E93-E97. | Case report<br>N=1<br>Stress fracture of the left fifth metatarsal bone after TKA, the fracture was treated with internal fixation using a screw and low-intensity pulsed ultrasound treatment.<br>follow-up: 2 year | | Larger studies included in table 2. |
| Fujioka H, Tanaka J, Yoshiya S et al. (2004) Ultrasound treatment of nonunion of the hook of the hamate in sports activities. Knee Surgery, Sports Traumatology, Arthroscopy 12:162-164. | Case report<br>n = 2<br>FU = 4 months | 2 baseball players reported disappearance of pain and bone union conformed by CT at end of 4 months of treatment. | Larger studies included in Table 2. |
| Fujishiro T, Matsui N, Yoshiya S et al. (2005) Treatment of a bone defect in the femoral shaft after osteomyelitis using low-intensity pulsed ultrasound. European Journal of Orthopaedic Surgery and Traumatology 15:244-246. | Case report<br>n = 1<br>FU = 6 weeks | After 2 months of ultrasound treatment, rapid bone growth with radiographic bridging of the bone defect was observed and the external fixator removed. Fracture was completely consolidated at 3 months. | Larger studies included in Table 2. |

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| Gan TY, Kuah DE, Graham KS, Markson G (2014). Low-intensity pulsed ultrasound in lower limb bone stress injuries: a randomized controlled trial. *Clin J Sport Med*; 24:457-60. doi:10.1097/JSM.0000000000000084 pmid: 24667169. | Double-blinded, randomised, placebo-controlled trial<br>N=23 stress fracture (tibia, fibula, metatarsal)<br>Non operative management<br>LIPUS 10 versus placebo 13 (sham device)<br>Follow-up: 12 weeks | There were no significant differences between the treatment and placebo conditions for changes in MRI grading (2.2 vs 2.4, *P* = 0.776) or bone marrow edema size (3 vs 4.1, *P* = 0.271). There were no significant differences between the treatment and placebo conditions for the 6 clinical parameters. | Included in systematic review (Stefan 2017) added to table 2. |
| Griffin XL (2016). Low intensity pulsed ultrasound for fractures of the tibial shaft. BMJ 355:i5652. | Editorial | Authors report important patient-centred outcomes with a precise estimate, showing that low intensity pulsed ultrasound is of no benefit to adults with tibial fractures treated with an intramedullary nail. It is time for us to make good use of their determination and abandon this ineffective treatment. | Editorial |
| Griffin XL; Costello I et al (2008). The role of low intensity pulsed ultrasound therapy in the management of acute fractures: a systematic review. J Trauma; 65(6):1446-52 (ISSN: 1529-8809) | Systematic review of low intensity pulsed ultrasound (LIPUS) in the management of acute long bone fractures. | Seven randomised controlled trials and two meta-analyses were retrieved using the search strategy. The literature supports the use of LIPUS in the treatment of acute fractures treated with plaster immobilization. | Most up to date systematic reviews included in table 2. |

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| Griffin L X, Smith N, Parsons M et al. (2014) Ultrasound and shockwave therapy for acute fractures in adults. Cochrane Database of Systematic Reviews: 2):CD008579. | Systematic review of RCTs low intensity ultrasound (LIPUS), high intensity focused ultrasound (HIFUS) and extracorporeal shockwave therapies (ECSW) as part of the treatment of acute fractures in adults. | 12 studies, involving 622 participants with 648 fractures, were included. 11 trials on LIPUS and 1 trial on ECSW. 4 trials included participants with conservatively treated upper limb complete fractures and 6 trials included participants with lower limb complete fractures; these were surgically fixed in four trials. 2 trials reported results for conservatively treated tibial stress fractures. One study of complete fractures found little evidence of a difference between the two groups in the time to return to work (mean difference (MD) 1.95 days favoring control, 95% confidence interval (CI) -2.18 to 6.08; 101 participants). Pooled estimates from two studies found LIPUS did not significantly affect the time to return to training or duty in soldiers or midshipmen with stress fractures (mean difference -8.55 days, 95% CI -22.71 to 5.61). After pooling results from eight studies (446 fractures), the data showed no statistically significant reduction in time to union of complete fractures treated with LIPUS (standardised mean difference (SMD) -0.47, 95% CI -1.14 to 0.20). Subgroup analysis comparing conservatively and operatively treated fractures raised the possibility that LIPUS may be effective in reducing healing time in conservatively managed fractures, but the test for subgroup differences did not confirm a significant difference between the subgroups. Pooled results from 8 trials (333 fractures) reporting proportion of delayed union or non-union showed no significant difference between LIPUS and control. Adverse effects directly associated with LIPUS and associated devices were found to be few and minor, and compliance with treatment was generally good. | More up to date reviews included in table 2. |

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| Gebauer D, Mayr E, Orthner E et al. (2005) Low-intensity pulsed ultrasound: effects on nonunions. Ultrasound in Medicine & Biology 31:1391-1402. | Case series (prospective cohort)<br><br>n = 67 established nonunion<br><br>FU (length of treatment) = 168 days (mean) | 85% (57/67) fractures clinically and radiographically healed. | Study included in systematic review (Leighton R 2017) added to table 2. |
| Gebauer D and Correll J. (2005) Pulsed low-intensity ultrasound: a new salvage procedure for delayed unions and nonunions after leg lengthening in children. Journal of Pediatric Orthopedics 25:750-754. | Case series<br><br>n = 17<br><br>FU = up to 12 months | All cases healed within 3-12 months. | Larger studies included in Table 2. |
| Giannini S, Giombini A, Moneta MR et al. (2004) Low-intensity pulsed ultrasound in the treatment of traumatic hand fracture in an elite athlete. American Journal of Physical Medicine & Rehabilitation 83:921-925. | Case report<br><br>n = 1<br><br>FU = 2 months | Goalkeeper able to go back to training after 24 days of treatment. Complete healing confirmed by radiography at 2 months. | Larger studies included in Table 2. |
| Gold SM and Wasserman R. (2005) Preliminary results of tibial bone transports with pulsed low intensity ultrasound (Exogen). Journal of Orthopaedic Trauma 19:10-16. | Case series<br><br>n = 8<br><br>FU = 12.4 months (mean) | External fixation index reduced by 1.21%. | Larger studies included in Table 2. |
| Handolin L, Kiljunen V, Arnala I et al. (2005) Effect of ultrasound therapy on bone healing of lateral malleolar fractures of the ankle joint fixed with bioabsorbable screws. Journal of Orthopaedic Science 10:391-395. | RCT<br><br>n = 22 (11 ultrasound vs 12 sham)<br><br>FU = 42 days | % Bone healing at 9 weeks: difference of means: 0.038 (95% CI: -0.29 to 0.365) | Included in systematic review reported in Table 2. |

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| Handolin L, Kiljunen V, Arnala I et al. (2005) No long-term effects of ultrasound therapy on bioabsorbable screw-fixed lateral malleolar fracture. Scandinavian Journal of Surgery: SJS 94:239-242. | RCT<br><br>n = = 16(8 ultrasound vs 8 sham)<br><br>FU = 18 months | No differences observed in clinical outcomes between groups. | Subset of Handolin 2005 patients included in systematic review added to table 2. |
| Hannemann PFW, Mommers EHH et al (2014). The effects of low-intensity pulsed ultrasound and pulsed electromagnetic fields bone growth stimulation in acute fractures: a systematic review and meta-analysis of randomized controlled trials. Archives of Orthopaedic and Trauma Surgery, Volume 134, Issue 8, pp 1093–1106 | Systematic review and meta-analysis of randomised controlled trials comparing pulsed electromagnetic fields (PEMF) or low-intensity pulsed ultrasound (LIPUS) bone growth stimulation with placebo for acute fractures.<br>Variety of bone injuries (fresh, malunions or nonunions in all types of bones) | Seven hundred and thirty-seven patients from 13 trials were included. Pooled results from 13 trials reporting proportion of nonunion showed no significant difference between PEMF or LIPUS and control. With regard to time to radiological union, we found heterogeneous results that significantly favoured PEMF or LIPUS bone growth stimulation only in non-operatively treated fractures or fractures of the upper limb. Furthermore, we found significant results that suggest that the use of PEMF or LIPUS in acute diaphyseal fractures may accelerate the time to clinical union. | Most up to date systematic reviews added to table 2.<br>PEMF and LIPUS data analysed together. |
| Heckman JD, Ryaby JP, McCabe J et al. (1994) Acceleration of tibial fracture-healing by non-invasive, low-intensity pulsed ultrasound. Journal of Bone & Joint Surgery - American Volume 76:26-34. | RCT patients with closed or grade I open fractures of the tibial shaft<br>**97** (48 vs 49) low-intensity pulsed ultrasound (daily 20 minute session through a window in the cast for 20 weeks or until investigator considered the fracture to have healed) width 200μs, 1.5MHz sine waves, repetition rate 1 kHz and intensity 30 $mW/cm^2$] vs sham control.<br>Follow-up: ultrasound group: 250 days (mean); sham group: 284 days (mean) | At the end of the treatment, there was a statistically significant decrease in the time to clinical healing (86 +/- 5.8 days in the active-treatment group compared with 114 +/- 10.4 days in the control group) (p = 0.01) and also a significant decrease in the time to over-all (clinical and radiographic) healing (96 +/- 4.9 days in the active-treatment group compared with 154 +/- 13.7 days in the control group) (p = 0.0001). The patients' compliance with the use of the device was excellent, and there were no serious complications related to its use. | Included in Busse 2009 added to table 2 |

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| Hemery X, Ohl X et al (2011). Low-intensity pulsed ultrasound for non-union treatment: a 14 case series evaluation. Orthopedic and Traumatologic Surgery Research. 97-1, 51-57. | Retrospective case series<br>N=14 surgically treated long-bone non-union.<br>LIPUS | Bone consolidation was obtained in 11 of the 14 cases (79%), and within 3 months of treatment in 27% (3/11), within 6 months in 27% (3/11) and within 9 months in 46% (5/11). There were no treatment-linked complications. There was no significant correlation between interval to initiation of ultrasound treatment and bone consolidation. Associated sepsis or atrophy did not significantly impact treatment efficacy. | Larger studies included in table 2. |
| Huber M, Prantl L (2012).Successful treatment of nonunion in severe finger injury with low-intensity pulsed ultrasound (LIPUS): a case report. Journal of Medical Case Reports 2012, 6:209. | Case report | LIPUS was successfully used in a 19-year-old Caucasian man with a nonunion of his ring finger after injury and first treatment with K-wire osteosynthesis. | Larger studies included in table 2. |
| Jensen JE. (1998) Stress fracture in the world class athlete: a case study. Medicine & Science in Sports & Exercise 30:783-787. | Case report<br>n = 1<br>FU = 6 weeks | After 3 weeks of treatment a gymnast was able to return to training and full competition at 6 weeks. | Larger studies included in Table 2. |
| Jingushi S, Mizuno K, Matsushita T et al. (2007) Low-intensity pulsed ultrasound treatment for postoperative delayed union or nonunion of long bone fractures. Journal of Orthopaedic Science 12:35-41. | Case series (prospective cohort study)<br>n = 72 established nonunion<br>FU = 11.5 months | When ultrasound started within 6 months of most recent operation, 89.7% of all fractures healed. | Study included in systematic review (Leighton R 2017) added to table 2. |
| Jones CP, Coughlin MJ, and Shurnas PS. (2006) Prospective CT scan evaluation of hindfoot nonunions treated with revision surgery and low-intensity ultrasound stimulation. Foot & Ankle International 27:229-235. | Case series<br>n = 13 (19 joints)<br>FU = 16.3 months (mean) | Result: One non-union, 5 partial unions and 13 complete unions at follow-up. | Larger studies included in Table 2. |

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| Abouddi J, J Schroeder et al (2015). Low-Intensity Pulsed Ultrasound Bone Stimulator Treatment for Symptomatic Distal Phalangeal Shaft Fracture Nonunion. The Journal of Bone and Joint surgery. 5:e78 | Case report<br>N=2 cases of symptomatic distal phalangeal fracture nonunion that were treated with a course of digital splinting and daily external low-intensity pulsed ultrasound (LIPUS) treatment. | Osseous union, symptom resolution, and full range of motion were successfully achieved in both cases without surgery. | Larger studies included in table 2. |
| Manufacturer registry data from USA (Heppenstell 1999, unpublished) reported in<br>Medicare Services Advisory Committee. (2001) Low intensity ultrasound treatment for acceleration of bone fracture healing: Exogen bone growth stimulator. Report 52- | Case series<br><br>n = 313 (nonunions)<br><br>FU = 9 months | 74% (232/313) healed at 9 months<br>Mean healing time: 152±4.2 days | Larger studies included in Table 2.<br><br>Not published in a peer reviewed journal. |
| Manufacturer data from Germany (Gebauer 1998, unpublished) reported in<br>Medicare Services Advisory Committee. (2001) Low intensity ultrasound treatment for acceleration of bone fracture healing: Exogen bone growth stimulator. Report 52- | Case series<br><br>n = 41(nonunions)<br><br>FU = 9 months | 82.9% (34/41) healed at 9 months<br>Mean healing time: 160±10 days | Larger studies included in Table 2.<br><br>Not published in a peer reviewed journal. |
| Lerner A, Stein H, and Soudry M. (2004) Compound high-energy limb fractures with delayed union: our experience with adjuvant ultrasound stimulation (exogen). Ultrasonics 42:915-917. | Case series<br><br>n = 17<br><br>FU = up to 72 months | 16 fractures healed within 13-52 weeks despite severe soft-tissue injuries and varying degrees of tissue loss. | Larger studies included in Table 2. |

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| Lüthje P and Nurmi-Lüthje I. (2006) Non-union of the clavicle and delayed union of the proximal fifth metatarsal treated with low-intensity pulsed ultrasound in two soccer players. Journal of Sports Medicine & Physical Fitness 46:476-481. | Case report<br><br>n = 2<br><br>FU = 3 months | 2 soccer players treated for 3 months reported excellent end results (confirmed by MRI and radiography) and continued to play at the same level. | Larger studies included in Table 2. |
| Kristiansen TK, Ryaby JP et al (1997). Accelerated Healing of Distal Radial Fractures with the Use of Specific, Low-Intensity Ultrasound. A Multicenter, Prospective, Randomized, Double-Blind, Placebo-Controlled Study. The Journal of Bone and Joint Surgery. VOL. 79-A, 7, 961-973. | RCT<br>Patients with dorsally angulated fractures (negative volar angulation) of the distal aspect of the radius that had been treated with manipulation and a cast<br>30 LIPUS vs 31 placebo<br>Follow-up: 16 weeks | The time to union was shorter with ultrasound than those that were treated with the placebo 61 ± 3 days compared with 98 ± 5 days; $p < 0.0001$). Radiographic stage of healing also was significantly accelerated with ultrasound as compared with placebo. Treatment with ultrasound was associated with a significantly smaller loss of reduction (20 ± 6 per cent compared with 43 ± 8 per cent; $p < 0.01$), as determined by the degree of volar angulation, as well as with a significant decrease in the mean time until the loss of reduction ceased (12 ± 4 days compared with 25 ± 4 days; $p < 0.04$). | Study included in systematic reviews added to table 2. |
| Kumahashi N, Uchio Y, Iwasa J et al. (2008) Bone union of painful bipartite patella after treatment with low-intensity pulsed ultrasound: Report of two cases. Knee 15:50-53. | Case report<br><br>n = 2<br><br>FU = 4 months | Patellar pain disappeared within 2 months of treatment in both cases and bone union confirmed by radiography at 4 months. | Larger studies included in Table 2. |
| Lee SY, Niikura T et al (2016). Treatment of ununited femoral neck fractures in young adults using low-intensity pulsed ultrasound: Report of 2 cases. International Journal of Surgery Case Reports 21, 59–62. | Case report<br>N=2<br>Two cases of ununited femoral neck fractures in young adults treated with low-intensity pulsed ultrasound (LIPUS). | After 6 to 8 months LIPUS treatment the delayed and non-union fractures were completely consolidated. | Larger studies included in table 2. |

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| Leung KS, Lee WS, Tsui HF et al. (2004) Complex tibial fracture outcomes following treatment with low-intensity pulsed ultrasound. Ultrasound in Medicine & Biology 30:389-395. | RCT<br>Patients with open tibial fractures and high-energy-induced complex tibial fractures immobilised with internal or external fixators. **30** (16 vs 14)<br>Low-intensity pulsed ultrasound (daily 20 minute session for 90 days, width 200μs, 1.5MHz sine waves, and repetition rate 1 kHz and intensity 30 mW/cm$^2$) vs sham control.<br>Follow-up: 9 months | The LIPUS-treated group showed statistically significantly better healing, as demonstrated by all assessments. Complications were minimal in the LIPUS group. There were two cases of delayed union, with one in each group. There were two cases of infection in the control group. The delayed-union cases were subsequently treated by LIPUS and the infection cases were treated with standard protocol. Fracture healing in these patients was again treated by LIPUS. | Included in systematic review added to table 2. |
| Lenza M, Belloti JC (2009). Conservative interventions for treating middle third clavicle fractures in adolescents and adults (Review). *Cochrane Database of Systematic Reviews* 2009, Issue 2. Art. No.: CD007121. DOI:<br>10.1002/14651858.CD007121.pub2. | Cochrane review | The third trial, which evaluated therapeutic ultrasound in 120 participants, was also underpowered but had a low risk of bias. The trial found no statistically significant difference between low-intensity pulsed ultrasound and placebo in the time<br>to clinical fracture healing (mean difference -0.32 days, 95% CI -5.85 to 5.21 days) nor in any of the other reported outcomes. | Study on LIPUS included in Busse 2009 review. |
| Martinez de Albornoz P, Khanna A et al (2011); The evidence of low-intensity pulsed ultrasound for *in vitro*, animal and human fracture healing, *British Medical Bulletin*, Volume 100, Issue 1, 1, Pages 39–57, | Systematic review<br>Evidence on in vitro and animal and human studies included. | The evidence *in vitro* and animal studies suggests that LIPUS produces significant osteoinductive effects, accelerating the healing process and improving the bone-bending strength. The evidence in human trials is controversial in fresh, stress fractures and in limb lengthening. LIPUS is effective in delayed unions, in smokers and in diabetic population. There is heterogeneity among *in vitro*, animal studies and their application to human studies. Further randomised controlled trials of high methodological quality are needed. | Most up to date systematic reviews included in table 2. |

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| Mayr E, Frankel V, and Ruter A. (2000) Ultrasound--an alternative healing method for nonunions? Archives of Orthopaedic & Trauma Surgery 120:1-8. | Retrospective review (registry data)<br>n = 1317 patients with delayed unions (951) and non-unions (366)<br>Low-intensity pulsed ultrasound (daily 20 minute session, width 200µs, 1.5MHz sine waves, repetition rate 1 kHz and intensity 30 $mW/cm^2$).<br><br>Follow-up (fracture age): up to 755 days | The overall success rate for delayed unions was 91% (average healing time 129 ± 2.7 days) and for nonunions 86% (average healing time 152±5.3 days). Patient medication with calcium channel blockers, nonsteroidal anti-inflammatory drugs, renal or vascular insufficiency and steroids is a negative predictor for healing nonunions. Patients who were smokers during ultrasound therapy had lower healing rates than those who never smoked. | Larger studies included in table 2. |
| Massari L, Caruso G et al (2009). Pulsed electromagnetic fields and low intensity pulsed ultrasound in bone tissue. Clinical Cases in Mineral and Bone Metabolism; 6(2): 149-154. | Review | Many clinical studies agree in confirming that biophysical stimuli are able to lead to healing in 75-85% of patients with nonunions. Prospective, randomised<br>and double-blind studies show that by employing biophysical<br>stimuli the time needed for a fresh fracture to heal can be reduced "on average" by 25-38%. | Review |
| Mehta S, Long K et al (2015). Low-intensity pulsed ultrasound (LIPUS) can decrease the economic burden of fracture non-union. Journal of Medical Economics. Vol18-7, 542-549. | Retrospective cohort study<br>N=1158 patients<br>Surgery versus LIPUS | Surgery Only' patients used significantly more healthcare services. In the year following intervention, 'Surgery Only' patients had total medical costs $6289 higher than 'LIPUS Only' patients (Mean = $11,276 vs $4986; $p < 0.0001$). Outpatient costs accounted for >68% of overall costs in both cohorts, and outpatient costs were significantly higher among the 'Surgery Only' cohort (Mean = $7682 vs $4196; $p < 0.0001$). Total inpatient costs were also significantly higher among the 'Surgery Only' cohort (Mean = $3302 vs $381; $p < 0.0001$). | Economic costs on non-unions |

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| Mundi R, Petis S et al (2009). Low-intensity pulsed ultrasound: Fracture healing. Indian Journal of Orthopaedics. 43(2), 132-140. | Systematic review | The types of fractures studied among these seven trials included lateral malleolar, radial, and tibial fractures. 3 of the 7 trials found that LIPUS significantly reduces healing time compared with placebo, whereas the other four did not find a statistically significant difference. There is a substantial level of inconsistency in the findings of several RCTs evaluating the efficacy of LIPUS as an adjunct for fracture healing. Although LIPUS has proven to be effective in certain trials for accelerating fracture healing, no definitive statement can be made regarding its universal use for all fracture types and methods of fracture care. | Most up to date studies included in table 2. |
| Moghaddam A, Yildirim TM et al (2016). Low intensity pulsed ultrasound in the treatment of long bone nonunions: Evaluation of cytokine expression as a tool for objectifying non-union therapy. Journal of Orthopaedics 12, 206-12. | Prospective comparative study<br>N=23 nonunions<br>N=11 successful LIPUS therapy versus 8 unsuccessful LIPUS therapy.<br>Follow-up: 3 months | Blood analysis: The TGF-β1 serum concentration increased from the pre-treatment value to 1 week within the unsuccessful group. Otherwise, no significant differences between groups in measured cytokines during LIPUS therapy could be detected. Our findings suggest that LIPUS does not lead to a significant increase in cytokine levels in patients with nonunions. It is likely that “successful” treatment can be attributed to spontaneous healing. Our results suggest that LIPUS is not a proper treatment for long bone nonunions | Analysis of serum cytokine expression. |
| Nolte PA, van der Krans A, Patka P et al. (2001) Low-intensity pulsed ultrasound in the treatment of nonunions. Journal of Trauma-Injury Infection & Critical Care 51:693-702. | Case series (prospective cohort study)<br><br>n = 29 established nonunions<br><br>FU (fracture age)= up to 398 days | 86% (25/29) non-union cases healed in an average of 22 weeks. | Study included in systematic review (Leighton R 2017) added to table 2. |

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| Nolte P, Anderson R et al (2016). Heal rate of metatarsal fractures: a propensity-matching study of patients treated with low-intensity pulsed ultrasound (LIPUS) vs surgical and other treatments. Injury. 47 (11), 2584-2590. | Retrospective observational cohort study (LIPUS registry data were propensity-matched to metatarsal fracture patients from a health claims database)<br>N=594 metatarsal fractures were treated with LIPUS, including 161 Jones fractures. | LIPUS-treated patients were more likely to: be overweight or obese; be male; have open fracture; and smoke (all, $P < 0.0001$), suggesting that these variables were perceived as nonunion risk factors by prescribing physicians. After propensity-matching, none of these differences between the registry and the health claims database remained significant. The heal rate with LIPUS treatment was 97.3%, comparable to the heal rate of 95.3% among claims patients in 2011 who did not receive LIPUS ($P = 0.0654$). When fresh fractures (0–90 days) and delayed unions (91–365 days) were analyzed separately, the LIPUS fresh fracture heal rate was superior to claims patients ($P = 0.0381$), and the delayed union heal rate was comparable. After exclusion of registry patients who received surgery, heal rate with LIPUS alone (97.4%) was significantly better ($P < 0.0097$) than the heal rate for matched patients in 2011 (94.2%). LIPUS significantly improved the heal rate of metatarsal fractures <1 year old without surgery ($P = 0.0097$). Metatarsal fractures treated with LIPUS alone have a heal rate comparable to fractures treated by surgical intervention. | Retrospective study with registry data from 1994-1998. |

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| Ota T, Itoh S et al (2017). Comparison of treatment results for Mallet finger fractures in children between low-intensity pulsed ultrasound stimulation and Ishiguro's method. American association for hand surgery.1-6. | Comparative case series<br>N=19 displaced mallet finger fractures in children.<br>Ishiguro's method involves extension block and arthrodesis of the distal interphalangeal (DIP) joint with pinning (n=11) and LIPUS (n=8) | The duration needed for fracture healing was longer, however, active extension and flexion of the DIP joint were significantly larger in the LIPUS group compared with those in the pinning group. Functional recovery was excellent in all cases in the LIPUS group; however, recovery was good in 3 cases and excellent in 8 cases in the pinning group. Extension of the DIP joint was significantly larger when pins were removed in 35 or lesser days postoperatively compared with cases in which pin fixation was continued for more than 35 days. LIPUS therapy may be recommended as an option to treat type I mallet finger in children for whom initiation of treatment was delayed up to 8 weeks. When Ishiguro's method is applied to the displaced mallet fracture in children, arthrodesis of the DIP joint for more than 5 weeks should be avoided to prevent flexion contracture. | Small study with lack of control group. |
| Ota T, Itoh S et al (2017). The efficacy and safety of combination therapy of low-intensity pulsed ultrasound stimulation in the treatment of unstable both radius and ulna fractures in children. Bio-Medical Materials and Engineering. 28, 545-553. | Retrospective study<br>N=44 (25 children with both radius and ulna fracture diaphysis (mid-R&U) and 19 metaphysis (dist-R&U) fractures, treated with intramedullary nailing followed by cast and splint mobilization. 13 in mid R&U and 8 in dist R&U were combined with LIPUS stimulation. | Periosteal callus appeared significantly earlier after surgery in the LIPUS-treated groups than in the group without LIPUS treatment. The duration of external fixation was significantly shorter in the dist-R&U fracture group treated with LIPUS stimulation compared with that in the mid-R&U fracture group without LIPUS treatment. The time span needed for bone union in the groups with LIPUS stimulation was significantly shorter than in the groups without LIPUS stimulation. LIPUS stimulation can lead to a reduction of treatment periods of unstable forearm fractures safely after operation even in children. | Small retrospective study not randomised. |

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| Oda, Kohtaroh, Ohba, Tetsuro, Ebata, Shigeto and Haro, Hirotaka. Low-Intensity Pulsed Ultrasound and Halo Immobilization Is an Effective Treatment for Nonunion Following Traumatic Spondylolisthesis of the Axis. Journal of neurological surgery reports (78) 4 e119-e122 2017. | Case report describes traumatic spondylolisthesis that resulted in nonunion, angulation, and displacement after treatment with a cervical collar for 3 months, and treated with halo immobilization and low-intensity pulsed ultrasound (LIPUS). | Radiographs and computed tomography showed conclusive evidence of bone union after 10 weeks of treatment with halo immobilization. No adverse events were observed. This is the first report describing that the combination of halo immobilization and LIPUS therapy might be a safe, effective, and feasible method by which to treat cervical spine fractures. | Larger studies included in table 2. |
| Pigozzi F, Moneta MR, Giombini A et al. (2004) Low-intensity pulsed ultrasound in the conservative treatment of pseudoarthrosis. Journal of Sports Medicine & Physical Fitness 44:173-178. | Case series<br><br>n =15 established nonunion<br><br>Follow-up = up to 24 weeks | Mean healing time: 94.7±43.8 days | Study included in systematic review (Leighton R 2017) added to table 2. |
| Rocca GJD (2009). The science of ultrasound therapy for fracture healing. Indian Journal of Orthopaedics. 43(2), 121-126. | Review to establish basic science evidence of therapeutic role of lipus in fracture healing. | A large body of cellular and animal research exists which reveals that LIPUS may be beneficial for fracture healing and for promotion of fracture healing in compromised tissue beds. | General review |
| Ricardo M. (2006) The effect of ultrasound on the healing of muscle-pediculated bone graft in scaphoid non-union. International Orthopaedics 30:123-127. | RCT<br>Patients with fractures of the scaphoid treated with vascular pedicle bone graft for non-union.<br>n = **21** (10 vs 11) low-intensity pulsed ultrasound (daily 20 minute session with signal intensity 30 mW/cm$^2$) vs sham control.<br>Follow-up: 2.3 years (mean) | Time to healing 56±3.2 days versus 94±4.8 days; p <0.001. 66.7% (14/21) patients were very satisfied with the results of surgery. 71.4% (15/21) had occasional; pain or discomfort with strenuous activity. 52.4% (11/21) returned to their previous occupation and leisure activity with mild limitation. | Included in systematic reviews reported in Table 2. |

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| Riboh JC, Leversedge FJ (2012). The Use of Low-Intensity Pulsed Ultrasound Bone Stimulators for Fractures of the Hand and Upper Extremity. The Journal of Hand Surgery. 37,7, 1456-61. | Review | Critical review of literature suggests that the evidence supporting LIPUS for the treatment of acute fractures might be better than that evaluating its use for the treatment of delayed union or nonunions of fractures. | Review |
| Rutten S, Nolte PA, Guit GL et al. (2007) Use of low-intensity pulsed ultrasound for posttraumatic nonunions of the tibia: a review of patients treated in the Netherlands. Journal of Trauma-Injury Infection & Critical Care 62:902-908. | Case series<br><br>n = 71 established tibial nonunions.<br><br>FU (fracture age)= 257 days (mean) | Healing rate of 73% (52/71). Ultrasound treatment shows a statistically significant higher healing rate compared with the chance of spontaneous healing ($p < 0.0001$). | Study included in systematic review (Leighton R 2017) added to table 2. |
| Rutten S, Nolte PA et al (2008). Low-intensity pulsed ultrasound increases bone volume, osteoid thickness and mineral apposition rate in the area of fracture healing in patients with a delayed union of the osteotomized fibula. Bone 43-2, 348-354. | Biopsies were obtained from 13 patients (9 female, 4 male; age 42-63) with a delayed union of the osteotomized fibula after a high tibial osteotomy, treated for 2-4 months with or without LIPUS in a randomised prospective double-blind placebo-controlled trial. | Our results suggest that LIPUS accelerates clinical fracture healing of delayed unions of the fibula by increasing osteoid thickness, mineral apposition rate, and bone volume, indicating increased osteoblast activity, at the front of new bony callus formation. Improved stability and/or increased blood flow, but probably not increased angiogenesis, might explain the differences in ossification modes between LIPUS-treated delayed unions and untreated controls. | Histology and histomorphometri c analysis. |
| Maeda S, Tsuda E et al (2014). Histological evaluation of low-intensity pulsed ultrasound on osteochondritis dissecans of the humeral capitellum. Asia-Pacific Journal of Sports Medicine, Arthroscopy, Rehabilitation and Technology 2 56-62 | Case series<br>N=15 Hhistopahologically evaluate the effect of LIPUS irradiation on elbow OCD.<br>LIPUS group n=7, vs 8 control. | LIPUS stimulation increased the expression levels of OPN in elbow OCD. | Histological findings. |

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| Sakuma Y; Iwamoto T et al (2014). Ununited fracture of the hook of hamate treated with low-intensity pulsed ultrasound in an older middle-aged patient. Clin J Sport Med; 24(4):358-9 | Case series<br>N=1 fracture at the base of the hook of hamate in middle aged patient.<br>Low-intensity pulsed ultrasound without a splint. | Bone union was confirmed 12 months after the ultrasound treatment started. | Larger studies included in table 2. |
| Schortinghuis J, Bronckers AL, Gravendeel J et al. (2008) The effect of ultrasound on osteogenesis in the vertically distracted edentulous mandible: a double-blind trial. International Journal of Oral & Maxillofacial Surgery 37:1014-1021. | RCT<br><br>n = 9 (5 ultrasound vs 4 sham)<br><br>FU = 44 months (mean) | No difference between groups. | Included in systematic review reported in Table 2. |
| Schofer MD, Block JE, Aigner J, Schmelz A (2010). Improved healing response in delayed unions of the tibia with low-intensity pulsed ultrasound: results of a randomized sham-controlled trial. *BMC Musculoskelet Disord*;11:229. doi:10.1186/1471-2474-11-229 pmid: 20932272. | RCT multi-centre randomised sham-controlled trial<br>Non-union (Tibia)<br>Operative management<br>LIPUS n=51 versus Sham n=50<br>Follow-up: 16 weeks | Based on log-transformed data, mean improvement in BMD was 1.34 (90% confidence interval (CI) 1.14 to 1.57) times greater for LIPUS-treated subjects compared with sham (p = 0.002). A mean reduction in bone gap area also favored LIPUS treatment (p = 0.014). | Included in systematic review (Stefan 2017) added to table 2. |
| Snyder BM, Conley J (2012). Does low-intensity pulsed ultrasound reduce time to fracture healing? A meta-analysis. The American Journal of Orthopaedics. 41 (2) E12-19. | Meta-analysis of RCTs (LIPUS versus placebo) on acceleration of fracture healing<br>Skeletally matured patients with at least 1 fracture | 5 RCTs involving 209 patients (266 fractures) included. Results showed a mean reduction in fracture healing time of 36 days. Meta-analysis failed tests for heterogeneity. Subgroup analyses based on non-operative, operative and tibial fractures did not reveal the source of heterogeneity. These results corroborate inconclusive evidence by 2 previous reviews and strengthen the call for further research. | Most up to date systematic review included in table 2. |

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| Teoh KH, Whitham R et al (2018). The use of low-intensity pulsed ultrasound in treating delayed union of fifth metatarsal fractures. The Foot (in-press, accepted manuscript, available online January 2018) | Retrospective review<br>N=30<br>LIPUS following a delayed union of fifth metatarsal fracture<br>Follow-up: 3 years | 27 (90%) patients went on to progress to union clinically and radiologically following LIPUS treatment. Smoking (p = 0.014) was predictive of non-union. Assuming that we had 10 delayed unions a year and 6 went on to non-union as previously suggested by a systematic review, the cost savings of using LIPUS (90% success rate; 10 LIPUS machine and surgery for 1 non-union) vs operative intervention (surgery for 6 non-union) equates to a cost saving of £7765 a year. | Larger studies with efficacy data are included in table 2 and economic costs are outside the remit of IP programme. |
| Tomaru M, Osada D et al (2014). Treatment of hook of the hamate fractures in adults using low intensity pulsed ultrasound. Hand Surg. 19, 433. | Case report<br>N=2 delayed unions and one nonunion of hook of the hamate fractures in adults were treated with low-intensity pulsed ultrasound (LIPUS). | In all cases, bony union was confirmed on carpal tunnel radiographs or computed tomography at the final follow-up time of eight and 36 months after injuries. | Larger studies included in table 2. |
| Tajali Bs, Houghton P et al (2012). Effects of Low-Intensity Pulsed Ultrasound Therapy on Fracture Healing: A Systematic Review and Meta-Analysis. American Journal of Physical Medicine & Rehabilitation: Volume 91 - Issue 4 - p 349–367 | Systematic Review and Meta-Analysis on effects of low-intensity pulsed ultrasound (LIPUS) on bone regeneration.<br>All types of fractures (fresh, delayed union, nonunion, distraction osteogenesis)<br>23 studies were included (RCTs, non-controlled, cohort studies), all bones, all outcomes. | The time of third cortical bridging was statistically earlier following LIPUS therapy in fresh fractures (mean random effect, 2.263; 95% CI, 0.183–4.343, *P* = 0.033). LIPUS can stimulate radiographic bone healing in fresh fractures. Although there is weak evidence that LIPUS also supports radiographic healing in delayed unions and nonunions, it was not possible to pool the data because of a paucity of sufficient studies with similar outcome measures. | Most up to date studies included in table 2. |

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| Watanabe Y, Matsushita T et al (2010). Ultrasound for fracture healing: current evidence. J Orthop Trauma.24 Suppl 1:S56-61. doi: 10.1097/BOT.0b013e3181d2efaf. | Systematic review | The beneficial effect of acceleration of fracture healing by LIPUS is considered to be larger in the group of patients or fractures with potentially negative factors for fracture healing. The incidence of delayed union and nonunion is 5% to 10% of all fractures. For delayed union and nonunion, the overall success rate of LIPUS therapy is approximately 67% (humerus), 90% (radius/radius-ulna), 82% (femur), and 87% (tibia/tibia-fibula). LIPUS likely has the ability to enhance maturation of the callus in distraction osteogenesis and reduce the healing index. The critical role of LIPUS for fracture healing is still unknown because of the heterogeneity of results in clinical trials for fresh fractures and the lack of controlled trials for delayed unions and nonunions. | Most up to date studies included in table 2. |

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| Watanabe Y, Arai Y et al (2013). Three key factors affecting treatment results of low-intensity pulsed ultrasound for delayed unions and nonunions: instability, gap size, and atrophic nonunion. Journal of Orthopaedic Science<br>Volume 18, Issue 5, pp 803–810 | Retrospective cohort study<br>N=151<br>101 delayed unions<br>50 nonunions<br>LIPUS only<br>Follow-up: 1 year | Delayed union group (*n* = 101): Seventy-five delayed unions (74.3 %) united without an additional major surgical intervention. Failure of LIPUS therapy was associated with types of nonunion (atrophic/oligotrophic vs. hypertrophic, relative risk 23.72 [95 % CI 1.20–11.5], *p* < 0.01), instability at fracture site (unstable vs. stable, relative risk 3.03 [95 % CI 1.67–5.49], *p* < 0.001), and maximum fracture gap size not less than 9 mm (relative risk 3.30 [95 % CI 1.68–6.45]). Nonunion group (*n* = 50): Thirty-four nonunions (68.0 %) united without an additional major surgical intervention. Failure of LIPUS therapy was associated with method of fixation (intramedullary nail vs. others, relative risk 4.50 [95 % CI 1.69–12.00], *p* < 0.001), instability at fracture site (unstable vs. stable, relative risk 4.56 [95 % CI 2.20–9.43], *p* < 0.0001), and maximum fracture gap size not less than 8 mm (relative risk 5.09 [95 % CI 1.65–15.67]). | Study included in systematic review (Leighton R 2017) added to table 2. |
| Walker NA, Denegar CR (2007). Low-intensity pulsed ultrasound and pulsed electromagnetic field in the treatment of tibial fractures: a systematic review. Journal of Athletic Training 2007; 42(4): 530-535 | Systematic review on effectiveness of low-intensity pulsed ultrasound (LIPUS) or pulsed electromagnetic fields (PEMF) for fracture healing<br>Studies before 2001 included | Low-intensity pulsed ultrasound (LIPUS; five studies): Three studies reported statistically significant faster radiographic and clinical healing in patients treated with LIPUS compared with placebo. Two studies reported no significant difference in all outcomes. | Most up to date systematic reviews included in table 2. |

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| Uchiyama Y, Nakamura Y, Mochida J et al. (2007) Effect of low-intensity pulsed ultrasound treatment for delayed and non-union stress fractures of the anterior mid-tibia in five athletes. Tokai Journal of Experimental and Clinical Medicine 32:121-125. | Case series<br>N=5 delayed and non-union stress fractures at the anterior mid-tibia in athletes.<br>LIPUS treatment<br><br>Follow-up: 7.4 months (mean) | Patients returned to full sports activity at an average of 3 months after the onset of treatment (range, 2 to 4 months). Absence of pain was achieved at an average of 3.8 months (range, 2 to 5 months), and disappearance of bone umbauzone was achieved at an average of 11 months (range, 8 to 14 months). | Larger studies included in table 2. |
| Zura R, Rocca GJD et al (2015). Treatment of chronic (>1 year) fracture nonunion: Heal rate in a cohort of 767 patients treated with low-intensity pulsed ultrasound (LIPUS). Injury Volume 46, Issue 10, Pages 2036-2041 | Cohort study (FDA registry data)<br>Fracture non-union<br>N=767 | Heal rate for chronic nonunion patients (*N* = 767) treated with LIPUS was 86.2%. Heal rate was 82.7% among 98 patients with chronic nonunion ≥5 years duration, and 12 patients healed after chronic nonunion >10 years (HR = 63.2%). There was more loss to follow-up, non-compliance and withdrawal in chronic nonunion patients than all other patients ($p < 0.0001$). Age was the only factor associated with failure to heal among chronic nonunions ($p < 0.004$). Chronic nonunion patients averaged 3.1 surgical procedures prior to LIPUS, but some LIPUS-treated patients were able to heal without revision surgery. Among 91 patients who had LIPUS ≥90 days after their last surgery, HR averaged 85.7%, and the time from last surgery to index use of LIPUS averaged 449.6 days. LIPUS enhanced heal rate for fractures that had been nonunion for at least 1 year, including fractures that had been nonunion >10 years. LIPUS resulted in successful healing in the majority of nonunions without further surgical intervention. | Study included in systematic review (Leighton R 2017) added to table 2. |

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| Zura R, Xu ZJ et al (2017). When is a fracture not "fresh"? Aligning reimbursement with patient outcome after treatment with low-intensity pulsed ultrasound. Journal of Orthoapedic Trauma. 31:248-251. | Prospective cohort study.<br>N=5983 FDA mandated post market surveillance registry.<br>LIPUS, 20 min/d. | We estimated the time point at which a fracture responds to LIPUS as well as during the first week after fracture. There was significant bone-to-bone variation; metatarsal was "fresh" until week 7, ankle until week 9, humerus until week 10, and femur and radius until week 12. Healing was significantly affected by patient age, body mass index, and open fracture (all $p \leq 0.02$). Our results suggest that fractures of the metatarsal, femur, humerus, ankle, and radius respond to LIPUS treatment, as if they were still fresh at least 6 weeks longer than the eligibility allowed under current coverage policies. | Registry data reported in table 2a (Zura 2015) |