# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## INTERVENTIONAL PROCEDURES PROGRAMME

## Interventional procedure overview of low-intensity pulsed ultrasound to promote healing of fresh fractures at low risk of non-healing

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.

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## 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 fresh fractures at low risk of non-healing.

### *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. Several factors may influence how well fractures heal including stability of the fracture, its blood supply and patient nutrition.

### *What the procedure involves*

The aim of low-intensity pulsed ultrasound (LIPUS) is to reduce fracture healing time and avoid non-union by delivering micro-mechanical stress to the bone to stimulate bone healing.

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; 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/$cm^2$ 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

## *Fresh fractures*

### Functional outcomes

#### *Time to return to work (number of days)*

In a meta-analysis of 12 randomised controlled trials (RCTs; 1,099 patients) comparing LIPUS with placebo or no treatment in adults with fresh fractures, results from pooled data (2 studies) showed that LIPUS did not reduce the time to return to work (standard mean difference [SMD]: 0.06, 95% confidence interval [CI] −0.14 to 0.27, p=0.56, $I^2$=0%). [2]

In a meta-analysis of 26 RCTs of LIPUS compared with sham or no device in patients with any kind of fracture or osteotomy (6 studies at low risk of bias and 20 studies at high risk of bias), pooled results from 3 trials (2 fresh fracture studies and 1 stress fracture study) showed that compared with the control, LIPUS did not statistically significantly reduce time to return to work or active duty (percentage difference 2.7%, 95% CI −7.7 to 14.3%; $I^2$=0%; p=0.76, 392 patients; moderate certainty). Only 1 trial assessed time to return to work with time-to-event analysis and found no statistically significant effect (hazard ratio 1.11 favouring control, 95% CI 0.82 to 1.50; 343 patients).[1]

#### *Time to full weight bearing (number of days)*

In the meta-analysis of 26 RCTs, the pooled results of 3 trials (operative fresh fractures) showed no statistically significant effect of LIPUS on full weight bearing (percentage difference −16.6%; 95% CI −44.9 to −26.1%; $I^2$=95%, p=0.001, 513 patients). One trial at high risk of bias suggested a benefit (percentage difference −40.0%; 95% CI −48.4 to −30.3%; p<0.001, 30 patients) and differed from the results of 2 RCTs at low risk of bias, which showed that LIPUS did not decrease days to weight bearing (percentage difference 4.8%; 95% CI −4.0 to 14.4%; 483 patients, $I^2$=0%, p=0.37, high certainty). Only 1 trial assessed time to full weight bearing with a time-to-event analysis and found no statistically significant effect (hazard ratio 0.87 favouring LIPUS, 95% CI 0.70 to 1.08; 451 patients).[1]

In the meta-analysis of 12 RCTs, results from pooled data (3 studies) showed that LIPUS did not reduce the time to full weight bearing (SMD: −0.76, 95% CI −1.92 to 0.4, p=0.02, $I^2$=91%).[2]

#### *Other functional outcomes*

In the meta-analysis of 26 RCTs, other functional outcomes (including return to leisure activities, return to household activities, return to level of function before injury, and physical function measured with a multidimensional questionnaire in 2 fresh fracture studies) were not statistically significantly affected by use of LIPUS, nor did they show substantial inconsistency.[1]

**Quality of life (measured by SF-36 physical component summary scores)**

In the meta-analysis of 12 RCTs, results from pooled data (2 studies) showed that LIPUS improved the SF-36 physical component summary scores compared with placebo (SMD: 0.2, 95% CI 0.37 to 0.02, p=0.02, $I^2$=0%). [2]

**Time to radiographic or clinical healing or fracture union (days)**

In the meta-analysis of 26 RCTs, radiographic healing effect varied substantially among studies. Two trials (Busse 2016, 2014 on fresh fractures) used time-to-event analysis to assess time to radiographic healing and showed no statistically significant effect of LIPUS (hazard ratio 1.06 in favour of control, 95% CI 0.86 to 1.32; $I^2$=0%; 532 patients). [1]

In the meta-analysis of 12 RCTs, results from pooled data (11 trials, n=887) showed that LIPUS statistically significantly reduced the time to fracture union (SMD: 0.65, 95% CI [1]1.13 to [1]0.17, p<0.01, $I^2$=89%). The effect of LIPUS was different between time to radiographic fracture union (9 studies; SMD: −0.55, 95% CI −1.01 to 0.09, p=0.02, $I^2$=83% and the time to clinical union (2 studies; SMD: −1.07, 95% CI −3.14 to 1, p=0.31, $I^2$=97%; P=0.63 for interaction).[3] Subgroup analyses showed that LIPUS was effective for fractures treated with conservative management (SMD: −1.08, 95% CI −1.82 to 0.34, p<0.01, $I^2$=90%) but not effective for fractures treated with operative management (SMD: −0.25, 95% CI −0.78 to 0.28, p=0.35, $I^2$=78%; p=0.07 for interaction).[3] LIPUS was effective on upper limb fractures (SMD: −1.08, 95% CI −2.05 to −0.11, p=0.03, $I^2$=92%) but not lower limb fractures (SMD: −0.39, 95% CI −0.91 to 0.13, p=0.14, $I^2$=83%; p=0.22 for interaction). LIPUS reduced time to fracture union when treatment duration was less than 6 months (SMD: −0.87, 95% CI −1.72 to −0.02, p=0.04, $I^2$=91%) but when the duration was up to the time of healing the effect of LIPUS was not statistically significant (SMD: −0.39, 95% CI −0.91 to 0.14, p=0.15, $I^2$=82%; p=0.34 for interaction).[2]

In a cohort study of 4,190 patients with fresh fractures treated with LIPUS, early use of LIPUS was associated with fracture healing in 96% (4,032/4,190) of patients. Days to treatment and days on treatment were statistically significantly shorter for patients whose fractures healed (p<0.0001). Logistic estimates of the odds ratio for healing were equivalent for patients aged 30–79 years, and all age cohorts had a healing rate more than 94%. Open fracture, current smoking, diabetes, vascular insufficiency, osteoporosis, cancer, rheumatoid arthritis, and prescription non-steroidal anti-inflammatory drugs all reduced healing rate, but older patients (60 years or more) had similar healing rates to the population as a whole.[3]

**Incidence rate of delayed union and non-union**

In the meta-analysis of 12 RCTs, results from pooled data (8 trials, n=773) showed that LIPUS did not reduce the incident rate of delayed union and non-union (risk ratio [RR] 1.02, 95% CI 0.60 to 1.74, p=0.94, $I^2$=14%). Subgroup analyses showed that treatment duration did not have an effect (less than 6 months RR 0.76, 95% CI 0.34 to1.69, p=0.5, $I^2$=0% and time until healing RR 1.16, 95% CI 0.49 to 2.73, p=0.73, $I^2$=33%; p=0.48 for interaction); there were no significant differences between operative (RR 1.12, 95% CI 0.61 to 2.06, p=0.71, $I^2$=15%) and conservative management (RR 0.57, 95% CI 0.11 to 3.01, p=0.51, $I^2$=34%; p=0.45 for interaction); nor between upper (RR 0.94, 95% CI 0.29 to 3.01, p=0.91, $I^2$=0%) and lower limb subgroups (RR 0.96, 95% CI 0.49 to 1.89, p=0.92, $I^2$=25%; p=0.96 for interaction).[2]

**Pain reduction at 4 to 6 weeks**

In the meta-analysis of 26 RCTs, pooled effect from 4 trials (with fresh fractures) assessing pain at 4 to 6 weeks follow-up (using a visual analogue scale, from 0 to 100) showed no statistically significant effect of LIPUS on pain reduction but there was high heterogeneity (mean difference −6.92, 95% CI −15.39 to 1.55, $I^2$=91%, p=0.001, 654 patients). In 1 trial at high risk of bias, there was a suggested benefit (mean difference −28.12, 95% CI −37.05 to −19.19; 28 patients) while in 3 trials at low risk of bias there was no statistically significant effect of LIPUS (mean difference 0.93, 95% CI −2.51 to 0.64; 626 patients, $I^2$=0%, p=0.94). Other outcomes for pain including pain intensity (assessed at multiple time points in 2 studies) and number of painful days (in 2 studies), did not show a statistically significant effect of LIPUS nor substantial inconsistency.[1]

**Number of subsequent operations**

In the meta-analysis of 26 RCTs, neither the pooled risk ratio (RR 0.80; 95% CI 0.55 to 1.16; $I^2$=0%, p=0.75, 10 trials [7 fresh fractures and 3 distraction osteogenesis], 693 patients, moderate certainty) nor the pooled risk difference (3%, 95% CI 7 to 2%; $I^2$=0%, p=0.64, 10 trials, 740 patients) showed a statistically significant effect with LIPUS[1].

## *Distraction osteogenesis*

In a meta-analysis of 4 RCTs (n=118 patients with tibia defects) with a moderate to high risk of bias comparing distraction osteogenesis plus LIPUS as an adjunct therapy with standard distraction osteogenesis, there was a statistically significant reduction in the treatment time in favour of LIPUS (mean difference, −15.236 d/cm; p<0.0001; random effects model 95% CI −19.902 to −10.569 d/cm; $I^2$=0%; $T^2$=0) when applied during distraction and consolidation phases. The mean difference in trials with a high risk of bias was −11.917 d/cm (95% CI −21.163 to −2.672 d/cm; $I^2$=0%; $T^2$=0) and in trials with an unclear risk of bias was −26.370 d/cm (95% CI −21.776 to −10.965 d/cm; $I^2$=0%, $T^2$=0). One RCT for mandible defects showed no statistically significant effect of LIPUS on distraction osteogenesis.[4]

In a double-blind RCT comparing LIPUS as an adjunct therapy with standard distraction osteogenesis (n=32) with a placebo ultrasound device (n=30), there was no difference in regenerate maturation index (days/cm; defined as the time to removal of the frame after adjusting for length of distraction) between the groups as per the per protocol (LIPUS 66.9±24.7 versus placebo 56.8±24.7, 95% CI −3.2 to 23.4, p=0.054) or intention-to-treat analysis (LIPUS 65.8±24.7 versus placebo 60.8±27.3, 95% CI −8.2 to 18.2, p=0.226). Smoking status was the only covariate that increased the time to removal of the frame (hazard ratio 0.47, 95% CI 0.22 to 0.97, p=0.042).[5]

## *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 17.8 to 33.6%, $I^2$=85%). The effect differed statistically significantly between the 12 trials at high risk of bias (percentage difference 32.8%, 95% CI 25.3 to 39.5%; $I^2$=78%; 446 patients) and the 3 trials at low risk of bias (percentage difference 1.7%, 95% CI 8.8 to 11.2%, $I^2$=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 greatest 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 union and non-union 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]

# 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 statistically significant interaction with risk of bias on the risk difference scale (p=0.75)[1].

## *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 fresh fractures at low risk of non-healing. 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 fresh 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 6,926 patients from 4 systematic reviews[1-2, 4, 6], 1 randomised controlled trial[5] and 1 cohort study[3]. There is an overlap of studies in the systematic reviews. Some of the studies also included patients in whom LIPUS had been used for other indications, including patients with primary non-union and patients 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 fresh fractures at low risk of non-healing

## Study 1 Schandelmaier S (2017)[1]

**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 (n=1565)<br>**Studies included according to types of fractures**<br>**Operatively managed fresh fractures** (n=7 studies, 726 patients)<br>(Busse 2016, 2014, Kamath 2015, Leung 2004, Emami 1999, Handolin 2005a, 2005b)<br>**Non-operatively managed fresh fractures** (n=6 studies, 441 patients)<br>(Heckman 1994, Kristiansen 1997, Liu 2014, Lubbert 2008, Mayr 2000,Patel 2014)<br>**Non-operatively managed stress fractures** (n=2 studies, 70 patients)<br>(Gan 2014, Rue 2004)<br>**Operatively managed non-unions** (n=3 studies, 142 patients)<br>(Schofer 2010, Ricardio 2006, Rutten 2012)<br>**Distraction osteogenesis** (n=6 studies) **Osteotomy** (n=2 studies) (total 215 patients)<br>(Tsumaki 2004, Schortinghuis 2008, 2005, Salem 2014, Dudda 2011, El-Mowafi 2005)<br>(Urita 2013-shortening, Zacherl 2009 –deformity correction)<br>**Fracture locations:** Tibia (14 studies, n=1,019 patients), radius (3, n=193), clavicle (1, n=120), fibula (3, n=57), hallux (1, n=52), scaphoid (2, n=51), mandible (3, n=45), ulna (1, n=27), femur (1, n=10), metatarsal (1, n=7) |
| Age and sex | Varied across studies; mean age 39.5 years (range 30–68 years); Sex: 25% female (range 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 (manufacturer 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 was consistent with that 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 were excluded from the analysis (12 trials). 6 trials were considered to be at low risk of bias and the remaining 20 trials to be at high risk of bias.

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

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

**Other issues**: the authors note that subgroup analysis and meta-regression for radiographic healing found no effect modification based on clinical subgroups. Therefore they 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.

The 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=26**

**Fracture treated with LIPUS compared with control (sham device or no device)**

**Results for fresh fractures (including stress fractures and distraction osteogenesis)**

**Functional recovery**

**Mean difference in days to return to work**

Pooled analysis from 3 trials (2 fresh fracture studies [Busse 2016, Lubbert 2008] and 1 stress fracture study [Rue 2004]) showed that compared with the control, LIPUS did not statistically significantly reduce time to return to work or active duty (percentage difference 2.7%, 95% CI −7.7 to 14.3%; $I^2$=0%; p=0.76; 392 patients; moderate certainty).

Only 1 trial (Busse 2016) assessed time to return to work with time-to-event analysis and found no statistically significant effect (hazard ratio 1.11 favouring control, 95% CI 0.82 to 1.50; 343 patients).

**Mean difference of days to full weight bearing**

Pooled analysis from 3 trials (of operative fresh fractures) showed no statistically significant effect on full weight bearing with LIPUS treatment (percentage difference -16.6%; 95% CI -44.9 to -26.1%; $I^2$=95%, p=0.001, 513 patients).

One trial (Leung 2004) at high risk of bias suggested a benefit (percentage difference -40.0%; 95% CI -48.4 to -30.3%; p<0.001, 30 patients) and differed from the results of 2 RCTs (Emami 1989, Busse 2016) at low risk for bias, which showed that LIPUS treatment did not decrease days to weight bearing (percentage difference 4.8%; 95% CI -4.0 to 14.4%; 483 patients, $I^2$=0%, p=0.37, high certainty).

Only 1 trial (Busse 2016) assessed time to full weight bearing with a time-to-event analysis and found no statistically significant effect (hazard ratio 0.87 favouring LIPUS, 95% CI 0.70 to 1.08; 451 patients).[1]

**Other functional outcomes**: return to leisure activities [pooled estimate p=0.061], return to household activities [pooled estimate p=0.722], return to level of function before injury [HR 1.00], and physical function measured with a multidimensional questionnaire SF-36 [p=0.30]) (Busse 2016, Lubbert 2008) were not statistically significantly affected by use of LIPUS, nor did they show substantial inconsistency.

**Mean difference in pain reduction** (all instruments transformed to 0-100 visual analogue scale).

The pooled effect from 4 trials (with fresh fractures) assessing pain at 4 to 6 weeks follow-up showed no statistically significant effect of LIPUS treatment on pain reduction but there was high heterogeneity (mean difference -6.92, 95% CI -15.39 to 1.55, $I^2$=91%, p=0.001, 654 patients).

1 trial at high risk of bias (Patel 2014), suggested a benefit (mean difference -28.12, 95% CI -37.05 to -19.19, 28 patients) while in 3 trials at low risk of bias (Lubbert 2008, Busse 2014, Busse 2016) there was no statistically significant effect of LIPUS treatment (mean difference -0.93, 95% CI -2.51 to 0.64; 626 patients, $I^2$=0%, p=0.94).

Two other small studies that could not be included in the meta-analysis (Rutten 2012 and Urita 2012) assessed pain intensity (narratively in 1 and with a modified instrument of unclear scale and variance) at 5 months and reported no effect.

**Other outcomes for pain** including pain intensity assessed at multiple time points (Busse 2016, 2014) and number of painful days (Gan 2014, Leung 2004) did not show a statistically significant effect of LIPUS nor substantial inconsistency**.**

**Number of subsequent operations related to fracture**

The pooled risk ratio (of 10 trials [7 fresh fracture studies and 3 distraction osteogenesis studies] showed a reduction with LIPUS (11.4% (43/376] versus 15.1% [55/364], RR 0.80; 95% CI 0.55 to 1.16; $I^2$=0%, p=0.76; 7 trials, 693 patients, moderate certainty) and the pooled risk difference also showed a reduction with LIPUS (RD 3%, 95% CI 7 to 2%; $I^2$=0%, 10 trials, 740 patients) but the effect was not statistically significant.

**Time to radiographic healing**

**Percentage difference in days to radiographic healing**

Two trials (Busse 2016, 2014 on fresh fractures) used time to event analysis methods and showed no significant effect of LIPUS (hazard ratio 1.06 in favour of control, 95% CI 0.86 to 1.32; $I^2$=0%; 532 patients).

**Results for all types of fractures (including fresh conservatively or operatively managed fractures, stress fractures, osteotomies, delayed unions or non-unions)**

**Time to radiographic healing after fracture treated with LIPUS compared with control (sham device or no device)**

**Percentage difference in days to radiographic healing by clinical subgroups:**

Accelerated radiographic healing with LIPUS was reported in 15 trials (percentage difference in days to radiographic healing 26%, 95% CI 17.8% to 33.6%; $I^2$=85%). The effect differed significantly between the 12 trials at high risk of bias (percentage difference 32.8%, 95% CI 25.3 to 39.5%; $I^2$=78%; 446 patients) and the 3 trials at low risk of bias (percentage difference 1.7%, 95% CI 8.8 to 11.2%, $I^2$=10%; 483 patients; interaction P<0.001).

The effect of LIPUS on days to radiographic healing did not differ significantly across clinical subgroups (interaction P=0.13, or between high and moderate compliance with treatment (interaction P=0.99).

In our multivariable meta-regression, which included risk of bias, clinical subgroups, and compliance with treatment, the only significant effect modifier was the risk of bias (P=0.005).

Another 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 versus 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**

| Outcome | Study results (95% CI) and measurements | Absolute effect estimates | | | Quality of evidence | Narrative summary |
|---|---|---|---|---|---|---|
| | | No ultrasound | LIPUS | Difference (95% CI) | | |
| 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: CI, confidence interval; HR, hazard ratio; LIPUS, low-intensity pulsed ultrasound.

## Study 2 Lou S (2017)[2]

**Details**

| | |
|---|---|
| Study type | **Systematic review (including meta-analysis)** |
| Country | China |
| Recruitment period | 12 RCTs from 1994 to 2016 |
| Study population and number | n=**12 RCTs (1,099 adults, sample size ranged from 20 to 501)** with fresh fractures (different fracture locations)<br>Studies included:<br>**Operative fresh fractures** (n=6)<br>(Busse 2016, 2014, Leung 2004, Emami 1999, Handolin 2005a, 2005b)<br>**Non-operative fresh fractures** (n=6)<br>(Heckman 1994, Kristiansen 1997, Liu 2014, Lubbert 2008, Mayr 2000, Strauss 1999) |
| Age and sex | Varied across studies |
| Study selection criteria | **Study selection:** quasi-randomised and randomised controlled trials (RCTs) comparing treatment with LIPUS to placebo (sham or no treatment) in adults with fresh fractures (fractures within 2 weeks), reporting outcomes such as function; time to fracture union (days); functional recovery (score), incidence rate of delayed union and non-union (%), time to full weight bearing and time to return to work (days). Studies of any duration, conducted at any time, published or unpublished in any language were included.<br>Patients with post-corticotomy were excluded. Trials comparing LIPUS with other interventions were excluded.<br>Data sources: Medline, Embase, Cochrane Library and Cochrane trials registry searched from January 1980 to November 2016. |
| Study characteristics and technique | LIPUS as only treatment or an adjunctive therapy - frequency: 1.5MHz; form: pulsed; impulse length: 200ms; signal repetition frequency: 1kHz; and intensity: 30mW/cm$^2$. Trials where LIPUS was used as an adjunctive therapy to non-surgical or surgical treatments were also included.<br>Duration of treatment lasted 28 to 365 days for 20 minutes a day in all except 2 studies (15 minutes in 1 study and 20 minutes twice a day in another study). Most patient received LIPUS within 7 days.<br>5 studies used conservative treatment (plaster cast to maintain reduction) and probe was applied through a cast window.<br>Comparator was a placebo (sham ultrasound) or no additional treatment. |
| Follow-up | **Varied across studies** |
| Conflict of interest/source of funding | None, no specific grant from any funding agency. |

**Analysis**

**Follow-up issues**: high loss of follow-up in included studies.

**Study design issues**: Systematic review was performed according to the recommendations of the Cochrane Handbook, reported on the basis of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and registered on the PROSPERO International prospective register of systematic reviews. Two authors independently selected studies, extracted data and performed the meta-analysis. Any disagreements were resolved through discussion or seeking input from an independent third author. Optimal statistical approaches and measures were used. Subgroup analyses and sensitivity analysis was also done to explore heterogeneity. Summary standard mean difference (SMD) and the risk ratio (RR) with their 95% confidence intervals (CI) were calculated with a random effects model. The $I^2$ statistic was used to assess the heterogeneity. Risk of bias was assessed by the Cochrane risk-of-bias tool. Overall quality of the evidence was assessed using the GRADE system.

Limitations: most trials did not have protocols, one trial was only a published abstract, a quasi-randomised method was used in 2 trials, concealment of treatment allocation was not adequately reported in 2 trials, patients were not blinded to treatment in 3 trials, outcome assessors/caregivers were not blinded to treatment in 1 trial and high number of patients were lost to follow-up (3 trials). The strength of the evidence according to GRADE was limited and the evidence for each outcome was high to moderate. Too few studies were included in the subgroup analyses.

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

**Other issues**: Authors state that the time to fracture union results are consistent with other meta-analysis and the minimum clinically important difference has not been well established. Therefore the results should be interpreted with caution.

**Key efficacy and safety findings**

| Efficacy |
| --- |
| Number of patients analysed: **RCTs included in meta-analysis n=12**<br>**Time to fracture union (11 studies, n=887)**<br>Time to fracture union between LIPUS and placebo groups: SMD: -0.65, 95% CI -1.13 to-0.17, p<0.01, $I^2$=89%<br><br>**Subgroup analysis using different treatments**<br>LIPUS was effective for fractures treated with conservative management (5 studies) (SMD: -1.08, 95% CI -1.82 to -0.34, p<0.01, $I^2$=90%).<br>LIPUS was not effective for fractures treated with operative management (6 studies) (SMD: -0.25, 95% CI -0.78 to 0.28, p=0.35, $I^2$=78%). Subgroup differences test did not indicate that results were statistically significantly different from each other (p=0.07 for interaction).<br><br>**Subgroup analysis based on upper and lower limb**<br>LIPUS was effective on upper limb fractures (4 studies) (SMD: -1.08, 95% CI -2.05 to -0.11, p=0.03, $I^2$=92%.<br>LIPUS was not effective on lower limb fractures (7 studies) (SMD: -0.39, 95% CI -0.91 to 0.13, p=0.14, $I^2$=83%.<br>Subgroup differences test show that findings not statistically significantly different from each other (P=0.22 for interaction).<br><br>**Subgroup analysis based on radiological union and clinical union**<br>The effect of LIPUS treatment was different for time to radiographic fracture union (9 studies) (SMD:-0.55, 95%CI -1.01 to -0.09, p=0.02, $I^2$=83%) and the time to clinical union (2 studies) (SMD:-1.07, 95%CI -3.14 to 1, p=0.31, $I^2$=97%). Test for subgroup differences did not show that results were statistically significantly different from each other (P=0.63 for interaction).<br><br>**Subgroup analysis based on duration of treatment less than 6 months and time until healing**<br>LIPUS treatment reduced time to fracture union when the duration of treatment was <6 months (6 studies) (SMD: -0.87, 95%CI -1.72 to -0.02, p=0.04, $I^2$=91%) but when the duration was until the time for healing the effect of LIPUS was not statistically significant (5 studies) (SMD: -0.39, 95% CI: -0.92 to 0.14, p=0.15, $I^2$=82%). Test for subgroup differences showed that the duration of treatment did not affect the effect of LIPUS P=0.34 for interaction).<br><br>**Quality of life (measured by SF-36 physical component summary scores) (2 studies)**<br>Results from pooled data (2 studies, Busse 2014, 2016) showed that LIPUS treatment improved the SF-36 physical component summary scores compared with placebo (SMD: 0.2, 95% CI 0.37 to 0.02, p=0.02, $I^2$=0%).<br><br>**Functional recovery**<br>**Time to full weight bearing (3 studies)**<br>Pooled data (from 3 studies, Busse 2016, Emami 1999, Leung 2004) show that LIPUS treatment did not reduce the time to full weight bearing (SMD: -0.76, 95% CI -1.92 to 0.4, p=0.02, $I^2$=91%).<br><br>**Time to return to work (2 studies)**<br>Pooled data (from 2 studies, Busse 2016, Lubbert 2008) showed that LIPUS treatment did not reduce the time to return to work (SMD: 0.06, 95% CI -0.14 to 0.27, p=0.56, $I^2$=0%).<br><br>**Incident rate of delayed union and non-union (8 studies, n=773)**<br>Results showed that LIPUS treatment did not reduce the incident rate of delayed union and non-union (RR: 1.02, 95% CI 0.60 to 1.74, p=0.94, $I^2$=14%).<br><br>**Subgroup analysis based on treatment duration**<br>Treatment duration<6 months (4 studies) (RR 0.76, 95% CI 0.34 to 1.69, p=0.5, $I^2$=0%.<br>Treatment time until healing (4 studies) (RR 1.16, 95% CI 0.49 to 2.73, p=0.73, $I^2$=33%), p=0.48 for interaction. |

**Upper and lower limbs**

The findings from upper limb (1 study) (RR 0.94, 95% CI 0.29 to 3.01, p=0.91, $I^2$=0%) and lower limb (7 studies) (RR 0.96, 95% CI 0.49 to 1.89, p=0.92, $I^2$=25%) subgroups were not statistically significantly different from each other (p=0.96 for interaction).

**Operative and conservative management**

There were no significant differences between operative management (6 studies) (RR 1.12, 95% CI 0.61 to 2.06, p=0.71, $I^2$=15%) and conservative management (2 studies) (RR 0.57, 95% CI 0.11 to 3.01, p=0.51, $I^2$=34%) (p=0.45 for interaction).

Abbreviations used: CI, confidence interval; LIPUS, low-intensity pulsed ultrasound, RR, risk ratio; SMD, standard mean difference.

## Study 3 Zura R (2015)[3]

### Details

| | |
|---|---|
| Study type | **Prospective cohort study (FDA mandated post market surveillance registry)** |
| Country | USA |
| Recruitment period | 1994-1998 |
| Study population and number | n=5,765 patients with fresh fracture (<90 days old) |
| Age and sex | Average age 43.3 years; male 58.4% |
| Study selection criteria | Inclusion criteria: four distinct elements were required to report a patient: date fracture occurred, date treatment began, date treatment ended, and a dichotomous outcome of healed versus failed by clinical and radiological criteria.<br>Patients with delayed union or non-union (90-365 days old) or with treatment resistant fracture non-union (>365 days old) were not included in the analysis. |
| Study characteristics and technique | LIPUS (EXOGEN 2000+) as an adjuvant treatment for 20 minutes/day. |
| Follow-up | **Not reported** |
| Conflict of interest/source of funding | 3 authors are paid consultants of Bioventus and 2 authors are employees of Bioventus. All funding was provided by Bioventus LLC. |

### Analysis

**Follow-up issues**: 13% (740/5,765) patients were lost to follow-up; 5.3% (304/5,765) withdrew from treatment, 5.8% (333/7,565) were deemed non-compliant and 3.4% (25/5,765) died, or (159/7,565) were missing an outcome.

**Study design issues**: large registry set up and maintained by a third party consultant. Retrospective analysis of treatment data for the last 20 years, patient data from the registry were individually reviewed and validated by a registered nurse in a blinded fashion. Data were used to calculate 2 variables of interest: days to treatment (DTT) and days on treatment (DOT). Primary outcome was the impact of age on fracture heal rate. Logistic regression was used to model the odds ratio of non-union, covariates in the model included age, gender, body mass index, open fracture and smoking.

**Study population issues**: patients lost to follow-up were significantly younger than patients with a treatment outcome ($p<0.0004$), somewhat heavier ($p<0.002$), smoked for a longer period ($p<0.0002$) but did not differ in other ways.

## Key efficacy and safety findings

Efficacy

Number of patients analysed: **4,190 patients with fresh fractures (0-90 days)**

**Heal rate**

**Comparison of fresh fractures ( 0-90 days ): healed versus not healed**

| | Healed (±SD) | N or % | Not healed (±SD) | N or % | P value |
|---|---|---|---|---|---|
| % (n) | | 96.2% (4032/4190) | | 3.8% (158/4190) | |
| Age (years) | 43.2±8.1 | 4000 | 47.7±16.7 | 157 | 0.0009 |
| DTT (mean) | 38.3 ±24.3 | 4013 | 47.1±27.3 | 157 | 0.0001 |
| DOT (mean) | 115.6±83.1 | 4032 | 193.0±119.7 | 158 | <0.0001 |
| Open versus closed fracture % | 669 versus 3212 | 17.2% | 41 versus 108 | 27.5% | 0.002 |
| Number of medications (mean) | 0.4±0.7 | 2639 | 0.7±0.9 | 108 | 0.003 |
| Number of medical comorbidities (mean) | 1.4±0.7 | 727 | 1.4±0.5 | 36 | NS |

**Effect of patient age on heal rate (%)**

Data shows that age did not have any effect on fracture heal rate, among patients 30 or older. The heal rate is significantly higher than the overall heal rate in patients aged 20-29 years of age (P<0.003). Logistic estimates of the odds ratio for healing are equivalent for patients aged 30-79 years, and all age cohorts had healing rate>94%.

**Effect of patient age and BMI on heal rate**

A decrease in heal rate is seen with increased weight, obese patients more than 60 years old have a lower heal rate than younger obese or older people who are not obese. Patients under age 20 years and underweight have the highest heal rate.

**Impact on type of fracture (closed or open) and type of bone fractured**

Open fractures, as well as fractures of the tibia/fibula, femur, humerus, clavicle, radius/ulna and metacarpal had significantly lower heal rate than the average of all bones when treated with LIPUS. Fractures of the metatarsal, radius, scaphoid, ankle, fibula and ulna had significantly better heal rates than average when treated with LIPUS.

**Impact of comorbidities and use of medications**

Current smoking, diabetes, vascular insufficiency, osteoporosis, cancer, rheumatoid arthritis, and prescription of NSAIDs, all reduced healing rate but older patients (>60) had similar healing rates to the population as a whole.

Abbreviations used: DTT, days to treatment; DOT, days on treatment; LIPUS, low-intensity pulsed ultrasound; NSAIDs, non-steroidal anti-inflammatory drugs; NS, not significant; SD, standard deviation.

## Study 4 Raza H (2016)[4]

**Details**

| | |
|---|---|
| Study type | **Systematic review (including meta-analysis)** |
| Country | Canada |
| Recruitment period | 5 studies from 2004 to 2014 |
| Study population and number | n=**5 randomised clinical trials (4 tibial distraction osteogenesis and 1 mandible distraction osteogenesis) (127 patients)**<br>Studies included: (Tsumaki 2004, El-Mowafi and Mohsen 2005, Schortinghuis 2008, Dudda 2011, Salem and Schmelz 2014))<br>Sample sizes: range 9-42 patients. |
| Age and sex | LIPUS: mean age range 32-68 years, control groups 29-68 years; sex: not reported |
| Study selection criteria | **Study selection:** randomised clinical trials on patients undergoing distraction osteogenesis of any anatomic region, having LIPUS during any phase of distraction osteogenesis that examined the effect of LIPUS on distraction osteogenesis compared to conventional distraction osteogenesis with no adjuvant therapy, reporting reduced treatment time of the procedure and any other methods for evaluating the time effect of LIPUS on bone regeneration and maturation were included.<br>Data sources: Medline, Embase, Cochrane, DARE, HTA database, NHS economic evaluation database, American college of physicians journal club, and Scopus were searched (inception to October 2014), no language restrictions, and manual searches of references in articles were done. |
| Study characteristics and technique | LIPUS as an adjuvant treatment during any phase of distraction osteogenesis (phase of application varied among studies).<br>Intensity (30 mW/cm2) and duration (20 min/day) was same across studies.<br>LIPUS applied during both phases of treatment in 2 trials (Schortinghuis 2008, Salem and Schmelz 2014) only during distraction in 1 trial (Dudda 2011) and only during consolidation in 2 trials (Tsumaki 2004, El-Mowafi and Mohsen 2005).<br>Conventional distraction procedure with no adjuvant therapy was used in the control groups. |
| Follow-up | **Varied across studies** |
| Conflict of interest/source of funding | Not reported |

**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 any disagreement was resolved through consensus. Data extracted independently by 3 reviewers, combined and any discrepancies were resolved by re-examining and consensus. Methodological quality of studies was assessed according to Cochrane collaboration tool for assessing risk of bias in RCTs. The primary outcome of interest was reduced treatment time. Data were pooled using a random effects meta-analysis model when more than 3 trials were eligible for a quantitative analysis and considering the differences in interventions and measurement tools. The pooled effect estimate was considered significant at $p<0.5$. Clinical and statistical heterogeneity was examined.

Limitations: Studies included were small (no justification given for sample size calculation), with significant heterogeneity and a moderate to high risk of bias. Concealment of treatment allocation was not reported. Different methods were used to evaluate the effects of LIPUS (3 studies measured the healing index, 1 study measured bone mineral density on the callus and 1 study performed bone and radiographic analysis) in different phases of distraction osteogenesis. Only 4 trials were included in the analysis.

**Study population issues**: studies were fairly comparable, patient age and size of bony defects varied across studies.

**Key efficacy and safety findings**

Efficacy

Number of patients analysed: **4 trials (118 patients with tibial distraction osteogenesis) were included in the meta-analysis.**

| | **Tsumaki 2004** | **El-Mowafi and Mohsen 2005** | **Schortinghuis 2008** | **Dudda 2011** | **Salem and Schmelz 2014** |
|---|---|---|---|---|---|
| **LIPUS (n)** | 21 | 10 | 5 | 16 | 12 |
| **Control (n)** | 21 | 9 | 4 | 20 | 9 |
| **Treated bone** | Tibia | Tibia | Mandible, vertical distraction | Tibia | Tibia |
| **Mean bony defect size** | | | | | |
| LIPUS | 0.5 | 6.1 | 0.46 | 7.0 | 7.9 |
| Control | 0.5 | 6.1 | 0.58 | 6.3 | 7.9 |
| **Mean healing index d/cm** | | | | | |
| LIPUS | 205 | 30.0 | 116.95 | 32.8 | 33.0 |
| Control | 217 | 48.0 | 105.34 | 44.6 | 45.0 |

**Effect of LIPUS on the healing index during tibial distraction osteogenesis (stratified by the risk of bias)**
**Tibia:** A statistically significant difference for reduced treatment time between distraction osteogenesis with LIPUS and standard distraction osteogenesis was seen (mean difference -15.236 d/cm; random effects 95% CI, -19.902 to -10.569 d/cm; $I^2$=0%, $T^2$=0, P<0.001).
The combined mean differences in trials with a high risk of bias (2 studies) were -11.917 d/cm; 95% CI -21.163 to -2.672 d/cm; $I^2$=0%; $T^2$=0) and in trials with an unclear risk of bias (2 studies) -26.370 d/cm; 95% CI -21.776 to -10.965 d/cm; $I^2$=0%, $T^2$=0. There was no difference between trials with a high versus an unclear bias (p=0.415).

**Mandible: 1 RCT (Schortinghuis 2008)** performed vertical distraction and showed no significant differences between the groups.
Microradiography: gap fill area- LIPUS (0.6±0.2mm$^2$) versus control (2.7±2.8mm$^2$)
Radiodensity of calcified tissue: LIPUS (36.9 ±13.3mm$^2$) versus control (39.4±9.5mm$^2$)
Histologic analysis: total gap fill length – LIPUS (0.4±0.5mm) versus control (2.3±2.3mm); p>0.05

Abbreviations used: LIPUS, low-intensity pulsed ultrasound; RCT, randomised controlled trial.

## Study 5 Simpson AHRW (2017)[5]

### Details

| | |
|---|---|
| Study type | **Randomised controlled trial** |
| Country | UK |
| Recruitment period | 2003-6 |
| Study population and number | n=**62 adult patients undergoing limb lengthening or bone transport by distraction osteogenesis**<br>**LIPUS (n=32) versus placebo ultrasound device (n=30)** |
| Age and sex | LIPUS: mean age 37.8 years, control group 37 years; sex: LIPUS 31% (10/32) versus control 7% (2/30) |
| Study selection criteria | **Study selection:** skeletally mature patients requiring tibial lengthening of between 2.5 cm and 10 cm, presented for leg lengthening in whom corticotomy was to be within the proximal metaphysis of the tibia and distal to the tibial tuberosity were included.<br>Exclusion criteria: those with associated injuries, alcoholics, users of non-steroidal anti-inflammatory drugs, patients with a pathological fracture or systemic disease that affected bone healing, pregnant women and those unable to comply to protocol. |
| Study characteristics and technique | LIPUS (EXOGEN 2000+) as an adjuvant treatment 20 days after distraction osteogenesis was used for 20 minutes.<br>Standardised corticotomy was performed in the proximal tibial metaphysis and a circular lizarov frame was used in all patients at the site of lengthening. The rate of distraction was standardised. Treatment was continued through the maturation phase.<br>Control group: conventional distraction procedure with placebo therapy was used. |
| Follow-up | **Not reported** |
| Conflict of interest/source of funding | No conflicts of interest; study received grant from Smith and Nephew. |

### Analysis

**Follow-up issues**: there were a number of protocol violations in the treatment (n=2) and placebo groups (n=5) (p=0.249). In 3 patients a second operation was done after 14 days, in 1 patient a stimulating agent was used at the site of the regenerate, incomplete preoperative documentation was noted in 1, systemic disease in 1 and 1 patient withdrew from study.

**Study design issues**: study was conducted in 4 centres, patients were randomised by a computer generated randomisation scheme on a 1:1 basis and stratified by centre. The technique was similar in both groups; patients and surgeons were blinded to the form of treatment they were randomised, treatment and placebo devices were identical, the assessor was blinded to the allocation of treatment. Compliance with the device was also assessed. The primary outcome was the time to removal of the frame after adjusting for the length of distraction in days/cm for both per protocol and the intention to treat groups. This was determined by radiographs taken at 4 weekly intervals and assessed using standardised criteria. Weight bearing was also measured using standardised scales. Both per protocol and intention to treat analysis were done.

**Study population issues**: there were no significant differences in age, BMI and smoking status between the 2 groups. There was a higher percentage of women in the placebo group.

**Key efficacy and safety findings**

Efficacy

Number of patients analysed: **62** (**LIPUS group [n=32] versus control [n=30]**)

Primary outcome: maturation of the regenerate

| | **Per protocol analysis** | | | | **Intention-to-treat analysis** | | | |
|---|---|---|---|---|---|---|---|---|
| | **Active (n=30)** | **Placebo (n=25)** | **95% CI** | **P value** | **Active (n=32)** | **Placebo (n=30)** | **95% CI** | **P value** |
| Distraction length (cm), mean±SD | 4.3±2.4 | 4.3±1.8 | -1.2 to 1.1 | 0.515 | 4.4±2.3 | 4.3±1.7 | -1.0 to 1.1 | 0.578 |
| Time to regenerate maturation from treatment with LIPUS to removal of frame (days), mean±SD | 257.7±101.9 | 227±102.7 | -24.4 to 86.6 | 0.211 | 256.6±101.2 | 233.8±98.3 | -27.9 to 73.5 | 0.394 |
| RMI (days/cm), mean±SD | 66.9±24.7 | 56.8±24.7 | -3.2 to 23.4 | 0.054 | 65.8±24.7 | 60.8±27.3 | -8.2 to 18.2 | 0.226 |

**Secondary outcomes**
**Factors affecting bone healing**
The smoking status was the only covariate which increased the time to removal of the frame (hazard ratio 0.47, 95% CI 0.22 to 0.97, p=0.042.

**Compliance with device**
75% of patients were more than 50% compliant with treatment regime. Multi-linear regression analysis showed no significant correlation between compliance with LIPUS use (0.262) or time (p=0.664) of the application of device with the maturation of the regenerate (RMI $R^2$=0.07).

**Weight bearing**
The initial weight bearing was not statistically significantly different for the treatment (n=29) and placebo (n=30) groups (29.1±16.4 kg and 32.2±21.4 kg, p=0.543).

Abbreviations used: CI, confidence interval; LIPUS, low-intensity pulsed ultrasound; RCT, randomised controlled trial; RMI, regenerate maturation index; SD, standard deviation

## 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 8-501])** 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 trial registers were also searched. |
| Study characteristics and technique | LIPUS treatment compared with either a sham or untreated control.<br>All trials used LIPUS at a peak pressure of 30 mW/cm2. LIPUS was applied for 20 minutes every day on an outpatient basis, 1 trial applied twice daily and 1 trial used only for 15 minutes.<br>Duration of treatment varied among the trials 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 analysis was done and heterogeneity was examined using the $I^2$ statistic (>50% considered to represent substantial heterogeneity).

Time to 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.

Two 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 treatment 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 treatment did not accelerate fracture union (mean difference -26.34; 95% CI 2.06 to -54.73; $I^2$=82%; overall effect p=0.07) compared to those with non-operatively managed fresh fractures and/or impaired fractured healing (4 studies) (mean difference -56.51; 95% CI -11.23 to -101.78; $I^2$=98%, overall effect p=0.01).<br><br>The greatest 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; $I^2$=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 the effectiveness of LIPUS on the process of fracture healing/union (bone formation) and functional recovery. The evidence is mainly for adult and skeletally mature patients.
- The duration of exposure to low-intensity pulsed ultrasound varied across the trials, which may affect outcomes.
- Many systematic reviews have assessed the effectiveness of LIPUS on bone healing but provided no definitive conclusions. Reviews had different inclusion criteria, evaluation techniques, and focused on different outcomes and indications. Most of the evidence was from randomised controlled trials. However, their quality was generally poor due to limitations such as high loss to follow-up, lack of blinding and allocation concealment, use of surrogate measures and potential publication bias.
- All systematic reviews have suggested that trials are at high risk of bias, poorly reported and do not report outcomes important to patients, suggesting that further research is needed. Only a few trials have reported important patient outcomes such as quality of life and functional recovery.
- There is a lack of evidence on the clinical effect of LIPUS on bone healing for distraction osteogenesis and fresh fractures. Most of the evidence is related to tibial fractures.

## Existing assessments of this procedure

The medical services advisory committee 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 before skeletal maturation and that the efficacy data were 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

- 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
- Low-intensity pulsed ultrasound to promote fracture healing. NICE interventional procedures guidance 374 (2010). Available from https://www.nice.org.uk/guidance/IPG374. This guidance is currently under review and is expected to be updated in 2018.

### Technology appraisals

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

### NICE guidelines

- Fractures (non-complex): assessment and management. NICE guideline 38 (2016). Available from https://www.nice.org.uk/guidance/NG38
- Fractures (complex): assessment and management. NICE guideline 37 (2016). Available from https://www.nice.org.uk/guidance/NG37
- Hip fracture: management. NICE clinical guideline 124 (2011). Available from https://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 https://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 fracture healing were submitted and can be found on the NICE website

## *Patient commentators' opinions*

NICE's Public Involvement Programme will send questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). When NICE has received the completed questionnaires, these will be 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:
  - NCT00744861 EXO-SPINE: A prospective, multicentre, 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.

  - ISRCTN90844675, Pulsed ultrasound to speed up healing after intramedullary nailing of tibia fractures. Study type: randomised controlled trail; LIPUS applied daily for 3 months versus standard of care; n=210 with closed or open fractures of tibia; Location: Germany; status: completed but unpublished.

- JPRN-UMIN000002005- (further details not available).

## References


1. 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
2. Lou S, Houchen Lv, Zhirui Li et al (2017). The effects of low-intensity pulsed ultrasound on fresh fracture: A meta-analysis. Medicine 96:39 9e8181
3. Zura R, Mehta S et al (2017). A cohort study of 4190 patients treated with low-intensity pulsed ultrasound (LIPUS): findings in the elderly versus all patients. BMC Musculoskeletal Disorders. 16: 45, 1-10.
4. Raza H, Saltaji H et al 92016). Effect of low-intensity pulsed ultrasound on distraction osteogenesis treatment time: A meta-analysis of randomized clinical trials. J Ultrasound Med; 35:349-58.
5. Simpson AHRW, Keenan G et al (2017). Low-intensity pulsed ultrasound does not influence bone healing by distraction osteogenesis. The Bone and Joint Journal, 9-B; 494-502.
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) | 03/10/2017 | Issue 10 of 12, October 2017 |
| Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library) | 03/10/2017 | Issue 9 of 12, September 2017 |
| HTA database (Cochrane Library) | 03/10/2017 | Issue 4 of 4, October 2016 |
| MEDLINE (Ovid) | 03/10/2017 | 1946 to September Week 3 2017 |
| MEDLINE In-Process (Ovid) | 03/10/2017 | October 02, 2017 |
| EMBASE (Ovid) | 03/10/2017 | 1974 to 2017 Week 40 |
| PubMed | 03/10/2017 | n/a |
| JournalTOCS | 03/10/2017 | n/a |

Trial sources searched on 06/02/2017

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched on 06/02/2017

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search
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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=20170202-20171231

# 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, Bhandari M, Einhorn TA, et al (2014). Trial to re-evaluate ultrasound in the treatment of tibial fractures (TRUST): a multicenter randomized pilot study. *Trials*; 15:206. doi: 10.1186/1745-6215-15-206 pmid: 24898987. | RCT (multicenter, concealed, blinded randomized trial)<br>N=51 fresh fracture (tibia)<br>Operative management<br>LIPUS n=23 versus sham device n=28<br>Follow-up: 1 year | Our overall rate of recruitment was approximately 0.8 patients per center per month and site investigators successfully adhered to the study protocol and procedures. Our rate of follow-up at one year was 84%. Patient compliance, measured by an internal timer in the study devices, revealed that 39 (76%) of the patients were fully compliant and 12 (24%) demonstrated a greater than 50% compliance. Based on patient feedback regarding excessive questionnaire burden, we conducted an analysis using data from another tibial fracture trial that revealed the Short Musculoskeletal Function Assessment (SMFA) dysfunction index offered no important advantages over the SF-36 Physical Component Summary (PCS) score. No device-related adverse events were reported. | Study included in systematic review (Stefan 2017) included in table 2. |

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|---|---|---|---|
| Busse JW, Bhandari M, Einhorn TA, et al (2016). TRUST Investigators writing group.<br>Re-evaluation of low intensity pulsed ultrasound in treatment of tibial fractures (TRUST):<br>randomized clinical trial. *BMJ* 2016;355:i5351.pmid: 27797787. | RCT (concealed, randomized, blinded, sham controlled clinical trial with a parallel group design)<br>N=501 fresh fracture (tibia)<br>Operative management<br>LIPUS n=250 versus sham device n=251<br>Follow-up: 1 year | SF-36 PCS data were acquired from 481/501 (96%) patients, for whom we had 2303/2886 (80%) observations, and radiographic healing data were acquired from 482/501 (96%) patients, of whom 82 were censored. Results showed no impact on SF-36 PCS scores between LIPUS and control groups (mean difference 0.55, 95% confidence interval −0.75 to 1.84; P=0.41) or for the interaction between time and treatment (P=0.30); minimal important difference is 3-5 points) or in other functional measures. There was also no difference in time to radiographic healing (hazard ratio 1.07, 95% confidence interval 0.86 to 1.34; P=0.55). There were no differences in safety outcomes between treatment groups. Patient compliance was moderate; 73% of patients administered ≥50% of all recommended treatments. | Study included in systematic review (Stefan 2017) 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 randomized 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. |

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| 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. |

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| 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. |
| 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>n = 127 (63 ultrasound vs 64 sham)<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>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. |

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| Dudda M, Hauser J, Muhr G, Esenwein SA (2011). Low-intensity pulsed ultrasound as a useful adjuvant during distraction osteogenesis: a prospective, randomized controlled trial. *J Trauma*; 71:1376-80. doi:10.1097/TA.0b013e31821912b2 pmid: 22071933. | prospective, randomized controlled trial<br>n=36 distraction osteogenesis (Tibia)<br>operative management<br>LIPUS during distraction n=16 versus control n=20 (no sham device)<br>Follow-up: 35 weeks | Average transport distance was 7.0 cm in the ultrasound group and 6.3 cm in the control group. Mean Paley index for the ultrasound group was 1.09 mo/cm and 1.49 mo/cm for the control group. Mean distraction consolidation index for the ultrasound group was 32.8 d/cm and 44.6 d/cm for the control group. The calculated indices indicated no significant statistical difference between the two groups ($p < 0.116$) but the fixator gestation period could be decreased for 43.6 days in the treatment group. | Included in systematic review (Stefan 2017) added to table 2. |
| Emami A, Petren-Mallmin M, and Larsson S. (1999) No effect of low-intensity ultrasound on healing time of intramedullary fixed tibial fractures. Journal of Orthopaedic Trauma 13:252-257. | RCT patients with fresh closed or Gustilo grade I open tibial shaft fractures fixed with a reamed and statically locked intramedullary rod.<br>N =**32** (15 vs 17)<br>low-intensity pulsed ultrasound (daily 20 minute session for 75 days, width 200µs, 1.5MHz sine waves, repetition rate 1 kHz and intensity 30 mW/cm$^2$) vs sham control<br>Follow-up: 12 months | The time until the first visible callus averaged 40 ± 3 days for the active group and 37 ± 3 days for the placebo ($p = 0.44$). The healing time, defined as radiologic bridging of three cortices, was on average 155 ± 22 days (median 113 days) for the active treatment group and 125 ± 11 days (median 112 days) for the placebo group ($p = 0.76$) as assessed by the radiologist and 128 ± 13 days for the active group and 114 ± 9 days for the placebo group ($p = 0.40$) as evaluated by the orthopaedic surgeon. | Included in systematic review 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. |

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| 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><br>n = 1<br><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. |
| 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, randomized, 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 versus 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 randomized 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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| 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. |
| 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. |

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| 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 randomized 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 non-unions in all types of bones) | Seven hundred and thirty-seven patients from 13 trials were included. Pooled results from 13 trials reporting proportion of non-union 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 |
| 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. |
| 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>n = 313 (non-unions)<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>Not published in a peer reviewed journal. |

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| 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>n = 41(non-unions)<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>Not published in a peer reviewed journal. |
| Liu Y, Wei X, Kuang Y, et al (2014). Ultrasound treatment for accelerating fracture healing of the distal radius. A control study. Acta Cir Bras; 29:765-70. doi:10.1590/S0102-86502014001800012 pmid: 25424299. | RCT<br>N=81 fresh fracture of distal radius<br>Non operative management<br>LIPUS 41 versus control 40<br>Follow-up: 12 weeks | Clinical fracture healing time in ultrasound group was significantly shorter than that in the control group (32.04 ± 2.58d vs. 40.75 ± 5.12d, p <0.01). In addition, the grey value changes of fracture sites of the ultrasound group were much higher than that of the control group. The reposition effects of fracture healing had no difference between the two groups (p >0.05). | Included in systematic review (Stefan 2017) added to table 2. |
| Kinami Y, Noda T et al (2013). Efficacy of low-intensity pulsed ultrasound treatment for surgically managed fresh diaphyseal fractures of the lower extremity: multicentre retrospective cohort study. Journal of Orthopaedic Science. | Retrospective<br>cohort study<br>n=141 patients surgically treated for diaphyseal fractures of the femur or tibia<br>LIPUS on surgically managed fresh fractures (n=78) versus control (n=63). | There was no significant difference between the groups in terms of distribution of cases by fracture site, fracture type, soft tissue condition, fixation method. Analyses comparing subgroups, however, showed significant differences between the two groups, particularly in relation to type C fractures, regardless of whether all cases or only closed-fracture cases were analysed: there was an approximately 30 %reduction in the union period for type C fractures in the LIPUS group. There were also cases requiring reoperation due to lack of stability, even among the type C fractures. | Multicentre retrospective study with no randomisation. |

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| 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>n = 2<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. |
| 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. |

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| 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: 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 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. |
| Lubbert PH, van der Rijt RH, Hoorntje LE et al. (2008) Low-intensity pulsed ultrasound (LIPUS) in fresh clavicle fractures: a multi-centre double blind randomised controlled trial. Injury 39:1444-1452. | RCT<br><br>n = 101 (52 ultrasound vs 49 sham)<br><br>FU = not reported | No differences in time to subjective clinical healing, resumption of daily activities, sports or professional work, visual analogue pain score and use of pain medication.<br><br>Skin irritation reported in one patient in ultrasound group and 1 patient in the sham group. One patient in each group died 1+ year after treatment (car accident and motorcycle accident) | Included in systematic reviews reported in Table 2. |
| El-Mowafi H and Mohsen M. (2005) The effect of low-intensity pulsed ultrasound on callus maturation in tibial distraction osteogenesis. International Orthopaedics 29:121-124. | RCT<br>n = 20 patients with tibial defects ranging from 5 cm to 8 cm with distraction osteogenesis low-intensity pulsed ultrasound stimulation (30 mW/cm2)onto the bone lengthening site (group A, n=10) while rigid fixation was maintained in the remaining patients (group B, n=10).<br>FU = not reported | The mean healing index in group A was 30 (27–36) days/cm while it was 48 (42–75) days/cm in group B. In group B, one patient failed to consolidate the regenerated bone. Low intensity pulsed ultrasound stimulation is highly effective in achieving maturation of bone and reducing time of distraction osteogenesis. | Included in systematic reviews added to Table 2. |

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| 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 randomized controlled trials of high methodological quality are needed. | Most up to date systematic reviews 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 non-unions. Prospective, randomized<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 |
| 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 to 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. |

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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 9LIPUS) 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 non-union 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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| 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 non-union<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 |
| 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 non-unions of fractures. | Review |
| 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 Histopahologically 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. |
| 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. |

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| Salem KH, Schmelz A (2014). Low-intensity pulsed ultrasound shortens the treatment time in tibial distraction osteogenesis. *Int Orthop*;38:1477-82. doi:10.1007/s00264-013- 2254-1 pmid:24390009. | RCT<br>N= 21 distraction osteogenesis (Tibia)<br>Operative management<br>LIPUS n=12 versus control n=9 (no sham device)<br>Follow-up: not reported | Patients in the LIPUS group needed a mean of 33 days to consolidate every 1 cm of new bone in comparison to 45 days in the control group. The healing index was therefore shortened by 12 days/cm in the LIPUS group. This means that callus maturation was 27 % faster in the LIPUS group. The fixator time was shortened by 95 days in the LIPUS group. The overall daily increase in radiographic callus density was 33 % more in the LIPUS group than in the control group. | 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. |
| 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 non-unions, 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 non-union is 5% to 10% of all fractures. For delayed union and non-union, 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 non-unions. | Most up to date studies included in 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 to placebo. Two studies reported no significant difference in all outcomes. | Most up to date systematic reviews included in table 2. |
| 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>FU = 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. |

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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 impacted 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) |