

# Low intensity pulsed ultrasound (LIPUS) for bone healing: a clinical practice guideline

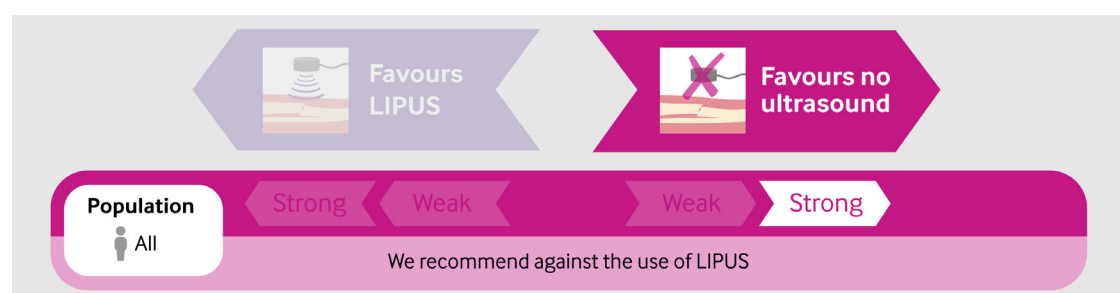
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**Does low intensity pulsed ultrasound (LIPUS) accelerate recovery in adults and children who have experienced bone fractures or osteotomy (cutting of a bone)? An expert panel rapidly produced these recommendations based on a linked systematic review triggered by a large multi-centre randomised trial in adults with tibial fracture.**

Fracture is common (see box on p 3). Bones can also be broken for medical reasons; osteotomy is a procedure whereby a bone is cut to shorten, lengthen, or to change its alignment. Following osteotomy, the bone has similar healing problems as traumatic fractures, and may require more extensive recovery.<sup>1</sup>

Irrespective of age, location, and mechanism of the broken bone, whether it is managed with or without surgery, and whether it heals as expected or with delay, the idea of speeding or enhancing this healing to minimise symptoms and inconvenience for the patient is appealing. Bone stimulators such as LIPUS and electromagnetic field therapy might promote bone healing by stimulating bone growth (osteogenesis) in long or other bones.

Guidance from independent organisations on use of LIPUS for bone healing is scarce, but data suggest the device is commonly used in clinical practice (see box on p 3). Prices vary across countries, each device costing between US\$1300 and \$5000 (based on US and UK).

The TRUST randomised controlled trial published in *The BMJ* on 25 October 2016 found that the addition of LIPUS to standard care in 501 adult patients undergoing surgery for fresh tibial fracture did not improve functional recovery or accelerate radiographic healing at one year follow up compared with a sham device.<sup>9</sup> The *BMJ* Rapid Recommendations team believed that the TRUST trial, if considered in a new systematic review and meta-analysis,

## WHAT YOU NEED TO KNOW

- LIPUS is used for bone healing for people who have had fractures or osteotomy
- LIPUS is costly to purchase
- A new trial and linked systematic review provides moderate to high certainty evidence to support a strong recommendation against the use of LIPUS for bone healing
- Further research is unlikely to alter the evidence
- Healthcare administrators and funders may consider de-implementation of LIPUS as a performance indicator in quality improvement initiatives

## LINKED ARTICLES IN THIS *BMJ* RAPID RECOMMENDATIONS CLUSTER

- Schandelmaier S, Kaushal A, Lytvyn L, et al. Low intensity pulsed ultrasound for bone healing: systematic review of randomized controlled trials. *BMJ* 2017;356:j656  
Review of all available randomised trials that assessed LIPUS versus sham device or no device that informed the recommendation made by the panel
- MAGICapp ([www.magicapp.org](http://www.magicapp.org))  
Expanded version of the results with multilayered recommendations, evidence summaries, and decision aids for use on all devices

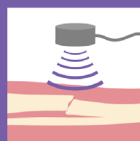
could change practice. Previous systematic reviews had concluded that potential benefits of LIPUS on bone healing were highly uncertain, with calls for trials with safeguards against bias and a focus on outcomes important to patients.<sup>10 11</sup> The linked publications in this package (see "Linked articles" box) synthesise the latest evidence and translate it for clinical care.

## Population



Adults and children with a fracture or osteotomy

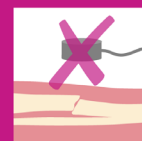
## Choice of intervention



### LIPUS

Low intensity pulsed ultrasound, used to stimulate bone growth (osteogenesis)

or



### No ultrasound

Standard care without ultrasound

## Recommendations

### Population

### Favours LIPUS

### Favours no ultrasound



All

Strong

Weak

Weak

Strong

Why? ▼

We recommend against the use of LIPUS

### Comparison of benefits and harms

#### Favours LIPUS

#### No important difference

#### Favours no ultrasound

	Number of days (mean)		Evidence quality
Days to radiographic healing	147	No important difference 150	★★★★ Moderate
Days to return to work	205	No important difference 200	★★★★ Moderate
Days to full weight bearing	73	No important difference 70	★★★★ High
	Mean value		
Pain score (0–100, lower better)	39	No important difference 40	★★★★ High
	Events per 1000 people		
Subsequent operations	128	No important difference 160	★★★★ Moderate
Device-related adverse effects	0	No important difference 0	★★★★ High

### Key practical issues

#### LIPUS

Usually used for 15–20 minutes each day for 14 to 140 days

Device can be cumbersome to travel with

Health insurance may not cover cost

#### No ultrasound

No practical issues

### Preferences and values

The panel unanimously agreed that all or nearly all informed patients would elect not to apply LIPUS.

### Resourcing

LIPUS is a costly device which does not represent a wise use of health resources.

### Other considerations

LIPUS may be burdensome to use. This is reflected in the TRUST trial, in which many patients reported limited compliance.

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### Background information

#### Bone fracture

- More than one in three people have a fracture at some point in their life
- Each year around four per 100 people of all ages experience a fracture<sup>2</sup>
- Some 5-10% of these experience delayed healing or non-union of the fracture<sup>3</sup>

#### LIPUS

- Guidance
  - 1994 US Food and Drug Administration (FDA) approved LIPUS for fracture healing and, in 2000, for treatment of established non-unions<sup>4</sup>
  - 2010 UK National Institute for Health and Care Excellence (NICE) issued a statement supporting the use of LIPUS to reduce fracture healing time and to provide clinical benefit, particularly in circumstances of delayed healing and non-union<sup>5</sup>
- Data on use
  - A Canadian survey of 450 trauma surgeons in 2008 found that nearly half of respondents were using bone stimulators to manage tibial fractures. Of those, about half used electro-magnetic field therapy and the other half used LIPUS<sup>6</sup>
  - Global revenues for bone stimulators were about US\$400m 2004.<sup>7</sup> In 2007, sales from LIPUS were around \$250m in the US<sup>8</sup>
  - We found no data to describe whether use has changed over time

### The evidence

Evidence requested from the panel to inform recommendations:

- A new rapid systematic review of the effects of LIPUS added to standard care for a variety of fractures and osteotomies<sup>16</sup>
- A systematic literature search on patients' values and preferences, which did not identify any relevant studies (see appendix 4 on bmj.com).

### Systematic review of LIPUS for all fracture healing

The data from the TRUST trial<sup>9</sup> were included in a linked systematic review of randomised trials of LIPUS compared with sham device or no device on patient-important outcomes in patients with a fracture or osteotomy. Fig 1 shows details about the trials and characteristics of included patients.<sup>16</sup>

We judged that the systematic review provides evidence of moderate to high certainty that LIPUS has little or no impact on time to return to work, time to full weight bearing, pain, the number of subsequent operations, or time to radiographic healing (see infographic on p 2). We were confident that there was little risk of adverse events from the device, based on nine trials that reported this outcome.

For return to work, time to full weight bearing, and number of subsequent operations, our certainty in the evidence is moderate (rather than high) because of imprecise estimates of effect, where confidence intervals

## DATA SOURCES

Use this information to gauge how similar your patients' conditions are to those of people studied in the trials

NUMBER OF TRIALS

26

NUMBER OF PATIENTS

1565

### TYPES OF FRACTURE OR OSTEOTOMY

Operatively managed fresh fractures	7	726
Non-operatively managed fresh fractures	6	441
Stress fractures	2	70
Non-union	3	142
Osteotomy	8	215

### EXCLUSIONS

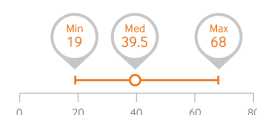
Infections	Multiple fractures
Pathologic fractures	
Large gap between bone ends after fixation	

### FRACTURE LOCATIONS

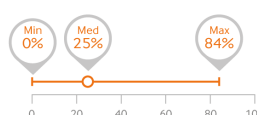
Tibia	14	1019
Radius	3	193
Clavicle	1	120
Fibula	3	57
Hallux	1	52
Scaphoid	2	51
Mandible	3	45
Ulna	1	27
Femur	1	10
Metatarsal	1	7

### PATIENT CHARACTERISTICS

#### MEAN AGE



#### SEX % women



3 of 26 trials were explicitly free of industry funding



No patient involvement reported in trial design

Fig 1 | Characteristics of patients and trials included in systematic review of LIPUS






PRACTICAL ISSUES	
	Low intensity pulsed ultrasound (LIPUS)
 PROCEDURE	<div>Patient operated device</div> <div>Portable device that emits ultrasound that cannot be heard or felt</div> <div>A probe (also called transducer) is applied to area of fracture, directly on skin using a gel to conduct the ultrasound</div> <div>If a cast is used, a window can be created to give access to the area</div> <div>Used for 20 minutes each day for 14 to 140 days or until healed</div>
 TESTS & VISITS	<div>Device usually obtained from orthopaedic clinic or directly from the manufacturer</div> <div>A prescription from a family physician or orthopaedic surgeon is typically required</div> <div>Follow up is the same for patients using LIPUS as for standard care</div>
 ADVERSE EFFECTS, INTERACTIONS & ANTIDOTE	<div>The gel used for the probe may rarely result in skin irritation</div> <div>Should not be used in proximity to a cardiac pacemaker</div>
 COST & ACCESS	<div>The LIPUS device costs about US\$1 300–5 000; some devices can be re-used</div> <div>Health insurance may not cover the cost of the device</div>
 TRAVEL & DRIVING	<div>Device can be cumbersome to travel with and may require authorisation for transport in cabin luggage of aircraft</div>

Fig 2 | Practical issues about use of LIPUS

included potentially important benefit and harm (see forest plots (figs 2-7) in the linked systematic review).<sup>16</sup> The observed heterogeneity in the effect sizes between trials for time to weight bearing, pain, and radiographic healing was explained by considering risk of bias: studies with serious methodological limitations due to lack of blinding (no use of sham device) suggested a benefit, whereas studies without such limitations did not (see subgroup analyses in the linked systematic review).<sup>16</sup> For these outcomes, we therefore based our conclusions on the trials with low risk of bias. The estimates for typical (prognostic) outcomes for patients not treated with LIPUS were informed by the control arm of the TRUST trial, which enrolled patients with tibia fractures in the US and Canada and was at low risk of bias.

Understanding the recommendation

We unanimously agreed to issue a strong recommendation against LIPUS for patients with any bone fractures or osteotomy. We have moderate to high certainty of a lack of benefit for outcomes important to patients, and, combined with the high costs of treatment, LIPUS represents an inefficient use of limited healthcare resources.

HOW THE RECOMMENDATION WAS CREATED

Our international guideline panel included orthopaedic and musculoskeletal trauma surgeons, physiotherapists, general internists, methodologists, and people with lived experience of bone fractures including one who used LIPUS (see appendix 1 on bmj.com for list of panel members). No person had financial conflicts of interest; intellectual and professional conflicts were minimised and managed according to *BMJ* Rapid Recommendations standards (see appendices 2 and 3 on bmj.com).

We followed the *BMJ* Rapid Recommendations procedures for creating a trustworthy recommendation.<sup>12 13</sup> We discussed and agreed on the clinical outcomes of most importance to patients and clinicians a priori, and the systematic review authors focused their reporting on these. The outcomes chosen for LIPUS were:

- Functional recovery (such as time to return to work and time to full weight bearing)
- Pain
- Subsequent operations
- Complications.

The patient representatives judged radiographic healing as a less important outcome. It was included because many clinicians would consider radiographic healing to inform their management decisions. Some patients may feel reassured by observing radiographic healing, with increased confidence in resuming activities such as weight bearing and return to work.

Before seeing the evidence, we agreed on what would constitute an important benefit from using LIPUS for these outcomes, and how patient values and preferences might vary between persons. Guided by patients on our panel, we agreed that most people want at least a possibly important benefit in functional recovery time or pain to make the time and expense of using LIPUS worthwhile. Reduced adherence with the device in the TRUST trial suggests that LIPUS can be burdensome to patients.<sup>9</sup>

We applied the GRADE system to critically appraise the evidence and move from evidence to recommendations (appendix 3).<sup>14</sup> We considered the balance of benefits, harms, and burdens of the procedure; the quality of evidence for each outcome; the typical and expected variation in patient values and preferences; resources; feasibility; and acceptability—details of our reasoning are summarised in the infographic and discussed further in the text.<sup>15</sup> Recommendations can be strong or weak, for or against a course of action. We place a low value on speculative benefits of treatments. Thus, when available evidence suggests no benefit, or only very low quality evidence suggests benefit and moderate or high quality evidence shows appreciable adverse effects, burden, or cost, the panel would make a strong recommendation against an intervention.

A particular challenge for the panel was to determine to what extent the most trustworthy evidence—coming from trials of patients with fresh tibial and clavicle fractures managed operatively—could be applied to adults with different types of fracture or osteotomies. Trials including patients with stress fractures, non-union, and osteotomies were either at high risk of bias or did not contribute sufficient outcome data to the systematic review. After extensive deliberations, the panel found no compelling anatomical or physiological reasons why LIPUS would probably be beneficial in these other



# HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE



Four people with lived experience of bone fractures, one of whom had used LIPUS, were full panel members, participated in the teleconferences and email discussions, and met all authorship criteria. These panel members identified important outcomes and led the discussions about values and preferences. Return to work or regular activities and pain were weighed as of higher importance for patients than radiographic healing. The panel identified key practical issues including concerns with cost and access to LIPUS, as well as the burden of therapy. In light of the lack of efficacy, one patient panel member remarked, and the others agreed, that discussing LIPUS would unnecessarily take valuable time from the patient-clinician encounter, which is often already too short.

patient populations. For example, if LIPUS on fresh fractures does not decrease the incidence of non-unions, it is unlikely to exert a beneficial effect in the conversion of non-unions into healed bones. Furthermore, osteotomies have the same biological response as for traumatic fractures. An additional challenge faced by the panel was that no trials included children. Paediatric fractures typically heal faster and have lower rates of non-union; thus, any potential benefit of LIPUS for children is likely to be even smaller than that for adults. The panel concluded that the evidence was applicable to all of these groups, and did not downgrade their certainty in the evidence.<sup>20</sup>

In response to peer review comments, the panel again considered the applicability to other fractures and populations, in particular non-union fractures. Reviewers pointed to differing healing methods in non-union, and the potential that smaller effect sizes could make a difference to patients. Non-union is the result of impaired bone health, as seen in smokers and diabetics,<sup>21</sup> or due to mechanical reasons such as large bone defects. There was high quality evidence showing a lack of benefit in accelerating healing for fresh fractures, thus it is unlikely that LIPUS would improve outcomes in patients with non-union. Given the panel's judgment of an implausible benefit of LIPUS for patients with non-union, the panel chose to make a strong recommendation against LIPUS also for these patients.

## Practical considerations

Patients with fractures may experience pain and limited mobility, particularly in the first two to three months. Driving and physical activity are limited during the recovery period. Figure 2 outlines the key practical issues for those considering LIPUS as an adjunct therapy in the management of bone fractures.

## Costs and resources

LIPUS does not represent an efficient use of health resources for individuals or health funders, given its lack of benefit on outcomes important to patients and its purchasing costs. Healthcare organisations that currently pay for LIPUS may reasonably choose to stop reimbursements based on best current evidence and our strong recommendation against LIPUS.

## Future research

It is unlikely that new trials will alter the evidence. Fracture research should focus on other interventions that have a greater probability to speed up healing, such as surgical application of adjuvant biomaterials or extracorporeal shock wave therapy.<sup>22,23</sup> Further trials of treatments for non-union fractures would be better compared with operative stabilisation, with or without autologous bone grafts. Research should also address de-implementation strategies for the use of LIPUS for bone healing.<sup>24</sup>

**Competing interests:** All authors have completed the *BMJ* Rapid Recommendations interests form. The *BMJ* Rapid Recommendations team judged that no panel member declared financial, professional, or academic interests that precluded authorship. The declared interests for each panel member are in appendix 2 on bmj.com. No panel members declared any financial conflicts of interest related to this clinical question, specifically no financial ties to the bone stimulators industry. B Mollon uses bone stimulators in practice. T Agoritsas, RAC Siemieniuk, B Mollon, S Schandelmaier, L Lytvyn, and PO Vandvik participated in writing the complementary systematic reviews that formed the evidence base for this guideline. B Mollon was a co-author on a systematic review on this topic published in *The BMJ* in 2009, for which R Poolman wrote the editorial. No other panel member has previously formally made statements regarding LIPUS. This article was edited by H MacDonald at *The BMJ* who had no relevant financial or intellectual interests.

**Transparency:** R Poolman affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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