Low Intensity Pulsed Ultrasound (LIPUS)

The application of ultrasound energy at much **lower** levels than is the current clinical norm is starting to gain ground as a therapeutic possibility. Clearly the applied energy is the same, it is the 'dose' which is different – most importantly, the intensity (W/cm^2) – which is **MUCH** lower – typically 2 or 3 times lower than the lowest setting on most regular clinical machines, with the most common application being at 30mW cm^{-2} (which is 0.03 W cm^{-2}).

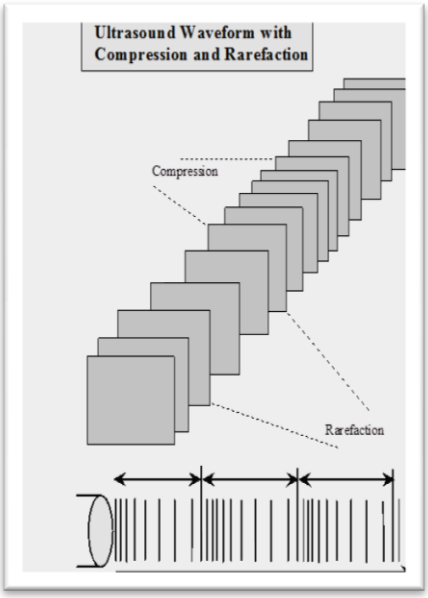
At the present time, the strongest evidence for the clinical application of this modality is in relation to fracture healing, which is the area that this information sheet will concentrate on. It is argued – quite reasonably – that IF it works this well on bone lesions, then it should also be effective on other soft tissue lesions (ligament, tendon etc) but at the present time, the published research in this field is limited.

Examples of LIPUS devices available in the UK are illustrated below :

	
Exogen Device (Smith & Nephew)	**Osteotron Device (EMS Physio)**

LIPUS vs Regular Therapy Ultrasound

Ultrasound (US) is a form of **MECHANICAL** energy. Mechanical vibration at increasing frequencies is known as sound energy. The normal human sound range is from 16Hz to something approaching 15-20,000 Hz (in children and young adults). Beyond this upper limit, the mechanical vibration is known as **ULTRASOUND**. The frequencies used in therapy are typically between 1.0 and 3.0 MHz (1MHz = 1 million cycles per second).



Sound waves are **LONGITUDINAL** waves consisting of areas of **COMPRESSION** and **RAREFACTION**. Particles of a material, when exposed to a sound wave will oscillate about a fixed point rather than move with the wave itself. As the energy within the sound wave is passed to the material, it will cause oscillation of the

particles of that material. Clearly any increase in the molecular vibration in the tissue can result in heat generation, and ultrasound can be used to produce thermal changes in the tissues, though current usage in therapy does not focus on this phenomenon (Williams 1987, Baker et al 2001, ter Haar 1999, Nussbaum 1997, Watson 2000, 2008).

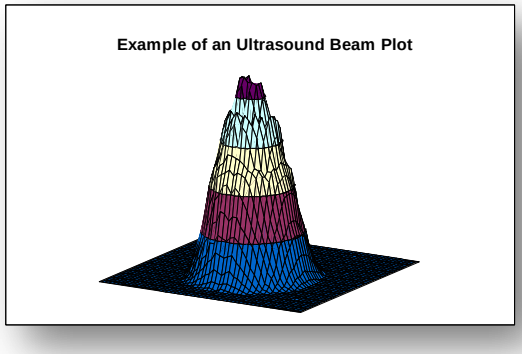
In addition to thermal changes, the vibration of the tissues appears to have effects which are generally considered to be ***'non thermal'*** in nature, though, as with other modalities (e.g. Pulsed Shortwave) there must be a thermal component however small.

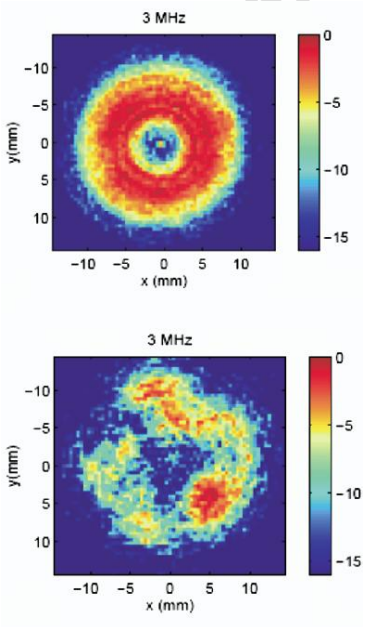
Low Intensity Pulsed Ultrasound (LIPUS) is clearly ultrasound energy, but delivered at a much lower intensity (W cm^{-2}) than traditional ultrasound energy. There are other differences with the output of LIPUS devices, but this the most obvious issue.

Whilst a typical therapy machine will offer an operating frequency choice of 1MHz or 3MHz, the LIPUS fracture healing evidence has been generated almost exclusively at 1.5MHz. Both the Exogen and Osteotron devices offer LIPUS at this frequency, though the Osteotron device also offers a 0.75MHz (optional extra) probe which, it is suggested, would be effective for the more deep seated lesions (e.g. femur). No evidence has been identified for clinical trials with LIPUS at frequencies other than 1.5MHz, and therefore it is currently not known whether 'other' frequencies are effective, not as effective, or possibly more effective.

BNR - inequality of the Ultrasound Beam

As the beam emerges from the treatment head, the energy across the beam profile is not 'even' - there are areas of higher and areas a lower intensity. When the intensity is set on a therapy ultrasound device, it would certainly not be the case that every part of the beam, even as it emerges, would actually be at that intensity. The 'inequality' of the beam strength - or the 'beam unevenness' is represented by the Beam Nonuniformity Ratio (or BNR). In the ideal world this value would be, or be close to 1.0 (which means that there is equal power across the entire beam profile. In reality, most therapy ultrasound machines will have a typical BNR of between 4 and 6 (the smaller the better). If the BNR has a value of 5 for example, it would mean that the 'strongest' parts of the beam would be at 5 x greater power than the mean power of the beam. One of the reasons for needing to employ a 'moving treatment head' application technique is to ensure that the 'strongest' parts of the beam are not always applied to the same part of the tissue - the treatment head movement helps to 'even out' the beam inequality.





A 'typical' beam plot can be seen in the diagram above and examples of 2 'real' beam X sectional plots from different transducers (at 3 MHz) from the Johns et al (2007) paper are illustrated (left) .

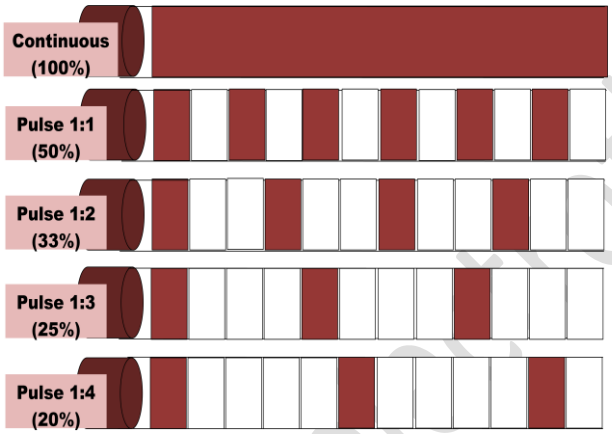
A recent analysis of clinical machines (Johns et al, 2007) identified that the BNR was in the range, 2.79-5.85 at 1 MHz and ranged from 2.51 to 4.56 for the 3.3MHz devices tested.

If (as with LIPUS treatments for fractures, the treatment head needs to kept stationary for prolonged periods (typically 20 minutes), a LOW BNR is an essential safety issue.

The LIPUS devices for fracture healing have a low BNR - the Exogen being 4.0 (max) and the Osteotron being 3.0 or 3.5 depending on which applicator is employed.

Ultrasound Pulsing

Ultrasound on standard therapy machines can be delivered in a continuous or a pulsed mode, with pulse mode variations on many, if not all machines. LIPUS devices, having a narrow clinical application, tend not to offer such a wide range of pulse options.



Typical pulse ratios are 1:1 and 1:4 though others are available. In 1:1 mode, the machine offers an output for 2ms followed by 2ms rest. In 1:4 mode, the 2ms output is followed by an 8ms rest period. The adjacent diagram illustrates the effect of varying the pulse ratio.

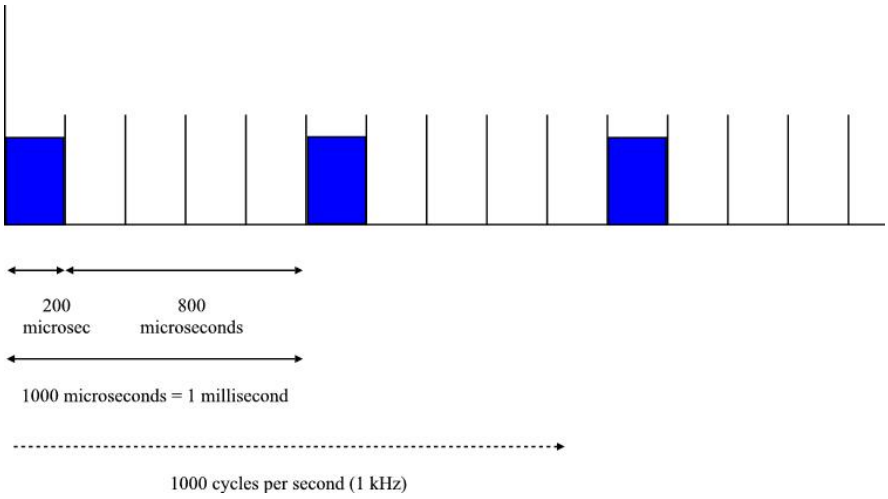
Until recently, the pulse duration (the time during which the machine is on) was almost exclusively 2ms (2 thousandths of a second) with a variable off period. Some machines now offer a variable on time though whether this is of clinical significance has yet to be determined.

Some manufacturers describe their pulsing in terms of a percentage rather than a ratio (1:1 = 50% 1:4 = 20% etc). The pulse ratio - duty cycle percentage equivalence is shown in the table below:

Mode	Pulse Ratio	Duty Cycle
Continuous	N/A	100%
Pulsed	1:1	50%
	1:2	33%
	1:3	25%
	1:4	20%
	1:9	10%

LIPUS machines typically deliver their ultrasound pulsed at 20% (1:4) and at 1000Hz (1kHz) - therefore there are 1000 cycles per second, each cycle is thus 1/1000 of a second (i.e. a millisecond). In that millisecond, there will be 20% ultrasound and 80% not ultrasound. The ultrasound 'on' cycle

will therefore be 0.2 milliseconds (200 microseconds or 200μs) followed by a 'gap' of 0.8 milliseconds (or 800 μs). The Osteotron device additionally offers a 100Hz pulse option.



1kHz pulsing with LIPUS devices

Ultrasound Intensity

The intensity (strength in general terms - power density to be very specific) at which ultrasound is applied in regular clinical applications ranges from about 0.1 through to 1.0 W cm^{-2}. Some applications (researched and evidenced as being effective) will use intensities of up to 2.5 W cm^{-2}, and although not 'common' is certainly deemed to be a safe application mode and can be very effective in some clinical circumstances.

The power density clearly represents how much power is being applied (the Watts) and how concentrated it is (the cm^2).

With the LIPUS devices for fracture healing applications, as mentioned in the introduction, one of the key differences is that the power density is much LOWER than with the traditional ultrasound treatments. Almost all of the LIPUS research has used 0.03 W cm^{-2} (which is sometimes expressed as 30mW cm^{-2}).

A typical therapy machine is not able to be set at power densities below 0.1 W cm^{-2} . It is not therefore know whether a standard therapy ultrasound machine can deliver a low enough 'dose' to be effective in this clinical area. At the moment, the available evidence would suggest that the sound energy that it delivers would be 'too strong' for the job in hand. Whilst there have been some (limited) animal experimentation (e.g. Warden et al 2006), this approach has yet to be formally evaluated in a human patient clinical trial.

The Exogen device (patient, take home, portable version) offers no power density options (it is always at 30mW cm^{-2}) whereas the Osteotron device offers additional power options at 45 and 60 mW cm^{-2} - though as for as the clinical evidence goes, none can be currently identified which supports the use of these higher dose options. It is suggested that they might / will be more effective for the deeper bone problems - which has logic, just lacks evidence at the present time.

Ultrasound for Fracture Healing : Mechanism of Action

A considerable amount of research has been carried out to try and identify the mechanism by which LIPUS ultrasound applications can 'enhance' fracture repair. Necessarily, a high proportion of these studies are based on cell, lab and animal research, but they have served to provide an ever increasing picture of what is happening. It is suggested that this research area will continue to develop, and it is highly likely that additional information will continue to be published for some time to some yet - which will either add 'new pathways' to the existing ones or provide additional transduction or cytokine or gene expression data. It is appreciated that for many therapists, this is not the most important part of the 'story' and thus the following section will provide a summary rather than a fully explanation!

Useful summary and review papers can be found in : Claes and Willie (2007); Della Roca (2009); Jingushi (2009); Lu et al (2009); Warden (2003)

The mechanisms which have been sufficiently well evidenced to justify their inclusion are listed below with some key references

Jungushi et al (2007) suggest that LIPUS is responsible for cell differentiation effects as a primary mechanism of effect rather than cellular upregulation or proliferation. They identify increased matrix synthesis, earlier expression of Type II procollagen and also prostaglandin expression and an increased chondrocyte differentiation all being associated with LIPUS exposure. This results in an earlier callus mass, though not an increased (volume) of callus.

Other papers do appear to provide evidence for an increase in cell upregulation and proliferation. It is generally considered that the LIPUS energy has an effect at cell membrane level where mechanoreceptors (integrins) respond and result in various upregulation and expressions.

COX2 (Naruse et al, 2010) expression is increased. This is essential in the PGE2 pathway (it is necessary for PGE2 production), and both COX2 and PGE2 are known to be essential in fracture repair. Leung et al (2004) demonstrated increased expression of VEGF, a strong angiogenic stimulator and both Naruse et al (2010) and Sant Anna et al (2005) demonstrated increased expression of BMP2; BMP4; BMP6 and BMP7 (linked with TGFβ) and linked to differentiation of stem cells (mesynchymal cells) into bone and cartilage. (BMP = Bone Morphogenic Protein).

There is an increased cell division in periosteal cells in the inflammatory stage (Leung et al, 2004) and in increased differentiation of chondrocytes triggered via a TGFβ pathway (as above) (Ebisawa et al 2004). Upregulation of endochondral ossification (Kokubu et al, 1999, Sena et al, 2005) Increased osteoblast differentiation (Lai et al, 2010), increased bone mineralisation (Leung et al, 2004) and increased rate of callus remodelling (Freeman et al 2009) have all been demonstrated as being associated with LIPUS exposure.

The Della Rocca (2009) review includes some additional information relating these and other gene expressions to the fracture healing pathway.

Other studies which contribute to the evidence base in this area include Nolte et al (2001) who identify an increase in ossification activity, Ryaby et al (1991) with increased TGFβ synthesis. The

increased expression of Type II collages from the chondrocytes is linked to a TGFβ pathway (Mukai et al, 2005). The Kokubu et al (1999) study reiterates the essential contribution made by both COX2 and PGE2 to the fracture healing process. COX2 regulates PGE2 production, reinforced by the results obtained by Tang et al (2006). Both Reher et al (2002) and Warden et al (2001) identify NO and pGE2 pathways as being significantly involved in LIPUS fracture healing pathways.

This would be consistent with other proposed mechanisms of ultrasound action (ter Haar 1999) and the relationship between the use of NSAID's and tissue repair following injury.

Other elements described and identified include increased proliferation of periosteal cells, increased calcitonin expression, VEGF expression and alkaline phosphatase production (Leung et al, 2004). Wang et al (2004) argue that LIPUS exposure, resulting in increased VEGF, NO and HIF-1α (hypoxia inducible factor 1α) expression is an additional component of the stimulating pathway.

Without any further consideration of the detail of these mechanisms, it is clear that LIPUS energy, delivered to the fracture area results in an increased expression of several critical chemical mediators, growth factors and cytokines which have an essential role to play in the normal fracture healing sequence. It is evidenced that the LIPUS does not change the events of fracture repair but rather increases the expression of these various factors, and thereby stimulates the normal sequence. The resulting increased production of collagen, differentiation of cell types and change in callus production appears therefore to be a secondary effect as a result of the expression and upregulation functions.

Ultrasound for Fracture Healing : Clinical Issues

Numerous recent papers have identified the benefits of using therapeutic ultrasound for both normally healing (fresh) fractures and those that demonstrate either a delayed union or non union (e.g. Mayr et al 2000, Busse et al 2002, Warden et al 1999). Ultrasound has been historically considered to be a contraindication is these circumstances, though the exact reason for this remains unclear. Given the volume and quality of the published evidence, it would be entirely inappropriate for fractures to remain on the contraindication list.

NICE Guidance :

NICE provide numerous documents (freely available from their website - listed with the references) which identify the potential value of LIPS from both fresh fractures and those with delayed and no union. They concentrate on the established dose (1.5MHz; pulse 200μs; delivered at 20% duty cycle (1kHz); 30 mW cm^{-2}; 20 minutes daily, usually as a patient delivered treatment (home based) with coupling gel as a contact medium between the treatment applicator and the skin.

Their 2010 review included a meta analysis of 1910 patients from one previous meta analysis (13 RCT's)(Busse et al, 2006) plus an additional 4 RCT's not included in the first meta analysis (Heckman et al, 1994; Emami et al, 1999; Leung et al, 2004; Ricardo, 2006), a comparative study (Coughlin et al, 2008) and a case series (Mayr et al, 2000). Full details are provided in the NICE document together with other research which they excluded for this work.

The Busse et al (2006) meta analysis (13 RCT's) reported an overall reduction in mean healing time of 34% (CI 21 - 44%) for patients receiving LIPUS compared with a sham treatment. The Heckman study (1994) involved tibial fractures, 33 patients treated with LIPUS and 34 in a sham group. They reported a significant increased rate of healing (96 days LIPUS group, 54 days sham group). The Leung et al (2004) study with 30 patients (16 LIPUS, 14 sham) with tibial fractures report an average time to full weight bearing of 9.3 weeks in the treated group and 15.5 weeks in the sham group (significant difference). The Coughlin et al (2008) study also involved 30 patients undergoing subtalar arthrodesis (15 LIPUS, 15 standard management) reported a significant difference in the number of patients healed at 9 weeks - 63% in the LIPUS group compared with 43% in the standard management group.

The Mayr et al (2000) review (case series) involved 1317 patients all of whom received LIPUS and an 89% overall healing rate, subdivided into 91% mean healing rate for the delayed unions and 86% for the non unions.

Some of these studies are considered in further detail below. The point here is that the NICE analysis of fracture healing rates from the available evidence is totally coincident with my own work. The NICE analysis also includes sections on return to function, safety and infection. NICE do state that although the data was derived from RCT's, some was of poor quality (low patient numbers, lack of blinding, publication bias).

The NICE conclusions (phrased differently for the patient guidance and the 'medical' guidance suggests that this treatment may provide significant benefit for patients with non union and delayed healing fractures in whom surgical intervention may be avoided and recovery of limb function may be accelerated. It is advised that non union and delayed healing long bone fractures, particularly of the tibia would be most likely to benefit from this treatment. It is considered that this treatment had the potential to be cost saving compared with standard management. Additionally, it is suggested that this treatment may be of some benefit in patients with fresh fractures, though there were concerns with regards the cost implications.

Clinical Trial Information

A recent systematic review and meta-analysis (Busse et al 2002) (as reported in the NICE section above) has carefully considered the evidence in respect to the effect of low intensity pulsed ultrasound on the time to fracture healing. They conclude that the evidence from randomised trials where the data could be pooled (3 studies, 158 fractures) that the time to fracture healing was significantly reduced in the ultrasound treated groups than in the control groups and the mean difference in healing time was 64 days.

Warden et al (1999) published a review paper concluded that from animal and human studies, the use of ultrasound could accelerate the rate of fracture repair by a factor of 1.6.

Heckman et al (1994) demonstrated a 38% reduction in the healing time for tibial fractures using a LIPUS device whilst Kristiansen et al (1997) demonstrated a 30% acceleration in healing for fractures of the radius.

Jensen (1998) identifies the beneficial effects of ultrasound in the treatment (as opposed to the diagnosis) of stress fractures with an overall success rate of 96%. The report fails to identify all relevant data for consideration and must therefore be considered with some caution in terms of 'quality evidence'.

Mayr et al (2000) report a series of outcomes when using low intensity pulsed ultrasound for patients with delayed unions (n=951) and non unions (n=366). The overall success rate for the delayed unions was 91% for the delayed and 86% for the non unions.

The authors undertook an interesting stratified analysis of their patients, and identified that those who were using non steroidal anti inflammatory drugs, calcium channel blockers or steroids had a less favourable outcome, a finding that could be considered to be consistent with several research publications that have tried to identify the mechanism by which the ultrasound could bring about fracture healing acceleration and other wider research concerning the adverse influence of NSAID's on tissue repair (e.g. Tsai et al 2004, Evans & Butcher2004).

A more recent paper (Rutten et al 2007) demonstrated a 73% union rate in their group of tibial non unions (n=71 patients) which is clearly much better than the most optimistic spontaneous healing rate in this group (usually cited at between 5 and 30%).

The use of such low doses has been shown to result in non significant increases in tissue temperature. ***Using higher ultrasound doses could have an adverse effect on the fracture healing process*** and the low intensity pulsed system is considered to be effective and safe for this patient group. Reher et al (1997) demonstrated a stimulative effect at low dose (0.1 W cm-2) whilst an inhibitory effect at a higher dose (1 – 2 W cm-2). Chang et al (2002) demonstrated that the effect of low intensity pulsed ultrasound in these circumstances was achieved by non thermal mechanisms rather than as a phenomenon secondary to thermal effects.

Both Tis et al (2002) and Sakurakichi et al (2004) have evaluated the use of ultrasound as a component of treatment (in an animal model) during distraction osteogenesis, and both have demonstrated significant benefits. Cook et al (2001) have demonstrated similar benefits following spinal fusion surgery and Tanzer et al (2001) have shown that the use of ultrasound in combination with porous intramedullary implants is also beneficial. There are many other studies concerning the use of US and bone repair, but essentially the published work shows a consistent benefit, and the use of low intensity pulsed ultrasound for patients with bone related disorders, including normally healing fractures, stress fractures, delayed and non unions and as a post surgical intervention should be considered positively.

One study (Schortinghuis et al 2004) that employed the SAFHS ultrasound system yet failed to demonstrate a significant effect (following deliberate bone injury – rat model) is probably related to the additional inclusion of a PTFE membrane – a GoreTex® like material). This would almost certainly not enable adequate ultrasound energy transmission due to the porous nature of the material, and the consequent air trapping, leading to ultrasound energy reflection.

The Warden et al (1999) paper provides a useful review and another useful review of this field can be found in Pounder and Harrison (2008).

Summary and Conclusion

There is good lab, cell, animal and clinical (RCT and other) evidence to support the use of LIPUS in patients with fractures. It has demonstrated benefit for fresh fractures, those with delayed healing and those with established non union. In current clinical practice, it is most commonly employed for those with fracture healing problems (though in elite sport for example, it is routinely used on most, if not all fractures given that speed of healing and rapid return to sport is a time critical activity).

The intervention is supported by the NICE guidance, and thus would constitute a recognised 'evidence based' treatment. It is not routinely incorporated into therapy practice, though it is suggested that this position should change in the near future. The treatment need not involve ' therapy time' beyond setting up the treatment and teaching the patient how to manage the device. The treatment is best delivered using a home based, patient delivery system. The effective treatment dose is known and well established (summarised as 1.5MHz; 0.03 W cm^{-2}; 20% duty cycle at 1kHz; 20 minutes; daily).

There is currently not enough evidence to support the use of a 'regular' therapy ultrasound machine to deliver this treatment. Not only are most therapy machines completely unable to deliver the evidenced therapy, the treatment needs to be delivered on a daily basis, and this therefore may be an ineffective use of a therapy machine which is 'in demand' in a department or clinic.

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LIPUS Mechanisms

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Web Resources :

NICE LIPUS data

There are several NICE documents available with regards the use of LIPUS for fracture healing. This page will make a useful start point, and other documents can be found via the links from here :

http://publications.nice.org.uk/low-intensity-pulsed-ultrasound-to-promote-fracture-healing-ipg374

LIPUS Manufacturer and Distributor pages

Exogen (Smith and Nephew) :

global.smith-nephew.com/master/EXOGEN_ULTRASOUND_BONE_HEALING_SYSTEM.htm

Osteotron (EMS Physio) :

www.emsphysio.co.uk/124_osteotron-iv.htm