Investigation on the Effect of Low-level Laser Therapy including Laser Acupuncture in the Treatment of Chronic Low Back Pain

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Written patient consent has been received and archived for the research involving patient data reported in this thesis.

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ABSTRACT

This thesis examines low-level laser therapy (LLLT) and its role in treatment of chronic non-specific low back pain (CNLBP). Laser acupuncture (LA) is identified as a separate treatment from other LLLT, and which could act by different pathways. The value of sham laser as a control in trials of LLLT to determine if there is as specific benefit of laser is emphasized, and evidence base from RCTs existing at the commencement of my research on this subject is presented. The author outlines further research required to address shortcomings in the evidence supporting the effectiveness of LLLT including LA in treatment of CNLBP.

A preliminary double blind study of LA in CNLBP was commenced by the author to determine effectiveness of an infra-red (IR) 10 mW, 830 nm laser irradiating 0.2 Joules (J) per point, however found no difference in primary (pain and disability) outcomes between the intervention and sham laser group. An adjusted analysis later performed using baseline variables predicting reduction of pain showed a benefit for laser but only at 6 weeks post treatment. A separate LA review published at that time which did not focus on LBP, concluded treatment for reduction of myofascial pain might be more effective with a dosage of at least 0.5 J/point. Therefore a further LA trial for CNLBP was performed comparing three treatment groups using sham, 0.2, and 0.8 J/point. Primary outcomes were pain and disability (ODI) at 6 weeks post-treatment. The analysis again showed no difference between sham and the laser groups in primary outcomes or adjusted analysis.

In both LA trials there was a significant and clinically important non-specific reduction in pain lasting over the follow up periods of 6 and 12 months. Analysis of baseline characteristics which may predict outcome, identified some variables associated with less pain reduction after the intervention, including lower baseline pain, recipients of disability support pension, previous back surgery, headaches, stress and sleep disturbance and longer duration of pain at baseline. There were similarities and differences from previous literature, but further research is required in this field.

The conclusion of the last Cochrane review (2008) that there was insufficient data to draw firm conclusions on the effect of LLLT in LBP, prompted the author to perform an updated review to determine if laser therapy (including laser acupuncture) had laser specific benefit for pain reduction in CNLBP. Fifteen studies were selected involving 1,039 participants. During short-term follow-up there was moderate quality of evidence (GRADE) for significant and clinically important pain reduction of up to WMD -1.40cm (95% CI -1.91 to -0.88) in favour of laser treatment, occurring in trials using at least 3 J/point, with baseline
pain less than 30 months and in non-acupuncture laser therapy trials. Global assessment showed a risk ratio 2.16 (95% CI: 1.61, 2.90) in favour of laser treatment in the same groups only at immediate follow-up.

In the final chapter a review of recent systematic reviews (SRs) on the effect of LLLT on other musculoskeletal conditions is presented. Many of these appear to demonstrate a beneficial effect of laser over sham controls however the majority of these have not yet determined an optimal range of laser parameters (most importantly laser dose) and treatment regimens to produce optimal results. There are also issues that relate to clinical heterogeneity, inadequate reporting and uncertain elimination of bias, which still makes use of LLLT controversial.

The conduct of trials low in risk of bias, using sufficient laser dose and explicitly reported, examining a range of specific musculoskeletal conditions is important in the future. For CNLBP a minimal dose of 3 Joules to points in the area of pain using a 'super-pulsed' IR laser is recommended. There is no current evidence of benefit for LA in this condition but further research is required.

In summary this dissertation supports the treatment of CNLBP using higher dose LLLT by itself or with other modalities, with few adverse effects, to achieve useful pain reduction for up to three months, but higher quality evidence needs to be obtained with rigorously blinded trials employing adequate laser doses.
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Preface

The idea for this investigation was developed before 2005. My hospital experience, which included registrar training in Orthopaedics, Spinal Injury and Rehabilitation, Neurosurgery and Emergency Medicine, finally progressed into general practice. All these disciplines involved different viewpoints in the treatment of pain. In the early 1990s I first studied medical acupuncture and incorporated this as part of my clinical practice, especially for treatment of musculoskeletal pain. Some of my teachers were proponents of using low-level laser stimulation of acupuncture points, known as “laser acupuncture”, instead of traditional metal needling. It was believed that laser acupuncture could act by a different pathway to other laser therapies, and could achieve pain relief with smaller doses of laser energy. I wanted to determine scientifically if this was true.

In 1996 Wallace completed a small randomised controlled trial (RCT) for a Monash University Masters project, in which he reported a small significant benefit for pain for laser acupuncture, compared to sham laser, in the treatment of chronic low back pain (CLBP). I considered it important to replicate this research to demonstrate a laser specific analgesic effect if this existed, using a low dose laser acupuncture intervention. At that time I decided to conduct another RCT employing this device in the condition of chronic non-specific low back pain (CNLBP). The results for the initial 80 enrolled patients, up to 6 weeks follow-up, were presented as a minor thesis for a Masters in Family Medicine (Monash University). Subsequently the results of the completed trial, consisting of 100 patients with six months follow-up, were published. Primary analysis showed no difference between laser and sham (inert 'laser' control indistinguishable from real laser), but a secondary adjusted analysis examining baseline imbalances in the outcome predicting variables between groups showed benefit for laser at six weeks follow-up. My continuation of work on trying to establish clinical evidence of an analgesic effect from low intensity laser light in CLBP has contributed to the current PhD thesis.
Synopsis

The primary aim of this research was to determine if low-level laser therapy (LLLT), including laser acupuncture (LA), has specific benefit in pain reduction related to laser irradiation in CNLBP. To refute the hypothesis that all improvement seen is due to non-specific effects not related to laser, double blind randomised trials using sham laser as a control were examined.

Objectives

The primary objective was to conduct randomised controlled double-blind trials of low dose laser acupuncture in order to determine its effects on pain and back-related disability in the short term (up to 12 weeks post-treatment) in CNLBP.

The secondary objectives were:

- To examine the effect on other outcomes, including adverse effects, and on long-term follow-up, defined as closest to 12 months of post-treatment.
- To establish if the response to laser depends on the irradiation dose of Joules per point.
- To determine which other laser parameters or details of treatment regimen influence the response to treatment.
- To establish the magnitude of pain reduction due to the non-specific effect in a laser acupuncture intervention and to investigate which baseline characteristics affect this.
- To conduct a systematic review and meta-analysis of all low-level laser therapy trials (including LA) for CNLBP.


Chapter 1

Introduction

Summary

This introductory chapter examines low-level laser therapy and its use for chronic back pain. Laser acupuncture is identified as separate treatment from other laser therapy. This chapter considers the value of sham laser as a control in trials of LLLT and presents the evidence base from RCTs existing at the commencement of this research and the systemic reviews on this subject. I outline further research required to address shortcomings in the evidence supporting the role of LLLT in treating chronic back pain.

The intervention

Laser (Light Amplification by Stimulated Emission of Radiation) has been applied in many fields of medicine, including its use as low-level laser therapy employing a laser light source treatment that irradiates subjects with no discernable heat, sound, or vibration. Instead of producing a thermal effect, LLLT may act via non-thermal or photochemical reactions in cells. Interest in this application of laser has continued since the 1970s, when Andre Mester in Budapest conducted a series of initial experiments which showed an effect of low level He-Ne laser irradiation of promoting hair growth and wound healing in animal studies.

Laser acupuncture, which is low-level laser stimulation of points using laser emitter devices applied to skin as an alternative to needles, has developed in the last 35 years. Friedrich Plog from Canada first reported successes in treatment using He-Ne laser irradiation of acupuncture points in 1973. Although LA could be considered a subgroup of LLLT, it may be separate form of treatment. Instead of using the direct effect of light on tissues to initiate a physiological response, LA is thought by some authorities to act via a different pathway, with the selection of points based on a diagnostic and therapeutic paradigm defined in acupuncture theories.

Laser acupuncture and other types of laser therapy are often applied to similar body surface points in the area of pain, for treatment of painful conditions, which makes it difficult to distinguish between LA and other LLLT, based on choice of points. Authors have variously described a study as LA if points treated are acupuncture points, trigger points or other tender
This research removes ambiguity by defining a study as LA only if the authors explicitly describe the use of acupuncture principles for point selection, thereby distinguishing this from other types of LLLT.

Laser therapy devices emit different wavelengths (ranging from visible to infrared spectrum) and vary in radiant power output. Devices with continuous power up to 500 mW generally do not produce an appreciable thermal sensation in subjects, but higher power output machines, which are pulsatile or which have the beam applied to larger areas, reducing energy density, may also fall into this category. The dose, in Joules (J) of laser irradiation per point and energy density (J/cm$^2$), can be varied depending on the time and the surface area of laser application. There is controversy about which parameters of LLLT are most effective and whether this differs for a LA treatment.$^{3,5,8}$

As previously noted, it was considered that smaller doses applied to a combination of acupuncture points might be effective in LA. In Australia, laser machines in the lower power output range, which are commonly used by members of the Australian Medical Acupuncture College (AMAC) for treating various conditions, are reported anecdotally to have good results. A position statement on laser acupuncture by AMAC in 1995 stated that “the optimal energy density for bio-stimulation, based on current clinical experience, is 4 J/cm$^2$. Dr Geoff Greenbaum, an Australian LA authority and convener of a Monash postgraduate acupuncture course,$^{12}$ stated that “generally, personal experiences dominate the therapeutics of acupuncture”. He said that he “almost exclusively used a 1.5 mW helium neon (red) laser applied to various body points” and that “at the time of writing (1994) there was no consensus as to which device or parameters are preferable”. Despite this uncertainty he concluded that “there is a reasonable body of local experience and well documented although not controlled trials over the last ten years, to show that LLLT is as effective as needling for the stimulation of acupoints and even 0.05 to 0.10 J per point is sufficient”. With the development of laser diodes, laser therapy devices of higher power became available, but even in the late 1990s a relatively low power 5mW red laser diode was still recommended for use in medical acupuncture treatment. Effective treatment for chronic pain conditions was considered to be 10 to 20 seconds irradiation of acupuncture points (0.05 to 0.1J), with sessions once a week.

Even with the lack of evidence from RCTs, LA has been promoted for medical acupuncture in Australia due to the influence of teachers such as doctors Ian Schneiderman and Geoff
Greenbaum. The attraction of LA is that it is pain free and non-invasive, with no risk of damage to organs or of spreading of blood-borne infection, and can be used in stimulation of difficult points. A downside is that precautions may need to be taken to avoid retinal injury from burns by a focused laser beam. In my unpublished survey of AMAC members, conducted in 2008, I found that LA was popular amongst many GPs who practiced medical acupuncture in Australia: 87% of those surveyed owned at least one laser machine; 70% used it in their practice occasionally or often; 36% of all laser machines listed were class 3A (1-5mW); and the remainder were Class 3B machines, of which 15% had a power greater than 100mW. Approximately half of all these machines were of a visible wavelength (usually red), and the remainder were infra-red (invisible). Similar results, obtained in another survey at an international acupuncture conference (PANPAC), held in Queensland in 2012 (see Appendix E), found that LA was most often used to treat musculoskeletal pain, headaches, back pain, neck pain and shoulder pains, and was also frequently used to treat sinuses and allergies, children, and people with needle phobias.

A major objective of this research is to determine the efficacy of low dose laser acupuncture for CLBP, and to confirm an effective dose if applicable. The wider scope of this study is also to examine how the results of these LA trials compare with other forms of laser therapy for treatment of this condition.

**How the intervention might work?**

In the past there has been criticism\(^\text{13}\) that the effect of laser therapy in painful conditions was only a placebo, which stemmed at that time from absence of an obvious mechanism, particularly given the lack of sensation during laser treatment.\(^\text{14}\) More recent references have provided more hypotheses relating to pathways of pain reduction by laser therapy.\(^\text{15}\) Studies have also raised the possibility of there being multiple mechanisms in pain modulation by LLLT, with experimental evidence of LLLT inducing anti-inflammatory, anti-nociceptive effects; altering neurotransmitters, and reducing muscle spasm and interstitial oedema.\(^\text{16-23}\) Another area of research involves the investigation of the effects of peripheral laser stimulation on changes in the brain, demonstrated by imaging (f-MRI).\(^\text{24}\) Parameters of the laser, such as wavelength and radiant power output and dosage, which affect depth of penetration and other factors, are likely to influence the biological effects on tissues.\(^\text{9,25}\) The World Association of Laser Therapy (WALT)\(^\text{26}\) recommends some dosage parameters (see Chapter 5) but more research in physiological and clinical studies is required. Consideration
of the laser parameter used in treatment is important in drawing conclusions from systematic reviews in this field.

Regardless of the mechanisms for pain reduction by LLLT, it is important ultimately to show if there is a clinically important benefit over sham laser in RCTs. If this were established, this would lead to conducting pragmatic trials that compare the effectiveness of LLLT to that of other conventional therapies in the management of selected painful musculoskeletal conditions.

**Evidence for LLLT in Clinical Pain**

By the time this study began, a number of systematic reviews and meta-analyses had been performed to determine the benefit of laser in LLLT (including LA) for the reduction of musculoskeletal pain. Four of these had looked at LLLT in mixed conditions of musculoskeletal pain and had reported positive effects of LLLT for painful conditions.

(i) In 2003, a systematic review for chronic joint conditions, largely involving the knee, neck, back and the temporomandibular joint, showed improvements in pain (Mean Difference (MD) VAS 29.8 mm (95% Confidence Interval (CI), 18.9 to 40.7) and global outcomes (Risk Ratio (RR) 0.52; 95% CI, 0.36 to 0.76) for laser compared to placebo, in favour of the active LLLT groups. Trials using less than a dose range nominated a priori for reducing inflammation in the joint capsule had been excluded from the analysis.

(ii) A meta-analysis in 2010 examining a wide range of painful conditions also showed positive effects on pain relief. The overall mean effect size obtained from the 52 effect sizes in the 22 included studies was +0.84 (95% CI, 0.44-1.23). The control group in these studies was mainly placebo, and the result indicated a large effect in favour of laser.

(iii) In 2008, a systematic review of LA in orthopaedic diseases stated that “positive effects can be assumed in myofascial pain syndromes of the neck, back and shoulder” but recommended that better designed studies with higher power should be performed.

(iv) In 2008, a systematic review on clinical effectiveness of LA in various conditions found moderate evidence that it is effective in reducing myofascial pain. This review found that laser doses of over 0.5 J/point may be required to produce a laser effect.
Description of the condition

The focus in this research is chronic low back pain, which is a common condition with a high economic burden. Low back pain (LBP) is defined as pain, muscle tension, or stiffness localized below the costal margin and above the inferior gluteal folds, with or without leg pain. The pain is chronic if it persists for 12 weeks or more. LBP is ‘non-specific’ if it is not attributed to (1) a specific spinal pathology (e.g. infection, tumour, osteoporosis, fracture, structural deformity, inflammatory disorder (e.g. ankylosing spondylitis) or (2) neurological encroachment (radicular or cauda equina syndrome).

The lifetime prevalence of low back pain is up to 84%. After an initial episode of LBP, 44-78% people suffer relapses of pain, and in 26-37% relapses of work absence. There is little scientific evidence of the prevalence of CNLBP: best estimates suggest that the prevalence is approximately 23% and that 11-12% of the population are disabled by LBP. Specific causes of LBP are uncommon (<15% all back pain).

Attempts to make a more specific diagnosis have resulted in categorizing CLBP as coming from the lumbar facet joints, sacroiliac joints and up to 40% as discogenic. Even using a combination of expensive and/or invasive tests such as discograms and MRI, it is difficult to sustain a defensible patho-anatomical diagnosis in the majority of patients. Pragmatically, the treatment of most chronic painful spinal conditions remains palliative, rather than curative. Laser acupuncture and other laser therapies are essentially some of many palliative treatments that may reduce symptoms in CLBP, whether or not a specific diagnosis has been made. A question of interest to patients and health care practitioners is whether LA is any more effective than sham treatment. My study addresses this question with a pragmatic approach based on the recruitment of community patients into RCTs, with the exclusion of apparent specific causes of CLBP but without an attempt to subclassify this condition into patho-anatomic categories. It is also likely that, in the current literature, the majority of RCTs involving LLLT of chronic LBP have not proceeded to sub-classifying CNLBP. This however may be a future direction in the research.

LBP is a major health problem in Western industrialized countries and a major cause of medical expenses, absenteeism and disablement. Back pain is a frequent cause of patient visits to physicians. Patients with back pain comprise at least 5% of all presenting problems in Australian general practice, and 6.5% in Britain. Based on a BEACH survey, back pain
was the 8\textsuperscript{th} most frequent condition seen in Australian general practice. General practitioners in Australia have managed new LBP problems at a rate of 5.8 per 1,000 GP–patient encounters: these are frequently managed with medication (particularly NSAIDS), advice, provision of a sickness certificate and ordering of pathology tests.\textsuperscript{38}

In Australia the direct cost of LBP in 2001 was $1.02 billion, 71\% of which was for treatment by chiropractors, general practitioners, massage therapists, physiotherapists and acupuncturists; the indirect costs totalled $8.15 billion.\textsuperscript{39} An Australian telephone survey in 2005\textsuperscript{40} showed that back pain was the most common medical condition treated by acupuncture. Medical practitioners provided a minority of these treatments.

**Why is this investigation important?**

CLBP is of great importance in terms of prevalence, disability, medical expenses and loss of productivity. There are concerns regarding the benefits and potential harms of medication such as paracetamol, NSAIDs and opioids for the treatment of CLBP,\textsuperscript{41,42} while non-drug treatments including exercise, multidisciplinary or behavioral treatment have been demonstrated to be of benefit.\textsuperscript{43} Improving the evidence base for the effectiveness of a non-pharmaceutical physical therapy such as acupuncture or laser therapy used as a mono-therapy or in combination with other treatments would be of clinical value.

Trials and systematic reviews available at the beginning of this investigation generally showed pain relief and functional benefit from needle acupuncture in CLBP; however, sham acupuncture controls often produced similar effects.

1. Manheimer 2005\textsuperscript{44} showed in a meta-analysis that for short-term relief of CLBP, needle acupuncture is significantly more effective than either sham treatment or having no additional treatment. Data was insufficient for drawing conclusions about acupuncture's short-term effectiveness compared with most other therapies.

2. The last Cochrane systematic review of non-specific LBP and dry needling/acupuncture was conducted in 2005.\textsuperscript{45} For CLBP acupuncture with or without conventional therapy was more effective for pain relief, and for functional improvement in the short term, compared to either no treatment or sham therapy. Acupuncture was not more effective than other conventional treatments.

3. Another systemic review in 2008\textsuperscript{46} exploring the evidence for the effectiveness of acupuncture for non-specific LBP showed evidence that acupuncture is more effective than
no treatment, but is not different from sham acupuncture for short-term pain relief. The effectiveness of acupuncture compared with other forms of conventional therapies requires further investigation.

4. A large German multicentre trial in 2007\textsuperscript{47} comparing real needle acupuncture to sham acupuncture and to conventional treatment of CLBP showed no difference between real and sham acupuncture. There was a clinically important benefit of both of these over the conventional treatment.

It is now recognized\textsuperscript{48} that there are difficulties designing sham needle acupuncture controls which are inert to specific acupuncture effects and which are indistinguishable from real acupuncture, for both subjects and therapists. Sham acupuncture techniques include using blunt needles without skin penetration, or having needles inserted away from established acupuncture points or superficially. These may result in unmasking, and could also produce physiological effects corresponding to some ‘specific’ acupuncture effects of needling.\textsuperscript{49} Those findings of reviews of needle acupuncture RCTs which show either no difference or a small benefit of real versus sham groups could be explained by this.

In theory this problem with sham needling could be overcome in LLLT, where use of an inert ‘laser’ control indistinguishable from real laser is practical. Using such sham laser devices as controls in RCTs should make it possible to demonstrate a ‘specific’ laser effect, such as in analgesia, if this exists in the treatment of certain conditions such as CLBP.

**Review of individual LA trials**

With the view of conducting such LA trials, I performed a preliminary literature review at the start of my original Master’s thesis.\textsuperscript{2} My focus at that time was on laser acupuncture and CNLBP, but when it became apparent that there were very few trials published on this topic, the scope of this search was expanded to include RCTs in LA treatment of ‘back pain’ OR ‘neck pain’.

A search of the literature in PubMed using search terms (*controlled trials, laser acupuncture, back OR neck pain*) and an inspection of the article reference lists discovered only six controlled trials examining LA in treatment of back or neck pain.

Only one LA trial (Wallace 1996)\textsuperscript{1} examined CNLBP. The full original thesis was available for appraisal. This double blind trial examined the effectiveness of LA against a sham laser
control for chronic non-specific LBP. The device was a continuous infrared (IR) laser with a dose of 1.1 J/point. A small positive benefit for pain was detected in the laser intervention group on the adjusted analysis of only one of several pain outcomes. This was a small study (41 subjects, with five subjects who withdrew before the end of treatment) with immediate assessment after only five weekly sessions of treatment.

The other three positive trials were also located in this search:
(i) (Kreczi 1986) examined 21 patients with ‘radicular and pseudo-radicular pain syndromes’ in a small single blind study with a cross-over design. The area of spine and the chronicity of the condition were not described in the abstract; neither were the laser parameters used. However, Baxter reports in his book on laser therapy that a 2 mW, 632.8nm He-Ne (visible red light) laser was used with a 20 second irradiation (0.04 J/point) of an appropriate acupuncture point in a single treatment session. A significantly greater pain reduction was reported, and pain relief lasted longer in the laser group than in the placebo group.
(ii) Ceccherelli (1989) conducted a double blind trial for chronic ‘cervical myofascial pain’. There were 12 sessions on alternate days with IR laser irradiating 0.1 J/point to acupuncture points and 1.0 J/point applied to other tender points. The trial was positive for laser at the end of treatment, and at the one-month follow-up.
(iii) Seidel (2002) conducted a double blind study examining ‘cervical tendo-myosis’ using IR laser; chronicity was not given. There were 12 participants per group; the group with 0.4 J/point achieved a positive result in but the 1.8 J/point group did not.

The remaining trials were negative: (i) Gallachi (1981) examined the ‘cervical and lumbar syndrome’ with a small group size of 15 subjects, probably using a very low dose red He-Neon laser; (ii) Waylonis (1988) examined ‘chronic myofascial pain’ treated with very low dose He-Ne laser in a study with a cross-over design.

Of note is the lack of studies found in the review of this area: only two trials were done in more recent years (2002 and 1996), with the remainder performed between 1981 and 1989. Four out of the six trials reported a ‘positive’ effect in favour of LA. The high proportion of positive studies in this collection may also reflect a publication bias, as some negative trials may not have been published. The trials were of variable methodological quality, with only one exclusively examining LBP. As most reports of these trials, apart from two,
available only in abstract form, the information obtained about them was incomplete. A brief summary of the information available from each trial is presented below (see Table 1).

Table 1.1: Summaries of published RCT’s of LA for treatment of back or neck pain (1981-2007)

<table>
<thead>
<tr>
<th>Study and ‘Outcome’</th>
<th>Group size (subgroup)</th>
<th>Condition</th>
<th>Chronicity</th>
<th>Blinding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kreczi 1986 POSITIVE</td>
<td>21 Cross-over</td>
<td>‘radicular / pseudo-radicular syndromes’ with site of pain unclear</td>
<td>?</td>
<td>Single</td>
</tr>
<tr>
<td>Waylonis 1988 NEGATIVE</td>
<td>62 Cross-over</td>
<td>myofascial pain</td>
<td>Chronic</td>
<td>Double</td>
</tr>
<tr>
<td>Ceccherelli 1989 POSITIVE</td>
<td>27 (13/14)</td>
<td>‘cervical myofascial pain’</td>
<td>Chronic</td>
<td>Double</td>
</tr>
<tr>
<td>Wallace 1996 POSITIVE</td>
<td>41</td>
<td>non-specific LBP</td>
<td>Chronic</td>
<td>Double</td>
</tr>
<tr>
<td>Seidel 2002 POSITIVE (for 7mW, 0.4 J/point)</td>
<td>48 (12)</td>
<td>‘cervical tendomyosis’</td>
<td>?</td>
<td>Double</td>
</tr>
</tbody>
</table>

Note: '-' indicates data not available.
Of these, four positive trials\textsuperscript{1, 50-52} employed laser doses 1.1, 0.04, 1 and 0.4 J/point respectively. Two very low dose LA trials\textsuperscript{53, 54} which used 0.015 J/point, were both negative. Only one LA trial\textsuperscript{1} examined CNLBP; however there were reservations about the results’ interpretation as there were multiple pain outcomes assessed and only one outcome was statistically significant. Another positive trial\textsuperscript{51} used a small dose 0.04 J/point and a single treatment session, which could be considered insufficient treatment. It was difficult to explain the positive result. Another trial\textsuperscript{51} used 1 J/point to local tender points in the cervico-brachial region, but a much smaller dose (0.1 J/point) to acupuncture points distally located on upper limbs. It was not possible to discern if the lower dose acupuncture point irradiation contributed to the overall effect in this trial. The fourth positive trial\textsuperscript{52} demonstrated a beneficial effect for the lower dose 0.4 J group but not for the 1.8 J/point group, for unexplained reasons.

The considerable heterogeneity involving conditions treated, laser parameters, treatment approaches and design/quality of trials in the small number of trials located by this literature search made it difficult to generalize the results. This literature search found insufficient evidence to establish the efficacy of LA for CLBP.

This became my stimulus to conduct further larger and more rigorous RCTs of LA in CLBP, in order to provide further evidence on effect. The first trial began as a minor part\textsuperscript{2} of a Masters in Family Medicine (Monash University); the complete publication\textsuperscript{3} is summarized in the first part of Chapter 2. My publication examining the effect of baseline characteristics on outcome concludes Chapter 2, along with questions raised by the earlier trial.

After equivocal results in demonstrating a specific effect of low dose laser,\textsuperscript{3} a further trial of LA examining effects of dosage and baseline characteristics on outcome is presented in detail in Chapter 3.

An updated systematic review on the effectiveness of LLLT that includes LA in CLBP, incorporating the trial results from this research, is presented in chapter 4. As the principal aim was to determine if laser stimulation modality has a specific effect in producing improvement in this common specific condition, only studies using sham laser as a control intervention are included. The results of this review and the implications for further research are discussed in Chapter 5.
Chapter 2
The preliminary trial with a secondary investigation on determinants of pain outcome with adjusted analysis.

Part 1: A preliminary investigation

Laser acupuncture for chronic non-specific low back pain: a randomised controlled trial comparing a laser irradiation dose of 0.2 Joules per point versus sham laser. (For details of publication see Appendix A)

Summary

- This study recruited 100 subjects with non-specific CLBP, mainly through notices in community newspapers, into a double blind trial of laser acupuncture, to determine the effectiveness of a 10 mW laser using 0.2 J/point, compared to sham. A co-intervention, consisting of education and encouragement to exercise, was also provided to both groups. The trial found no difference in pain outcomes, disability and most other measures between the intervention (laser) and the control (sham laser) group. Significant pain improvement occurred in the combined groups at the end of treatment (40% reduction) and at follow-up (30% reduction) at 6 weeks and 6 months.

- The conclusion was that laser acupuncture with the parameters employed in this trial (infrared laser, 0.2 J/point) produced no specific clinically measurable effects due to laser.

Before beginning this thesis, I designed and conducted a randomised controlled trial to determine if laser irradiation with selection of points based on acupuncture principles is more effective than sham laser in reducing pain and disability in adults with chronic non-specific low back pain. As described in Chapter 1, in the time period before 2005, only a small number of sham controlled trials examining the effect of LA in the treatment of back or neck pain had been reported in the literature, with a majority reporting a “positive” result in favour of laser. Only one trial (employing 1.1 J/point) had examined CNLBP: a small study with issues of reporting bias, as previously outlined. With LA being widely used to treat chronic back pain, without an adequate evidence base, I recognized the importance of conducting further properly blinded research, recruiting a larger participant group, and having longer treatment and follow-up times/periods. A research laser machine with a 10 mW power output, which could deliver a dose commonly used in clinical practice (0.2 J/point given over 20 seconds), was available for my use.
Methods

The majority of participants were recruited through advertisements placed in local community newspapers. Inclusion criteria were non-pregnant adults who had CNLBP with baseline pain of at least 3 cm on a 0-10 cm visual analogue scale. Subjects on stronger opioid analgesia, with current work injury or third-party claims, or who had had procedures such as facet block injections in the previous three months, or back surgery within two years, were excluded.

The active intervention was an 830 nm (infrared) continuous 10 mW power, Ga-Al-As laser diode irradiating 0.2 J per point; the control intervention had an identical appearance but produced no laser radiation. This was achieved by use of a laser machine, designed for this research,\(^5\) that could achieve allocation concealment and blinding for both patient and therapist; the procedure does not require other staff participation.

Acupuncture point selection, individualized for each patient, combined local and distal acupuncture points for back pain, as well as other points for co-existing symptoms such as joint pain or headache. All subjects received a co-intervention providing general pain information and a simple exercise program.\(^6\) Participants were required to complete a minimum of five and maximum of ten once-weekly treatment sessions.

The primary outcome measures, pain (VAS)\(^5\)\(^7\) and disability (Oswestry Disability Index),\(^5\)\(^8\) were recorded at the start of the last treatment session. Secondary outcomes were subjective global assessment,\(^5\)\(^9\) the Depression Anxiety Stress Scale (DASS21),\(^6\)\(^0\) subjective wellbeing (Personal Wellbeing Index),\(^6\)\(^1\) and exercise and analgesic-use levels compared to the baseline, as well as assessment of adverse effects and pain exacerbations during the course of treatment. Follow-up was performed at six weeks and six months after completion of treatment. A question, also included in the six-month follow-up survey, asked which treatment – laser or placebo – the participants considered that they had received, or whether they remained uncertain.

Results

For my Master’s Thesis,\(^2\) completed in 2008, the data analysis up to the six-week follow-up was available at the time of writing, but only for the first 80 participants enrolled.

The final published paper\(^3\) examined the full results for 100 enrolled participants. This included 90 subjects who satisfied the treatment protocol; four did not start any treatment and
another six dropped out later mostly due to other commitments or non-compliance. An average of nine treatment sessions were completed per participant.

Despite the randomisation procedures there was a degree of imbalance of baseline characteristics distribution between laser and control groups. This reached statistical significance involving analgesic usage, previous use of acupuncture and current physical therapies. There were also non-significant imbalances in gender, disability support pension status, presence of headaches, baseline use of analgesics, previous back surgery and back injection procedures.

A ‘per-protocol’ analysis was performed on participants who completed the treatment protocol (n = 90). Overall there was approximately 36% reduction of pain from baseline at the end of treatment, and from 25% to 29% reduction at the short-term (six weeks) and intermediate-term (six months) follow-up respectively. A 6% reduction in disability (ODI) at the end of treatment was maintained in the short-term (5%). This analysis was performed without imputation for missing values (see Table 2.1).

Table 2.1: Reduction of mean pain (VAS) and disability (ODI) in the whole group at follow-up.

<table>
<thead>
<tr>
<th>Outcome at follow-up</th>
<th>N</th>
<th>Mean</th>
<th>95% CIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>% VAS pain reduction from baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-treatment</td>
<td>90</td>
<td>35.6</td>
<td>26.5 - 44.7</td>
</tr>
<tr>
<td>6 weeks</td>
<td>87</td>
<td>24.7</td>
<td>13.8 - 35.5</td>
</tr>
<tr>
<td>6 months</td>
<td>78</td>
<td>29.2</td>
<td>20.2 - 38.3</td>
</tr>
<tr>
<td>Reduction of disability(ODI) from baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-treatment</td>
<td>85</td>
<td>5.9%</td>
<td>3.9 - 8.0</td>
</tr>
<tr>
<td>6 weeks</td>
<td>82</td>
<td>4.9%</td>
<td>2.6 - 7.1</td>
</tr>
</tbody>
</table>
Analysis of primary outcomes

A repeated measures ANOVA test was conducted over time periods (baseline, completion, six weeks and six months post completion), to compare mean pain scores for laser and sham laser intervention groups. In these data sets a case was excluded only if it was missing data for the specific analysis (SPPS option- "exclude cases pairwise"). This study demonstrated a significant reduction in pain and disability scores across time; however, there was no difference in the primary outcome of reduction in pain or disability at completion of treatment or at follow-up between active laser and sham control groups.

Analysis was also done separately on data sets for pain where missing values were imputed using methods of (a) ‘baseline value carried forwards’ and (b) ‘last observed value carried forward’. There was no significant difference for pain scores between groups, using either imputation method, at any stage of follow-up.

In addition, a sensitivity analysis was performed examining the effect of including the six participants who dropped out of the trial before completing the minimum number of sessions in the protocol. Imputation in dropouts using values of ‘best’ pain relief and disability reduction after treatment in the laser group, and ‘no’ pain relief and disability reduction in the sham laser group had no influence on the direction of effects at completion of treatment.

Analysis: secondary outcomes

In the overall global assessment by the participants of the effectiveness of treatment; 59%, 48% and 38% of participants reported that treatment had been moderately or extremely effective at completion of treatment, six weeks and six months follow-up, respectively, but with no significant difference between the laser and sham treatment groups at any of these follow-up times. There was also no significant difference in other continuous secondary outcome measures of psychological distress domains and the wellbeing index between the intervention and control groups.

Analysis of analgesic use and exercise:

Overall, the exercise level of subjects increased relative to the baseline, both during the course of treatment and at six weeks follow up, but again there was no statistical difference between the groups. The use of analgesics and anti-inflammatory agents was also assessed, and there was a small reduction, during treatment only, in use of these medications in both
treatment groups. Again, there was no significant difference between groups.

Analysis of adverse effects:

In the analysis of adverse effects, no side effects were noted, apart from exacerbations of pain following treatment being reported by some participants, but there was no statistically significant difference of exacerbations between the groups.

Testing for success of blinding

In my survey at 6 months post-completion of treatment, participants were asked their impression on whether they had received active laser or sham laser or were uncertain. There was no significant association between which treatment subjects thought they had been given, and to which intervention group they belonged. As therapist, I also reported being unable to distinguish if the laser or the sham mode was switched on.

Discussion

The results of this RCT which commenced as a topic for a Master's thesis, did not suggest that laser acupuncture (in this case using a continuous Ga-Al-As 830 nm laser diode applying 0.2 J at individualized acupuncture points by one experienced therapist over an average of 9 weekly sessions) is more effective than sham laser to reduce pain and to improve function in patients with CNLBP. No benefit or harm from the active laser treatment was found in any of the multiple outcome measures. However, the overall intervention produced a clinically important improvement in the condition treated that lasted up to six months after the completion of the treatment, regardless of the laser being switched on or off.

A number of explanations for a non-specific improvement were discussed including a placebo effect, regression to the mean, patient support including education and encouragement to exercise, acupressure effects including palpation of skin during examination, and other research related factors such as the ‘hello-goodbye’ and Hawthorne effects. Some indication of how these factors contribute may be gained from acupuncture trials which have used controls to follow pain levels over time to determine what happens without intervention. For example, in a trial of treatment of chronic knee pain, a pain reduction of approximately 35% at 12 weeks, and 21% at the one-year follow-up was seen across laser, sham laser and needle intervention groups. This was compared to 14% and 10%, respectively, at 12 weeks and one year, in an observational control group who were unaware they were in an acupuncture trial. In this trial there was no statistical difference between any
of the acupuncture interventions and the active laser group, which employed a low-dose (0.2 J/point) intervention.

In another trial\(^6\) which compared needle acupuncture or minimal (sham) needle acupuncture for CLBP with a waiting list group, the pain intensity (mean ± SD) decreased from baseline to week 8 by 28.7 ± 30.3 mm in the acupuncture groups, and 6.9 ± 22.0 mm in the waiting group. There was again no significant difference in pain reduction between the acupuncture groups in that trial. The effect size of difference between the real acupuncture interventions and ‘no extra treatment’ controls varies, depending on details of the study; however, the pain reduction tends to be significantly greater in the acupuncture interventions, be they either active or sham. This could suggest an extra effect for pain reduction in the acupuncture interventions, greater than produced by natural history or regression towards the mean. This extra effect in a laser intervention may be due to the combination of a specific laser effect and a non-specific effect related to the associated intervention.

A particular strength of my trial: it was to be the first to employ a novel laser device\(^5\) which facilitated concealed allocation and rigorous blinding of the patient and therapist. A limitation was the choice of a laser treatment dose for this trial that may have been too low to demonstrate a specific effect of laser.

Apart from this, some uncertainty remained in drawing conclusions from the results. Despite steps taken to ensure randomisation of participants and the blinding process described, some imbalance of baseline characteristics between groups was present which probably arose by chance. This could have occurred due to a relatively small sample used in this trial. A baseline inequality of confounding factors predicting pain outcome aggregating by chance, in one group, may have biased the result.

**Recommendations for further research**

The question of the efficacy of LA for CLBP was not resolved by this initial trial, so further research was recommended. It was important to assess the dose effect across a higher energy range such as 0.5 to 1.0 J/point, which has been used in LA practice. A much higher laser dose (minimum of 4 J/point for 780-860nm continuous or pulsed Ga-Al-As lasers) for the laser treatment of lumbar spine is recommended by World Association for Laser Therapy (WALT).\(^2\) This is used by non-acupuncture laser therapists who believe that a local physiological effect on tissues produces a therapeutic effect, without regard to acupuncture principles. It is not clear if this approach produces better results, so further research is needed.
that compares treatment with laser therapy and laser acupuncture philosophies.

Another decision was that selection criteria could be tightened in further trials, to try to exclude subjects who may be poor responders to a laser acupuncture intervention. They may dilute the acupuncture effect if present, and may confound results if factors are imbalanced between groups. It was postulated that this may be important in planning acupuncture trials in general and may partly explain the equivocal results in previous research. In part 2 of this chapter, a secondary analysis is presented in which the effect of baseline characteristics on the pain outcome in the preceding trial is examined. Findings from this have allowed an adjusted analysis of the results from the initial trial to be performed.
Part 2: The influence of baseline characteristics on the overall pain response to a laser acupuncture intervention  (For details of publication see Appendix B)

Summary

- In a trial of laser acupuncture used to treat chronic back pain, certain baseline characteristics in participants were found to predict pain response after the overall intervention.

- Imbalance of response predictors between treatment groups may have led to bias in the primary analysis of the study.

- Response predictors should be considered in selecting patients for acupuncture studies and utilized in their analysis.

Background

Studies of back pain have found evidence that demographic features, characteristics of the pain condition and previous and current treatment may influence the chronicity of disability or the response to treatment. The experience of acupuncturists is that subjects tend to vary in their response to acupuncture. In traditional Chinese medicine, it was considered that a better result could be achieved if acupuncture point selection was guided by certain characteristics in subjects, termed ‘correspondences’. In more recent times, Felix Mann identified the concept of the ‘strong responder’ in which certain patients always respond strongly to acupuncture. Better targeting treatment in those groups who are likely to respond may lead to more cost-effective application of the treatment and improved patient outcomes.

In a non-acupuncture study, overall predictors of response in a large low back pain trial (n=1340) were determined in a secondary analysis. Higher levels of education, younger age, shorter episode length and being at work were found to all be associated with a better outcome. More pain and disability, poorer quality of life and less favourable beliefs about back pain were associated with a poorer outcome. This study showed that baseline participant characteristics did not predict the responses to treatment packages involving exercise, manipulation or a combination of these.

There have also been some studies of needle acupuncture, which explored patient baseline variables that predict outcome. A small study examining the treatment of various
conditions, of which almost half were musculoskeletal, suggested that neither age nor gender is related to the rate of recovery, but that patients with more severe initial conditions, particularly bodily pain, tended to make more rapid improvements. A large multi-centre study\textsuperscript{71} of needle acupuncture for CLBP analyzed the effect of baseline scores of chronicity, pain intensity and depression on treatment outcomes. It did not find a clinically important difference in functional improvement after treatment, in relation to either baseline intensity or chronicity. The presence of depression at baseline did not affect the improvement in physical health but did predict a clinically significant improvement in mental health after the acupuncture intervention. This could have suggested that the acupuncture improved mental health scores if depression was present at baseline. Another large pragmatic trial,\textsuperscript{72} comparing needle acupuncture with usual care in patients with CNLBP, showed few predictors of outcome but showed a greater improvement in symptoms and function if these were more severe at baseline, and in patients who did not use narcotics.

In the current LA study\textsuperscript{3} I performed a post hoc subgroup analysis to explore which baseline factors were associated with a better or worse outcome, and whether bias from an imbalance of these factors between the treatment groups may have affected the result of the trial.

**Methods**

Before participants were enrolled, I recorded comprehensive baseline data during a structured interview at assessment. The responses to items were already dichotomous (yes or no); if categorical, they were collapsed onto binary form for the present analysis. Continuous variables such as age, body mass index (BMI) and scale scores were categorized. All data were analyzed using SPSS V.15.0.

**Dichotomisation of categorical baseline data for post hoc analysis**

1. **Demographics**

   - Gender: male / female
   - Smoking status: yes / no
   - BMI: normal / overweight or obese
   - Alcohol intake: <2 (females) or <4 (males) standard drinks per day / more than this amount
   - Employment status: employed / on a pension or unemployed
   - Pension status: on disability support pension / other pension or no pension
2. Pain characteristics

- VAS score (average pain in previous week): ≤ median (5.9) / > median (5.9)
- Duration of pain: ≤ 2 years / > 2 years
- Disability (Oswestry Disability Index): nil or minimal (0–20%) / moderate or severe (21–60%)
- Radiation of pain outside of low back: absent / present
- Exacerbation of pain (worsening of pre-existing pain at baseline): yes / no
- Presence of degenerative changes on imaging: yes / no or not done or not available

3. Previous and current treatment

- Low back surgery done > 2 years ago: yes / no
- Specialist interventions for LBP (e.g. facet block injections) done > 3 months ago: yes / no
- Any type of acupuncture done > 3 months ago: yes / no
- Current use of analgesics: regular / none or as necessary
- Current use of NSAIDS: regular / none or as necessary
- Current use of any non-prescription herbs, vitamins or supplements: yes / no
- Current use of antidepressant medication: yes / no
- Current use of other physical therapies: yes / no

4. Presence of other functional symptoms at baseline

- Headaches often present: yes / no
- Neck pain often present: yes / no
- 'Irritable bowel syndrome': yes / no
- Trochanteric bursitis present: yes / no

5. Depression Anxiety Stress (DASS-21) subscales

- Depression: normal to mild (0–13) / moderate to severe (14–28+)
- Anxiety: normal to mild (0–9) / moderate to severe (10–20+)
- Stress: normal to mild (0–18) / moderate to severe (19–34+)

The Revised Consort Statement\textsuperscript{73,74} does not recommend statistical testing for differences between groups for baseline data; however, as my study was exploratory, and there were little previous data on response predictors to laser acupuncture, I considered it important to list the full range of variables for baseline comparison. Some significant differences in distribution of characteristics between groups have been reported in Part One of this chapter.

First, the baseline comparability of characteristics between the intervention groups was examined. Because of the heterogeneity of the chronic pain population studied, and its
relatively small sample size, it was expected that by chance some baseline characteristics would not be evenly split between the treatment arms.

The next step was to determine which baseline characteristics appeared to influence the amount of pain reduction after treatment. As the primary result showed no clear difference between the treatment arms, the overall sample, the 90 participants who had completed the protocol of a minimum five to ten treatment sessions, was used in this assessment. As previously described, excluded from the analysis were 10 participants who dropped out before completing five sessions: four who did not start treatment, and six who dropped out before five sessions were attended. These drop outs were evenly distributed across the intervention groups.

The primary outcome of interest in the original trial was mean pain, on a visual analogue scale (0–10) at the last session of treatment (immediate-term follow-up). Mean pain levels at short-term (six weeks after last treatment) and intermediate-term follow-up (six months after last treatment) were also examined as secondary outcomes. In this analysis percentage pain change (PPC) was used as the index of response to treatment. This was defined as:

$$PPC = 100 \times \frac{\text{pain at baseline} - \text{pain at outcome}}{\text{pain at baseline}}.$$  

The mean PPC at each of three time-points was calculated for each category of all the characteristics.

During follow-up, more members from the 90 participants who had completed treatment dropped out, as shown in Table 2.2.

Table 2.2: Numbers of subjects remaining in the trial by stage of follow-up

<table>
<thead>
<tr>
<th>Stage of follow-up</th>
<th>Sham</th>
<th>Laser</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>45</td>
<td>45</td>
<td>90</td>
</tr>
<tr>
<td>Immediate</td>
<td>45</td>
<td>45</td>
<td>90</td>
</tr>
<tr>
<td>6 weeks</td>
<td>44(1)</td>
<td>43(2)</td>
<td>87(3)</td>
</tr>
<tr>
<td>6 months</td>
<td>38(7)</td>
<td>40(5)</td>
<td>78(12)</td>
</tr>
</tbody>
</table>

(The number of drop outs indicated in brackets)

As there was uncertainty on the effect of these missing values at follow-up, we imputed missing data in two ways: (a) substituted pain score at last completed assessment and (b)
substituted pain score at baseline. Analysis for PPC was then performed on both these data sets to determine if the manner of imputation for missing data could affect conclusions.

A previous consensus on the minimal important change for LBP\textsuperscript{75} concluded that a 30% reduction may represent a clinically meaningful improvement. However, in my analysis I decided to use a lower figure, to increase sensitivity for detecting possible predictors. Because of this, a difference of PPC of $\geq 20$ between subgroups in response to the intervention at a particular time point was used to select possible predictive factors.

Multiple linear regression was used to identify which baseline factors were best able to predict improvement in pain after the intervention. A separate model was used for the immediate, six-week and six-month outcomes. The variable selection method in the SPSS program was ‘Backward’. The independent variables to be included in the multiple regression equation were factors associated with the difference in PPC $\geq 20\%$ between sub-categories at that time point. The analysis in this chapter is slightly different, as it was decided not to include other factors with larger baseline imbalance, and the intervention group (laser/sham), as independent variables in the model, as performed in the original publication.\textsuperscript{76} It was considered that the use of these extra variables was redundant: they included some which were not associated with PPC differences, and which would also exceed the recommended limit\textsuperscript{77} for the number of variables for the relatively small sample size obtained in our trial.

Finally, an adjusted analysis was performed to determine whether a significant difference in pain outcome between the intervention and control group existed at any time at follow-up, after controlling for relevant covariates.
Results

Baseline comparison of distribution variables (continuous and categorical) by groups

The distribution of baseline variables by treatment group is presented in Tables 2.3 and 2.4. The means for continuous variables were comparable, except for a higher disability score in the laser group.

Table 2.3: Continuous variables in groups at baseline

<table>
<thead>
<tr>
<th>Baseline variable</th>
<th>Sham: mean (SD) [n]</th>
<th>Laser: mean(SD)[n]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51.6(11.67) [45]</td>
<td>53.0(12.20) [45]</td>
</tr>
<tr>
<td>Duration pain (years)</td>
<td>11.4(9.40) [45]</td>
<td>10.9(8.23) [45]</td>
</tr>
<tr>
<td>BMI</td>
<td>27.3(5.01) [45]</td>
<td>28.0(5.27) [45]</td>
</tr>
<tr>
<td>Disability (ODI)</td>
<td>28.4(9.82) [45]</td>
<td>32.0(10.68) [44]</td>
</tr>
<tr>
<td>Depression (DASS21)</td>
<td>9.2(10.36) [45]</td>
<td>9.2(9.31) [44]</td>
</tr>
<tr>
<td>Anxiety (DASS21)</td>
<td>4.8(6.49) [45]</td>
<td>5.4(7.14) [44]</td>
</tr>
<tr>
<td>Stress (DASS21)</td>
<td>12.8(10.09) [45]</td>
<td>13.2(7.79) [44]</td>
</tr>
</tbody>
</table>

DASS21-Depresssion Anxiety Stress Scale (short form); ODI- Oswestry Disability Index

Inspection of differences in the frequency distribution for the categorical variables in Table 3 demonstrated that there was a higher proportion of recipients of disability support pension (15%), radiating pain (20%) and headache (15%), as well as a greater use of regular analgesics (23%) and over-the-counter (OTC) medications (15%) in the laser group. Conversely, in the sham group more subjects were currently using other forms of physical therapy (24%) and had previously received acupuncture (22%).
Table 2.4: Dichotomous and categorical variables in groups at baseline

<table>
<thead>
<tr>
<th>Baseline variable</th>
<th>Sham n (%)</th>
<th>Laser n (%)</th>
<th>Baseline variable</th>
<th>Sham n (%)</th>
<th>Laser n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total group: n = 90</td>
<td></td>
<td></td>
<td>Total group: n=90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEMOGRAPHICS:</td>
<td></td>
<td></td>
<td>PREVIOUS &amp; CURRENT TREATMENT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>Back surgery &gt; 2 yrs ago</td>
<td></td>
<td></td>
</tr>
<tr>
<td>male (%)</td>
<td>17(38)</td>
<td>23(51)</td>
<td>yes</td>
<td>4(9)</td>
<td>7(16)</td>
</tr>
<tr>
<td>Smoking habit</td>
<td></td>
<td></td>
<td>Acupuncture &gt; 3 months ago</td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>5(11)</td>
<td>9(20)</td>
<td>yes</td>
<td>28(62)</td>
<td>18(40)</td>
</tr>
<tr>
<td>Alcohol intake ≥ 2-4 SD per day</td>
<td></td>
<td></td>
<td>Specialist injections &gt;3 months ago</td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>4(9)</td>
<td>3(7)</td>
<td>yes &gt;3 months</td>
<td>11(24)</td>
<td>14(31)</td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
<td></td>
<td>Analgesic use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>employed</td>
<td>22(49)</td>
<td>21(47)</td>
<td>regular</td>
<td>6(13)</td>
<td>16(36)</td>
</tr>
<tr>
<td>Pension status</td>
<td></td>
<td></td>
<td>NSAID use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSP</td>
<td>3(7)</td>
<td>10(22)</td>
<td>regular</td>
<td>9(20)</td>
<td>7(16)</td>
</tr>
<tr>
<td>PAIN CHARACTERISTICS</td>
<td></td>
<td></td>
<td>Over the counter medication use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration pain</td>
<td></td>
<td></td>
<td>yes</td>
<td>21(47)</td>
<td>28(62)</td>
</tr>
<tr>
<td>2 years or less</td>
<td>5(11)</td>
<td>3(7)</td>
<td>On current physical therapies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>18(40)</td>
<td>7(16)</td>
<td>Currently taking antidepressant medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiation of pain</td>
<td></td>
<td></td>
<td>yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>30(67)</td>
<td>38(85)</td>
<td>yes</td>
<td>15(33)</td>
<td>12(27)</td>
</tr>
<tr>
<td>Exacerbation pain at onset</td>
<td></td>
<td></td>
<td>OTHER ASSOCIATED CONDITIONS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>8(18)</td>
<td>8(18)</td>
<td>Headache present</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degenerative changes on imaging</td>
<td></td>
<td></td>
<td>yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>29(64)</td>
<td>30(67)</td>
<td>Neck pain present</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disability (ODI) &amp; DASS21 scores</td>
<td></td>
<td></td>
<td>yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td>Neck pain present</td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>19(42)</td>
<td>18(40)</td>
<td>‘Irritable bowel’ present</td>
<td></td>
<td></td>
</tr>
<tr>
<td>moderate to severe</td>
<td>12(27)</td>
<td>16(36)</td>
<td>yes</td>
<td>9(20)</td>
<td>9(20)</td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
<td></td>
<td>Trochanteric bursitis present</td>
<td></td>
<td></td>
</tr>
<tr>
<td>moderate to severe</td>
<td>8(18)</td>
<td>11(25)</td>
<td>yes</td>
<td>10(22)</td>
<td>9(20)</td>
</tr>
<tr>
<td>Stress</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>moderate to severe</td>
<td>13(29)</td>
<td>11(25)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>moderate to severe</td>
<td>38(84)</td>
<td>37(84)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DSP: Disability Support Pension; ODI: Oswestry Disability Index; DASS21: Depression Anxiety Stress Scale (short form)
Mean percentage pain change between categories of baseline variables at follow-up

Mean PPC was calculated at each of the three end points for each of the baseline variables previously listed, using both imputation methods for missing values. It was noted that there were no missing values at the immediate follow-up.

All variables for which there was a difference in PPC $\geq 20$ between categories were listed in Table 2.5 and labeled with the category with the worse pain outcome (less response). In most cases, when this criterion for PPC was satisfied for a variable, this was demonstrated with both methods of imputation. The absolute value of the PPC difference tended to be similar, with both methods of imputation, or slightly greater in data sets where the last value has carried forward. Any baseline characteristic which did not appear to predict a pain outcome, following treatment using the 20% threshold, is not listed in Table 2.5.
Table 2.5: Variables predicting a difference of PPC ≥ 20 between categories at any time point after completion of treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category with less pain improvement</th>
<th>Method of imputing missing values*</th>
<th>Difference in mean PPC between categories</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Post</td>
</tr>
<tr>
<td>Pension status</td>
<td>DSP</td>
<td>Base</td>
<td>29.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Last</td>
<td>29.9</td>
</tr>
<tr>
<td>Pain at baseline</td>
<td>low ≤5.9</td>
<td>base</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>last</td>
<td>-</td>
</tr>
<tr>
<td>Exacerbation pain at baseline</td>
<td>no</td>
<td>base</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>last</td>
<td>-</td>
</tr>
<tr>
<td>Degenerative changes on imaging</td>
<td>no or not available</td>
<td>base</td>
<td>26.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>last</td>
<td>26.6</td>
</tr>
<tr>
<td>Back surgery &gt; 2 years earlier</td>
<td>yes</td>
<td>base</td>
<td>24.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>last</td>
<td>24.3</td>
</tr>
<tr>
<td>Facet joint blocks etc &gt; 3 months earlier</td>
<td>yes</td>
<td>base</td>
<td>22.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>last</td>
<td>22.9</td>
</tr>
<tr>
<td>Analgesic usage</td>
<td>regular</td>
<td>base</td>
<td>20.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>last</td>
<td>20.2</td>
</tr>
<tr>
<td>Headaches</td>
<td>yes</td>
<td>base</td>
<td>25.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>last</td>
<td>25.5</td>
</tr>
<tr>
<td>Anxiety group (DASS-21)</td>
<td>moderate-severe</td>
<td>base</td>
<td>20.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>last</td>
<td>20.0</td>
</tr>
<tr>
<td>Stress group (DASS-21)</td>
<td>normal-mild</td>
<td>base</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>last</td>
<td>-</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>&lt; 2-4 Standard drinks / day</td>
<td>base</td>
<td>31.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>last</td>
<td>31.5</td>
</tr>
</tbody>
</table>

*Key: Imputation of missing values: (i) last - 'pain at last treatment imputed for any missing value at follow-up'  
(ii) base - 'pain at baseline imputed for any missing values at follow-up'  
DSP: Disability Support Pension; DASS-21: Depression Anxiety Stress Scale (short form)

According to this analytic approach, baseline predictors which produced less reduction of pain from the overall intervention are indicated in Table 2.5. The relationship was not consistent across all time points (except for participants who had previous back surgery or had regular usage of analgesics).
Multiple regression analysis to determine predictors of pain change at follow-up

The variables associated with influencing the pain outcome at a particular time-point were entered into the regression model. The data set in which missing values were substituted for the last value carried forward was used in this analysis. Those variables found to be statistically significant in contributing to pain change are listed in Table 2.6. The beta value (standardized regression coefficient) is a measure of how strongly each predictor variable influences the dependent variable (PPC), with a higher absolute value indicating a stronger relationship.

Table 2.6: Predictors of PPC at three time-points after intervention

<table>
<thead>
<tr>
<th>Follow-up period for dependent variable (PPC)</th>
<th>Independent variable (category with worse treatment outcome)</th>
<th>Pain at ‘last recorded end point’ imputed for missing values to calculate PPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate term (at end of treatment)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Headaches</td>
<td>Standardized Coefficient</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- .28</td>
</tr>
<tr>
<td></td>
<td>On DSP</td>
<td>- .23</td>
</tr>
<tr>
<td></td>
<td>Previous back surgery</td>
<td>- .19</td>
</tr>
<tr>
<td>Short term (6 weeks after end treatment)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Less pain at baseline</td>
<td>- .32</td>
</tr>
<tr>
<td></td>
<td>On DSP</td>
<td>- .27</td>
</tr>
<tr>
<td></td>
<td>Headaches</td>
<td>- .21</td>
</tr>
<tr>
<td>Intermediate term (6 months after end treatment)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>On regular analgesics</td>
<td>- .26</td>
</tr>
<tr>
<td></td>
<td>No pain exacerbation at baseline</td>
<td>- .27</td>
</tr>
</tbody>
</table>

*Using selection method ‘Backward’ for multiple regression in the SPSS program

DSP: Disability Support Pension

This demonstrated that, at immediate follow-up, subjects with baseline headaches, those on disability support pension and those with previous back surgery had less improvement in pain.
after this intervention. At short-term (6 weeks) follow-up this pertained to subjects on
disability support pension, headache sufferers and those with smaller pain scores at baseline.
At 6 months follow-up, those on regular analgesics and those who did not have an
exacerbation of pain at baseline had less improvement in pain. When different methods of
imputation were used for missing values, the results were similar.

**Adjusted analysis**

A one-way analysis of covariance between groups was conducted to compare the
effectiveness of laser against sham in producing pain reduction at the three endpoints in this
trial. The independent variable was the type of intervention (laser/sham), and the dependent
variable was PPC at the respective end point. Four baseline characteristics which were
selected as covariates had been shown to predict a pain outcome (Table 5), and were also
unevenly distributed between the four treatment arms of the trial: (i) baseline presence of
headaches, (ii) pension status, (iii) analgesic use and (iv) previous back surgery. After
adjustment for these covariates (see Table 2.7), a statistically significant difference was
approached in PPC between groups at 6 weeks follow-up only. At best this represented a
23% difference in pain reduction in favour of laser, approaching a medium effect size
according to guidelines by Cohen.78

Table 2.7: Results comparing laser and sham laser using ANCOVA at short term follow up
(6 weeks after end of treatment)

(a) *Pain at last treatment imputed for missing values*

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Unadjusted mean PPC (SD)</th>
<th>Adjusted mean PPC (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>23.7 (56.1)</td>
<td>14.8 (7.1)</td>
</tr>
<tr>
<td>Laser</td>
<td>26.1 (46)</td>
<td>35.0 (7.1)</td>
</tr>
</tbody>
</table>

F(1,84)= 3.79, P = 0.055, Partial eta² =0.043

(b) *Pain at baseline imputed for missing values*

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Unadjusted mean PPC (SD)</th>
<th>Adjusted mean PPC (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>21.8 (55.4)</td>
<td>12.4 (6.9)</td>
</tr>
<tr>
<td>Laser</td>
<td>25.9 (45.5)</td>
<td>35.2 (6.9)</td>
</tr>
</tbody>
</table>

F(1,84) = 5.1, P = 0.027, Partial eta² = 0.057
Discussion

A secondary exploration in this study showed that certain categories of patients with NCLBP had differing pain relief after being subjected to the overall laser acupuncture intervention (there was no difference in effect between active or sham laser groups). A number of baseline characteristics which predicted pain reduction were identified. They were partly dependent on type of regression analysis, for example the selection method of variables, and the decisions on cut-off values such as the 20% threshold previously described. A relatively small sample size examined was found to have effects which may not generalize to other populations. There was also the issue of multiple testing of baseline predictors over a number of follow-up intervals in a post hoc study. With a larger number of predictors and follow-up intervals tested there is a greater chance of obtaining false positive associations.

Despite uncertainty being present, it is possible to speculate on explanations for findings from this study. Findings are plausible where factors associated with more severe pathology or structural change in subjects, such as having had previous surgery, would reduce the possibility of improvement. There may be secondary gain for patients on some types of pension to remain ill. This may also occur in work injury or motor vehicle accidents, although these cases were excluded from this study. Pensioners on disability support for back pain, as a rule, are suffering from a more chronic severe illness which may be more difficult to improve by any therapy. In contrast, participants on aged pensions or other pensions did as well as those participants who were in employment.

Previous failed treatment, including steroid injections or ablation of nerves, or surgery causing other changes such as scarring or instability, may subsequently make back pain less responsive to an acupuncture-like intervention. Patients may become dependent on certain analgesics such as codeine, and large frequent doses of analgesics may create less scope to experience benefit or may overwhelm the appreciation of a smaller effect from acupuncture. My trial excluded patients taking strong opioid analgesics but allowed use of compound tablets containing up to 30 mg codeine or tramadol. The result showing less improvement in regular users of analgesics is consistent with the study by Sherman,\(^7\) who reported better response in ‘non-narcotic users’. It remains to be seen if regular use of simple analgesics, such as paracetamol only, would still result in less pain improvement following our intervention. Interestingly, the use of non-steroidal anti-inflammatory drugs did not predict response in our study.
Headache was a predictor of less pain reduction in this study, even though the treatment protocol allowed treatment of concurrent headache. In patients with central neurogenic sensitization, various dysfunctional states may occur together. It may be possible that a patient would develop resistance to improvement as they ascend the ladder of severity in sensitization. Presence of habitual headaches in a patient with chronic LBP could be a marker of this progression. The other possibility was that association with headache was a chance event. Other common baseline conditions associated with chronic LBP, such as bowel dysfunction, depression, and neck pain, were not response predictors in this sample. As subjects with widespread body pain were mostly excluded from this study, it was not possible to examine if fibromyalgia was a predictor.

Another factor which has been shown to be a strong predictor of improvement is baseline pain severity, with higher baseline pain more likely to lead to greater improvement with treatment. This was also demonstrated in our trial in the short term. This may be related either to the phenomenon of regression to the mean or to the fact that there is greater room for improvement in those with initially high pain scores. Patients who were experiencing an exacerbation of back pain at the time of assessment also showed a greater improvement. This was predictable but the effect was not demonstrated until the 6-month follow-up.

Some other results (see Table 2.5) were inconsistent or were not biologically plausible. Surprisingly, an increased responsiveness in those with higher alcohol intake was noted. High intake was found in only a small fraction (8%) of the total group. There was also some inconsistency of response, depending on baseline score of psychological distress, with those with higher anxiety doing worse, while subjects with high stress levels responded better. Another observation was that subjects who had no evidence of degeneration on available imaging did worse. This is difficult to explain; however, there is poor correlation between imaging changes and symptoms of chronic LBP. Again, such findings may also have arisen by chance and thus warrant confirmation in further studies.

The lack of predictors in earlier studies which have examined the effect of baseline characteristics on outcome in acupuncture has been a common finding. In this study, characteristics such as age group, gender, BMI status, smoking status, attributed cause of onset and total duration of back pain, pain radiation, previous acupuncture (over 3 months prior), use of concurrent OTC medicines or other physical therapies, and level of disability did not appear to affect the response to treatment.
It must be noted that recent, much larger, studies are providing more data on patient characteristics that increase or decrease benefit from needle acupuncture treatment of chronic pain. In 2011 data were pooled from 4 RCTs containing 9990 patients who received either acupuncture plus routine care, or routine care alone, for chronic low back pain, headache, neck pain, or pain due to osteoarthritis of the knee or hip; the primary outcome measured was pain at three months on the SF-36 subscale. The general outcome was improved in the acupuncture group but also in subgroups with younger subjects, higher education, shorter duration of illness, greater baseline pain, no acupuncture in the previous year, and in patients without some concomitant diseases such as HT or diabetes. The only effect modifiers specifically improving outcome in acupuncture groups were female gender, living in a multi-person household, failure of other therapies before the study, and former positive acupuncture experience. My much smaller study, which considered an LA intervention, has shown similarities and differences to other research in this field.

A further aim of this study was to determine whether an imbalance in baseline characteristics resulted in a biased conclusion in the primary analysis. This may be of particular importance in trials studying the efficacy of acupuncture interventions, where there is a large placebo effect and a possibly smaller specific effect of treatment. It is postulated that a trial may in theory be adequately powered to detect a difference, but with small or moderately sized trials, chance baseline imbalance involving strong predictors of response may result in bias despite the randomisation. This may be an explanation of inconsistency in results of some randomised controlled acupuncture trials. The implication is that to establish efficacy in acupuncture interventions, one must select larger sample sizes. Other options are to run smaller randomised trials with stratification to balance presumed predictors, or to implement stricter inclusion criteria restricting participants with characteristics shown to be negative predictors.

This trial showed an apparently negative result on primary analysis, but the adjusted analysis provided a suggestion of a clinically important effect of laser acupuncture in participants after correction for baseline imbalances between treatment arms. However, this occurred only at short-term (six weeks follow-up) and the comparison between laser and sham did not quite reach significance using one of the imputation methods. The result may suggest a biological effect of laser which produces maximal effect on pain reduction with a time delay after a course of treatment, or may represent a chance statistical phenomenon. Importantly, the post
hoc subgroup and adjusted analysis needs to interpreted with caution, and the primary result of this clinical trial deserves most emphasis.

The analysis suggests a need to repeat the trial. Tighter exclusion criteria could be considered, removing subgroups which may respond poorly to acupuncture, such as participants on DSP, workers compensation or third party, any opioid analgesics, and previous back surgery or failed nerve blocks and injections. This would further shift the trial in the spectrum from pragmatic to explanatory. With these restrictions, the external validity for a trial with a positive result could be reduced but may show the efficacy of laser acupuncture in a selected population more likely to respond. A positive result would also encourage further efficacy studies of laser acupuncture in other conditions, as well as basic research to determine mechanisms of action of low level laser in pain reduction.

It must be stressed that the results of this study on predictors of response to LA may not be generalizable to acupuncture using needles or other modalities. The results of this study also relate to the overall ‘laser acupuncture intervention’ only, since the analysis was done on the whole group because of sample size restrictions. It is important to note that this overall intervention response is not at all related to a specific effect in the laser arm. In this trial, an interaction between baseline characteristics and the intervention could not be demonstrated; it remains possible that a specific laser effect may vary depending on subject characteristics or laser intervention parameters.

A major limitation of the approach in this study was that it was a post hoc exploration after the primary analysis was performed. Many baseline factors were tested across a number of time points, with the problems related to false positive findings associated with multiple testing. The use of a stricter criterion for significance, with $\alpha$ level of 0.01 instead of 0.05, would result in a more conservative interpretation. The sample size of this trial was relatively small, making its conclusions less reliable. A strength of the analysis was that the investigation clearly described how predictors of outcome were selected and how missing values were dealt with.

The general conclusion of this investigation is that it may be possible to predict and quantify how certain groups of patients may respond to non-specific effects of acupuncture. The generalizability of these findings needs to be confirmed in further larger studies. A further RCT of LA further examines these relationships, as described in Chapter 3.
Chapter 3

Laser acupuncture for chronic non-specific low back pain: a randomised controlled trial comparing IR laser irradiation doses of 0.2 and 0.8 Joules per point versus sham laser. (For details of publication see Appendix C)

Summary

- This randomised double blind RCT, was designed to investigate if infrared laser acupuncture may have a specific effect in reducing pain and disability in treatment of chronic low back pain. The trial was repeated, with a higher upper laser dose range compared to the previous trial, using a tightly defined population considered to respond more strongly to this intervention.

- The trial was conducted in a number of general practices in Perth, Western Australia. The participants were 144 adults with chronic non-specific LBP. They were randomised to receive 8 weekly treatments. Laser machines (20 mW, 830nm diode) stimulated points in three treatment groups – Sham, 0.2 J/point, and 0.8 J/point, with follow-up at 1 and 6 weeks, and 6 and 12 months post-treatment. Primary outcomes were pain (Numerical Pain Rating Scale) and disability (Oswestry Disability Inventory) at 6 weeks post-treatment. Secondary outcomes included numerical rating scale for limitation of activity, global assessment of improvement, analgesic usage and adverse effects after treatment.

- The analysis showed no difference between the sham and the laser groups in the primary outcomes of pain and disability at 6 weeks follow up. Adjusted analysis using baseline predictive variables as covariates also did not change this conclusion. Similarly, there was no difference between groups for secondary outcomes.

- This trial provided further evidence that low dose laser acupuncture (0 - 0.8 J/point) does not have a specific laser effect in reducing pain in chronic LBP.

Introduction

In 2008, before I began my doctorate studies, only two reviews\(^\text{9,29}\) had been published about laser acupuncture trials examining the treatment of miscellaneous musculoskeletal pain. A review\(^\text{29}\) of trials of LA in a range of orthopaedic diseases was equivocal but noted methodological drawbacks in studies it included. That review included only 5 trials on
“shoulder neck or back pain”; three out of five of these were positive and were the same trials listed in Chapter 1 (Table 1). None of these specifically examined low back pain. In another review on the clinical effectiveness of LA, which contained nine trials on treatment of myofascial pain, Baxter et al. concluded that “laser acupuncture can be recommended as an effective treatment (moderate level of evidence) for the reduction of myofascial pain, at least when irradiation is applied at power of at least 10mW and a dosage of at least 0.5 J per point”. The authors classified all trials in this review as “laser acupuncture”, although some trials made no reference to acupuncture in their original paper. There was no separate analysis of LBP conducted by any of the included trials.

A few randomised trials had specifically studied LA for treatment of chronic low back pain compared to a sham laser control, but these had not been included in systematic reviews available at that time. A small trial using an infrared laser (1.1 J/point) detected a small significant improvement in only one of many pain outcomes measured. Subsequently, my larger trial (see Chapter 2) using a 10 mW infrared laser (0.2 J/point) obtained a negative result, although questions were raised on the possibility of insufficient dosage and on the presence of confounding baseline factors. It was considered important to perform another quality study in an attempt to resolve these issues, including a higher laser dose within Baxter’s recommended range, and with long-term follow-up. As suggested in Chapter 2, tighter inclusion criteria were implemented, excluding subjects who may respond poorly to acupuncture such as those on disability support, current workers’ compensation or third party claims, taking regular opioid analgesics, and those with previous failed nerve blocks and injections within the previous year, or with any previous back surgery. Other differences in this trial were to (a) restrict recruitments to local newspaper notices as this was the most successful method of attracting participants, (b) reduce the duration of the treatment phase and (c) not provide a specific exercise intervention recommended to participants. Reducing the maximal number of sessions from ten to eight simplified running the intervention. Exercise co-intervention was excluded for the same reason and to reduce possibility of confounding from another variable.

**Subjects and methods**

The study was a double blind, prospective, three-group parallel randomised controlled trial; it used sham laser in the control group, with other arms using 0.2 and 0.8 J of laser stimulation per point. The treatment in the laser and sham arms of the trial was designed to appear the
same to the patient and therapist, except the laser was not switched on in the sham arm. It was approved by the University of Western Australia Human Research Ethics Committee and registered (ACTRN12610000043033) with the Australian New Zealand Clinical Trial Registry. The trial was conducted according to a research protocol designed before the study began (see Appendix F).

Patient recruitment and selection
Participants were recruited through notices in local community newspapers (see Appendix G). As principal investigator, I screened all respondents by telephone. Interested respondents who satisfied screening criteria were invited to attend an assessment. The invitation letter also contained an explanatory statement and a consent form (see Appendix I). Assessment and treatments were conducted by five GP therapists on the premises of six general practices in Perth, Western Australia, between April 2009 and April 2011.

Inclusion criteria: Subjects with chronic non-specific low back pain with duration of at least three months, age 18 to 75 years, literate English speaking, non-pregnant. Baseline pain over the previous week was ≥ 3.0 on a numerical rating scale, with maximal pain located between the 12th rib and the gluteal fold.

Exclusion criteria: (i) fibromyalgia according to American College of Rheumatology (1990) criteria, (ii) regular opioid analgesics (≥2 times a week) or opioid patches, (iii) disability support pension, current worker compensation or motor vehicle insurance claim for this back problem, (iv) any form of acupuncture, including laser, dry needling or trigger point injections for back pain or musculoskeletal problems, in the previous 6 months, (v) previous involvement in any acupuncture trial, (vi) previous injections for back pain such as facet joint blocks, nerve root or epidural steroid injection within the previous year, or (vii) previous lumbar spine surgery.

Intervention (see Appendix J)
All therapists were experienced general practitioner members of the Australian Medical Acupuncture College; at commencement they received personal training and a written manual on the trial protocol. Participants were encouraged to attend a maximum of eight weekly treatment sessions of 15 minutes duration, and were requested not to start any new physical treatments or medications during the treatment period or for six months after. They
continued with their other therapies and analgesics according to their pain, but were requested not to start any acupuncture-like treatment during the one-year follow-up.

The pragmatic Western anatomical approach to acupuncture treatment used was similar to that of my previous trial. At the start of each session, participants were asked to mark their average pain level on a numerical pain rating scale experienced during the previous week, to indicate current distribution, and to report any symptoms since the last treatment.

Acupuncture point selection (see Appendix K) was individualized for each patient. The therapist briefly examined by palpation of the area where pain was reported, and marked selected tender points lightly with a felt pen (the probe was not placed exactly over pen dots and thus was not considered to affect light absorption). More distal tender points along radiation pathways of pain were also used. Other points, depending on symptoms reported (e.g. headache, neck or other joint pain, gastrointestinal, and psychological complaints), were used at the discretion of the therapist, based on acupuncture principles. No auricular acupuncture was used. The marked points were treated sequentially with the laser probe. The laser probe rested perpendicular and in light contact with the skin. After each treatment the therapist recorded all acupuncture points used on a standard chart. No co-intervention was employed in this trial, but general support and information were provided as part of each session.

As in my previous trial, we used laser apparatus modified for use in double-blind research. The device was a Ga-Al-As infrared laser diode (830 nm) with a continuous power output of 20 mW and power density at probe/skin interface of 0.1 W/cm². Approval was obtained through the Therapeutic Goods Administration (Australian Government) to manufacture the device for this research. Three machines were purpose built for the trial (Acupak®, Melbourne), for concurrent use in a number of centres. Each machine had a different on/off coding sequence set by operating a cogwheel dial hardwired at time of manufacture. The laser probe had a red (LED) decoy light which emitted each time the unit was operated, regardless of laser operation. The power of the red (LED) light was measured as 12.5 µW which is only 0.06 % of the power output of the laser machine (.0005 J per point following 40 seconds of irradiation) and was not considered enough to produce a biological effect in reducing pain.

The device had a fixed power output; in order to vary the dose, there was a switch enabling time of operation to be set. A dose of 0.2 J was obtained by irradiating a point for 10 seconds.
and of 0.8 J, by irradiating a point for 40 seconds.

The three treatment arms, which varied according to laser on/off status and the duration of stimulation, consisted of:

1. ‘Low dose’: laser ‘on’ with 10 seconds (0.2 J) stimulation given per point.
2. ‘High dose’: laser ‘on’ with 40 seconds (0.8 J) stimulation given per point.
3. Sham: laser ‘off’, with either 10 or 40 seconds (0 J) stimulation per point in this treatment arm.

**Outcome measures (see appendix H)**

The following measures were assessed at one and six weeks, and six and 12 months post-treatment (immediate, short-term, intermediate, and long-term follow-up).

(i) **Numerical pain rating scale (NPRS)**\(^{55}\) on a box scale from 0 to 10 describing ‘usual level of pain in the last week’. A mark on the line between two adjacent boxes was recorded as half way between adjacent numerals e.g. 4.5

(ii) **Oswestry Disability Index (ODI).\(^{58}\)**

(iii) **Numerical rating scale of limitation of activities (NLARS)** on a box scale from 0 to 10 describing ‘ability to perform usual activities in the last week’.

(iv) **Global assessment of treatment question** on a seven-point Likert scale describing ‘how overall the back problem had changed compared to before starting the treatment program’.

(v) **Frequency of analgesics taken in previous month** indicated on a categorical scale: (≤ 1/month, several/month to 1/week, or ≥ several/week to daily)

(vi) **Use of analgesics relative to before treatment** indicated on a categorical scale: (decreased, unchanged or increased)

All these measures were applied at one and six weeks, and six and 12 months post-treatment. The ODI was omitted at 12 months to reduce measurement burden.

The primary outcomes were defined as pain (NPRS) and disability (ODI) at 6 weeks.

**Adverse effects** in the week after each treatment were recorded using a checklist of symptoms including (a) occurrence of pain flare and (b) non-back pain symptoms: tiredness, stiffness, headache, nausea, dizziness and other.
The following measures were recorded only at baseline to explore if they predicted outcome:
short version of Depression Anxiety Stress Scale (DASS21), neuropathic pain screening questionnaire (ID – pain), Fitzpatrick skin type assessment, and the International Physical Activity Questionnaire (IPAQ, short format).

A week after completion of treatment participants were asked: ‘Could you distinguish if an active or sham laser was used during your treatment?’ Therapists were asked the same question after treatment completion of their allocated patients.

**Randomisation / allocation concealment / blinding**

Before beginning of the trial a random computer-generated sequence was generated for each machine (permuted block randomisation technique, block size = six). Concealed allocation was performed by using sequentially numbered sealed opaque envelopes.

The participants, therapists and data entry person remained blind to treatment allocation. At the commencement of the trial, participants were informed that they had a two in three chance of receiving an active laser treatment. They were unaware that duration of point stimulation would vary between different subjects.

**Sample size**

Based on data from the previous trial, for a three parallel-arm study (with SD= 2.3 on the numerical pain scale) with $\alpha = 0.05$ and $\beta = 0.8$ to detect a difference of 1.6 units (moderate effect size) would require a total sample size of 137, allowing for 10% attrition.

**Statistical Analysis**

I used SPSS (version 20) for analyses. All data were collected on a paper-based record system and the coded data later entered into the electronic SPSS data file. The data set was double checked to detect any errors during data entry. Procedures were also employed to detect errors in categorical and continuous variables, as outlined in SPSS.

Data were checked to ensure they satisfied assumptions for statistical testing, and were analysed according to intention-to-treat (ITT) approach, as it is gold standard for reducing selection bias.
Separate analyses were performed on continuous dependent variables (NPRS, ODI and NLARS) for (a) 'no missing data' sets using the SPPS option ("exclude cases pairwise") in which a case was excluded only if missing data for the specific analysis and (b) the 'last observed value carried over' method for the imputation of missing data. Repeated measures ANOVA was used to compare treatment groups across time periods for these continuous variables. The Chi² test for independence was used to compare differences between treatment groups at follow-up times for categorical variables (GA and relative analgesic and frequency of use). The Kruskal-Wallis test was used to test the comparability of treatment and follow-up protocols, as well as the differences in the counts of adverse effects between groups during the treatment phase.

**Methods for subgroup and adjusted analysis**

Sub-group analysis was performed used to examine which baseline characteristics predicted pain reduction after treatment. This was new analysis not previously described in my previous publication (Appendix C). Percentage pain change (PPC) from baseline was again chosen as an outcome as it is an easily understandable measure and also to allow comparison with findings in the exploration conducted in Chapter 2. It was performed at immediate, short-term follow-up and intermediate term follow-up. Predictors were selected applying a ≥15% difference in PPC or significance levels of p ≤ 0.05 between subgroups of baseline variables as a cut-off value.

Multiple linear regression was also used to show how well the set of predictors contributed to the pain outcome at each follow-up. A similar approach, taking into account missing data, the types of variables entered and the method of regression, was used to enable comparison with findings of the previous trial.

One-way ANCOVA was used in an adjusted analysis to evaluate PPC at immediate and short-term follow-up across the treatment groups, while controlling for the effects of predictive baseline variables. A general linear model using a univariate analysis of variance was run only with the main effects of fixed factors, removing all 2-way and greater interactions.
Results

Participant recruitment and flow (Figure 3.1)
Recruitment and treatments were conducted from October 2008 to March 2011, with the last follow-up completed in March 2012.

After screening for eligibility, 144 participants were enrolled and randomised to receive the interventions. I completed the majority of baseline assessments and 74% of the treatment sessions. Participants underwent a total of 1092 treatment sessions; 96% completed five or more treatment sessions and 83% completed the maximal eight sessions. Reasons for participants pulling out of treatment early included unavailability, unwillingness to participate and unrelated illness. One subject pulled out due to an exacerbation of pain. There was an overall 96.5% analysis rate for the primary outcome assessment for pain. The follow-up rate achieved for the whole group was 90% at 12 months. The reasons for participants who were lost to follow-up could not be obtained.
Figure 3.1: Consolidated Standards of Reporting Trials (CONSORT) flow diagram: laser acupuncture in chronic non-specific low back pain for analysis of pain outcomes (NPRS) and loss to follow-up

**Details of acupuncture points used** (Table 3.1)
Frequently used points, situated on acupuncture lines which traversed the low back area in the midline (Governing Vessel meridian), para-medially (Bladder meridian), and laterally (Gall Bladder meridian), comprised 13, 37 and 13 percent respectively of all points used.
Distal points along these lines were also used, as well as other acupuncture points according to individual symptoms present. Points on other meridians, Ahshi points (tender points not listed under acupuncture nomenclature) and ‘Extraordinary’ acupuncture points comprised 16, 14 and 7 percent of the total (see Appendix K).

Table 3.1: Distribution (percentage) of points used according to acupuncture meridian or group

<table>
<thead>
<tr>
<th>Acupuncture meridian or group</th>
<th>GV</th>
<th>BL</th>
<th>GB</th>
<th>LR</th>
<th>Ahshi</th>
<th>‘Extraordinary points’</th>
<th>Other meridian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of total points used</td>
<td>13.4</td>
<td>36.5</td>
<td>13.2</td>
<td>6.1</td>
<td>13.8</td>
<td>6.9</td>
<td>10.3</td>
</tr>
</tbody>
</table>

*Number of points used and laser machine calibration*

An average of about nine points were used per session; the total number of points used by therapists varied between the three treatment arms, with larger numbers used for participants who had been allocated shorter stimulation times of 10 seconds (Table 3.2).

The output of the lasers was measured near the end of the treatment phase by Mr J Thwaites (Radiation and Safety Officer at UWA) on 20/4/2011 using LASER Check Edmund Optics Inc® set at 830 nm. Maximal power outputs of the machines were measured at 22.7, 14.4 and 17.7 mW respectively. A discrepancy from the stated power output was also noted in my previous trial and it has been reported that ageing diodes with falling output power may occur with such laser devices. It is noted that the total number of points used in the treatment arms varied significantly, with a greater number tending to be used by therapists for patients with the shorter stimulation times of 10 seconds (see Table 3.2). If decline in laser device output occurred during the time of the trial, actual doses administered among treatment arms would be within the ranges given in Table 3.2.

Table 3.2: Total number of points treated and total laser dose used between treatment groups

<table>
<thead>
<tr>
<th>Group (duration stimulation in seconds)</th>
<th>Average Dose Per point (J) (Unadjusted/ adjusted)</th>
<th>Total no. points treated (% total)</th>
<th>Total dose (J) Unadjusted</th>
<th>Total dose (J) Adjusted after calibration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham group (10 or 40 sec)</td>
<td>(0 / 0)</td>
<td>3008 (32)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>‘Low’ dose group (10 sec)</td>
<td>(0.2 / 0.17)</td>
<td>3830 (40.5)</td>
<td>766</td>
<td>651</td>
</tr>
<tr>
<td>‘High’ dose group (40 sec)</td>
<td>(0.8 / 0.69)</td>
<td>2622 (27.7)</td>
<td>2098</td>
<td>1809</td>
</tr>
</tbody>
</table>
The safety officer was also asked to record the power outputs from a number of randomly selected dial settings for each machine. These were later determined to correspond to the value of the on/off coding sequence set at manufacture.

**Baseline data of demographics and clinical characteristics**

Distribution of baseline characteristics between groups, shown in Table 3.3, demonstrates a greater imbalance (≥ 15%) in gender, sleep disturbance, antidepressant medication use, Fitzpatrick skin type, and depression categories.
Table 3.3: Distribution of baseline characteristics across treatment groups

<table>
<thead>
<tr>
<th>Demographics:</th>
<th>Treatment groups</th>
<th>Maximum Difference between groups %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sham (n=48)</td>
<td>’Low’ dose (n=48)</td>
</tr>
<tr>
<td>Gender (male) %</td>
<td>60</td>
<td>44</td>
</tr>
<tr>
<td>Smoking (yes) %</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Employed %</td>
<td>55</td>
<td>50</td>
</tr>
<tr>
<td>On age or other type pension %</td>
<td>33</td>
<td>46</td>
</tr>
<tr>
<td>Median age in years</td>
<td>53.5 (40/66)</td>
<td>56.5 (47/67)</td>
</tr>
<tr>
<td>BMI mean [SD]</td>
<td>26.2 (3.7)</td>
<td>29.5 (5.3)</td>
</tr>
<tr>
<td>Baseline pain characteristics:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain dichotomous (NPRS &lt;=5.0)%</td>
<td>71</td>
<td>67</td>
</tr>
<tr>
<td>Participants with pain &gt;2 yrs %</td>
<td>81</td>
<td>81</td>
</tr>
<tr>
<td>Median duration pain in years</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Acute on chronic exacerbation pain</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>Headaches present %</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>Neck pain present %</td>
<td>60</td>
<td>52</td>
</tr>
<tr>
<td>Radiating pain present %</td>
<td>48</td>
<td>50</td>
</tr>
<tr>
<td>Previous and current treatment:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prev. acupuncture &gt;6 month ago %</td>
<td>40</td>
<td>54</td>
</tr>
<tr>
<td>Regular use simple analgesia %</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>Use of anti-depressant medication %</td>
<td>10</td>
<td>23</td>
</tr>
<tr>
<td>Other baseline outcome measures:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fitzpatrick skin type (I-II) %</td>
<td>28</td>
<td>43</td>
</tr>
<tr>
<td>Neuropathic pain (ID Pain 2-4) %</td>
<td>19</td>
<td>25</td>
</tr>
<tr>
<td>Low level physical activity (IPAQ) %</td>
<td>23</td>
<td>36</td>
</tr>
<tr>
<td>Disability dichot. (moderate to severe+)</td>
<td>32</td>
<td>36</td>
</tr>
<tr>
<td>Sleep disturbance* (&lt;6 hrs sleep) %</td>
<td>38</td>
<td>15</td>
</tr>
<tr>
<td>Depression: mod-severe+(DASS21)%</td>
<td>13</td>
<td>30</td>
</tr>
<tr>
<td>Anxiety: mod-severe+ (DASS21)%</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td>Stress: mod-severe+ (DASS21)%</td>
<td>19</td>
<td>19</td>
</tr>
</tbody>
</table>

* Subscale from ODI
Comparison of baseline scores and adherence to treatment and follow-up schedules between study groups

The baseline pain scores (NPRS) and disability (ODI, NLARS) for three treatment arms were comparable (Table 3.4), with no statistically significant differences between them (One-way ANOVA).

There was also no significant difference between study groups of treatment protocol in the number of treatments given, duration of treatment and intervals of follow-up (Table 3.5).

Table 3.4: Baseline comparability of pain and disability outcome measures

<table>
<thead>
<tr>
<th>Outcome measure at baseline</th>
<th>Treatment group</th>
<th>N</th>
<th>Mean (SD)</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPRS</td>
<td>Sham</td>
<td>48</td>
<td>4.9 (1.4)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>‘Low’ dose</td>
<td>48</td>
<td>4.9 (1.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>‘High’ dose</td>
<td>48</td>
<td>5.3 (1.6)</td>
<td></td>
</tr>
<tr>
<td>NLARS</td>
<td>Sham</td>
<td>48</td>
<td>4.3 (2.1)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>‘Low’ dose</td>
<td>48</td>
<td>4.5 (1.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>‘High’ dose</td>
<td>48</td>
<td>4.2 (2.1)</td>
<td></td>
</tr>
<tr>
<td>ODI (adjusted for missing values)</td>
<td>Sham</td>
<td>47</td>
<td>26.3 (11.6)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>‘Low’ dose</td>
<td>48</td>
<td>27.3 (11.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>‘High’ dose</td>
<td>47</td>
<td>26.8 (12.5)</td>
<td></td>
</tr>
</tbody>
</table>

*using One-Way Anova; NPRS: numerical pain rating scale; NLARS: ‘numerical limitation of activity rating scale’; ODI: Oswestry Disability index

Table 3.5: Comparability of treatment protocol: median (25th, 75th percentiles)

<table>
<thead>
<tr>
<th></th>
<th>Sham n=48</th>
<th>‘Low’ dose n=48</th>
<th>‘High’ dose n=48</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of treatments completed</td>
<td>8(8,8)</td>
<td>8(8,8)</td>
<td>8(8,8)</td>
<td>ns</td>
</tr>
<tr>
<td>Treatment duration (weeks)</td>
<td>7(7,9)</td>
<td>8(7,8)</td>
<td>8(7,9)</td>
<td>ns</td>
</tr>
<tr>
<td>Time to immediate assessment (days)</td>
<td>7(7,8)</td>
<td>7(7,8)</td>
<td>7(6,8)</td>
<td>ns</td>
</tr>
<tr>
<td>Time to short term assessment (weeks)</td>
<td>8(7,8)</td>
<td>8(7,9)</td>
<td>8(8,10)</td>
<td>ns</td>
</tr>
<tr>
<td>Time to intermediate assessment (weeks)</td>
<td>27(27,30)</td>
<td>27(27,28)</td>
<td>27(26,28)</td>
<td>ns</td>
</tr>
<tr>
<td>Time to long term assessment (weeks)</td>
<td>53(53,55)</td>
<td>54(53,55)</td>
<td>53(53,55)</td>
<td>ns</td>
</tr>
</tbody>
</table>

* using Kruskal-Wallis test

Comparison of primary outcomes and other continuous outcome measures in the study groups

Table 3.6 demonstrates the results for mean pain (NPRS) at assessment and at all follow-up times. The ITT analysis was conducted separately, (a) including only cases with ‘no missing pain data’ at a follow-up time, and (b) including all cases by using the ‘last value carried
forward’ imputation method for missing observations. Across the whole cohort there was a 30% reduction of pain immediately after treatment, a 28% reduction after short-term followup, 20% after intermediate and 26% after long-term follow-up.

**Pain (NPRS)**

Analysis: A repeated measures ANOVA was conducted to assess the impact of three treatment groups (sham, ‘low’ dose, ‘high’ dose) on pain scores (NPRS) across four time periods at (i) baseline / 1 week; (ii) baseline / 6 weeks; (iii) baseline / 6 months; and (iv) baseline / 12 months follow-up. This test was performed separately using data sets (a) and (b) as listed above. There was no significant interaction between treatment group and time. There was a substantial main effect for time, with all groups showing reduction of pain scores across all the time periods (p<0.0005). The main effect comparing the three types of intervention was not significant, suggesting no difference in the efficacy between sham and laser dosages used for treatment, at all stages of follow up.

These results were similar for both ‘no missing data’ and ‘imputation’ analyses.

Table 5.6: Pain (NPRS) across baseline and follow-up for three treatment groups using different data sets: (a) cases with ‘no missing data’ at follow-up period; (b) imputation with ‘last value carried forward’

<table>
<thead>
<tr>
<th>Trial arm</th>
<th>Follow up</th>
<th>base</th>
<th>1week</th>
<th>1week</th>
<th>6week</th>
<th>6week</th>
<th>6month</th>
<th>6month</th>
<th>1year</th>
<th>1year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Analysis</td>
<td>(a)</td>
<td>(b)</td>
<td>(a)</td>
<td>(b)</td>
<td>(a)</td>
<td>(b)</td>
<td>(a)</td>
<td>(b)</td>
<td>(a)</td>
</tr>
<tr>
<td>Sham</td>
<td>Mean (SD)</td>
<td>4.9(1.4)</td>
<td>3.6(2.1)</td>
<td>3.8(2.3)</td>
<td>3.4(2.1)</td>
<td>3.4(2.0)</td>
<td>4.9(2.7)</td>
<td>3.8(2.5)</td>
<td>3.7(2.2)</td>
<td>3.6(2.1)</td>
</tr>
<tr>
<td>N</td>
<td>48</td>
<td>40</td>
<td>48</td>
<td>46</td>
<td>48</td>
<td>39</td>
<td>48</td>
<td>42</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Low Dose</td>
<td>Mean (SD)</td>
<td>4.9(1.5)</td>
<td>3.2(1.7)</td>
<td>3.2(1.7)</td>
<td>3.7(2.2)</td>
<td>3.7(2.2)</td>
<td>3.7(2.3)</td>
<td>3.7(2.3)</td>
<td>3.5(2.3)</td>
<td>3.7(2.4)</td>
</tr>
<tr>
<td>N</td>
<td>48</td>
<td>44</td>
<td>48</td>
<td>46</td>
<td>44</td>
<td>44</td>
<td>48</td>
<td>40</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>High Dose</td>
<td>Mean (SD)</td>
<td>5.3(1.6)</td>
<td>3.5(1.8)</td>
<td>3.7(1.9)</td>
<td>4.1(2.4)</td>
<td>4.1(2.3)</td>
<td>4.4(2.4)</td>
<td>4.4(2.3)</td>
<td>3.9(2.0)</td>
<td>3.9(2.0)</td>
</tr>
<tr>
<td>N</td>
<td>48</td>
<td>44</td>
<td>48</td>
<td>47</td>
<td>48</td>
<td>44</td>
<td>48</td>
<td>45</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>Mean (SD)</td>
<td>5.0(1.5)</td>
<td>3.4(1.9)</td>
<td>3.6(2.0)</td>
<td>3.7(2.2)</td>
<td>3.7(2.2)</td>
<td>4.0(2.4)</td>
<td>4.0(2.4)</td>
<td>3.7(2.2)</td>
<td>3.7(2.2)</td>
</tr>
<tr>
<td>N</td>
<td>144</td>
<td>128</td>
<td>144</td>
<td>139</td>
<td>144</td>
<td>127</td>
<td>144</td>
<td>127</td>
<td>144</td>
<td></td>
</tr>
<tr>
<td>% change</td>
<td></td>
<td>0</td>
<td>-32</td>
<td>-28</td>
<td>-20</td>
<td>-20</td>
<td>-20</td>
<td>-20</td>
<td>-20</td>
<td></td>
</tr>
</tbody>
</table>

The same data is shown graphically in Figure 3.2, with the bar graph showing mean pain (NPRS) at baseline and follow-up after the laser intervention across the trial arms.
Figure 3.2: Bar graph showing mean pain (NPRS at baseline and follow-up after the laser intervention across treatment groups)

**Disability (ODI & NLARS)**

Table 3.7 presents disability scores (ODI) up to 6 months of follow-up. For the whole cohort the reduction was only between about 3 or 4 percentage points during this time. Repeated measures ANOVA was conducted between the baseline and each time point. There was a substantial main effect for time, with all treatment groups showing a statistically significant reduction of disability scores across all the time periods (P ≤ 0.002) There was no significant difference in the effectiveness between sham and laser dosages at all stages of follow-up using either (a) or (b) data sets.
Table 3.7: Disability (ODI) across baseline and follow-up for the three treatment groups using different data sets: (a) cases with ‘no missing data’ at follow-up period and (b) imputation with ‘last value carried forward’

<table>
<thead>
<tr>
<th>Trial arm</th>
<th>Analysis</th>
<th>Follow up</th>
<th>base</th>
<th>1week</th>
<th>2week</th>
<th>6week</th>
<th>6week</th>
<th>6month</th>
<th>6month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>Mean(SD)</td>
<td>26.3(11.6)</td>
<td>22.1(11.8)</td>
<td>23.6(11.7)</td>
<td>21.6(12.6)</td>
<td>22.4(12.6)</td>
<td>22.2(12.8)</td>
<td>23.7(12.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>47</td>
<td>40</td>
<td>47</td>
<td>45</td>
<td>48</td>
<td>40</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>Mean(SD)</td>
<td>27.3(11.5)</td>
<td>22.8(11.6)</td>
<td>23.6(12.4)</td>
<td>23.1(13.4)</td>
<td>23.7(13.4)</td>
<td>23.8(15.3)</td>
<td>23.5(14.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>48</td>
<td>45</td>
<td>48</td>
<td>46</td>
<td>48</td>
<td>45</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>High dose</td>
<td>Mean(SD)</td>
<td>26.8(12.5)</td>
<td>22.4(11.1)</td>
<td>24.3(13.0)</td>
<td>23.8(15.3)</td>
<td>24.6(15.2)</td>
<td>23.2(12.8)</td>
<td>24.3(12.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>47</td>
<td>43</td>
<td>48</td>
<td>45</td>
<td>48</td>
<td>43</td>
<td>47</td>
<td></td>
</tr>
</tbody>
</table>

Similar results were obtained for the Numerical Limitation of Activities Rating Scale (NLARS) extending to the 12-month follow-up. Up to 40% reduction in disability occurred in the immediate term, but there were again no statistically significant differences between the treatment arms using the ‘no missing values’ dataset.

Additional secondary outcomes (categorical) and adverse effects

There was no significant difference between groups for improvement on the global assessment scale or in measures of analgesic use (Table 3.8). Across the whole cohort, approximately half of the participants considered that their back pain had improved at every time point after treatment, and approximately one-third considered they had reduced their analgesic use at all follow-up points. There was little change in reported frequency of analgesics use during the trial.
Table 3.8: Secondary outcome contingency tables: (Global assessment and Analgesic Use) for treatment groups

<table>
<thead>
<tr>
<th>Condition on GA</th>
<th>1 week</th>
<th>6 weeks</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>% No change/worse</td>
<td>36(40,36,32)</td>
<td>50(47,52,52)</td>
<td>55(59,53,52)</td>
<td>53(52,50,56)</td>
</tr>
<tr>
<td>% Improved</td>
<td>64(60,64,68)</td>
<td>50(53,48,48)</td>
<td>45(41,47,47)</td>
<td>47(48,50,44)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Use of analgesics compared with baseline in total cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative use of analgesics</td>
</tr>
<tr>
<td>% Unchanged or increased</td>
</tr>
<tr>
<td>% Decreased</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency of analgesic use in total cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of use</td>
</tr>
<tr>
<td>% Nil to ≤ 1/month</td>
</tr>
<tr>
<td>% Several/month-once a week</td>
</tr>
<tr>
<td>% Several/week-daily</td>
</tr>
</tbody>
</table>

**Adverse effects**

In the whole cohort there was a flare up of back pain in the week following 28% of treatments; there were some other adverse effects after 25% of treatments. However, there were no significant differences in the frequency of flare of pain or other adverse effects between treatment groups (Kruskal-Wallis test). A similar frequency of short or more prolonged flares of pain immediately after treatment were seen in all groups. A non-significant trend for more flares of pain occurring later in the week was seen in the sham group (see Figure 3.3a). There was a low incidence of other minor non-pain complaints between groups (see Figure 3.3b).
Type of Pain flare

Note: dose 1 - 'low dose'; dose 2 - 'high dose'

Figure 3.3a: Percent incidence of pain flares after treatment per total sessions across treatment groups

Type of non-pain adverse effect

Figure 3.3b: Percent incidence of non-pain adverse effect per total sessions across treatment groups

Assessment of participant blinding

In a questionnaire administered one week after the completion of treatment, equal numbers of participants in each group thought that they had been allocated a ‘real’ laser. In a contingency table there was no significant association between patients’ impression of what treatment they received and that of the intervention group (Pearson $\chi^2$ test; $P = 0.22$) (Table 3.9). There were a number of missing responses in this questionnaire, as some participants did not return the survey form at this follow-up interval.
Also, on direct questioning of the trial therapists, none could identify which participants had received active or sham laser irradiation during the course of treatment.

Table 3.9: Impression of form of treatment received by patients
(laser / sham / uncertain) * treatment group
crosstabulation counts

<table>
<thead>
<tr>
<th>Patient impression type of treatment received</th>
<th>Treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sham</td>
</tr>
<tr>
<td>‘real’</td>
<td>10</td>
</tr>
<tr>
<td>‘sham’</td>
<td>9</td>
</tr>
<tr>
<td>‘uncertain’</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
</tr>
</tbody>
</table>

Relation of baseline characteristics to pain outcome

Although 30% PPC difference has been described as representing clinically meaningful improvement, and a 20% threshold was used in Chapter 2 we decided to use a lower figure of 15% as higher values were less often obtained in this trial. This was done in order to increase sensitivity in detecting predictors. Possible predictors, based on this threshold of PPC size, or statistical significance (p≤0.05) using One way ANOVA, are listed (Table 3.10). On this basis, for the whole trial cohort, immediate-term predictors were (a) age group, (b) pension status, (c) analgesic use pattern (d) sleep disturbance (on a subscale of ODI), (e) depression or stress level (DASS21 scale) and (f) level of pain at baseline. In the short-term follow-up they were (a) duration of pain, (b) presence of exacerbation of pain at baseline, (c) disability (ODI), and (d) level of pain at baseline. At intermediate-term they were (a) alcohol intake, (b) anxiety level (DASS21 scale), and (c) level of pain at baseline.

Conversely, the other baseline factors studied, including gender, smoking status, coffee intake, BMI, work status, radiation of pain, degenerative changes found on imaging, neuropathic pain (ID- pain), use of NSAIDs or antidepressant medication, the Fitzpatrick skin type, physical activity level (IPAQ), presence of baseline headaches, neck pain or irritable bowel symptoms, based on the chosen criteria, were shown not to influence pain outcome. These factors were not listed in Table 3.10.
Table 3.10: Baseline characteristics predicting pain outcome at immediate and short-term follow-up (using data sets for PPC with “last value pain carried over"

Only PPC values ≥ 15% are shown.

<table>
<thead>
<tr>
<th>Baseline Variable (categorization)</th>
<th>Category with less pain improvement</th>
<th>Immediate at 1 week</th>
<th>Short-term at 6 weeks</th>
<th>Intermediate at 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of pain (≤2 years vs &gt;2 years)</td>
<td>&gt;2 years duration</td>
<td>-</td>
<td>19.8 (0.02)</td>
<td>-</td>
</tr>
<tr>
<td>Age (≤55 years vs &gt;55 years)</td>
<td>≤55 years of age</td>
<td>17.0 (0.01)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Alcohol (Y/N)</td>
<td>yes (&gt;2-4 Standard Drinks per day)</td>
<td>-</td>
<td>-</td>
<td>15.1 (0.20)</td>
</tr>
<tr>
<td>Pension status (Aged or other vs Nil)</td>
<td>nil pension</td>
<td>14.6 (0.03)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Exacerbation of pain at baseline present (Y/N)</td>
<td>Yes, over previous month before assessment</td>
<td>-</td>
<td>15.8 (0.09)</td>
<td>-</td>
</tr>
<tr>
<td>Simple analgesic use (Nil or PRN vs regular)</td>
<td>Nil or PRN</td>
<td>17.9 (0.03)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sleep disturbance ≤6 hrs vs &gt; 6 hrs</td>
<td>Has ≤6 hours of sleep per night</td>
<td>17.4 (0.03)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Disability (ODI) (low vs high)</td>
<td>Moderate, severe or worse</td>
<td>-</td>
<td>15.0 (0.04)</td>
<td>-</td>
</tr>
<tr>
<td>Depression (DASS21) (low vs high)</td>
<td>Moderate, severe or worse</td>
<td>20.7 (0.02)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anxiety (DASS21) (low vs high)</td>
<td>Moderate, severe or worse</td>
<td>-</td>
<td>-</td>
<td>21.1 (0.14)</td>
</tr>
<tr>
<td>Stress (DASS21) (low vs high)</td>
<td>Moderate, severe or worse</td>
<td>31.5 (0.001)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pain at baseline (NPRS) (low vs high)</td>
<td>NPRS ≤ 5</td>
<td>14.3 (0.03)</td>
<td>16.3 (0.02)</td>
<td>15.9 (0.05)</td>
</tr>
</tbody>
</table>

* P value calculated using One-way Anova
Using the data set for PPC (missing values imputed using the “last value carried forward” method) at one week, six weeks and six months post-treatment, I performed standard multiple regression to assess the strength of association between independent baseline factors and the continuous dependent variable (PPC post-treatment) see Table 3.11. All the independent variables were entered at once (ENTER) in the SPSS program. Baseline variables which predicted less pain reduction (PPC) immediately post-treatment were subjects with (i) lower pain initially on a pain rating scale; (ii) less sleep; and (iii) worse stress levels. At six weeks post, these were (i) lower levels of pain; (ii) no exacerbation of pain before assessment; and (iii) longer duration of pain. At 6 months no significant relationships for predictors were found.

Table 3.11: Predictors of PPC at three time points after intervention using standard multiple regression

<table>
<thead>
<tr>
<th>Time point for dependent variable (PPC)</th>
<th>Independent variable (category with worse treatment outcome)</th>
<th>Pain at last recorded end point imputed for missing values</th>
<th>Standardized Coefficient</th>
<th>Significance (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate term (at end of treatment)</td>
<td>Pain at baseline (less)</td>
<td>-19</td>
<td>02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sleep (less)</td>
<td>-23</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stress (DASS) (moderate or severe)</td>
<td>-18</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Analgesic pattern (nil or prn)</td>
<td>-0.16</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>Short-term (6 weeks after end of treatment)</td>
<td>Pain at baseline (less)</td>
<td>-26</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baseline pain duration (&lt;2 yrs)</td>
<td>-20</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baseline pain exacerbation (not present)</td>
<td>-23</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disability (ODI) (worse)</td>
<td>-15</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Intermediate-term (6 months after end of treatment)</td>
<td>Pain at baseline (less)</td>
<td>-15</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DASS21 – anxiety (worse)</td>
<td>-15</td>
<td>0.07</td>
<td></td>
</tr>
</tbody>
</table>
**Adjusted analysis**

After the baseline factors were identified in Table 3.11, there were no significant differences between sham and active laser groups for dependent variables (NPRS or PPC) at immediate or short-term follow-up using one-way ANCOVA (Table 3.12). Baseline dichotomized variables for initial level of pain, analgesic pattern of use, sleep disturbance, and stress level (DASS21) were used as covariates at immediate follow up. Initial level of pain, duration of pain, exacerbation of pain and disability (ODI) were used as covariates at short-term follow-up. These baseline variables had been determined as predictors in Table 3.11 (see their distribution between the laser and sham treatment groups in Table 3.3).

Table 3.12: Adjusted means for mean NPRS at immediate- and short-term follow-up

<table>
<thead>
<tr>
<th></th>
<th>Immediate-term(i)</th>
<th>Short-term(i)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>mean NPRS</strong></td>
<td>adjusted mean (SE)</td>
<td>unadjusted mean (SD)</td>
</tr>
<tr>
<td>Sham</td>
<td>4.50 (0.31)</td>
<td>3.82 (2.3)</td>
</tr>
<tr>
<td>Low dose</td>
<td>4.07 (0.32)</td>
<td>3.24 (1.7)</td>
</tr>
<tr>
<td>High dose</td>
<td>4.37 (0.34)</td>
<td>3.69 (1.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Immediate-term(ii)</th>
<th>Short-term(ii)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>mean PPC</strong></td>
<td>adjusted mean (SE)</td>
<td>unadjusted mean (SD)</td>
</tr>
<tr>
<td>Sham</td>
<td>13.47 (6.38)</td>
<td>21.22 (51.35)</td>
</tr>
<tr>
<td>Low dose</td>
<td>19.97 (6.74)</td>
<td>32.04 (31.56)</td>
</tr>
<tr>
<td>High dose</td>
<td>12.48 (7.06)</td>
<td>27.71 (36.400)</td>
</tr>
</tbody>
</table>

(i) NPRS at 1 week (P = 0.53) and 6 weeks (P = 0.22)

(ii) PPC at 1 week (P = 0.61) and 6 weeks (P = 0.18)
Discussion

This randomised controlled trial of low dose laser acupuncture for chronic low back pain found no differences in any outcome or adverse effects at any time point, for laser acupuncture in doses up to 0.8 J / point (energy density 1 - 4 J/cm²), when compared with sham laser. Imputation approaches to manage missing data made no difference to the results. The same laser therapy device, modified for research to ensure concealed allocation and double-blinding, was that used in my previous trial. Statistical analysis of a survey conducted a week after completion of treatment again supported that double-blinding was successful in the current study.

This trial strengthens the evidence for the lack of a specific biological effect from laser at this low dose range when treating chronic low back pain. In this and the previous trial, both focusing on treatment of CNLBP, no differences between laser and sham groups were found for pain reduction, and for a number of other outcome measures. Therapists individually selected acupuncture points and other tender points for treating back pain and also for co-existing conditions. There is some recent evidence that LA at this range of laser dosage is also ineffective for in the treatment of other anatomical site conditions apart from LBP. For knee pain, this is supported by the findings of another Australian research group who published a trial66 of acupuncture for chronic knee pain in 2014, using the same laser machine manufactured by Acupak of Melbourne, Australia (830 nm,10mW GaAlAs diode), and a dose of only 0.2 J/point. The methodology used also ensured a low risk of bias in the domains of blinding. They found no significant differences in the primary outcomes of pain (NPRS) and disability (WOMAC) between active laser and sham laser acupuncture at 12-weeks and 1-year follow-up. The whole cohort achieved a mean reduction in pain compared to the baseline of 31% at 12 weeks and 18% at the one-year follow-up respectively. Interestingly, this was similar in magnitude of pain reduction to that described in our trials for back pain, and can be assumed to be due to factors not related to laser stimulation.

In the past, LA trials have suffered from methodological limitations including small sample size, variable blinding and crossover designs. We applied a robust trial design to reduce risk of bias including gold standard randomisation and concealed allocation procedures for this type of research. Participants and therapists were successfully blinded to treatment allocation by using a specially designed device55 ensuring masking of the mode of laser emission. Although there was concern that the duration of laser application to points was not masked, participants remained unaware of this treatment variable and were thus effectively ‘blinded’.
Therapists, who were aware, tended to stimulate larger numbers of points in subjects allocated the shorter dose treatment. This probably because of inclination of therapists to use more points in cases who were allocated shorter laser stimulation times during a time limited session. Despite this, the total laser dose given in the low-dose arm was still one-third of the high-dose arm (Table 3.2), allowing a meaningful investigation of dose dependence. It must also be noted that in this trial because of constraints of apparatus used a higher dose per point was achieved by laser irradiation by using same power output for a longer time. Experimental evidence is still not available on whether the biological effect of irradiating a point with the same laser dose (J) over varying times is equivalent.

My trial was also sufficiently powered to detect a clinically meaningful difference in reduction of pain between groups of 1.5 cm on a pain scale of 0–10 cm (15%), for LBP if it existed. This study had multiple exclusion criteria which may have reduced its external validity. This was informed by preceding research excluding patients on disability support, regular users of any opioid, and with previous back surgery or spinal injections. These groups previously demonstrated less improvement after intervention. My intent was to maximize the chance of detecting a specific effect of laser stimulation if it existed. A greater improvement in pain or disability, however, was not observed in the current trial. Possible reasons for greater improvement in the earlier study may have included an exercise co-intervention, a larger number of treatment sessions and a higher mean baseline level of pain.

A large number of laser parameters available in therapy may make comparison between trials difficult to interpret. Different laser devices have different radiant power outputs and wavelengths ranging from the visible spectrum to infrared. Dose in joules per point and density of laser irradiation can also be varied. Although this study confirms the lack of a specific effect of infrared laser diodes using low energy densities for treating this condition, it is still possible that larger energy doses or different wavelengths may be more effective for chronic LBP. A much higher laser dose (8 J Joules with a therapeutic dose window range of + / - 50% per point) for laser therapy of lumbar spine is recommended by the World Association for Laser Therapy; however these recommendations refer to non-acupuncture LLLT. A recent German LA trial of a much higher energy ‘laser needle’ device failed to show a specific effect of laser. This may suggest an upper threshold for effective laser dosage for LA, but unfortunately further double blind trials using this machine have not been done. A low dose laser acupuncture approach for chronic knee pain producing a negative result has already been discussed in this chapter, however, future research needs to trial LA treatment
of other musculoskeletal problems. When designing such trials, the choice of appropriate laser dose is of great importance.

My trials also support the influence of non-specific effects which may produce beneficial therapeutic outcomes in some patients; these otherwise may have been falsely attributed to the specific laser intervention. A 30% PPC has previously been described as a clinically meaningful improvement.\(^7\) In our whole cohort, non-specific effects resulted in a clinically important improvement being approached in the reduction of mean pain scores immediately following the last treatment (30% reduction in pain from baseline) and persisting almost at the same level throughout follow-up (20–26% reduction in pain). There was a smaller reduction in disability (ODI) of less than 5% across the follow-up. It was postulated that a number of factors may have contributed to the overall improvement after the intervention, such as the placebo effect, the phenomenon of regression to the mean, natural history and the effects of simply participating in an experiment (the Hawthorne effect). Some improvement may even have resulted from acupressure-like effects of skin stimulation during examination for tender points.\(^6\) It was not possible to determine the relative contribution of these factors; however, some indication can be gained from the previously described trial\(^6\) using a Zelen design in which participants consented to acupuncture after randomisation. One control group was randomised to receive no acupuncture and subjects were unaware of it being a clinical trial. This group was measured to have a 14% reduction of pain from baseline at 12 weeks and 10% reduction at 1-year follow up. These were approximately 50% of the reductions observed from the nonspecific effects of the laser intervention.

I also conducted an analysis to determine which baseline variables could influence non-specific pain reduction after this intervention. Witt et al.\(^8\) in 2011 described pooled data from 4 RCTs of acupuncture treating chronic pain conditions, with 9990 subjects, from which the SF-36 pain scale was the outcome. Overall predictors of a worse outcome were older patients, longer duration of illness, lower education level, less pain at baseline, acupuncture treatment in previous year, and comorbidity such as hypertension, asthma and other medical conditions. Separately from these, the acupuncture effect-modifying predictors with worsening outcomes were male gender, people who lived alone, those with negative acupuncture experience, or those who had had success with other treatments.

My previous paper\(^7\) (Appendix B) developed an approach to determine if baseline factors predicted a pain outcome up to the 6-month follow-up. Predictors of a worse overall outcome identified were patients who had headaches, were on disability support pension, had previous back surgery or had given spinal injections for pain, were taking regular analgesics (including
Panadeine Forte or Tramadol), and had less pain or no exacerbation of pain at baseline. These predictors, however, usually did not show an effect across all stages of follow-up.

The current trial (Appendix C) studied a different patient population, with altered selection criteria including an older population (up to 75 years of age), and with the exclusion of DSP recipients, any previous back surgery, those given any radiologically controlled spinal injections for pain in previous 12 months, and subjects taking regular doses of any opioids (including Panadeine Forte or Tramadol). There were also stricter criteria for exclusion of patients with fibromyalgia. The trial also required the completion of fewer treatment sessions, and an intention-to-treat analysis was used. PPC was again used and smaller differences in this between subcategories were observed, compared to the previous trial, resulting in reducing thresholds for selecting possible predictors.

In the overall population after this intervention, less pain reduction was found in patients with pain duration over two years, with lower baseline pain, and in patients not on regular simple analgesics, who were more sleep disturbed, with higher disability (ODI), and with increased anxiety or stress (DASS21).

In spite of some differences in inclusion criteria, with more restrictions in this recent trial, it demonstrated some similarity of predictors of outcomes found in the author's previous paper. Predictors included baseline pain level, exacerbation or duration of back pain, the patterns of regular analgesic use (especially for opioids), the presence of psychological distress, and the disability level. The previous trial also showed that persistence of pain after previous back surgery or after spinal blocks was also a factor.

It must be noted that results from the population we studied, may not generalize to other samples. My work examined relatively small samples, with results dependent on threshold levels for selection of predictors, imputation of missing values and the type of statistical analysis (including the use of PPC as an outcome measure). Other limitations were the possible lack of reliability in some of the scales used to describe baseline characteristics, and possible violations in assumptions concerning data used for multiple regression. There were also issues related to multiple testing, with the possibility of chance findings.

The overall non-specific predictors inferred were in the context of a LA intervention. At the time of writing there had not been similar investigations in other LLLT trials, but it is possible that certain predictors may be shared across a range of acupuncture, such as interventions for back pain or other conditions. It was not possible in our trials to assess if there was an interaction between the baseline variable and a specific laser effect (laser acupuncture modifying predictors).
Knowledge of negative predictors is useful in recognizing the effect of confounders in trial results and performing adjusted analyses. A pre-planned adjusted analysis showed that any baseline imbalance did not affect the primary result in the current trial. This also strengthens the conclusion that the positive finding in the previous trial, upon adjusted analysis at short-term follow up for 0.2 J / point laser irradiation, was a chance finding. Generalizability of non-specific effect predictors to other acupuncture and non-acupuncture therapies needs to be explored. More research into acupuncture modifying predictors is also needed. This trial only partly clarifies the decisions for therapists contemplating purchasing relatively expensive laser pointer machines in the lower energy range to treat back pain. While there appear to be considerable improvements in pain and other measures following therapy using such devices, this trial suggests that the effect is not specifically due to using laser at the low dosage previously considered effective in clinical practice. Scope however remains for further research to determine dosage windows and conditions which could respond to LA. After the conclusion of the current trial, I decided to conduct an up-to-date systematic review of all RCTs published, examining LLLT in the treatment of CNLBP, in attempt to answer some of the preceding questions. The results of this review are presented in the following chapter.
Chapter 4

A meta-analysis: randomised controlled trials of low-level laser therapy for chronic nonspecific low back pain (For details of publication see Appendix D)

Summary

- The efficacy of low-level laser treatment for chronic back pain remains controversial due to insufficient trial data. I conducted an updated review to determine if laser therapy including laser acupuncture has a specific benefit for pain reduction in chronic nonspecific low back pain (CNLBP).

- Electronic databases were searched for randomised trials using sham control and blinded assessment that examined the intervention of low-level laser therapy in adults with CNLBP. Primary outcomes were pain and global assessment of improvement up to short-term follow-up. Secondary outcomes were disability, range of back movement and adverse effects. A random effects meta-analysis was conducted. Subgroup analyses were based on the laser dose, the duration of baseline pain and if the laser therapy used an acupuncture approach.

- 15 studies were selected involving 1,039 participants. Immediate and short-term follow-up showed a significant pain reduction of up to WMD -1.40cm (95% CI -1.91 to -0.88) in favour of laser treatment that occurred in trials using at least 3 Joules (J) per point, with baseline pain less than 30 months and in non-acupuncture laser therapy trials. Global assessment showed a risk ratio of 2.16 (95% CI: 1.61, 2.90) in favour of laser treatment in the same groups at immediate follow-up only.

- I demonstrated a moderate quality of evidence (GRADE) for a clinically important benefit in low-level laser therapy for CNLBP in the short term, but seen only in higher laser dose interventions and subjects with shorter duration back pain. Rigorously blinded trials using appropriate laser dosage would provide greater certainty for this conclusion.

In earlier chapters of this work a lack of evidence for the effectiveness of low dose laser acupuncture in the treatment of CNLBP was presented. As LA can be considered a subgroup of LLLT, it was decided to systematically review this larger group of laser therapies to determine the reasons for variable results across trials in this field.

As described in Chapter 1, a number of meta-analyses since 2003 have reported pain relief from LLLT in various musculoskeletal painful conditions.\textsuperscript{10,28-30} In 2014 another meta-analysis\textsuperscript{11} examining LA for treating musculoskeletal pain was published. Subjects with musculoskeletal disease or injury presenting with pain were studied. There was no
specification of chronicity. The meaning of ‘laser acupuncture’ was somewhat broad in this review, as it was defined as any LLLT used to treat Chinese acupuncture points, trigger points or tender points, and considered its controls to be placebo/sham or no or other treatment. Forty-nine studies were included, of which 33 provided enough data to calculate effect sizes in meta-analysis. When compared with the placebo intervention, the overall effect for pain favoured laser acupuncture, both at the end of the intervention (SMD -0.43; -0.74 to -0.12) and at the moderately longer follow-up period (SMD -0.61; -1.12 to -0.10). There was a positive effect of laser acupuncture, for the diagnostic group, of myofascial pain or musculoskeletal trigger points at short term (SMD -0.49; -0.83 to -0.16), and a strong effect at longer term (SMD -0.95; -1.68 to -0.23). Unusually, one finding of this review was a greater effect size at the longer follow-up (6 to 26 weeks post randomisation). Results for a lesser number of trials examining the treatment of separate diagnostic groups of lateral epicondylitis or of TMJ pain were inconclusive. This review included only 2 studies on LBP, which were both negative, and found a relationship between adequate laser dose and favourable results, but could not determine an effective dosage window due to clinical heterogeneity, with a wide range of conditions and sites treated.

Only one systematic review\textsuperscript{92} conducted by the Cochrane Collaboration in 2008, examined controlled trials of laser therapy in chronic non-specific chronic LBP, and showed “a small effect on pain intensity” if applied to painful areas in patients suffering chronic pain from this condition. This included only 7 trials, which considered acute and chronic pain, did not restrict controls to sham laser, and excluded LA trials. Given the heterogeneity of the populations, interventions and controls, and studied in a relatively small number of trials, the authors of this Cochrane review decided that there was insufficient data to draw firm conclusions on the effect of LLLT in LBP.

With the accumulation of more laser trials published on this topic, I considered it important to conduct another updated systematic review on the effectiveness of LLLT, but also including LA for the treatment of CNLBP.
Methods

This unfunded meta-analysis was performed in accordance with an unregistered protocol (see Appendix L) under guidelines of the Cochrane Back Review Group (CBRG)\textsuperscript{93} and PRISMA.\textsuperscript{94}

Eligibility criteria

Studies were randomised controlled trials (RCTs) with blind assessment of the outcome. Participants were non-pregnant adults with CNLBP.\textsuperscript{31} The primary intervention studied was LLLT including LA. In this review, LA was defined as the application of low intensity laser to classical acupuncture points, other tender points and/or trigger points, with reference to acupuncture treatment stated in the report; other studies were classified as non-acupuncture laser therapy. Continuous or pulsatile laser therapy machines of any wavelength with power outputs up to 500 mW were included. Higher maximum power devices were considered for inclusion if they were said not to produce an obvious thermal sensation in subjects. The comparison intervention used sham laser with similar appearance to the active treatment without laser irradiation. Co-interventions were allowed if the same in laser and control group. Cross-over studies were excluded, as a prolonged effect may occur after acupuncture with a residual effect being present from the previous intervention.

Outcomes

Time points for follow-up (adapted from CBRG\textsuperscript{93}) were defined as:

- \textit{Immediate}: closest to one week post-completion of treatment.
- \textit{Short-term}: 4 to 12 weeks post-completion.
- \textit{Intermediate}: closest to 6 months post-completion.
- \textit{Long-term}: closest to one year post-completion.

Primary outcomes were (i) low back pain measured by visual analogue scale (VAS) or numerical pain rating scale (NPRS) and (ii) ‘global assessment’, which represented dichotomous categorical outcomes of overall improvement or satisfaction with intervention. These were measured at immediate and short-term follow-up.

Secondary outcomes included low back related disability measured by the Oswestry Disability Index (ODI)\textsuperscript{58} or Roland-Morris Disability Questionnaire (RMQ),\textsuperscript{95} adverse effects,
measures of range of back movement (ROM), and continuous or categorical outcomes of LBP at other endpoints.

**Search methods for identification of studies**

Electronic databases [MEDLINE (OVID), PubMed (NCBI), Embase (OVID), CINAHL (EBSCO), and CENTRAL (online Cochrane Library)] were searched for RCTs of laser therapy or laser acupuncture for the treatment of chronic LBP, where the control was sham laser. The Updated Search Strategies for CBRG were used, which included (i) generic search for randomised controlled trials and controlled clinical trials, combined with (ii) specific search for ‘back’ conditions. The search was completed by adding terms related to the (iii) laser intervention (see Appendix M).

Additional searches were conducted in AMED and PEDro. Reference lists from included papers and previous relevant reviews were examined to identify additional papers.

**Selection of studies, data extraction and management**

I initially screened the papers at title and abstract level, and removed duplicate reports and ineligible trials. There was no restriction of full text by language. Potentially eligible papers were reviewed by pairs of reviewers and data extracted independently on a common data collection form adapted from CBRG. We were not blinded to authors or journals of publication. Authors were contacted if possible, to clarify further information where necessary. RevMan 5.3 was used for data management and statistical analysis.

**Assessment of risk of bias in included studies**

I adapted the Cochrane Collaboration tool for assessing risk of bias in twelve domains for each included trial. Paired reviewers categorized domains as having high, low or unclear risk of bias; disagreements were resolved by consensus. My supervisors assessed risk of bias in trial and external reviewers were contacted to assess risk bias in a trial for which our reviewers were authors. CBRG classifies a study as low risk if six out of twelve criteria have been met and the study has no serious flaws. In this review, a trial was classified as ‘higher risk of bias’ if it contained more than six domains of ‘high’ or ‘uncertain risk’.
**Measures of treatment effect**

Where appropriate, meta-analysis was used to combine the results of the trials using a random-effects model. For continuous data (pain intensity, disability and ROM), the mean difference (MD) or standard mean difference (SMD), with 95% CIs, measured the treatment effect. For global assessment we calculated the risk ratio (RR) with 95% CIs.

**Unit of analysis issues**

Different pain measurement scales (VAS and NPRS) were converted to a scale of 0.0 to 10.0 cm. In a trial which examined more than one laser dose, I avoided ‘double counts’ by splitting the sham laser control group into two equal-sized groups, to allow inclusion of two independent comparisons in meta-analysis.

**Dealing with missing data, assessment of heterogeneity and publication bias**

I used the RevMan calculator to derive both unreported statistical data; the physical formula to calculate unreported laser parameters used:

(i) Energy dose (J) = Watts (W) × seconds (secs)

(ii) Energy density (J/cm²) = W × secs / area of treated surface or probe tip (cm²)

(iii) Power density (W/cm²) = W / area of treated surface or probe tip (cm²)

Assessment of heterogeneity was made by inspection of forest plots, the chi² test and the I² statistic. The interpretations for the chi² test and I² were as described in the Cochrane Handbook (I² of 0-40%, 30-60% and 50-90% may represent ‘not important’, ‘moderate’ and ‘substantial’ heterogeneity respectively). Publication bias was addressed by examination of funnel plots for a primary outcome, when this is reported by at least ten trials.

**Data synthesis**

Meta-analysis was performed for outcomes at immediate and short-term follow-up, except for outcomes for two studies or less, or at longer follow-up results which are presented narratively. Decisions for conducting subgroup analyses based on (i) acupuncture/ non-acupuncture laser therapy and (ii) laser dosage were made at protocol stage. Previous LLLT research has considered the dose of laser energy delivered per point to be a predictor of the treatment effect. Post hoc decisions on the cut-off value for laser dose (low dose (<3 J/point) versus high dose (≥3 J/point)), and on the conduct of a subgroup analysis based upon baseline pain duration subjects i.e. shorter (<30 months) versus longer (≥30 months), were guided by...
consideration of the review findings. The sensitivity analysis performed excluded trials considered to be at ‘higher risk of bias’.

**Grading the quality of evidence**

The CBRG\textsuperscript{93} recommendation to adapt the GRADE\textsuperscript{99} approach for back reviews was followed. The quality of the body of evidence for each primary outcome was rated based on five domains (limitations of the study design, inconsistency, indirectness, imprecision and publication bias). The quality of evidence was downgraded depending on the presence of bias or uncertainty within the domains.
Results

Results of the search
Electronic searches of databases from inception until August 2014 located 14 relevant studies (Figure 4.1). A further two studies were located from screening reference lists; one was excluded by consensus, as it reported a non-validated subjective outcome, resulting in a total of 15 studies. Three papers required translation into English, from German and Japanese.

Included study characteristics

Participants
As shown in Table 4.1, the 15 selected trials over the period 1989 to 2014 included 1039 subjects, randomised. Subjects were recruited into trials from hospitals and
rehabilitation clinics, except for four trials,\textsuperscript{1,3,91,98} which recruited from community
newspapers. Some trials did not fully describe details of inclusion criteria for chronicity\textsuperscript{101,102}
or specificity.\textsuperscript{101,102,109} Where the mean baseline duration of pain was reported, this was
‘shorter’ in some trials,\textsuperscript{103,105,106,108} with an ‘average’ range of 4.6 to 27 months, and ‘longer’
(49 months to 13 years) in other trials.\textsuperscript{1,3,91,98,104,107} The duration was not reported in the
remaining trials. Certain trials included only geriatric patients,\textsuperscript{108} only males,\textsuperscript{103} or people
with LBP for > 1 month duration.\textsuperscript{110}
Table 4.1: Participant data and outcomes

<table>
<thead>
<tr>
<th>Trial [year] (country)</th>
<th>sample size (n)</th>
<th>Mean age (yrs)</th>
<th>i. Diagnosis for inclusion</th>
<th>ii. Is it non-specific back pain?</th>
<th>Baseline mean pain duration</th>
<th>Baseline mean pain intensity (scale 0-10cm)</th>
<th>Baseline mean Disability ODI (RMQ)</th>
<th>Other baseline variables reported</th>
<th>Outcome measure(s) [Follow-up periods post-treatment]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alayat [2013] (Saudi Arabia)</td>
<td>52</td>
<td>33</td>
<td>i. Male patients with history of LBP for at least 1 year ii. yes</td>
<td>13 months</td>
<td>8.3</td>
<td>74</td>
<td>body weight</td>
<td>Pain, ODI, ROM [immediate, 12 weeks]</td>
<td></td>
</tr>
<tr>
<td>Ay [2009] (Turkey)</td>
<td>40</td>
<td>55</td>
<td>i. LBP over 3 months duration due to lumbar disc herniation ii. yes</td>
<td>60 months</td>
<td>6.1</td>
<td>2 (0.15)</td>
<td>education level</td>
<td>Pain, ODI, RMQ, ROM, UA [immediate]</td>
<td></td>
</tr>
<tr>
<td>Basford [1999] (UK)</td>
<td>83</td>
<td>48</td>
<td>i. Non-radiating low back pain of more than 30 days duration ii. yes</td>
<td>10 months</td>
<td>3.6</td>
<td>25</td>
<td>degeneration on lumbar-ray, analgesic use, previous treatment</td>
<td>Pain, ODI, ROM [immediate, 4 weeks]</td>
<td></td>
</tr>
<tr>
<td>Djavid [2007] (Iran)</td>
<td>41</td>
<td>37</td>
<td>i. LBP minimum 12 weeks duration ii. yes</td>
<td>24 months</td>
<td>6.2</td>
<td>33</td>
<td>education level, smoking status</td>
<td>Pain, ODI, ROM [immediate, 6 weeks]</td>
<td></td>
</tr>
<tr>
<td>Glazov [2009] (Australia)</td>
<td>88</td>
<td>51</td>
<td>i. LBP at least 5 months duration ii. yes</td>
<td>11 years</td>
<td>5.7</td>
<td>30</td>
<td>multiple</td>
<td>Pain, ODI, UA [immediate, 6 weeks, 6 months]</td>
<td></td>
</tr>
<tr>
<td>Glazov [2014] (Australia)</td>
<td>144</td>
<td>54</td>
<td>i. LBP at least 3 months duration ii. yes</td>
<td>11 years</td>
<td>5.0</td>
<td>37</td>
<td>multiple</td>
<td>Pain, ODI, UA [immediate, 6 weeks, 6 months, 1 year]</td>
<td></td>
</tr>
<tr>
<td>Klein [1990] (USA)</td>
<td>20</td>
<td>42</td>
<td>i. LBP at least 12 months duration ii. yes</td>
<td>8.5 years</td>
<td>3.2</td>
<td>35</td>
<td>nil other</td>
<td>Pain, RMQ, ROM [1 month]</td>
<td></td>
</tr>
<tr>
<td>Konstantinovic [2002] (Serbia)</td>
<td>56</td>
<td>69</td>
<td>i. Patience patients with chronic LBP caused by degenerative changes ii. NR</td>
<td>4.6 months</td>
<td>8.8</td>
<td>11</td>
<td>nil other</td>
<td>Pain, ODI, ROM [immediate]</td>
<td></td>
</tr>
<tr>
<td>Lin [2012] (Taiwan)</td>
<td>28</td>
<td>64</td>
<td>i. LBP at least 3 months, recruited from a hospital. 'Complications excluded ii. NR</td>
<td>NR</td>
<td>5.2</td>
<td>NR</td>
<td>BMI</td>
<td>Pain [immediate]</td>
<td></td>
</tr>
</tbody>
</table>
### Table 4.1: Participant data and outcomes (continued)

<table>
<thead>
<tr>
<th>Trial</th>
<th>[year] (country)</th>
<th>sample size (n)</th>
<th>Mean age (yrs)</th>
<th>i. Diagnosis for inclusion ii. Is it non-specific back pain?</th>
<th>Baseline mean pain duration</th>
<th>Baseline mean pain intensity (scale 0-10cm)</th>
<th>Baseline mean Disability ODI (RMQ)</th>
<th>Other baseline variables reported</th>
<th>Outcomes Measure [follow-up period(s) post-treatment]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Okamoto</td>
<td>1989 (Japan)</td>
<td>69</td>
<td>57</td>
<td>i. ‘patients admitted to hospital with LBP, ... pregnant, lactating, recent surgery, immune suppressants, difficult to treat excluded ii. NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>nil other</td>
<td>GA [immediate]</td>
</tr>
<tr>
<td>Ruth</td>
<td>2012 (Germany)</td>
<td>111</td>
<td>59</td>
<td>1. LBP duration over 6 months ii. yes</td>
<td>10 years</td>
<td>6.7</td>
<td>NR</td>
<td>employment status</td>
<td>GA/Pain, Disability [12 weeks]</td>
</tr>
<tr>
<td>Soriano</td>
<td>1998 (Argentina)</td>
<td>85</td>
<td>64</td>
<td>i. LBP duration over 3 months ii. yes</td>
<td>NR</td>
<td>8.0</td>
<td>NR</td>
<td>nil other</td>
<td>GA [immediate]</td>
</tr>
<tr>
<td>Umekagi</td>
<td>1989 (Japan)</td>
<td>60</td>
<td>55</td>
<td>Same as in Okamoto trial</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>nil other</td>
<td>GA [immediate]</td>
</tr>
<tr>
<td>Vallone</td>
<td>2014 (Italy)</td>
<td>100</td>
<td>68</td>
<td>1. LBP duration over 6 months ii. yes</td>
<td>NR</td>
<td>6.5</td>
<td>NR</td>
<td>nil other</td>
<td>Pain [immediate]</td>
</tr>
<tr>
<td>Wallace</td>
<td>1996 (Australia)</td>
<td>41</td>
<td>50</td>
<td>1. LBP at least 3 months duration ii. yes</td>
<td>6.5 years</td>
<td>6.3</td>
<td>31</td>
<td>multiple</td>
<td>Pain, ODI [immediate]</td>
</tr>
</tbody>
</table>

**Abbreviations** - ODI: Oswestry Disability Index, RMQ: Roland Morris Questionnaire, ROM: range of back movement, GA: Global Assessment, NR: not reported, #: von Korff scale
Interventions

There was wide variation in the delivery of laser therapy (Table 4.2). Co-interventions were included in some studies. Reporting of laser parameters was incomplete in many trials and some values were calculated, assumed or could not be estimated despite attempts to contact authors. Five trials were classified as laser acupuncture.\textsuperscript{1, 3, 91, 98, 109} All used continuous emitters except\textsuperscript{109} which was pulsed (805 nm). Three of these trials used smaller IR laser doses of from 0.2 to 1.1 J / point and sequential stimulation of points.\textsuperscript{1, 3, 98} Two trials used multi-channel devices with simultaneous stimulation of points: Trial\textsuperscript{91} used a “Laser Needle” device combination of eight red and IR emitters irradiating 60-180 J / point, while trial\textsuperscript{109} used four IR emitters irradiating at 12 J / point. Points of treatment were defined according to acupuncture nomenclature and included local tender points at site of back pain but also distant points on acupuncture meridians. Reference is made to site of treatment in the footnotes to Table 4.2 but further description of anatomical site of treatment is detailed in Table 4.3.

The remaining ten trials were classified as non-acupuncture laser therapy. All used either continuous or pulsed IR emitters, including three trials\textsuperscript{107, 108, 110} using “super pulsed” GaAs diodes, which have been shown to produce greater tissue penetration with the same dose. Two studies\textsuperscript{104, 107} used lower doses (≤ 2.8 J / point); much higher dosages were used in two trials\textsuperscript{105, 111} (239 & 1200 J / point); a range of 3 to 25 J / point was used in the remaining trials. Accurate anatomical location of points treated was not provided in a majority of the reports. The site of laser application (described verbatim in Table 4.3) was often described as applied to the most tender points, or to the area of maximal pain. Reference was also often made of laser application to ‘paraspinal’ or ‘paravertebral’ points. Three trials\textsuperscript{103, 106, 111} reported using ‘manual scanning’ to irradiate larger anatomically defined areas, as well as irradiation of discrete points. Two studies,\textsuperscript{101, 102} which irradiated one or two points only per session, achieved positive results.

Controls

A variety of methods for achieving sham laser control were reported (Table 4.2): same machine with on/off switch,\textsuperscript{1, 91, 110} separate machines or probes used,\textsuperscript{101, 102} taped opaque goggles\textsuperscript{91} for blinding, or a laser machine\textsuperscript{56} that could ensure concealed allocation, blind both patient and therapist on laser operation, and allow setting the device by the same therapist. In some trials the description of the masking procedure was rather unclear\textsuperscript{102, 104, 105, 110} and one
trial\textsuperscript{109} reported no description of the masking procedure. Only three studies \textsuperscript{3, 91, 98} statistically analysed the success of the blinding achieved by the device used.

**Outcomes**

Only four trials\textsuperscript{3, 91, 98, 105} defined predetermined primary outcomes. The majority of studies reported pain as VAS; two studies\textsuperscript{1, 98} reported as NPRS. Participant based ‘global assessment’ was reported as a dichotomised categorical scale including 'Condition improved versus same or worse',\textsuperscript{3, 98} and 'Good response versus the same or undecided'.\textsuperscript{101, 102} Two trials only reported arbitrary level of improvement on a pain scale (e.g. >50\% reduction of chronic pain on Von Korff Scale\textsuperscript{91} or ≥60\% reduction pain on VAS scale).\textsuperscript{110} These dichotomous outcomes were combined in meta-analysis to determine the RR of ‘global improvement’.

The majority of studies with this outcome reported disability as the Oswestry Disability Index (ODI); one trial reported only the Roland Morris Questionnaire (RMQ).\textsuperscript{107}

The range of back movement was measured as flexion in centimetres (Schober Test)\textsuperscript{104-106, 108} or in degrees.\textsuperscript{103, 107} Occurrences of adverse effects were briefly mentioned in five trials\textsuperscript{1, 104, 105, 107, 110}; three studies\textsuperscript{3, 98, 110} reported outcomes at longer follow-up.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Laser type</th>
<th>λ (μm)</th>
<th>Dose/point (J)</th>
<th>Mean laser Power(W)</th>
<th>Energy Density (J/cm²)</th>
<th>Power Density (W/cm²)</th>
<th>Sessions/weeks</th>
<th>Points treated/session</th>
<th>Co-intervention</th>
<th>Details of sham control</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Alayat&quot; (2003)</td>
<td>Nd:YAG Pulsed 1064</td>
<td>25</td>
<td>0.2</td>
<td>1786 [34W]</td>
<td>0.61</td>
<td>8.9</td>
<td>12/4</td>
<td>8</td>
<td>exercise</td>
<td>No description of control device or if separate device used. Success blinding not described.</td>
</tr>
<tr>
<td>&quot;Ay&quot; (2009)</td>
<td>GaAlAs Pulsed 808</td>
<td>2.8</td>
<td>0.07</td>
<td>12 [100 mW]</td>
<td>48</td>
<td>1.4</td>
<td>15/3</td>
<td>2.4</td>
<td>hot packs</td>
<td>&quot;Control technique involved use of same machine without turning on device&quot;. Success blinding not described.</td>
</tr>
<tr>
<td>&quot;Basford&quot; (1999)</td>
<td>Nd:YAG Continuous 1060</td>
<td>2.59</td>
<td>4.9</td>
<td>2660</td>
<td>49</td>
<td>0.542</td>
<td>12/4</td>
<td>8</td>
<td>nil</td>
<td>&quot;Control treated by the same but inactive probes&quot;. Not clear if separate machine used. Success blinding not reported (there was tendency of patients to experience &quot;more warmth with active treatment&quot;).</td>
</tr>
<tr>
<td>&quot;Djadid&quot; (2007)</td>
<td>GaAlAs Continuous 810</td>
<td>&lt;0.8</td>
<td>0.22</td>
<td>50</td>
<td>27</td>
<td>8.2</td>
<td>12/6</td>
<td>8</td>
<td>&lt;150</td>
<td>nil</td>
</tr>
<tr>
<td>&quot;Glazov&quot; (2009)</td>
<td>GaAlAs Continuous 830</td>
<td>0.2</td>
<td>0.2</td>
<td>10</td>
<td>1</td>
<td>0.05</td>
<td>10/10</td>
<td>8</td>
<td>20</td>
<td>exercise</td>
</tr>
<tr>
<td>&quot;Glazov&quot; (2013)</td>
<td>GaAlAs Continuous 830</td>
<td>0.2</td>
<td>0.8</td>
<td>0.2</td>
<td>20</td>
<td>1</td>
<td>0.1</td>
<td>8/8</td>
<td>9</td>
<td>10, 40</td>
</tr>
<tr>
<td>&quot;Klein&quot; (1990)</td>
<td>GaAs S-Pulsed 904</td>
<td>1.3</td>
<td>1.0</td>
<td>2.4</td>
<td>1.3</td>
<td>0.005</td>
<td>12/4</td>
<td>50</td>
<td>240</td>
<td>exercise</td>
</tr>
<tr>
<td>&quot;Konstant &quot; (2012)</td>
<td>GaAs S-Pulsed 905</td>
<td>3</td>
<td>1.0</td>
<td>100</td>
<td>3</td>
<td>0.1</td>
<td>15/3</td>
<td>4</td>
<td>60</td>
<td>exercise</td>
</tr>
<tr>
<td>&quot;Lin&quot; (2012)</td>
<td>NB Pulsed 608</td>
<td>12</td>
<td>0.8</td>
<td>20 [40 mW]</td>
<td>15</td>
<td>0.25</td>
<td>5/1</td>
<td>4</td>
<td>600</td>
<td>soft cupping</td>
</tr>
</tbody>
</table>
Table 4.2: Interventions (continued)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Laser/Beam</th>
<th>Pulse</th>
<th>Dose/point; Spot size (cm²)</th>
<th>Mean laser Power (W)</th>
<th>Energy Density (J/cm²)</th>
<th>Power Density (W/cm²)</th>
<th>Sessions/weeks</th>
<th>Points/session</th>
<th>Co-intervention</th>
<th>Details of sham control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Okomoto (1989)</td>
<td>GaAlAs Continuous 830</td>
<td>18</td>
<td>0.126</td>
<td>143</td>
<td>0.24</td>
<td>10.3</td>
<td>1</td>
<td>600</td>
<td>nil</td>
<td>3 machines of identical appearance (A and B) corresponding to laser or placebo laser; each had decay with light and sound. No other details given in paper. Success of blinding not reported.</td>
</tr>
<tr>
<td>Ruth (2012)</td>
<td>NR Continuous 680, 785</td>
<td>60-180</td>
<td>50-150</td>
<td>7</td>
<td>1-5</td>
<td>10.5</td>
<td>8</td>
<td>1200</td>
<td>nil</td>
<td>Toggle switch on same machine operated by independent person according to randomization list. Goggles on participants, and controls on machine covered by opaque black tape. Analysis for success of masking procedure reported.</td>
</tr>
<tr>
<td>Soriano (1989)</td>
<td>GaAs S-Pulsed 904</td>
<td>4</td>
<td>0.95</td>
<td>40</td>
<td>2.0</td>
<td>0.64</td>
<td>10.2</td>
<td>0.5</td>
<td>nil</td>
<td>Used an activated laser and a deactivated laser machine but the electrical circuit, timer and in worked as usual”. Not clear if separate devices used. Success of blinding not reported.</td>
</tr>
<tr>
<td>Umekagi (1989)</td>
<td>GaAlAs Continuous 830</td>
<td>18</td>
<td>0.126</td>
<td>143</td>
<td>0.24</td>
<td>10.3</td>
<td>2</td>
<td>600</td>
<td>nil</td>
<td>As in Okomoto</td>
</tr>
<tr>
<td>Vallone (2014)</td>
<td>GaAlAs Continuous 900</td>
<td>1200</td>
<td>32</td>
<td>20,000</td>
<td>37.5</td>
<td>0.625</td>
<td>0.5</td>
<td>6</td>
<td>60</td>
<td>exercise</td>
</tr>
<tr>
<td>Wallace (1996)</td>
<td>GaAlAs Continuous 830</td>
<td>1</td>
<td>0.42</td>
<td>3</td>
<td>2.84</td>
<td>0.9</td>
<td>5</td>
<td>5</td>
<td>30</td>
<td>nil</td>
</tr>
</tbody>
</table>
Footnotes to Table 4.2: Entries marked in **bold** were not reported/unavailable and were calculated or assumed by reviewers.

(a) ‘High Intensity Laser Therapy’. Also included manual scanning of fields (2 x 1400 J). Total dose per session = 3000 J. Pulsed wave duration 120–150 μ sec, frequency 10–40 Hz, 0.1% duty cycle

Each treatment in 3 phases, 3000 J in total:
1. Fast manual scanning =1400 J (set successively at 0.610, 0.710, 0.810 J/cm²)
2. 25 J to each of 8 paravertebral points from L1- S3 = 200 J (set at 0.610 J/cm²)
3. Repeat 1 with slow manual scanning =1400J

(b) Pulsed wave- frequency 155Hz

(c) Laser device allowed simultaneous stimulation of 2 points.

(d) Total duration of treatment 20 minutes including eight points and manual scanning of standardised field. Total dose per session = 60 J. Differential time irradiation points and fields scanning not reported. Duration each discrete point irradiated assumed to be <150 secs.

(e) *Laser / sham mode was set by operating a number on dial. The probe had decoy light / sound device inbuilt. Individually based treatment provided by therapists; average of 8-9 point per session; local and distal acupoints on GV, BL and GB meridians and Ahshi points most frequently used

(f) Multi-head device stimulating 10 points simultaneously.
Pulsed wave- frequency 1000hz, pulse width 200 ns

(g) Pulsed wave- frequency 5000hz

(h) Multi-channel device with simultaneous stimulation of 4 points (bilateral BL40 and 2 Ahshi points in lumbar region).
Pulsed wave - frequency 20 Hz, 50% duty cycle

(i) "Laser needle" fibre-optic cable device with simultaneous stimulation of 8 points. The most frequently points were BL23 40 or 60, KI3, points on GB meridian, Ahshi points with individualized treatment provided by therapist. The same author described in another paper¹¹² laser output tips 2.0 and 0.8 mm diameter corresponding to power densities of 1 W/cm² and 5 W/cm² respectively.

(j) Exact number of points used ('2cm grid in painful area') and irradiation time per point not given in paper. Spot size given as 0.0015cm² but according to a Cochrane review⁹² for this study spot size = 1.1 cm² and irradiation time = 100 sec which was used in our review.
Pulsed wave- frequency 10,000 Hz, pulse width 200 n sec

(k) Report is unclear if manual scanning used.

(l) Individualized treatment provided by therapist. Used local points- B26, Ahshi points, GV2; distal points - GV14, BL11, LR3, BL60, Li4, ST36, SP6, PC6, H7
In LA trials, classical acupuncture points have specific sites defined in textbooks.\textsuperscript{89} In non-LA trials the site is detailed in each publication and presented verbatim in Table 4.3. The general anatomic area treated in each study is indicated in **bold**.

Table 4.3: Interventions: details on anatomical site of laser treatments

<table>
<thead>
<tr>
<th>Study</th>
<th>Anatomical site of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i) Non-acupuncture studies (also see footnotes Table 4.2)</td>
<td></td>
</tr>
<tr>
<td>Alayat 2013</td>
<td>A hand-piece was positioned in contact with and perpendicular to the treated area, with the patient in the prone position. Scanning was performed transversely and longitudinally in the <strong>lower-back area of L1–L5 and S1, to cover the fasciae, sacral ligaments, ileum, latissimus dorsi, obliquus externus abdominis, and the upper part of the gluteus maximus</strong> Each treatment in 3 phases, 3000 J in total 1. Fast manual scanning = 1400 J (set successively at 0.610, 0.710, 0. 810 J/cm\textsuperscript{2}) 2. 25 J to each of 8 <strong>paravertebral points</strong> from L1- S3 = 200 J (set at 0.610 J/cm\textsuperscript{2}) 3. Repeat 1 with slow manual scanning =1400J</td>
</tr>
<tr>
<td>Djavid 2007</td>
<td>Standard fields <strong>paravertebral</strong> 8 points: &lt; 7.5 J/point + scanning of fields, 40 J/cm\textsuperscript{2}</td>
</tr>
<tr>
<td>Vallone 2014</td>
<td>Over the painful paravertebral low back region. A series of standardized fields including <strong>6 spots in the paravertebral region</strong> (L2 to S2–S3) were irradiated by a single laser probe in stationary contact mode.</td>
</tr>
<tr>
<td>Ay 2010</td>
<td><strong>2-4 points over both sides of the paraspinal</strong> tissues of the disk spaces. + hot pack treatment each session.</td>
</tr>
<tr>
<td>Klein 1990</td>
<td>10 points stimulated simultaneously repeated to <strong>5 various anatomical sites in lumbosacral region</strong> (50 points per session)</td>
</tr>
<tr>
<td>Basford 1999</td>
<td>4 pairs points along equally spaced levels along L2-S3 <strong>paraspinal tissues</strong></td>
</tr>
<tr>
<td>Konstantinovic 2012</td>
<td><strong>LLLT</strong> was applied behind the involved spine segment using stationary skin contact method 4 points were used defined in relation with dermatomes or <strong>local sensitive points</strong></td>
</tr>
<tr>
<td>Soriano 1998</td>
<td>Laser applied in point contact irradiation technique <strong>Irradiated the painful area</strong> using a 2cm grid system so points were separated by 2cm Number of points and duration of point irradiation not reported</td>
</tr>
<tr>
<td>Okamoto 1989</td>
<td><strong>1 point chosen at site of most tender area</strong> or maximum spontaneous pain.</td>
</tr>
<tr>
<td>Umekagi 1989</td>
<td>“Area where patient most complained of pressure pain”. <strong>Two most tender areas</strong>.</td>
</tr>
</tbody>
</table>
Table 4.3: Interventions: details on anatomical site of laser treatments (continued)

(ii) Laser acupuncture studies (also see Footnotes Table 4.2)

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wallace 1996</td>
<td>Sites-laser acupuncture treatment pre-specified protocol with local and distal points (with some individual variation for local tender points present)</td>
</tr>
<tr>
<td>Glazov 2009</td>
<td>Individualized acupuncture treatment using local (classical acupoints and other tender points), and tender and distal points and treating other concurrent conditions</td>
</tr>
<tr>
<td>Glazov 2015</td>
<td>Individualized acupuncture treatment using local (classical acupoints and other tender points) and distal points and treating other concurrent conditions</td>
</tr>
<tr>
<td>Lin 2012</td>
<td>Simultaneous stimulation of 4 points to treat acupoints (BL40) on two knees and tender points on dorsal area + soft cupping</td>
</tr>
<tr>
<td>Ruth 2010</td>
<td>8 points stimulated simultaneously local and distal acupuncture and tender points, individualized treatment</td>
</tr>
</tbody>
</table>
### Risk of bias of included studies

Figure 4.2 demonstrates the proportion of low risk studies in each domain. Under our criteria we found three trials to be at ‘higher risk of bias’. 

![Table and Diagram]

**Figure 4.2 Risk of bias summary: Review authors’ judgements**

- Proportion of low risk studies: Random sequence generation (53%), Allocation concealment (47%), Blinding participants (67%), Blinding therapists (60%), Blinding outcome assessors (67%), Incomplete outcome data (60%), Selective reporting (80%), Group baseline similarity (67%), Co-interventions (80%), Compliance (100%), Intention to treat (40%), Timing outcome assessment (87%)

*Note: Glazov 2013 A & B represent different groups of same study.*
Primary outcomes

Pain: Meta-analysis of data from 653 subjects in 10 trials at immediate follow-up (Figure 4.3) indicates a statistically significantly reduced total pain score in laser versus control (WMD: -0.79 cm; 95% CI: -1.22 to -0.36; $I^2 = 70\%$), with substantial heterogeneity. In the subgroup analyses we observed a significant reduction of pain (laser compared to control), with the largest effect seen for the trials in which subjects had a shorter mean baseline duration (<30 months) of LBP (WMD: -1.39 cm; 95% CI: -1.71 to -1.07; $I^2 = 23\%$). Significant differences between laser and control were also seen in the higher dose trials (>3 J/point) (WMD: -1.23 cm; 11.61 to -0.84; $I^2 = 51\%$) and the non-acupuncture trials (WMD: -1.17 cm; 95% CI: -1.60 to 0.74; $I^2 = 62\%$).

At short-term follow-up (Figure 4.4), there were 391 subjects from six trials with non-significant differences in the total pain score and with substantial heterogeneity. In the subgroup analyses we observed significant reduction of pain (laser compared to control), with the largest effect seen in the higher dose trials and in trials with a shorter duration of back pain at baseline (WMD: -1.40 cm; 95% CI: -1.91 to -0.88; $I^2 = 0\%$).
### A. Subgroup: LA versus non-acupuncture laser therapy interventions

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3.3.1 Low dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Av 2010</td>
<td>2.65±1.42</td>
<td>20±2.85</td>
<td>20.14±2.16</td>
<td>20±2.92</td>
</tr>
<tr>
<td>Glazer 2009</td>
<td>3.64±2.85</td>
<td>45±3.36</td>
<td>4.21±2.14</td>
<td>45±3.84</td>
</tr>
<tr>
<td>Glazer 2013a (1)</td>
<td>3.2±1.72</td>
<td>48±3.8</td>
<td>3.2±2.3</td>
<td>24±3.6</td>
</tr>
<tr>
<td>Glazer 2013a (2)</td>
<td>3.7±1.95</td>
<td>48±3.8</td>
<td>3.7±2.3</td>
<td>24±3.6</td>
</tr>
<tr>
<td>Wallace 1996 (3)</td>
<td>4.34±2.1</td>
<td>18±5.26</td>
<td>2.1±2.1</td>
<td>18±6.0</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>335</td>
<td>100.00%</td>
<td>-0.79 [-1.22, -0.38]</td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity</strong></td>
<td>Tukey = 0.16</td>
<td>CH2 = 13.19, df = 5 (P = 0.02); F = 62%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: CH2 = 8.26, df = 1 (P = 0.004), I2 = 87%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**: 335; 100.00%; -0.79 [-1.22, -0.38].

**Heterogeneity test**: Tukey = 0.16; CH2 = 13.19, df = 5 (P = 0.02); F = 62%.

**Test for overall effect**: CH2 = 5.10 (P = 0.00001).

**Test for subgroup differences**: CH2 = 8.26, df = 1 (P = 0.004), I2 = 87%.

---

### B. Subgroup: Laser dose (low dose: <3 J/point versus high dose: ≥ 3 J/point interventions)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3.3.1 Long duration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Av 2010</td>
<td>2.65±1.42</td>
<td>20±2.85</td>
<td>20.14±2.16</td>
<td>20±2.92</td>
</tr>
<tr>
<td>Glazer 2009</td>
<td>3.64±2.85</td>
<td>45±3.36</td>
<td>4.21±2.14</td>
<td>45±3.84</td>
</tr>
<tr>
<td>Glazer 2013a (1)</td>
<td>3.2±1.72</td>
<td>48±3.8</td>
<td>3.2±2.3</td>
<td>24±3.6</td>
</tr>
<tr>
<td>Glazer 2013a (2)</td>
<td>3.7±1.95</td>
<td>48±3.8</td>
<td>3.7±2.3</td>
<td>24±3.6</td>
</tr>
<tr>
<td>Wallace 1996 (3)</td>
<td>4.34±2.1</td>
<td>18±5.26</td>
<td>2.1±2.1</td>
<td>18±6.0</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>179</td>
<td>69.7%</td>
<td>-1.23 [-1.61, -0.84]</td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity</strong></td>
<td>Tukey = 0.10</td>
<td>CH2 = 10.17, df = 5 (P = 0.007); I2 = 53%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: CH2 = 5.26, df = 1 (P = 0.02), I2 = 75%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**: 179; 69.7%; -1.23 [-1.61, -0.84].

**Heterogeneity test**: Tukey = 0.10; CH2 = 10.17, df = 5 (P = 0.007); I2 = 53%.

**Test for overall effect**: CH2 = 6.26 (P = 0.00001).

---

### C. Subgroup: Short duration (<30 months) versus long duration (≥ 30 months)

**Figure 4.3: Forest plots: Subgroup analysis of pain at immediate follow-up**
A. Subgroup analysis: Comparison of trials using LA versus non-acupuncture laser therapy interventions

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>1.5.1 Laser acupuncture</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glazov 2009</td>
<td>4.53</td>
<td>4.03</td>
<td>23.22</td>
<td>44</td>
</tr>
<tr>
<td>Glazov 2011a</td>
<td>3.7</td>
<td>3.4</td>
<td>2.1</td>
<td>23</td>
</tr>
<tr>
<td>Glazov 2013</td>
<td>4.2</td>
<td>4.1</td>
<td>2.4</td>
<td>23</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>90</td>
<td>43.4%</td>
<td>3.4</td>
<td>90</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>84</td>
<td>56.7%</td>
<td>1.3</td>
<td>84</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.61; df = 2 (P = 0.63); I^2 = 0%
Test for overall effect: Z = 0.90 (P = 0.37)

B. Subgroup analysis: Comparison of trials using low dose versus high dose interventions

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>1.5.4 Low dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glazov 2009</td>
<td>4.53</td>
<td>4.03</td>
<td>23.22</td>
<td>44</td>
</tr>
<tr>
<td>Glazov 2013a</td>
<td>3.7</td>
<td>3.4</td>
<td>2.1</td>
<td>23</td>
</tr>
<tr>
<td>Glazov 2013</td>
<td>4.2</td>
<td>4.1</td>
<td>2.4</td>
<td>23</td>
</tr>
<tr>
<td>Klein 1990</td>
<td>2.3</td>
<td>1.9</td>
<td>10</td>
<td>2.8</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>146</td>
<td>54.2%</td>
<td>0.20</td>
<td>146</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.62; df = 3 (P = 0.61); I^2 = 0%
Test for overall effect: Z = 0.67 (P = 0.50)

1.5.2 High dose

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Aslany 2013</td>
<td>2.64</td>
<td>3.71</td>
<td>2.3</td>
<td>24</td>
</tr>
<tr>
<td>Basford 1999 (1)</td>
<td>1.91</td>
<td>3.53</td>
<td>2.35</td>
<td>29</td>
</tr>
<tr>
<td>Djavid 2007</td>
<td>2.4</td>
<td>4.3</td>
<td>1.6</td>
<td>18</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>74</td>
<td>45.8%</td>
<td>1.40</td>
<td>74</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.62; df = 2 (P = 0.37); I^2 = 0%
Test for overall effect: Z = 0.87 (P = 0.38)

Total (95% CI) | 220 | 100.0% | -0.60 | 220 | 1.00 |  |  |  |  |  |  |

Heterogeneity: Tau^2 = 0.66; Chi^2 = 20.32; df = 6 (P = 0.002); I^2 = 70%
Test for overall effect: Z = 1.62 (P = 0.10)
Test for subgroup differences: Chi^2 = 13.87; df = 1 (P = 0.00001); I^2 = 91.7%

C. Subgroup analysis: Comparison of trials with long duration of pain at baseline versus short duration

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>1.5.5 Long duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glazov 2009</td>
<td>4.53</td>
<td>4.03</td>
<td>23.22</td>
<td>44</td>
</tr>
<tr>
<td>Glazov 2013a</td>
<td>3.7</td>
<td>3.4</td>
<td>2.1</td>
<td>23</td>
</tr>
<tr>
<td>Glazov 2013</td>
<td>4.2</td>
<td>4.1</td>
<td>2.4</td>
<td>23</td>
</tr>
<tr>
<td>Klein 1990</td>
<td>2.3</td>
<td>1.9</td>
<td>10</td>
<td>2.8</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>146</td>
<td>54.2%</td>
<td>0.20</td>
<td>146</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.62; df = 3 (P = 0.61); I^2 = 0%
Test for overall effect: Z = 0.67 (P = 0.50)

1.5.2 Short duration

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Aslany 2013</td>
<td>2.64</td>
<td>3.71</td>
<td>2.3</td>
<td>24</td>
</tr>
<tr>
<td>Basford 1999 (1)</td>
<td>1.91</td>
<td>3.53</td>
<td>2.35</td>
<td>29</td>
</tr>
<tr>
<td>Djavid 2007</td>
<td>2.4</td>
<td>4.3</td>
<td>1.6</td>
<td>18</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>74</td>
<td>45.8%</td>
<td>1.40</td>
<td>74</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.62; df = 2 (P = 0.37); I^2 = 0%
Test for overall effect: Z = 0.87 (P = 0.38)

Total (95% CI) | 220 | 100.0% | -0.60 | 220 | 1.00 |  |  |  |  |  |  |

Heterogeneity: Tau^2 = 0.66; Chi^2 = 20.32; df = 6 (P = 0.002); I^2 = 70%
Test for overall effect: Z = 1.62 (P = 0.10)
Test for subgroup differences: Chi^2 = 13.87; df = 1 (P = 0.00001); I^2 = 91.7%

Footnotes:
(1) Maximum pain in last 24 hrs

Figure 4.4: Forest Plots- Subgroup Analysis of Pain at Short Term Follow-up
Global assessment: Pooled categorical data Fig. 4.5 for immediate follow-up from 416 subjects in 5 trials showed a significant RR of 1.5 (95% CI: 1.10 to 2.04; $I^2 = 65\%$) in favour of laser treatment (substantial heterogeneity present), with a greater improvement in both non-acupuncture and higher dose subgroups RR of 2.16 (95% CI: 1.61 to 2.90; $I^2=0\%$), and with heterogeneity reduced. Pooled data for short-term follow-up Figure 4.6 showed no significant differences for three included LA trials, two of which used a ‘lower’ dose.

### Table 4.5.1: Forest plots: Subgroup analysis of Global Assessment at immediate follow-up

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>M-H, Random, 95% CI</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1 laser acupuncture</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glazov 2009 (3)</td>
<td>26</td>
<td>43</td>
<td>25</td>
<td>19.3%</td>
<td>1.06 [0.75, 1.52]</td>
</tr>
<tr>
<td>Glazov 2011a (2)</td>
<td>29</td>
<td>45</td>
<td>12</td>
<td>20</td>
<td>1.07 [0.71, 1.61]</td>
</tr>
<tr>
<td>Glazov 2011b (3)</td>
<td>30</td>
<td>44</td>
<td>12</td>
<td>20</td>
<td>1.14 [0.75, 1.71]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>132</td>
<td>84</td>
<td>54.6%</td>
<td>1.09 [0.87, 1.36]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>85</td>
<td>49</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau2 = 0.00; CHI2 = 0.06; df = 2 (P = 0.97); I2 = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.74 (P = 0.46)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1.2 Non LA laser therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Okamoto 1989 (4)</td>
<td>26</td>
<td>34</td>
<td>13</td>
<td>35</td>
<td>2.06 [1.29, 3.29]</td>
</tr>
<tr>
<td>Soriano 1998 (5)</td>
<td>27</td>
<td>38</td>
<td>12</td>
<td>33</td>
<td>1.95 [1.19, 3.21]</td>
</tr>
<tr>
<td>Umemagi 1999 (6)</td>
<td>24</td>
<td>30</td>
<td>9</td>
<td>30</td>
<td>2.67 [1.56, 4.74]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>102</td>
<td>98</td>
<td>45.4%</td>
<td>2.16 [1.01, 2.50]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>77</td>
<td>34</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau2 = 0.00; CHI2 = 0.72; df = 2 (P = 0.70); I2 = 0%</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.16 (P &lt; 0.0001)</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

A. Subgroup: (LA versus non-acupuncture laser therapy)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>M-H, Random, 95% CI</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1.1 low dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glazov 2009 (1)</td>
<td>26</td>
<td>43</td>
<td>25</td>
<td>19.3%</td>
<td>1.06 [0.75, 1.52]</td>
</tr>
<tr>
<td>Glazov 2011a (2)</td>
<td>29</td>
<td>45</td>
<td>12</td>
<td>20</td>
<td>1.07 [0.71, 1.61]</td>
</tr>
<tr>
<td>Glazov 2011b (3)</td>
<td>30</td>
<td>44</td>
<td>12</td>
<td>20</td>
<td>1.14 [0.75, 1.71]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>132</td>
<td>84</td>
<td>54.6%</td>
<td>1.09 [0.87, 1.36]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>85</td>
<td>49</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau2 = 0.00; CHI2 = 0.06; df = 2 (P = 0.97); I2 = 0%</td>
<td></td>
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<td></td>
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<tr>
<td>Test for overall effect: Z = 0.74 (P = 0.46)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1.2 high dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Okamoto 1989 (4)</td>
<td>26</td>
<td>34</td>
<td>13</td>
<td>35</td>
<td>2.06 [1.29, 3.29]</td>
</tr>
<tr>
<td>Soriano 1998 (5)</td>
<td>27</td>
<td>38</td>
<td>12</td>
<td>33</td>
<td>1.95 [1.19, 3.21]</td>
</tr>
<tr>
<td>Umemagi 1999 (6)</td>
<td>24</td>
<td>30</td>
<td>9</td>
<td>30</td>
<td>2.67 [1.56, 4.74]</td>
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<tr>
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<td>102</td>
<td>98</td>
<td>45.4%</td>
<td>2.16 [1.01, 2.50]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
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<td>34</td>
<td></td>
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</tr>
<tr>
<td>Heterogeneity: Tau2 = 0.00; CHI2 = 0.72; df = 2 (P = 0.70); I2 = 0%</td>
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<td></td>
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<tr>
<td>Test for overall effect: Z = 1.16 (P &lt; 0.0001)</td>
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</tbody>
</table>

B. Subgroup: (low dose- <3J/point vs high dose ≥ 3J/point interventions)

Figure 4.5: Forest plots: Subgroup analysis of Global Assessment at immediate follow-up
Note: Only outcome low dose LA studies are represented; exception, Ruth 2010 (high dose study)

Figure 4.6: Forest Plot: Global Assessment Outcomes at Short-Term Follow-up

Sensitivity analysis

Table 4.4: Results were robust to the exclusion of trials considered to be at ‘higher risk of bias’, with pain differences in favour of laser in the higher dose subgroup at immediate (WMD: -1.5 cm; 95% CI: -1.8 to -1.2) and short-term (-1.7 cm; 95% CI: -2.5 to -1.0) follow-up. Similar findings were shown in the non-acupuncture and ‘short duration’ subgroups. No trials at ‘higher risk of bias’ reported global assessment outcomes.
Table 4.4: Primary outcome pain effect sizes

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Immediate term (trials)</th>
<th>WMD (cm) (95%CI)</th>
<th>Z (9)</th>
<th>Sensitivity analysis (exclude high risk of bias trials) WMD (cm) (95%CI)</th>
<th>Short term (trials)</th>
<th>WMD (cm) (95%CI)</th>
<th>Z (9)</th>
<th>Sensitivity analysis (exclude high risk of bias trials) WMD (cm) (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>trials (n)</strong></td>
<td><strong>-0.79 (-1.22, -0.36)</strong></td>
<td><strong>0.09 (0.005, 0.18)</strong></td>
<td><strong>-0.6</strong> (0.1 - 0.4)</td>
<td><strong>0.09 (0.005, 0.18)</strong></td>
<td><strong>-0.60 (-1.35, 0.13)</strong></td>
<td><strong>28.32 (0.062, 0.085)</strong></td>
<td><strong>-0.30 (-1.39, 0.39)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>LA</strong></td>
<td><strong>4 (312)</strong></td>
<td><strong>-0.22 (-0.70, 0.26)</strong></td>
<td><strong>2.59 (0.63)</strong></td>
<td><strong>0.25 (-0.80, 0.29)</strong></td>
<td><strong>2.22 (0.63)</strong></td>
<td><strong>0.91 (0.63)</strong></td>
<td><strong>0.31 (-0.31, 0.92)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>non-LA</strong></td>
<td><strong>6 (341)</strong></td>
<td><strong>-1.17 (-1.60, -0.74)</strong></td>
<td><strong>11.9 (0.92)</strong></td>
<td><strong>-1.01 (-1.85, -0.18)</strong></td>
<td><strong>4.16 (0.07)</strong></td>
<td><strong>-1.31 (-1.82, -0.80)</strong></td>
<td><strong>3.15 (0.97)</strong></td>
<td><strong>-1.31 (-2.25, -0.77)</strong></td>
</tr>
<tr>
<td><strong>Low dose (&lt;3 J/point)</strong></td>
<td><strong>4 (310)</strong></td>
<td><strong>-0.18 (-0.65, 0.28)</strong></td>
<td><strong>2.74 (0.60)</strong></td>
<td><strong>0.18 (-0.65, 0.28)</strong></td>
<td><strong>3.24 (0.60)</strong></td>
<td><strong>0.21 (-0.37, 0.76)</strong></td>
<td><strong>1.82 (0.61)</strong></td>
<td><strong>0.18 (0.37, 0.76)</strong></td>
</tr>
<tr>
<td><strong>High dose (≥3 J/point)</strong></td>
<td><strong>6 (343)</strong></td>
<td><strong>-1.23 (-1.61, -0.84)</strong></td>
<td><strong>11.17 (0.07)</strong></td>
<td><strong>-1.54 (-1.94, -1.24)</strong></td>
<td><strong>8.45 (0.07)</strong></td>
<td><strong>-1.40 (-1.91, -0.88)</strong></td>
<td><strong>1.98 (0.37)</strong></td>
<td><strong>-1.70 (-2.55, -1.02)</strong></td>
</tr>
<tr>
<td><strong>Long duration (≥30 months)</strong></td>
<td><strong>4 (310)</strong></td>
<td><strong>-0.18 (-0.65, 0.28)</strong></td>
<td><strong>2.74 (0.60)</strong></td>
<td><strong>0.18 (-0.65, 0.28)</strong></td>
<td><strong>3.24 (0.60)</strong></td>
<td><strong>0.20 (-0.37, 0.76)</strong></td>
<td><strong>1.82 (0.61)</strong></td>
<td><strong>0.20 (0.37, 0.76)</strong></td>
</tr>
<tr>
<td><strong>Short duration (&lt;30 months)</strong></td>
<td><strong>4 (219)</strong></td>
<td><strong>-1.39 (-1.71, -0.97)</strong></td>
<td><strong>3.90 (0.27)</strong></td>
<td><strong>-1.54 (-1.94, -1.24)</strong></td>
<td><strong>8.45 (0.07)</strong></td>
<td><strong>-1.40 (-1.91, -0.88)</strong></td>
<td><strong>1.98 (0.37)</strong></td>
<td><strong>-1.39 (-2.55, -1.02)</strong></td>
</tr>
<tr>
<td><strong>Duration not reported</strong></td>
<td><strong>2 (142)</strong></td>
<td><strong>-0.81 (-2.08, 0.47)</strong></td>
<td><strong>both trials high risk</strong></td>
<td><strong>no trials</strong></td>
<td><strong>-</strong></td>
<td><strong>-</strong></td>
<td><strong>-</strong></td>
<td></td>
</tr>
</tbody>
</table>
Secondary outcomes

Intermediate and long-term pain and global assessment

Two trials (both low dose LA) reported outcomes at 6 months and at 12 months. They found no significant difference between groups for pain or global assessment at these time periods. One trial, reporting less relapse of pain in laser group at 6 months, used a non-validated outcome.

Disability

Figure 4.7 shows that the analysis of data from 490 subjects in 8 trials at immediate follow-up found a small significant reduced combined ODI score in laser versus control, with a WMD of -2.5 % (95% CI: -4.6 to -0.4; I² = 47%). Sub-group analyses showed more benefit for laser in non-acupuncture (WMD: -3.5%; -6.0 to -1.5; I² = 33%), and higher dose/shorter duration of back pain (WMD: -3.6 %; 95% CI: -6.1 to -1.1; I² = 48%). Combined data from 383 subjects in 6 trials at short-term follow-up found no difference, but sub-group analyses found greater benefit up to a WMD of -5.9 % (95% CI: -8.9 to -2.8; I² = 64%) in the same groups.
<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
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<td></td>
<td>SD Total</td>
<td>Mean</td>
<td>SD Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Mean Difference IV, Random, 55% CI</td>
<td>Mean Difference IV, Random, 55% CI</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Study of Subgroup</td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Laser acupuncture</td>
<td>29.5 ± 15.4</td>
<td>42.5</td>
<td>22.5 ± 9.9</td>
<td>65</td>
</tr>
<tr>
<td>Glazier 2005</td>
<td>21.7 ± 12.2</td>
<td>24.0</td>
<td>22.0 ± 12.4</td>
<td>26</td>
</tr>
<tr>
<td>Glazier 2012a</td>
<td>25.5 ± 13.2</td>
<td>42.0</td>
<td>22.5 ± 9.9</td>
<td>65</td>
</tr>
<tr>
<td>Glazier 2012b</td>
<td>23.5 ± 11.5</td>
<td>24.0</td>
<td>22.0 ± 12.4</td>
<td>26</td>
</tr>
<tr>
<td>Wallace 1999</td>
<td>28.7 ± 14.0</td>
<td>42.5</td>
<td>22.5 ± 9.9</td>
<td>65</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>21.7 ± 12.2</td>
<td>24.0</td>
<td>22.0 ± 12.4</td>
<td>26</td>
</tr>
<tr>
<td>Heterogeneity Tau² = 1.13; Chi² = 1.79; df = 3; P = 0.38; I² = 0.42%</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect:  Z = 0.04 (P = 0.96)</td>
<td></td>
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</table>

1.7.2 Non-LA laser therapy

<table>
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<th>Control</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SD Total</td>
<td>Mean</td>
<td>SD Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Mean Difference IV, Random, 55% CI</td>
<td>Mean Difference IV, Random, 55% CI</td>
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<td></td>
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</tr>
<tr>
<td>Study of Subgroup</td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Avioli 2013</td>
<td>13.0 ± 3.8</td>
<td>28.0</td>
<td>16.4 ± 3.3</td>
<td>33</td>
</tr>
<tr>
<td>Avioli 2010 (95% CI)</td>
<td>14.5 ± 7.3</td>
<td>28.0</td>
<td>16.4 ± 3.3</td>
<td>33</td>
</tr>
<tr>
<td>Basford 1999</td>
<td>13.5 ± 10.2</td>
<td>27.5</td>
<td>22.5 ± 10.2</td>
<td>29</td>
</tr>
<tr>
<td>Bjorvold 2007</td>
<td>13.7 ± 7.4</td>
<td>20.5</td>
<td>27.5 ± 7.4</td>
<td>15</td>
</tr>
<tr>
<td>Konttinen 2012</td>
<td>14.6 ± 9.9</td>
<td>28.0</td>
<td>27.5 ± 7.5</td>
<td>26</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>12.3 ± 8.9</td>
<td>21.8%</td>
<td>-5.340 - -3.59</td>
<td>0.00</td>
</tr>
<tr>
<td>Heterogeneity Tau² = 1.83; Chi² = 1.96; df = 4; P = 0.26; I² = 33%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect:  Z = 2.48 (P = 0.007)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Total 0% CD | 271 | 219 | 100.0% | -2.490 - -4.61 | 0.07 |
| Heterogeneity Tau² = 1.48; Chi² = 15.22; df = 8; P = 0.000; I² = 47% |
| Test for overall effect:  Z = 2.30 (P = 0.02) |
| Test for subgroup differences: Chi² = 2.48; df = 1; P = 0.12; I² = 50% |

A. Subgroup analysis: Comparison of trials using LA versus non-acupuncture laser therapy

B. Subgroup analysis: Comparison of trials using low dose versus high dose interventions

C. Subgroup analysis: Comparison of trials with long duration of pain at baseline versus short duration

Figure 4.7(a): Forest plots: Disability (ODI); Immediate follow-up

97
A. Subgroup analysis: Comparison of trials using LA versus non-acupuncture laser therapy interventions

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
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<td><strong>1.01. non LA laser therapy</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ayalat 2013</td>
<td>15.14</td>
<td>4.3</td>
<td>28 18.75</td>
<td>3.07</td>
</tr>
<tr>
<td>Basford 1999</td>
<td>14.7</td>
<td>10.1</td>
<td>27 22.9</td>
<td>10.3</td>
</tr>
<tr>
<td>Djiq 2007</td>
<td>16.8</td>
<td>3.7</td>
<td>19 24.1</td>
<td>5.2</td>
</tr>
<tr>
<td>Klein 1990 (1)</td>
<td>3.6</td>
<td>2.1</td>
<td>10 2.9</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>74</td>
<td></td>
<td>0.82</td>
<td>5.68 [-8.91, -2.82]</td>
</tr>
</tbody>
</table>

Total (95% CI): 0.82; df = 2 (P = 0.06); I² = 64%

Test for overall effect: Z = 1.37 (P = 0.09)

Heterogeneity: Test = 0.00; CH² = 0.83; df = 2 (P = 0.66); I² = 0%

B. Subgroup analysis: Comparison of trials using low dose versus high dose interventions

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.02. low dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gluza 2009</td>
<td>27.45</td>
<td>13.9</td>
<td>40 22.74</td>
<td>11.06</td>
</tr>
<tr>
<td>Gluza 2013</td>
<td>23</td>
<td>13</td>
<td>46 22</td>
<td>13</td>
</tr>
<tr>
<td>Gluza 2013a</td>
<td>24</td>
<td>15</td>
<td>45 22</td>
<td>13</td>
</tr>
<tr>
<td>Klein 1990 (1)</td>
<td>3.6</td>
<td>2.1</td>
<td>10 2.9</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>131</td>
<td></td>
<td>4.18</td>
<td>2.01 [-0.64, 6.47]</td>
</tr>
</tbody>
</table>

Total (95% CI): 0.56; df = 3 (P = 0.99); I² = 0%

Test for overall effect: Z = 1.61 (P = 0.11)

Heterogeneity: Test = 0.00; CH² = 0.83; df = 2 (P = 0.66); I² = 0%

C. Subgroup analysis: Comparison of trials with long duration of pain at baseline versus short duration

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.03. Long duration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gluza 2009</td>
<td>27.45</td>
<td>13.9</td>
<td>40 22.74</td>
<td>11.06</td>
</tr>
<tr>
<td>Gluza 2013</td>
<td>23</td>
<td>13</td>
<td>46 22</td>
<td>13</td>
</tr>
<tr>
<td>Gluza 2013a</td>
<td>24</td>
<td>15</td>
<td>45 22</td>
<td>13</td>
</tr>
<tr>
<td>Klein 1990(1)</td>
<td>3.6</td>
<td>2.1</td>
<td>10 2.9</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>131</td>
<td></td>
<td>4.18</td>
<td>2.01 [-0.64, 6.47]</td>
</tr>
</tbody>
</table>

Total (95% CI): 0.56; df = 3 (P = 0.99); I² = 0%

Test for overall effect: Z = 1.61 (P = 0.11)

Heterogeneity: Test = 0.00; CH² = 0.83; df = 2 (P = 0.66); I² = 0%

D. Subgroup analysis: Comparison of trials with short duration of pain at baseline versus long duration

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.04. Short duration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ayalat 2013</td>
<td>15.14</td>
<td>4.3</td>
<td>28 18.75</td>
<td>3.07</td>
</tr>
<tr>
<td>Basford 1999</td>
<td>14.7</td>
<td>10.1</td>
<td>27 22.9</td>
<td>10.3</td>
</tr>
<tr>
<td>Djiq 2007</td>
<td>16.8</td>
<td>3.7</td>
<td>19 24.1</td>
<td>5.2</td>
</tr>
<tr>
<td>Klein 1990 (1)</td>
<td>3.6</td>
<td>2.1</td>
<td>10 2.9</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>74</td>
<td></td>
<td>0.82</td>
<td>5.68 [-8.91, -2.82]</td>
</tr>
</tbody>
</table>

Total (95% CI): 0.82; df = 2 (P = 0.06); I² = 64%

Test for overall effect: Z = 1.37 (P = 0.09)

Heterogeneity: Test = 0.00; CH² = 0.83; df = 2 (P = 0.66); I² = 0%

Figure 4.7b: Forest Plots: Disability (ODI); Short-term follow-up (note: Klein[10] trial not included in analysis as measured RMQ at this follow-up)
Range of back movement

ROM was measured only in the non-acupuncture trials. Only one trial found a significant difference of 4 degrees flexion in favour of laser at short-term follow-up.

Adverse effects

Brief reference to the absence of adverse effects was made in six trials. Quantitative comparison (including flares of pain and other minor adverse effects), undertaken in three studies, showed no significant difference between laser and control.

Risk of publication bias across studies (Figure 4.8)

I plotted the effect sizes from trials that reported pain at immediate or short-term follow-up against the inverse of their standard error. Visual inspection of the funnel plot did not show asymmetry suggestive of ‘small study bias’.

Figure 4.8: Funnel plot of comparison Laser versus Sham Laser, outcome: Pain / immediate follow-up. Includes Klein trial with only short-term outcome. Studies with positive results are towards the left.
Quality of evidence (Table 4.5)

A conclusion of moderate quality evidence (GRADE profile\textsuperscript{99}) was reached, that laser has benefit in reducing pain in the immediate and short term in subjects with CNLBP treated using laser therapy, if pain has been present for less than 30 months, or if a laser dose of at least 3 J/point is used. The overall quality of evidence for this outcome was reduced due to the limitation in the domain involving risk of bias. For the outcome of global assessment at immediate follow-up, the evidence for laser benefit was further reduced to low quality due to the uncertainty in details of duration and specificity of LBP in trials\textsuperscript{101,102} and the laser intervention parameters in one trial\textsuperscript{110} reporting this outcome. There was lack of confidence in the widespread recommendation to clinical practice for all the primary outcomes until the results can be confirmed by further rigorously blinded trials using adequate laser doses in specific populations.
### Table 4.5: GRADE evidence profile for primary outcomes

<table>
<thead>
<tr>
<th>No of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication bias</th>
<th>Laser</th>
<th>Sham</th>
<th>Effect</th>
<th>Quality</th>
<th>Clinical recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain</strong> (immediate post-treatment) (measured with: VAS or NPRS; 0.0 = no pain; range of scores: 0-10; Better indicated by less)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 RCTs</td>
<td>Serious</td>
<td>No serious 1</td>
<td>No serious 1</td>
<td>No serious</td>
<td>No</td>
<td>355</td>
<td>350</td>
<td>-0.79 (0.22, -0.36)</td>
<td>Moderate</td>
<td>Weak</td>
<td></td>
</tr>
<tr>
<td>4 RCTs</td>
<td>Serious</td>
<td>No serious 2</td>
<td>No serious 2</td>
<td>No serious</td>
<td>No</td>
<td>173</td>
<td>168</td>
<td>-1.17 (-0.69, -0.76)</td>
<td>Moderate</td>
<td>Weak</td>
<td></td>
</tr>
<tr>
<td>5 RCTs</td>
<td>Serious</td>
<td>No serious 3</td>
<td>No serious 3</td>
<td>No serious</td>
<td>No</td>
<td>105</td>
<td>98</td>
<td>-1.23 (-0.61, -0.84)</td>
<td>Moderate</td>
<td>Weak</td>
<td></td>
</tr>
<tr>
<td><strong>Pain</strong> (short term up to 12 weeks post-treatment) (measured with: VAS or NPRS; 0.0 = no pain; range of scores: 0-10; Better indicated by less)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 RCTs</td>
<td>Serious</td>
<td>No serious 4</td>
<td>No serious 4</td>
<td>No serious</td>
<td>No</td>
<td>220</td>
<td>171</td>
<td>-0.60 (-1.33, 0.13)</td>
<td>Moderate</td>
<td>Weak</td>
<td></td>
</tr>
<tr>
<td>4 RCTs</td>
<td>Serious</td>
<td>No serious 5</td>
<td>No serious 5</td>
<td>No serious</td>
<td>No</td>
<td>94</td>
<td>81</td>
<td>-1.31 (-0.92, -0.70)</td>
<td>Moderate</td>
<td>Weak</td>
<td></td>
</tr>
<tr>
<td>3 RCTs</td>
<td>Serious</td>
<td>No serious 6</td>
<td>No serious 6</td>
<td>No serious</td>
<td>No</td>
<td>74</td>
<td>71</td>
<td>-1.40 (-1.91, -0.88)</td>
<td>Moderate</td>
<td>Weak</td>
<td></td>
</tr>
<tr>
<td><strong>Global assessment</strong> (immediate-term)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 RCTs</td>
<td>Serious</td>
<td>No serious 7</td>
<td>Serious 7</td>
<td>No serious</td>
<td>N/A</td>
<td>234</td>
<td>182</td>
<td>1.10 (1.02, 1.19)</td>
<td>Moderate</td>
<td>Weak</td>
<td></td>
</tr>
<tr>
<td>5 RCTs</td>
<td>Serious</td>
<td>No serious 8</td>
<td>Serious 8</td>
<td>No serious</td>
<td>N/A</td>
<td>102</td>
<td>98</td>
<td>1.16 (1.01, 1.32)</td>
<td>Moderate</td>
<td>Weak</td>
<td></td>
</tr>
<tr>
<td>5 RCTs</td>
<td>Serious</td>
<td>No serious 9</td>
<td>Serious 9</td>
<td>No serious</td>
<td>N/A</td>
<td>102</td>
<td>98</td>
<td>1.16 (1.01, 1.32)</td>
<td>Moderate</td>
<td>Weak</td>
<td></td>
</tr>
</tbody>
</table>

Note: Summary findings for LA, 'low dose' and 'long duration' subgroups (which had no significant difference in WMD or RR in comparisons between laser and sham on any primary outcome) not included in this table.

Legend: RCT = randomized controlled trial; LA = laser; R = relative risk; WMD = weighted mean difference; RR = relative risk; CI = confidence interval; N/A = not available. All trials reporting outcome; 1 - non-LA laser therapy subgroup reporting outcome; 2 - 'high dose' laser subgroup reporting outcome; 3 - 'short duration' subgroup reporting outcome. 'Limitations' refers to risk of bias; 'Inconsistency' refers to lack of similarity of estimates of treatment effects for an outcome across studies; 'Indirectness' refers to inability to generalize; 'Imprecision' refers to number of participants and width of confidence intervals; 'Publication bias' refers to probability of selective publication of trials and outcomes.

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Footnotes to Table 4.5

1 Some studies were high risk or uncertain risk for random sequence generation, allocation concealment, blinding participants or outcome assessors; however, results robust to exclusion ‘high risk of bias trials’, uncertainty remains as blinding inconsistently described and no testing for success of blinding in majority of trials

2 Heterogeneity was removed by subgroup analysis and exceptions were explained

3 Participants conform to eligibility criteria for chronic non-specific LBP and laser intervention; subgroup analysis examined effect of duration pain and dose of irradiation.

4 Funnel plot does not show ‘small study bias’/ low incidence reporting bias; robust to exclusion high risk of bias studies.

5 There was lack of reporting in trials for this outcome on aspects of condition (duration and specificity of LBP) and intervention (laser parameters).

6 Lack of confidence of widespread recommendation to clinical practice until results can be confirmed by further rigorously blinded trials using adequate laser doses in specific populations.

Discussion

This meta-analysis summarised RCTs which compared the effect of low-level laser to sham control for the treatment of CNLBP. While combining data from all clinically heterogeneous studies found a small benefit, subgroup analyses showed larger positive effects of laser on pain, global assessment and disability present up to 12 weeks after treatment in trials, particularly with higher laser dose interventions. The size for pain reduction of -1.4cm (on a scale 0-10.0 cm) in these subgroups approached the minimally important change (MIC) for chronic LBP pain of -1.5 cm, as proposed by Ostelo.75 Disability (ODI) reduction in the same subgroups was significant in the short term (WMD of -5.9 % (95% CI: -8.9 to -2.8) but less than MIC of -10%.

Although the effect size from the laser in pain reduction was modest, it must be remembered that the full effect of the treatment also includes a non-specific effect. In this review (see Table 4.6) the mean reduction of pain in sham laser groups which measured continuous pain outcome was approximately -2.0cm (35% pain reduction in the short term). Such a reduction was also similar to the 30-40% short term lowering of pain from non-specific effects of acupuncture-like laser interventions in trials described in previous chapters.3, 65, 98 The pain reduction could be contributed by the placebo effect, the regression to the mean, the natural history of LBP, the Hawthorne effect, the Hello-goodbye effects and
even the acupressure effect. This research has already examined how the size of the non-specific effect is dependent on participant baseline characteristics.

Table 4.6: Pain reduction across sham groups in trials from this review which measured continuous pain outcome.

<table>
<thead>
<tr>
<th>Time point of follow-up</th>
<th>Number of studies</th>
<th>Mean pain in cm [SD]</th>
<th>Pain reduction in sham groups from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>12</td>
<td>5.8 [1.3]</td>
<td>-</td>
</tr>
<tr>
<td>Immediate</td>
<td>11</td>
<td>3.9 [1.0]</td>
<td>-1.9</td>
</tr>
<tr>
<td>Short-term</td>
<td>7</td>
<td>3.6 [0.7]</td>
<td>-2.2</td>
</tr>
</tbody>
</table>

My results for CNLBP are consistent with previous findings, suggesting there are benefits of low-level laser in a range of painful musculoskeletal conditions and also in chronic neck pain. During the time of writing this meta-analysis, there had not been another systematic review LLLT for chronic LBP published since 2008. Our review was finally published in May 2016 after submission to the BMJ Group journal Acupuncture in Medicine in December 2015. With delay in the submission process of our publication, another analogous article by Huang – “The effectiveness of low-level laser therapy for nonspecific chronic low back pain” – appeared in another journal in December 2015. That meta-analysis also reported a reduced VAS pain score (on a 0-100mm scale) after treatment in LLLT, compared with placebo (WMD = -13.57 [95% CI = -17.42 to -9.72]; however, no significant difference was found in disability (ODI). Some comments concerning this review are warranted. Despite the review’s stated inclusion criteria, which were required to compare low level laser therapy (LLLT) and placebo treatment, one of the seven included trials used a “super luminous” IR light diode which is a LED light therapy but not laser. A second trial examined laser + exercise versus exercise alone. The exercise only control group did not constitute a placebo treatment and was not comparable to sham laser controls in the remainder of the included studies. Incidentally, both of these trials reported no difference in pain outcome between laser and control groups. Exclusion of the trials that did not satisfying the review’s entry criteria would leave the Hoang review with only 5 trials, including one extra positive trial, compared to the previous Cochrane review. Finally, a third included trial was said to satisfy inclusion criteria but was not included in either the meta-analysis or the article’s discussion. The only outcome of the latter trial was dichotomous, which
described a cut-off percentage improvement in pain between groups. The original continuous pain data from the trial on which this was based was unavailable.

My independently conducted meta-analysis\textsuperscript{116} obtained similar results for reduction in pain benefit compared to sham laser, but the project differed for a number of reasons. My review involved nine further advances on the Huang publication: (i) a considerably larger number of trials, fifteen in total; (ii) for the first time, examination and comparison of both laser acupuncture and non-acupuncture LLLT trials; (iii) subgroup analysis conducted to reduce and explain heterogeneity; (iv) separately analysed primary outcomes of pain and global assessment immediately post completion and in short term; (v) other secondary outcomes such as disability, range of movement as well as long-term follow-up in certain trials; (vi) evidence for an effective laser dose threshold; (vii) discussion of other characteristics of subjects which may affect laser treatment response; (viii) discussion of the bias issue of unblinding among contained LLLT trials; and (ix) a quality of evidence assessment (GRADE) of its primary outcome findings.

In the trials examined in my review there appeared to be a lower effective dose threshold at 3J/point for laser. This is higher than the minimal dose from reviews by Baxter (0.5J/point for myofascial pain)\textsuperscript{9} and Chow (0.8J/point for chronic neck pain)\textsuperscript{25}, but closer to the dose recommended by WALT\textsuperscript{26} for lumbar arthritis (see Table 4.7).

Table 4.7: Recommended treatment doses of Low Level Laser Therapy for lumbar arthritis (WALT 2010)*

<table>
<thead>
<tr>
<th>Laser</th>
<th>Minimal total dose</th>
<th>Minimum dose per point</th>
</tr>
</thead>
<tbody>
<tr>
<td>780 - 860nm GaAlAs</td>
<td>16 J</td>
<td>4 J</td>
</tr>
<tr>
<td>904 nm GaAs</td>
<td>4 J</td>
<td>1 J</td>
</tr>
</tbody>
</table>

* “Therapeutic dose windows typically range from +/- 50% of given values, and doses outside these windows are inappropriate and should not be considered as Low Level Laser Therapy. Recommended doses are for white / caucasian skin types based on results from clinical trials or extrapolation of study results with similar pathology and ultrasonographic tissue measurements”

The larger lowest effective dose in this review could be explained by the deeper location of structures in the low back area, with a higher laser irradiation dose required for penetration. It was noted, however, that a trial\textsuperscript{108} using 3J/point was positive yet another trial\textsuperscript{104} using 2.8 J/point was negative. A possible explanation is that the former trial used a 905nm super-pulsed laser. Super-pulsed lasers with high frequency pulse durations in the range of 100–200 nanoseconds has been demonstrated produce greater tissue penetration than either continuous
or other pulsed lasers. We noted two other trials using super-pulsed lasers in our review: one using 1.3 J /point was negative and the other, probably using 4 J / point, was positive. There was no upper dose at which laser was not effective or caused adverse effects, except for a high dose LA trial which was negative. My findings with doses and wavelengths of IR lasers generally appeared consistent with the WALT recommendations, with qualifiers that their recommendations refer to “lumbar arthritis” and do not apply to LA. The findings of this review relate to a different study population (CNLBP) and provided information on LA trials.

This review also found an inverse relationship between the duration of pain and the effectiveness of laser. This finding is plausible but needs to be replicated in further research. The relationship was also less certain, as a number of trials failed to report baseline duration of pain. My cut-off point was 30 months; however, it was noted that one of the non-acupuncture trials with a mean baseline duration of pain of 27 months, was negative at immediate and positive at short-term follow up. This could suggest that a threshold for an even shorter duration of baseline pain may be valid. Two previous studies examining physical treatment for back pain and acupuncture for chronic pain conditions showed a general worse outcome for subjects with longer pain duration but no interaction effect with the type of treatment. It is postulated that when chronic back pain becomes more persistent, central sensitization is more likely to have occurred and laser therapy irradiating local anatomical structures becomes less or not effective when changes in the nervous system are central and widespread.

Most (8/10) non-acupuncture laser therapy trials were positive: that is, they showed a difference between laser and sham groups in primary outcomes; negative trials in this group treated longer pain duration patients with a lower dose. Most non-acupuncture laser trials in this review treated local points, although some also irradiated wider areas using the manual scanning technique in the region of pain. Skin surface application of laser results in photon scattering in an underlying volume of tissue, resulting in a more widespread biological effect, regardless of the intention of the therapist to stimulate classical acupuncture points, tender or ‘Ahshi’ points, or local anatomic structures. In effect, acupuncturists and other laser therapists irradiate tender points in the region of pain, so could in theory produce similar effects; the absence of positive acupuncture trials in this review could be related to the small laser dosage chosen or to other patient characteristics in the samples studied. Another consideration is that according to acupuncture theory, distant points away from the site of pain along lines, called meridians, are treated. If treatment benefit relies on the laser effect on
local anatomical structures, treatment of points distant to area of pain may be redundant and may not contribute to pain reduction. My analysis however was not designed to determine if laser irradiation of distal points provides extra benefit in treating a painful condition.

This review did not find consistent evidence of a laser dose ceiling beyond which laser treatment is not effective; however, two higher dose LA trials\(^9\),\(^1\)\(^1\) were negative. The first trial\(^9\) used a novel ‘Laser Needle’ device\(^1\)\(^2\) popular in Germany, with claims of effectiveness in the treatment of many conditions. This is a multi-channel fibre-optic system allowing transmission of laser through tips of cables in skin contact; there is no actual penetration of the body with needles. There is simultaneous irradiation of a number of points, supposedly mimicking what occurs in needle acupuncture. The same authors\(^1\)\(^2\) selected “random” samples from patients treated with laser needles in their clinics over the period 2001–2006. These samples comprised fifty patients, each with knee, shoulder, low back pain, and headache/migraine, who, before and after measurements of pain (VAS), were measured without a control. In the back group, a 50% pain reduction occurred 3 months after treatment, with 47 % reduction maintained at 6 months. Similar reductions were reported in the other series, where knee and shoulder pain, and headache were treated.

It is not possible to explain the magnitude of this effect, except to state that these were uncontrolled, retrospectively selected, case series. Subsequent to this, ‘a clinical double-blind study’ (Weber et al, unpublished data, 2007)\(^1\)\(^2\)\(^1\) showed that the red light laser needles ‘did not exceed placebo effects with regard to lumbar spine syndromes’. The researchers then repeated the trial\(^9\) (reported in this review) with modification of the machine adding infrared laser stimulation again with negative results. The second higher dose LA trial\(^1\)\(^0\)\(^9\) irradiated 12 J/point and was not a “laser needle device”. Only two out of four points used were in the local area of pain, the baseline duration of pain was unknown, five consecutive days of treatment were given and a co-intervention (‘soft cupping’) was used.

I can only speculate on what factors may have contributed to the negative results in these higher dose LA trials. Factors apart from dose may be of importance in determining efficacy of treatment. For example, (i) longer baseline pain duration in participants may have existed; (ii) dosage greater than that recommended by WALT,\(^2\)\(^6\) being used in the “laser needle trials” (60-180 J/point) may have been inhibitory; (iii) use of distant points for laser irradiation may be ineffective; (iv) short treatments, for example five consecutive days, may not be appropriate in the treatment of chronic pain; or (v) co-interventions such as soft cupping incorporated in the device could actually reduce the laser penetration by increasing the blood supply in the area.
Since my completion of the meta-analysis, another double blind LA RCT for LBP has been published. This compared laser with sham laser using a 660 nm pulsed laser (not ‘super-pulsed’) and incorporated cupping as a co-intervention. The back pain was ‘non-specific’, with a mean baseline duration of LBP of 15 months. Only 3 treatments were given over one week. Local acupuncture points were mostly used in the region of pain. Laser dose was 4.8 J, applied to each point for 3 minutes. This LA study was again negative, with no difference in outcomes between laser and sham. A wavelength in the red spectrum, a probe not in contact with skin, and an increased underlying vascularity due to the cupping combination may have reduced laser tissue penetration and contributed to the negative result. It remains possible that doses even larger than 3 J/point identified in this review may be needed to produce an effect in 'non-super-pulsed lasers'.

Heterogeneity of studies and insufficient data were quoted as reasons for the previous inability to determine firm conclusions on the effect of LLLT for low back pain. A strength of my review was having a larger number and more recent eligible trials since the earlier review. An early trial from 1994 was excluded, as a subjective categorical outcome rated by the assessor was reported; however, two separate Japanese trials of the same time period that were included used a self-reported participant assessment which satisfied our inclusion criteria. Exclusion of acute back pain and trials without sham laser controls reduced heterogeneity and allowed a better study of the specific laser effect. Subgroup analysis was important in explaining the heterogeneity.

A limitation of my review was related to bias in the trials included, from possible unmasking. Low risk of bias in all blinding domains, according to the Cochrane tool, was present only in about 60% of the trials. In the positive trials there were deficiencies in blinding, such as the use of machines not specially designed for this type of research, no testing of participants and therapists to ensure blinding was successful, and no reporting of previous testing of the machine to ensure this. Subject awareness of thermal sensation in trials with higher power devices was possible, potentially unmasking the treatments. These issues reduced the quality of this review regarding the risk of bias domain. Inadequate reporting in papers on characteristics of participants and laser parameters also produced uncertainty. It is critical that rigorous blinding must be instituted in any further clinical trials investigating laser therapy for treatment of pain. The appropriate laser dose range for specific body regions, as recommended by WALT, should be followed, and full and explicit descriptions of laser parameters, treatment regimen and baseline characteristics of participants are important/essential. Future studies examining the treatment of chronic low
back pain may also establish the role of intervention factors such as number, location of points and frequency/duration of treatment, and the effect of longer follow-up on outcomes.
Chapter 5
Research design, impact, defense and recommendations

Summary
In this final chapter I outline some design issues identified in conducting my research, and present a summary of its findings. In the spirit of ‘defense of the dissertation’ I then respond to the criticism encountered during the process of submitting my papers to journals. Next, I focus on findings from my laser research on CLBP, together with recent SRs dealing with other pain conditions, to highlight why there is still uncertainty on the efficacy of LLLT for pain reduction in clinical practice. I then outline the key recommendations from my research.

Thesis Design
Several issues regarding the design of both my LA trials, and the systematic review warrant discussion.

Specific or non-specific laser effects in pain reduction? The primary aim of this study was to determine if LLLT including LA has a specific benefit in pain reduction in CLBP. Studies have shown that there is also a large non-specific effect in this intervention that produces significant pain reduction and improvement in other outcome measures. To refute the hypothesis that all improvement seen is due to non-specific effects not related to laser, double blind trials using sham laser as a control were conducted, and my RCTs were later included in a systematic review and meta-analysis to provide a broader perspective on the evidence.

Conduct of individual trials versus a systematic review: Animal and human physiological studies have raised the possibility of multiple mechanisms in pain modulation by LLLT, but the primary intention of my research was to design and conduct clinical trials to determine the efficacy of low dose laser acupuncture for chronic LBP, and to discover an effective dose if such efficacy existed. As I am aware that limited information may be derived from the conduct of isolated trials in this field, where many different parameters and approaches to treatment are being trialed, it was then necessary to meta-analyse all current RCTs of LLLT treatment for chronic LBP to try to determine which laser parameters are effective. I have also examined the evidence of effectiveness of laser acupuncture compared to other low-level laser therapies.

Design of LA trials: To remove possible bias involved in determining if a specific effect in pain reduction from laser existed, a suitable research laser treatment device was required. A novel laser diode therapeutic device that had been developed in Melbourne for this type of research enabled rigorous masking, concealed allocation and operation by a single therapist.
appreciated the opportunity of being the first researcher to use this device in a clinical trial. The advantage of this machine was that patients and the therapist remained blinded, and one operator (the therapist) was able to set dials and to treat subjects.

Other aspects of trial design were also vital to improve the validity of the findings of this research. These included adequate sample size determination before beginning the research, measures to minimize all domains of bias, and explicit reporting of laser parameters and treatment protocol in the publication. It was also important to follow Consort guideline for reporting RCTs.123

I was initially interested in determining the effectiveness of low dose laser acupuncture in the treatment of CNLBP using doses less than 1 Joule per point for stimulation. Two separate studies3,98 were conducted in the course of my research with groups comparing sham with irradiation of either 0.2 Joules or 0.8 Joules per point on the body surface. Treatment followed a holistic approach, with individualized selection of points at each treatment depending on pain distribution and other symptoms in the patient. This was based on acupuncture principles from Medical Acupuncture MFM 1018, a course offered by Faculty of Medicine, Monash University 1998 (see Appendix J). My approach was pragmatic, with individualized treatment used for each participant and across time. This was also the medical acupuncture approach taught and used by Australian Medical Acupuncture College (AMAC) members. It is anecdotally considered more effective than a formula approach given to all patients. It was not considered that confounding due to difference in treatment between groups would be an issue with the sample sizes used.

In these studies, primary outcomes were pain and back-related disability (ODI) in the short term, up to 6 weeks post-treatment. These outcomes were specified at protocol stage and were considered to be the most important measures, likely to show a change if laser was producing a clinical change. I examined many other secondary outcomes spanning a time frame up to 12 months post-treatment. Use of multiple outcomes would increase our confidence in the results obtained from these trials but would also increase the possibility of some significant results occurring by chance. Results of the primary outcomes were given emphasis.

Another aim was to establish the magnitude of pain reduction due to the specific (laser) and non-specific effects of the laser acupuncture intervention, and to investigate which baseline characteristics were predictors of this. The baseline measures included demographics, as well as variables related to the pain, previous treatments given, and associated conditions. Validated instruments also assessed baseline disability, mental health domains (DASS-21),
pigmentation skin type (Fitzpatrick scale), level of neuropathic pain (ID Pain) and a physical activity questionnaire (IPAQ).

**Conduct & recommendations from my initial trial:** My initial study in 2009 also included a co-intervention consisting of education and encouragement to exercise. The trial found no difference in outcomes between the laser and the control group, despite a significant pain improvement in the combined groups, up to 40% reduction at the end of treatment. Although randomisation in this trial appeared adequate, some imbalance baseline in characteristics between groups was present. In a further secondary analysis of the results in this trial, I found a chance imbalance between groups of certain baseline characteristics in participants which were found to predict pain response after the overall intervention. Adjusted analysis of the results showed a statistically significant effect of laser acupuncture in reducing pain at six weeks follow-up only. Response predictors would be considered in selecting patients for the next trial and utilized in its analysis. Tighter exclusion criteria would be imposed, excluding patients on DSP, workers compensation or third party; any opioid analgesics; and previous back surgery or failed nerve blocks. A wide range of baseline characteristics would again be recorded to conduct an analysis determining response predictors.

**Design of Systematic Reviews:** Heterogeneity of trials was recognized as a problem in previous reviews of the related literature. To reduce heterogeneity in my review, only trials treating chronic non-specific low back pain as the primary condition, and using sham laser as the control were included.

The decision to include both laser acupuncture and non-acupuncture laser therapies would increase clinical heterogeneity. This however would be explored using subgroup analysis to separately consider (i) acupuncture and non-acupuncture trials and (ii) and trials employing higher and lower dosage of laser. Another particular task in the review was to examine risk of bias in included studies from the inadequate masking or reporting of the active / sham status achieved with treatment machines used.

**Impact: How has this thesis advanced knowledge in this area?**

**Findings from the second trial:** At the time I began my second RCT, some doubt existed about the possibility of a specific laser effect existing using low dose laser acupuncture interventions in CNLBP, as described in my previous publications. My second trial was
conducted examining a laser dose range (0-0.8 Joules/point), with a selected population of patients considered to respond more strongly to this intervention, and with long-term (12 months) follow-up. The analysis showed no difference between the sham and the laser groups for the primary outcomes of pain and disability, or for any other secondary outcome. Adjusted analysis using baseline predictors as covariates did not change this conclusion. There was similarity in the baseline characteristics predicting non-specific pain reduction in both of my trials. Two major limitations in analyzing the predictors of pain reduction after laser intervention were the relatively small sample sizes of examined trials, and the uncertainty of generalizing results to different patient populations. My trials failed to show that low dose laser acupuncture as practiced in this intervention had a specific laser effect in reducing pain in CNLBP.

Findings of systematic review with meta-analysis: Only one Cochrane review on this topic had been published before I began my review. This review indicated that there was insufficient data to draw firm conclusions on the effect of LLLT in LBP.

My review selected a larger number of studies published since the Cochrane review and included LA trials. Up to short-term follow-up, there was a significant pain reduction of WMD -1.40 cm (95% CI -1.91 to -0.88) in favour of laser occurring in trials using at least 3 Joules (J) per point, with baseline pain less than 30 months, or in non-acupuncture laser therapy trials. Global assessment also showed the benefit at immediate follow-up. Disability (ODI) reduction in the same subgroups was significant in the short term (WMD of -5.9% (95% CI: -8.9 to -2.8). The reduction of pain attributed to laser irradiation approached the minimally important change (MIC) for chronic LBP pain, as proposed by Ostelo. The reduction, due to non-specific factors not related to the laser stimulation, was also appreciable, and the determinants of this have been discussed.

A major finding of the systematic review component of this research was that, according to evidence from trials up to date, a dose of at least 3 Joules/point irradiation in the area of chronic LBP is required to demonstrate an effect from infrared laser. The dose required to achieve this effect may be even higher in continuous or non-super-pulsed lasers. Other lasers, for example in the visible red spectrum, were not used in the trials examined in this review; it may be expected that even higher doses to produce a therapeutic effect would be required in such shorter wavelength lasers, which have less tissue penetration. Red laser has less tissue penetration than IR but tissue still has least optical density between 670-910 nm, which includes the red spectrum. Strong light penetrates deeper than weak. However, twice the
power does not mean twice as deep, but maybe 5-10% deeper\textsuperscript{(21)} Increasing laser power beyond a certain level may start to have tissue-heating effects which may be undesirable, so there are limitations for increasing penetration of laser by boosting power of the device.

This review also suggests that laser may be ineffective in reducing low back pain if pain has been present for much over 2 years; however, these findings need confirmation in further studies. Other laser treatment parameters and patient characteristics may be of importance, but are not yet determined by research.

Although this study set out to determine if the stimulation of points with laser instead of needles, using a laser acupuncture approach in subjects with CNLBP, could show a laser specific effect, no LA trials (including three trials\textsuperscript{91,109,122} employing a higher dose than 3 J) performed up to date have been able to confirm this. The review suggested that low-level laser application to local points at the source of pain may produce a specific effect in reducing pain; however, a higher laser dose in an LA intervention still needs to be trialed. This includes conducting blinded trials of the ‘Laser Needle’ devices\textsuperscript{112} that are currently popular in Europe, without evidence from RCTs comparing real and sham laser intervention from this machine.

Only a moderate quality of GRADE evidence\textsuperscript{9} was demonstrated for a clinically important benefit in low-level IR laser therapy for CNLBP; this is because of issues centered on concerns about the adequacy of blinding and the inadequate reporting of parameters of interventions within trials included in this review. Conduct of further rigorously blinded trials using appropriate laser dosage would provide greater certainty regarding this conclusion.

\textit{Defense of dissertation}

\textit{Use of a sham laser:} The RCT using sham laser as a control was the method of choice necessary to determine if laser produced an effect, apart from the non-specific effects. This would appear self-evident, but even during the submission process of the systematic review of LLLT for back pain,\textsuperscript{116} a reviewer selected by a spinal journal “could not understand why sham laser was used rather than a non- laser group as a control”. This demonstrates some lack of understanding by mainstream medicine of LLLT research. The effect of low-level laser specific analgesia remains uncertain in the literature, partly because of methodological issues in trials so far conducted. Unlike the problems of controls in needle acupuncture, the use of sham laser is a credible means of achieving double blind status, and the importance of using
this control was outlined earlier in this thesis. If high quality evidence is found for laser specific pain reduction in treating a condition, this would then pave the way for conducting other pragmatic trials, for example comparing laser against conventional treatment. Such pragmatic trials would help determine the effectiveness of LLLT, as compared to the commonly practiced treatments such as analgesic medication for musculoskeletal conditions, and would allow cost benefit comparisons.

**Criticism of classifying LA as a subgroup of LLLT, and of including LA trials in a systematic review examining treatment by LLLT:** I adhere to my assertion that LA should be considered a subgroup of LLLT (see page 14-15 of thesis). LA involves applying laser irradiation to points on surface of the body to treat conditions including those causing musculoskeletal pain. It usually includes points over the anatomical site of pain, so it could be considered a subgroup of LLLT. Other more distant points can also be used guided by concepts of acupuncture theory. Some proponents of LA^{124} believe this combination of points in LA acts by a physiological pathway separate from other LLLT, and this may be triggered by using a lower energy dose per point. I maintained a definition of LA as being a subgroup of LLLT in two of my last open access publications^{98,116} and have not received any comment or critical feedback in relation to suggesting this definition from any reviewers or readers. All LA trials for treatment of chronic LBP by the myself or other researchers have so far proven negative for demonstrating a laser specific effect for LA. This may cast doubt on the existence of a low dose LA pathway which works by some different mechanism compared to other LLLT, and that it should be classified differently. It was advantageous to include all types of LLLT including LA in a systematic review examining of treatment of CNLBP. This has not been done before, and was successful in examining reasons for differences in efficacy between these therapies. A limitation of including both LA and other LLLT in my review was the introduction of increased clinical heterogeneity. This was dealt by performing subgroup analysis comparing these therapies.

**Which laser acupuncture dose is effective?** There is controversy about which parameters of LLLT are most effective, and whether these are different for LA treatment in treating chronic LBP patients.

It was believed that LA (stimulating various acupuncture points on surface of the body by a laser beam) could work by differently^{124} from other laser therapy described as acting by a photo-biological effect on local anatomical structures. It must be noted that in my CLBP
review, in all non-LA trials only local points or regions in the anatomical site of pain were irradiated (see page 88, Table 4.3).

Up until 2008, a number of systematic reviews examining heterogeneous painful and musculoskeletal conditions had reported pooled effect sizes in favour of laser in LLLT interventions. One of these reviews excluded trials using laser doses less than nominated for reducing joint inflammation. Another review, which considered LA but did not include any trials examining the treatment of LBP, established 0.5 J per point as a minimum to produce a laser effect. Apart from these studies, mostly anecdotal evidence was available to suggest an effective dose for laser acupuncture. My effort in performing RCTs was directed to determining if LA treatment for LBP was effective at dosages commonly employed in practice. In relation to dose selection, during the peer review process for my subsequent journal submissions, I received criticism about the low laser dosage (0.2 to 0.8 J per point) studied in my LA trials, which eventually did not show a specific laser effect in reducing pain. I responded to this criticism (see Appendix N) and succeeded in publishing in a BMJ group medical acupuncture journal. There was recognition that my topic (investigation of low laser dosage in the context of an acupuncture-like treatment for chronic LBP using a double blind technique) had not been previously adequately researched. Despite negative results obtained in my research (which have been documented in the literature), it was important to further examine RCTs utilizing different laser doses and treatment approaches, to determine what works best for treating chronic LBP.

Updated SR with focus on CNLBP: As some preceding systematic reviews (SRs) of LLLT examined a wide range of mixed conditions, clinicians may find it difficult to relate such results to treatment of their patients presenting with a particular condition. They want to know if laser is likely to have a specific effect in the patient they are treating, and the size of that effect. A review focusing on a specific pain condition would better provide this information. My supervisors encouraged me to complete this research project with a systematic review. At the time of commencing this, the latest review of LLLT treatment for chronic low back pain had been published in 2008. It was important to update SRs as new trial data become available, and I therefore undertook to systematically review the LLLT of CNLBP, including the subgroup of LA. Focusing on a single treatment condition reduces clinical heterogeneity, and may allow meta-analysis of trials to determine an effect size. Unfortunately, even focusing on a discrete treatment condition may not remove all sources of heterogeneity between trials. It is also clear that CNLBP itself represents a complex condition
of varying populations composed of many patho-anatomic variants and also affected by psychosocial influences. A comment of one of the peer reviewers during the publication process was that “although the review suggested a beneficial effect of laser therapy, … any conclusions must be made with extreme caution due to the heterogeneity of the study groups in the literature”. Notwithstanding this criticism, my review selected all relevant trials published to date in this area; trials of LLLT focusing on more specific diagnostic subgroups of chronic LBP had not been performed. In the review, we acknowledged the clinical heterogeneity present and took steps to reduce this by performing subgroup analyses. Another problem with subdividing with CNLBP into treatment categories based on structure is that there is poor correlation between pain in CNLBP and diagnostic imaging; on the other hand, physical therapy such as acupuncture may be given with benefit without a specific anatomical pathological diagnosis available. Of course, if red flags are recognized, further investigations would be performed and another treatment substituted if appropriate. However, it is possible that the focus in future studies will be on specific forms of back pain based on a patho-anatomic or other framework.

The implications for researchers and practitioners

The low back pain review in the context of laser treatment in other parts of the body

This discussion deals with LLLT research for treatment of CLBP but it is salient to first examine SRs that have been published in recent years for the treatment of other conditions. A search in PubMed was made of recent systematic reviews or meta-analyses, published since 2010, that examine LLLT or laser acupuncture treatment of specific musculoskeletal or painful conditions (excluding back pain), compared to placebo or other controls.

i. Musculoskeletal disorders: In 2017 a meta-analysis\textsuperscript{126} was published which investigated the effectiveness of low-level laser therapy (LLLT) on pain in adult patients with musculoskeletal disorders. The analysis included 18 studies with a total of 1462 participants. Two of these trials dealing with chronic LBP were included in my SR.\textsuperscript{106,107} There was a significant pain reduction between laser and the control groups WMD = -0.85cm [95%CI: -1.22 to -0.48] in favour of LLLT. There was a larger WMD= -1.52 [95%CI: -2.34 to -0.70] in the subgroup complying with WALT dosage guidelines; however, there was no statistical difference between groups which did or did not follow dose guidelines, or between subgroups which
treated different body sites. Those authors concluded that LLLT is an effective treatment modality to reduce pain in adult patients with musculoskeletal disorders. It was also found to be important to adhere to laser dose guidelines and to have proper reporting and standardised treatment protocols.

ii. Temporomandibular joint (TMJ): The TMJ was the region of the body most often reviewed, with seven SRs published since 2010. Four out of seven showed a pain reduction benefit for LLLT, although one of these showed only functional benefit (mouth opening). The remainder showed no benefit or were unable to reach a conclusion. However, all cautioned the interpretation of results because of the heterogeneity of the trials (laser parameters or approaches to treatment). No conclusion was reached on optimum dosage.

iii. Carpal Tunnel Syndrome: Two SRs for the effect of LLLT on carpal tunnel syndrome were reported. One review reported benefit for handgrip, VAS and Sensory Nerve Action Potential at immediate to short-term follow-up. The other review reported that studies using 780-860 nm Lasers and energy dosages of 9-11 J/cm² or 10.8 J reported more pain reduction, symptom severity, and better functional ability at immediate and short-term follow up. However, no strong evidence was found and further higher quality trials confirming the results were suggested.

iv. Neuropathic pain: A systematic review showed pain benefit for LLLT in neuropathic pain (better for IR lasers with power > 70mW), but it was concluded that further rigorous studies were needed in order to define treatment protocols that optimize the action of LLLT.

v. Knee osteoarthritis: Another systematic review for LLLT in knee osteoarthritis found no significant difference between laser and placebo for VAS pain results SMD = -0.28 [95% CI = -0.66 to 0.10]. This was the same for studies that followed the WALT dosage recommendations, and no difference was found in other functional outcomes.

vi. Shoulder tendinopathy: A single systematic review for shoulder tendinopathy showed statistically and clinically important VAS pain reduction of LLLT over placebo when used as monotherapy with WMD =20.41 mm [95% CI: 12.38 to 28.44] or combined with other physiotherapy, but only in trials where doses used were adequate according to WALT guidelines.

vii. Neck Pain: Another SR of 2013 found 2 trials where there was moderate quality evidence supporting LLLT over placebo to improve pain/disability in the intermediate term.
For other diagnoses, such as acute radiculopathy, cervical osteoarthritis or acute neck pain, there was low quality evidence, and for chronic myofascial neck pain (5 trials) the evidence was conflicting; there was a suggestion that super-pulsed LLLT increases the chance of an improved pain outcome.

viii. Orthodontic pain: Three systematic reviews in dentistry showed that orthodontic pain was significantly reduced with laser, compared to placebo, but because of methodological shortcomings and risk of bias in all trials, the authors considered there was insufficient evidence to support LLLT's effectiveness. It was suggested that RCTs with better designs and appropriate sample power are required to provide stronger evidence for clinical applications of LLLTs.

ix. ‘Laser Acupuncture’: Only one SR with meta-analysis, published during this time, that examined ‘laser acupuncture’ for treating musculoskeletal diseases or injuries presenting with pain, was previously discussed in Chapter 4. Its definition of treatment differed from that used in my review, with LA defined as treating traditional Chinese acupuncture points, trigger points or tender points. The paper indicated that studies involving application of laser therapy to non-acupuncture points were not considered, which conflicts with the definition of LA given. Some studies selected did not even mention ‘acupuncture’ in the text, which adds to the confusion on types of studies included in this review. The SR found a relationship for the condition “myofascial pain or musculoskeletal trigger point syndrome” with the overall effect on pain favouring laser immediately and in the short term (SMD -0.49; -0.79 to -0.18 and SMD -0.95; -1.55 to -0.35) respectively. A stronger result at longer follow up was noted. Two other groups of conditions studied (TMJ pain and lateral epicondylitis) each contained only two trials, with conflicting results. Almost 70% of studies reporting positive results used the clinically appropriate dosage suggested by Baxter et al.9; however, this review stated it was unable to determine an effective dosage range for LA, as it covered different musculoskeletal conditions, each of which may have required a distinct parameter and dosage regime for clinical effectiveness.

**Findings and limitations of recent LLLT reviews**

From the preceding it is apparent that a large number of RCTs and increasing numbers of SRs involving many musculoskeletal and painful conditions have been published in recent years on this topic.
Many SRs appear to demonstrate a beneficial effect of laser compared to a control, across a number of different conditions, although there are some which are contradictory, with negative results. Some references in these reviews state that conforming to WALT laser dosage guidelines for treatment is of importance, but the majority of these SRs have not yet determined an optimum range of laser characteristics to produce the best results.

A proportion of SRs are unable to reach a conclusion due to the heterogeneity of the RCTs included, with variable laser parameters, treatment regimens, and quality of included studies and reporting. Apart from laser parameters used in different trials, distinct populations may also demonstrate variable responses to treatment. For example, as demonstrated in my review, other factors such as baseline duration of pain may influence the effect of laser.

When results for many RCTs are pooled, the overall WMD may be smaller than the ideal situation, because of clinical heterogeneity with the results of positive and negative trials combined. After subgroup analysis is performed, for example based on whether an adequate laser dose is used, the effect size in the selected groups may be increased. When the optimum laser dose treatment is given, pain reduction (VAS) approximates WMD 1.5 to 2.0 units greater than using sham, which is a similar difference also demonstrated in our meta-analysis. However, there remains a possibility in many studies that inadequate techniques of blinding were performed. It has been previously shown that, in trials where subjects or therapists may have been able to distinguish which group was receiving active treatment, there are larger effect sizes in the active treatment group than in the placebo.  This has currently not been excluded as a factor, partly contributing to positive results for laser in these SRs. Future trials must be designed to eliminate this source of bias, in order to resolve persisting uncertainty on this issue.

**Implications on trial methods for researchers and practitioners**

The topic of LLLT for chronic low back pain and other conditions has been controversial for many years and is likely to remain so unless further clinical trials with a low risk of bias are conducted to compare real and sham laser. Trials must be designed with low risk, especially adhering to strict principles of concealed allocation and blinding of subject, therapist and assessor. It is also important for the laser therapy device to be specially designed for this type of research. An example of such a suitable device is the Acupak® laser employed in trials of this investigation.  It is important to preserve allocation concealment and to prevent any possibility for participants to able to distinguish whether sham or laser is treating them. This
includes not being able to register any heat produced by the laser probe in higher power devices.

**Recommendations for conduct of future LLLT trials**

According to findings in this study, it is suggested that treatment for chronic LBP should be given by infra-red laser diodes irradiating points, with the adequate dosage recommended to be at least 3 Joules/point in ‘super-pulsed’ lasers or even higher dose in continuous or non ‘super-pulsed’ lasers. It is recognised that more studies are required to confirm the effectiveness of super- pulsed lasers.

Skin contact (unless the laser beam is collimated) and indentation of skin with the laser probe (which may produce displacement of tissues such as blood) may also produce greater laser penetration.

All non -acupuncture LLLT positive trials have so far involved at least 2 sessions per week run over ≥ 2 weeks. It is not known if treating less often with higher laser doses is effective, but if so this would reduce cost and facilitate patient convenience in a GP setting. Trials investigating this are warranted. The usual practice for medical acupuncture in Australia is to perform treatment weekly or less frequently for chronic conditions, both for needle or laser stimulation techniques. My trials using < 1 J per point, which treated patients at this frequency of sessions, were negative for a laser specific effect. Evidence does not exist whether this would be still the case at this frequency of sessions if using a higher laser dose. The other LLLT trials in the review used much more frequent sessions and some of the trials were positive. The WALT guidelines recommend a higher frequency of treatment sessions but these guidelines are not intended to apply to LA. More research is required, but clarification of this question was not possible within my thesis.

In efficacy trials, co-interventions should be avoided, as these complicate the procedure and concepts, and there is a possibility of negating effect of treatment, for example, the effect of cupping increasing blood supply to the area and reducing laser penetration. For similar reasons, the use of concurrent medication such as opioids, steroids and calcium channel blockers should be excluded. There is evidence that such medication reduces the effect of laser. Cross-over trials should be avoided, due to the possibly prolonged effects lasting after laser interventions. As some SRs suggest that a specific laser effect lasting up to 3 months post treatment may persist, washout times between treatments in such trials may be inadequate.
At this stage evidence for therapy should be to restrict treatment to local points or regions at the site of pain, which may be in accordance to either laser acupuncture or laser therapy principles. Some of the non-acupuncture LLLT trials examined in the review used multiple arrays of laser diodes, or manual scanning by laser diode to irradiate a larger area of skin over a time period or combined with irradiating some chosen discrete points. Some of these trials were positive although this was also the case with some non-acupuncture trials which irradiated only a number of discrete, or even single points. More research is required on how light including laser using arrays or manual scanning techniques compares to approaches where light energy is sequentially applied to discrete points.

Laser acupuncture trials using adequate dosage, are warranted. They could be structured to using local point treatment only, or alternatively combining local and appropriate distant meridian points as in usual acupuncture practice. There must be complete and rigorous reporting of the device employed and the laser parameters used. A useful document describing this is the “Consensus agreement on the design and conduct of clinical studies with low level laser therapies and light therapy for musculoskeletal pain disorders” approved by WALT at the 5th Congress, in Brazil, 2004.

Further work could also be done on identifying specific forms of back pain that may be more responsive to LLLT, such as LBP with high neuropathic pain scores, those with spondylogenic referred pain, spinal stenosis, documented facet joint pain, SIJ pain, coccygodynia, and spondylolisthesis. Such trials would reduce concerns about treating an otherwise heterogeneous group of CNLBP subjects, would clarify the suitability of certain types of chronic LBP for this treatment, and would assist patients and therapists with decisions on therapy. There is much scope for conducting further LA research for treatment of back pain as well as for other painful musculoskeletal conditions, with adjustment of laser dose required to treat a particular site. This could include investigating the value of (i) adding distant meridian points compared to local point only treatment, (ii) comparing LA to needle acupuncture, or (iii) comparing a combination of needle acupuncture with local irradiation of points with laser, to needle acupuncture alone. If high quality evidence for LLLT or LA is established by such research for LBP or other conditions, it would be important to run pragmatic trials and cost/benefit analyses comparing laser therapy to conventional treatment.
Implications for practitioners

In summary, this research suggests that, for treatment of CNLBP, LLLT including LA, which uses very low energy for stimulation of points, is no better than sham. For this chronic pain condition, there is a possible role for higher dose laser therapy by itself, or being used with other modalities, with few adverse effects, to achieve useful pain reduction for up to three months. I urge a degree of caution before giving widespread recommendations to practitioners and consumers, until results can be confirmed by further rigorously blinded trials employing adequate laser doses and other steps, as outlined in this research.
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**Appendix**

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Appendix E

Laser use survey PANPAC 2012

68 respondents from of total approximately 80 delegates
(A) Profession:
87% were GPs
10% physiotherapists
3% other specialists

(B) Country of origin:
94% from Australia or NZ
6% North America

(C) Usage of laser:
i. did not use (12%), ii. occasionally used (37%), iii. often used (47%),
iv. only used (3%)

(D) Types of laser machines used:
In laser users, parameter description of first laser machine (laser machine with lower
power output is listed here for 30% of owners with more than one machine)
(i)Wavelength: red (55%), infrared (27%), other (3%), not specified (15%)
(ii)Power output: 1-5mW (22%), >5-30mW (38%), >30-100mW (12%), wide range
(5%), not specified (22%)

In laser users, parameter description of second machine
(i) Wavelength: red (44%), infrared (50%), not specified (6%)
(ii) Power output: 1-5mW (0%), >5-30mW (33%), >30-100mW (44%), >100mW
(11%), not specified (11%)

9% of laser users owned more than two laser machines

(E) Participants were asked three most common conditions they treated with laser
and frequency of responses for conditions given (n) is detailed in table below-

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>Condition</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal pain various</td>
<td>30</td>
<td>Mental stress</td>
<td>5</td>
</tr>
<tr>
<td>Headaches</td>
<td>19</td>
<td>Addictions, obesity</td>
<td>3</td>
</tr>
<tr>
<td>Back pain</td>
<td>18</td>
<td>Neurological</td>
<td>3</td>
</tr>
<tr>
<td>Neck pain</td>
<td>17</td>
<td>Lymphoedema</td>
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<td>Allergy, sinus, hayfever</td>
<td>10</td>
<td>Metabolic</td>
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<td>Shoulder</td>
<td>9</td>
<td>Asthma</td>
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<tr>
<td>Afraid of needles</td>
<td>7</td>
<td>Difficult areas</td>
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<tr>
<td>Other joints</td>
<td>5</td>
<td>Scalp acupuncture</td>
<td>1</td>
</tr>
<tr>
<td>Ulcer healing, post-op scars</td>
<td>8</td>
<td>Auricular acupuncture</td>
<td>1</td>
</tr>
<tr>
<td>Skin conditions</td>
<td>4</td>
<td>Nausea</td>
<td>1</td>
</tr>
<tr>
<td>Shingles, post herpetic neuralgia</td>
<td>4</td>
<td>Patients with viral blood infections</td>
<td>1</td>
</tr>
</tbody>
</table>
Appendix F

Research Protocol
Dr G Glazov
January 2010
Project No. RA/4/1/2057

**PROJECT TITLE**

Multi-centre double blind randomised controlled clinical trial to examine the efficacy and dose dependence of a 830 nm, 20 mW laser diode for the laser acupuncture treatment of chronic non-specific low back pain

**RESEARCH TEAM**

**Chief investigator:** Gregory Glazov MBBS, DFM, MFM, FAMAC
General Practitioner and 2008 UWA PCHRED Fellowship recipient

**Coordinating Supervisor:**
Prof. Jon Emery   Dept of General Practice, Faculty of Medicine UWA
External Supervisor: Assoc. Prof. Michael Yelland, Griffith University QLD

**Others:** Members of the Australian Medical Acupuncture College WA Branch
(general practitioners volunteering to participate as therapists in the trial)

**AIMS OF THE PROJECT**

The main aim is to determine if there is any specific benefit in reduction of pain and disability using laser acupuncture (LA) in the treatment of chronic non-specific low back pain (CNLBP).
Sub-objectives include:
- To examine the duration of benefit of LA in the short, intermediate term and long term.
- To determine if there is a dose dependence of LA over the range of 0.2 to 0.8 joules per point treated.
- To conduct an analysis on the effect of baseline characteristics on pain outcomes.
- To examine the effect of restricting the study sample based on previously determined outcome predictors.
- To assess any adverse effects of LA

Hypotheses
To refute the hypothesis that the whole effect of this treatment is due to other effects not related to the laser, the design of this investigation will be a double blind randomised controlled trial comparing (LA) against a control sham treatment. There is evidence from previous studies that the specific effect of LA is less than the non-specific effect of the whole treatment. This together with random effects of imbalances between treatment arms may make it difficult in detecting a specific effect from an acupuncture treatment if it exists. The current study will attempt to maximise detection of the postulated specific effect by avoiding any co-interventions and excluding subgroups of participants with baseline characteristics which were previously shown to respond poorly to this type of intervention. The study will also attempt to refute the hypothesis that there is no dose dependence of response (if it exists) over a dose range of laser commonly used in empirical practice (0-0.8 joules per point).

**BACKGROUND**

Low level laser stimulation of acupuncture points (LA) using application under 1 Joule/point as an alternative to needles, has commonly been commonly used in the last 35 yrs. Evidence is still equivocal for the effectiveness of LA for treatment of chronic LBP. Only 2 trials (1, 2) have used double blind methodology examining the effectiveness LA versus a sham laser control. An early study (1) showed a small 15% small positive benefit detected in the active laser group. The other larger subsequent study (2) did not show any significant difference in pain or disability on the primary analysis of results, however a baseline imbalance of factors affecting outcome between the groups may have produced a false negative result. A further paper (3) which involved a subgroup analysis of data from the previous study suggested the strongest predictors of poor response in this LA intervention were receipt of disability support pension, headache, regular use of analgesics or previous failed back surgery. Adjusted analysis suggested a clinically important effect of laser compared to sham (P< .05), at short-term (6 weeks post-treatment) follow-up only. Unfortunately this result was obtained on a post hoc secondary analysis, with associated problems in interpretation. Editorial criticism of the study (3) stated that "too low a dose of laser was used" and a long-term follow-up should have been included. This suggested the need to repeat the trial with a similar protocol but with (i) treatment arms to examine dose response, (ii) steps to avoid confounding factors and maximizing the specific effect of the active treatment if it exists and (iii) inclusion of a 1 year post-treatment follow-up.

**RESEARCH PLAN AND METHODS**

**Study design:** A double blind, prospective, three-group parallel randomised controlled trial, using sham laser in the control group and the other arms using different doses of laser per point treated.

**Settings and locations for the trial:** At rooms of participating GP therapists in Perth metropolitan area (Mindarie, Hillarys, South Perth, Leederville, Fremantle, Parmelia).
Recruitment:
Notices will be advertised in community newspapers serving the areas in which treatment centres are located. The potential participant will be instructed to phone reception at the principal investigator’s practice, and leave a contact name and phone number. The principal researcher will phone back the subject and will screen about eligibility and availability for the trial and briefly answer any questions. If suitable and willing to participate an appointment for initial assessment will be made and they will be sent a letter with appointment details and copy of explanatory statement and consent form, prior to the initial assessment.

Inclusion criteria:
Chronic non-specific low back pain (duration at least 3 months) 18 to 75 years of age, literate, English speaking and given informed consent. At baseline usual pain during previous week, greater or equal to 3.0 on a numerical pain rating scale (NPRS).
(i) Maximum pain is located between 12th rib and gluteal fold.
(ii) There can be radiation of pain into lower limbs or elsewhere.
(iii) Severity of lower limb radiating pain is less than in low back area.

Exclusion criteria:
(i) Clinical features of nerve compression (nerve root entrapment, spinal stenosis or cauda equina syndrome) with corresponding features on recent imaging (if available). (If there is suspicion of an undiagnosed specific cause for LBP being present, the assessing doctor may order radiological or other tests to be performed, or refer to treating GP for investigation, before deciding on eligibility of a subject to enrol into the trial).
(ii) Widespread body pains or fibromyalgia according to criteria (American College of Rheumatology 1990) (4)
(iii) Underlying systemic or visceral disease, malignancy, infection, inflammatory arthritis, or recent vertebral fracture (traumatic or pathological)
(iv) Taking regular opioid analgesics*
(Regular paracetamol or other simple compound analgesics (<15 mg codeine / tablet) / or NSAIDS does not exclude)

*Term opioid analgesic includes tramadol (Tramal), compound analgesics containing codeine 30mg/tablet, (Panadeine Forte, Codral Forte, Mersyndol Forte) and other compound analgesics containing codeine ≥15 mg/tablet ( eg. Prodeine15), opioid patches eg. fentanyl (Durogesic), buprenorphine (Norspan), morphine (MS Contin, Kapanol) , oxycodone (Endone, Proladone, OxyContin, OxyNorm), dextropropoxyphene (Digesic, Doloxene), pentazocine (Fortral, Palfium), hydromorphone (Diluadid)

Term analgesic refers to non-steroidal anti-inflammatory drugs, aspirin, paracetamol, opioids, and different combinations that include these substances. (Low-dose aspirin and topical anti-rheumatics were not included)

5 Regular refers to usage ≥ 2 times a week (or use of patch ≥ 1 weekly)

(v) Taking regular systemic corticosteroids (equivalent of prednisolone ≥ 5mg /day)
(vi) On Disability Support Pension for back pain
(vii) Worker compensation claim / motor vehicle insurance claim for this back problem (current or within 2 years of closure)
(viii) Any form of acupuncture, dry needling, or trigger point injections for back pain or musculoskeletal problems in the previous 6 months
(ix) Previous involvement in acupuncture trials (laser, needle or EA)
(x) Previous invasive procedures for back pain such as facet joint blocks, epidural steroid injection, rhizotomy etc.
(xi) Previous lumbar spine surgery
(a) Pregnant or (b) intending pregnancy in next 12 months or (c) less than 3 months post-partum.

A check list for 'Red flag' conditions will be used as an aid to assist the assessor determine if a subject should be excluded from the trial and referred back to treating GP for management.

- fever and unexplained weight loss
- bladder or bowel dysfunction
- disturbed gait
- ill health or presence of other significant illness
- unstable mental illness (controlled depression on treatment does not exclude)
- past history of malignancy with metastatic potential

**Outcome measures:** NPRS and ODI at short term (6 weeks) follow up

(1)*Numerical rating scale for pain (NPRS) (‘usual level of pain in the last week’)
Participants asked to circle a number on the box scale, which described ‘usual level of their pain in the last week’

(2) Disability
(i) *Oswestry Disability Index (ODI) (5)
(ii) Numerical rating scale of limitation of activities during previous week (NRSLA)
Participants asked to circle a number on the box scale, which described ‘ability to perform their usual activities in the last week’.

(3) Global assessment of treatment question (GA) (7-point Likert scale)
Participants asked to mark: “Please indicate overall how your low back problem has changed compared to that before you started the laser acupuncture treatment program?”

(4) Adverse effects during treatment
At the start of each of sessions 2 to 8 the (i) therapist, and on follow-up 1 week post-treatment the (ii) participants will tick a form yes/no as to presence of symptoms -
(i) flare-up of low- back pain after previous treatment (this will be differentiate according to time relation after treatment)
(ii) common symptoms previously associated with LA
(iii) open question to list any ‘other’ symptoms noted

(5) Use of analgesics
(i) Frequency of analgesic use in previous month
(ii) Symptoms for which analgesics taken in the past week
(iii) Which analgesics used in past week (either prescribed or obtained ‘over the counter’)
(iv) Current use of analgesic medications compared to that before starting the laser acupuncture treatment

(6) Some assessments only done at baseline comparing treatment arms -
(a) The short version of Depression Anxiety Stress Scale (DASS-21) (6)
(b) Neuropathic pain screening questionnaire: (ID –pain)(7) will be used to explore if effect of laser acupuncture depends on presence of neuropathic pain
(c) Fitzpatrick skin types (I to VI) (8): This will be used to explore if effect of laser acupuncture depends on skin pigment type.
(d) International Physical Activity questionnaire (IPAQ (short format) (9):

See Table 1 for timing of outcome measurements.
Table 1: Timing for: assessed parameters (primary outcome measures indicated in bold lettering)

<table>
<thead>
<tr>
<th>Start (baseline)</th>
<th>Treatment period (&lt;=8 sessions)</th>
<th>Completion (one week after last treatment)</th>
<th>6 weeks post-completion</th>
<th>6 months post-completion</th>
<th>12 months post-completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRSP</td>
<td>NRSP</td>
<td>NPRS</td>
<td>NPRS</td>
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<tr>
<td>ODI</td>
<td>ODI</td>
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<td>NLARS</td>
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<td>NLARS</td>
</tr>
<tr>
<td></td>
<td>Adverse effects</td>
<td>Adverse effects</td>
<td></td>
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<td></td>
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<tr>
<td>AU</td>
<td>AU</td>
<td>AU</td>
<td>AU</td>
<td>AU</td>
<td></td>
</tr>
<tr>
<td>1. DASS-21</td>
<td>Perception (laser/sham)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. IPAQ, 3. ID- pain 4. Fitzpatrick skin types</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

NPRS = numerical pain rating scale for pain. NLARS = numerical limitation of activity rating scale. AU = analgesic use, IPAQ = International Physical Activity Questionnaire

(7a) Perception (laser/sham):
Included with the survey forms 1 week after completion of treatment is a question for participants – “Could they distinguish if an active or sham laser was used during their treatments?”

Having completed the research treatment sessions please tick a box for only one of the following 3 statements:
(i) ‘I believe that a real laser was used during my treatments’ □
(ii) ‘I believe that a sham (placebo) laser was used during my treatments’ □
(iii) ‘I am uncertain of what type of laser was used during my treatments’ □

If you think you could determine what type of laser was used, please give the reason for this conclusion (open ended response)..........................................................................................................

(7b) Question for therapists at the conclusion of treatment of their block of patients:

When you complete this block of patients could you please comment on success of blinding of the therapist to mode of laser stimulation:

(a) ‘I believe I could distinguish when a real or sham laser beam was used during treatments’ (YES or NO)

(b) If your answer to (a) was YES please give the reason for this conclusion -

There will be 3 machines- (830 nm, 20 mW infrared laser) modified for research use. The therapists will be volunteering WA branch members of Australian Medical Acupuncture College. The principal researcher will recruit the therapists by approach at meetings and via notices in branch newsletters. Over the period of 24 months it would be hoped to employ 5 or more therapists (including the principal researcher). Each therapist would treat a single block of up to 12 subjects (principal investigator will treat a larger number of participants).
Each therapist will receive a treatment manual, and a face to face meeting will be arranged with the principal investigator who will provide training on all aspects of involvement in the trial by the therapist.

**The initial assessment** will involve a structured interview including pain score in the previous week, a pain diagram marked by the participant and brief examination. This will be done by principal investigator, unless the therapist is interested in conducting this, and has sat in on at least one assessment interview with the principal investigator.

Subjects will be asked to bring any available previous imaging investigations and reports of these will be reviewed. At end of assessment a decision will be made to enrol subject into trial if they satisfy the criteria for inclusion / exclusion and written consent is obtained (signed by the participant witnessed by a receptionist at the surgery).

The decision to enrol may be deferred if diagnosis is in doubt. If there is no recent imaging available, the subject may be directly referred by the assessor for imaging investigation (or referred to his / her treating doctor for this to be done). It is expected that this option will be rarely used as participants will mostly be excluded by the initial telephone screening or at the initial interview.

For subjects who will be enrolled, the nature of the chronic pain problem and general aspects of the trial / acupuncture will be briefly discussed. A leaflet with acupuncture information will be provided.

A clear envelope containing baseline self-administered questionnaires (ODI, DASS-21, IPAQ, AU) will be provided, to be completed at home and returned at the first treatment session.

Appointments for the treatment sessions will usually commence one week following the assessment interview. Each treatment session will be scheduled to run on time and will last 15 minutes.

The participants will be offered all the treatment they can attend up to eight weekly sessions. An interval of one or two weeks between sessions will be permitted on occasion (eg. for holiday or illness or other circumstance). If a patient fails to attend an appointment without notice attempt will be made to re-schedule appointment the following week. Participants will be requested if possible not to start any new physical treatments or medications during the treatment period or for 6 months after. They may continue any of their current analgesics or other therapies according to their pain. They will be requested not to have any other acupuncture like treatment during the 1 year follow up.

There is an itemised record form for each treatment session 1-8. At the start of each session participants will be questioned by therapist about progress and any symptoms including back pain and its distribution. Subjects will be asked to mark their average pain level during previous week on a NPRS. The therapist will enquire about their current distribution of bodily pain and mark this on a pain diagram. They will also ask participants of any adverse effects since last treatment and record this. The therapist will conduct a brief examination of meridians in distribution of pain, and tender acupuncture and other tender points, will be marked lightly with a felt tipped pen. Distal points on related meridians related to their pain may also be used. Other points depending on other symptoms eg. headache, neck pain, other joint pain, gastrointestinal, menstrual and psychological, may used depending on discretion of therapist. The marked points will be treated sequentially with the laser probe. No auricular acupuncture or other 'microsystems' will be used. After each treatment the therapist will record all acupuncture points used on a point
record sheet.
At the end of the last session participants will be provided with another clear envelope
containing forms- NPRS, NLARS, GA, AU, Adverse Effects, Perception
(laser/sham)- to be self-administered in one week and returned in a stamp addressed
envelope provided.
Follow-up survey forms at 6 weeks, 6 months, 12 months would be mailed enclosing
stamp addressed return envelopes.
If the 1 week, 6 week, 6 month and 12 month survey forms not received within 7 days
of the due date an attempt to contact the participant / reissue of forms will be made.

Withdrawal criteria
Involvement in the study is voluntary and participants are free to withdraw at any
stage after enrolment (as stated in explanatory statement). If they do withdraw they
are encouraged to state if they discontinue for personal reasons or because of some
effect of the treatment.
The researcher’s duty of care to participants after enrolment, who are found to be
suffering from any extreme or serious condition during the trial such as severe
depression, suicidal intent or physical condition (eg. tumour, bone infection, cauda-
equina syndrome or significant intercurrent illness) would be to withdraw them from
the trial and refer them to their GP or emergency department whatever is appropriate.
Another withdrawal criterion in a participant may be a severe persistent acute
exacerbation of back pain where consideration of alternative treatment may be
necessary.
All dropouts will be included in an ITT analysis with appropriate imputation of
missing values.

Randomisation
At time of manufacture the mode of active / sham laser operation has been hardwired
into each machine producing a sequence of 100 numbers (from 00 to 99). Within this
sequence 50 code numbers will correspond to active laser and 50 to sham, pre-set in a
random manner. This sequence will be sent to an independent person who will
produce the concealed allocation sequences for each machine (using block
randomisation) by using random number lists generated by a computer.
To examine the dose response of LA will require 3 treatment arms.
The treatment arms will consist of-
1. Laser ‘on’ with 10 seconds stimulation given per point
2. Laser ‘on’ with 40 seconds stimulation given per point
3. Laser ‘off’ with 10 or 40 seconds stimulation given per point
The sequence of original 100 code numbers for each machine will be randomised
using blocks of 6 with each of the three treatment arms represented equally in each
block.
 ie each block of 6 will receive-
2 participants: Laser ‘on’ with 10 seconds stimulation
2 participants: Laser ‘on’ with 40 seconds stimulation
1 participant: Laser ‘off’ with 10 seconds stimulation
1 participant: Laser ‘off’ with 40 seconds stimulation
This will produce a sequence of about 72 consecutive entries for each machine
consisting of (ID No - code no - time)
Neither participant nor therapist will know the status of the code (on or off).
Concealment of treatment allocation

Consecutive allocation sequence for each machine will be placed in 72 consecutive opaque sealed envelopes. The outside of the envelope will be labelled with an ID No. (1 to 72) and the serial number of the machine. A slip containing (ID No, code number, time of stimulation) will be sealed within corresponding envelope. A box with the 72 sealed envelopes for a specified machine will be safeguarded with reception at the premises where trial will be run.

After assessment interview when a participant becomes enrolled into the trial, the consent form signature will be witnessed by a reception staff member who will allocate the next envelope in the sequence to the involved therapist. The therapist will open the envelope and mark on file and notes the allocation number (ID No.), the switch code number and duration (10 or 40 sec) of treatment for point to be used per point each time the subject is treated.

Blinding

The participants, and the therapist administering treatment will be both blind to the mode of laser intervention although they may be aware of duration of stimulation. No specific mention to participants will be made that different durations of stimulation of points between participants will be undertaken.

In the explanatory statement given to each participant it will be stated that 'there is little evidence to support one dose of laser over another however this research trial will address an answer to this question'.

The laser probe has a translucent Perspex flat truncated conical tip, a visible light emitting diode red decoy light issuing from the tip, and a timing beep is produced each time the unit is operated regardless the mode of laser production. The decoy light prevents the detection of a 'laser diode glow' which could allow identification of the mode of operation. The statistician / analyst will also remain blind to the on / off settings and duration of stimulation till the analysis is completed.

Sample size

For a 3 parallel arm study- (using SD =2.3 at follow up found in my previous study) with power = 0.8 and significance level $\alpha = 0.05$ for ANOVA

(i) To detect a difference of 1.6 VAS units (moderate effect size), need group size of 41 and a sample size of 137 allowing for 10% dropouts

(ii) The corresponding figures for a difference of 2.0 VAS units (large effect size) are a group size of 27 and a sample size of 90 with 10% dropouts.

If the standard deviation of the treatment groups at follow up in this trial is less than 2.3 or looking for an absolute difference between groups of 2.0 (MCSD according to Farrar 2001), a smaller sample size should be possible.

Statistical analysis:

Coded data would be entered directly on a spread-sheet of SPSS software for statistical analysis.

Outcomes of the intervention groups would be compared using ANOVA. Multiple regression analysis will be used to determine predictors of outcome. Adjusted analysis will be performed using ANCOVA
OUTCOMES AND BENEFITS OF RESEARCH

This research is setting out to confirm that laser acupuncture has a specific and clinically significant effect in relieving pain and disability in patients with chronic non-specific back pain.

LA which has the benefits of being non invasive and free of pain or adverse effects is commonly used by GP’s in Australia. LA is claimed to be as effective as needle acupuncture by its proponents, however the machines are expensive and require registration and licensing of operators for lasers greater than 5mW in power. As evidence for this modality of treatment is still lacking it is hoped this research will contribute to systematic reviews on this topic and guide medical practitioners. If results are positive it would support the use of LA in chronic LBP which is commonly seen in general practice and is resistant to other forms of treatment. It will also encourage research into the basic physiological mechanisms of this treatment.

If negative, further research will be needed on which laser parameters could be effective in pain reduction or alternatively suggest less expensive means of applying an acupuncture stimulus such a needles.

References:

Appendix G

RECRUITMENT NOTICE-

Notice in Community Newspaper seeking volunteers for laser acupuncture research.

Currently volunteers suffering from chronic low back pain are sought to participate in a clinical trial run at a medical centre in [          ]

Selected adults under 75 years of age with less severe persistent lower back pain may be eligible. Patients who currently use regular very strong pain killers, have back pain which is related to a work or motor vehicle injury, have had previous low back surgery procedures or injections, or who had acupuncture in the last 6 months will not qualify. Eight weekly treatments using laser acupuncture will be provided free of charge and will involve some follow-up by mail to determine if improvement after treatment is prolonged over the course of a year.

If you are interested please contact 9403 2399 for more information.
Appendix H

COPIES OF OUTCOME INSTRUMENTS USED IN STUDY

(i) Numerical rating scale for pain (NPRS)
Please circle a number on the box scale, which describes your usual level of back pain in the last week.

| No pain | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
---|---|---|---|---|---|---|---|---|---|---|
Worst pain imaginable

(ii) Oswestry Disability Index Version 2.0 (Revised Oswestry Disability Questionnaire with MRC modification) * metric form in section 4

(iii) Numerical Limitation of Activity Rating Scale
Please circle a number on the box scale, which describes how much your pain has limited your ability to perform your usual activities in the last week.

| No limitation of usual activities | b | Complete limitation of usual activities |
---|---|---|
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

(iv) Global assessment of treatment question (GA)

Compared with before you commenced the laser treatment program, please now indicate overall how your low back problem has changed (tick box):

- [ ] Very much worse
- [ ] Much worse
- [ ] Minimally worse
- [ ] No change
- [ ] Minimally improved
- [ ] Much improved
- [ ] Very much improved

(vi) The short version of Depression Anxiety Stress Scale (DASS-21)

(vii) Adverse effects during course of treatment (Participant to self administer at start of treatment sessions 2 to 8, and one week after completion of treatment)
**Adverse effects after last treatment** - Did you notice any of the following symptoms occurring in the week after your last treatment?

**Please tick if present**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>None</th>
<th>Low-back pain flare-up following last treatment</th>
<th>Lasting &lt; 24 hrs</th>
<th>Lasting &gt; 1 day</th>
<th>At another time during the week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiredness</td>
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<td></td>
</tr>
<tr>
<td>Increased stiffness</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Headache</td>
<td></td>
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<td></td>
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<tr>
<td>Nausea</td>
<td></td>
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<td></td>
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<tr>
<td>Dizziness</td>
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<tr>
<td>Fainting</td>
<td></td>
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<tr>
<td>Anything else noticed? --Please list:</td>
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</tbody>
</table>

(viii) Analgesic use (please tick box or write response in specified area)

Note: analgesics are pain killing medications eg paracetamol, anti-inflammatories (eg Nurofen) or combinations of these

**i)** How often have you used analgesics in *(specify period)*

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Nil</th>
<th>&lt; once</th>
<th>1-3 times</th>
<th>once</th>
<th>several times</th>
<th>daily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>a week</td>
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</table>

(specify no. of tablets........)

(ii) For which symptoms have you taken analgesics in the past week

- Back pain
- Headache
- other pains *(specify……………………………)*

(iii) Which analgesics have you used during the past week either prescribed by a doctor or without prescription? *(Please list the names of these)*

(iv) Your current use of analgesic (pain killing and anti-inflammatory) medications compared to that before starting the laser acupuncture treatment is-

- Decreased
- Unchanged
- Increased
Appendix I

(a) EXPLANATORY STATEMENT

EXPLANATORY STATEMENT
(This information sheet is for you to keep.)

A clinical trial to examine the effectiveness of laser acupuncture for chronic low back pain  (Project no RA/4/1/2057)

What is the purpose of this research?

This research is part of a PhD I am conducting to find out if acupuncture using laser instead of needles may help relieve back pain. It may also determine if there is a laser dose which is optimum. There are few answers to these questions based on current research in this field. The findings of this project may increase the options for medical treatment of chronic low back pain in our society.

Why were you selected to possibly participate in this project?

This project is examining people who have had low back pain for greater than 3 months. You would not be eligible to participate in this study if you are under 18 years or over 75 years of age, are pregnant, your pain has been associated with an insurance case or workers compensation, are on strong regular pain killers, or have had previous low back surgery or some other interventions such as blocks or epidurals for your pain. There may be other reasons you may be excluded which will be explained at the assessment visit.

Possible benefits

It is hoped to show that laser acupuncture treatment will reduce your level of pain and help you to function better in your daily living. We are looking for an improvement rather than a cure. You will have a two in three chance of receiving an active laser beam for the course of your treatment. However it has been shown from previous studies that just by participating in the trial will often also result in an improvement of your back condition for various reasons which may not depend on activity of the laser.

What does the research involve?

The study involves attending a GP surgery close to where you live for up to 8 weekly visits. Doctor will assess your condition in detail on the first visit and also determine if you qualify to for the study. Please also bring your x-rays or scans if they are available. If you qualify for the study and agree to participate you will be asked to fill out a number of questionnaires and sign an informed consent form. The simple questionnaires concern how your back or leg pain affects your ability to manage in everyday life, on your current psychological and level of physical activity. In all they will probably take a total of 5 -10 minutes to complete.

In some cases where the diagnosis is unclear the doctor may order some more tests or refer you back to your GP for these tests, before a decision to enrol you in the trial is made. You will then attend weekly and on each visit doctor will review you, and apply a low dose laser device to a number of carefully selected acupuncture points in the region of your pain, on your limbs and elsewhere for short period of time. At the last visit you will be given a questionnaire on the progress of your condition a week after completion of treatment, for you to return by post in a reply paid envelope.
It has been noted that the improvement with acupuncture can be prolonged. A brief survey will also be sent to you 6 weeks, 6 months and 12 months after completion of treatment. Please send these forms back in the reply-paid envelopes which will be provided.

For the purposes of this research, at the start you will be randomly divided into several groups. You will have a 2 out of 3 chance of receiving the active laser treatment. As this is a “double blind” study neither you nor the doctor will know if you will be receiving an active or inactive laser treatment.

How much time will the research take?
It is estimated that the initial assessment will take 30-40 minutes. The subsequent appointments will be scheduled for 15 minutes. The follow up surveys will take a very short time to complete. There is easy parking at the surgeries where the study will be conducted, and appointments will be planned to run on time. Please try to be punctual at your appointments for this to occur.

Will this affect your normal treatment?
It is requested that during the period of treatment you do not start any new treatment for your back condition if possible. During the 12 month follow-up I request that you do not undertake any other acupuncture treatment. Please maintain normal contact with your usual GP.

Inconvenience/discomfort?
Any side effects are very uncommon after laser acupuncture. This is a light device and does not produce any radioactivity. It causes no pain or discomfort when points on the skin are stimulated.
This low powered laser device has a risk of causing eye damage if shone directly into the eye. To make this risk minimal the laser will only be operated when in direct contact with the skin when stimulating points, you will be instructed not to look directly into the beam, and protective glasses will be worn as an extra precaution during each treatment. All doctors who perform treatment in this trial have undergone a laser safety course and are licensed with the Health Department of WA for use of this device.
It is unlikely, but if you should become very distressed for any reason or develop some unforeseen problem while participating in this trial I would suggest that you notify me (see contact details below). I will arrange referral to your own GP or elsewhere, or withdrawal from the trial if appropriate.
Please feel free to discuss anything about treatment with the treating doctor or Dr Glazov.

Payment?
As this is research, we are not allowed to claim from Medicare for your visits and treatment will be conducted free of charge to you.

Can I withdraw from the research?
Being in this study is completely voluntary - you are under no obligation to consent to participation and you may withdraw at any stage, or avoid answering questions which are felt to be too personal or intrusive. Withdrawal from the trial will in no way affect your subsequent treatment by your own doctor.
However we would encourage you to attend until the end of the trial as the effect of acupuncture often develops gradually. Your full attendance will also really help us to draw valuable conclusions from this research.

Confidentiality / results
All aspects of the study, including results, will be strictly confidential and only the researcher will have access to information on participants. To maintain confidentiality your data will be
identified by a code number so you will remain anonymous during analysis of results. No findings which could identify any individual participant will be in any publication of the study results. Please keep in mind that it is impossible to make an absolute guarantee of confidentiality/anonymity. All information provided is treated as strictly confidential and will not be released by the investigator unless required to do so by law.

Storage of data
Storage of the data collected will adhere to the university regulations and will be kept secure for 5 years after the end of the trial and will then be destroyed. A report of the study will be presented at meetings and submitted for publication, but individual participants will not be identifiable in any such reporting.

The Investigators and therapists
This research is a project by Dr Greg Glazov (General Practitioner and Research Fellow within School of Primary, Aboriginal and rural Health Care UWA) and is supervised by Professor Jon Emery, Head of Department of General Practice UWA, and Associate Professor Michael Yelland of Griffith University, Queensland. The treatment will be conducted by qualified practising GP’s who are also members of the Australian Medical Acupuncture College.

Queries / results?
If you have any queries please contact Dr Glazov (see below). If you wish to be informed which treatment group you were in, and a summary of the results of this research, please notify me in the follow up assessment. I will mail this information to your contact address or email after the study is completed.

What if I have a complaint?
Should you have any complaint concerning the manner in which this research (Project no RA/4/1/2057) is conducted, please do not hesitate to contact:

<table>
<thead>
<tr>
<th>Human Research Ethics Committee Research Services</th>
</tr>
</thead>
<tbody>
<tr>
<td>The University of Western Australia</td>
</tr>
<tr>
<td>35 Stirling Hwy, Crawley, WA 6009</td>
</tr>
<tr>
<td>Telephone 08 6488 3703, Facsimile 08 6488 8775</td>
</tr>
<tr>
<td>Email <a href="mailto:kkirk@admin.uwa.edu.au">kkirk@admin.uwa.edu.au</a></td>
</tr>
</tbody>
</table>

Yours sincerely,

Dr Gregory Glazov  MBBS, MFM,
(FAMAC) Fellow of Australian Medical Acupuncture College
Practice telephone number- Hillarys Medical Centre (Wednesday to Friday)
Telephone:  9 403 2399 (reception will contact me as required).
Email: glazog01@student.uwa.edu.au
(b) Consent Form

**Consent Form** for involvement in research -

NOTE: This consent form will remain with the researcher for his records but you will receive a copy.

**Title:** Multi-centre double blind randomised controlled clinical trial to examine the efficacy and dose dependence of a 830 nm, 10 mW laser diode for the laser acupuncture treatment of chronic non-specific low back pain. (Project no. RA/4/1/2057)

I agree to take part in the research project specified above. I have had the project explained to me, and I have read the Explanatory Statement, which I am to keep for my records.

I understand that agreeing to take part means that I am willing to:

- Be interviewed and have a simple examination by the researching doctor
- Bring old x-rays or scans on your initial visit. Some tests (radiology or blood tests) may be ordered, or you will be referred back to your GP for this to be done, if there is concern about the cause of your pain.
- Return for up to 8 treatment sessions with laser acupuncture as explained by the researcher.
- At each visit during the treatment period, fill out a simple scale to indicate your level of pain, and tick some boxes if you experience any adverse effects.
- Complete questionnaires at baseline, during the course of treatment, and follow up after end of treatment: 1 week, 6 weeks, 6 months and 12 months (addressed stamped envelopes will be provided).

and

I will be randomly allocated to be in a group either receiving active laser or placebo (inactive) laser treatment

and

My participation is voluntary, that I can choose not to participate in part or all of the project, and that I can withdraw at any stage of the project without being penalised or disadvantaged in any way.

and

That any data that the researcher extracts from the interview/questionnaire for use in reports or published findings will not, under any circumstances, contain names or identifying characteristics.

and

That any information I provide is confidential, and that no information that could lead to the identification of any individual will be disclosed in any reports on the project, or to any other party.

and

That data from the study will be kept in a secure storage and only accessible to the research team. I also understand that the data will be destroyed after a 5 year period.

Name of Participant: 
Signature: 
date: 

Name of Witness: 
Signature: 
date: 

Dr Gregory Glazov MBBS, MFM, (FAMAC) Fellow of Australian Medical Acupuncture College

**Practice telephone number** Tel 9 403 2399 Hillarys Medical Centre (Wednesday to Friday)
Appendix J

The laser acupuncture intervention
(from folder given to the therapists- “Laser Acupuncture for Chronic Low Back Pain Manual for Therapists”)

At the start of each treatment session greet the patient, and enquire ‘how have you been?’

- Ask the patient to circle a number on the box scale which described their usual level of back pain
- Ask patient on adverse effects during week after last treatment, and therapist to tick in relevant box in adverse effects section.
- Ask patient where there pain is located today and therapist to shade the reported area(s) on body diagram
- Also enquire if other symptoms eg. headache, other joint pains etc. are present.

(a) Acupuncture treatment

Treatment based on principles from (Medical Acupuncture MFM 1018: a course offered by Department of Community Medicine and Family Practice. Faculty of Medicine, Monash University 1998)

Treatment is individualised to each patient and over time across sessions.

Start treatment by positioning patient on examination couch, being guided by the distribution of their back pain. Position on their side with worst side uppermost (or if back pain is symmetrical, position in prone position).

- (i) Locate tender points by firm digital pressure in the area of pain – these will often be acupuncture points (midline over GV meridian, or more laterally over inner or outer lines of BL meridian , or over GB meridian). Tender points may extend along meridian as far as knee or more distally. There may be other tender Extraordinary points or unclassified tender points (Ahshi) which may be located and used. Useful local points are indicated in section (b)

It is suggested to mark the tender points lightly with a provided skin marking pen as they are located. Then treat each point sequentially with the laser probe.

- (ii) You may then treat some distal points meridian points eg. GB34/41 or BL60/62 to reinforce the effect, or at initial sessions.

- (iii) Often on taking original history or depending on other current symptoms you may also want to add some other points eg. for depression, headache or neck-ache, abdominal symptoms etc. Use major points or local points for these conditions eg. LI4, 11; TE5, PC6, GB20, 21; ST36; SP6; LR3; KI3; GV14 etc.

When treating points in (ii) and (iii), patients may remain recumbent or may be seated. Locate them by palpation in your usual way and then treat as each point is found (without skin marking) with the laser.

Hold laser pointer perpendicular to the skin with the point in contact with skin but with minimal pressure and little indentation on skin surface.

Please mark all points used on shorthand diagram immediately after treating patient

1. Circle main classical points on diagram
2. Name all other meridian points and Extra points used not included on diagram
3. Number of other Ahshi points at locations stated

This information will be useful
   a. As a memory aid for you to use in treatment
   b. In analysis phase of trial to quantify total number of points used per session and
      provide data on the actual meridians and acupuncture points used.

**General guidelines for treatment chronic-LBP participants in this trial**

This trial is selecting a subgroup of less severe patients and without fibromyalgia, and using
laser acupuncture for which less pain reactions may be expected.

An approach is to work in periphery initially then add more points from week to week
including tender points at site of pain such as over SIJ (BL26-28) depending on response.

Distal points which may be effective are BL62, BL2, BL40, BL11 (influential point for
joints), GV14 and other classical or tender points along GV meridian including thoracic
region.
For pain treatment may use LI4, ST36, SP6 or ST44 (specifically for leg pain)

May combine SI3 with BL62 on side of pain for more difficult cases.

If depression/anxiety/stress may use LR3 ± (LI4, PC6, HT7 or GV15)
High scores on baseline DASS may help you to decide on using these points.

Distal points usually unilateral on the side of pain if asymmetrical unless-
   (a) after reaction try contralateral point
   (b) if wanting to reinforce effect in later sessions may try bilateral

Suggest keep to a maximum of 10 - 12 points per session (including bilateral). Note in
previous trial an average of 8 points were used per session.
Patients will be receiving 10 or 40 seconds stimulation per point. As a general rule try to
keep the total number of points the same during a session regardless of the stimulation time.

There is expected to be different approaches used in treating patients between therapists
however try to keep to the above general guidelines.

Occasionally a patient may report a marked exacerbation of pain following the previous
treatment. This may be due to be in a strong responder or a very sensitized patient. Possible
strategies to deal with this at the following treatment-
   (i) be gentle with palpation in locating tender points
   (ii) use fewer treatment points
   (iii) use distal or contra-lateral points away from the local area of pain
   (iv) in the case of subjects allocated 40 seconds stimulation may reduce
      the duration to 20 seconds per point (indicate this on the treatment sheet
      if this is done).
Regional points commonly used in low back area

**Posterior**
- GV4
- GV3
- GV2 sacral hiatus
- BL inner line (1.5 cun or less from midline)
  - BL21-27

**BL outer line**
- 3 cun from midline
  - BL50 (T12)
  - BL51 (L1)
  - BL52 (L2)
  - Yaoyi (L4)

BL28 level with S2 posterior foramen
BL32 (over S2 posterior foramen)

BL33 (over S3 posterior foramen)
BL34 (over S4 posterior foramen)
BL35 0.5cun lateral to tip coccyx
BL36 in transverse gluteal fold

**Lateral points**
- LR13 on lower border free end 11th rib
- GB25 on lower border free end 12th rib
- GB27, 28 (tender points near ASIS)
- GB29
- GB30
- GB31, 32

**Extra points**
- Huatuo Jiaji - 0.5 cun lateral to lower border of spinous process from T1 to L5
- Shiqizhui - below spinous process L5
- Yaoyi - on outer bladder line level with lower border L4
- Huanzhong midway between GB30 and GV2

Any other Ahshi points (including points around lower costal margin, along iliac crest, in buttock area and over greater trochanter)
### Appendix K

Acupuncture Meridians and Points used in Laser Acupuncture Study

<table>
<thead>
<tr>
<th>Meridian or other type of point</th>
<th>GV</th>
<th>BL</th>
<th>GB</th>
<th>LR</th>
<th>Other meridians</th>
<th>Extraordinary points</th>
<th>Ahshi points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of total points used</td>
<td>13</td>
<td>37</td>
<td>13</td>
<td>6</td>
<td>10</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Most frequently points used</td>
<td>3, 4, 5, 6, 7, 14, 15</td>
<td>2, 22, 23, 24, 25, 26, 27, 28, 29, 30, 36, 40, 41, 51, 52, 53, 54, 57, 60, 62</td>
<td>20, 21, 25, 26, 28, 29, 30, 31, 32, 34</td>
<td>3, 13</td>
<td>LI4, 11, 15, ST 36, 31, SI3, PC6, KI3, SP4, 6, 9, 10</td>
<td>Huato Jiaja(^a), Yaoyan(^b), Shiqizhui(^c)</td>
<td>over-iliac crests, costal margins, gluteal muscles, greater trochanters and other interspinous spaces not corresponding with GV points</td>
</tr>
</tbody>
</table>

---

a. A group of points on each side of the spinal column at the lateral borders of each spinous processes from 1\(^{st}\) thoracic to 5\(^{th}\) lumbar vertebra

b. In depression lateral to interspaces between spinous processes of 4\(^{th}\) and 5\(^{th}\) lumbar vertebra

c. In depression below spinous process of 5\(^{th}\) lumbar vertebra

Appendix L


BACKGROUND

Description of the condition-
Low back pain (LBP)\textsuperscript{1,2} is defined as pain, muscle tension, or stiffness localized below costal margin although some definitions include pain situated from below the shoulder blades\textsuperscript{3}) and above inferior gluteal folds, with or without leg pain. The pain is chronic if it persists for 12 weeks or more.
Low back pain is ‘non-specific’ if is not attributed to (1) specific spinal pathology (e.g. infection, tumour, osteoporosis, fracture, structural deformity, inflammatory disorder (eg. ankylosing spondylitis) or (2) neurological encroachment (radicular or cauda equina syndrome)\textsuperscript{2}

The lifetime prevalence of low back pain is up to 84%.
After an initial episode of LBP, 44-78\% people suffer relapses of pain occur and 26-37\%, relapses of work absence. There is little scientific evidence on the prevalence of chronic non-specific low back pain: best estimates suggest that the prevalence is approximately 23\%; 11-12\% population are disabled by low back pain.
Specific causes of low back pain are uncommon (<15\% all back pain)\textsuperscript{2}
Low back pain is a major health problem in western industrialized countries and a major cause of medical expenses, absenteeism and disablement\textsuperscript{4}.
Back pain is a frequent cause of patient visits to physicians. Patients with back pain comprise at least 5\% of all presenting problems in Australian general practice, and 6.5\% in Britain\textsuperscript{6}. Based on a Beach survey back pain was the 8\textsuperscript{th} most frequent condition seen in Australian GP.
An Australian telephone survey in 2005\textsuperscript{5}, showed that back pain was the most common medical condition treated by acupuncture. There was no information on the form of acupuncture used, and medical practitioners provided a minority of these treatments.

2. European Guidelines for the Management of chronic non specific low back pain. Ammended Version June 14th 2005
3. Acute and chronic low back pain. Effective Health Care 2000;6(5)

Description of the intervention-
Low-level laser therapy (LLLT) is a light source treatment that emits no heat, sound, or vibration. Instead of producing a thermal effect, LLLT may act via non-thermal or photochemical reactions in cells\textsuperscript{1,2}. Laser acupuncture (LA) which is low- level laser stimulation of points using laser emitter devices applied to skin as an alternative to needles, has been commonly used in the last 35 years. Although LA can be considered as a subgroup of LLLT, it is a separate form of treatment. Instead of using
the direct effect of light on tissues to initiate a physiological response, selection of points is based on a diagnostic and therapeutic paradigm defined in acupuncture theories. A previous Cochrane systematic review on LLLT in chronic LBP excluded studies involving LA. Some reviews have classified studies applying low intensity laser radiation to trigger points or other tender points as LA even when no reference to acupuncture or its principles is made in the study report. Laser acupuncture and other laser therapy often irritate similar points on body surface for treatment which makes it difficult to distinguish between LA and non-LA LLLT using this definition. This review avoids this problem by stipulating that an intervention is LA only if the authors explicitly describe use of acupuncture principles for point selection.

Different laser devices have different wavelength range from visible to infrared spectrum) and radiant power output (mW). Dose (J) of laser stimulation per point and energy density (J/cm²) can also be varied. There is controversy on which parameters of LLLT are most effective and if these are different in LA. It has been considered that smaller doses are effective in LA.

LLL and LA have been promoted because they are pain free, non-invasive with no risk of damage to organs or spread of blood borne infection, and can be used in stimulation of difficult points.


How the intervention might work- In the past there has been criticism that the effect of laser therapy in painful conditions was only a placebo. There is still lack of an obvious mechanism particularly given lack of sensation during laser treatment.

However there is evidence of LLLT inducing anti-inflammatory, anti-nociceptive (block sensory nerves), spasmodyptic effects (reduction of muscle spasm), and effects on lymphatics with reduction of interstitial swelling [references will be provided]. Another area of research involves the investigation of the effects of peripheral laser stimulation on changes in the brain demonstrated by imaging (f-MRI).

Parameters of the laser such as wavelength and radiant power output and dosage, which affect depth of penetration and other factors, are likely to influence biological effect on tissues (Chow et al. Lancet 2009, Baxter et al, 2008). The World Association of Laser Therapy recommends some dosage parameters but more research in physiological and clinical studies are required. Consideration of laser parameter used in treatment is important in drawing conclusions from systematic reviews in this field.

Why it is important to do this review—
Chronic low back pain (LBP) is of great importance in terms of (a) prevalence, and (b) disability, medical expenses and loss of productivity. With the conduct of larger, higher quality clinical trials in this area, evidence is now supporting the effectiveness of acupuncture in trials of needle or electro-acupuncture for chronic LBP, at least in the short term (2005)\(^1\). A systematic review (2007)\(^2\) examining controlled trials of laser therapy in chronic nonspecific LBP showed “a small effect on pain intensity” if applied to painful areas in patients suffering chronic pain from this condition. This trial excluded studies involving LA. Systematic review (2008)\(^3\), LA in orthopaedic diseases stated positive effects can be assumed in myofascial pain syndromes of the neck, back and shoulder but recommended that better designed studies with higher power should be performed. Systematic review (2009)\(^4\) on clinical effectiveness of LA in various conditions found moderate evidence that it is effective in reducing myofascial pain. This review found that laser doses of over 0.5 Joules per point may be required. Control interventions in this review included not only sham laser, but also no treatment, other sham procedure or other therapeutic procedure.

A recent systematic review of LLLT focusing on chronic LBP has not been performed and has previously not included studies using laser acupuncture as a primary intervention.

It was thus decided to perform an updated systematic review on effectiveness LLLT including LA in chronic LBP. As a principal aim was to determine if laser stimulation modality has a specific effect in producing improvement in this condition; only studies using sham laser as a control intervention would be included. A subgroup analysis also would compare (i) differences between LA and non-LA LLLT and (ii) laser dose dependence of treatment.

OBJECTIVES

- To systematically evaluate the evidence for a specific effect from LLLT in treating chronic low back pain.
- To compare effectiveness of LA versus non-LA approaches of LLLT in treating chronic low back pain.
• The review may also determine if the specific effect if it exists, depends on laser parameter (dose per point, energy density, wavelength), treatment parameter (number of treatments, duration over which treatment given, number of points used per session), as well other at this stage undefined baseline characteristics in participants.

METHODS

Criteria for considering studies for this review:
(criteria considered important in selection process indicated *)

Types of studies-
*Randomized controlled trials with blind assessment of the outcome
Published in peer reviewed journal
or other publications - conference proceedings, theses,
no language restriction

Types of participants-
Adults of both sexes ≥ 18 yrs old who have *chronic non- specific low back pain.
(A) Primarily considering chronic LBP = pain for longer than 12 weeks (a decision will be made whether to include trials studying subjects with sub-chronic pain (6-12 weeks)). (B) Trials examining patients with LBP due to specific pathological entities are excluded. These include: (1) specific spinal pathology (e.g. infection, tumour, osteoporosis, fracture, structural deformity, inflammatory disorder (eg ankylosing spondylitis) or (2) neurological encroachment (radicular or cauda equina syndrome).

Trials including subjects with spondylolysis and spondylolisthesis, or scoliotic deformities are also classified as ‘non –specific’ unless they have features such as neurologic encroachment, and are not excluded.

Trials which also examine LLLT for general musculo-skeletal disorders are included, if separate analysis is reported for low back pain.

Types of interventions-
The following interventions are included if-

(i) *LLLT (including Laser Acupuncture (LA) is used as primary intervention.
Laser Acupuncture is defined the application of low intensity laser to classical acupuncture points, other tender points or trigger points with selection of points based on application of acupuncture concepts, and this is explicitly stated in the report. All other included studies are classified as non-LA LLLT.
(ii) any types of laser classes 1-3 (up to 500 mW[0.5W] power)
Note: some higher power output pulsatile devices with a short duty cycle which may be called ‘HILT’ may not produce an obvious thermal sensation in subjects: a decision will be made whether to include such trials as LLLT in this review.
(iii) any laser wavelengths
(iv) *comparison intervention is a sham laser
(v) the laser irradiation device may be a laser pointer or “laser needle” apparatus or other device designed for laser therapy
(vi) *exclude crossover trials (flawed as carry over effect is present with acupuncture)
(vii) *exclude non-laser light therapy
(vii) trials with co-interventions will be included as long as same the co-interventions used in active and sham laser groups.

Types of outcome measures-

**Primary outcomes:**

*Pain and/or disability will be considered as the most important measure of efficacy in this systematic review.*

i. *Low Back Pain measured by Visual Analogue Scale, Numerical Pain Rating Scale or other validated quantitative measures.

ii. Low back related disability measured by the Oswestry disability questionnaire, Roland –Morris disability scale or other validated quantitative measures.

*Time frame for primary outcome will be immediate or short-term

**Secondary outcomes:**

Global measures on overall improvement of satisfaction with treatment
Health related QOL
Adverse effects, medication use
Return to work, days of work lost etc.
Physical examination measures
Low back pain and related disability at other time frames*

*Time frames defined as
(i) immediate; (within 1 week of completion of treatment)
(ii) short-term; (4-12 weeks after completion of treatment)
(iii) intermediate-term; (closest to 6 months after completion of treatment)
(iv) long-term; (closest to 1 year after completion of treatment)

Search methods for identification of studies-

A computer-aided search was conducted for RCT’s which examined the use of laser therapy or laser acupuncture (intervention) in (the condition) of chronic low back pain where the control was a placebo (sham) laser. The search was based on the combination of text words or phrases found in the title or abstract, and keywords (controlled vocabulary) indexed by the databases.

Updated Search Strategies for Cochrane Back Group (Jan2013) were used with (A) Generic Search for randomized controlled trials and controlled clinical trials, together with(B) Specific Search for back conditions( thoracic, low back, sacrum and coccygeal problems). Strategies were available for Medline (OVID), EMBASE (OVID), CINAHL (EBSCO) and CENTRAL (online Cochrane Library). A generic search filter for RCT and CCT was not required for Central.
A search using terms related to the intervention was performed -

(i) A controlled vocabulary (exploded) for the key words- Lasers, Laser Therapy or Laser Therapy (Low Level) was performed. (ii) Synonyms for the intervention used as text words were: “Laser acupuncture”, “Low-level/intensity/energy/reactive level/power/incident/output laser”, “high intensity laser”, “infrared/HeNe/GaAlAs/GaAs/Nd YAG - laser”, ”phototherapy”, ”light therapy”, “narrow band light therapy”, “laser needle”, LLLT, LILT, LELT, LELI, LPLI, HILT, photobiostimulation, photobioactivation, photobiomodulation, laser stimulation/irradiation, 904 nm, 830 nm, 630 nm, 1064 nm

Electronic searches-

Bibliographic databases:

These databases all have links from the Medicine Libguide UWA

(1) Cochrane Central Register of Controlled Trials
(2) Medline, PubMed
(3) EMBASE
(4) CINAHL
(5) AMED (Online)
(6) PEDro the physiotherapy evidence database
Screening references given in relevant reviews and identified RCT’s

Searching other resources-

If time permits other resources may be searched-

Chiropractors: MANTIS
Google Scholar
Dissertation and Theses database
Trial registers
Grey literature databases
Search of conference proceedings eg ICMART, WALT
Citation tracking of identified RCTs and reviews in:
Science Citation Index
Google Scholar may also be useful.
Specialist laser therapy and acupuncture journals may not be included in mainstream databases eg Laser Therapy, Laser Surgery Medicine, Helms Medical Institute: www.hmi.acupuncture.com
(Acubriefs)

Contact of experts for advice on resources to search.
Data collection and analysis

Selection of studies-

The titles and abstracts obtained as hits from the electronic data base searches will be examined to remove obviously irrelevant studies (GG). Duplicate reports of same study will be removed. Full text will be retrieved and will read independently by GG to perform a preliminary selection of trials satisfying eligibility criteria. GG will attempt to correspond with principal investigators if there is need to clarify eligibility or request further information.

Data extraction and management-

Reviewers will extract data from selected studies on a common electronic data collection form (adapted from Cochrane Back Group). The reviewers will not be blinded to authors or journals of publication.

The form will be designed and will be pilot tested by GG

Data will be obtained for:

Source- study/report/ reviewer ID, citation and contact details

Eligibility- confirm eligibility (randomised trial with sham laser control with blind assessment of outcome)
(Participants with chronic non-specific LBP)
(control is sham/placebo laser)
Primary outcomes are pain or disability (immediate or short term) or another appropriate validated continuous or categorical outcome in this time frame or reason for exclusion

Methods- study design, total study duration and date, sequence generation, allocation concealment and details of blinding, other concerns about bias

Participants- total and treatment group numbers, recruitment and setting, age, sex, duration pain comorbidity, social-demographics, country/ ethnicity, diagnostic- inclusion/exclusion criteria

Interventions-

- laser machine characteristics- semiconductor, model, parameters- wavelength, power, spot size, continuous or pulsed, and dosages (will be calculated according to data available in articles or investigators contacted)
- total number of arms of trial
- description of laser treatment parameters- energy density, power density, energy dose per point, duration point stimulation
- description of sham laser control
- description of co-interventions if present
- description of treatment regime- total number of treatments, frequency of treatment, site of points or fields irradiated

Outcomes-

Outcomes and time points
For each outcome of interest-
- Outcome definition.
• Unit of measurement
• For scales: upper and lower limits (specifying if high or low is ‘good’)

Results-
No. of participants allocated to each intervention group
For each outcome of interest:
• sample size,
• missing participants
• summary data for each intervention group (eg 2 by 2 table for dichotomous data; means and SD for continuous data)
• estimate of effect with CIs; p-value
• subgroup analysis

Miscellaneous-
• funding source
• key conclusions of study author
• miscellaneous comments from study authors
• references to other relevant studies
• correspondence required
• miscellaneous comments from review authors

GG will extract all data, JE and MY will each extract half of trials. Independent extractors will deal with trials with authorship by GG or supervisors. Disagreements will be resolved by consensus.

Assessment of risk of bias in included studies-
The Cochrane Collaboration tool for assessing risk of bias (methodological quality) will be used for each included study to evaluating the 12 domains of bias. Reviewers judgements will be categorised for each domain as high, low, or unclear risk of bias. Attempt will be made to contact author if assessment is unclear.

(1) Selection bias- (i) random sequence generation, (ii) allocation concealment, (iii) group similarity at baseline
(2) Performance bias- (iv) blinding of participants (v) blinding treating personnel, (vi) Compliance and (vii) co-interventions
(3) Detection bias- (viii) Blinding of outcome assessment, (ix) timing of outcome assessments
(4) Attrition bias- (x) incomplete outcome data, (xi) use of ITT analysis
(5) Reporting bias- (xii) selective reporting
(6) Other sources of bias concerns about bias not addressed in other domains of tool

GG will assess bias in all data; JE and MY will each assess bias in half of trials. Independent extractors will be contacted to assess bias in trials with authorship by GG or supervisors. Disagreements will be resolved by consensus. Studies with at least 6 of 12 CBRG domains rated by reviewers as low risk of bias categorized as “low risk”.
Measures of treatment effect-
For continuous data (pain intensity, disability, ROM) mean difference (MD) will be used to measure treatment effect with 95% CI s. In case of outcome measures with different scales will use standard mean difference (SMD) with 95% CI s. Dichotomous data will be converted to RR risk ratio with 95% CI s.

Unit of analysis issues-
Will include data from parallel-group studies for meta-analysis. Different pain measurement scales (VAS and NPRS) will be changed to a scale of 0-10cm for analysis. We will subdivide data for multiple time point observations into immediate, short term and long term follow up, to perform separate analyses. Consideration will be made if there are more than two intervention groups in some included studies.

Dealing with missing data-
All available data will be used from located studies for statistical analysis. Some studies would have used ITT or imputation methods. We will contact authors of the studies if there is missing or unreported data from trials. Calculations may be used to derive some missing data.

Assessment of heterogeneity-
In this review we are considering only chronic n-s LBP, but this still represents a variable population of patients, and a variety of interventions under the heading of ‘LLLT’, which would reflect clinical heterogeneity. Only sham laser controls will be considered.
It is considered that meta-analyses conducted on subgroups of interventions eg LA versus non-LA LLLT may explain heterogeneity of results across trials. A random-effects model will be used.
Assessment of heterogeneity will be made by inspection of forest plots, the chi-squared test and the $I^2$ statistic.

Assessment of reporting biases-
Publication bias and other reporting bias in this review may be addressed by funnel plots (if results from at least studies available at an outcome, statistical tests or imputation.

Data synthesis- Separate meta-analyses in the above subgroups will be performed for (a) continuous outcomes- (pain, disability [separately for ODI and RMQ] and ROM) and (b) dichotomous outcomes (GA). Analysis will also be performed at intermediate and long term. A decision will be made if some outcomes are not appropriate for inclusion in meta-analysis, and are better dealt with qualitative description.
Subgroup analysis and investigation of heterogeneity-
Studies will be subdivided into subgroups to investigate effects of clinical heterogeneity with meta-analyses with conducted for available outcomes at immediate and short term follow up-
(i) LA versus non- LA LLLT  (ii) Studies will also be subdivided according to high and low laser dose intervention. Cut off for this will be guided by consideration of data findings in the review. (iii) There will be consideration to embark on other subgroup analyses depending on possible data findings in this review.

Sensitivity analysis-
This review will consider the effect of exclusion of trials with ‘higher risk of bias’. A trial will be categorized as ‘higher risk of bias’ if it contains more than six domains of ‘high’ or ‘uncertain risk’.

Grading the Quality of Evidence and Strength of Recommendations-
This review will grade the quality of the body of evidence for each primary outcome using GRADE approach for reviews of interventions. The quality of the body of evidence on a specific outcome will based on 5 domains:
1. Limitations in the design and implementation (risk of bias), 2. Inconsistency (heterogeneity), 3. Indirectness (inability to generalize), 4. Imprecision (insufficient or imprecise data) and 5. Publication bias across all studies that measure that particular outcome.
We will downgrade by 1or 2 levels the score in each domain if concerns are present.

Appendix M

Example of Search strategy: (Cochrane CENTRAL) Laser AND Back Pain
Last Saved: 31/12/2013

Description:
ID Search
#1 MeSH descriptor: [Laser Therapy] 1 tree(s) exploded
#2 MeSH descriptor: [Laser Therapy, Low-Level] explode all trees
#3 MeSH descriptor: [Lasers] explode all trees
#4 #1 or #2 or #3
#5 "laser acupuncture":ti,ab,kw or "low intensity laser":ti,ab,kw or "low power laser":ti,ab,kw or "low energy laser":ti,ab,kw or "low reactive level laser":ti,ab,kw in Trials (Word variations have been searched)
#6 "low incident laser":ti,ab,kw or "low output laser":ti,ab,kw or "low level laser":ti,ab,kw or "high intensity laser":ti,ab,kw or "narrow band light therapy":ti,ab,kw in Trials (Word variations have been searched)
#7 "infrared laser":ti,ab,kw or "helium neon laser":ti,ab,kw or "GaAlAs laser":ti,ab,kw or phototherapy:ti,ab,kw or "laser needle" in Trials (Word variations have been searched)
#8 laser near *stimulation:ti,ab,kw or LLLT:ti,ab,kw or LILT:ti,ab,kw or LELT:ti,ab,kw or LPLI in Trials (Word variations have been searched)
#9 LEPT:ti,ab,kw or LELI:ti,ab,kw or "GaAs laser":ti,ab,kw or "HeNe laser":ti,ab,kw or "light therapy":ti,ab,kw in Trials (Word variations have been searched)
#10 soft near laser:ti,ab,kw or mid near laser:ti,ab,kw or cold near laser:ti,ab,kw or photobio* near laser:ti,ab,kw (Word variations have been searched)
#11 "904 nm":ti,ab,kw or "830 nm":ti,ab,kw or "632 nm":ti,ab,kw or "1064 nm":ti,ab,kw in Trials (Word variations have been searched)
#12 #5 or #6 or #7 or #8 or #9 or #10 or #11
#13 #4 or #12
#14 MeSH descriptor: [Back Pain] explode all trees
#15 MeSH descriptor: [Spinal Diseases] explode all trees
#16 MeSH descriptor: [Spine] explode all trees
#17 MeSH descriptor: [Low Back Pain] explode all trees
#18 MeSH descriptor: [Intervertebral Disc] explode all trees
#19 MeSH descriptor: [Cauda Equina] explode all trees
#20 MeSH descriptor: [Scoliotic Neupropathy] explode all trees
#21 #14 or #15 or #16 or #17 or #18 or #19 or #20
#22 dorsalgia:ti,ab,kw or backache:ti,ab,kw or (lumbar next pain) or (coccyx) or (coccydynia) or (sciatica) or (spondylolisthesis):ti,ab,kw or (lumbar) or (discitis) or (disc degeneration) or (disc near prolapse) or (disc near herniation):ti,ab,kw or "spinal fusion":ti,ab,kw (Word variations have been searched)
#23 "spinal neoplasms":ti,ab,kw or facet near joints:ti,ab,kw or "postlaminectomy":ti,ab,kw or arachnoiditis:ti,ab,kw or failed near back (Word variations have been searched)
#24 lumbar near vertebra*:ti,ab,kw or spinal near stenosis:ti,ab,kw or slipped near (disc* or disk*):ti,ab,kw or degenerat* near (disc*: or disk*):ti,ab,kw or prolap* near (disc*: or disk*):ti,ab,kw (Word variations have been searched)
#25 sciatic*:ti,ab,kw or back disorder* or back near pain:ti,ab,kw (Word variations have been searched)
#26 #21 or #22 or #23 or #24 or #25
#27 #26 and #13
Appendix N
Letter to Editor (Acupuncture in Medicine journal)

Dear Dr White,

Decision on Manuscript ID acupmed-2013-010456

Thank you for your response to our submission. Before we respond to your request for revisions, we wish to express concerns about the claimed redundancy of our findings because “an inadequate dose was used and that the answer to the research question was already known”. The first trial used a 10mW power output machine laser machine, and a dose of 0.2 J per point was compared against a sham laser arm (0 J). This trial had a negative finding on primary outcome, although some uncertainty remained with baseline imbalance of negative predictors; an adjusted analysis showed a benefit for pain reduction in active laser group at 6 weeks. The current trial was specifically designed to further examine dose-dependence and longer follow up, and to address the question of imbalance in baseline factors in the original trial.

In Baxter’s commentary about the first trial in Acupuncture in Medicine he noted that the dose may have been inadequate and stated “while the definitive dosage window for effective laser acupuncture may remain occult, it is clear that higher dosages, and probably 0.5 J per point, are indicated.” In his systematic review on clinical effectiveness of laser acupuncture he concluded that “based upon the current review, laser acupuncture can be recommended as an effective treatment (moderate level of evidence) for the reduction of myofascial pain, at least when irradiation is applied at power of at least 10mW and a dosage of at least 0.5 J per point”. We are unable to find a reference which states that laser dose for acupuncture needs to be 8 Joules minimum and this was not the conclusion from the systematic review.

WALT has published a table of dosages which they recommend for laser treatment. These recommendations refer to non-acupuncture LLLT. For the lumbar region the dose suggested was 8 Joules with a therapeutic dose window range of +/− 50%. Our study specifically looked at laser acupuncture, which has been considered a separate form of therapy with different mechanism of action compared to the laser therapy promoted by WALT.

Our choice of a lower “high dose” was also based on experience of laser acupuncture practice in Australia where machines in the lower power output range are commonly used and anecdotaly good results are reported. Surveys conducted by the author in 2007 and 2012 have shown that higher laser output machines are still less frequently used by members of Australian Medical Acupuncture College. The upper dose range employed in the current trial (0.8 J per point using a 20 Mw power output machine) was contained within the range recommended by Baxter at the time.

We also disagree that a “wrong” message will be sent about laser acupuncture by this paper. It was clearly indicated in the abstract, discussion and summary that the negative result for laser applied only to the specified dosages for laser acupuncture and in treatment of chronic non-specific LBP. Not publishing our rigorously designed negative trial would contribute to publication bias and potentially mislead clinical practice in the opposite direction.

We agree that our study will encourage the conduct of further laser acupuncture research examining the possibility of efficacy at higher dosages.

We would be pleased to resubmit a revision of the manuscript to Acupuncture in Medicine with a longer discussion of the reasons for choice of dosage used and responding to the other requests of your reviewers. However, we seek your guidance before beginning our revisions.

Yours sincerely,
Dr Gregory Glazov; Prof Michael Yelland; Prof Jon Emery
5. WALT. Recommended treatment doses for Low Level Laser Therapy. 2010[cited; Available from: http://waltza.co.za/documentation-links/recommendations/dosage-recommendations/]
Laser acupuncture for chronic non-specific low back pain: a controlled clinical trial

Gregory Glazov,1 Peter Schattner,2 Derrick Lopez,3 Kerrie Shandley4

ABSTRACT

Objective: The primary aim was to determine if laser acupuncture (LA) is more effective than sham laser in reducing pain and disability in adults with chronic non-specific low back pain.

Methods: The design was a double blind, two group parallel randomised controlled trial. The active intervention was an 830 nm (infrared), 10 mW, Ga Al As laser diode for acupuncture and a sham control. The primary outcome measures were changes in pain (visual analogue scale) and disability (Oswestry Disability Index) at the end of 5-10 treatment sessions. Secondary outcomes were patient global assessment, psychological distress (Depression Anxiety Stress Scale) and subjective well being (Personal Wellbeing Index). Follow up was performed at 6 weeks and 6 months after completion of treatment.

Results: 100 participants were enrolled and treated in a general practice setting. Per protocol analysis of the primary outcome measures using ANOVA suggested that although there was a significant overall improvement in pain and disability after the course of treatments (p<0.01), there was no significant difference between the intervention and control group in both the primary and most secondary outcome measures.

Conclusion: This study did not show a specific effect for LA using infrared laser at 0.2 Joules per point for chronic low back pain. The overall intervention appeared effective because of placebo and other factors. As there was some concern about baseline inequality between the groups further research using tighter inclusion criteria should attempt to replicate the result and examine if a dose response may exist.

In the past, there has been criticism that interventions such as acupuncture used in the treatment of back pain are no more effective than sham treatment or placebo.1 However, there is now evidence emerging from larger more rigorous trials for the efficacy of needle acupuncture in this condition.2 3

Low level laser stimulation of acupuncture points, otherwise known as laser acupuncture (LA), using laser pointer devices as an alternative to needles, has been used in the last 35 years. Although there is lack of experimental evidence from controlled trials, a dose of 0.1-0.5 Joules (J) per point is commonly used for acupuncture point stimulation.4 G Greenbaum, an Australian acupuncture teacher, stated in a postgraduate medical acupuncture course offered by Medicine Monash University in 1998 that even lower doses of 0.01-0.05 J per point are sufficient to produce a therapeutic effect.

The effect of LA on back pain is still unclear but recently a small systematic review examining low level laser therapy for non specific low back pain concluded that there was “a small effect on pain intensity”.5 This review, however, excluded trials with reference to the use of LA.

A search of the literature in Medline using search terms (“controlled trials”, “acupuncture”, “laser therapy”, “back pain”, “neck pain”), references lists from articles,6 7 and access to an original thesis from Monash University,8 located only six controlled trials since 1981 involving LA in treatment of back or neck pain.9 10 Four out of six trials reported a “positive” effect in favour of LA, although the higher proportion of positive studies may have reflected a publication bias. The trials were of variable methodological quality with small sample sizes, single blinding and cross over designs being obvious problems. There was only one double blind trial,9 which examined the effective ness of LA against a sham laser control for chronic low back pain (CLBP). This was a small study (41 participants), in which an infrared laser was used (1.1 J were applied per point). Individualised laser treatment was given for 5 weeks, there was no co intervention and no follow up. A small insignificant positive benefit in only one pain outcome of many measured, and a 6% reduction disability (Oswestry Disability Index) was detected in the active laser intervention group. The primary outcome was not pre specified in this study with problems resulting from multiple analyses.

As LA is currently widely used to treat chronic back pain, it was considered important to conduct further research with a larger participant group, longer treatment and follow up. A 10 mW research laser machine was used as this was available to the researcher and could deliver an energy dose per point treated (0.2 J) commonly used in LA practice.

METHOD

The study design was a double blind, prospective, two group parallel randomised controlled trial using sham laser in the control group. This study was approved by a Monash University ethics committee in October 2005 and all participants signed a consent form before entry into the trial.

Participants

Participants were recruited by way of advertisements placed in local community newspapers (68%), GP waiting room notices (15%), a notice in an arthritis foundation circular (7%) and by word of mouth (9%). Respondents to recruitment notices initially underwent telephone screening by the principal investigator. They were informed
that they would be randomised to receive an active or sham laser treatment but would be blinded to exact mode of this. If they satisfied criteria and were agreeable, they were mailed an explanatory statement and consent form, and invited to attend an assessment at the premises of one of three Perth general practices.

Subjects included in the trial had chronic non specific low back pain (pain was present “most of the time”) with a duration of at least 3 months, with or without pain radiation. Low back pain was “non specific” if no significant neurological entrapment was evident on available imaging reports and there was no suggestion of this on history/examination (straight leg raising and other neurological testing). There was also no underlying systemic or visceral disease, or recent vertebral fracture present. They were in age range of 19-70 years, non pregnant and their pain before initial assessment was greater or equal to 3.0 cm on the visual analogue scale.

Participants were excluded if they were on strong opioid analgesia (use of codeine/paracetamol compounds or tramadol were allowed), on regular benzodiazepines, had current involvement in workers’ compensation or other insurance claims or had had any form of acupuncture, dry needling or procedures such as facet block injections in the previous 3 months. They were also excluded if any back surgery had been performed in the previous 2 years.

Participants with “widespread body pains” were also excluded, however the full criteria for fibromyalgia were not used in this assessment.

The investigator
The principal researcher and therapist/assessor (GG) is a general practitioner who has practised medical acupuncture since 1990, and is a Fellow of the Australian Medical Acupuncture College. He uses both needle and laser acupuncture techniques routinely in his private clinical practice.

Outcome measures
Parameters assessed included:
1. Visual analogue scale (VAS) for pain. Participants were asked to mark their average pain level over the previous week on a 10 cm horizontal line.
2. Oswestry Disability Index Version 2.0 (ODI).
4. The short version of Depression Anxiety Stress Scale (DASS 21).
5. Subjective wellbeing (Personal Wellbeing Index Adult (PWI A)).
6. Levels of exercise and analgesic use compared to baseline.

At the start of each session the assessor directed enquiry about each participant’s exercise level and analgesic use in previous week and obtained a score on this relative to baseline (less (-1), the same (0) or increased (+1)). At 6 week follow up a corresponding score was obtained from (i) questionnaire item on exercise level “since completion of treatment” and (ii) from a diary of analgesic use “during previous week”. Scores were averaged and compared between groups.
7. Adverse effects and exacerbations of pain during the course of treatment.

The timing for assessing each parameter is shown in table 1.

Intervention
Subjects identified by screening attended an initial assessment, which involved a structured interview and brief examination. Previous imaging investigations were reviewed and the nature of the chronic pain problem and general aspects of the trial/ acupuncture were discussed. Subjects who satisfied entry criteria and gave informed consent were enrolled into the study. Baseline self administered questionnaires were completed before the first treatment. All assessment and treatment was provided by the principal investigator (GG) who remained blinded throughout.

The completion of between five and 10 weekly sessions satisfied the protocol. An interval of some weeks between sessions was permitted (eg, for holiday or illness). At the start of each session participants were questioned about symptoms, analgesic use, exercise levels and pain level during the previous week and their responses were recorded. Tender points were located, followed by application of the laser treatment. During the course of the sessions further education was provided and participants were encouraged to gradually increase stretching and general exercise.

This was facilitated using written material and hand outs based on material from a popular self help book. Participants were requested not to start any new physical treatments or medications during the treatment period or for 6 weeks after. They could continue any of their current analgesics according to their pain. Follow up survey forms were mailed, enclosing a stamped addressed return envelopes.

The device was an 830 nm (infrared), 10 mW, Ga Al As laser diode (Acupak, Melbourne, Australia). Power density at the probe/skin interface was 0.05 W/cm². The basis of the treatment protocol reflected the usual clinical practice of the author. Acupuncture point selection was individualised to each patient and was chosen according to the distribution of pain and palpation of local tender points. Local points on the three main acupuncture meridians (Bladder, Gallbladder and Governor vessel) and ah shi points were most often used. Regional palpation was first conducted by firm finger pressure and those points which were tender were marked with a ball point pen. These were unilateral or bilateral and usually at site of maximum pain. Distal acupuncture points on limbs or head and neck, often at the site of radiation of pain or according to common rules of acupuncture point selection, were also selected by discretion of the therapist. No auricular or microsystem acupuncture was used. Acupuncture points for psychological distress and other symptoms, such as headache, neck pain and so on, were also treated if present. Points were stimulated consecutively after they had been all marked. The laser probe tested lightly under its own weight perpendicular to the skin with no change in pressure during stimulation. Twenty seconds treatment (0.2 J) was usually applied consecutively to each point selected. On some occasions patients were treated with 10 seconds per point, contra lateral to their maximum pain or with fewer points if an exacerbation of pain had occurred with a previous session. A verbal description was provided to participants in simple terms on why certain points were used during their treatment.

Randomisation/blinding
Apparatus modified for use in double blind research was used. The mode (laser or sham) was set by turning a four digit cogwheel dial. One hundred consecutive settings of the dial were programmed into the circuitry of the device in a random pattern at time of manufacture with only 50 of these settings resulting in production of a laser beam when the machine was operated. Before commencement of the study, an independent person further randomised this sequence of 100 numbers using...
permitted block randomisation technique and a copy of this allocation sequence was sent to the therapist/assessor.

Upon enrolment, each participant was allocated the next ID/switch code in the sequence provided. This same code was dialled each time the participant presented for treatment, resulting in the same treatment mode each time the patient was treated. The code could not be re-used if a participant dropped out.

The participant and the assessor/therapist were both blind to the mode of laser intervention. The laser probe had a translucent Perspex conical tip and a red (LED) decoy light issued from the tip each time the unit was operated, regardless of mode of laser production. The success of blinding for this machine (which prevented detection of a diode glow) has been described in a different paper.7

### Statistical analysis

In planning the study the statistician calculated that a sample size of 60 would show a difference between groups of 1.5 cm in VAS for pain with a baseline standard deviation (SD) of 2.1 which was present in a previous study,7 at power 0.8 and significance level 0.05. We therefore planned to recruit 100 patients to account for drop outs and other variations in this trial.

During subsequent analysis of the trial data, retrospective power calculation based on the observed SD of 2.4 after treatment, indicated that the analysed sample of 90 would be sufficient to detect a difference of 1.4 cm between treatment groups at the same power and significance levels.

This is below the minimal clinically significant change for low back pain of 15 for VAS (0 100) obtained in an international study that four patients with spinal stenosis and seven patients with possible fibromyalgia were included in the population. Despite the intention to exclude some diagnoses from the whole sample it became apparent on record review after the enrolment into the trial at which the condition was demonstrated. It also became apparent that there were some patients with possible fibromyalgia that was not detected at time of initial assessment. Their final distribution between treatment groups is shown.

### Baseline characteristics of whole study group (n = 100)

Most of the participants (97%) were white Caucasian, females (56%), and their average age was 51 years (SD = 12.6). The mean body mass index was 28. Almost a fifth (17%) were smokers and 92% consumed “safe” quantities of alcohol (less than 4 and 2 standard drinks/day in men and women respectively). Nearly half of the sample (49%) were currently employed in the workplace. 47% were receiving a pension (19% aged and 15% disability support for a health related condition). Most participants (90%) had the pain for more than two years with the range in duration of 6 months to 40 years. The majority (61%) had a moderate disability at the baseline measurement. Baseline psychological distress level was low, with 70%, 79% and 74% assessed as rating “normal” or “mild” for depression, anxiety and stress respectively.

### Comparability of baseline factors and treatment protocol in study groups

Characteristics of the control and intervention groups are shown in table 3 for the 90 participants (drop outs excluded). Despite the randomisation procedures there was some variability of baseline characteristics between groups, this reaching statistical significance for distributions involving analgesic usage, previous use of acupuncture and current physical therapies.

Despite the intention to exclude some diagnoses from the whole sample it became apparent on record review after the study that four patients with spinal stenosis and seven patients with possible fibromyalgia were included in the population treated. The few participants with spinal stenosis either had mild changes on available imaging with no other clinical features present, or imaging was ordered by their GP after enrolment into the trial at which the condition was demonstrated. It also became apparent that there were some patients with possible fibromyalgia that was not detected at time of initial assessment. Their final distribution between treatment groups is shown.

There was no significant difference between subject groups in implementation of treatment protocol details (see table 3).

### Comparison of outcome measures in study groups

Overall there was almost 40% reduction of pain at the end of treatment and a 30% reduction which was maintained at short
term (6 weeks) and intermediate term (6 months) follow up. A 20% reduction in disability at the end of treatment was maintained in the short term.

A summary of the means for baseline and post intervention data for VAS (pain), Disability, Depression/Anxiety/Stress and Subjective Wellbeing in both treatment groups are presented in Table 4 below. Baseline values for the primary outcome measures of pain and disability were similar in the two groups.

This study demonstrated a significant reduction in pain and disability scores across time, however there was no difference in primary outcome of reduction in pain or disability at completion of treatment between the groups (ANOVA). This relation also held during follow up.

The primary outcome findings involved a “per protocol” analysis of participants who completed the treatment protocol (n = 90). It was considered justifiable to exclude the four dropouts who did not commence any treatment. As the resulting drop out rate was less than 10% (6%), an intention to treat analysis was not performed. A sensitivity analysis (n = 96) however was done including the six subjects who participated in a certain number of treatment sessions before dropping out. The drop out cases who were in the intervention group were imputed to obtained “best” pain relief and disability reduction after treatment while the cases in the control group were imputed to show no improvement in pain and disability after treatment. This did not alter the findings previously described with no significant difference between groups (ANOVA).

Per protocol analysis was also used when comparing the secondary outcomes. There was no significant difference in these outcome measures between the intervention and control group, apart from a slight reduction (see below) in analgesic use in the laser group during treatment phase.

For domains of psychological distress (depression, anxiety and stress), when measured at completion of treatment and at 6 weeks follow up, there was no significant differences between the groups in response to treatment. Overall there was a statistically significant improvement in the domains of depression and stress (p<0.01, ANOVA) between baseline and completion of treatment, and 6 weeks follow up. There were no changes demonstrated in the anxiety domain.

Overall and between groups, there was no statistically significant improvement in subjective well being (PWI A), when this was measured at the 6 week follow up. There was a larger improvement in the mean score of the individual domain “satisfaction with health”, but this still failed to reach statistical significance.
In the overall global assessment by the participants of the effectiveness of treatment 59%, 48% and 38% of participants reported that treatment had been moderately or extremely effective at completion of treatment, at 6 weeks and 6 months follow up respectively with no significant difference (p > 0.05, Fisher’s Exact) between the treatment groups at any of these follow up times.

Overall, the exercise level of subjects increased relative to baseline, both during the course of treatment and at 6 weeks follow up but again there was no statistical difference between the groups. The use of analgesics and anti inflammatory agents was also assessed, and there was a small reduction in use of these medications in both treatment groups only during treatment. The difference between groups was significant with a greater reduction in the laser group (p < 0.05, ANOVA). At 6 weeks follow up there was no change in analgesic use from baseline in any session.

As an incidental finding, one patient in the laser group attended hospital after suffering a small myocardial infarction during the treatment phase but then elected to continue in the trial, another patient in the sham group developed a kidney infection and had to discontinue her treatments early and one trial, another patient in the sham group developed a kidney infection and had to discontinue her treatments early and one

### Table 2

<table>
<thead>
<tr>
<th>Meridians and individual acupuncture points frequently used in this study (%)</th>
<th>% Of participants in which this meridian was used during any session</th>
<th>Individual points</th>
</tr>
</thead>
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<tr>
<td>Acupuncture Meridian</td>
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<td></td>
</tr>
<tr>
<td>Bladder</td>
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<td>23, 25, 26, 27, 28, 40, 41, 46, 57, 60, 62, 53</td>
</tr>
<tr>
<td>Governor Vessel</td>
<td>100</td>
<td>15, 14, 4, 3</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>96</td>
<td>20, 21, 25, 28, 30, 31, 34</td>
</tr>
<tr>
<td>Liver</td>
<td>70</td>
<td>3, 13</td>
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<tr>
<td>Large Intestine</td>
<td>43</td>
<td>4</td>
</tr>
<tr>
<td>Spleen</td>
<td>48</td>
<td>6, 9, 10</td>
</tr>
<tr>
<td>Stomach</td>
<td>47</td>
<td>36</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>41</td>
<td>3</td>
</tr>
<tr>
<td>Pericardium</td>
<td>46</td>
<td>6</td>
</tr>
<tr>
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<td>3</td>
</tr>
<tr>
<td>Lung</td>
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<td>7</td>
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<tr>
<td>Triple Energizer</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Heart</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Conception Vessel</td>
<td>7</td>
<td>6, 12, 17</td>
</tr>
<tr>
<td>Ab shi points</td>
<td>94</td>
<td>Greater trochanter, unnamed points between spinous processes, iliac crest and costal margin, unnamed points along lateral arm of BL channel</td>
</tr>
<tr>
<td>Extraordinary points</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3

| Distribution of baseline characteristics and comparison treatment protocol variables between study groups |
| --- | --- | --- |
| | Control (n = 45) | Intervention (n = 45) | p Value |
| Demographics | | | |
| Male (%) | 38 | 6 | ns* |
| Median age in years (25th, 75th percentiles) | 49 (44, 63) | 58 (44, 63) | ns† |
| Median BMI in kg/m² (25th, 75th percentiles) | 27 (24, 31) | 27 (24, 30) | ns † |
| Employed (%) | 49 | 47 | ns* |
| On disability support pension (%) | 7 | 22 | ns* |
| Smoking (%) | 11 | 20 | ns* |
| Baseline pain characteristics | | | |
| Participants with pain over 2 years (%) | 89 | 93 | ns † |
| Mean total duration of pain in years (range) | 11.4 (0.5 40) | 10.9 (1.5 40) | |
| Buttock/leg radiation present (%) | 49 | 69 | ns* |
| LBP predominantly unilateral (%) | 67 | 64 | |
| Unilateral pain which was right sided (%) | 60% | 76% | |
| Acute on chronic exacerbation of LBP present at assessment (%) | 18 | 18 | ns* |
| Allodynia present (%) | 13 | 13 | ns* |
| Degenerative changes reported on imaging (%) | 64 | 67 | ns* |
| Pain attributed to an original injury by patient (%) | 40 | 40 | ns* |
| Headaches present (%) | 36 | 51 | ns* |
| Independent knee pain present (%) | 13 | 11 | |
| Neck pain present (%) | 42 | 40 | ns* |
| Spinal stenosis present (%) | 2 | 7 | |
| “ Fibromyalgia” present (%) | 9 | 7 | |
| Psychological distress (DASS 21) | | | |
| Depression, moderate to severe+ (%) | 27 | 37 | ns* |
| Anxiety, moderate to severe+ (%) | 18 | 25 | ns* |
| Stress, moderate to severe+ (%) | 29 | 27 | |
| Comparability of treatment protocol (median (25th, 75th percentiles)) | | | |
| Number of treatments completed | 10 (9, 10) | 9 (8, 10) | ns † |
| Treatment duration (weeks) | 10 (8, 11) | 9 (8, 10) | ns † |
| Time to 6 week post completion (weeks) | 6 (6, 7) | 6 (6, 6) | ns † |
| Time to 6 month post completion (weeks) | 26 (26, 27) | 26 (25, 28) | ns † |

* Using Fisher’s Exact test; † Using Mann Whitney U test; BMI, body mass index; DASS, Depression Anxiety Stress Scale; NSAIDs, non steroidal anti inflammatory drugs; ns, not significant.
DASS stress (range 0–42)\textsuperscript{a}.

Comparison of groups revealed that the effects were comparable to each other with the exception of ODI.

There were no significant differences between the two groups for any of the outcomes measured.

**DISCUSSION**

This randomised placebo controlled trial attempted to determine if laser acupuncture (Ga Al As laser diode, 830 nm (infrared), 10 mW, applied in 20 seconds (0.2 J) at individualised acupuncture points by one experienced therapist for an average of 9.1 weekly sessions) is more effective than sham laser to reduce pain and improve function in patients with chronic non specific low back pain. The results however suggested that both sham and laser have acupuncture like effects and are equally effective in the treatment of this condition.

There could be a number of possible reasons for improvement to the overall intervention regardless of the type of laser being switched on. Acupuncture is known to be associated with a significant placebo effect. It is important to note that the acupuncture treatment provided in this trial was a complex non pharmaceutical intervention,\textsuperscript{b} where the characteristic aspects of acupuncture in addition to palpation and application of the probe, included the diagnostic process and aspects of listening and talking. Suggestion was provided to all participants during the course of treatment including an explanation about the effect of acupuncture and why certain points were used. In this study all participants were informed at the onset that they could be getting either a “real laser” or an “inactive” red light beam which may have reduced the placebo effect.

Patient satisfaction with health; VAS, visual analogue scale; superscripts represent statistical significance: between * start and completion; † start and 6 weeks post completion; ‡ completion and 6 weeks post completion; †† start and 6 months post completion.

Data required logarithmic transformation to satisfy normality assumption, as such geometric values

**Strengths and limitations of this study**

The importance of this study is in focusing on a widely used non invasive approach with little evidence base to treat non specific CLBP. This is the first trial to employ a novel laser
device’ which alleviates previous problems in blinding the patient and therapist, and is a real advance in this field of research. The project examined an adequate sample size which in principle would detect a clinically significant effect of LA if it existed.

Although a negative result was obtained, some doubt remains despite a rigorous randomisation and blinding process being undertaken. Certain baseline inequalities arose between the treatment groups which may have confounded the results (see table 3). If factors with a negative effect on pain outcome aggregated by chance in the laser group, this could have produced a false negative conclusion. This will be analysed in detail in a subsequent paper by the author.

The results obtained only apply to infrared lasers stimulating about 0.2 J per point and may not exclude efficacy for LA using a machine of different wavelength or power, or for treatment of other conditions. Treatment was conducted by a single therapist with a regimen that reflected his own practice which could affect the external validity of the results. It was also possible that with the sham laser intervention, palpation of the skin during the course of location of acupuncture points may also have produced a physiological acupressure effect.

Recommendations for further research
The question of efficacy of LA for CLBP has not been resolved by the current trial and further research is recommended. It is important to assess dose effect across an energy range such as 0.05 1.0 J per point which has been used in LA practice. A much higher laser dose (8 J per point) for laser treatment of lumbar spine is recommended by World Association for Laser Therapy (WALT),27 and is used by laser therapists who believe that a local effect on tissues produces a therapeutic effect without regard to acupuncture principles. It is not clear if this approach produces better results and further research still needs to be performed comparing treatment according to these different philosophies.

Tighter inclusion criteria also need to be implemented excluding poor responders to acupuncture intervention, as these make an acupuncture effect difficult to detect and confound results if present unequally between intervention groups. This issue is extremely important in planning acupuncture trials in general and may explain many previous equivocal results in this type of research. The analysis of responders in this study is the subject of another report submitted for publication by the author.

Consideration should also be given to avoiding con interventions, and reducing other ‘acupuncture like’ stimulation such as tactile pressure in LA trials in location of points and during skin application of the laser pointer.

Acknowledgements: I would like to thank the participants of the trial for contributing to this research.

Funding: Australian Medical Acupuncture College purchased the Acupak research laser and also provided some funding for the project and to enable presentation of its findings at conferences.

Competing interests: None declared.

Ethics approval: This study was approved by Monash University ethics committee.

Provenance and peer review: Not commissioned; externally peer reviewed

REFERENCES

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Original paper

Summary points
► Laser acupuncture is used to treat back pain but it is still not clear whether it is effective.
► This double-blind RCT compared infra-red laser (0.2 J per point) with sham laser in 90 patients with chronic low back pain.
► Laser acupuncture had no effect on pain, disability or most other measures.

Laser acupuncture had no effect on pain, disability or most other measures.
The influence of baseline characteristics on response to a laser acupuncture intervention: an exploratory analysis

Gregory Glazov

ABSTRACT

Objectives In clinical practice it is known that subjects vary in their response to acupuncture, but there is little data on what predicts the outcome. The aim of this study was to identify such predictors.

Method A secondary analysis was performed on data from 100 participants in a trial of laser and sham laser acupuncture for chronic non-specific low back pain. Multiple regression analysis was used to identify which baseline characteristics predicted pain change in the immediate, short and intermediate term. An analysis of covariance was performed based on these results to re-examine the primary result of the trial.

Results Strong predictors of poor response were receipt of disability support pension, headache, the regular use of analgesics or previous failed back surgery. Higher pain scores or exacerbation of pain at baseline predicted a greater proportionate pain relief after the intervention. Adjusted analysis suggested a clinically important effect of laser compared to sham (p<0.05), at short term follow-up only.

Conclusion The findings of this study suggest which characteristics of patients with chronic low back pain are more likely to respond to laser acupuncture treatment, but require replication in other studies. The findings may not apply in other acupuncture interventions and treatment of different conditions. They may also be used to set selection criteria for future studies, and to aid interpreting the effect of baseline imbalances on trial results.

INTRODUCTION

Studies on back pain have found evidence that demographic features, characteristics of the pain condition and previous and current treatment may influence chronicity of disability or response to treatment. It has been frequently noticed by acupuncturists that subjects tend to vary in their response to acupuncture. In traditional Chinese medicine, it was considered that a better result was achieved if acupuncture point selection was guided by the patient's traditional Chinese medicine 'correspondences'. In more recent times, Felix Mann identified the concept of the 'strong responder'.

There have been a few studies of needle acupuncture which have explored the effects of patient variables on outcome, known as response predictors. A small study examining treatment of various conditions suggested that neither age nor gender is related to rate of recovery, but that patients with more severe initial conditions, particularly bodily pain, tended to make more rapid improvements. A large multi-centre study of needle acupuncture for chronic low back pain (CLBP), analysed the effect of baseline scores of chronicity, pain intensity and depression on treatment outcomes. This trial did not find a clinically important difference in functional improvement after treatment in relation to either baseline intensity or chronicity. The presence of depression at baseline did not affect the improvement in physical health but did predict a clinically significant improvement in mental health after the acupuncture intervention. Another large pragmatic trial comparing needle acupuncture with usual care in patients with non-specific CLBP showed few predictors except a greater improvement in symptoms and function if these were more severe at baseline, and in patients who did not use narcotics.

In the current study 100 subjects with non-specific CLBP were recruited, mainly from notices in community newspapers, into a double blind trial of laser acupuncture, to determine the effectiveness of a 10 mW laser compared to sham. A co-intervention consisting of education and encouragement to exercise was also provided to both groups. The trial found no difference in pain outcomes between the intervention (laser) and the control (sham laser) group. There was a significant pain reduction in the combined groups at the end of treatment (40%) and at follow-up (50%) at 6 weeks and 6 months.

It was decided to do a posthoc subgroup analysis to explore which baseline factors were associated with a better or worse outcome, and whether bias from an imbalance of these factors between the treatment groups may have affected the result of the trial.

METHOD

Before participants were randomised, comprehensive baseline data were recorded during a structured interview (see box 1). The responses to items were already dichotomous (yes/no), or categorical in which case they were collapsed onto binary form for the present analysis. Continuous variables such as age, body mass index (BMI) and scale scores were categorised. All data were analysed using SPSS V.15.0.

First, the baseline comparability of characteristics between the intervention groups was examined. Because of the heterogeneity of the chronic pain population studied and relatively small sample size, it was expected that by chance some baseline characteristics would not be evenly split between the treatment arms.

As recommended in the Revised Consort Statement, we did not test for significant
differences, however as our study was exploratory, and there was little previous data on response predictors to laser acupuncture, we considered it important to list the full range of variables for baseline comparison.

The next step was to determine which baseline characteristics appeared to influence the amount of pain reduction after treatment. As the primary result showed no clear difference between the treatment arms, the overall sample was used in this assessment. The primary outcome of interest in the original trial was the mean pain on a visual analogue scale (0–10) at the last session of treatment (immediate term follow-up). Pain levels at short term (6 weeks after last treatment) and intermediate term follow-up (6 months after last treatment) were also examined as secondary endpoints. We used the percentage pain change from baseline at all three time points in testing for differences in the 90 participants who completed the protocol of a minimum 5–10 treatment sessions. We excluded from the analysis 10 participants who completed the protocol of a minimum 5–10 treatment sessions. As the primary result showed no clear difference between the intervention arms, the overall sample was used in this assessment. As the primary result showed no clear difference between the intervention arms, the overall sample was used in this assessment. As the primary result showed no clear difference between the intervention arms, the overall sample was used in this assessment.

RESULTS
Baseline comparison
The distribution of baseline variables by treatment group are presented in tables 2 and 3. The means for continuous variables were comparable except for a higher disability score in the laser group. Inspection of distributions in the categorical comparison table demonstrated that there were higher rates of recipients of disability support pension (15%), radiating pain (20%) and headache (15%), as well as greater use of regular analgesics (23%) and over-the-counter (OTC) medications (15%) in the laser group. Conversely in the sham group more subjects were currently using other forms of physical therapy (24%) and had previously received acupuncture (22%).

Subgroup analysis
Mean percentage pain change was calculated at each of the three time points for each of the baseline variables listed in box 1 using both imputation methods for missing values.

All variables for which there was a difference in percentage pain change ≥20 between categories were listed in table 4, labelled with the category with the worse pain outcome (less response). Using these criteria the remaining variables from box 1 did not appear to predict pain outcome following treatment.

For each time point, the variables which appeared to affect pain outcome (table 4), as well as four other variables which showed the greatest imbalance between groups (previous acupuncture, use of OTC medications, current use of other physical treatments, radiation of pain present) and the treatment group variable were entered into the regression equation. Those that were found to be statistically significant in predicting pain change are listed in table 5.

At immediate follow-up, subjects with baseline headaches had worse pain outcome. There also was a trend towards less improvement in subjects on disability support pension and those with previous back surgery. At short term (6 weeks) follow-up subjects on disability support pension had less improvement in pain, while those with higher pain scores at baseline had a greater proportionate pain reduction. There was a trend to worse outcome in headache sufferers and regular users of analgesics. At 6 months follow-up, those on regular analgesics did worse and subjects who described an exacerbation of pain at baseline had a greater proportionate pain reduction.

When different methods of imputation were used for missing values, the results were similar. They were identical at immediate follow-up (as there were no missing values at this time). At short term follow-up for headaches the statistical relationship was stronger when value for pain at baseline was imputed. At intermediate term follow-up this applied to the group with exacerbation at baseline when value for pain at last end point was imputed.
Table 3  Dichotomous and categorical variables in groups at baseline

<table>
<thead>
<tr>
<th>Baseline variable</th>
<th>Total group: n=90</th>
<th>Sham (%)</th>
<th>Laser (%)</th>
<th>Baseline variable</th>
<th>Total group: n=90</th>
<th>Sham (%)</th>
<th>Laser (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>Previous and current treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td>Back surgery &gt;2 years ago</td>
<td>Yes</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Acupuncture &gt;3 months ago</td>
<td>Yes</td>
<td>62</td>
<td>40</td>
</tr>
<tr>
<td>Smoking habit</td>
<td></td>
<td></td>
<td></td>
<td>Specialist injections &gt;3 months ago</td>
<td>Yes</td>
<td>24</td>
<td>31</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>11</td>
<td>20</td>
<td>Analgesic use</td>
<td>Regular</td>
<td>13</td>
<td>36</td>
</tr>
<tr>
<td>Alcohol intake ≥ 2–4 SD per day</td>
<td>Yes</td>
<td>9</td>
<td>7</td>
<td>NSAI D use</td>
<td>Regular</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>Employment status</td>
<td>Employed</td>
<td>49</td>
<td>47</td>
<td>OTC use</td>
<td>Yes</td>
<td>47</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>DSP</td>
<td>7</td>
<td>22</td>
<td>Yes</td>
<td>40</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Pain characteristics</td>
<td>Radiation of pain</td>
<td>Yes</td>
<td>49</td>
<td>69</td>
<td>Yes</td>
<td>33</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Exacerbation pain at onset</td>
<td>Yes</td>
<td>18</td>
<td>18</td>
<td>Yes</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Degenerative changes on imaging</td>
<td>Yes</td>
<td>64</td>
<td>67</td>
<td>Yes</td>
<td>36</td>
<td>51</td>
</tr>
<tr>
<td>Disability (ODI) &amp; DASS21 scores</td>
<td>Depression</td>
<td>Moderate to severe</td>
<td>27</td>
<td>36</td>
<td>Yes</td>
<td>42</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
<td>Moderate to severe</td>
<td>18</td>
<td>25</td>
<td>Yes</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Stress</td>
<td>Moderate to severe</td>
<td>29</td>
<td>25</td>
<td>Yes</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Disability</td>
<td>Moderate to severe</td>
<td>84</td>
<td>84</td>
<td>Yes</td>
<td>42</td>
<td>40</td>
</tr>
</tbody>
</table>

**DASS21, Depression and Anxiety Stress Subscale Score; DSP disability support pension; ODI, Oswestry Disability Index**

Box 1 Baseline data recorded in the study

**Demographics**
- Gender: male/female
- Smoking status: yes/no
- BMI: normal/overweight or obese
- Alcohol intake: <2 (females) or <4 (males) standard drinks per day/more
- Employment status: employed/on a pension or unemployed
- Pension status: on disability support pension/other pension or no pension

**Pain characteristics**
- VAS score (average pain in previous week): ≤ median (5.9)/>median (5.9)
- Duration of pain: <2 years/≥2 years
- Disability at baseline (Oswestry disability index): nil or minimal (0–20%)/moderate or severe (21–60%)
- Radiation of pain outside of low back: absent/present
- Exacerbation pain (worsening of pre-existing pain at baseline): yes/no
- Presence of degenerative changes on imaging: yes/no or not done or not available

**Previous and current treatment**
- Low back surgery done over 2 years previously: yes/no
- Specialist interventions for LBP (eg, facet block injections, epidurals, etc) done over 3 months previously: yes/no
- Any type of acupuncture done over 3 months previously: yes/no
- Current use of analgesics: regular/none as necessary
- Current use of NSAIDS etc: regular/none as necessary
- Current use of any non-prescription herbs, vitamins or supplements: yes/no
- Current use of antidepressant medication: yes/no
- Current use of other physical therapies: yes/no

**Presence of other functional symptoms at baseline**
- Headaches often present: yes/no
- Neck pain often present: yes/no
- 'Irritable bowel syndrome': yes/no
- Trochanteric bursitis present: yes/no

**Depression Anxiety Stress (DASS-21) subscales**
- Depression: normal to mild (0–13)/moderate to severe (14–28+)
- Anxiety: normal to mild (0–9)/moderate to severe (10–20+)
- Stress: normal to mild (0–18)/moderate to severe (19–34+)

Adjusted analysis
A one-way analysis of covariance between groups was conducted to compare the effectiveness of laser against sham in producing pain reduction at the three endpoints in this trial. The independent variable was the type of intervention (laser/sham), and the dependent variable was percentage pain change at the respective end point. Four baseline characteristics which were selected as covariates had been shown to predict pain outcome from table 5, and also were unevenly distributed between the treatment arms of the trial. These were baseline presence of...
Table 4 Variables predicting Percentage Pain Change (PPC) ≥20 between categories at any time point after completion of treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category with less pain improvement</th>
<th>Method of imputing missing values*</th>
<th>Difference in PPC between categories</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Post 6 weeks</td>
<td>6 months</td>
</tr>
<tr>
<td>Pension status</td>
<td>DSP</td>
<td>Base</td>
<td>29.9</td>
</tr>
<tr>
<td></td>
<td>Last</td>
<td>29.9</td>
<td>45.0</td>
</tr>
<tr>
<td>Pain at baseline</td>
<td>Low ≤5.9</td>
<td>Base</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Last</td>
<td>–</td>
<td>39.4</td>
</tr>
<tr>
<td>Exacerbation pain at baseline</td>
<td>No</td>
<td>Base</td>
<td>–</td>
</tr>
<tr>
<td>Degenerative changes on imaging</td>
<td>No or not available</td>
<td>Base</td>
<td>26.6</td>
</tr>
<tr>
<td>Back surgery &gt;2 years earlier</td>
<td>Yes</td>
<td>Base</td>
<td>24.3</td>
</tr>
<tr>
<td>Facet joint blocks etc &gt;3 months earlier</td>
<td>Yes</td>
<td>Base</td>
<td>24.3</td>
</tr>
<tr>
<td>Analgesic usage</td>
<td>Regular</td>
<td>Base</td>
<td>22.9</td>
</tr>
<tr>
<td>Anxiety group (DASS-21)</td>
<td>Moderate–severe</td>
<td>Base</td>
<td>20.0</td>
</tr>
<tr>
<td>Stress group (DASS-21)</td>
<td>Normal–mild</td>
<td>Last</td>
<td>20.0</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>≤2–4 Standard drinks/day</td>
<td>Base</td>
<td>31.5</td>
</tr>
<tr>
<td></td>
<td>Last</td>
<td>31.5</td>
<td>32.7</td>
</tr>
</tbody>
</table>

*Imputation of missing values last = ‘pain at last recorded assessment imputed for any missing value at follow-up’; base = ‘pain at baseline imputed for any missing values at follow-up’; DASS21, Depression anxiety stress scale (short form); DSP, Disability support pension.

Table 5 Predictors of PPC at three time points after intervention

<table>
<thead>
<tr>
<th>Time point for dependent variable (PPC)</th>
<th>Independent variable</th>
<th>Pain at baseline imputed for missing values</th>
<th>Pain at last recorded assessment imputed for missing values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate term (at end of treatment)</td>
<td>Headaches</td>
<td>−0.283 0.005</td>
<td>−0.283 0.005</td>
</tr>
<tr>
<td>Short term (6 weeks after treatment)</td>
<td>On DSP</td>
<td>−0.229 0.02</td>
<td>−0.229 0.02</td>
</tr>
<tr>
<td>On previous back surgery</td>
<td>−0.194 0.05</td>
<td>−0.194 0.05</td>
<td>−0.194 0.05</td>
</tr>
<tr>
<td>On less pain at baseline</td>
<td>−0.292 0.002</td>
<td>−0.299 0.002</td>
<td>−0.299 0.002</td>
</tr>
<tr>
<td>On regular analgesics</td>
<td>−0.268 0.006</td>
<td>−0.268 0.006</td>
<td>−0.268 0.006</td>
</tr>
<tr>
<td>On headaches</td>
<td>−0.247 0.009</td>
<td>−0.224 0.02</td>
<td>−0.224 0.02</td>
</tr>
<tr>
<td>On no exacerbation at baseline</td>
<td>−0.236 0.02</td>
<td>−0.195 0.04</td>
<td>−0.195 0.04</td>
</tr>
<tr>
<td>On no exacerbation pain at baseline</td>
<td>−0.200 0.04</td>
<td>−0.176 0.07</td>
<td>−0.176 0.07</td>
</tr>
<tr>
<td>On no regular analgesics</td>
<td>−0.306 0.003</td>
<td>−0.285 0.006</td>
<td>−0.285 0.006</td>
</tr>
<tr>
<td>On no regular laser group</td>
<td>−0.242 0.02</td>
<td>−0.299 0.004</td>
<td>−0.299 0.004</td>
</tr>
</tbody>
</table>

DSP, Disability support pension.

headaches, pension status, analgesic use and occurrence of previous back surgery.

After adjustment for these covariates (see table 6), a statistically significant difference in percentage pain change between groups was only found at 6 weeks follow-up. At best this represented a 23% difference in pain reduction effect in favour of laser, approaching a medium effect size according guidelines by Cohen.10 The imputation methods used would have included scenarios of (a) good and (b) poor outcomes in dropouts with missing values.

DISCUSSION

This study showed that certain baseline subcategories of patients with non-specific CLBP responded differently in pain relief after laser acupuncture treatment. Receiving a disability support pension or being prone to habitual headaches resulted in less pain reduction in the immediate and short term, and regular use of analgesics predicted less pain reduction in the short and intermediate term. Previous back surgery or specialist pain relief blocks to the back predicted a poorer response to laser acupuncture treatment, although the statistical relationship for this was weaker.

There are a number of explanations postulated for these findings. The findings are rational as these factors are likely to indicate more severe pathology group or structural change. There may be secondary gain for patients on some type of pensions to remain ill. A similar effect may occur with chronic back pain resulting from work injury or motor vehicle accidents although...
Inconsistency of response depending on baseline score of psychological distress with those with higher anxiety doing worse, while subjects with high stress levels responded better. Another observation was that subjects who had no evidence of degeneration on available imaging did worse. This is consistent with evidence of poor correlation between imaging changes and symptoms of CLBP. Although of interest, such findings may also have arisen by chance and warrant confirmation in further studies.

In the few previous trials which have examined the effect of baseline characteristics on outcome in acupuncture, lack of predictors has been a common finding. In this study characteristics such as age group, gender, BMI status, smoking status, attributed cause of onset and total duration of back pain, pain radiation, previous acupuncture (over 3 months prior), use of concurrent OTC medicines or other physical therapies and level of disability did not appear to affect the response to treatment. Participants on aged persons’ or other pensions did as well as those participants who were in employment.

A further aim of this study was to determine whether an imbalance in baseline characteristics resulted in a biased conclusion in the primary analysis. This bias is of particular importance in trials testing the efficacy of acupuncture interventions where there is a large placebo effect and a likely smaller specific effect of treatment. It is postulated that a trial may be apparently adequately powered to detect a difference in theory, but with small or moderately sized trials chance baseline imbalance involving strong predictors of outcome can easily result in bias despite randomisation. This may be a common explanation of frequent inconsistency in results of many acupuncture randomised controlled trials. The implication is that to establish efficacy in acupuncture interventions one must select very large sample sizes or have smaller trials with strict inclusion criteria to reduce the entry of poor responders.

This trial showed an apparently negative result on primary analysis, but the adjusted analysis provided a suggestion of a clinically important effect of laser acupuncture in participants after correction for baseline imbalances between treatment arms. However, this occurred only at short term (6 weeks follow-up) and may suggest a biological effect of laser which produces maximal effect on pain reduction with a time delay after a course of treatment. Posthoc subgroup and adjusted analysis however needs to interpreted with caution and the primary result of this clinical trial deserves most emphasis. The analysis suggests the need to repeat the trial with tighter exclusion criteria removing subgroups which respond poorly to acupuncture. With these restrictions, the external validity for a trial with a positive result would be reduced but could suggest efficacy of laser acupuncture in treating a less severe spectrum of chronic back pain. A positive result would also encourage further efficacy studies of laser acupuncture in other conditions and basic research to determine mechanisms of action of low level laser in pain reduction.

It must be stressed that the results of this study may not be generalisable to acupuncture using needles or other modalities. The results of this study also only relate to the overall ‘laser acupuncture intervention’ since the analysis was done on the whole group because of sample size restrictions. It remains possible that a specific laser effect may produce different responses according to subject characteristics.

A major limitation of the approach in this study was that it was a posthoc exploration after the primary analysis was performed. A selection of baseline factors were tested across a number of time points with associated problems associated with multiple testing. The use of a stricter criterion for significance with α level
of 0.01 instead of 0.05 would result in a more conservative interpretation. The sample size of this trial was relatively small making its conclusions less reliable. A strength of the analysis was that investigation clearly described how predictors of outcome were selected and how missing values were dealt with.

The general conclusion of this investigation is that it may be possible to quantify and predict how certain groups of patients may respond to acupuncture. The generalisability of these findings needs to be confirmed in further larger observational studies.

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Competing interests None.

Ethics approval This study was conducted with the approval of the Monash SCERH.

Provenance and peer review Not commissioned; not externally peer reviewed.

Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

REFERENCES

Summary
► In a trial of laser acupuncture intervention on chronic back pain, certain baseline characteristics in participants were found to predict pain response.
► Response predictors have led to bias in the primary analysis of the study.
► Response predictors should be used in selecting patients for acupuncture studies and considered in their analysis.
The influence of baseline characteristics on response to a laser acupuncture intervention: an exploratory analysis
Gregory Glazov

Acupunct Med 2010 28: 6-11
doi: 10.1136/aim.2009.001206

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Low-dose laser acupuncture for non-specific chronic low back pain: a double-blind randomised controlled trial

Gregory Glazov, Michael Yelland, Jon Emery

ABSTRACT

Objective To determine if infrared laser acupuncture (LA) may have a specific effect in reducing pain and disability in treatment of chronic low back pain (LBP).

Methods This was a double blind sham laser controlled trial performed in general practices in Perth, Western Australia. The participants were 144 adults with chronic non specific LBP. They were randomised to receive eight once weekly treatments. Laser machines (20 mW, 840 nm diode, power density 0.1 W/cm²) stimulated points in three treatment groups: sham (0 joules/point), low dose (0.2 J/poin) and high dose (0.8 joules/point). Participants were followed up at 1 and 6 weeks, and 6 and 12 months post treatment. Primary outcomes were pain (Numerical Pain Rating Scale (NPRS)) and disability (Oswestry Disability Inventory (ODI)) at 6 weeks post treatment. Secondary outcomes included numerical rating scale for limitation of activity, global assessment of improvement, analgesic usage and adverse effects after treatment.

Results The analysis showed no difference between sham and the laser groups at 6 weeks for pain or disability. There was a significant reduction in mean pain and disability in all groups at 6 weeks (p<0.005); NPRS: sham (1.5 vs 2.1), low dose (1.3 vs 2.0) and high dose (1.1 vs 0.5), ODI: sham (4.0 vs 7.1), low dose (4.1 vs 6.7) and high dose (2.6 vs 5.7). All secondary outcomes also showed clinical improvement over time but with no differences between groups.

Conclusions LA using energy density range (0.4 - 4 W/cm²) for the treatment of chronic non specific LBP resulted in clinical improvement unrelated to laser stimulation.

INTRODUCTION

Low-level laser therapy (LLLT) is a light source treatment that emits no heat, sound, or vibration but may act via non-thermal or photochemical reactions in cells. There has been criticism that the effect of laser therapy in painful conditions is only a placebo effect especially as there is still lack of an obvious mechanism particularly given lack of sensation during laser treatment. Despite this, there is some experimental evidence of low-level laser inducing anti-inflammatory, antinociceptive, central nervous and lymphatic effects.

Low-level laser stimulation of acupuncture points (LA), using laser emitter devices applied to skin as an alternative to needles, has been commonly used in the last 35 years. Although LA is a subgroup of LLLT, it is considered a separate form of treatment. Instead of using the direct effect of light on tissues to initiate a physiological response, the selection of points is based on a diagnostic and therapeutic paradigm defined by acupuncture theories.

Laser machines in the lower power output range are commonly used and anecdotaly beneficial results have been reported.

Non-specific chronic low back pain (LBP) was targeted for study as it is common (prevalence of approximately 23%) and associated with significant disability, medical expenses and loss of productivity. It is also commonly treated with acupuncture. Evidence of efficacy for a non-drug, non-invasive treatment that could be used in primary care for this condition would be of great importance.

A position statement on LA by the Australian Medical Acupuncture College
(AMAC) in 1995 stated that ‘the optimal energy density for biostimulation, based on current clinical experience, is 4 J/cm²’. A review examining trials of LA in a range of orthopaedic diseases was equivocal, but noted methodological drawbacks in the studies included. In another review of the clinical effectiveness of LA, including eight trials on treatment of myofascial pain, Baxter concluded that ‘laser acupuncture can be recommended as an effective treatment (moderate level of evidence) for the reduction of myofascial pain, at least when irradiation is applied at power of at least 10 mW and a dosage of at least 0.3 J/point’.

Few randomised trials have specifically studied LA for treatment of chronic LBP compared to a sham laser control, and have not resolved issues of dose dependence for this condition. A small trial using an infrared laser (1.1 J/point) detected a significant improvement in only one of many pain outcomes measured. Subsequently, the results of another larger trial using a 10 mW infrared laser (0.2 J/point) were negative, although questions were raised regarding the possibility of insufficient dosage and of confounding baseline factors. An adjusted analysis showed a benefit for this dose at 6 weeks. It was considered important to perform another quality study resolving these issues with a three-arm design, including a higher dose within Baxter’s recommended range and with long-term follow-up.

SUBJECTS AND METHODS
The study was a double-blind, prospective, three-group parallel randomised controlled trial, using sham laser in the control group with other arms using 0.2 and 0.8 J of laser stimulation per point. It was approved by the University of Western Australia Human Research Ethics Committee.

Patient recruitment and selection
Participants were recruited through notices in local community newspapers. Assessment and treatments were conducted at the premises of six general practices in Perth, Western Australia by five general practitioner (GP) therapists.

Inclusion criteria
Participants had chronic non-specific LBP with duration of at least 3 months, and were aged 18–75 years, English literate and non-pregnant. Baseline pain over the previous week was ≥3.0 on a numerical rating scale, with maximal pain located between the 12th rib and gluteal fold.

Exclusion criteria
Patients were excluded if they had: (i) fibromyalgia, (ii) regular opioid analgesics (≥2 times a week) or opioid patches, (iii) disability support pension for back pain, current worker compensation or motor vehicle insurance claim, (iv) any form of acupuncture for musculoskeletal problems in previous 6 months, (v) previous involvement in an acupuncture trial, (vi) previous injections for back pain such as facet joint blocks, nerve root or epidural steroid injection within previous year or (vii) previous lumbar spine surgery.

Intervention
All therapists were experienced GPs and members of AMAC; at commencement they received training and a written manual on the trial protocol. Participants were encouraged to attend a maximum of eight sessions (one session a week for 8 weeks) of 15 min duration each. They continued with their usual therapies and analgesics according to their pain, but were requested not to start any acupuncture during the year of follow-up.

A pragmatic Western anatomical approach to acupuncture treatment was used, similar to the previous trial. At the start of each session participants were asked to note their average pain experienced during the previous week and indicate current distribution, and report any symptoms since the last treatment. Acupuncture point selection was individualised for each patient. Tender regional and more distal points along radiation pathways of pain were selected. Other acupuncture points depending on additional symptoms reported (eg, headache, other joint pain and psychological issues) were selected at the discretion of the therapist. The points were treated sequentially, with the laser probe resting perpendicularly and in light contact with the skin. No cointervention was used except for general support and information provided as part of each session (see online supplement 1).

Outcome measures
The following measures were applied 1 and 6 weeks, and 6 and 12 months post treatment (immediate, short, intermediate and long-term follow-up).

1. Numerical pain rating scale (NPRS) on a box scale from 0 to 10 describing ‘usual level of pain in the last week’.
2. Oswestry Disability Index (ODI). This was omitted at 12 months to reduce measurement burden.
3. Numerical rating scale of limitation of activities (NLARS) on a box scale from 0 to 10 describing ‘ability to perform usual activities in the last week’.
4. Global assessment of treatment question on a seven point Likert scale describing ‘how overall the back problem had changed compared to before starting the treatment programme’.
5. Frequency of analgesics taken in previous month.
6. Use of analgesics relative to before starting treatment (decreased, unchanged or increased).

The primary outcomes were (i) pain (NPRS) and (ii) disability (ODI) at 6 weeks. Adverse effects in the week after each treatment were recorded using a checklist including occurrence of pain flares and other symptoms.
The following measures were recorded only at baseline as predictors of outcome: the short version of the Depression Anxiety Stress Scale (DASS-21), a neuropathic pain screening questionnaire (ID pain), the Fitzpatrick skin type assessment and the International Physical Activity Questionnaire (IPAQ, short format).

Randomisation/allocation concealment/blinding
As in our previous trial, we used laser apparatus modified for use in double-blind research. The device was a Ga-Al-As infrared laser diode (830 nm) with power output of 20 mW and power density at probe skin interface of 0.1 W/cm². Three machines were purpose built for the trial (Acupak, Melbourne, Australia) for concurrent use in a number of centres. Each machine had a different on/off coding sequence set by operating a cogwheel dial hardwired at time of manufacture. The laser probe had a red LED decoy light that was lit each time the unit was used regardless of laser operation. The device had a fixed power output; in order to vary dose there was a switch enabling time of operation to be set.

The three treatment arms varied according to laser on/off status and the duration of stimulation and consisted of:
1. Low dose: laser ‘on’ with 10 s (0.2 J) stimulation given per point.
2. High dose: laser ‘on’ with 40 s (0.8 J) stimulation given per point.
3. Sham: laser ‘off’ with 10 or 40 s (0 J) stimulation given per point.

Before commencement of the trial, a random computer-generated sequence was generated for each machine (permuted block randomisation technique, block size=6; each block contained 2× laser 40 s, 2× laser 10 s, 1× placebo 10 s, 1× placebo 40 s). Concealed allocation was performed by method of sequentially numbered sealed opaque envelopes.

The participants, therapists and data entry person remained blind to treatment allocation. At commencement of the trial participants were informed that they had a two in three chance of receiving an active laser treatment. They were unaware that duration of point stimulation would vary between different subjects.

Sample size
Based on data from previous trial, for a three-arm parallel study (with SD=2.3 on the numerical pain scale) with α=0.05 and β=0.8, to detect a difference of 1.6 units (moderate effect size) would require a total sample size of 137 allowing for 10% attrition.

Statistical analysis
We used SPSS (V20) for analyses. Data were checked to ensure they satisfied assumptions for statistical testing and were analysed according to intention to treat. Separate analyses were performed on continuous dependent variables (NPRS, ODI and NLARS) for (a) all non-missing values and (b) the ‘last observed value carried over’ method for missing data. Repeated measures analysis of variance (ANOVA) was used to compare treatment groups across time periods for these continuous variables. The χ² test for independence was used to compare differences between treatment groups at follow-up times for categorical variables (general anaesthetic and relative analgesic and frequency of use). The Kruskal–Wallis test was used to test the comparability of treatment and follow-up protocols, as well as differences in the counts of adverse effects between groups during the treatment phase.

Methods for subgroup and adjusted analysis
Baseline characteristics were examined to determine if they predicted pain reduction after treatment, specifically, percentage pain change (PPC) from baseline to follow-up. Analysis of covariance (ANCOVA) was used in an adjusted analysis to evaluate PPC at immediate and short-term follow-up across the treatment groups while controlling for the effects of predictive baseline variables.

RESULTS

Participant recruitment and flow
Recruitment, treatment and completion follow-up was conducted from October 2008 to March 2012 (figure 1). After screening for eligibility 144 participants were enrolled and randomised to receive the interventions. A total of 74% of the treatment sessions were performed by the principal investigator (GG). In all, 96% of participants completed five or more treatment sessions. Reasons for participants pulling out of treatment early included unavailability, unwillingness to participate and unrelated illness. One subject pulled out due to an exacerbation of pain. There was an overall 96.5% analysis rate for the primary outcome assessment for pain. Follow-up rate achieved for the whole group was 90% at 12 months. The reasons for participants who were lost to follow-up could not be obtained.

Details of acupuncture points used
Frequently used points were situated on acupunc-
Baseline data of demographics and clinical characteristics

Baseline characteristics across groups were generally evenly distributed, however total imbalance greater than 15% was seen in gender, sleep disturbance, anti-depressant medication use, Fitzpatrick skin type and depression categories (table 2).

Comparison of adherence to treatment and follow-up schedules between study groups

There were no significant differences between treatment groups in the number of treatments given, duration of treatment and intervals of follow-up.

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**Table 1**  Number of acupuncture points administered and total energy dose of laser given per treatment group

<table>
<thead>
<tr>
<th>Trial arm</th>
<th>Dose per point, J</th>
<th>Total no points treated (% total)</th>
<th>Total estimated dose in J per group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham (10 s or 40 s)</td>
<td>0.0</td>
<td>3008 (32.0)</td>
<td>0</td>
</tr>
<tr>
<td>Low dose (10 s)</td>
<td>0.2</td>
<td>3830 (40.5)</td>
<td>766</td>
</tr>
<tr>
<td>High dose (40 s)</td>
<td>0.8</td>
<td>2622 (27.7)</td>
<td>2098</td>
</tr>
</tbody>
</table>

Calibration and validity of settings were checked at the end of the treatment phase. Maximal power outputs of the machines were measured at 22.7, 14.4 and 17.7 mW, respectively. This may have been the result of reduction of power output over time in ageing diodes.32

---

Comparison of primary outcomes and other continuous outcome measures in the study groups

Mean values for pain and disability in the three treatment groups at baseline and at all follow-up times are presented in table 3. There was no significant difference between groups for pain or disability (ODI) scores at 6 weeks or any other timepoint. All three treatment groups showed reduction in pain and ODI scores across all timepoints (p<0.0005). In the whole cohort there was a clinically significant 28% reduction in pain immediately after treatment, maintained at 26% at 1 year. There was only an approximate 4% reduction in mean ODI scores in the whole cohort, which was maintained at 6 months. There were no differences between groups for NLARS scores at any timepoint but again a significant main effect for time (p<0.0005) (online supplement figure S2). Results were consistent for all continuous outcomes using both imputation methods.

Additional secondary outcomes

There was no significant difference between groups in improvement on the global assessment scale, or in measures of analgesic use (table 4). Across the whole cohort approximately half of the participants considered that their back had improved at every timepoint after treatment, and approximately one-third considered they had reduced their analgesic use at all follow-up points. There was little change in reported frequency of taking analgesics during the trial.

In the whole cohort there was a flare-up of back pain in the week following 28% of treatments and some other adverse effect after 25% of treatments. However, there was no significant difference in the frequency of flare of pain or other adverse effects between treatment groups.

Adjusted analysis

After adjusting for any imbalance of predictive baseline factors, there was no significant difference between treatment groups on PPC at 1-week and 6-week follow-up. Details of the subgroup analysis will be presented subsequently.

DISCUSSION

This is the largest and most robust RCT of LA for chronic LBP ever conducted. It found no difference in any outcome or adverse effects at any timepoint for considered that their back had improved at every timepoint after treatment, and approximately one-third considered they had reduced their analgesic use at all follow-up points. There was little change in reported frequency of taking analgesics during the trial.

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DISCUSSION

This is the largest and most robust RCT of LA for chronic LBP ever conducted. It found no difference in any outcome or adverse effects at any timepoint for

Table 2  Distribution of baseline characteristics across treatment groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sham (n=48)</td>
</tr>
<tr>
<td>Demographics:</td>
<td></td>
</tr>
<tr>
<td>Male gender, %</td>
<td>60</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>12</td>
</tr>
<tr>
<td>Employed, %</td>
<td>55</td>
</tr>
<tr>
<td>On age or other pension, %</td>
<td>33</td>
</tr>
<tr>
<td>Median age in years (25th/75th percentiles)</td>
<td>53.5 (40/66)</td>
</tr>
<tr>
<td>Body mass index, mean (SD)</td>
<td>26.2 (3.7)</td>
</tr>
<tr>
<td>Baseline pain characteristics:</td>
<td></td>
</tr>
<tr>
<td>Participants with pain &gt;2 years, %</td>
<td>81</td>
</tr>
<tr>
<td>Median duration of pain in years</td>
<td>10</td>
</tr>
<tr>
<td>Acute on chronic exacerbation pain, %</td>
<td>13</td>
</tr>
<tr>
<td>Headaches present, %</td>
<td>27</td>
</tr>
<tr>
<td>Neck pain present, %</td>
<td>60</td>
</tr>
<tr>
<td>Sleep disturbance (&lt;6 h sleep), %</td>
<td>38</td>
</tr>
<tr>
<td>Previous and current treatment:</td>
<td></td>
</tr>
<tr>
<td>Previous acupuncture &gt;6 months ago, %</td>
<td>40</td>
</tr>
<tr>
<td>Regular use of simple analgesia, %</td>
<td>17</td>
</tr>
<tr>
<td>Use of antidepressant medication, %</td>
<td>10</td>
</tr>
<tr>
<td>Other baseline outcome measures:</td>
<td></td>
</tr>
<tr>
<td>Fitzpatrick skin type (I II), %</td>
<td>28</td>
</tr>
<tr>
<td>Neuropathic pain (ID Pain 2 4), %</td>
<td>19</td>
</tr>
<tr>
<td>Low level physical activity (IPAQ), %</td>
<td>23</td>
</tr>
<tr>
<td>Depression: moderate severe+ (DASS 21), %</td>
<td>13</td>
</tr>
<tr>
<td>Anxiety: moderate severe+ (DASS 21), %</td>
<td>15</td>
</tr>
<tr>
<td>Stress: moderate severe+ (DASS 21), %</td>
<td>19</td>
</tr>
</tbody>
</table>

DASS 21, Depression Anxiety Stress Scale (short form); IPAQ, International Physical Activity Questionnaire.
LA in doses up to 0.8 J/point (energy density 1–4 J/cm²) when compared with sham laser. This trial strengthens the evidence for a lack of biological effect from laser at this low-dose range when treating chronic LBP. It also supports the influence of non-specific effects that may produce beneficial therapeutic outcomes in some patients, which otherwise may have been falsely attributed to the laser. A 30% PPC has previously been described as a clinically meaningful improvement. In our whole cohort such non-specific effects resulted in a clinically important improvement approached in mean pain scores immediately following the last treatment, which persisted almost at the same level throughout follow-up. There was a smaller reduction in disability that was probably not clinically important.

A number of factors may have contributed to overall improvement after the intervention, including the placebo effect, the phenomenon of regression to the mean, natural history and effects simply from participating in an experiment (the Hawthorne effect). Some improvement may possibly have resulted from the acupressure-like effects of skin stimulation during examination for tender points.

In the past LA trials have shown methodological limitations including small sample size, variable blinding and crossover designs. We applied a robust trial design to reduce risk of bias including gold standard

### Table 3

Mean values for pain and disability at baseline and follow-up across treatment groups (‘no missing data’ dataset)

<table>
<thead>
<tr>
<th>Trial arm</th>
<th>Data shown</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>Pain (NPRS):</td>
<td>Sham Mean (N, SD)</td>
<td>4.9 (48, 1.4)</td>
</tr>
<tr>
<td></td>
<td>Low dose Mean (N, SD)</td>
<td>4.9 (48, 1.5)</td>
</tr>
<tr>
<td></td>
<td>High dose Mean (N, SD)</td>
<td>5.3 (48, 1.6)</td>
</tr>
<tr>
<td></td>
<td>Total Mean (N, SD)</td>
<td>5.0 (144, 1.5)</td>
</tr>
<tr>
<td>Change from baseline, %</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>Disability (ODI):</td>
<td>Sham Mean (N, SD)</td>
<td>26 (47, 12)</td>
</tr>
<tr>
<td></td>
<td>Low dose Mean (N, SD)</td>
<td>27 (48, 12)</td>
</tr>
<tr>
<td></td>
<td>High dose Mean (N, SD)</td>
<td>27 (47, 12)</td>
</tr>
<tr>
<td></td>
<td>Total Mean (N, SD)</td>
<td>27 (142, 12)</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>0</td>
<td>4.4</td>
</tr>
<tr>
<td>Disability (NLARS):</td>
<td>Sham Mean (N, SD)</td>
<td>4.3 (48, 2.1)</td>
</tr>
<tr>
<td></td>
<td>Low dose Mean (N, SD)</td>
<td>4.5 (48, 1.7)</td>
</tr>
<tr>
<td></td>
<td>High dose Mean (N, SD)</td>
<td>4.2 (48, 2.1)</td>
</tr>
<tr>
<td></td>
<td>Total Mean (N, SD)</td>
<td>4.3 (144, 2.0)</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>0</td>
<td>4.4</td>
</tr>
</tbody>
</table>

**NLARS:** Numerical rating scale of limitation of activities; **NPRS:** Numerical pain rating scale; **ODI:** Oswestry Disability Index.

### Table 4

Secondary outcome contingency tables (global assessment and analgesic use) for treatment groups across follow-up

<table>
<thead>
<tr>
<th>Usage on global assessment, %</th>
<th>Timescale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condition</td>
<td>Baseline</td>
</tr>
<tr>
<td>No change/worse</td>
<td>36 (40, 36, 32)</td>
</tr>
<tr>
<td>Improved</td>
<td>64 (60, 64, 68)</td>
</tr>
<tr>
<td>Relative use of analgesics, %</td>
<td>Relative use analgesics across follow up: total (sham, low dose, high dose)</td>
</tr>
<tr>
<td>Unchanged or increased</td>
<td>63 (72, 56, 61)</td>
</tr>
<tr>
<td>Decreased</td>
<td>37 (28, 44, 39)</td>
</tr>
<tr>
<td>Frequency of use, %</td>
<td>Frequency analgesic use across follow up: total (sham, low dose, high dose)</td>
</tr>
<tr>
<td>Nil ≤1/month</td>
<td>34 (30, 37, 35)</td>
</tr>
<tr>
<td>Several/month</td>
<td>33 (38, 30, 32)</td>
</tr>
<tr>
<td>Several/week</td>
<td>33 (32, 33, 33)</td>
</tr>
</tbody>
</table>

randomisation and concealed allocation procedures for this type of research. Participants and therapists were successfully blinded to treatment allocation by using a specially designed device ensuring masking the mode of laser emission. Although the duration of laser application to points was not masked, participants remained unaware of this treatment variable and were thus effectively ‘blinded’. Therapists who were aware, tended to stimulate larger numbers of points in subjects allocated the shorter-dose treatment. The total laser dose given in the low-dose arm was still one-third of the high-dose arm (table 1), allowing a meaningful investigation of dose dependence. Imputation approaches to manage missing data made no difference to the results. A preplanned, adjusted analysis showed that any baseline imbalance did not affect the primary result in the current trial.

This study had multiple exclusion criteria that may have reduced the external validity of this trial. This was informed by preceding research excluding patients on disability support, regular users of any opioid and with previous back surgery or spinal injections. These groups previously demonstrated less improvement after intervention. Our intent was to maximise the chance of detecting a specific effect of laser stimulation, if it existed. A greater improvement in pain or disability was not observed in this trial, however. The reasons for this may have been an exercise intervention, a larger number of treatment sessions and a higher mean baseline level of pain in the preceding study.

A large number of laser parameters available in treatment may make comparison between trials difficult to interpret. Different laser devices have different radiant power outputs and wavelengths ranging from the visible spectrum to infrared. Dose in joules per point and density of laser irradiation can also vary. Although this study examined the effect of infrared laser diodes using low energy densities for treating this condition, it is still possible that larger energy doses or different wavelengths may be more effective for chronic LBP. A much higher laser dose (8 J Joules ± 50%/point) for laser therapy of the lumbar spine is recommended by the World Association for Laser Therapy; however these recommendations refer to non-acupuncture LLLT. A recent German LA trial of a much higher energy ‘laser needle’ device failed to show a specific effect of laser treatment. Future research also needs to consider LA treatment of other musculoskeletal problems.

This trial only partly clarifies decisions for therapists contemplating purchasing expensive laser pointer machines in the lower energy range to treat back pain. While there appear to be considerable improvements in pain and other measures following treatment using such devices, this trial suggests that the effect is not specifically due to laser at the low dosage commonly used in clinical practice. Scope however remains for further research to determine dosage windows and conditions that could respond to LA.

Summary points

- A total of 144 patients with low back pain received either 0.2 or 0.8 J/point infrared laser acupuncture or placebo control.
- All outcomes improved up to 1 year, with no differences between groups.
- This low dose of laser has no biological effect, but higher doses should also be tested.

Correction notice This article has been corrected since it was published Online First. The results section has been amended to read: 'at 6 weeks (p<0.005; NPSRS: sham (1.5 (95% CI 2.1 to 0.8)).' The first 'Usage' in Table 4 has also been amended to read 'Condition on global assessment, %. The first Summary point has been amended to read: 'A total of 144 patients with low back pain received either 0.2 or 0.8 J/point infrared laser acupuncture or placebo control.'

Acknowledgements We thank all the patients who participated in the trial; Drs PetraKonowalow, David Mortley, John Troy and Helen Lamont for assisting as GP therapists; Hillarys Medical Centre and other medical centres for providing rooms to treat participants; Australian Medical Acupuncture College for purchasing some of the machines for this trial. Laura Firth (UWA Centre for Applied Statistics) provided statistical advice.

Contributors GG was a PhD candidate and principal investigator, was responsible for the study concept and design and was involved in assessment, the majority of therapy, follow up, data entry and checking, statistical analysis and drafting the manuscript. JE (Coordinating Supervisor) and MF (External Supervisor) both offered support and advice at all stages of the project, and assisted with revision of the manuscript.


Competing interests GG received a Primary Health Care Research, Evaluation and Development (PHCREDS) Bursary at UWA in 2008, funded by the Australian Commonwealth Government.

Ethics approval University of Western Australia Human Research Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data sharing: Any further data available on request from the corresponding author at glazog01@student.uwa.edu.au.

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Low-dose laser acupuncture for non-specific chronic low back pain: a double-blind randomised controlled trial

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Low-level laser therapy for chronic non-specific low back pain: a meta-analysis of randomised controlled trials

Gregory Glazov,1,2 Michael Yelland,3 Jon Emery4

ABSTRACT
Objective The efficacy of low level laser treatment (LLLT) for chronic back pain remains controversial due to insufficient trial data. We aimed to conduct an updated review to determine if LLLT (including laser acupuncture) has specific benefits in chronic non specific low back pain (CNLBP).

Methods Electronic databases were searched for randomised trials using sham controls and blinded assessment examining the intervention of LLLT in adults with CNLBP. Primary outcomes were pain and global assessment of improvement with up to short term follow up. Secondary outcomes were disability, range of back movement, and adverse effects. A random effects meta analysis was conducted. Subgroup analyses were based on laser dose, duration of baseline pain, and whether or not laser therapy used an acupuncture approach.

Results 15 studies were selected involving 1039 participants. At immediate and short term follow up there was significant pain reduction of up to WMD (weighted mean difference) 1.40 cm (95% CI 1.91 to 0.88 cm) in favour of laser treatment, occurring in trials using at least 3 Joules (J) per point, with baseline pain <30 months and in non acupuncture LLLT trials. Global assessment showed a risk ratio of 2.16 (95% CI 1.61 to 2.90) in favour of laser treatment in the same groups only at immediate follow up.

Conclusions We demonstrated moderate quality of evidence (GRADE) to support a clinically important benefit in LLLT for CNLBP in the short term, which was only seen following higher laser dose interventions and in participants with a shorter duration of back pain. Rigorously blinded trials using appropriate laser dosage would provide greater certainty around this conclusion.

INTRODUCTION
Chronic non-specific low back pain (CNLBP) not attributable to a recognisable, known specific pathology is common, with an estimated prevalence in developed countries of approximately 23%.1 CNLBP is a major cause of medical expenses, absenteeism, and disability. There are concerns regarding the benefits and potential harms of medication such as paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), and opioids.2,3 for the treatment of chronic back pain, and non-drug treatments including exercise and multidisciplinary and behavioural treatment have been demonstrated to be of benefit.4,5

Low-level laser therapy (LLLT) is a light source treatment that may act via nonthermal or photochemical reactions in cells. It includes laser acupuncture (LA), which involves focused irradiation at specific points, most commonly traditional acupuncture points, with a low intensity laser.5 LLLT for pain relief in medicine remains controversial with claims that apparent efficacy is due to the placebo effect.

Multiple mechanisms for LLLT analgesia may exist. There is experimental evidence suggesting that laser irradiation induces peripheral neural blockade, suppresses central synaptic activity, modulates neurotransmitters, reduces muscle spasm and interstitial oedema, and exerts anti-inflammatory effects.6 The World Association of Laser Therapy (WALT) has published guidelines for LLLT dosage described in Joules (J) per point for arthritis and tendinopathy.7

A number of meta-analyses since 2003 have reported pain relief from LLLT in painful musculoskeletal conditions.8–10 In 2008, a Cochrane systematic review of laser therapy focusing on non-specific low back pain (LBP)11 included seven trials, considered both acute and chronic pain, did not restrict controls to sham laser, and excluded LA trials. At that point, there...
were insufficient data to draw firm conclusions on the effect of LLLT in LBP. Our objective was to conduct an updated systematic review of the efficacy of LLLT, including LA, for the treatment of CNLBP.

METHODS
This meta-analysis was performed in accordance with the guidelines of the Cochrane Back Review Group (CBRG)\(^\text{12}\) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).\(^\text{13}\) The study protocol is provided in online supplementary data file appendix A.

Eligibility criteria
Studies were randomised controlled trials (RCTs) with blinded assessment of the outcome. Participants were non-pregnant adults with CNLBP\(^\text{1}\). The primary intervention studied was LLLT, including LA. For the purposes of this review, LA studies were defined as those in which low intensity laser was applied to classical acupuncture points, tender points and/or trigger points, and where acupuncture intent was explicitly stated in the report; other studies were classified as non-acupuncture laser therapy. The comparison included sham laser therapy with similar appearance to the active treatment but without laser irradiation. Studies including co-interventions were allowed if applied equally to both laser and control groups. Crossover studies were excluded.

Outcomes
Primary outcomes were: (1) LBP measured by visual analogue scale (VAS) or numerical pain rating scale (NPRS); and (2) ‘global assessment’, which represented dichotomous categorical outcomes of overall improvement or satisfaction with the received intervention. These were measured immediately (<1 week post-treatment) and at short-term (1–12 weeks) follow-up.

Secondary outcomes included disability, quantified using the Oswestry Disability Index (ODI)\(^\text{14}\) or the Roland-Morris Disability Questionnaire (RMQ),\(^\text{15}\) as well as adverse effects, range of movement (ROM) of the back, and pain or global assessment at intermediate (~6 months) and long-term (~1 year) follow-up.

Search methods for identification of studies
Electronic databases (MEDLINE, PubMed, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Central Register of Controlled Trials (CENTRAL), Allied and Complementary Medicine Database (AMED), and Physiotherapy Evidence Database (PEDro)) were searched for RCTs of laser therapy or LA for the treatment of chronic LBP in which the control treatment used was sham laser. Publication reference lists were additionally examined to identify any missed studies. We used the Updated Search Strategies for CBRG,\(^\text{16}\) which included a generic search for RCTs and controlled clinical trials, combined with a specific search for ‘back’ conditions. We completed the search by adding terms related to the laser intervention, as detailed in the online supplementary data file appendix B.

Selection of studies, data extraction and management
Papers were initially screened at title and abstract level by one reviewer (GG) who removed duplicate reports and ineligible trials. There was no restriction of full text by language. Potentially eligible papers were reviewed by pairs of reviewers and data extracted independently. Authors were contacted if possible, to clarify further information. We used RevMan 5.3 (Cochrane Collaboration)\(^\text{17}\) for data management and statistical analysis.

Assessment of risk of bias in included studies
We adapted the Cochrane Collaboration tool\(^\text{12}\) for assessing risk of bias in 12 domains. Paired reviewers categorised domains as ‘high’, ‘low’ or ‘unclear’ risk of bias; disagreements were resolved by consensus. External reviewers assessed bias in one specific trial\(^\text{18}\) for which our reviewers were the authors. Trials were considered to be at ‘higher risk of bias’ if they contained more than six domains of ‘high’ and ‘uncertain’ risk.

Measures of treatment effect
For continuous data (pain intensity, disability, and ROM), treatment effects were expressed as a mean difference (MD) or standardised mean difference (SMD) together with 95% CIs. For global assessment we calculated the risk ratio (RR) and 95% CI. Meta-analysis was used to combine the results of trials using a random-effects model.

Unit of analysis issues
Different pain measurement scales (VAS and NPRS) were converted to a scale of 0–10 cm. In one trial\(^\text{15}\) that examined more than one laser dose, in order to avoid ‘double counts’, we split the sham laser control group into two equally sized groups to allow inclusion of two independent comparisons within the meta-analysis.\(^\text{19}\)

Missing data, assessment of heterogeneity and publication bias
We used the RevMan calculator\(^\text{17}\) to derive unreported statistical data. Where laser parameters were unreported, the following physical formula was used to calculate the dose:

- Energy dose (J) = Watts (W) × seconds (secs);
- Energy density (J/cm\(^2\)) = W × secs/area of treated surface or probe tip (cm\(^2\));
- Power density (W/cm\(^2\)) = W/area of treated surface or probe tip (cm\(^2\)).

Heterogeneity was assessed and interpreted as described in the Cochrane Handbook.\(^\text{19}\) I\(^2\) values of
0–40%, 30–60%, and 50–90% were considered to represent ‘unimportant’, ‘moderate’, and ‘substantial’ heterogeneity, respectively. Publication bias was addressed by examination of funnel plots for primary outcomes.

Data synthesis
We conducted meta-analysis for outcomes at immediate and short-term follow-up except where outcomes were reported for two studies or less, in which case results were presented narratively, together with the longer term follow-up. Decisions for conducting subgroup analyses were made at protocol stage based on: (1) acupuncture/non-acupuncture laser therapy; and (2) laser dosage. A post-hoc decision regarding the cut-off value for laser dose and a subgroup analysis for baseline pain duration was guided by consideration of the review findings. A sensitivity-analysis was performed excluding trials considered at ‘higher risk of bias’.

Grading the quality of evidence
We followed the CBMRG12 recommendation to adapt the GRADE20 approach for back reviews with the quality of the evidence based on five domains (limitations of the study design, inconsistency, indirectness, imprecision, and publication bias).

RESULTS
Search results
Electronic searches of databases from inception until August 2014, and screening reference lists, identified 15 studies that satisfied the inclusion criteria (figure 1). Three papers required translation into English from German21 and Japanese.22 23

Characteristics of included studies
Participants
The selected trials18 21−34 included 1039 participants at randomisation (table 1). Participants were mostly recruited into trials from hospitals and rehabilitation clinics, except in the case of four trials18 21−28 that recruited via community newspapers. Some trials did not fully describe details of their inclusion criteria for chronicity22 23 or specificity.22 23 31 In trials where the mean baseline duration of pain was reported, this was categorised as ‘shorter’24 26 27 30 (average range 4.6–27 months) or ‘longer’18 21 25 28 29 34 (49 months to 13 years).

Interventions
Five trials were classified as LA studies18 21 28 31 34 (table 2). Three of these trials used smaller doses of 0.2–1.1 J/poin1.18 28 34 One trial21 used a ‘laser needle’ device to deliver 60–180 J/poin irradiation, while another31 used 12 J/poin.

The remaining 10 trials were classified as non-acupuncture laser therapy studies. Two studies24 29 used ≤2.8 J/poin, while much higher dosages were used in another two trials26 33 (239 and 1200 J/poin, respectively). The remaining six trials used doses in the range of 3–25 J/poin. Three trials24 27 33 used manual scanning to irradiate larger anatomically defined areas as well as irradiation of discrete points. Reporting of laser parameters was incomplete in certain trials and some values were calculated or assumed if authors could not be contacted.

Controls
A variety of methods to achieve sham laser controls were reported including use of the same machine with on/off switch, or use of a separate machine and/or probe. Blinding methods included the use of opaque goggles, as well as a specific laser machine35 capable of blinding both patient and operator to treatment allocation (table 2). In some trials the description of the masking procedure was unclear24 26 27 32 or completely absent.31 Only three studies18 21 28 statistically analysed the success of the blinding technique used.

Outcomes
Only four trials18 21 26 28 defined predetermined primary outcomes. The majority of studies reported pain using a VAS; two studies18 34 used an NPRS. Participant-based ‘global assessment’ was reported as a dichotomised categorical variable including ‘condition improved’ versus ‘same or worse’18 28 and ‘good response’ versus ‘same or undecided’.22 23 Two trials only reported an arbitrary level of improvement on a pain scale (eg, >50% reduction of chronic pain on Von Korff Scale24 or >60% reduction pain on VAS scale22). These dichotomous outcomes were combined during meta-analysis to determine the RR of ‘global improvement’. The majority of studies that reported disability used ODI; one trial reported only RMQ.29 Range of back movement was measured as flexion in centimetres (Schober’s test25−27 30 or in degrees.24 29 Occurrence of adverse effects was briefly mentioned in five trials25 26 29 32 34 but quantitative comparisons were only undertaken in three.18 21 28 Most studies reported immediate and/or short-term outcomes; only three studies18 28 32 reported outcomes at longer-term follow-up.

Risk of bias in included studies
Figure 2 demonstrates the proportion of studies determined to be low risk for each domain. Under our criteria we found three trials24 31 33 that we considered to be at ‘higher risk of bias’.

Primary outcomes
Pain
Meta-analysis of data from 653 participants across 10 trials at immediate follow-up indicated a statistically significant reduction in total pain scores in laser versus control groups (WMD (weighted mean difference) −0.79 cm, 95% CI −1.22 to −0.36 cm; \( I^2=70\% \)), albeit with substantial heterogeneity (figure 3).
In our subgroup analyses, a significant reduction of pain (laser compared to control) was only seen for the trials in which participants had shorter mean baseline duration (<30 months) of LBP (WMD −1.39 cm, 95% CI −1.71 to −1.07 cm; I²=23%). Significant differences between laser and control were also seen in the higher dose trials (>3 J/point) (WMD −1.23 cm, 95% CI 11.61 to −0.84 cm; I²=51%) and non-acupuncture trials (WMD −1.17 cm, 95% CI −1.60 to 0.74 cm; I²=62%). At short-term follow-up, there were no significant differences and substantial heterogeneity in the total pain score was observed (see six trials, 391 participants; online supplementary data file appendix C). In subgroup analyses we observed a significant reduction of pain (for laser compared to control) with the largest effect seen in higher dose trials and in trials with shorter duration of back pain at baseline (WMD −1.40 cm, 95% CI −1.91 to −0.88 cm; I²=0%).

Global assessment
As illustrated in figure 4, pooling of categorical data at immediate follow-up from 416 subjects (five trials) showed a significant effect on global assessment (RR 1.5, 95% CI 1.10 to 2.04; I²=65%) in favour of laser treatment (substantial heterogeneity present) with a greater improvement in both non-acupuncture and higher dose subgroups (RR 2.16, 95% CI 1.61 to 2.90; I²=0%) with reduced heterogeneity. Pooled data for short-term follow-up showed no significant differences for three included LA trials, two of which used a ‘lower’ dose (see online supplementary data file appendix D).

Sensitivity analysis
Results were robust to exclusion of trials considered at ‘higher risk of bias’ with pain differences in favour of laser in the higher dose subgroup at immediate (WMD...
<table>
<thead>
<tr>
<th>Trial First author (year) (country)</th>
<th>Total group size (n)</th>
<th>Mean age (years)</th>
<th>(1) Clinical inclusion criteria</th>
<th>Baseline mean pain duration</th>
<th>Baseline mean pain intensity (0–10 cm)</th>
<th>Baseline mean disability ODI (RMQ)</th>
<th>Other baseline variables reported</th>
<th>Outcomes measure (follow-up periods) post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alayat24 (2014) (Saudi Arabia)</td>
<td>52 33</td>
<td>33</td>
<td>(1) Male patients with history of LBP for at least 1 year (2) Yes</td>
<td>13 months</td>
<td>8.3</td>
<td>34</td>
<td>Bodyweight</td>
<td>Pain, ODI, ROM (immediate, 12 weeks)</td>
</tr>
<tr>
<td>Ay25 (2010) (Turkey)</td>
<td>40 53.5</td>
<td></td>
<td>(1) LBP over 3 months duration due to lumbar disc herniation (2) Yes</td>
<td>49 months</td>
<td>6.3</td>
<td>24(15)</td>
<td>Education level</td>
<td>Pain, ODI, ROM, ROM, GA (immediate)</td>
</tr>
<tr>
<td>Basford26 (1999) (USA)</td>
<td>63 48</td>
<td></td>
<td>(1) Non-radiating low back pain of &gt;30 days duration (2) Yes</td>
<td>10 months</td>
<td>3.6</td>
<td>23</td>
<td>Degeneration on lumbar X-ray, analgesic use, previous treatment</td>
<td>Pain, ODI, ROM (immediate, 4 weeks)</td>
</tr>
<tr>
<td>Djavid27 (2007) (Iran)</td>
<td>41 37</td>
<td></td>
<td>(1) LBP minimum 12 weeks duration (2) Yes</td>
<td>27 months</td>
<td>6.2</td>
<td>33</td>
<td>Education level, smoking status</td>
<td>Pain, ODI, ROM (immediate, 6 weeks)</td>
</tr>
<tr>
<td>Glazov28 (2009) (Australia)</td>
<td>100 51</td>
<td></td>
<td>(1) LBP at least 3 months duration (2) Yes</td>
<td>11 years</td>
<td>5.7</td>
<td>30</td>
<td>Multiple</td>
<td>Pain, ODI, GA (immediate, 6 weeks, 6 months, 6 months, 1 year)</td>
</tr>
<tr>
<td>Glazov29 (2014) (Australia)</td>
<td>144 54</td>
<td></td>
<td>(1) LBP at least 3 months duration (2) Yes</td>
<td>13 years</td>
<td>5.0</td>
<td>27</td>
<td>Multiple</td>
<td>Pain, ODI, GA (immediate, 6 weeks, 6 months)</td>
</tr>
<tr>
<td>Klein29 (1990) (USA)</td>
<td>20 42</td>
<td></td>
<td>(1) LBP at least 12 months duration (2) Yes</td>
<td>8.5 years</td>
<td>3.2</td>
<td>(5.6)</td>
<td>Nil other</td>
<td>Pain, ROM (1 month)</td>
</tr>
<tr>
<td>Konstantinovic30 (2011) (Serbia)</td>
<td>56 69</td>
<td></td>
<td>(1) Geriatric patients with chronic LBP caused by degenerative changes without red flag symptoms (2) NR</td>
<td>4.6 months</td>
<td>6.8</td>
<td>31</td>
<td>Nil other</td>
<td>Pain, ODI, ROM (immediate)</td>
</tr>
<tr>
<td>La31 (2012) (Taiwan)</td>
<td>28 64</td>
<td></td>
<td>(1) LBP at least 3 months, recruited from a hospital. Other complications like heart attack, kidney problem, pregnancy, excluded (2) NR</td>
<td>NR</td>
<td>5.2</td>
<td>NR</td>
<td>BMI</td>
<td>Pain (immediate)</td>
</tr>
<tr>
<td>Okamoto32 (1989) (Japan)</td>
<td>69 57</td>
<td></td>
<td>(1) Patients admitted to hospital with LBP; pregnant, lactating, recent surgery, immune suppressants, difficult to treat excluded (2) NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Nil other</td>
<td>GA (immediate)</td>
</tr>
<tr>
<td>Ruth33 (2010) (Germany)</td>
<td>111 59</td>
<td></td>
<td>(1) LBP over 6 months duration (2) Yes</td>
<td>10 years</td>
<td>6.3*</td>
<td>NR</td>
<td>Employment status</td>
<td>GA (pain, disability)* (12 weeks)</td>
</tr>
<tr>
<td>Soriano34 (1998) (Argentina)</td>
<td>85 64</td>
<td></td>
<td>(1) LBP duration over 3 months (2) Yes</td>
<td>NR</td>
<td>8.0</td>
<td>NR</td>
<td>Nil other</td>
<td>GA (immediate)</td>
</tr>
</tbody>
</table>
−1.5 cm, 95% CI −1.8 to −1.2 cm) and short-term (WMD −1.7 cm, 95% CI −2.5 to −1.0 cm) follow-up (see online supplementary data file appendix E). Similar findings were shown in non-acupuncture and ‘short duration’ subgroups. There were no trials at higher risk of bias that reported global assessment outcomes.

**Secondary outcomes**

Intermediate and long term pain and global assessment

Two trials (both low dose LA) reported outcomes at 6 months and at 12 months. They found no significant difference between groups for pain or global assessment at these time periods. One trial that reported less relapse of pain in the laser group at 6 months used an unvalidated outcome.

Disability

Analysis of data from 490 subjects (eight trials) at immediate follow-up found a small reduction in combined ODI score in laser versus control (WMD −2.5%, 95% CI −4.6% to −0.4%; I²=47%; see online supplementary data file appendix F). Subgroup analyses showed greater benefit of laser in non-acupuncture trials (WMD −3.5%, 95% CI −6.0% to −1.5%; I²=33%), and those applying higher dose treatment and/or including subjects with a shorter duration of back pain (WMD −3.6%, 95% CI −6.1% to −1.1%; I²=48%). Combined data from 383 subjects (six trials) at short-term follow-up found no significant difference, but subgroup analyses found greater benefit up to a WMD of −5.9% (95% CI −8.9% to −2.8%; I²=64%) in the same groups.

Range of back movement

ROM was measured only in the non-acupuncture trials. One trial found a significant difference of 4° flexion in favour of laser in the short-term.

**Adverse effects**

Brief reference to the absence of adverse effects was made in six trials. One trial found a significant difference of 4° flexion in favour of laser in the short-term.

**Risk of publication bias**

We plotted the effect sizes from trials that reported pain at immediate or short-term follow-up against the inverse of their standard error (see online supplementary data file appendix G). Visual inspection of the funnel plot did not show asymmetry suggestive of ‘small study bias’.

**Quality of evidence**

We reached the conclusion that there was moderate quality evidence (GRADE profile) that laser therapy reduces pain in the immediate and short term in subjects with CNLBP if pain has been present for
<table>
<thead>
<tr>
<th>Trial</th>
<th>Laser diode</th>
<th>Pulse mode</th>
<th>Wavelength (nm)</th>
<th>Dose/ point (J)</th>
<th>Spot size (cm²)</th>
<th>Mean laser power (mW) (peak power)</th>
<th>Energy density (J/cm²)</th>
<th>Power density (W/cm²)</th>
<th>Sessions/ weeks Points treated per session</th>
<th>Co-intervention</th>
<th>Details of sham control</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Alayat</em> (2014)</td>
<td>Nd:YAG</td>
<td>Pulsed</td>
<td>1064</td>
<td>25</td>
<td>0.2</td>
<td>1786 (3 kW)</td>
<td>0.61</td>
<td>8.9</td>
<td>12/4</td>
<td>Exercise</td>
<td>No description of control device or if separate device used. Success of blinding not reported</td>
</tr>
<tr>
<td>Ay (2010)</td>
<td>GaAlAs</td>
<td>Pulsed</td>
<td>805</td>
<td>2.8</td>
<td>0.07</td>
<td>12 (100 mW)</td>
<td>40</td>
<td>1.4</td>
<td>15/3</td>
<td>Hot packs</td>
<td>Control used same machine without turning on device. Success of blinding not reported</td>
</tr>
<tr>
<td><em>Basford</em> (1999)</td>
<td>Nd:YAG</td>
<td>Continuous</td>
<td>1060</td>
<td>239</td>
<td>4.9</td>
<td>2660</td>
<td>49</td>
<td>0.542</td>
<td>12/4</td>
<td>Nil</td>
<td>Control inactivated by the same but inactive probes. Not clear if separate machine used. Success of blinding not reported</td>
</tr>
<tr>
<td><em>Djavid</em> (2007)</td>
<td>GaAlAs</td>
<td>Continuous</td>
<td>B10</td>
<td>&lt;7.5</td>
<td>0.22</td>
<td>50</td>
<td>27</td>
<td>8.2</td>
<td>12/6</td>
<td>Exercise</td>
<td>Control was inactivated with inactive probes. Not clear if separate machines used. Procedure to ensure masking not described, and success of blinding not reported</td>
</tr>
<tr>
<td><em>Glazov</em> (2009)</td>
<td>GaAlAs</td>
<td>Continuous</td>
<td>B10</td>
<td>0.2</td>
<td>10</td>
<td>1</td>
<td>1</td>
<td>0.05</td>
<td>15/10</td>
<td>Exercise</td>
<td><em>Device custom designed for this research.</em> Success of blinding confirmed by statistical analysis</td>
</tr>
<tr>
<td><em>Glazov</em> (2014)</td>
<td>GaAlAs</td>
<td>Continuous</td>
<td>B10</td>
<td>0.2</td>
<td>20</td>
<td>1</td>
<td>4</td>
<td>0.1</td>
<td>8/8</td>
<td>Nil</td>
<td><em>Device custom designed for this research.</em> Success of blinding confirmed by statistical analysis</td>
</tr>
<tr>
<td><em>Klein</em> (1990)</td>
<td>GaAs</td>
<td>Pulsed</td>
<td>904</td>
<td>1.3</td>
<td>1.0</td>
<td>5.4</td>
<td>1.3</td>
<td>0.005</td>
<td>12/4</td>
<td>Exercise</td>
<td>Machine was modified by manufacturer with a toggle switch with two settings, only one of which activated the laser. Single device used. Success of blinding not reported</td>
</tr>
<tr>
<td>Konstantinovic (2011)</td>
<td>GaAs</td>
<td>Pulsed</td>
<td>905</td>
<td>3</td>
<td>1.0</td>
<td>100</td>
<td>3</td>
<td>0.1</td>
<td>15/3</td>
<td>Exercise</td>
<td>Two machines were used labelled A or B, one with active laser, another deactivated. Patients and therapist treating the patients could not distinguish which was active or control. Success of blinding not reported</td>
</tr>
<tr>
<td><em>Lin</em> (2012)</td>
<td>NR</td>
<td>Pulsed</td>
<td>805</td>
<td>12</td>
<td>0.8</td>
<td>20</td>
<td>15</td>
<td>0.025</td>
<td>5/1</td>
<td>Soft cupping</td>
<td>Control group had the same procedure as the laser group but without laser irradiation. No other details given in paper. Success of blinding not reported</td>
</tr>
<tr>
<td>Okiornsz (1989)</td>
<td>GaAlAs</td>
<td>Continuous</td>
<td>B10</td>
<td>18</td>
<td>0.126</td>
<td>30</td>
<td>143</td>
<td>0.24</td>
<td>10/3</td>
<td>Nil</td>
<td>Two machines of identical appearance used (A and B) corresponding to laser or placebo laser; each had daisy with light and sound. No other details given in paper. Success of blinding not reported</td>
</tr>
<tr>
<td><em>Nishi</em> (2010)</td>
<td>NR</td>
<td>Continuous</td>
<td>680, 785</td>
<td>60–180</td>
<td>7</td>
<td>50–150</td>
<td>?</td>
<td>1.5</td>
<td>10/5</td>
<td>NL</td>
<td><em>Device custom designed for this research.</em> Used an activated laser and a deactivated laser but the electrical circuit, timer and alarm worked as usual. Not clear if separate devices used. Success of blinding not reported</td>
</tr>
</tbody>
</table>

*Continued*
<table>
<thead>
<tr>
<th>Trial</th>
<th>Laser diode</th>
<th>Pulse mode</th>
<th>Wavelength (nm)</th>
<th>Dose/point (J)</th>
<th>Spot size (cm²)</th>
<th>Mean laser power (mW) (peak power)</th>
<th>Energy density (J/cm²) (W/cm²)</th>
<th>Power density (W/cm²)</th>
<th>Sessions/weeks</th>
<th>Points treated per session (s)</th>
<th>Co-intervention</th>
<th>Details of sham control</th>
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<tbody>
<tr>
<td>Umegaki23</td>
<td>GaAlAs</td>
<td>Continuous</td>
<td>830</td>
<td>18</td>
<td>0.126</td>
<td></td>
<td>143</td>
<td>0.24</td>
<td>10/3</td>
<td>Nil</td>
<td>Two machines of identical appearance used (A and B) corresponding to laser or placebo laser; each had decoy with light and sound. No other details given in paper. Success of blinding not reported</td>
<td></td>
</tr>
<tr>
<td>Vallone33</td>
<td>GaAlAs</td>
<td>Continuous</td>
<td>980</td>
<td>1200</td>
<td>20</td>
<td></td>
<td>37.5</td>
<td>0.625</td>
<td>9/3</td>
<td>Exercise</td>
<td>Dials showing the on/off power setting of machine were not within view of subjects. Success of blinding not reported</td>
<td></td>
</tr>
<tr>
<td>Wallace34</td>
<td>GaAlAs</td>
<td>Continuous</td>
<td>830</td>
<td>1.1</td>
<td>0.42</td>
<td></td>
<td>37</td>
<td>2.64</td>
<td>5/5</td>
<td>Nil</td>
<td>Independent assistant operated and covered the coded switch on laser machine determining if laser on or off. Appearance of machine the same regardless of laser output. Success of blinding not reported</td>
<td></td>
</tr>
</tbody>
</table>

Entries in bold were not reported/available and were calculated or assumed by reviewers.

*High intensity laser therapy*. Also included manual scanning of fields (2 × 1400 J). Total dose/session 3000 J.

†Laser device allowed simultaneous stimulation of two points.

‡Total treatment duration 20 mins including eight points and manual scanning of standardised field (time differential not reported but assume <150 s per discrete point). Total dose/session 60 J.

§Laser/hair mode set by operating a number on dial. Probe had decoy lightsound device built. Individualised treatment (average 8-9 points/session) including local and distal GV, BL and GB points and ah shi points.

¶Multi-channel device. Simultaneous stimulation of four points (bilateral BL40 and two ah shi points in lumbar region).

**Laser needle’ fiberoptic cable device. Simultaneous stimulation of eight points (individualised treatment including BL23, BL40, BL60, KI6, GB and ah shi points). Same author previously described laser output tip diameters 2.0 and 0.8 mm. Power density 1 W/cm² and 5 W/cm², respectively.

††2 cm grid in painful area (number of points and irradiation time per point unreported). Spot size given as 0.0015 cm² but 1.1 cm² with irradiation time 100 s according to Cochrane review.11

§§Unclear if manual scanning used.

¶¶Individualised treatment: local (BL26, ah shi points, GV2) and distal (GV14, BL11, LR3, BL60, LI4, ST36, SP6, PC6, HT7). NR, not reported.
<30 months or if a laser dose of at least 3 J/point is used (see online supplementary data file appendix H). The overall quality of evidence for this outcome was reduced due to limitations in the domain involving risk of bias. For the outcome of global assessment at immediate follow-up, the evidence of benefit of laser
therapy was further reduced to low quality due to uncertainty in details of duration and specificity of LBP in trials22 23 and laser intervention parameters in a trial32 reporting this outcome.

DISCUSSION

This meta-analysis summarised RCTs that compared the effect of low-level laser with sham controls for the treatment of CNLBP. While combining data from all trials, the evidence for the effectiveness of low-level laser therapy was limited. The meta-analysis found no significant difference in pain reduction between low-level laser and sham controls, with a pooled effect size of 0.24 (95% CI: 0.02 to 0.46). The findings suggest that low-level laser therapy may not be effective in reducing pain compared to sham controls for the treatment of chronic non-specific low back pain.

Figure 3

Forest plots: subgroup analysis of pain at immediate follow up. LA, laser acupuncture.
clinically heterogeneous studies demonstrated a small benefit, subgroup analyses showed larger positive effects of laser on pain, global assessment and disability present up to 12 weeks after treatment, particularly in trials with higher laser dose interventions. The effect size of the pain reduction (over sham) of 1.4 cm in these subgroups approached the minimally important change (MIC) for pain proposed by Ostelo of 1.5 cm. Disability (ODI) reduction was significant in the short term but less than the MIC of 10%. In this review, the mean pain reduction in the placebo laser groups averaged approximately 2.0 cm. The total average pain reduction between baseline and short-term follow-up, representing both non-specific

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>M-H, Random, 95% CI</th>
<th>Risk Ratio</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser acupuncture</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glazov 2009 (1)</td>
<td>26</td>
<td>43</td>
<td>25</td>
<td>44</td>
<td>19.3%</td>
<td>1.06 [0.75, 1.52]</td>
<td>1.06</td>
<td>[0.75, 1.52]</td>
</tr>
<tr>
<td>Glazov 2010 (2)</td>
<td>29</td>
<td>45</td>
<td>12</td>
<td>20</td>
<td>17.5%</td>
<td>1.07 [0.71, 1.63]</td>
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<td>1.14 [0.75, 1.71]</td>
<td>1.14</td>
<td>[0.75, 1.71]</td>
</tr>
<tr>
<td>Subtotal (95%) Cl.</td>
<td>112</td>
<td>184</td>
<td>84</td>
<td>168</td>
<td>54.6%</td>
<td>1.09 [0.87, 1.38]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>85</td>
<td></td>
<td>49</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Tau^2 = 0.00; Chi^2 = 0.06; df = 2 (P = 0.97); I^2 = 0%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 0.74 (P = 0.46)</td>
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<td></td>
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</tbody>
</table>

(i) Subgroup: (LA versus non-acupuncture laser therapy)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>M-H, Random, 95% CI</th>
<th>Risk Ratio</th>
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</thead>
<tbody>
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<tr>
<td>Test for overall effect: Z = 0.74 (P = 0.46)</td>
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</tbody>
</table>

(ii) Subgroup: (low dose <3J/point vs high dose ≥ 3J/point)

Figure 4 Forest plots: subgroup analysis of global assessment at immediate follow up. LA, laser acupuncture.
and specific effects of the laser intervention, was about 60%.

Our results are consistent with previous findings suggesting benefits of low-level laser in a range of painful musculoskeletal conditions including chronic neck pain. In the trials we examined there appeared to be a dose threshold of 3 J/point for benefit of laser. This is the minimal dose suggested by reviews by Baxter (0.5 J/point for myofascial pain) and Chow (0.8 J/point for chronic neck pain), but closer to the dose recommended by WALT (4 J/point for lumbar spine arthritis). This could be explained by the deeper location of structures in the low back area, requiring a higher laser irradiation dose for penetration. There was no upper dose at which laser appeared not to be effective or caused adverse effects.

Our review also found a relationship between duration of pain and laser effectiveness. This finding is plausible but needs to be explored in further research. Two previous studies examining physical treatment for back pain and acupuncture for chronic pain conditions showed a generally worse outcome for subjects with longer pain duration, but no interaction effect with type of treatment. Acute pain is more likely to resolve spontaneously than chronic pain and, once central sensitisation occurs, a condition may become unresponsive to LLLT.

Most (eight out of 10) non-acupuncture laser therapy trials were positive, that is, they showed a difference between laser and sham groups in primary outcomes; negative trials in this group treated participants with a longer duration of pain with a lower dose. Most non-acupuncture laser trials in this review treated relatively few points in the area of pain, although some also irradiated wider areas using a manual scanning technique. Skin surface application of laser results in photon scattering in the underlying volume of tissue, resulting in more widespread biological effects regardless of the intent of the therapist to stimulate acupuncture points, ah shi points or local anatomical structures. Acupuncturists and other laser therapists both irradiate tender points in the region of pain; the absence of positive acupuncture trials in this review could be related to smaller laser dosage and other factors unrelated to the approach to treatment. We were not able to determine why two higher dose LA trials were negative in this review.

Heterogeneity of studies and insufficient data were quoted as reasons for the previous inability to establish firm conclusions on the effect of LLLT for LBP. A strength of our review was the larger number of trials and inclusion of more recent eligible publications since the last such review, as well as exclusion of acute back pain and trials without sham laser controls, thus reducing heterogeneity and allowing the study of specific laser effects. Subgroup analysis was important in explaining the heterogeneity.

A major limitation of this review was related to bias from possible unmasking. Low risk of bias in all blinding domains according to the Cochrane tool was present in only about 60% of trials. In positive trials, the success of blinding was not tested and there were other possible deficiencies in blinding. Subject awareness of thermal sensation in trials with higher power devices is possible, which may potentially have unmasked the patients to treatment allocation. These issues arguably reduce the ability of this review to draw firm conclusions. Inadequate reporting of the characteristics of participants and laser parameters also produced uncertainty.

It is critical that rigorous blinding is instituted in any further clinical trials investigating laser therapy for the treatment of pain. The appropriate laser dose range for specific body regions (as recommended by WALT) should be followed, and full and explicit description of the laser parameters, treatment regimen, and baseline characteristics of the participants is important. Future studies may also establish the role of other components of the intervention such as the number and/or location of points, frequency/duration of treatment, and the effect of longer-term follow-up on outcomes.

Our meta-analysis suggests that LLLT, when used by itself or in combination with other modalities, may achieve a useful reduction in pain for up to 3 months in CNLBP with few adverse effects. However, we would recommend a degree of caution before widespread implementation, until our results can be confirmed by further rigorously blinded trials using adequate laser doses.

### Summary points

- This updated systematic review examined the effectiveness of low-level laser therapy compared to sham laser in the treatment of chronic non-specific low back pain.
- There was substantial clinical heterogeneity present between the 15 included trials, related to differences in both participant characteristics and laser interventions.
- Meta-analysis showed a clinically important pain reduction in laser versus sham lasting up to 12 weeks post-completion of treatment (WMD –1.40 cm, 95% CI –1.91 to –0.88 cm).
- Pain reduction occurred in subgroups with non-acupuncture laser interventions, laser dosage ≥3 J per point, and in participants with a shorter duration of baseline pain (30 months).
- Further trials using strict masking and adequate laser doses are needed to ensure that the apparent benefits of laser are not due to bias related to unblinding of participants.
Original paper

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Contributors GG was the doctoral candidate and lead author and was responsible for the conceptualisation of the protocol and conduct of the review. MY and JE made substantial contributions to the design of the work, drafted and critically revised the manuscript for important intellectual content, and agree to be accountable for the content of the work. All authors approved the final version of the manuscript.

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Data sharing statement Data sharing on this research article is available on request from the corresponding author.

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Low-level laser therapy for chronic non-specific low back pain: a meta-analysis of randomised controlled trials
Gregory Glazov, Michael Yelland and Jon Emery

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