Supplementary Data File

Appendix A PROTOCOL

A Meta-analysis: LLLT (including LA) for treatment of Chronic Non-Specific LBP (Last revised July 2014)

BACKGROUND

Description of the condition-
Low back pain (LBP)[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[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)[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)[2]
Low back pain is a major health problem in western industrialized countries and a major cause of medical expenses, absenteeism and disablement[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[6]. Based on a Beach survey back pain was the 8th most frequent condition seen in Australian GP.
An Australian telephone survey in 2005[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.

1.van Tulder M, Koes B. Low back pain (chronic). Clin Evid 2006; 15:419-22
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)
4. van Tulder MW, Koes BW, Bouter LM, A cost of illness study of back pain in the Netherlands. Pain 1995; 63:233- 40
5. Xue CL, Zhang AL, Lin V, Myers R, Polus B. Acupuncture, chiropractic and osteopathy use in Australia: a national population survey. BMC Public Health 2008; 8:1
6. Murtagh JE. General practice. Sydney: McGraw-Hill Book Company Australia Pty Ltd; 1994. p. 257.

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 [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 [3]. 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 irradiate 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 / cm^2) 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.

LLLT 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.

1. Basford JR. Low-energy laser therapy: controversies and new research findings. Lasers Surg Med 1989;9.
2. Baxter GD, Bell AJ, Allen JM, Ravey J. Low-level laser therapy: current clinical practice in Northern Ireland. Physiotherapy 1999;77.
3. Chow R. Letter to the editor. Laser acupuncture studies should not be included in systematic reviews of phototherapy. Photomed Laser Surg 2006;24(1):69.

How the intervention might work-

In the past there has been criticism [1] 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[2].

However there is evidence of LLLT inducing anti-inflammatory, anti-nociceptive (block sensory nerves), spasmolytic 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[3], Baxter et al, 2008[4]). The World Association of Laser Therapy[5] 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.

1. Devor M. What's in a laser beam for pain therapy? [editorial]. Pain 1990;43:139.
2. Baldry PE. Acupuncture, Trigger points and Musculoskeletal Pain.3rd ed. Edinburgh:Churchill Livingstone, 2005:308
3. Chow R, Johnson M, Lopes-Martins R, Bjordal J. Efficacy of low-level laser therapy in the management of neck pain: a systematic review and meta-analysis of randomised placebo or active-treatment controlled trials. *The Lancet* 2009; **374**(9705): 1897-908.
4. Baxter DG et al. Clinical effectiveness of laser Acupuncture: a systematic review J Acup Meridian Stud 200870.
5. WALT. Recommended anti-inflammatory dosage for Low Level Laser Therapy. [Online]. 2005 Aug [?2007]; Available from: URL:http://www.walt.nu/images/stories/files/Scientific-Secretary-Report-2006.pdf

Why it is important to do this review-

Chronic -LBP is of the great importance in terms (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 way 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.

1. Furlan AD, van Tulder MW, Cherkin DC, Tsukayama H, Lao L, Koes BW, et al.
Acupuncture and dry needling for low back pain, Cochrane Database Syst Rev 2005; Jan 25;(1):CD001351.
2. Yousefi-Nooraie R, Schonstein E, Heidari K, et al. Low level laser therapy for nonspecific low-back pain. *Cochrane Database Syst Rev* 2008; (2): CD005107.
3. Schuller BK, Neugebauer EA. [Evidence for laser acupuncture in cases of orthopedic diseases: A systematic review.] [Article in German] Schmerz 2008;22(1):9-15.
4. Baxter GD,Bleakley C,McDonough. Clinical effectiveness of laser acupuncture: a systematic review. J Acupunc Meridian Stud 2008;1(2):65-82

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

Note: 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 musculoskeletal 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-
Number 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 CI s ; 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[1] approach for reviews of interventions. The quality of the body of evidence on a specific outcome will be 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.

1. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. *BMJ* 2004; 328:1490.

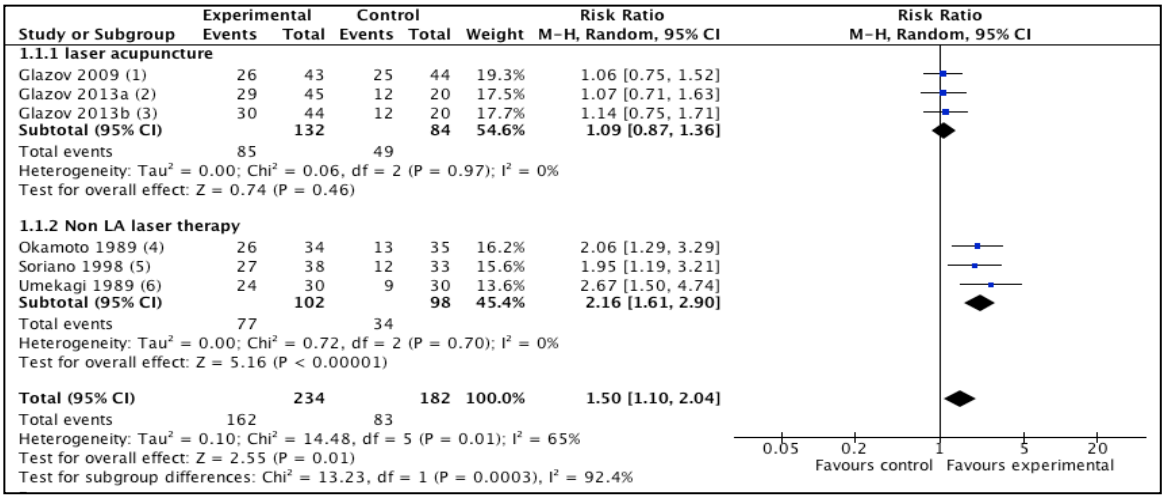
Appendix B

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

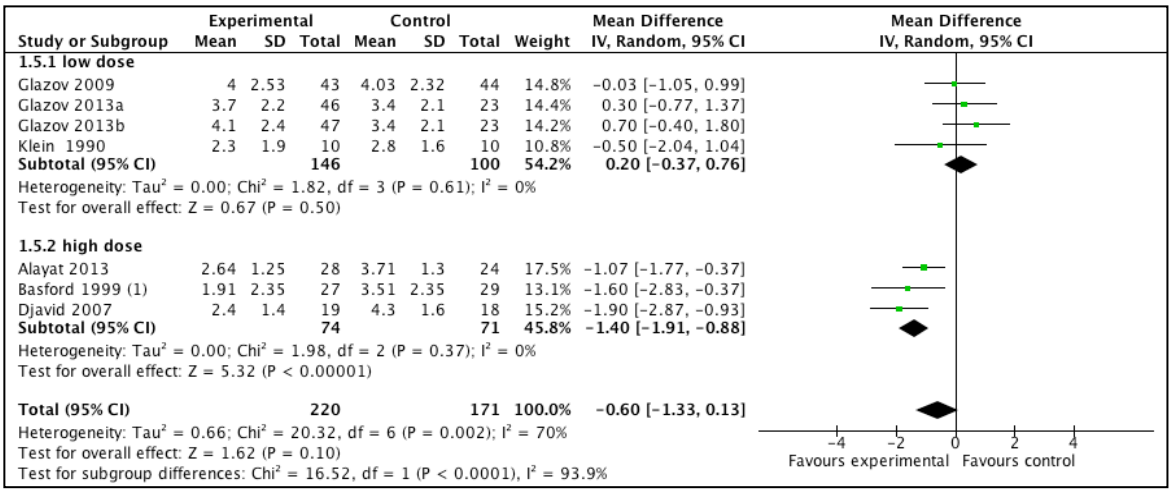
Description:
ID Search
#1 MeSH descriptor: [Laser Therapy] 1 tree(s) exploded
#2 MeSH descriptor: [Laser Therapy, Low-Level] explode all trees
#3 MeSH descriptor: [Lasers] explode all trees
#4 #1 or #2 or #3
#5 "laser acupuncture":ti,ab,kw or "low intensity laser":ti,ab,kw or "low power laser":ti,ab,kw 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: [Sciatic Neuropathy] 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 (spondylosis):ti,ab,kw or (lumbago) 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 C

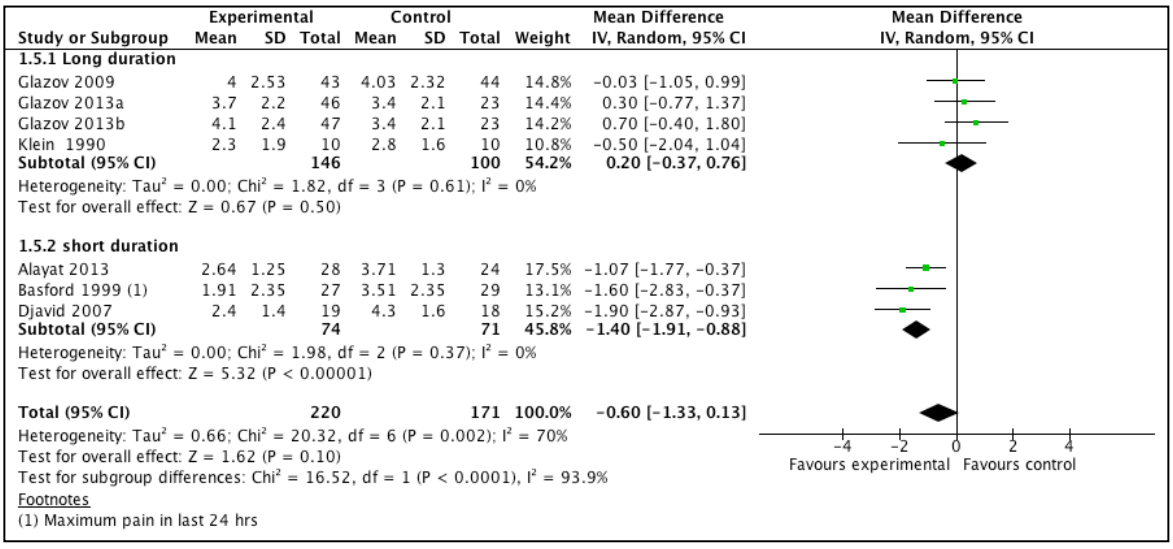
Forest Plots: Subgroup Analysis of Pain at Short Term Follow-up



(i)Subgroup analysis: Comparison of trials using LA versus non- LA laser therapy interventions



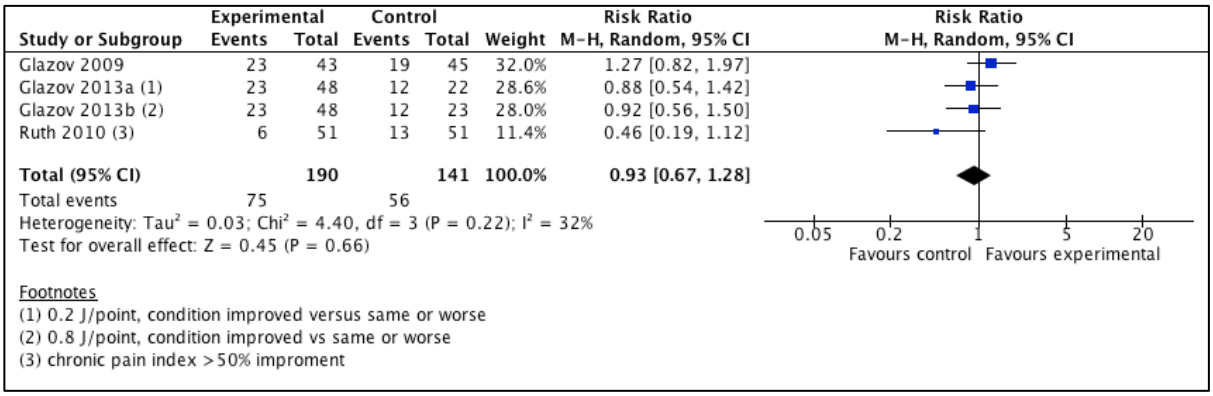
(ii) Subgroup analysis: Comparison of trials using low dose versus high dose interventions



(iii) Subgroup analysis: Comparison of trials with long duration of pain at baseline versus short duration

Appendix D

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



note: At this only outcome low dose LA studies represented, except Ruth 2010 (high dose study)

Appendix E

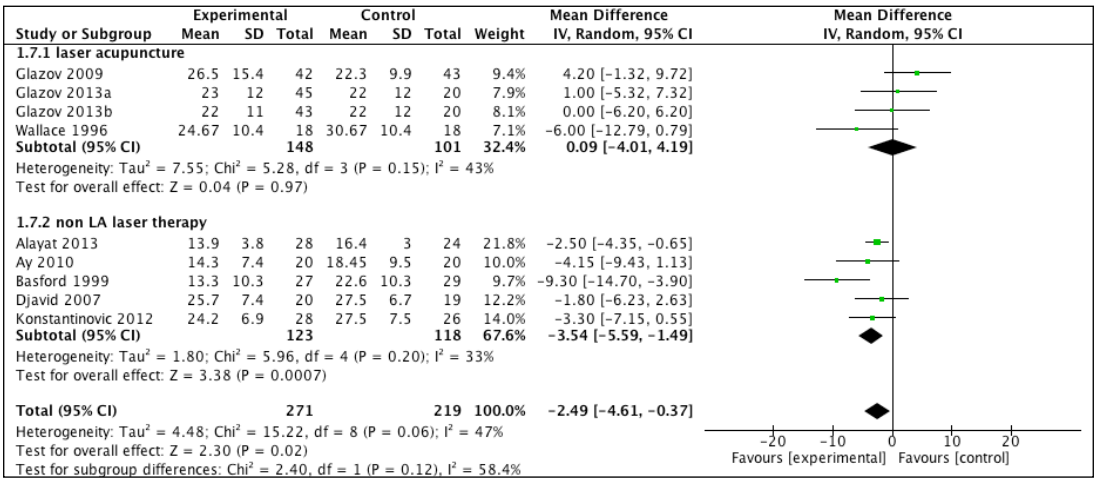
Primary outcome pain effect sizes

a. Subgroup analysis at immediate/short term follow up
b. Sensitivity analysis

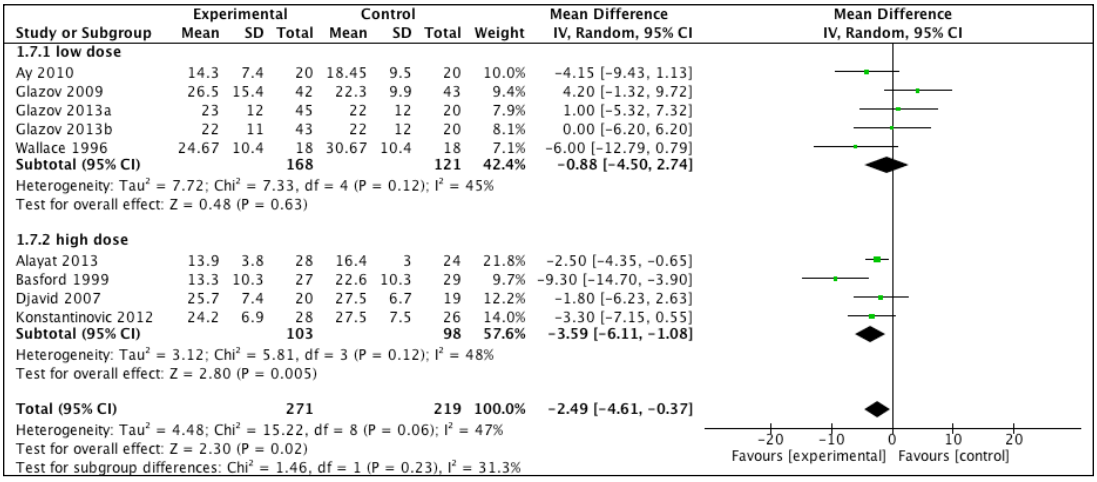
Subgroups	Immediate term				Short term			
	trials (n)	WMD[cm] (95%CI)	χ^2 (p) [I^2]	WMD(95%CI) Sensitivity analysis (exclude high risk of bias trials)	Trials (n)	WMD[cm](95%CI)	χ^2 (p) [I^2]	WMD[cm](95% Sensitivity analysis (exclude high risk of bia trials)
total	10(653)	-0.79 (-1.22, -0.36)	33.09 (0.0003) [70%]	-0.68 (-1.31, -0.04)	6(391)	-0.60(-1.33, 0.13)	20.32 (0.002) [70%]	-0.50(-1.39, 0.3
LA	4(312)	-0.22 (-0.70,0.26)	2.59 (0.63) [0%]	-0.25 (-0.80, 0.29)	2(226)	0.31(-0.31, 0.92)	0.91 (0 .63) [0%]	0.31(-0.31, 0.92
non- LA	6(341)	-1.17 (-1.60, -0.74)	13.19 0.02 [62%]	-1.01 (-1.85, -0.18)	4(165)	-1.31(-1.82, -0.80)	3.15 (0.37) [5%]	-1.51(-2.25, -0.
low dose (<3 J/point)	4(310)	-0.18(-0.65, 0.28)	2.74 (0.60) [0%]	-0.18 (-0.65,0.28)	3(246)	0.20(-0.37, 0.76)	1.82 (0.61) [0%]	0.20(-0.37, 0.76
high dose (≥3 J/point)	6(343)	-1.23(-1.61, -0.84)	10.17 (0.07) [51%]	-1.54 (-1.84, -1.24)	3(145)	-1.40(-1.91, -0.88)	1.98 (0.37) [0%]	-1.70(-2.55, -1.
long duration (≥30 months)	4(310)	-0.18(-0.65, 0.28)	2.74 (0.60) [0%]	-0.18 (-0.65, 0.28)	3(246)	0.20(-0.37, 0.76)	1.82 (0 .61) [0%]	0.20 (-0.37, 0.7
short duration (<30 months)	4(210)	-1.39(-1.71, -1.07)	3.90 (0.27) [23%]	-1.54 (-1.84, -1.24)	3(145)	-1.40(-1.91, -0.88)	1.98 (0.37) [0%]	-1.79(-2.55, -1.
duration not reported	2(142)	-0.81(-2.08, 0.47)		both trials high risk	no trials	-	-	-

Appendix F

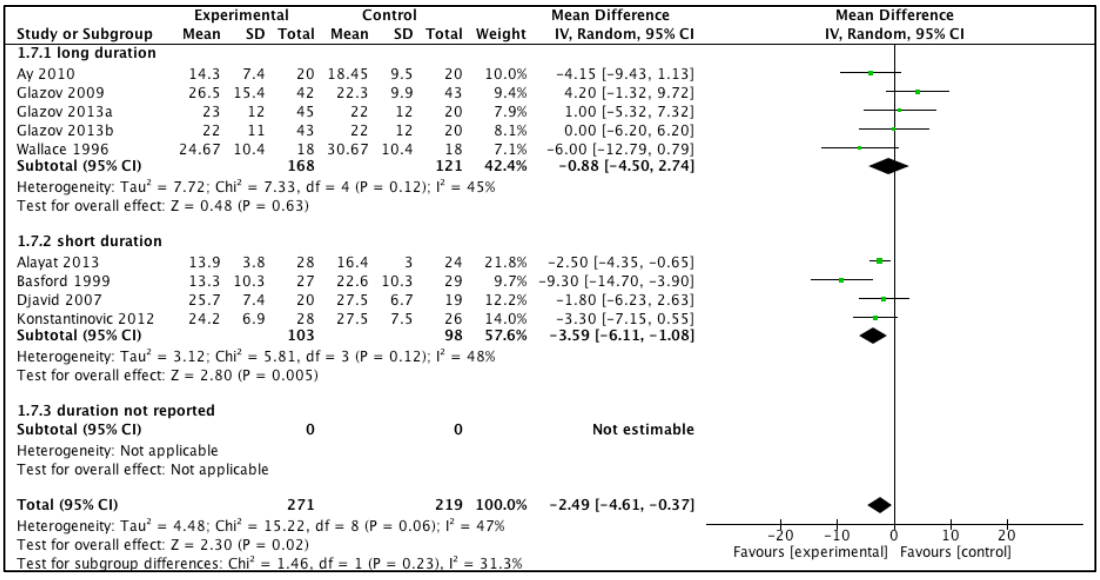
Forest plots for disability (ODI) outcomes



(i)Subgroup analysis: Comparison of trials using LA versus non- LA laser therapy interventions

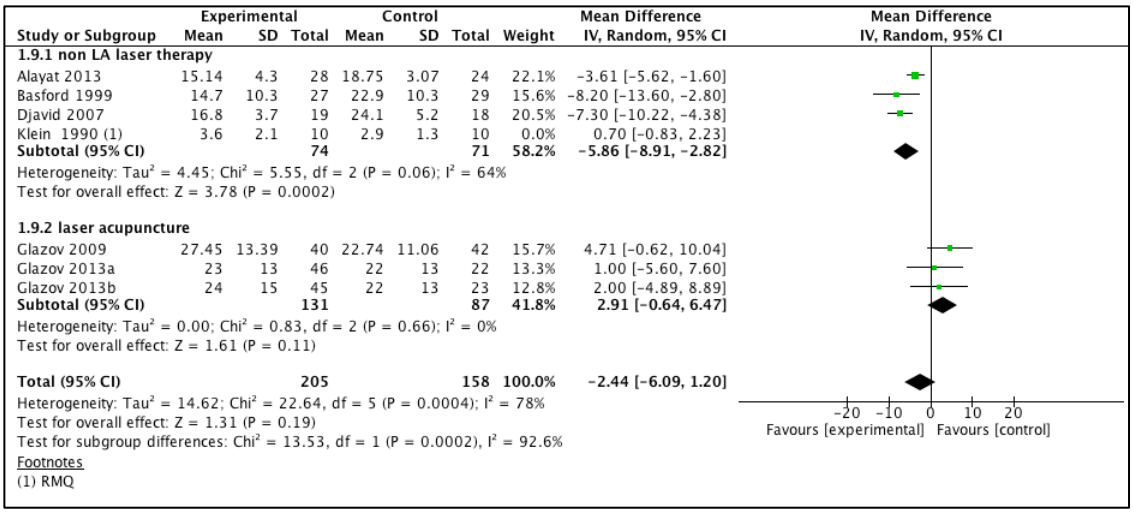


(ii) Subgroup analysis: Comparison of trials using low dose versus high dose interventions

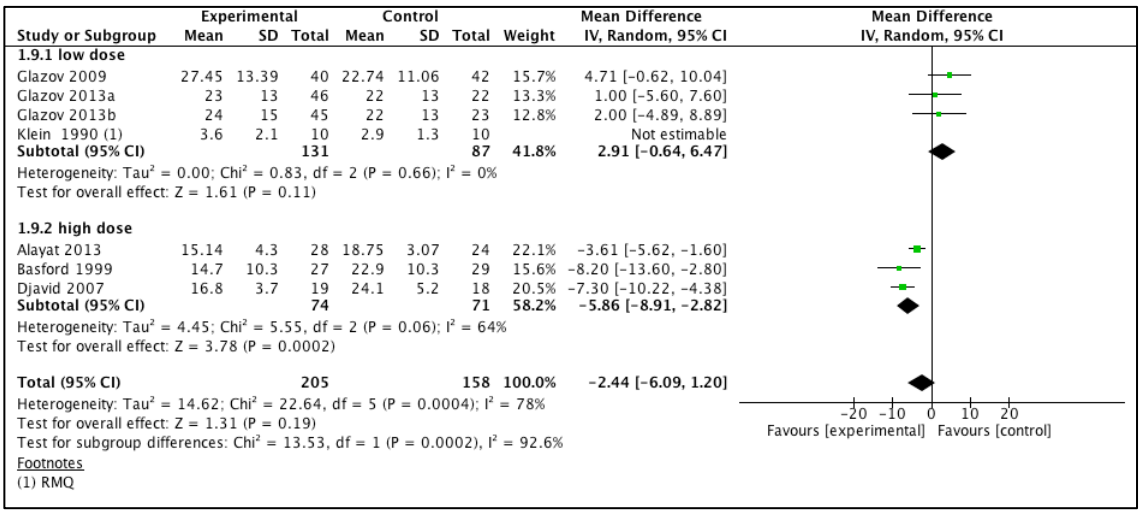


(iii) Subgroup analysis: Comparison of trials with long duration of pain at baseline versus short duration

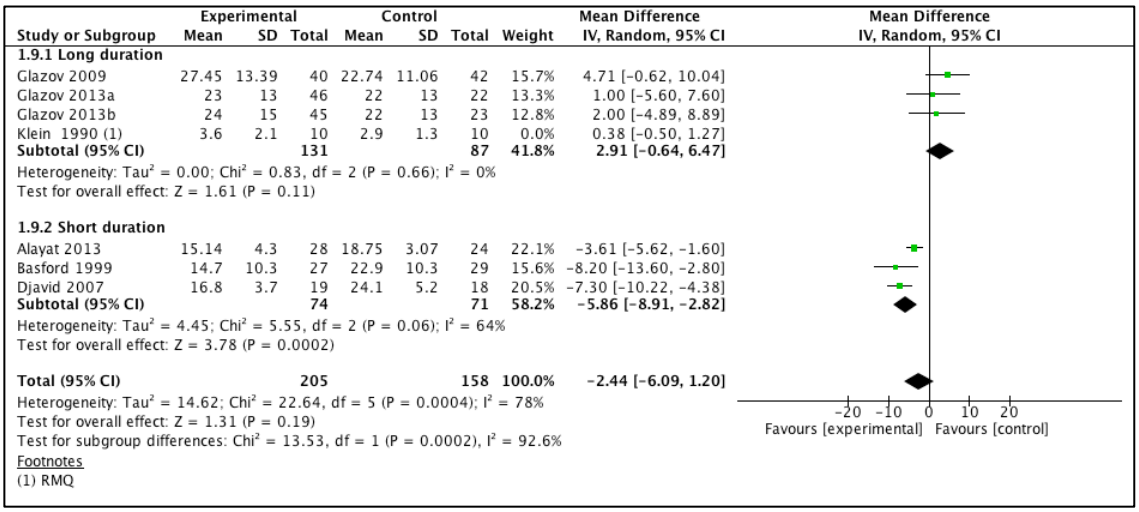
(a)Forest plots: Disability(ODI); Immediate follow-up



(i)Subgroup analysis: Comparison of trials using LA versus non- LA laser therapy interventions



(ii) Subgroup analysis: Comparison of trials using low dose versus high dose interventions



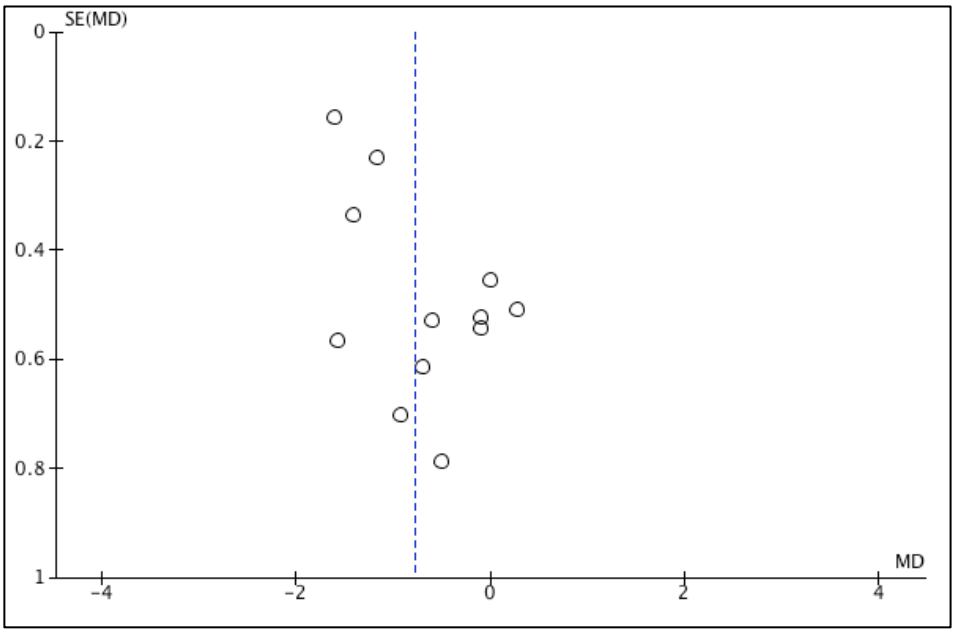
(iii) Subgroup analysis: Comparison of trials with long duration of pain at baseline versus short duration

(b)Forest Plots: Disability(ODI); Short-term follow-up

(note: Klein[28] trial not included in analysis as measured RMQ at this follow-up)

Appendix G

Funnel Plot



Funnel plot of comparison Laser versus Sham Laser, outcome: Pain / immediate follow-up Includes Klein[28] trial with only short-term outcome. Studies with positive results are towards the left.

Appendix H

GRADE evidence profile for primary outcomes

Quality assessment							Summary of findings				Quality	Clinical recommen
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Laser	Sham	Relative RR (95% CI)	Absolute WMD (95%CI)		
Pain (immediate post- treatment) (measured with: VAS or NPRS ; 0.0 = no pain; range of scores: 0-10; Better indicated by less)												
10[&]	RCTs	Serious[1]	No serious[2]	No serious[3]	No serious	No[4]	353[&]	300[&]	–	-0.79(-1.22, -0.36)[&]	O⊕⊕⊕ Moderate	Weak[6]
6[#]							173[#]	168[#]		-1.17(-1.60, -0.74)[#]		
6[*]							174[*]	169[*]		-1.23(-1.61, -0.84)[*]		
4[$]							103[$]	98[$]		-1.39(-1.71, -1.07)[$]		
Pain (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)												
6[&]	RCTs	Serious[1]	No serious[2]	No serious[3]	No serious	No[4]	220[&]	171[&]	–	-0.60(-1.33, 0.13)[&]	O⊕⊕⊕ Moderate	Weak[6]
4[#]							84[#]	81[#]		-1.31(-1.82, -0.80)[#]		
3[*]							74[*]	71[*]		-1.40(-1.91, -0.88)[*]		
3[$]							74[$]	71[$]		-1.40(-1.91, -0.88)[$]		
Global assessment (immediate- term)												
5[&]	RCTs	Serious[1]	No serious[2]	Serious[5]	No serious	N/A	234[&]	182[&]	1.50(1.10,2.04)[&]	–	OO⊕⊕ Low	Weak[6]
3[#]							102[#]	98[#]	2.16(1.61,2.90)[#]			
3[*]							102	98[#]	2.16(1.61,2.90)[#]			

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

Legend:
& all trials reporting outcome
# non-LA laser therapy subgroup reporting outcome
* 'high dose' laser subgroup reporting outcome
$ '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
'Indirectedness' 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

Footnotes:
[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.