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

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Summary

Background Neck pain is a common and costly condition for which pharmacological management has limited evidence of efficacy and side-effects. Low-level laser therapy (LLLT) is a relatively uncommon, non-invasive treatment for neck pain, in which non-thermal laser irradiation is applied to sites of pain. We did a systematic review and meta-analysis of randomised controlled trials to assess the efficacy of LLLT in neck pain.

Methods We searched computerised databases comparing efficacy of LLLT using any wavelength with placebo or with active control in acute or chronic neck pain. Effect size for the primary outcome, pain intensity, was defined as a pooled estimate of mean difference in change in mm on 100 mm visual analogue scale.

Findings We identified 16 randomised controlled trials including a total of 820 patients. In acute neck pain, results of two trials showed a relative risk (RR) of 1·69 (95% CI 1·22–2·33) for pain improvement of LLLT versus placebo. Five trials of chronic neck pain reporting categorical data showed an RR for pain improvement of 4·05 (2·74–5·98) of LLLT. Patients in 11 trials reporting changes in visual analogue scale had pain intensity reduced by 19·86 mm (10·04–29·68). Seven trials provided follow-up data for 1–22 weeks after completion of treatment, with short-term pain relief persisting in the medium term with a reduction of 22·07 mm (17·42–26·72). Side-effects from LLLT were mild and not different from those of placebo.

Interpretation We show that LLLT reduces pain immediately after treatment in acute neck pain and up to 22 weeks after completion of treatment in patients with chronic neck pain.

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Introduction

Chronic pain is predicted to reach epidemic proportions in developed countries with ageing populations in the next 30 years.[1] Chronic neck pain is a highly prevalent condition, affecting 10–24% of the population.[2–5] Economic costs of this condition are estimated at hundreds of millions of dollars,[2] creating an imperative for evidence-based, cost-effective treatments. Low-level laser therapy (LLLT) uses laser to aid tissue repair,[6] relieve pain,[7] and stimulate acupuncture points.[8] Laser is light that is generated by high-intensity electrical stimulation of a medium, which can be a gas, liquid, crystal, dye, or semiconductor.[9] The light produced consists of coherent beams of single wavelengths in the visible to infrared spectrum, which can be emitted in a continuous wave or pulsed mode. Surgical applications of laser ablate tissue by intense heat and are different from LLLT, which uses light energy to modulate cell and tissue physiology to achieve therapeutic benefit without a macroscopic thermal effect (sometimes termed cold laser). LLLT is non-invasive, painless, and can be easily administered in primary-care settings. Incidence of adverse effects is low and similar to that of placebo, with no reports of serious events.[10,11]

Research into the use of LLLT for pain reduction[12,13] and tissue repair[14,15] spans more than 30 years. However, reports do not identify this therapy as a potential treatment option,[16] possibly because of scepticism about its mechanism of action and effectiveness.[17] Research from the past decade suggests that LLLT produces anti-inflammatory effects,[18–21] contributing to pain relief. Cochrane reviews of the efficacy of LLLT in low-back pain[22] and rheumatoid arthritis[23] have been unable to make firm conclusions because of insufficient data or conflicting findings. However, effectiveness depends on factors such as wavelength, site, duration, and dose of LLLT treatment. Adequate dose and appropriate procedural technique are rarely considered in systematic reviews of electrophysical agents. Research into the dose-response profile of LLLT suggests that different wavelengths have specific penetration abilities through human skin.[17,24,25] Thus, clinical effects could vary with depth of target tissue. We have shown the importance of accounting for dose and technique in systematic reviews of transcutaneous electrical nerve stimulation[26] and LLLT,[11,21] and our approach is an acknowledged means of establishing efficacy.[27]

The only systematic review focusing solely on LLLT in treatment of neck pain included four randomised controlled trials, and concluded that there was evidence of short-term benefit of LLLT at infrared wavelengths of 780, 810–830, and 904 nm.[28] A Cochrane review of physical medicine for mechanical neck disorders, since

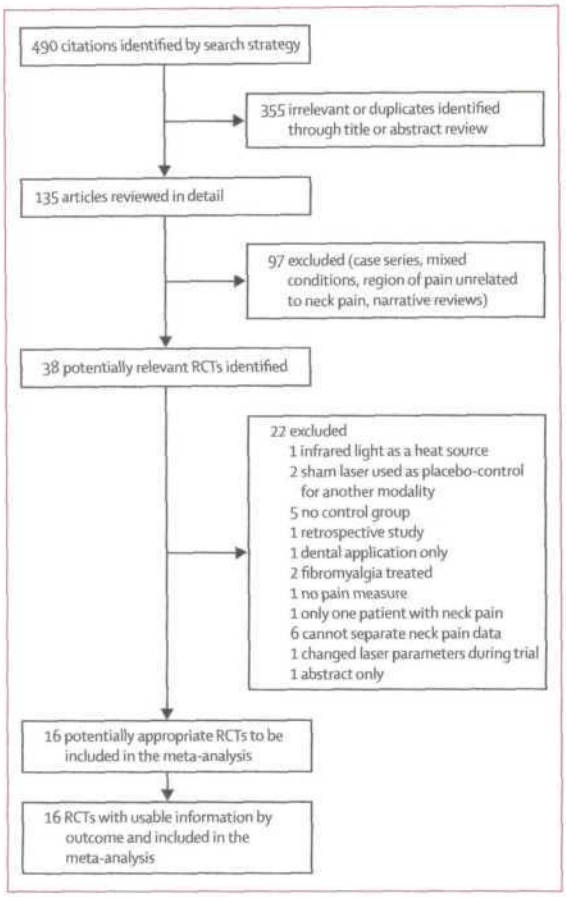

Figure 1: Selection process
RCT=randomised controlled trial.

withdrawn because much time had passed without an update, included three LLLT trials, for which outcomes did not differ from those of placebo.[29] The same investigators did a meta-analysis[30] of 88 randomised controlled trials of conservative treatments for acute, subacute, and chronic mechanical neck disorders, which included eight trials using LLLT. They concluded that LLLT has intermediate and long-term benefits.

These reviews did not identify treatment variables associated with positive outcomes, include non-English language publications, or quantitatively assess data.[28,30] We have therefore undertaken a new systematic review and meta-analysis of LLLT in neck pain to establish whether LLLT relieves acute and chronic neck pain and to systematically assess parameters of laser therapy to identify treatment protocols and dose ranges (therapeutic windows) associated with positive outcomes.

Methods

Search strategy and selection criteria

We did a search of published work without language restriction using Medline (January, 1966, to July, 2008), Embase (January, 1980, to July, 2008), Cinahl (January, 1982, to July, 2008), the Physiotherapy Evidence Database (January, 1929, to July, 2008), Biosis (January, 1926, to July, 2008), Allied and Complementary Medicine (January, 1985, to July, 2008), and the Cochrane Central Register of Controlled Trials (second quarter of 2008). Keywords used for neck pain and related conditions were: "neck pain/strain", "cervical pain/strain/syndrome", "cervical spondylosis/itis", "cervicobrachial (pain/disorder/syndrome)", "myofascial (pain/disorder/syndrome)", "trigger points", "fibromyalgia", "whiplash/WAD", "osteoarthritis/arthritis", and "zygaphophyseal/ZG joints". We combined these keywords with synonyms for LLLT: "low-level/low-energy/low reactive-level/low-intensity/low-incident/low-output/infrared/diode/semiconductor/soft or cold or mid/visible"; "laser therapy", "(ir)radiation", "treatment"; "low-energy photon therapy"; "low output laser"; "LLLT"; "LILT"; "LEPT"; "LELT"; "LILI"; "LELI"; "LPLI"; "biostimulation"; "photobio/stimulation/activation/modulation"; "light therapy"; "phototherapy"; "narrow band light therapy"; "904 nm"; "830 nm"; "632 nm"; "1064 nm"; "GaAs"; "GaAlAs"; "HeNe"; and "defocused CO_2". We consulted experts and searched reference lists of retrieved reports and textbooks for additional references.

Citations were screened and full reports of potentially relevant studies obtained. We applied inclusion and exclusion criteria, assessed methodological criteria, and extracted data including trial characteristics, demographic data, laser parameters, pain outcome measures, and co-interventions. Non-English language studies were translated by JMB.

We included randomised or quasi-randomised controlled trials of LLLT for acute or chronic neck pain as defined by trial investigators, and identified by various clinical descriptors included under the term non-specific neck pain.[31] These diagnostic labels included neck strain, neck sprain, mechanical neck disorders, whiplash, neck disorders, and neck and shoulder pain. We also used surrogate terms for neck pain, such as myofascial pain and trigger points.[32,33] Study participants were restricted to those aged 16 years and older. We excluded studies in which specific pathological changes could be identified, such as systemic inflammatory conditions—eg, rheumatoid arthritis, localised or generalised fibromyalgia, neck pain with radiculopathy, and neck pain related to neurological disease. We excluded abstracts and studies for which outcome measures for neck pain could not be separated from data for other regions of the body. Two reviewers (RTC, JMB) independently undertook the search of published work, screened studies, and extracted data. Any disagreements between reviewers were resolved by consensus with other team members acting as arbiters (RABL-M, MIJ).

Investigators had to have used a laser device that delivered irradiation to points in the neck identified by tenderness, local acupuncture points, or on a grid at predetermined points overlying the neck. Control groups had to have been given either placebo laser in which an

	n	Design	Diagnosis	Jadad score	Control	Sites treated	Cointerventions	Primary pain outcome measure
Ceccherelli et al (1989)[43]	27	DB RCT	Cervical myofascial pain	3	Placebo	Tender points in neck and distal acupuncture points	NR	VAS
Flöter et al (1990)[45]	60	DB, RCT	Cervical osteoarthritis	3	Placebo	Tender points in neck	NR	VAS
Taverna et al (1990)[32]	40	DB, RCT	Chronic myofascial pain	3	Placebo	Tender points in neck	NR	Graded subjective assessment: no change to optimum
Toya et al (1994)[53]	39	DB, RCT	Cervical pain complex	5	Placebo	Site not specified	No physical or medical therapy allowed	Graded subjective assessment: exacerbation to excellent
Soriano et al (1996)[39]	71	DB, RCT	Acute cervical pain	3	Placebo	Site not specified	No NSAIDs or other medical or physical therapy allowed	Graded subjective assessment: exacerbation to excellent
Laakso et al (1997)[49]	41	DB, RCT	Neck pain with trigger points in neck	3	Placebo	Three most painful trigger points	Simple analgesic drugs allowed as needed; NSAIDs, corticosteroids, tricyclic antidepressants excluded; no physical therapies	VAS
Özdemir et al (2001)[50]	60	DB, RCT	Neck pain related to neck osteoarthritis	3	Placebo	Six arbitrary points over neck muscles	NR	VAS
Seidel and Uhlemann (2002)[51]	48	DB, RCT	Chronic cervical syndrome	3	Placebo	Local neck points and distal acupuncture points	Acupuncture not allowed less than 6 months before inclusion; drug therapy unchanged during trial	VAS
Hakgüder et al (2003)[47]	62	DB, RCT	Neck pain with one trigger point	3	Exercise with LLLT and exercise alone	One active trigger point in levator scapulae or trapezius	NR	VAS
Chow et al (2004)[42]	20	DB, RCT	Neck pain (non-specific)	5	Placebo	Multiple tender points in cervical spine and attachments	Simple analgesic drugs allowed; no physical therapies	VAS
Gur et al (2004)[46]	60	DB, RCT	Chronic myofascial pain in the neck	5	Placebo	Up to ten trigger points	NR	VAS
Ilbuldu et al (2004)[48]	40	DB, RCT	Myofascial pain syndrome	2	Placebo and needling	Trigger points in upper trapezius	Simple analgesic drugs as needed; exercise to all groups	VAS
Altan et al (2005)[41]	53	DB, RCT	Cervical myofascial pain syndrome	3	Placebo	Three trigger points bilaterally and one trigger point in trapezius	No NSAIDs or analgesic drugs; exercise in both groups	VAS and graded assessment
Aigner et al (2006)[40]	45	SB, RCT	Acute whiplash injury	0	Placebo	Local and distal acupuncture points	Both groups wore cervical collar; paracetamol and chlormezanone	Assessment of subjective pain symptoms
Chow et al (2006)[52]	90	DB, RCT	Non-specific neck pain	5	Placebo	Local tender points	Simple analgesic drugs allowed; no physical therapies	VAS
Dundar et al (2007)[44]	64	DB, RCT	Cervical myofascial pain syndrome	3	Placebo	Three trigger points bilaterally	No NSAIDs or analgesic drugs	VAS

n=number of patients. DB=double blind. RCT=randomised controlled trial. NR=not reported. VAS=visual analogue scale. NSAIDs=non-steroidal anti-inflammatory drugs. SB=single blind.

Table 1: **Study design and outcome measures**

identical laser device had an active operating panel with the laser emission deactivated or an active treatment control (eg, exercise). We also included trials in which an active control was used as a co-intervention in placebo and real laser groups.

To be eligible for inclusion, a study had to compare pain relief along a 0–100 mm visual analogue scale, a numerical rating scale, or by patient-reported improvement (eg, categorical report of no change to complete relief of pain) as a primary outcome measure before and after laser therapy. Functional measures of disability (eg, neck pain disability questionnaire) were assessed as secondary outcome measures. We also examined adverse events where reported, although did not specify these a priori. Duration of follow-up was assessed and defined as short term (<1 month), medium-term (1–6 months), and long term (>6 months).

Assessment of methodological quality and heterogeneity

Reviewers assessed all studies for methodological quality on the basis of Jadad criteria (maximum score 5).[34] Jadad criteria allocate a point each for randomisation, double-blind design, and description of dropouts. If randomisation and double-blind concealment are assured, an additional 2 points are added. If randomisation or double-blind concealment is not assured, a point is deducted for each. A trial with a score of 3 or more is regarded as high quality. Data from trials with scores of 3 or more were grouped and analysed separately from those scoring less than 3.

We assessed clinical heterogeneity by considering population difference in age, sex, duration of symptoms, and outcomes. Clinical judgment was used to establish whether trials were sufficiently similar to allow pooling

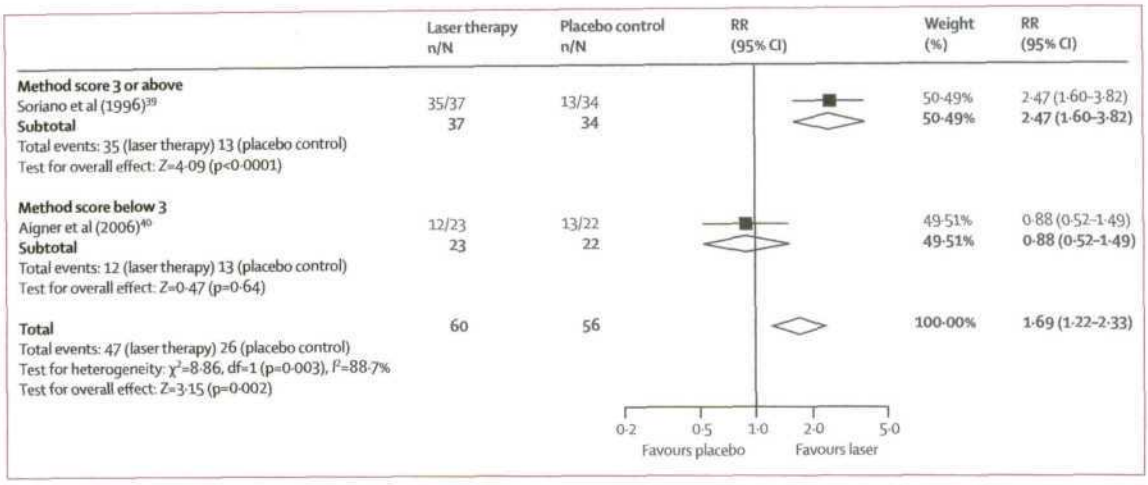

Figure 2: **Relative risk of improvement in acute neck pain in laser-treated versus control groups in two randomised trials reporting categorical data**
RR=relative risk.

of data. The specific parameters of laser devices, application techniques, and treatment protocols were extracted and tabulated by laser wavelength. Details for power output, duration of laser irradiation, number of points irradiated, and frequency and number of treatments were listed. When specific details were not reported, calculations were made from those described in the report when possible. When crucial parameters were not reported, we contacted manufacturers of laser devices and trial investigators to obtain missing information. Not all data were available because of the time elapsed since publication of some studies. Heterogeneity was qualitatively assessed for these factors by an expert in laser therapy (JMB).

We used five levels of evidence to describe whether treatment was beneficial: strong evidence (consistent findings in several high-quality randomised controlled trials); moderate evidence (findings from one high-quality randomised controlled trial or consistent findings in several low-quality trials); limited evidence (one low-quality randomised trial); unclear evidence (inconsistent or contradictory results in several randomised trials); and no evidence (no studies identified).[35]

Statistical analysis

Effect size for the primary outcome, pain intensity, was defined as a pooled estimate of the mean difference in change in mm on a 100 mm visual analogue scale between the mean of the treatment and the placebo groups, weighted by the inverse of the SD for every study—ie, weighted mean difference of change between groups. Variance was calculated from the trial data and given, with 95% CI, in mm on visual analogue scale. For categorical data, reported pain relief was dichotomised into two categories (improvement or no improvement), and we calculated relative risk (RR) of improvement, with 95% CI. For the secondary outcome, disability, effect size was defined as the standardised mean difference, which was a combined outcome measure without units—ie, the standardised mean difference in change between active laser groups and placebo groups for all included trials, weighted by the inverse of the variance for each study.[36]

Mean differences of change for laser-treated and control groups and their respective SDs were included in the statistical pooling. If variance data were not reported as SDs, they were calculated from the trial data of sample size and other variance data values such as p values, *t* values, SE, or 95% CI. Results were presented as weighted mean difference between laser-treated and control with 95% CI in mm on visual analogue scale—ie, as a pooled estimate of the mean difference in change between the laser-treated and control groups, weighted by the inverse of the variance for each study.[37] Statistical heterogeneity was assessed for significance ($p<0\cdot05$) with Revman 4.2, and χ^2 and *F* values greater than 50%. For categorical data, we calculated combined RRs for improvement, with 95% CI. A fixed effect model was used unless statistical heterogeneity was significant ($p<0\cdot05$), after which a random effects model was used. Publication bias was assessed by graphical plot.[38] Revman 4.2 was used for statistical analysis and Microsoft Excel 2003 (version 11) to plot dose-response curves.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 16 randomised controlled trials of a possible 38 that were suitable for inclusion, and that included 820 patients (figure 1). Two trials[39,40] provided data for laser therapy of acute neck pain, one treating acute whiplash-associated disorders and one treating acute neck pain of no defined cause. The other 14 trials reported response of chronic non-specific neck pain without radiculopathy to

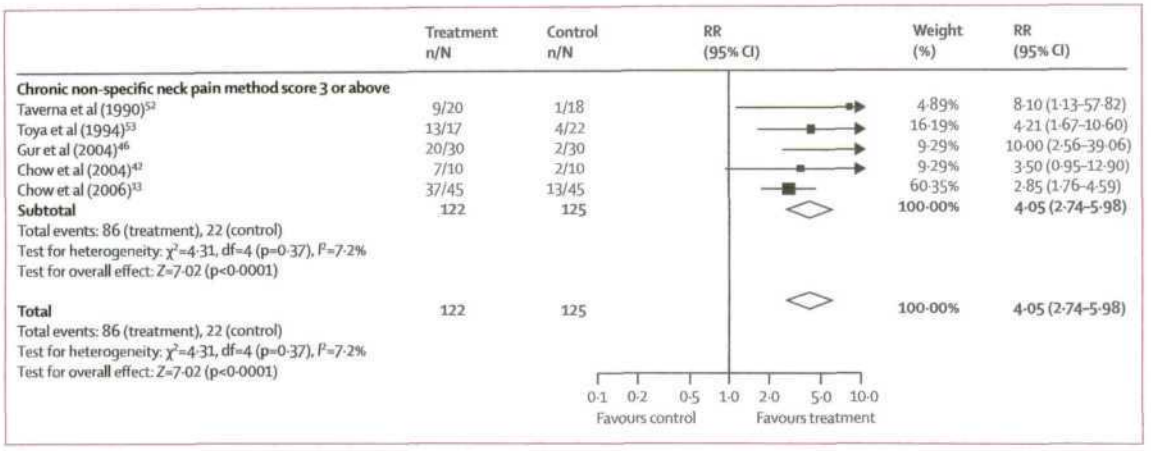

Figure 3: **Relative risk of global improvement in laser-treated versus control groups in five trials reporting categorical data for improvement in chronic pain**
RR=relative risk.

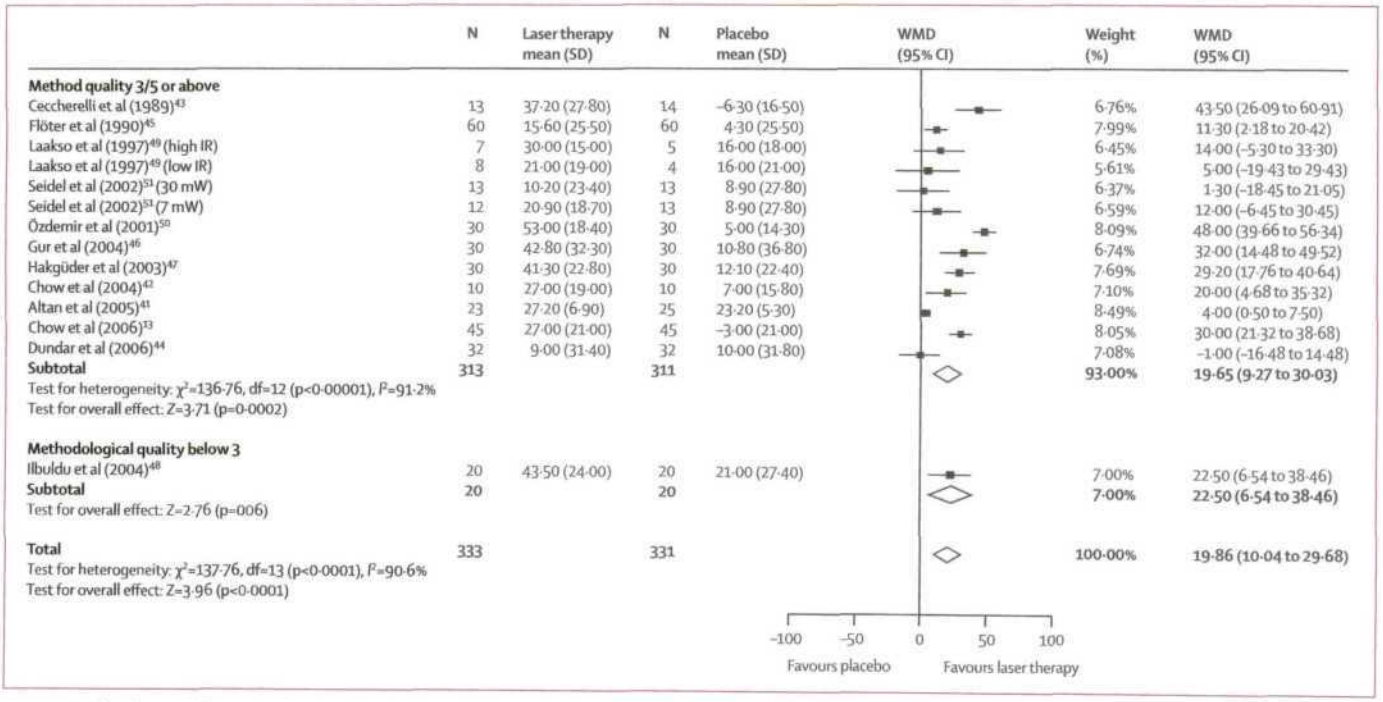

Figure 4: **Weighted mean difference in chronic pain reduction on 100 mm visual analogue scale between laser-treated and placebo-treated groups from 11 randomised trials grouped according to Jadad criteria**
WMD= weighted mean difference. IR=infrared.

laser therapy.[13,41–53] Of the studies included, 648 (79%) of the sample of patients with chronic neck pain were women, and patients had a mean age of 43 years (SD 9·8), mean symptom duration of 90 months (SD 36·9), and mean baseline pain of 56·9 mm (SD 7·5) on a 100 mm visual analogue scale in any trial. Co-interventions were inconsistently reported (table 1). Ten trials reported co-interventions, and six studies did not report or limit co-interventions. Of the studies reporting co-interventions, five groups of investigators explicitly excluded use of concurrent physical therapies, and four excluded use of non-steroidal anti-inflammatory drugs. Four studies allowed use of simple analgesic drugs as needed. Methodological quality assessment values for the trials by Jadad scoring ranged from 0 to 5 (table 1).

Analysis of categorical data for immediate before and after LLLT effects showed that LLLT groups in the two trials[39,40] of acute neck pain had a significant RR of 1·69 (95% CI 1·22–2·33) for improvement immediately after treatment versus placebo (figure 2). Methodological quality varied between these two studies. Five trials of chronic neck pain reported categorical data, and all were

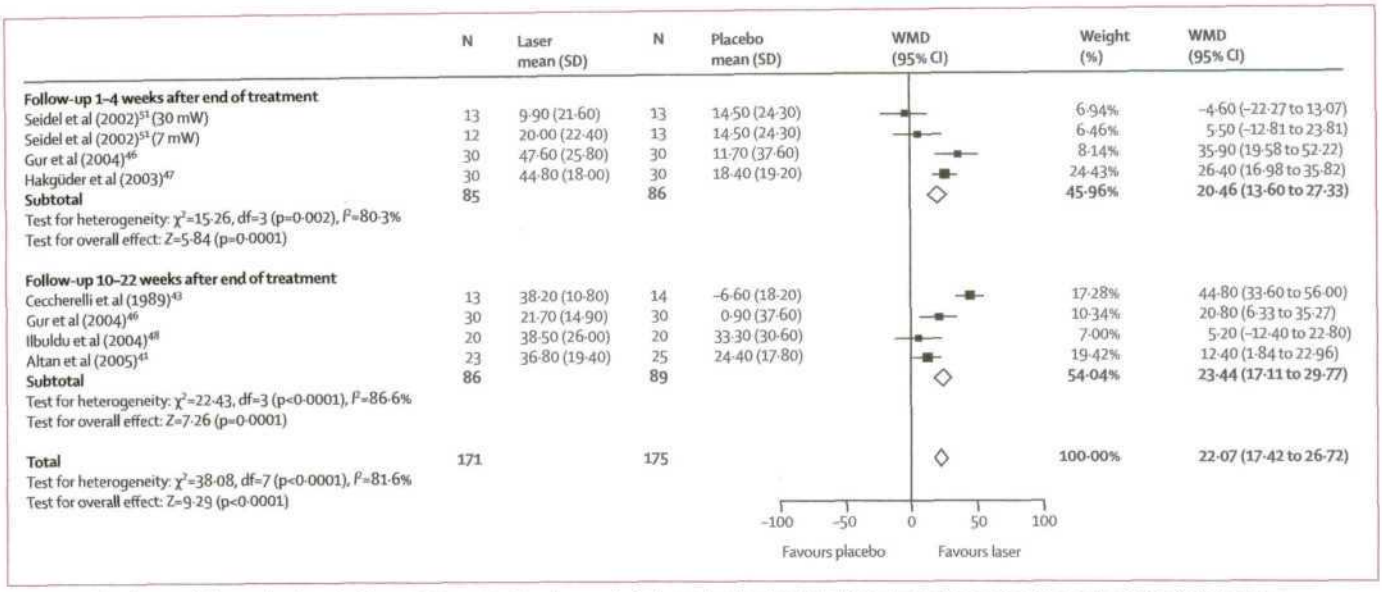

Figure 5: **Weighted mean difference in pain reduction on 100 mm visual analogue scale between placebo-treated and laser-treated groups in seven trials reporting follow-up data**
WMD= weighted mean difference.

high-quality trials with methodological scores of 3 or more. RR of pain improvement with LLLT was 4·05 (2·74–5·98) compared with placebo at the end of treatment (figure 3).

Analysis of data from visual analogue scale showed that in patients in 13 groups in 11 trials, irrespective of methodological quality, pain intensity was reduced by a mean value of 19·86 mm (10·04–29·68) compared with placebo groups (figure 4). Seven trials with eight LLLT groups provided follow-up data for 1–22 weeks after end of treatment (figure 5). The pain-relieving effect in the short term (<1 month) persisted into the medium term (up to 6 months). Five studies provided evidence for improvement in disability at end the of LLLT treatment (figure 6). Several questionnaire-based outcome measures were used—specifically, the neck pain and disability scale,[54] Northwick Park neck pain questionnaire,[55] short form 36,[56] Nottingham health profile,[57] and neck disability index.[58]

Positive publication bias, which tends to exclude negative studies, was not apparent on testing (figure 7).[38] The plot has an aggregation in the lower left quadrant of several small studies with results showing no or only small changes in visual analogue scale.[59] If publication bias towards only positive studies was present, few studies would lie in this position and small studies would have exaggerated positive outcomes. The slight asymmetry might be partly due to a negative publication bias, the small number of studies, and because we have included the most reported studies so far.

We subgrouped trials according to a-priori protocol in acute and chronic categories for the statistical analyses. Within these categories, we noted small variations between trials in patient characteristics such as baseline pain, symptom duration, age, and sex, and we did not detect any clinical heterogeneity (data not shown). Laser parameters and application techniques, including treatment protocols, were heterogeneous (table 2). Laser irradiation was applied to an average of 11 points (range 3–25) in the neck. Energy delivered per point ranged from 0·06 to 54·00 J, with irradiation durations of 1–600 s. Patterns of treatment ranged from a one-off treatment to a course of 15 treatments, which were administered daily to twice a week. On average, participants received a course of ten treatments. Visible (632·8 and 670·0 nm) and infrared (820–830, 780, and 904 nm) wavelengths were used at average power outputs ranging from 4 to 450 mW, in pulsed and continuous wave mode.

When trials with significant results in favour of LLLT were subgrouped by wavelength, doses and irradiation times seemed fairly homogeneous within narrow ranges (table 3). We noted a distinct dose-response pattern for each wavelength for which LLLT is effective within a narrow therapeutic window. For 820–830 nm, mean dose per point ranged from 0·8 to 9·0 J, with irradiation times of 15–180 s. For 904 nm doses, mean dose per point was 0·8–4·2 J, with irradiation times of 100–600 s. Investigators who used doses outside the minimum (0·075 J and 0·06 J)[40,49] and maximum (54 J)[44] limits of these ranges did not show any effect of LLLT, lending further support to a dose-dependent response for LLLT in neck pain.

Significant heterogeneity exists in categorical data for improvement from two studies[39,40] of acute neck pain (p=0·003, χ^2=8·86, I^2=88·7%). This finding could be attributable to the low dose per point used in one study.[40,62] We noted no heterogeneity between trials of chronic neck

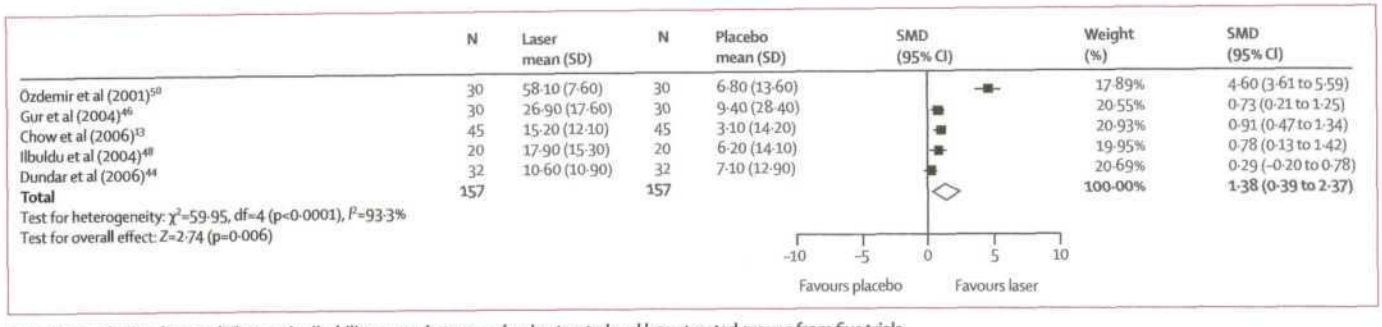

Figure 6: **Standardised mean difference in disability scores between placebo-treated and laser-treated groups from five trials**
SMD=standardised mean difference.

pain reporting on categorical data (p=0·37, χ^2=4·31, I^2=7·2%).

For continuous data from 100 mm visual analogue scale in chronic neck pain, we detected significant heterogeneity across all wavelengths (p<0·0001, χ^2=137·76, I^2=90·6%). However, when heterogeneity was addressed separately by wavelengths, most heterogeneity could be accounted for by variations in doses and application procedures. Removal of the study[44] that used a very high dose from the disability analysis eliminated statistical heterogeneity (p=0·31, χ^2=3·61, I^2=16·9%). For pain intensity on 100 mm visual analogue scale for 820–830 nm wavelength, this study caused heterogeneity together with results of a second study[50] that showed a highly significant effect, without obvious reasons for heterogeneity. After removal of both studies from the 820–830 nm analysis, statistical heterogeneity was eliminated (p=0·12, χ^2=10·20, I^2=41·2%), but the overall effect remained similar, with narrower confidence intervals after (22·0 mm [14·5–29·6]) than before (21·6 mm [10·3–32·9]) removal.

For 904 nm wavelength, statistical heterogeneity was evident for analysis of pain intensity on 100 mm visual analogue scale (p=0·00001, χ^2=28·37, I^2=89·4%). The only study in the review using a scanning application procedure in contact with the skin had weaker than average results.[45] Contrary to other laser application procedures, this method irradiates the target area intermittently. Few studies compare scanning irradiation with stationary irradiation, and most LLLT studies have used a stationary laser beam. Another study using 904 nm wavelength[41] with non-significant results has been criticised for absence of laser testing and calibration, and the actual dose used remains uncertain.[63] Removal of these two trials from the 904 nm analysis of pain reduction on 100 mm visual analogue scale increased the overall effect from 20·6 mm (95% CI 5·2–36·2) to 37·8 mm (25·4–50·1).

50% of trials did not report side-effect data. Side-effects reported included tiredness, nausea, headache, and increased pain, but were mild and, apart from one study in which unusual tiredness occurred more in the laser group than in the placebo group (p>0·01),[42] did not differ from those of placebo.

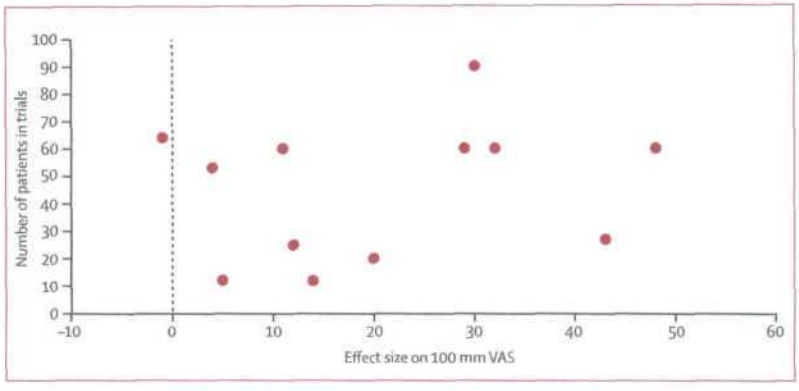

Figure 7: **Publication bias plot**
Plot of effect size between placebo and real laser groups within each trial versus their respective sample sizes. Red circles show one trial. VAS=visual analogue scale.

Discussion

Our results show moderate statistical evidence for efficacy of LLLT in treatment of acute and chronic neck pain in the short and medium term. For chronic pain, we recorded an average reduction in visual analogue scale of 19·86 mm across all studies, which is a clinically important change.[64,65] Categorical data for global improvement also significantly favoured LLLT. From our analysis, 820–830 nm doses are most effective in the range of 0·8–9·0 J per point, with irradiation times of 15–180 s. At 904 nm, doses are slightly smaller (0·8–4·2 J per point), with slightly longer irradiation times (100–600 s) than at 820–830 nm.

Our findings build on those of previous reviews of LLLT[28,30] by including non-English language studies, laser acupuncture studies in which local points were treated, and a quantitative analysis. Our search strategy has identified a greater number of studies than have previous reviews, and draws attention to the intrinsic difficulties in searching the topic of LLLT. Specifically, no accepted terminology exists for laser therapy. We have overcome this limitation by using as wide a range of synonyms as possible.

Moreover, many apparently disparate diagnostic terms are applied to patients presenting with neck pain. These terms suggest distinct clinical entities; however, there is strong evidence that a definitive diagnosis of the causes of neck pain is not possible in a clinical

	Wavelength (nm [mode])	Average output (mW)	J per point	Total time per point (s)	Frequency of treatment	Number of repetitions
Ceccherelli et al (1989)[43]	904 (p)	~25	1	~40	Three times per week on alternate days for 4 weeks	12
Flöter et al (1990)[45]	904 (p); 632·8 (cw)	20·5 (9·5 IR; 11·0 red HeNe)	1	600	Twice per week for 3 weeks	6
Taverna et al (1990)[52]	904 (p)	24	2	180–300	Six times per week for 2·5 weeks	15
Toya et al (1994)[53]	830 (cw)	60	NR	NR	One application only	1
Soriano et al (1996)[39]	904 (p)	40	4	100	Five times per week for 2 weeks	10
Laakso et al (1997)[49]	820 (p)	25	0·06; 0·40	1; 6	Three alternate days per week for 1·5 weeks	5
Laakso et al (1997)[49]	670 (p)	10	NR	4; 18	Three alternate days per week for 1·5 weeks	5
Özdemir et al (2001)[50]	830 (cw)	50	0·75	15	Five times per week for 2 weeks	10
Seidel and Uhlemann (2002)[51]	830 (cw)	7	0·42	60	Twice per week for 4 weeks	8
Seidel and Uhlemann (2002)[51]	830 (cw)	30	1·8	60	Twice per week for 4 weeks	8
Hakgüder et al (2003)[47]	780 (cw)	5	1	196	Five times for week for 2 weeks	10
Chow et al (2004)[42]	830 (cw)	300	9	30	Twice per week for 7 weeks	14
Gur et al (2004)[48]	904 (p)	11·2	0·18–1·80	180	Five times per week for 2 weeks	10
Ilbuldu et al (2004)[46]	632·8 (cw)	NR	2	NR	Three alternate days per week for 4 weeks	12
Altan et al (2005)[41]	904 (p)	4	0·5	120	Five times per week for 2 weeks	10
Aigner et al (2006)[40]	632·8 (cw)	5	0·075	15	Three times per week for 3 weeks	9
Chow et al (2006)[33]	830 (cw)	300	9	30	Twice per week for 7 weeks	14
Dundar et al (2006)[44]	830 (cw)	450	54	120	Five times per week for 3 weeks	15

p=pulsed. cw=continuous wave. IR=infrared. HeNe=helium-neon. NR=not reported.

Table 2: **Laser parameters and treatment regimen**

setting.[66,67] By using the term non-specific neck pain, which encompasses many descriptors,[31] we have addressed the clinical reality that patients presenting with neck pain can have several concurrent sources of pain from joints, muscles, and ligaments.

In addition to aggregating all included studies, irrespective of diagnostic label, we also combined data irrespective of the intended rationale for treatment, as long as neck muscles and spinal joints were exposed to laser irradiation. Transcutaneous application results in laser-energy scattering and spreading into a three-dimensional volume of tissue, up to 5 cm for infrared laser.[68] Since the same effect would be achieved with application of laser energy to acupuncture points, we also included data from studies in which local points in the neck were treated as part of the protocol. Evidence suggests that trigger points in the neck coincide with the location of acupuncture points in 70–90% of patients (eg, BL10, GB 20, GB21, and Ah Shi points).[69,70] Since trigger points and acupuncture points are characterised by tenderness, the treatment effect of laser irradiation to tender points, trigger points, or acupuncture points is likely to be the same. We did not distinguish any differences in subgroup analyses between these techniques. Thus, when treating neck pain with LLLT, irradiation of known trigger points, acupuncture points, tender points, and symptomatic zygapophyseal joints is advisable.

Dose assessment is crucial for interpretation of outcomes of LLLT studies, for which failure to achieve a dose in the recommended range has been identified as a major factor for negative outcomes.[71] The direct relation between positive outcomes of trials with adequate doses of laser irradiation for the appropriate condition has been shown in acute injury and soft-tissue inflammation,[21] tendinopathies,[72] rheumatoid arthritis,[73] lateral epicondylitis,[11] and osteoarthritis.[10]

Several crucial parameters of laser devices are needed to assess dose of laser irradiation, but these doses were inconsistently reported in the studies that we reviewed. No study provided all parameters identified as important by the Scientific Committee of the World Association of Laser Therapy.[74] In neck pain, however, there is little reason to believe that factors other than a plausible anatomical target, dose per point, and irradiation times are essential for efficacy of class 3B lasers (5–500 mW). We had sufficient data relating to each of these components of therapy, when combined with manufacturers' specifications, to identify a dose-response pattern for the number of joules per point and wavelength used and positive outcome. Subgrouping of studies by wavelength and ascending doses reduced apparent heterogeneity in treatment protocols and laser parameters, and showed a dose-response pattern with distinct wavelength-specific therapeutic windows. Most statistical heterogeneity disappeared when we excluded trials with small doses or flaws in treatment procedure from efficacy analyses. Additionally, a very high dose (54 J) of 830 nm LLLT used in one trial did not cause beneficial nor harmful effects.[44] This finding suggests not only that doses of this magnitude are higher than the therapeutic window, but also that LLLT is safe even if such an overdose is delivered. Frequency of treatments varied from daily to twice a week, raising questions about optimum treatment frequency.

Our analysis suggests that the optimum mean dose per point for 820–830 nm was 5·9 J, with an irradiation time of 39·8 s, and for 904 nm, 2·2 J delivered with an irradiation time of 238 s. We recommend a multicentre, pragmatic trial in an appropriately powered study to test the effectiveness of parameters of this order, with both pain intensity and functional improvement as outcome measures.

Data from seven trials were available for up to 22 weeks after the end of treatment, suggesting that positive effects were maintained for up to 3 months after treatment ended. Trials of knee osteoarthritis,[75] tendinopathies,[61,76] and low back pain reported similar longlasting effects of LLLT.[77,78] These results contrast with those for non-steroidal anti-inflammatory drugs in arthritis and spinal disorders, for which the effect ends rapidly when drug use is discontinued.[71] Reduction of chronic neck pain at the end of treatment of 19·86 mm and at follow-up of 23·44 mm on a visual analogue scale of 100 mm represents clinically significant pain relief.[64,65] This result compares favourably with those of pharmacological therapies that are widely used in treatment of neck pain, for which investigators have shown no conclusive evidence of benefit.[32] Intake of oral analgesic drugs was not systematically reported; however, randomisation within trials would keep the confounding effect of this factor to a minimum.

Half the studies obtained data for side-effects,[39,42,44–46,49,52,53] with tiredness reported in the laser-treated group in three studies,[42,46,49] which was significant in one study.[42] Since LLLT does not generate destructive heat, safety relates mainly to potential eye damage, dependent on class of laser device (classes 1–4), which is defined by analysis of several parameters. Safety glasses are required for classes 3B and 4 to eliminate this risk, and would be required for use in all studies. Systematic reporting of side-effects in future studies would also be recommended to clarify short-term and long-term safety aspects of LLLT.

Mechanisms for LLLT-mediated pain relief are not fully understood. Several investigations exploring the pleiomorphic tissue effects of laser irradiation provide plausible explanations for the clinical effects of LLLT. Anti-inflammatory effects of red and infrared laser irradiation have been shown by reduction in specific inflammatory markers (prostaglandin E_2, interleukin 1β, tumour necrosis factor α), in in-vitro and in-vivo animal studies and in man.[79] In animal studies, the anti-inflammatory effects of LLLT are similar to those of pharmacological agents such as celecoxib,[80] meloxicam,[81] diclofenac,[82] and dexamethasone.[80] Chronic neck pain is often associated with osteoarthritis of zygapophyseal joints,[83] which is manifested by pain, swelling, and restricted movement as clinical markers of local inflammation. Laser-mediated anti-inflammatory effects at this joint could result in decreased pain and increased mobility. The distance between skin surface and lateral aspect of the facet joint is typically 1·5–3·0 cm without pressure, and less with contact pressure (measured with ultrasonography [unpublished data, JMB]). Since 830 nm and 904 nm lasers penetrate to several centimetres,[24,84] anti-inflammatory effects at zygapophyseal joints are a plausible mechanism of pain relief.

Another possible mechanism of LLLT action on muscle tissue is a newly discovered ability to reduce oxidative stress and skeletal muscle fatigue with doses similar to those delivering anti-inflammatory effects. This effect has been reported in an animal study[85] and in human studies with biceps humeri contractions and different wavelengths.[86,87] Because muscle fatigue is usually a precursor of muscle pain, and chronic trapezius myalgia is associated with increased electromyograph activity during contractions and impaired microcirculation,[88] reduction of oxidative stress and muscular fatigue could be beneficial in patients with acute or chronic neck pain.

	Mean dose per point (J)	Mean irradiation time per point (s)
632·8 nm[48]	2	200
780 nm[47]	1	196
820–830 nm[33,43,50,53]	5·9 (3·4)	39·8 (30·3)
904 nm[35,41,43,45,46,52]	2·2 (1·6)	238 (184)

Data are mean (SD, when applicable). LLLT=low-level laser therapy.

Table 3: **Mean dose per point and irradiation times for wavelengths of LLLT used in studies with statistically significant results**

Inhibition of transmission at the neuromuscular junction could provide yet another mechanism for LLLT effects on myofascial pain and trigger points.[89,90] Such effects could mediate the clinical finding that LLLT decreases tenderness in trigger points within 15 min of application.[91] Laser-induced neural blockade is a further potential mechanism for the pain-relieving effects of LLLT.[92,93] Selective inhibition of nerve conduction has been shown in Aδ and C fibres, which convey nociceptive stimulation.[94,95] These inhibitory effects could be mediated by disruption to fast axonal flow in neurons[93] or inhibition of neural enzymes.[96]

These tissue effects of laser irradiation might account for the broad range of conditions that are amenable to LLLT treatment. Whether specific treatment protocols are necessary to elicit different biological mechanisms is unknown. Heterogeneity of treatment protocols might be due partly to variation in LLLT parameters and protocols, eliciting different effects. Whatever the mechanism of action, clinical benefits of LLLT occur both when LLLT is used as monotherapy[13,43] and in the context of a regular exercise and stretching programme.[46,47] In clinical settings, combination with an exercise programme is probably preferable. The results of LLLT in this review compare favourably with other widely used therapies, and especially with pharmacological interventions, for which evidence is sparse and side-effects are common.[16,32]

Contributors

RTC participated in the literature search, development of inclusion and exclusion criteria, selection of trials for inclusion in the analysis, methodological assessment, data extraction and interpretation, and writing of the report. MIJ participated in data analysis and interpretation, critically reviewed the report with special expertise in pain management, and contributed to writing of the report. RABL-M participated in data interpretation and analysis, and critically reviewed the report with respect

to the mechanism of action of laser, and relevance to neck pain. JMB participated in development of inclusion and exclusion criteria, translation of non-English language articles, methodological assessment, data analysis and interpretation, writing of the results section of the report, and supervised writing of the report as a whole.

Conflicts of interest

RTC is a member of the World Association for Laser Therapy (WALT), the Australian Medical Acupuncture College, the British Medical Acupuncture Society, the Australian Pain Society, the Australian Medical Association, and the Royal Australian College of General Practitioners. MIJ is a member of the International Association of the Study of Pain. RABL-M is funded by Fundação de Amparo do Estado de São Paulo (FAPESP, Brazil) and is scientific secretary of WALT, from which he has never received funding, grants, or fees. JMB is a member of the Norwegian Physiotherapy Association, Norwegian Sports Physiotherapy Society, Norwegian Society for Rheumatological and Orthopedic Physiotherapy, and has received research awards and grants from the Norwegian Manual Therapy Association, the Norwegian Neck and Back Congress, the Norwegian Research Council, the Norwegian Fund for Postgraduate Training in Physiotherapy, and the Grieg Foundation. He is also president of WALT, a position for which he has never received funding, grants, or fees.

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