Evidence Based Review

Low Level Laser Therapy (LLLT) for Musculoskeletal Pain

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Data Report Completed	**25/9/2014**

Important note:

- The purpose of this brief report is to summarise the best evidence for the effectiveness and safety of LLLT on musculoskeletal pain relief.
- It is not intended to replace clinical judgement or be used as a clinical protocol.
- A reasonable attempt has been made to find and review papers relevant to the focus of this report; however, it does not claim to be exhaustive.
- This document has been prepared by the staff of the Evidence Based Healthcare Team, ACC Research. The content does not necessarily represent the official view of ACC or represent ACC policy.
- This report is based upon information supplied up to June 2014.

Executive summary

Background

Low level laser therapy (LLLT) has been developed as a technology for pain management for decades. In response to a funding request, the Evidence Based Healthcare Team was asked to assess the effectiveness and safety of LLLT on musculoskeletal pain relief. The purpose of this evidence based review is to update ACC's 2000 review based on available recent systematic reviews on LLLT.

Search strategy

The search strategy covered several relevant sources to identify English language studies published since 2000. The manufacturers were also contacted to obtain additional information.

Selection criteria

- Types of studies: systematic review of randomised controlled trials (RCTs)
- Participants: Human participants with musculoskeletal pain
- Outcomes: Pain level

Methodology

All included studies were assessed for their methodological quality using the Scottish Intercollegiate Guideline Network (SIGN) level of evidence system.

Main results

Nine systematic reviews were selected in this report. Seven SRs provided conflicting evidence on efficacy of LLLT in a wide range of tendinopathies and joint disorders. Two SRs found evidence of moderate quality for effectiveness of LLLT on neck pain in the short and medium term. The optimal dose for a broad range of musculoskeletal conditions has not been fully understood. There is no direct evidence suggesting that LLLT is more effective than other treatments in terms of pain management.

Conclusions

- There is some evidence that LLLT is an effective treatment for a range of tendinopathy using World Association for Laser Therapy (WALT) recommended dosages.
- There is moderate evidence that LLLT is effective in the treatment of chronic neck pain.
- There is insufficient evidence to support the use of LLLT in the pain management of joint disorders.
- There are no significant safety concerns reported in the literature.

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List of Abbreviations

CI	Confidence interval
ES	Effect size
GPE	Global perceived effect
LET	Lateral elbow tendinopathy
LLLT	Low level laser therapy
mW	Milliwatt
MTrPs	Myofascial trigger points
nm	Nanometer
NSAIDs	Non-steroidal anti-inflammatory drugs
PEDro	Physiotherapy Evidence Database
QoL	Quality of life
RCT	Randomized controlled trial
RR	Relative risk
SR	Systematic review
TMJ	Temporomandibular joint
WMD	Weighted mean difference
WALT	World Association for Laser Therapy

1. BACKGROUNDS

1.1 Description of LLLT

LLLT is a non-invasive light source treatment that uses red and near-infrared monochromatic light to treat soft tissue injuries without increasing skin temperature. It has low energy output (between 1 and 1000mW) and generates a single wavelength of light (between 600 and 1100 nm) [1].

LLLT has been developed as a technology for pain management for more than 3 decades [2]. Several proposals have been made to explain how LLLT might work in terms of pain reduction. These mechanisms include a reduction of inflammation, an analgesic effect and peripheral nerve stimulation [3]. Treatment typically is delivered with a single laser probe or a laser cluster probe. The probe head of the device can be held in contact with the skin or at a small distance away over the target area, allowing the desired laser energy dose to be delivered. It appears that LLLT has a wide range of effects at the molecular, cellular, and tissue levels [4]. However, the exact mechanism of action remains to be fully elucidated, and the biological and medical effects of LLLT could vary with different clinical applications [3].

1.2 ACC's current position on LLLT

An evidence based review examining the effectiveness of LLLT in the management of a few musculoskeletal conditions was done by ACC in 2000. This review did not find clear evidence supporting LLLT as an effective treatment for musculoskeletal conditions. More importantly, the review found substantial positive evidence indicating that LLLT is an ineffective modality across a wide range of salient objective and subjective outcome measures. The results were consistent with previous studies and suggested that LLLT did not establish itself as an effective therapeutic tool at the time of the report [5,6]. However, during the last decade the number of published LLLT reports has rapidly increased. There is a necessity to reassess up-to-date evidence and evaluate the effects of LLLT on a broad range of musculoskeletal disorders.

ACC's 2000 recommendation was:

- Low-level laser therapy has no role for treating ACC claimants

1.3 Objective

In response to a funding request, the Evidence Based Healthcare Team was asked to assess the effectiveness and safety of LLLT on musculoskeletal pain relief. The purpose of this evidence based review is to update ACC's 2000 review based on recent systematic reviews on LLLT.

2. METHODS

2.1 Search methods for identification of studies

A search was conducted in May 2014 in the following databases:

- AMED (Allied and Complementary Medicine) <1985 to May 2014>
- Embase <1988 to 2014 May 16>
- Ovid MEDLINE In-Process & Other Non-Indexed Citations
- Ovid MEDLINE <1946 to Present>,
- PsycINFO <1967 to May Week 2 2014>
- Google scholar
- Web of Science
- PubMed
- Agency for Healthcare Research and Quality (AHRQ) database

Search terms included: pain, chronic pain, acute pain, disorder, low level/power/ intensity laser therapy/treatment, LLLT, Tendinitis/Tendinosis/Tendinopathy, Fibrositis/Myofascial Pain Syndrome, Fibromyositis, Musculoskeletal pain/disorder/disease

See Appendix 1 for the search strategy.

2.2 Criteria for considering studies for this review

- Types of studies: Systematic review of RCTs
- Types of participant: Human participants with musculoskeletal pain
- Types of interventions: Low level laser therapy
- Types of comparison: placebo, other treatments, or combination of treatments
- Types of outcome measures: Pain level

2.3 The following studies were excluded

- Abstract only
- Animal or laboratory study

- Narrative review, editorial or letter
- Non-English studies
- Systematic reviews before 2000

2.4 Level of evidence

Studies meeting the criteria for inclusion in this report were assessed for their methodological quality using the Scottish Intercollegiate Guideline Network (SIGN) level of evidence system[*]:

Table 1 SIGN level of evidence system

1++	High quality meta analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

[*] Scottish Intercollegiate Guidelines Network http://www.sign.ac.uk/

3. RESULTS

3.1 Study Selection

The initial electronic literature search identified 242 references. 221 articles were excluded on the basis of title and abstract evaluation for not satisfying the inclusion criteria, and duplication. After review of the full-text, 12 articles were excluded, leaving 9 eligible systematic reviews for inclusion in this report. The explanations for excluding these articles are described in Appendix 2.

3.2 Quality Assessment Using SIGN

Of the nine SRs which met the inclusion criteria, 3 looked at LLLT in the treatment of tendinopathy, 2 looked at LLLT in the treatment of neck pain, and 4 looked at LLLT in the treatment in joint disorders. The level of evidence is summarized in Table 2. For more detail analysis, see the evidence tables in Appendix 3

Table 2 The quality of the included systematic reviews

	Level of Evidence			
	1++	1+	1-	Total
Tendinopathy	0	2	1	3
Neck pain	1	1	0	2
Joint disorders	1	2	1	4
Total	2	5	2	9

3.3 Effectiveness

3.3.1 Tendinopathy

There was one SR which evaluated the effectiveness of low level laser treatment for treating pain in patients diagnosed with tendinopathy [7]. Another two SRs looking at lateral elbow tendinopathy (LET) were also located [8,9].

Table 3 RCTs covered by included SRs and evidence overlap for LLLT in the treatment of tendinopathy.

	RCTs	Subjects	Tumilty 2010	Bjordal 2008	Chang 2010	Results	Quality#
Lateral elbow tendinopathy	Basford 2000	47	√	√	√	0	Good
	Gudmundsen 1991	92		√		+	Good
	Haker 1990	49			√	0	Good

	Haker May 1991	49	√	√	√	0	Good
	Haker Nov 1991	58	√	√	√	+	Good
	Krasheninnikoff 1994	36	√	√	√	0	Good/Fair*
	Lam 2007	39	√	√	√	+	Good
	Løgdberg-Anderson 1997	142		√		+	Good
	Lundeberg 1987	57		√	√	0	Good/Poor*
	Oken 2008	58	√	√		+	Good
	Palmieri 1984	30		√		+	Good
	Papadopoulos 1996	29	√	√	√	-	Good/Fair*
	Stergioulas 2007	50	√	√	√	+	Good
	Vasseljen 1992	30	√	√	√	+	Good
	Hernandez-Herrero 2006	46	√			0	Fair
	Vasseljen May 1992	30	√			0	Good
Shoulder tendinitis	Vecchio 1993	35	√			0	Excellent
	England 1989	30	√			+	Good
Achilles tendinitis	Bjordal 2006	14	√			+	Excellent
	Costantino 2005	45	√			-	Good
	Darre 1994	89	√			0	Poor
	Stergioulas 2008	52	√			+	Good
	Tumilty 2008	20	√			0	Excellent
Superaspinatus tendinitis	Saunders 1995	24	√			+	Excellent
	Saunders 2003	36	√			+	Good
Various tendinopathies	Konstantinovic 1997	32	√			+	Poor
	Melagati 1994	32	√			+	Fair
	Muller 1993	48	√			0	Good
	Siebert 1987	64	√			0	Fair
De Quervains tenosynovitis	Sharma 2002	30	√			+	Good
Level of Evidence (SIGN)			1+	1+	1-		

Note: (-) results in favour of the placebo group; (0): non-significant results; (+) positive results for LLLT for at least one measurements. (*): disagreement existed between SRs. (#): The quality of evidence was assessed by SR authors.

The most comprehensive SR was done by Tumilty et al. in 2010 [7]. It reviewed 25 trials (n=1,023 participants), 22 of which were RCTs. Twenty trials scored 6 or more on the PEDro scale, which indicated high quality. Conflicting results were found in the SR. Twelve trials showed positive effects and 13 were inconclusive or showed no effect. Ten good quality studies with positive effects used LLLT dose within the WALT recommended range. Although there were sufficient data to undertake meta-analyses, the variation of interventions resulted in significant clinical heterogeneity between studies and could lead in turn to statistical heterogeneity. The authors therefore just reported two meta-analyses results. Pooled effect results of four high-quality trials revealed that grip strength was significantly improved in patients with lateral epicondylitis after low level laser treatment (WMD 9.59 kg, 95% CI 5.90 to 13.27). For patients with achilles tendinopathy, results from two high quality RCTs showed that the pain reduction effect was significant (WMD 13.64mm, 95% CI -26.17 to -1.11). The authors concluded that low level laser treatment was potentially effective in treating tendinopathy using WALT recommended dosages, but the overall evidence was inconclusive. This review was well-conducted and the authors' tentative conclusion seems justified. SIGN evidence level 1+

The second systematic review by Bjordal et al. [8] evaluated LLLT for the treatment of lateral elbow tendinopathy (tennis elbow). The SR included 13 RCTs (n=730 participants), one of which was of poor quality, the other studies met between 6 and 8 of the 10 quality criteria and were of acceptable methodological quality. Pooled effect results of ten RCTs showed a statistically significant improvement in pain at the end of LLLT treatment (WMD 10.2mm, 95% CI 3.0 to 17.5) and at 3 to 8 weeks of follow-up (WMD 11.80, 95% CI 7.64 to 16.07). There was also a significant increase in global improvement compared with placebo (RR 1.36, 95% CI 1.16 to 1.60). When the trials were subgrouped by technique and wavelength, there was a significant improvement in pain (WMD 17.2mm, 95% CI 8.5 to 25.9) and global improvement (RR 1.53, 95% CI 1.28 to 1.83) with tendon application 904nm LLLT. However, considerable heterogeneity in the treatment procedures for LLLT was reported. There was evidence of publication bias, which would likely to increase the pooled effect estimate in favour of LLLT. This appears to be a well conducted SR with low risk of bias: SIGN evidence level 1+.

Another 2010 SR by Chang et al. [9] compared the effectiveness of applying LLLT to tender points and acupuncture points in patients with lateral elbow tendinopathy. This SR assessed ten RCTs, 9 of which were also included in Bjordal’s SR. The results revealed that applying LLLT on tender points or myofascial trigger points (MTrPs) could effectively improve the effect size (ES) of pain reduction. By contrast, applying LLLT to acupuncture points resulted in no significant differences after treatment. LLLT also showed significant effects on increasing grip force, joint ROM and weight test. The authors concluded that using LLLT on tender points or MTrPs had better therapeutic effects than applying LLLT on acupuncture points in patients with lateral elbow tendinopathy. It is noteworthy that three studies using laser on acupuncture

points had high risks of bias (PEDro score: 3-5). They used LLLT with doses from 0.004 to 0.9J per point, which were lower than the doses applied to the tender points. The poor results may be caused by insufficient irradiation to the acupuncture points. Therefore, the authors' conclusions may be too strong and may not reflect the evidence. This review was assigned a 1- level of evidence with a high risk of bias.

3.3.2 Neck pain

Two SRs were identified.

Table 4 RCTs covered by included SRs and evidence overlap for LLLT in the treatment of neck pain.

RCTs	Subjects	Chow 2009	Gross 2013	Results	Quality#
Altan 2005	53	√	√	0	Good
Aigner 2006	45	√		0	Poor
Ceccherelli 1989	27	√	√	+	Good
Chow 2004	20	√	√	+	Excellent/Good*
Chow 2006	90	√	√	+	Excellent/Good*
Dundar 2007	64	√	√	0	Good
Flöter 1990	60	√		+	Good
Gur 2004	60	√	√	+	Excellent/Good*
Hakguder 2003	62	√	√	+	Good
Ilbuldu 2004	40	√	√	+	Poor
Konstantinovic 2010	60		√	+	Good
Laakso 1997	41	√		0	Good
Nilsson 1995	38		√	-	Fair
Özdemir 2001	60	√	√	+	Good
Seidel 2002	48	√	√	0	Good
Soriano 1996	71	√	√	+	Good
Taverna 1990	40	√	√	+	Good
Thorsen 1991	36		√	0	Fair
Thorsen 1992	47		√	-	Poor
Toya 1994	39	√		+	Excellent
Waylonis 1988	NR		√	0	Poor
Level of Evidence (SIGN)		1++	1+		

Note: (-) adverse results or results in favour of the placebo group; (0): non-significant results; (+) positive results for LLLT for at least one measurement; (*): disagreement existed between SRs. NR: Not reported. (#): The quality of evidence was assessed by SR authors.

A high quality (SIGN grade 1++) SR and meta-analysis of RCTs evaluated the immediate and intermediate term efficacy of LLLT in neck pain [10]. With the exception of two poor quality trials, the included trials fulfilled between 3 and 5 of Jadad scores and were considered as being of high quality. Of the 16 studies identified in this SR, two trials examined acute neck pain and suggested that LLLT improved pain outcomes compared to placebo (RR 1.69, 95% CI 1.22 to 2.33). Eleven trials reported changes in visual analogue scale and found a reduction of 19.86 mm (95% CI 10.04 to 29.68) after laser treatment. Results of categorical data from five trials of chronic neck pain showed an RR for pain improvement of 4.05 (95% CI 2.74 to 5.98) of LLLT versus placebo. Seven trials provided follow-up data, which suggested that the effect of pain relief persisted for up to 22 weeks. The data showed considerable clinical heterogeneity across all wavelengths. However, after removal of the studies most likely to have caused heterogeneity, statistical heterogeneity was eliminated and the overall effect remained similar with narrower confidence intervals. Therefore, this analysis strengthened the SR's conclusions that LLLT reduced pain in the short and intermediate term.

Another good quality SR (SIGN grade 1+) and meta-regression by Gross et al. [11] was located. The included 17 studies were slightly different from Chow's SR. Seven trials demonstrated low risk of bias. There was moderate quality evidence suggesting LLLT to be superior to placebo when applied to the chronic neck pain in terms of improving pain/disability/QoL/GPE at intermediate-term. For acute radiculopathy, cervical osteoarthritis or acute neck pain, low quality evidence suggested LLLT improves pain/function/QoL better than placebo. For chronic myofascial neck pain, evidence was conflicting and the authors suggested that further research was likely to have an important impact on the confidence in the estimate of effect. The meta-regression result suggests that super-pulsed LLLT might increase the chance of success in treatment of chronic myofascial neck pain. The review was generally well conducted but given the limitations of the included studies, and substantial heterogeneity, the authors' conclusions should be considered tentative.

3.3.3 Joint disorders

One SR looked at LLLT in the treatment of chronic joint disorders [12]. Two studies focus on temporomandibular joint (TMJ) [13,14]. One Cochrane review assessed the effects of LLLT in patients with non-specific low-back pain [15].

Table 5 RCTs covered by included SRs and evidence overlap for LLLT in the treatment of pain from joint disorders.

Joint	RCTs	Subject	Bjordal 2003	Petrucci 2007	Melis 2012	Yousefi-Nooraie 2008	Results	Quality#
Back	Basford 1999	63	√			√	+	Good
	Djavid 2007	61				√	0	Good
	Gur 2003	75				√	0	Fair
	Klein 1990	20	√			√	0	Good
	Longo 1991	80				√	0	Fair
	Soriano 1998	71	√			√	+	Good
	Toya 1994	115	√			√	+	Excellent
	Özdemir 2001	60	√				+	Good
TMJ	Bertolucci 1995-1	32	√		√		+	Good
	Bertolucci 1995-2	48			√		+	Fair
	Carrasco 2008	14		√	√		+	Good
	Carrasco 2009	60			√		0	Fair
	Conti 1997	20	√	√	√		+	Good
	da Cunha 2008	40		√	√		0	Good
	de Abreu 2005	30		√	√		0	Good
	Emshoff 2008	52		√	√		0	Excellent
	Gray 1994	55	√				+	Fair
	Kulekcioglu 2003	35		√	√		+	Good
	Marini 2010	99			√		+	Good
	Mazzetto 2007	48			√		+	Good
	Mazzetto 2010	40			√		+	Fair
	Shirani 2009	16			√		+	Good
	Venezian 2010	48			√		0	Good
Thumb	Basford 1987	81	√				0	Good
Knee	Bulow 1994	29	√				0	Good
	Gøtte 1995	40	√				+	Good
	Jensen 1987	29	√				0	Fair/Poor*
	Stelian 1991	50	√				+	Good
	Nivbrant 1992	30	√				+	Good
Level of Evidence (SIGN)			1+	1+	1-	1++		

Note: (-) adverse results or results in favour of the placebo group; (0): non-significant results; (+) positive results for LLLT for at least one measurement; (*): disagreement existed between SRs. (#): The quality of evidence was assessed by SR authors.

The 2003 SR done by Bjordal et al. [12] identified 14 trials with 695 patients to investigate whether LLLT of the joint capsule can reduce pain in finger, knee, spine and TMJ disorders. 12 of the 14 included studies had a PEDro score equal or larger than 6, which indicates high methodological quality. Before the reviewing procedures, the authors proposed a range of power densities and dose for the most common joints according to successful laboratory trials. Three studies which used doses lower than the suggested dose range found no significant difference between laser group and placebo group. The results of the remaining 11 trials showed there is a 29.8 mm (95% CI, 18.9 to 40.7) WMD of pain reduction on VAS in favour of the LLLT groups. The improvement of health status was also significantly in favour of the laser groups. (RR: 0.52; 95% CI 0.36 to 0.76). This SR was well conducted and was graded SIGN evidence level 1+.

The Cochrane review included seven small RCTs (sample sizes ranging from 20 to 80) investigating low-back pain, with the number of quality criteria met ranging from 6 to 11. Three studies compared showed a statistically significant improvement in pain reduction for LLLT in short-term and intermediate-term follow-up. But the mean reduction of pain scores was not clinically important [16]. One trial reported significant effect of reducing disability in favour of the intervention at short-term follow-up. This review also found that LLLT did not reduce pain more than exercise, with or without sham treatment for individuals with chronic low-back pain. Therefore, the authors concluded that there were insufficient data to support the clinical effectiveness of LLLT for low-back pain. Despite the clinical heterogeneity, the small sample sizes and the small clinical effect sizes, this SR was well-conducted with extensive subgroup analyses and consideration of heterogeneity (SIGN level of evidence 1++).

The 2011 SR by Petrucci et al. [14] examined a total of six RCTs carried out from 1997 to 2008 on LLLT for temporomandibular disorders (TMD). Two trials reported nonsignificant difference in pain reduction after laser treatment, while the rest of the trials reported significant difference between groups. In addition, a decrease in pain intensity was found in both active and placebo groups, but the reduction did not significantly differ between groups. Only one trial reported better results for the LLLT group in terms of mandibular range of motion. The authors concluded that there is no evidence to support the use of LLLT in the treatment of TMD. Based on the trials included in the review, the authors' overall conclusion does not seem unreasonable, but the evidence base was limited by number, quality, sample size and clinical heterogeneity. Thus, the conclusions should be interpreted with a degree of caution (SIGN level of evidence 1+).

A more recent SR by Melis et al. [13] also looked at the effect of LLLT on temporomandibular disorders. This SR assessed 14 RCTs carried out from 1995 to 2010, including all six RCTs in Retrucci's study. In eight trials, LLLT was found to be superior to placebo in improving pain intensity and mandibular range of motion. Conversely, eight trials reported no significant difference between the LLLT groups and the placebo groups (more than one trial was performed in some studies). The results also showed that six out of eight articles reported LLLT to be superior to placebo when applied on the TMJs, while one out of three reported LLLT to be superior to placebo when applied on the masticatory muscles. The authors concluded that LLLT may be more effective for the treatment of TMJ disorders, and less effective for the treatment of masticatory muscle disorders. However, this SR had a high risk of bias with a SIGN level of evidence 1-, and the conclusion may not be reliable.

3.4 Comparisons with other treatments

There is insufficient evidence to confirm whether LLLT is better than other common used treatments (such as NSAIDs, steroid injections, physiotherapy with various modalities, physical treatments and exercise interventions) for musculoskeletal pain. Only one SR performed a direct comparison between LLLT and exercise in the treatment of low-back pain. The authors found moderate evidence that LLLT did not reduce pain more than exercise [15].

Two SRs indirectly compared the efficacy of LLLT with pharmacological therapies. Bjordal et al. [8] suggested that LLLT should be considered as an alternative therapy to NSAIDs and corticosteroid injections in LET management due to the long-lasting effects of LLLT. Similarly, Chow et al. [10] reported that the clinically significant effect of LLLT for neck pain were able to be maintained for up to 22 weeks. This result compared favourably with those for pharmacological therapies, for which investigators had found inconclusive evidence of benefit.

3.5 Side effects

Side effects were mentioned in five SRs, three of which stated that there were no side effects or adverse events reported in the included RCTs related to LLLT during treatment or follow-up [8,12,14]. Two SRs looking at the effects of LLLT on neck pain reported some mild side effects, including tiredness, nausea, increased stiffness, headache and increased pain [10,11]. In addition, both of them included one trial that reported a significant increase in tiredness in the LLLT group. Chow et al. [10] also mentioned that low level laser might have the potential for eye damage. However, no reports of such an injury in human trials have been found.

3.6 Cost effectiveness

No SRs were found to determine whether LLLT is cost-effective compared to other pain relief treatments.

The cost of an LLLT device for medical use is between US$2000 and US$ 30,000 (See Appendix 4 for the cost of available LLLT devices in the market). Treatment costs vary depending on the target sites, dosage and the duration of the treatment. The cost of one 20-minutes treatment for pain relief is typically about NZ$40 with an average of 10 treatments given.

3.7 Additional findings

3.7.1 Cigna Medical Coverage Policy on LLLT

Cigna is a major international provider of medical, dental, disability, life and accident insurance. A recent Cigna Medical Coverage Policy for LLLT reviewed a number of published RCTs, SRs and international guidelines regarding to the effect of LLLT on various musculoskeletal and medical conditions, wound healing, and oral mucositis. It concluded that there is insufficient evidence in the published, peer-reviewed scientific literature to demonstrate that LLLT is effective for these conditions or other medical conditions. It was suggested that large, well-designed clinical trials are needed to demonstrate the effectiveness of LLLT for the proposed conditions. The details about Cigna Medical Coverage Policy on LLLT are as follow:

- Cigna Medical Coverage Policy: Low level laser therapy (Policy Number: 0115, July 2014)[17]

  Cigna **does not cover** low-level laser therapy (LLLT) for any indication because it is considered experimental, investigational or unproven.

3.7.2 Aetna Clinical Policy Bulletin on LLLT

Aetna is also a major global insurance company that offers health, life and accident insurance coverages to individuals. Website search found two Clinical Policy Bulletin updates related to LLLT. The details about Aetna Clinical Policy Bulletin on LLLT are as follow:

- Clinical Policy Bulletin: Cold Laser and High-Power Laser Therapies (Policy Number: 0363, June 2014)[18]

  Aetna considers cold laser therapy (also known as low-level laser therapy or class III laser) and high-power laser therapy (class IV therapeutic laser) experimental and investigational because there is **inadequate evidence** of the effectiveness of cold laser therapy and high-power laser therapy in pain relief (e.g. acute and chronic low back pain/neck pain, orthodontic pain, shoulder pain), wound healing,

or for other indications such as carpal tunnel syndrome, colorectal cancer, dentin hypersensitivity, elbow disorders, fibromyalgia, herpes labialis, lymphedema, musculoskeletal dysfunction, myofascial pain syndrome, neurological dysfunctions, patella-femoral pain syndrome, physical therapy (including rehabilitation following carpal tunnel release), rheumatoid arthritis, shoulder impingement syndrome, and tinnitus.

- Clinical Policy Bulletin: Infrared Therapy (Policy Number: 0604, September 2014)[19]

Aetna considers treatment with low-level infrared light (infrared therapy, Anodyne Therapy System) experimental and investigational for the treatment of the following indications because of **insufficient evidence** regarding the effectiveness of infrared therapy for these indications (not an all-inclusive list):

1) Acne
2) Back (lumbar and thoracic) pain
3) Bell's palsy
4) Central nervous system injuries
5) Chronic non-healing wounds
6) Diabetic macular edema
7) Diabetic peripheral neuropathy
8) Ischemic stroke
9) Lymphedema
10) Neck pain
11) Osteoarthritis
12) Parkinson's disease
13) Retinal degeneration
14) Stroke

3.7.3 Current international recommendations on LLLT

Literature search identified five guidelines and provided recommendations on LLLT in the treatment of a wide range of musculoskeletal pain. These recommendations are summarised in Table 6. Three guidelines either recommend against the routinely use of LLLT or are unable to make a recommendation due to insufficient or conflicting evidence. Two available guidelines recommend LLLT to be considered as a treatment option for patients with chronic low back pain and Achilles tendinopathy based on moderate evidence.

Table 6 Available recommendations on LLLT

Guidelines	Recommendations	Strength of evidence
Occupational medicine practice guidelines by American College of	**No recommendation** for or against the use of LLLT in the treatment of rotator cuff	Evidence that the intervention is effective is lacking, of poor quality, or conflicting and the balance of benefits, harms, and costs cannot be

Occupational and Environmental Medicine (ACOEM); 2011[20] .	tendinopathies. LLLT is **not recommended** to be used in patients with acute, subacute, or chronic knee pain LLLT is **not recommended** to be used in patients with acute and chronic low back pain because of high costs or high potential for harm to the patient. LLLT is **not recommended** to be used in patients with acute, subacute, or chronic lateral epicondylitis	determined. Recommendation against routinely providing the intervention. At least intermediate evidence was found that harms and costs exceed benefits based on limited evidence. The evidence is insufficient for an evidence-based recommendation. Recommendation against routinely providing the intervention to eligible patients. The EBPP found at least intermediate evidence that the intervention is ineffective, or that harms or costs outweigh benefits.
Occupational therapy practice guidelines for individuals with work-related injuries and illnesses by American Occupational Therapy Association (AOTA), 2009[21]	**No recommendation** for or against the use of LLLT in the treatment of epicondylitis, neck and shoulder pain **No recommendation** for or against the use of general hand, wrist, forearm conditions, rotator cuff tears	The literature review found at least fair evidence that the intervention can improve outcomes but concludes that the balance of the benefits and harm is too close to justify a general recommendation. Evidence that the intervention is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harm cannot be determined.
Guideline for the evidence-informed primary care management of low back pain, 2011[22]	**No recommendation** for or against the use of LLLT in patients with acute, subacute and chronic low back pain	There is insufficient evidence to make recommendations.
Management of chronic pain. A national clinical guideline by Scottish Intercollegiate Guidelines Network (SIGN), 2013[23]	LLLT **should be considered** as a treatment option for patients with chronic low back pain.	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
Achilles pain, stiffness, and muscle power deficits: Achilles tendinitis, 2010[24]	Clinicians **should consider** the use of LLLT to decrease pain and stiffness in patients with Achilles tendinopathy.	A single high-quality randomized controlled trial or a preponderance of level II studies support the recommendation

4 DISCUSSION

4.1 Nature and quality of the evidence

In this report, we found that most SRs of LLLT for musculoskeletal pain were of acceptable methodological quality. Six of eight included SRs have low or very low risk of bias. The results regarding the effectiveness of LLLT in the treatment of musculoskeletal pain vary by subtype of pain, LLLT parameters and trial protocols.

For tendinopathy, two well-conducted SRs and one SR with high risk of bias assessed 30 RCTs in total. Twelve RCTs reported non-significant findings, including two high quality RCTs. One fair quality and one good quality RCT reported findings significant in favour of the sham treatment or other non-laser interventions. 16 RCTs reported at least one positive outcome, including two high quality RCTs and two low quality RCTs.

For neck pain, two SRs with low and very low risk of bias showed moderate statistical evidence for efficacy of LLLT in the treatment of acute and chronic neck pain in the short and medium term. Of 21 RCTs included in these two SRs, two good quality RCTs and four poor quality RCTs reported non-significant findings, while very low quality evidence from two trials reported findings significantly in favour of the placebo groups. Of the 13 RCTs that reported positive outcomes, only one was a low quality RCT.

Three well-conducted SRs and one SR with high risk of bias reviewed 29 trials to examine the effect of LLLT versus control group in the treatment of joint disorders. Most trials were of acceptable methodological quality. 12 RCTs found no significant different between LLLT group and placebo groups at the end of treatment.

Although many studies reported potential benefits of LLLT in a variety of musculoskeletal pain conditions (45/79), differences in the clinical settings, study designs, measurements, and populations make it difficult for systematic and meta-analytic studies to confirm LLLT's actual outcomes of clinical efficacy and safety. Most RCTs included in the SRs have very small sample size, and only two RCTs have a sample size more than 100. This may have increased potential bias and weakened the scientific merit and clinical applicability of the trials reviewed. In addition, although positive effects were found among these studies, it is still not clear that the pain relief achieved was large enough to replace conventional therapies.

Additional findings showed that two major insurance companies considered LLLT experimental, investigational or unproven. Thus, both of them do not cover LLLT for musculoskeletal pain relief.

4.2 Dose-dependent effects of LLLT

Even though most of the included SRs suggested that the overall effectiveness of LLLT on pain relief was inconclusive, six SRs provided strong evidence that LLLT acts in a dose-dependent manner. The doses of laser irradiation were inconsistently reported in the RCTs included in our SRs, but positive outcome were more likely to be associated with the use of the recommended range [25]. Some researchers pointed out that poor results were caused by the lack of dosage consensus, such as insufficient irradiation [12]. Thus, the dose of LLLT, relating to wavelength, energy density and power, is crucial in the determination the effectiveness of LLLT.

One low quality SR suggested that different treatment points could impact on the effectiveness of LLLT. The authors concluded that using LLLT on tender points or trigger points had better therapeutic effects on lateral epicondylitis [9]. However, the dose used on acupuncture points was greatly lower than that on tender points. The negative results may therefore have been caused by insufficient irradiation. Since trigger points and acupuncture points are both characterised by tenderness, the effect of LLLT on tender point, trigger point or acupuncture point is more likely to be similar. Previous evidence also suggested that the acupuncture and myofascial trigger pain traditions have fundamental clinical similarities in the treatment of pain disorders [26].

4.3 Limitations

Methodological limitations of this systematic review include absence of RCTs and conference proceedings which may have led to relevant evidence being missed. Publication bias has not been discussed in this review. Although this report excluded SRs published in other languages, most included SRs did not have language restrictions.

The assessments including the extraction of data from included studies were performed by the principal reviewer only. However, the results were checked by the other reviewers.

5 CONCLUSIONS

Evidence statements

There is some evidence that LLLT is an effective treatment for a range of tendinopathy using WALT recommended dosages.

There is moderate evidence to support the use of LLLT in the treatment of chronic neck pain.

There is insufficient evidence to support the use of LLLT in the pain management of joint disorders.

There is no direct evidence suggesting that LLLT is more effective than other treatments in terms of pain management.

The dose of laser irradiation is crucial for the interpretation of the outcome of LLLT studies. However, it is not possible to make robust estimates of the optimal dose for a broad range of musculoskeletal conditions due to significant clinical heterogeneity.

LLLT is generally reported to be well tolerated and free of serious side effects by the existing literature.

Implication for practice

Use of WALT recommended dose range for different target soft tissues may increase the chance of a successful pain outcome.

LLLT is a non-invasive treatment that appears to be safe so long as devices are used according to the manufacturer's instructions.

Implication for research

More adequately powered, well-designed RCTs evaluating the optimal dosage parameters of LLLT in the treatment of musculoskeletal pain are warranted.

There is also a need for more high-quality trials or systematic reviews to do comparisons between LLLT and other pain management treatments.

Cost-effectiveness studies are recommended.

Recommendations for purchasing

Do not purchase the routinely use of LLLT in the treatment of tendinopathies and joint disorders. It may be prudent to wait until more definitive research is available before making purchasing recommendations.

Do not purchase the routinely use of LLLT for the treatment of chronic neck pain. However, it may be considered on a case by case basis where conventional treatment has failed on recommendation from a registered medical practitioner.

The Research team recommends that this review be considered by the ACC Purchasing Guidance Advisory Group (PGAG), so that the recommendations on purchasing LLLT can be formalised and disseminated throughout ACC.

6 APPENDIX

6.1 Appendix 1 Search strategy (Ovid)

1 exp Pain/ or (Pain* or disorder*).ti,ab. (3790888)

2 exp Acute Pain/ or Acute Pain*.ti,ab. (744498)

3 exp Chronic Pain/ or Chronic Pain*.ti,ab. (89128)

4 exp Tendinopathy/ or (Tendinitis or Tendinosis).ti,ab. (19422)

5 exp Fibromyalgia/ or (Fibrositis* or Myofascial Pain Syndrome* or Fibromyositis*).ti,ab. (24095)

6 exp Temporomandibular Disorder/ or (Temporomandibular* or Temporomandibular joint* or Temporomandibular Disorders*).ti,ab. (86439)

7 exp Musculoskeletal Abnormalities/ or Musculoskeletal Pain/ or Musculoskeletal Diseases/ or (Musculoskeletal adj3 disorder$).ti,ab. (27660)

8 1 or 2 or 3 or 4 or 5 or 6 or 7 (3501357)

9 meta-analysis as topic/ or Meta-Analysis.pt. or ((systematic adj3 literature) or systematic review* or meta-analysis* or meta-analyses or meta-analysed or meta-analyzed or meta-analysing or meta-analyzing).ti. or "cochrane database of systematic reviews".jn. or "research synthesis".ti. or ((information or data) adj2 synthesis).ti,ab. or (data adj2 extract*).ti,ab. or (medline or pubmed or psyclit or cinahl or (psycinfo not "psycinfo database") or "web of science" or scopus or embase).ti. (290575)

10 exp Laser Therapy/ or (low level laser or low power laser or low-level laser or low-power$ laser).ti,ab. (62378)

11 7 and 8 and 9 (247)

12 limit 11 to english language (242)

6.2 Appendix 2 Excluded study table

Study	Topic	Reason
Gam 1993	The effect of low-level laser therapy on musculoskeletal pain: a meta-analysis	**Systematic review was conducted before 2000**
de Bie 1998	Efficacy of 904 nm laser therapy in the management of musculoskeletal disorders: a systematic review.	**Systematic review was conducted before 2000**
Maia 2012	Effect of low-level laser therapy on pain levels in patients with temporomandibular disorders: A systematic review.	**Narrative review**
Kadhim-Saleh 2013	Is low-level laser therapy in relieving neck pain effective? Systematic review and meta-analysis.	**Narrative review.**
McNeely 2006	A systematic review of the effectiveness of physical therapy interventions for temporomandibular disorders.	**Types of interventions do not satisfy inclusion criteria**
Chow 2005	Systematic review of the literature of low-level laser therapy (LLLT) in the management of neck pain.	**Reviewed studies are updated by a recent systematic review by the same author**
Enwemeka 2004	The efficacy of low-power lasers in tissue repair and pain control: A meta-analysis study.	**Animal study**
Beckerman 1992	The efficacy of laser therapy for musculoskeletal and skin disorders: a criteria-based meta-analysis of randomized clinical trials.	**Systematic review was conducted before 2000**
Baxter 2008	Clinical effectiveness of laser acupuncture: A systematic review.	**Types of participant do not satisfy inclusion criteria.**
Fulop 2010	A meta-analysis of the efficacy of laser phototherapy on pain relief	**Cannot separate outcome of LLLT studies**
Brosseau 2004	Low level laser therapy (Classes I, II and III) for treating osteoarthritis	**Withdrawn from the Cochrane Library**
Bjordal 2006	**Low-Level Laser Therapy in Acute Pain: A Systematic Review of Possible Mechanisms of Action and Clinical Effects in Randomized Placebo-Controlled Trials**	**Types of participant are not satisfying inclusion criteria.**

6.3 Appendix 3 Evidence Tables

Reference and study design	Studies	Intervention/comparison	Measurements	Outcome	Comments & Level of Evidence
Chow et al, 2009 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 Lancet 2009; 374(9705), 1897-1908 UK/ Norway Included studies: Ceccherelli 1989 Flöter 1990 Taverna 1990 Toya 1994 Soriano 1996 Laakso 1997 Ozdemir 2001 Seidel 2002 Hakguder 2003 Chow 2004 Gur 2004 Ilbuldu 2004	Number of studies: N=16 Only one study was single blinded, the rest were double blinded. Total number of patients: n=820 Inclusion criteria: ▪ Randomised or quasi-randomised controlled trials of LLLT for acute or chronic neck pain. ▪ No language restrictions ▪ Patients ≥16 years old Exclusion criteria ▪ region of pain unrelated ▪ to neck pain ▪ specific pathological changes could be identified ▪ abstract only ▪ cannot separate neck pain data no pain measure Databases used: Medline (January, 1966, to July, 2008), Embase (January, 1980, to July, 2008), Cinahl (January 1982, to July, 2008), Physiotherapy Evidence Database (January, 1929, to July, 2008), AMED (January,1985, to July, 2008), and the Cochrane Central Register of Controlled Trials (second	Intervention: LLLT Length of intervention: Various, minimum: 1 application; maximum:7 weeks (1-15 repetitions) Comparison: placebo, exercise Co-interventions: • 6 did not report; • 5 excluded use of concurrent physical therapies; • 4 excluded use of non-steroidal anti-inflammatory drugs; • 4 allowed use of simple analgesic drugs as needed.	Pain reduction: • Chronic pain (n=11) Categorical data • Acute neck pain studies (n=2) • Chronic pain studies.(n=5) • Disability score (n=5) Follow up: • 1-4 weeks (n=4) • 10-22 weeks (n=4) • Total	WMD 19.9mm, 95% CI 10.0 to 29.7, p<0.0001, I^2=90.6% RR 1.69, 95% CI 1.22 to 2.33; I^2=89% RR 4.05, 95% CI 2.74 to 5.98; I^2=7% SMD 1.38, 95% CI 0.39 to 2.38; I^2=93% WMD 20.5mm, 95% CI 13.6 to 27.3, p=0.0001, I^2=80.3% WMD 23.4mm, 95% CI 17.1 to 29.8, p=0.0001, I^2=86.6% WMD 22.1mm, 95% CI 17.4 to 26.7, p<0.0001, I^2=81.6% Side-effect: Eight studies reported mild side-effect, including tiredness, nausea, headache and increased pain. Author's conclusion: LLLT reduces pain	Study type: Systematic review Quality: SIGN 1++ Comments: The review was well-conducted and the authors' tentative interpretation seems justified. The objectives and inclusion criteria of the review were clear and several relevant data source were searched. Statistical heterogeneity was assessed and explored using subgroup and sensitivity analyses. Study details were presented clearly, both statistical and clinical heterogeneity was assessed and the chosen method of synthesis appeared appropriate. The data showed considerable clinical heterogeneity across all wavelengths. However, after removal of the studies might cause heterogeneity, statistical

Altan 2005 Aigner 2006 Chow 2006 Dundar 2007	quarter of 2008), Experts were consulted, and reference lists of obtained reports and textbooks scanned. Methodological assessment of studies: Jadad scale Fixed or random effects: Both fixed effect model random effects model were used Heterogeneity: Statistical heterogeneity was tested using I^2 statistic, clinical heterogeneity was also considered			immediately after treatment in acute neck pain and up to 22 weeks after completion of treatment in patients with chronic neck pain.	heterogeneity was eliminated and the overall effect remained similar with narrower confidence intervals. Therefore, this analysis strengthened their conclusions.

Reference and study design	Studies	Intervention/comparison	Measurements	Outcome	Comments & Level of Evidence
Bjordal et al, 2008 A systematic review with procedural assessments and meta-analysis of Low Level Laser Therapy in lateral elbow tendinopathy (tennis elbow) BMC Musculoskeletal Disorders 9: 75 Norway/ Denmark/ Brazil/UK	Number of studies: N=13 Only one study was single blinded, the rest were double blinded. Total number of patients: n=730 Inclusion criteria: • Diagnosis: Lateral elbow tendinopathy, operationalised as pain from the lateral elbow epicondyle upon finger or wrist extension • Treatment: LLLT with wavelengths in the range 632-1064 nm, irradiating either the tendon pathology, acupuncture points or trigger points • Design: Randomised parallel group	Intervention: LLLT Length of intervention: Various Comparison: placebo, no treatment, or other treatments such as medication, exercise therapy or other electrotherapy modalities. Co-interventions:	Pain reduction (VAS) ▪ Overall (n=10) ▪ Tendon application 904nm (n=5) ▪ Tendon application 1064nm (n=3) ▪ Acupoint application 904nm (n=1) ▪ Tendon application 632nm compared to wrist brace (n=1)	WMD 10.2mm, 95% CI 3.0 to 17.5, p=0.005 WMD 17.2mm, 95% CI 8.5 to 25.9, p=0.0001 WMD 7.5mm, 95% CI 19.1 to 4.1, p=0.21 WMD 4.0mm, 95%CI -7.0 to 15.0, p=0.48 WMD 14mm, 95% CI 7.5 to 20.6, p<0.0001	Study type: Systematic review Quality: SIGN 1+ Comments: This review's inclusion criteria were clear. Several relevant databases were searched. The review processes were only partially reported. The statistical analysis seemed appropriate and clinical and statistical heterogeneity was

Included studies: Basford 2000 Gudmundsen 1991 Haker 1990 Haker 1991 Krashenninikoff 1997 Lam 2007 Løgdberg-Anderson 1997 Lundeberg 1987 Oken 2008 Palmieri 1984 Papadopoulos 1996 Stergioulas 2007 Vasseljen 1992	design or crossover design • Blinding: Outcome assessors should be blinded • Control group: Placebo control groups or control groups receiving other non-laser interventions with at least 10 persons per group • Specific endpoints for pain intensity or global improvement of health measured within 1 – 52 weeks after inclusion. Exclusion criteria • Not satisfying criteria for sample size in control group. • Not satisfying the criteria for specific endpoints and standard number of treatment. • Not satisfying blinding criteria. Databases used: MEDLINE, EMBASE, CINAHL, PEDro and the Cochrane Central Register of Controlled Trials (CENTRAL) Methodological assessment of studies: PEDro Scale Fixed or random effects: Random-effects for pain Fixed-effect meta-analysis for other outcomes. Heterogeneity: Both clinical and statistical heterogeneity		Global improvement: Overall (n=7) ▪ Tendon application 904nm (n=5) ▪ Tendon application 820nm (n=1) ▪ Acupoint application 904nm (n=1) Follow up: ▪ VAS (n=5) ▪ Global improvement (n=3) Side-effect: Side-effect did not report	RR 1.36, 95% CI 1.16 to 1.60, p=0.0002 RR 1.53, 95% CI 1.28 to 1.83, p < 0.00001 RR 1.10, 95% CI 0.63 to 1.91, p=0.74 RR 0.66, 95% CI 0.39 to 1.15, p=0.14 WMD 11.8 mm, 95% CI 7.5 to 16.1, p<0.00001 RR 1.68, 95% CI 1.32 to 2.13, p<0.0001 Author's conclusion: Low-level laser therapy administered directly to the lateral elbow tendon insertions, with an optimal dose of 904nm or possibly 634nm wavelength, either alone or in conjunction with an exercise regimen seemed to offer short-term pain relief and less disability in patients with tennis elbow.	considered. The authors' tentative conclusion, alongside their recommendations for future practice and research, reflect the evidence presented and seem likely to be reasonable.

	was considered. Statistical heterogeneity was tested using the χ^2 and I^2 statistics				

Reference and study design	Studies	Intervention/comparison	Measurements	Outcome	Comments & Level of Evidence
Petrucci 2007 Effectiveness of low-level laser therapy in temporomandibular disorders: A systematic review and meta-analysis Journal of orofacial pain 25: 298 Italy Included studies: Carrasco 2008 Conti 1997 da Cunha 2008 de Abreu 2005 Emshoff 2008 Kulekcioglu 2003	Number of studies: N=6 Two studies were single blinded, the rest were double blinded. Total number of patients: n=191 Inclusion criteria: • RCTs including placebo control group • Implementation of LLLT for chronic myogenous or arthrogenous temporomandibular pain • Adult human subjects (age > 18 yrs old) Exclusion criteria • LLLT conducted in association with other treatments or after surgical intervention on TMJ or in an invasive way • Patients with systemic diseases or pain not related to TMD. • Absence of complete data from baseline to the end of the follow-up • No definition of inclusion or exclusion criteria • No assessment of temporomandibular chronic pain by scale or score Databases used: PubMed, Science Direct, Cochrane Clinical	Intervention: LLLT Length of intervention: Various, minimum: 1-3 weeks or 3-20 sessions Comparison: placebo Co-interventions: Not report	Pain reduction ▪ VAS (n=5) ▪ Maximum vertical opening (n=2) ▪ Right lateral excursion (n=2) ▪ Left lateral excursion (n=2) Follow up: Follow up data did not report Side-effect: Side-effect did not report	WMD 7.77 mm, 95% CI -2.49 to 18.02, p=0.14 WMD 4.04 mm, 95% CI 3.06 to 5.02, p=0.00001 WMD 1.64 mm, 95% CI 0.10 to 3.17, p=0.04 WMD 1.90mm, 95%CI -4.08 to 7.88, p=0.53 Author's conclusion: There is no evidence to support the use of LLLT in the treatment of TMD.	Study type: Systematic review Quality: SIGN 1+ Reviewer's conclusion: This review addressed a clear question and used appropriate databases and search terms. Statistical heterogeneity was assessed. Confidence intervals were wide for some findings, which reduced the robustness of the results. Study details were presented and methods of analysis seemed appropriate given the small number of trials. The review was generally well conducted but limitations in the evidence base, potential publication bias and substantial heterogeneity mean that the authors' conclusions should be considered tentative.

	Trials Register, and PEDro. Methodological assessment of studies: PEDro Scale Fixed or random effects: Random-effects model Heterogeneity: Both clinical and statistical heterogeneity was considered. Statistical heterogeneity was tested using the I^2 statistics				

Reference and study design	Studies	Intervention/comparison	Measurements	Outcome	Comments & Level of Evidence
Chang 2010 Therapeutic Effects of Low-Level Laser on Lateral Epicondylitis from Differential Interventions of Chinese-Western Medicine: Systematic Review Photomedicine and Laser Surgery 28 (3), 327–336 Taiwan Included studies:	Number of studies: N=10 Single or double blinded. Total number of patients: n=449 Inclusion criteria: • the subjects were diagnosed as having LE of elbow with pain induced by resisted extension of the wrist • LLLT was used on the inflamed tendons, MTrPs, or acupuncture points as a treatment of LE • the study must have involved randomized grouping with single- or double-blind design • the control group must have received a non-laser or placebo laser treatment with zero output.	Intervention: LLLT Length of intervention: Various, 7-12 sessions Comparison: Non-laser or placebo. Co-interventions: Not reported	Primary measures: VAS (n=3) Secondary measures: Grasp force (n=3) Weight test (n=2) Painless ROM (n=2) Follow up (n=6) : VAS (n=3, 3 weeks-3 months) Grasp force (n=3, 3 weeks-3months) Weight test (n=2, 8 weeks-3months)	ES -0.71 95% CI -0.82 to -0.60, p<0.05 ES 0.7 95% CI 0.52 to 0.88, p<0.05 ES 0.58 95% CI 0.37 to 0.90, p<0.05 ES 1.27 95% CI 0.37 to 0.81, p<0.05 ES -1.06 95% CI -1.16 to -0.94, p<0.05 ES 1.09 95% CI 0.91 to 1.27, p<0.05 ES 0.55 95% CI 0.33 to 0.76, p<0.05	Study type: Systematic review Quality: SIGN 1- Comments: It was unclear whether action was taken to reduce reviewer error and bias in study selection and quality assessment. It was unclear if language restrictions were applied. The review processes were only partially reported. It was noteworthy that three studies conducting laser on acupuncture points had

Stergioulas 2007 Lam 2007 Basford 2000 Papadopoulos 1996 Krasheninnikoff 1994 Vasseljen 1992 Haker 1991 Haker 1991-2 Haker 1990 Lundeberg 1987	Databases used: MEDLINE, PubMed, CINAHL, (1980-February 2009). Methodological assessment of studies: PEDro scale Fixed or random effects: Not reported Heterogeneity: Not reported		Painless ROM (n=2 , 8 weeks-3months)	ES 0.72 95% CI 0.50 to 0.94, p<0.05 Side-effect: Not reported Author's conclusion: The current evidence justifying the therapeutic effects of LLLT on LE in Western medicine was better than that for TCM. More exact diagnosis of Ashi points and clinical RCTs will be needed to prove the effects of LLLT in TCM. LLLT on tender points and MTrPs would be more appropriate.	high risks of bias (PEDro score: 3-5). They used LLLT with dose from 0.004 to 0.9J per point, which were lower than the dose applying to tender points. The poor results may be caused by insufficient irradiation. Therefore, the authors' conclusions may be too strong and may not reflect the evidence.

Reference and study design	Studies	Intervention/comparison	Measurements	Outcome	Comments & Level of Evidence
Bjordal 2003 A systematic review of low level laser therapy with location-specific doses for pain from chronic joint disorders Australian Journal of Physiotherapy 49, 107-116 Norway/ Sweden	Number of studies: N=14 Double blinded. Total number of patients: n=695 Inclusion criteria: • joint disorder of more than six months duration or osteoarthritis verified by x-ray • random allocation of patients to groups • control group received identical placebo treatment, blind patients and outcome assessors	Intervention: LLLT Length of intervention: Various, 1-20 sessions; 1-10 weeks Comparison: Active placebo. Co-interventions: Anti-inflammatory drugs; exercises	Pain measures: VAS (n=7) Health Status (n=6): Follow up (n=6) : Blinded conditions (n=4) Unblinded conditions (n=2)	WMD 29.8 mm, 95%CI 18.9 to 40.7 RR 0.52, 95% CI 0.36 to 0.76, Pain relief for at least 3 weeks Pain relief for four to six months Side-effect: One trial reported an incident of transient	Study type: Systematic review Quality: SIGN 1+ Comments: This was a generally well conducted review. Appropriate quality assessment tools were applied to the RCTs and the results of this were clearly presented. The

Included studies: Basford 1987 Jensen 1987 Klein 1990 Nivbrant 1992 Bulow 1994 Gray 1994 Toya 1994 Bertolucci 1995 Gøtte 1995 Conti 1997 Soriano 1998 Basford 1999 Özdemir 2001 Stelian 1991	• laser exposure of skin overlying inflammatory joint capsule • outcome measure of pain and change in health status. Exclusion criteria • not irradiating the skin directly overlying the joint capsule Databases used: MEDLINE, Embase, CINAHL, PEDro and the Cochrane Controlled Trials Register (Central) for randomised controlled clinical trials. (1980- November 2001). Hand searching on national physiotherapy and medical journals from Norway, Denmark, Sweden, The Netherlands, Germany, Switzerland, England, USA, Canada and Australia. Methodological assessment of studies: PEDro scale Fixed or random effects: Random effects model were used Heterogeneity: Not reported			adverse effects for one patient in each group Author's conclusion: Based on the heterogeneity of the populations, interventions and comparison groups, we conclude that there are Insufficient data to draw firm conclusions on the clinical effect of LLLT for low-back pain. There is a need for further methodologically rigorous RCTs to evaluate the effects of LLLT compared to other treatments, different lengths of treatment, wavelengths and dosages.	authors acknowledged the heterogeneity in treatment procedures, co-intervention, laser parameters. Despite some review limitation, the authors' conclusions are likely to be reliable.

Reference and study design	Studies	Intervention/comparison	Measurements	Outcome	Comments & Level of Evidence
Yousefi-Nooraie 2008	Number of studies: N=7	Intervention: LLLT	Primary measures: Pain relief	LLLT > sham therapy (n=3)	Study type: Systematic

Low level laser therapy for nonspecific low-back pain Cochrane database of systematic reviews (2), CD005107-CD005107. Canada/Iran Included studies: Basford 1999 Djavid 2007 Gur 2003 Klein 1990 Longo 1991 Soriano 1998 Toya 1994	Total number of patients: n= 384 Inclusion criteria: • adults with acute subacute or chronic low-back pain • Trials that discussed musculoskeletal disorders were included if a separate analysis was reported for low-back pain Exclusion criteria • subjects with low-back pain caused by specific pathological entities Databases used: CENTRAL (The Cochrane Library 2005, issue 2), MEDLINE (1966 to November 2007), EMBASE (1988 to November 2007), CINAHL (1982 to November 2007), AMED (the Allied and Complementary Medicine Database, 1985 to March 2005) and PEDro- the physiotherapy evidence database (to November 2007) Methodological assessment of studies: The 11 criteria recommended by the Cochrane Back Review Group. Fixed or random effects: Fixed-effects model Heterogeneity: Clinical heterogeneity was considered	Length of intervention: Various, 7-12 sessions Comparison: Non-laser or placebo. Co-interventions: Not reported	Low back pain related disability Secondary measures: Relapse rate	LLLT+exercise = sham therapy (n=1) LLLT > sham therapy (n=1) LLLT+exercise = sham therapy (n=2) LLLT+exercise = sham therapy (n=2) LLLT < sham therapy (n=2)	review Quality: SIGN 1+ + Comments: The review question was stated clearly, and study design, participant, intervention and outcome criteria were all stated. The search appears comprehensive and it is therefore unlikely that any papers were missed. The characteristics and results of the primary trials were presented in adequate detail. Appropriate statistical techniques were used to combine the data. Despite the clinical heterogeneity, the small sample sizes and the small clinical effect sizes, this SR was well-conducted with consideration of heterogeneity.

Reference and study design	Studies	Intervention/comparison	Outcome & Results	Comments & Level of Evidence
Tumilty et al, 2010 Low Level Laser Treatment of Tendinopathy: A Systematic Review with Meta-analysis Photomedicine and Laser Surgery; 28(1), 3-16 New Zealand/ Northern Ireland/ Republic of Ireland/ US Included studies: Basford 2000 Haker May 1991 Haker Nov 1991 Hernandez-Herrero 2006 Konstantinovic 1997 Krasheninnikoff 1994 Lam 2007 Melagati 1994 Oken 2008 Papadopoulos 1996 Stergioulas 2007 Vasseljen 1992 Vasseljen May 1992 England 1989 Saunders 1995 Saunders 2003 Vecchio 1993	Number of studies: N=25 Only one study was single blinded, the rest were double blinded. Total number of patients: n=993 Inclusion criteria: ▪ Fully reported randomized controlled trials and controlled clinical trials ▪ No language restrictions ▪ Patients with tendinopathy and exhibited pain and=or functional disability Exclusion criteria ▪ Interventions based upon combinations of LLLT and other modalities were not considered for the review. to neck pain Databases used: The MEDLINE (1966-1st Aug 2008), PubMed (1950-1st Aug 2008), CINAHL (1982-1st Aug 2008), AMED (1985-1st Aug 2008), EMBASE (1988-1st Aug 2008), All EBM (Evidence Based Medicine) reviews, PEDro (Physiotherapy Evidence Database), and SCOPUS (1960-1st Aug 2008) Methodological assessment of studies: PEDro scale Fixed or random effects: Both fixed effect model random effects model were	Intervention: LLLT Length of intervention: Various Comparison: placebo, no treatment, or other treatments such as medication, exercise therapy or other electrotherapy modalities. Co-interventions: Various	Results: Conflicting results were found in this SR. There were 12 trials showed positive effects and 13 were inconclusive or showed no effect. Ten good quality studies with positive effects used LLLT dose inside the recommended range. Although there were sufficient data to undertake meta-analyses, the variation of interventions resulted in significant clinical heterogeneity between studies and could lead in turn to statistical heterogeneity (see figure 1). The authors therefore just reported two meta-analyses results. Pooled effect results of four high-quality trials revealed that grip strength was significantly improved in patients with lateral epicondylitis after low level laser treatment (WMD 9.59 kg, 95% CI 5.90 to 13.27). For patients with Achilles tendinopathy, results from two high quality RCTs showed that the pain reduction effect was significant (WMD 13.64mm, 95% CI -26.17 to -1.11). The authors concluded that low level laser treatment was potentially effective in treating tendinopathy using recommended doses, but the overall evidence was inconclusive. Side-effect: Not reported Author's conclusion: LLLT can potentially be effective in treating	Study type: Systematic review Quality: SIGN 1+ Comments: Search of multiple database. Data included non-English language studies. Full search strategies were reported. The quality of evidence was assessed using PEDro scale. Twenty trials scored at least 6 on the PEDro scale, which indicated high quality (PEDro scale ≥ 6). Statistical heterogeneity was assessed. The authors acknowledged some review limitations, including clinical and methodological heterogeneity, quality limitations in the RCTs. Overall the authors' conclusions reflected the evidence presented and are likely to be reliable.

Bjordal 2006 Darre 1994 Stergioulas 2008 Tumilty 2008 Costantino 2005 Muller 1993 Siebert 1987 Sharma 2002	used <u>Heterogeneity:</u> Statistical heterogeneity was tested using the chi-square test (I^2 statistic). Clinical heterogeneity was not tested.		tendinopathy using recommended dosages. However, the overall effect of LLLT was inconclusive. The 12 positive studies provide strong evidence that positive outcomes are associated with the use of current dosage recommendations for the treatment of tendinopathy.	

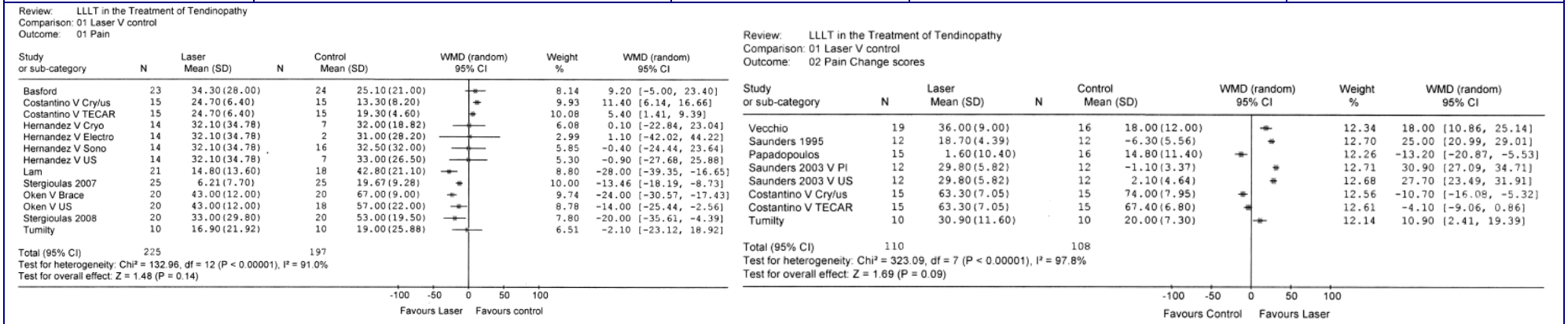

Figure 1 Pain analysis with all groups in all studies. When studies included more than two groups or an active control group, the non-laser treatments are shown after the author's name. US, ultrasound; Sono, sonophoresis; Electro, electrophoresis; Cryo, cryotherapy; Cryo=us cryoultrasound; TECAR, capacitive-resistive electric transfer therapy; Brace, tennis elbow brace; Pl, placebo.

Reference and study design	Studies	Intervention/comparison	Outcome & Results	Comments & Level of Evidence
Gross 2013 Low level laser therapy (LLLT) for neck pain: a systematic review and meta-	<u>Number of studies:</u> N=17 Five single-blinded trials, nine double-blinded, the rest did not report blinding. <u>Total number of patients:</u> n=919	<u>Intervention:</u> LLLT <u>Length of intervention:</u> Various	<u>Results:</u> 10 of 17 trials demonstrated high risk of bias (meeting six or more criteria). There was moderate quality evidence (n=2, 109 participants) suggesting LLLT to be superior	Study type: Systematic review Quality: SIGN 1+ Comments: The review question and

Regression The open orthopaedics journal 7: 396-419 Canada <u>Included studies:</u> Ceccherelli 1989 Taverna 1990 Soriano 1996 Ozdemir 2001 Seidel 2002 Hakguder 2003 Chow 2004 Chow 2006 Gur 2004 Ilbuldu 2004 Altan 2005 Dundar 2007 Konstantinovic 2010 Nilsson 1995 Thorsen 1991 Thorsen 1992 Waylonis 1988	<u>Inclusion criteria:</u> ▪ No language restrictions ▪ Patients ≥18 years old with acute, sub-acute or chronic neck pain categorized as simple non-specific mechanical neck pain <u>Exclusion criteria</u> ▪ neck disorders with definite or possible long tract (upper motor neuron) signs ▪ neck pain caused by other pathological entities ▪ headache not of cervical origin, but associated with the neck <u>Databases used:</u> MEDLINE, EMBASE, Manual Alternative and Natural Therapy, Cumulative Index to Nursing and Allied Health Literature, Index to Chiropractic Literature, and CENTRAL (Cochrane Library Issue 2, 2010) <u>Methodological assessment of studies:</u> 12 criteria for risk of bias, GRADE <u>Fixed or random effects:</u> random effects model <u>Heterogeneity:</u> Statistical heterogeneity was tested using I^2 statistic	<u>Comparison:</u> placebo, another intervention (i.e. exercise), or other treatment added to both arms of the trial (i.e. LLLT plus exercise versus sham LLLT plus exercise) <u>Co-interventions:</u> • not reported	to placebo when applied on the chronic neck pain in terms of improving pain/disability/QoL/GPE up to intermediate-term. For acute radiculopathy, cervical osteoarthritis or acute neck pain, low quality evidence suggested LLLT improves ST pain/function/QoL over a placebo. For chronic myofascial neck pain (n=5, 188 participants), evidence was conflicting; a meta-regression results suggests that super-pulsed LLLT may increase the chance of a successful pain outcome (see figure 1 and 2). <u>Side-effect:</u> Eight studies reported mild side-effect, including tiredness, nausea, headache and increased pain. <u>Author's conclusion:</u> Diverse evidence was found using LLLT for neck pain. LLLT may be beneficial for chronic neck pain/function/QoL. Larger long-term dosage trials are needed.	supporting inclusion criteria were clearly stated. The search strategy was clearly reported and a number of relevant sources were accessed. It appeared that each stage of the review process was performed in duplicate to minimise bias. Trial quality was assessed using appropriate criteria but only a small proportion was at low risk of bias. The review was generally well conducted but given the limitations of the included studies, and substantial heterogeneity, the authors' conclusions should be considered tentative.

Analysis of Variance					
SMD *vs* DT					
Source	DF	SS	MS	F	P
Regression	1	4.04	4.04	10.79	0.030
Residual Error	4	1.50	0.37		
Total	5	5.54			
SMD *vs* Energy Density					
Source	DF	SS	MS	F	P
Regression	1	0.18	0.18	0.14	0.728
Residual Error	4	5.36	1.34		
Total	5	5.54			
SMD *vs* D/Sess					
Source	DF	SS	MS	F	P
Regression	1	1.59	1.59	1.62	0.272
Residual Error	4	3.94	0.98		
Total	5	5.54			
SMD *vs* D/Prog					
Source	DF	SS	MS	F	P
Regression	1	0.95	0.95	0.83	0.414
Residual Error	4	4.59	1.14		
Total	5	5.54			

KEY: SMD standard mean difference; DF - drive force; SS - sum of squares; D/Sess - dose per session; D/Prog - dose per program; MS - mean square.

Figure 1 Meta-regression for four clinically relevant dosage factors yielded the following regression equation for drive technology (SMD = -2.70 + 1.74 DT).

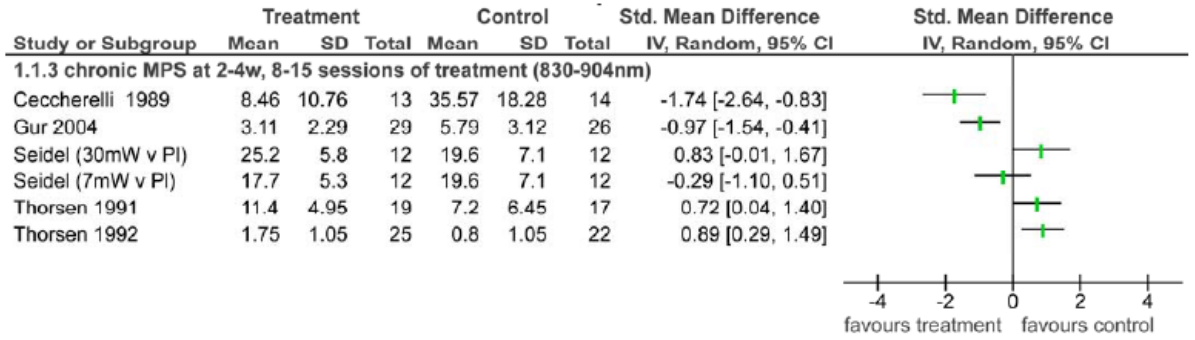

Figure 2 Chronic myofascial pain syndrome at 2 to 4w, 8 to15 sessions of treatment using a 830 nm or 904 nm LLLT wavelength

Reference and study design	Studies	Intervention/comparison	Outcome & Results	Comments & Level of Evidence
Melis 2012 Low level laser therapy for the treatment of temporomandibular disorders: A systematic review of the Literature CRANIO® 30: 304-312 Italy	Number of studies: N=14 Blinding of RCTs not report. Total number of patients: n=582 Inclusion criteria: • RCTs including placebo control group • Articles written in English • Human subjects Databases used: PubMed	Intervention: LLLT Length of intervention: Various, minimum: 1-3 weeks or 3-20 sessions The number of laser applications: Various, minimum: 3-20 applications Intervention duration: Varied between 10	Outcome assessed: pain intensity, mandibular function Results: Patients in 8 trials had pain intensity and mandibular function improvement of LLLT versus placebo. Conversely, eight trials reported no significant data between the two groups. Author's conclusion: Based on the results of this review, no	Study type: Systematic review Quality: SIGN 1- Reviewer's conclusion: Susceptible to bias because only one database searched (Pubmed). The literature search was limited by language and attempts did not appear to have been made to locate unpublished data, which meant that potentially relevant data may have been missed. The

Included studies: Bertolucci 1995-1 Bertolucci 1995-2 Conti 1997 da Cunha 2008 de Abreu 2005 Mazzetto 2007 Emshoff 2008 Kulekcioglu 2003 Carrasco 2008 Carrasco 2009 Shirani 2009 Marini I 2010 Mazzetto 2010 Venezian 2010	<u>Methodological assessment of studies:</u> CONSORT 2010 criteria <u>Fixed or random effects:</u> Not applicable <u>Heterogeneity:</u> Not reported	seconds and 10 minutes for each application. <u>Comparison:</u> placebo <u>Co-interventions:</u> Not report	definitive conclusions can be drawn on the efficacy of LLLT for the treatment of TMD. Many methodological differences among the studies, especially regarding the number and duration of laser applications and characteristics of the laser beam (wavelength, frequency, output), do not allow for standardized guidelines for effective treatment with LLLT. The only indication seems to be that LLLT is probably more effective for the treatment of TMJ disorders and less effective for the treatment of masticatory muscle disorders.	synthesis appeared to have been narrative. The authors' overall conclusion does not seem unreasonable, based on the trials included in the review, but the trials' variable quality and the nature of the synthesis, mean that there is some concern over its reliability.

6.4 Appendix 4 Cost of available LLLT devices in the market[†]

Product	Power Waveform and Wavelength	Price
TerraQuant TQ Solo	15,000mW@905nm, 60mw@875nm, 7.5 mW@660nm	$1,995
TerraQuant Pro	25,000mW@905nm, 60mw@875nm, 7.5 mW@660nm	$3,495
TerraQuant Elite	50,000mW@905nm, 60mw @ 875nm, 7.5 mW@660nm	$5,295
Erchonia PL5000	20mW@635nm	$12,000
Theralase	50,000 mW@905	$8,300
LZ30	900mW@808nm, 50mW@637nm	$4,250
LZ30-X	900mW@808nm, 190mW@637nm	$4,950
ML830	90mW@830nm	$4,495
Q1000ng	470-940nm 328mW to 64mW	$7,500
Thor-LX	200-2000mW@810nm, 30mW@660nm	$10,520
Medx Console	200mW@870nm, 500mW@633nm	$5,495
Omega Xp	200mW@820nm, 50mW@660nm, 100mW@915nm	$14,495
DJO Vectra Genesis	100mW - 1440mW@850nm, 670nm - 950nm	$5,000
Quantum Wave	100mW	$4,800
Apollo DT + 5000	5,000mW@810nm CW	$8,541
Apollo Portable +4000	4,000mW@810nm CW	$7,143
Apollo Handheld	2,000mW@810nm CW	$4,000
DioWave D10	10,000mW@980nm	$15,000
LiteCure LCT-1000	10,000mW@980nm	$15,000
K-Laser/K-1200	12,000mW@800nm and/or 970nm	$15,000
Cutting Edge	3300mW Pulsing	$30,000

[†] The information was obtained from http://www.coldlasers.org/therapeutic-office-systems/

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