A Meta-analysis of the Efficacy of Laser Phototherapy on Pain Relief

Andras M. Fulop, DPT, Seema Dhimmer, DPT, James R. Deluca, DPT, David D. Johanson, DPT, Richard V. Lenz, DPT, Keyuri B. Patel, DPT, Peter C. Douris, DPT, EdD, and Chukuka S. Enwemeka, PhD, FACSM

Objective: Laser phototherapy has been widely used to relieve pain for more than 30 years, but its efficacy remains controversial. To ascertain the overall effect of phototherapy on pain, we aggregated the literature and subjected the studies to statistical meta-analysis.

Methods: Relevant original studies were gathered from every available source and coded. Articles that met preestablished inclusion criteria were subjected to statistical meta-analysis, using Cohen's *d* statistic to determine treatment effect sizes.

Results: Fifty-two effect sizes were computed from the 22 articles that met the inclusion criteria. The resulting overall mean effect size was highly significant; $d = +0.84$ (95% confidence interval = 0.44-1.23). The effect size remained significant even when a high outlying *d* value was conservatively excluded from the analysis; $d = +0.66$ (95% confidence interval = 0.46-0.86). The fail-safe number associated with the overall treatment effect, that is, the number of additional studies in which phototherapy has negative or no effect on pain needed to negate the overall large effect size of +0.84, was 348.

Discussion: These findings warrant the conclusion that laser phototherapy effectively relieves pain of various etiologies; making it a valuable addition to contemporary pain management armamentarium.

Key Words: pain, meta-analysis, laser therapy, phototherapy, biostimulation

(*Clin J Pain* 2010;26:729–736)

It has been 40 years since Endre Mester of Hungary[1] first demonstrated the healing effects of laser phototherapy, and over 30 years since Friedrich Plog of Canada[2] independently showed that monochromatic light can be an effective alternative to invasive needle acupuncture for pain relief. Yet, the value of phototherapy as a clinical armamentarium remains contentious, even though pain of head and neck origin and those associated with carpal tunnel syndrome were the first conditions that earned phototherapy the approval of the US Food and Drug Administration. World-wide laser phototherapy has been used to relieve arthritic pain,[3–5] tendonitis and related muscle injury,[6–11] hemorrhoids,[12] carpal tunnel syndrome,[13–16] neck pain,[17] low back pain,[18] and Raynaud syndrome.[19] The mechanisms for light-induced pain relief have begun to emerge.

It has been postulated that photostimulation induces athermal photochemical reactions that alter the pain threshold of nociceptors.[20–22] Evidence abounds that phototherapy modulates inflammation by reducing prostaglandin E_2 concentrations,[23] inhibiting cyclo-oxygenase 2 in vitro,[23,24] and reducing tumor necrosis factor α.[10,25] It has also been shown that phototherapy enhances the release of endorphins.[26,27] A fourth mechanism is that it enhances local hemodynamics, thus aiding the removal of pain-causing substances from the site of lesion.[28,29] Yet, another mechanism relates to its capacity to increase cellular oxygenation[30–32] and mitochondrial adenosine triphosphate[2,33,34]; but how this mediates pain remains unclear.

Meta-analysis is a powerful statistical procedure for combining the results of 2 or more related studies to determine an overall treatment effect.[35] The resulting effect size of treatment yields a robust estimate of the true treatment effect compared with those derived from individual studies; permitting a better overview of the topic than would have been realized either by simply reviewing the literature, conducting a systematic review, or relying on the outcome of multiple studies.[36] These qualities render meta-analysis an objective quantitative review that can eliminate subjective assessment; thereby resolving most of the controversies concerning the clinical value of phototherapy on pain relief.

Earlier reviews and meta-analyses have shown that phototherapy relieves pain.[37,38] However, these studies relied on articles published before 2000. Since 2002, when the Food and Drug Administration approved laser phototherapy for the temporary relief of pain associated with head and neck pain, carpal tunnel syndrome, and arthritis, interest in phototherapy for pain relief has been high. Moreover, there has been a shift from treatment with laser-based devices to treatment with light-emitting diodes, which unlike lasers lack coherence. On account of these developments, we aggregated peer-reviewed articles published between January 2000 and December 2007 and used statistical meta-analysis to test the null hypothesis that contemporary treatments with phototherapy have no significant positive effect on pain relief. In particular, we were interested in determining whether the current literature supports or refutes the use of phototherapy for pain relief.

MATERIALS AND METHODS

Participants and Design

Original research articles investigating the effects of phototherapy on pain relief and published between January 2000 and December 2007 were aggregated, coded, and used

Received for publication May 10, 2009; revised November 23, 2009; accepted February 1, 2010.
From the College of Health Sciences, University of Wisconsin—Milwaukee, Milwaukee, WI.
Reprints: Chukuka S. Enwemeka, PhD, FACSM, College of Health Sciences, University of Wisconsin—Milwaukee, 2400 Hartford Avenue, Suite 898, Milwaukee, WI 53201 (e-mail: Enwemeka@uwm.edu).

in this study. The articles were obtained from libraries and online sources, including Medline, PubMed, Ovid literature search engine, and Psychology Information (PsycInfo). The terms used to identify the articles included "laser therapy," "photo bio-modulation," "light therapy," "low level laser therapy," "phototherapy," "pain," "pain control," and "pain management." Secondary sources included papers cited by articles retrieved from the above-mentioned sources, internet web pages, commercial search engines, and articles published in journals which were not available from the aforementioned databases.

Studies were included if they met the following criteria: (1) article was published in a peer-reviewed or scientific journal, (2) article was published between January 2000 and December 2007, (3) the study was completed in vivo using human participants only, (4) article stated or we were able to compute the following variables: power, power density, energy density, number of treatments given, duration of each treatment, frequency of treatment, beam and spot size, fluence (dose), size of the area treated, and mode of treatment (contact or noncontact mode), (5) the medical condition was clearly stated, (6) the study measured pain using a quantifiable scale or outcome, and (7) the wavelength and light source were identified. Articles were eliminated if any of the following exclusion criteria applied: (1) the study was conducted in vitro, (2) the article was a case study, (3) Cohen's *d* statistic could not be calculated from the data provided, or (4) members of the research team were unable to translate the article into English to compute Cohen's *d*.

Pilot Reliability Study and Data Coding

A coding form with a list of relevant parameters and related information was developed as shown in Table 1. Data from the studies that met inclusion criteria were then collected to establish a data pool. To ensure data accuracy, 6 raters were first trained; then a pilot study was conducted to determine the level of agreement among them as they ascertained the presence or absence of the parameters detailed in Table 1, and as they calculated the treatment effect sizes, that is, Cohen's *d*, from an initial set of 10 randomly selected studies. Raters were retrained with new sets of articles and retested for reliability until at least 90% agreement was attained.

Determination of Effect Size

Effect sizes were calculated using the formulae for computing Cohen's *d* statistic.[35,36] Cohen's *d* is defined as the difference between the means of the experimental group and the comparison group divided by the SD of the comparison group as follows:

$$d = \frac{x_1 - x_2}{SD_{comparison}}$$

TABLE 1. Treatment Parameters Identified in Each Study

Experimental participants	Power (W)
Condition treated	Power density (W/cm^2)
Independent variables	Energy density (J/cm^2)
Dependent variables	Number of treatments
Source of light	Frequency of treatments
Wavelength	Duration of treatments
Spot size	Pain outcome measurement
Distance from surface	Outcome
Dosage	

Where *d* stands for the effect size, x_1 is the mean of the treated group, x_2 is the mean of the comparison group, and $SD_{comparison}$ is the SD of the comparison group.

Where means and SDs were not reported but data was presented as percentages, a *d* value was calculated by first finding the associated *t* value with the following formula:

$$t = \frac{P_2 - P_1}{\sqrt{\frac{(P_2)(1-P_2)}{N_2} + \frac{(P_1)(1-P_1)}{N_1}}}$$

Where P_2 is the percent change of the treatment group, P_1 is the percent change of the comparison group, N_2 is the number of participants in the treated group, and N_1 is the number of participants in the comparison group.

The *t* value calculated was then converted to a *d* value using the following formula[35,36]:

$$d = \frac{2t}{\sqrt{df}}$$

Where *d* is the effect size, t is the *t* value, and df is the degree of freedom. The degree of freedom was determined with the formula[36]:

$$df = N_1 + N_2 - 2$$

N_1 and N_2 are the numbers of participants treated in the comparison group and the treated group, respectively.

The overall mean effect size was calculated by summing the *d* values obtained independently from each study and then divided by the total number of *d* values as follows:

$$d_{average} = \frac{\sum d}{N}$$

Where $d_{average}$ is the mean effect size, Σd is the sum of the effect sizes, and N is the total number of *d* values used.

Grubb's Extreme Studentized Deviation Test for Critical Outliers

To identify outlying *d* values, Grubb's test[39] or critical outliers was performed on the pool of calculated *d* values using the following formula:

$$z = \frac{[d_{average} - d]}{SD}$$

Where z is the z score for each individual *d* value, $d_{average}$ is the mean effect size, and SD is the SD of $d_{average}$. The z score was then compared with a critical *z* value obtained from Grubb's critical-z Table.

In further analysis, the effect sizes obtained from studies with repeated measurements of the same outcome variable were averaged to minimize undue influence of any

TABLE 2. Reviewed Outcomes of All Experimental/Quasi-experimental Studies

Category	No. Articles	No. (%) Articles With Positive Results	No. (%) Articles With Negative Results
Included studies	22	13 (59.1)	9 (30.9)
Excluded studies	28	23 (82.1)	5 (17.9)
Total (included and excluded studies)	50	37 (74.0)	14 (16.0)

TABLE 3. Outcome of Statistical Meta-analysis

Analysis	No. Papers	No. Effect Size	Cohen's *d*	95% Confidence Interval	Fail-Safe N (0.05 Criterion)	Fail Safe N (0.10 Criterion)
Overall	22	52	0.84	0.44-1.23	348	163
Outlier removed	21	51	0.66	0.46-0.86	256	118

one study on the overall effect size.[40] For example, if pain was measured on the same participants at 5 different time intervals in a particular study, the *d* values obtained were averaged to yield 1 *d* value instead of 5.[40] Finally, the overall *d* value obtained was considered small, medium, or large in accordance with the guideline provided by Cohen.[36] According to Cohen,[36] the values of 0.2, 0.5, and 0.8 indicate a small, medium, and large average effect size, respectively.

Calculation of the Fail-safe Number

Considering the likelihood that our meta-analysis did not include every relevant published report, we computed the fail-safe number (N_{fs}) associated with the overall *d* value obtained. From a statistical point of view, this is the number of nonsignificant studies that would be necessary to reduce the effect size resulting from this analysis to a nonsignificant value. Practically, it is the number of additional studies with effect sizes below our set criterion value that would have to be included in the meta-analysis to negate the outcome of this study. A set criterion value of 0.05 was used, statistical significance was set to 0.05, and the N_{fs} was calculated with the following formula:

$$N_{fs.05} = N(d - d_c)/d_c$$

Where N is the number of studies in the meta-analysis, d is the average effect size for the studies used, and d_c is the criterion value selected. For this meta-analysis, d_c was set to 0.05, the value of a nonsignificant small effect size.

RESULTS

We identified 22 articles from the 59 peer-reviewed papers that met the inclusion criteria. We excluded 9 papers from the analysis immediately because they were reviews,

TABLE 4. Conditions Treated and Variables Measured

Study	No. Participants	Condition Treated	Independent Variable	Dependent Variable(s)
Altan et al, 2005	53	Myofascial pain syndrome	Laser versus placebo	VAS, Pain 5-point scale and Tenderness on 18-point scale
Bingol et al, 2005	40	Shoulder pain	Laser versus placebo	Pain (VAS)
Brosseau et al, 2005	88	Osteoarthritis of the hand	Laser versus placebo	Pain (Auscan scale)
Chow et al, 2006	90	Chronic neck pain	Laser versus control	Pain (10 cm VAS scale)
Douris et al, 2006	27	Delayed onset muscle soreness	Laser versus Placebo, laser versus control	VAS McGill Pain Questionnaire
Dundar et al, 2007	64	Myofascial pain syndrome	Laser versus placebo	Pain (VAS)
Ekim et al, 2007	19	Carpal tunnel syndrome	Laser versus placebo	Pain (VAS)
Fikackova et al, 2007	80	Temporomandibular	Laser versus placebo	Pain reduction (%)
Gur et al, 2002	40	Fibromyalgia	Laser versus placebo	Pain (Likert scale) Skinfold tenderness
Gur et al, 2003a	75	Low back pain	Laser and exercise versus exercise	Pain (VAS)
Gur et al, 2003b	90	Osteoarthritis of the knee	Laser 3 J/2 J versus placebo	Pain at movement Pain at rest Pain at flexion
Gur et al, 2004	60	Myofascial pain syndrome	Laser versus Placebo	Pain (VAS)
Hakguder et al, 2003	62	Myofascial pain syndrome	Laser and stretching versus stretching	Pain (VAS)
Hirschl et al, 2004	48	Raynaud phenomenon	Laser versus Placebo	Pain intensity
Hopkins et al, 2004	22	Experimental wounds	Laser versus Placebo	Pain
Ozdemir et al, 2001	60	Cervical osteoarthritis	Laser versus Placebo	Pain and Neck Pain Disability Scale
Ozkan et al, 2004	25	Flexor tendon injuries	Laser and whirlpool versus	Pain (VAS)
Saunders, 2003	36	Supraspinatus tendonitis	Laser versus Control	Pain (VAS 100 mm Huskinssons)
Stergioulas, 2007	50	Lateral epicondylitis	Laser and plyometrics versus placebo and plyometrics	Pain (VAS)
Takas et al, 2006	20	Root planning	Laser versus Placebo	Pain (VAS)
Tascioglu et al, 2004	60	Osteoarthritis	Laser versus Placebo	Pain (VAS and WOMAC)
Zinman et al, 2004	50	Polyneuropathy	Laser versus Placebo	Pain (VAS)

VAS indicates visual analog scale; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

case studies, meta-analyses, lacked a control group, or did not measure pain on a quantifiable scale. An additional 28 papers were experimental or quasi-experimental; however, they too were excluded, as they lacked the numerical data needed to calculate treatment effect sizes. In several studies, data were presented as charts without descriptive summary data. Nonetheless, further analysis of these 28 papers showed that 23 (82.1%) demonstrated that phototherapy relieves pain; only 5 did not. In contrast, of the 22 articles included in our analysis, 13 (59.1%) found phototherapy to be effective in relieving pain, 9 did not; indicating that there was no bias in excluding the 28 studies from this analysis. Indeed, had it been possible to include the entire 50 experimental or quasi-experimental studies in the analysis, the outcome would have been more positive than reported below; as 36 (72%) of the 50 studies showed phototherapy to be effective in relieving pain, compared with the 59.1% of the studies used in this analysis (Table 2).

Ninety-six computable effect sizes were calculated from the 22 studies used. Fifty-two effect sizes were obtained when multiple *d* values from the same study were averaged to account for repeated measurements of the same variable over time, as detailed above. The overall mean effect size obtained from the 52 effect sizes was +0.84 (95% confidence interval 0.44-1.23). This finding indicates that phototherapy is highly effective for pain relief. The fail-safe number corresponding to this overall mean effect size was 348; meaning that 348 additional studies reporting a neutral or negative effect of phototherapy on pain would be needed to invalidate the outcome of this analysis (Table 3).

To permit a comparison of our results with those of Enwemeka et al[38] who used 0.10 as their set criteria, the fail-safe number was recalculated using 0.10 as the set criterion instead of the commonly used 0.05. The resulting fail-safe number was 163; a high number which again confirms that the likelihood of overturning the significant treatment effect size (+0.84) is minute.

When we removed the lone positively high outlying *d* value from the analysis, the resulting *d* value was 0.66 (95% confidence interval +0.46-+0.86). This finding again shows that phototherapy has a significant positive effect on pain relief. The fail-safe number associated with this effect size was 256 (118, if 0.10 is used as the set criterion).

To put our findings in perspective, we have included the conditions treated and the variables measured in the studies that were included in this analysis in Table 4. Similarly, the source of light, wavelength, power, power density, and energy density for each study are presented in Table 5, and Table 6 outlines the number, frequency, and duration of treatments, specific outcome data, and effect sizes for each study.

DISCUSSION

It is well recognized in meta-analysis that a treatment effect of +0.2 signifies a small effect size, +0.4 a medium effect size, and a value of +0.8 or greater indicates a large effect size of treatment.[36] Thus, the large effect size (+0.84) obtained in this analysis signifies that phototherapy is a highly effective form of treatment for pain relief. Even with our conservative approach of removing a high outlying *d* value, the treatment effect size remained significant. These results are consistent with the findings of Enwemeka et al[38] who reported a treatment effect size of +1.11 and a fail-safe number of 41 in their meta-analysis of articles published during the 30 years before year 2000. It should be noted that Enwemeka et al[38] did not control for outlying *d* values; moreover, their analysis was based on 9 articles that met their inclusion criteria. The effect size obtained in this meta-analysis would have likely been

TABLE 5. Source of Light, Wavelength, Power, Power, and Energy Density

Study	Source of Light	Wavelength (nm)	Power (W)	Power Density (W/cm^2)	Energy (J) or Energy Density (J/cm^2)
Altan et al, 2005	Ga-As	904	27 and 50 W	Not reported	Not reported
Bingol et al, 2005	Ga-As	904	Not reported	Not reported	2.98 J/cm^2
Brosseau et al, 2005	LLL Ga-As-Al	860	60 mW	3 W/cm^2	3 J/cm^2
Chow et al, 2006	Diolase device	830	300 mW	0.67 W/cm^2	Not reported
Douris et al, 2006	Dyantron solaris IR SLD	660 and 880	Not reported	100 mW/cm^2	8 J/cm^2
Dundar et al, 2007	LLL Ga-As-Al	830	450 mW	58 mW/cm^2	630 J
Ekim et al, 2007	Ga-Al-As	780	50 mW	Not reported	75 J
Fikackova et al, 2007	Ga-Al-As	830	400 mW	Not reported	Not reported
Gur et al, 2002	Ga-As laser	904	11.2 mW	Not reported	2 J/cm^2
Gur et al, 2003a	Not reported	Not reported	10W	Not reported	1 J/cm^2
Gur et al, 2003b	Ga-Ar infrared	904	20W	Not reported	30 J and 20 J
Gur et al, 2004	Ga-As laser	904	11.2 mW	Not reported	20 J/cm^2
Hakguder et al, 2003	Ga-As-Al	780	10 mW	Not reported	5 J/cm^2
Hirschl et al, 2004	Not reported	685	20 mW	Not reported	2 J/cm^2
Hopkins et al, 2004	46-diode cluster	820	Not reported	0.075 W/cm^2	8 J/cm^2
Ozdemir et al, 2001	Ga-As-Al	830	50 mW	Not reported	0.9 J/cm^2
Ozkan et al, 2004	Ga-As laser	904	27 W, 50 W	Not reported	Not reported
Saunders, 2003	Not reported	820	50 mW	Not reported	30 J/cm^2
Stergioulas, 2007	Ga-As	904	40 mW	Not reported	2.4 J/cm^2
Takas et al, 2006	R/IR	637-957	Not reported	Not reported	Not reported
Tascioglu et al, 2004	Ga-Al-As	830	50 mW	Not reported	15 J total
Zinman et al, 2004	TLC 5000	905	0-60 mW	Not reported	Not reported

Ga-Ar indicates gallium argon; Ga-As, gallium arsenide; Ga-As-Al, gallium arsenide aluminum; IR, infra red; LLL, low level laser; R, red.

TABLE 6. Number, Frequency, and Duration of Treatments, Data, and Cohen's *d*

Study	No. Treatments	Frequency of Treatments	Duration of Treatments	Specific Dependent Variable and Data	Cohen's *d*
Altan et al, 2005	10	Once/d for 10 d	2 min	Pain (VAS)	0.95
				Pain (VAS) 14 wk	2.43
				Pain 5-point scale	0.62
				Pain 5-point scale 14 wk	1.10
				Tenderness	−0.35
				Tenderness 14 wk	1.46
Bingol et al, 2005	10	5 times/wk	1 min	Pain (VAS) rate of change	0.41
				Pain (VAS) change in means	0.15
Brosseau et al, 2005	18	Thrice/wk	20 min	Pain (Auscan Scale) 3 wk	0.26
				Pain (Auscan Scale) 6 wk	0.34
				Pain (Auscan Scale) 3 mo	0.27
				Pain (Auscan Scale) 6 mo	0.085
Chow et al, 2006	14	Twice/wk for 7 wk	30 s per point	Pain (VAS)	9.80
Douris et al, 2006	4	Once/d ×4 d	80 s	McGill Experimental versus control	0.26
				McGill Experimental versus placebo	0.41
				Pain VAS Experimental versus control	0.74
				Pain VAS experimental versus placebo	0.86
Dundar et al, 2007	15	Once/d	2 min	Pain at rest (rate)	0.44
				Pain at movement (rate)	0.26
				Pain at night (rate)	0.00
				Pain at rest (difference)	−0.043
				Pain at movement (difference)	0.21
				Pain at night (difference)	0.21
Ekim et al, 2007	10	Once/d ×10 d	10 min	Pain VAS post-Tx	0.93
				Pain VAS 3 mo	0.73
Fikackova et al, 2007	10	"Within 1 mo"	Not reported	Pain reduction (%) at 10 J	0.37
				Pain reduction (%) at 15 J	0.37
Gur et al, 2002	10	Daily for 2 wk	3 min	Pain (Likert Scale)	0.92
				Skinfold tenderness	0.73
Gur et al, 2003a	20	5 times/wk; for 4 wk	30 min	Pain (VAS)	0.5
Gur et al, 2003b	10	Daily for 2 wk	5 min	Pain at movement, 4th wk, 1 versus 3	1.01
			5 min	Pain at movement, 8th wk	0.90
			5 min	Pain at movement, 12th wk	0.75
			3 min	Pain at movement, 4th wk, 2 versus 3	1.11
			3 min	Pain at movement, 8th wk	0.90
			3 min	Pain at movement, 12th wk	0.69
			5 min	Pain at rest, 4th wk, 1 versus 3	0.87
			5 min	Pain at rest, 8th wk	0.93
			5 min	Pain at rest, 12th wk	0.65
			3 min	Pain at rest, 4th wk, 2 versus 3	1.16
			3 min	Pain at rest, 8th wk	0.96
			3 min	Pain at rest, 12th wk	0.65
			5 min	Pain at flexion, 4th wk, 1 versus 3	0.68
			5 min	Pain at flexion, 8th wk	0.65
			5 min	Pain at flexion, 12th wk	0.82
			3 min	Pain at flexion, 4th wk, 2 versus 3	1.24
			3 min	Pain at flexion, 8th wk	1.05
			3 min	Pain at flexion, 12th wk	0.99
Gur et al, 2004	10	Daily ×2 wk	3 min	Pain (VAS) at rest, wk 2	1.03
				Pain (VAS) at rest, wk 3	1.04
				Pain (VAS) at rest, wk 12	0.75
				Pain (VAS) at movement, wk 2	0.82
				Pain (VAS) at movement, wk 3	0.95
				Pain (VAS) at movement, wk 12	0.75
				NPDS score, wk 2	0.71
				NPDS, wk 3	0.94
				NPDS, wk 12	0.67
Hakguder et al, 2003	62	Not reported	3 min	LLLT beneficial for pain	1.44
				3 wks later	1.55
Hirschl et al, 2004	15	5 times/wk ×3 wk	30-40 min	Pain intensity, wk 1	0.23
				Pain intensity, wk 2	0.37
				Pain intensity, wk 3	0.47
Hopkins et al, 2004	10	Once daily	2 min, 5 s	Pain day 1	−0.34
				Pain day 4	0.00
				Pain day 6	−0.19

(continued)

TABLE 6. (*continued*)

Study	No. Treatments	Frequency of Treatments	Duration of Treatments	Specific Dependent Variable and Data	Cohen's *d*
Ozdemir et al, 2001	10	Once daily for 10 × d	15 s per point	Pain level (VAS)	3.36
			(3 min total)	NPDS score	3.47
Ozkan et al, 2004	10	Once/d	130 s	Pain (VAS)	−0.72
Saunders, 2003	9	Thrice weekly for 3 wk	90 s	Pain (VAS 100 mm Huskinssons)	2.38
Stergioulas, 2007	12	Twice weekly × 4 wk, or Once/wk × 4 wk	30 s per Tx point	Pain (VAS) at rest, 8wk	0.26
				Pain at rest, 16 wk	0.26
				Pain at palpation, 8 wk	1.01
				Pain at palpation, 16 wk	0.89
				Pain on isometric testing, 8 wk	0.98
				Pain on isometric testing, 16 wk	1.18
				Pain during middle finger test, 8 wk	0.47
				Pain during middle finger test, 16 wk	0.38
				Pain during grip strength test, 8 wk	0.57
				Pain during grip strength test, 16 wk	1.08
Takas et al, 2006	4	One pre-Tx and one post-Tx	6 min pre and 10 min post	Pain (VAS) after treatment	0.30
				Pain (VAS) 24 h later	0.75
Tascioglu et al, 2004	10	Five times/wk × 2 wk	2 min	3 J, VAS, pain at rest, wk 3	0.016
				3 J, VAS, pain at rest, mo 6	−0.037
				3 J, VAS, pain at activity, wk 3	−0.058
				3 J, VAS, pain at activity, mo 6	−0.041
				1.5 J, VAS, pain at rest, wk 3	0.089
				1.5 J, VAS, pain at rest, mo 6	0.034
				1.5 J, VAS, pain at activity, wk 3	0.085
				1.5 J, VAS, pain at activity, mo 6	0.12
				3 J, WOMAC, pain at rest, wk 3	0.048
				3 J, WOMAC, pain at rest, mo 6	0.036
				1.5 J, WOMAC, pain at rest, wk 3	0.098
				1.5 J, WOMAC, pain at rest, mo 6	0.0051
Zinman et al, 2004	8	Twice/wk × 4 wk	5 min	Pain (VAS) wk 2	−0.09
				Pain (VAS) wk 6	0.47
				Pain (VAS) wk 8	0.26

LLLT indicates low-level laser therapy; NPDS, Northwick Park Dependency Score; Tx, treatment; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

higher than +0.84, had it been possible to include the 28 experimental studies that were excluded from this study. Twenty-three (82.1%) of the 28 papers excluded showed phototherapy to be significantly effective in pain reduction (Table 2); compared with 59.1% of the studies used in this analysis.

Compared with the 9 effect sizes computed from the 9 studies identified in the earlier study,[38] 52 effect sizes were computed from 22 articles in this study. The higher number of computable effect sizes and the larger number of relevant articles suggests a higher level of sophistication of articles published since 2000. Most contemporary articles measured pain outcomes at several time points or used multiple scales to estimate pain. Even after accounting for repeated measurements of the same outcome variable, the average number of computed effect sizes remained high. Furthermore, the total number of articles (22) with computable effect sizes published between January 2000 and December 2007 is more than twice the number of peer-reviewed articles (9) with computable effect sizes in the study by Enwemeka et al[38] which covered a 30-year period. This observation, which indicates that more articles have been published since 2000, also reflects the increasing acceptance of phototherapy as a clinical tool for pain relief.

Our findings strengthen earlier reports, which indicate that phototherapy is beneficial for pain relief, regardless of etiology.[3,4,6,7,17–19,27,37,38,41–43] For example, Brosseau et al[37] reviewed 13 clinical trials that examined the effects of laser phototherapy on pain relief in persons with either osteoarthritis or rheumatoid arthritis. They showed that, in patients with rheumatoid arthritis, phototherapy reduced pain by 70% and morning stiffness by 27.5 minutes relative to placebo; but functional assessment, range of motion, and local swelling did not differ between the 2 groups. The result for osteoarthritis was inconclusive, as the outcome of treatment seemed dependent on the parameters of treatment. Similarly, as detailed above, Enwemeka et al[38] used statistical meta-analysis to demonstrate that treatment with laser phototherapy moderately relieves pain of various etiologies.

The exact mechanisms by which phototherapy relieves pain continue to evolve. It has been shown that phototherapy increases local and systemic microcirculation thereby reducing swelling and pain. The increased blood flow is associated with nitric oxide synthesis.[8] Others have shown that phototherapy relieves pain by modulating key mediators of inflammation—for example, reducing the level of prostaglandin E_2 and inhibiting cyclo-oxygenase[23,24]—similar to the effects of nonsteroidal anti-inflammatory drugs and steroids. Furthermore, it has been postulated that photostimulation induces athermal photochemical reactions that modulate nerve transmission, thereby altering the pain threshold of nociceptors.[20–22] In addition, there

is evidence that phototherapy enhances the release of endorphins—the bodies endogenous pain relievers.[26,27] It is possible that a combination of these and other mechanisms are involved in the effect of phototherapy on pain relief. Thus, further studies are needed to clarify the mechanisms involved. As our study was limited to articles published in English, we recommend that future meta-analysis include articles published in other languages. Such effort could yield a significantly greater pool of articles even though the relatively few foreign language articles we examined had such limited information that it was not possible to compute effect sizes from them. Future studies on the effects of phototherapy on pain should include functional outcome instruments to bridge the gap between pain and its effect on function. As observed in Table 6, only 2 of the studies used functional-based outcome scales with the majority using visual analog pain scales.

Our findings warrant the conclusion that phototherapy effectively relieves pain of various etiologies; suggesting that it could be a valuable addition to contemporary pain management armamentarium. This finding does not suggest, however, that phototherapy should be used in isolation of other treatment strategies for musculoskeletal conditions. In contrast, standards of care for acute and chronic musculoskeletal pain such as the ones established by the Bone and Joint Decade Task Force[44] place an emphasis on multidisciplinary intervention strategies and self-management.

REFERENCES

1. Mester E, Ludany M, Sellyei M. The stimulating effect of low power laser ray on biological systems. *Laser Rev (Lond.)*. 1968;1–3.
2. Plog FMW. Biophysical application of the laser beam. In: Koebner HK. *Lasers in Medicine*. New York: John Wiley Publishers; 1980.
3. Ekim A, Armagan O, Tascioglu F, et al. Effect of low-level laser therapy in rheumatoid arthritis patients with carpel tunnel syndrome. *Swiss Med Wkly*. 2007;137:347–352.
4. Gur A, Cosut A, Sarac AJ, et al. Efficacy of different therapy regimes of low-power laser in painful osteoarthritis of the knee: A double-blind and randomized-controlled trail. *Laser Surg Med*. 2003;33:330–338.
5. Ozdemir F, Birtane M, Kokino S. The clinical efficacy of low-power laser therapy on pain and function in cervical osteoarthritis. *Clin Rheumatol*. 2001;20:181–184.
6. Douris P, Southard V, Ferrigi R, et al. Effect of phototherapy on delayed onset muscle soreness. *Photomed Laser Surg*. 2006;24:377–382.
7. Fikackova H, Dostalova T, Navratil L, et al. Effectiveness of low-level laser therapy in temporomandibular joint disorders: a placebo-controlled study. *Photomed Laser Surg*. 2007;25: 297–303.
8. Samoilova KA, Zhevago NA, Petrishchev NN, et al. Role of nitric oxide in the visible light-induced rapid increase of human skin microcirculation at the local and systemic levels: II. Health volunteers. *Photomed Laser Surg*. 2008;26:443–449.
9. Saunders L. Laser versus ultrasound in the treatment of supraspinatus tendinosis: randomized controlled trials. *Physiotherapy*. 2003;6:365–373.
10. Sousa LR, Cavalcanti BN, Marques MM. Effect of laser phototherapy on the release of TNF-α AND MMP-1 by endodontic sealer-stimulated macrophages. *Photomed Laser Surg*. 2009;27:37–42.
11. Stergioulas A. Low-level laser treatment can reduce edema in second-degree ankle sprains. *J Clin Laser Med Surg*. 2004;22: 125–128.
12. Trelles MA, Rotinen S. He/Ne laser treatment of hemorrhoids. *Acupunct Electrother Res*. 1983;8:289–295.
13. Naeser MA, Hahn KK, Lieberman BE, et al. Carpal tunnel syndrome pain treated with low-level laser and microamperes transcutaneous electric nerve stimulation: a controlled study. *Arch Phys Med Rehabil*. 2002;83:978–988.
14. Naeser MA. Photobiomodulation of pain in carpal tunnel syndrome: review of seven laser therapy studies. *Photomed Laser Surg*. 2006;24:101–110.
15. Weintraub MI. Noninvasive laser neurolysis in carpal tunnel syndrome. *Muscle Nerve*. 1997;20:1029–1031.
16. Wong E, Lee G, Zucherman J, et al. Successful management of female office workers with "repetitive stress injury" or "carpal tunnel syndrome" by a new treatment modality—application of low level laser. *Int J Clin Pharmacol Ther*. 1995;33:208–211.
17. Chow RT, Heller GZ, Barnsley L. The Effect of 300 mW, 830 nm laser on chronic neck pain: a double-blind, randomized, placebo-controlled study. *Pain*. 2006;124:201–210.
18. Gur A, Karakoc M, Cevik R, et al. Efficacy of low power laser therapy and exercise on pain and function in chronic low back pain. *Laser Surg Med*. 2003;32:233–238.
19. Hirschl M, Katzenschlager R, Francesconi C, et al. Low-level laser therapy in primary Raynaud's phenomenon-result of a placebo controlled, double blind intervention study. *J Rheumatol*. 2004;31:2408–2412.
20. Mendez TM, Pinheiro AL, Pacheco MT, et al. Dose and wavelength of laser influence on the repair of cutaneous wounds. *J Clin Laser Med Surg*. 2004;22:19–25.
21. Ohshiro T, Calderhead RG. Development of low reactive-level laser therapy and its present status. *J Clin Laser Med Surg*. 1991;9:267–275.
22. Walker J. Relief from chronic pain by low power laser irradiation. *Neurosci Lett*. 1983;43:339–344.
23. Honmura A, Ishii A, Yanase M, et al. Analgesic effect of GaAlAs diode laser irradiation on hyperalgesia in carrageenin-induced inflammation. *Lasers Surg Med*. 1993;13:463–469.
24. Sakurai Y, Yamaguchi M, Abiko Y. Inhibitory effect of low-level laser irradiation on LPS-stimulated prostaglandin E2 production and cyclooxygenase-2 in human gingival fibroblasts. *Eur J Oral Sci*. 2000;108:29–34.
25. Aimbiro F, Albertini R, Pacheco MT, et al. Low level laser therapy induces dose-dependent reduction of TNF-alpha levels in acute inflammation. *Photomed Laser Surg*. 2006;24:33–37.
26. Basford JR. Low-energy laser treatment of pain and wounds: hype, hope or hokum? *Mayo Clin Proc*. 1986;61:671–675.
27. Gibson KF, Kernohant WG. Lasers in medicine–a review. *J Med Eng Technol*. 1993;17:51–57.
28. Braverman B, McCarthy RJ, Ivankovich AD. Effect of helium-neon and infrared laser on wound healing in rabbits. *Lasers Surg Med*. 1989;9:50–58.
29. Mester E, Spiry T, Szende B. Effect of laser rays on wound healing. *Am J Surg*. 1971;122:532–535.
30. Karu TI. Photo-biological fundamentals of low-power laser therapy. *J Quantum Electron*. 1987;10:1703–1717.
31. Tam G. Low power laser therapy and analgesic action. *J Clin Laser Med Surg*. 1999;17:29–33.
32. Yu W, Naim JO, McGowan M, et al. Photomodulation of oxidative metabolism and electron chain enzymes in rat liver mitochondria. *Photochem Photobiol*. 1997;66:866–871.
33. Passarella S. He-Ne laser irradiation of isolated mitochondria. *J Photochem Photobiol B*. 1989;3:642–643.
34. Reddy GK, Stehno-Bittel L, Enwemeka CS. Laser photostimulation of collagen production in healing rabbit Achilles tendons. *Laser Surg Med*. 1998;22:281–287.
35. Wolf FM. *Meta-analysis: Quantitative Methods for Research Synthesis*. Newbury Park, CA: Sage; 1986.
36. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. New York: Academic Press; 1969.
37. Brosseau L, Welch V, Wells G, et al. Low level laser therapy for osteoarthritis and rheumatoid arthritis: a metaanalysis. *J Rheumatol*. 2000;27:1961–1969.

38. Enwemeka CS, Parker JC, Dowdy DS, et al. The efficacy of low-power lasers in tissue repair and pain control: a meta-analysis study. *Photomed Laser Surg*. 2004;22:323–329.
39. Barnett V, Lewis T. *Outliers in Statistical Data*. New York: Wiley; 1994.
40. Rosenthal R, Rubin DB. Meta-analytic procedures for combining studies with multiple effect sizes. *Psychol Bull*. 1986;99:400–406.
41. Gur A, Sarac AJ, Cevik R, et al. Efficacy of 984 nm gallium arsenide low-level laser in the management of chronic myofascial pain in the neck: a doubled-blind and randomized-controlled trial. *Laser Surg Med*. 2004;35:229–235.
42. Gur A, Karakoc M, Nas K, et al. Efficacy of low power laser therapy in fibromyalgia: a single-blind, placebo-controlled trial. *Lasers Med Sci*. 2002;17:57–61.
43. Hakguder A, Birtane M, Gurcan S, et al. Efficacy of low level laser therapy in myofascial pain syndrome: an algometric and thermographic evaluation. *Laser Surg Med*. 2003;33:339–343.
44. Walsh NE, Brooks P, Hazes JM, et al. Bone and Joint Decade Task Force for Standards of Care for Acute and Chronic Musculoskeletal Pain. Standards of care for acute and chronic musculoskeletal pain: the Bone and Joint Decade (2000–2010). *Arch Phys Med Rehabil*. 2008;89:1830–1845.

APPENDIX

Studies Included in the Meta-analysis

[1] Altan L, Bingol U, Aykac M, et al. Investigation of the effects of GaAs laser therapy on cervical myofascial pain syndrome. *Rheumatol Int*. 2005;25:23–27.

[2] Bingol U, Altan L, Yurtkuran M. Low-power laser treatment for shoulder pain. *Photomed Laser Surg*. 2005;23: 459–464.

[3] Brosseau L, Wells G, Marchand S, et al. Randomized controlled trial on low level laser therapy (LLLT) in the treatment of osteoarthritis (OA) of the hand. *Laser Surg Med*. 2005;36:210–219.

[4] Chow R, Heller G, Barnsley L. The effect of 300 mW, 830 nm laser on chronic neck pain: a double-blind, randomized, placebo-controlled study. *Pain*. 2006;124: 201–210.

[5] Douris P, Southard V, Ferrigi R, et al. Effect of phototherapy on delayed onset muscle soreness. *Photomed Laser Surg*. 2006;24:377–382.

[6] Dundar U, Evcik D, Samli F, et al. The effect of gallium arsenide aluminum laser therapy in the management of cervical myofascial pain syndrome: a double blind, placebo-controlled study. *Clin Rheumatol*. 2007;26:930–934.

[7] Ekim A, Armagan O, Tascioglu F, et al. Effect of low level laser therapy in rheumatoid arthritis patients with carpel tunnel syndrome. *Swiss Med Wkly*. 2007;137: 347–352.

[8] Fikackova H, Dostalova T, Navratil L, et al. Effectiveness of low-level laser therapy in temporomandibular joint disorders: a placebo-controlled study. *Photomed Laser Surg*. 2007;25:297–303.

[9] Gur A, Karakoc M, Nas K, et al. Efficacy of low power laser therapy in fibromyalgia: a single-blind, placebo-controlled trial. *Lasers Med Sci*. 2002;17:57–61.

[10] Gur A, Karakoc M, Cevik R, et al. Efficacy of low power laser therapy and exercise on pain and function in chronic low back pain. *Laser Surg Med*. 2003a;32: 233–238.

[11] Gur A, Cosut A, Sarac A, et al. Efficacy of different therapy regimes of low-power laser in painful osteoarthritis of the knee: a double-blind and randomized-controlled trail. *Laser Surg Med*. 2003b;33:330–338.

[12] Gur A, Sarac a, Cevik R, et al. Efficacy of 984 nm gallium arsenide low-level laser in the management of chronic myofascial pain in the neck: a doubled-blind and randomize-controlled trial. *Laser Surg Med*. 2004;35: 229–235.

[13] Hakguder A, Birtane M, Gurcan S, et al. Efficacy of low level laser therapy in myofascial pain syndrome: an algometric and thermographic evaluation. *Laser Surg Med*. 2003;33:339–343.

[14] Hirschl M, Katzenschlager R, Francesconi C, et al. Low-level laser therapy in primary Raynaud's phenomenon–result of a placebo controlled, double blind intervention study. *J Rheumatol*. 2004;31:12:2408–2412.

[15] Hopkins J, McLoda T, Seegmiller J, et al. Low-level laser therapy facilities superficial wound healing in humans: a triple-blind, sham-controlled study. *J Athl Train*. 2004;39:223–229.

[16] Ozdemir F, Birtane M, Kokino. The clinical efficacy of low-power laser therapy on pain and function in cervical osteoarthritis. *Clin Rheumatol*. 2001;20:181–184.

[17] Ozkan N, Atlan L, Bingol U, et al. Investigation of the supplementary effects of GaAs laser therapy on the rehabilitation of human digital flexor tendons. *J Clin Laser Med Surg*. 2004;22:105–110.

[18] Saunders L. Laser versus ultra sound in the treatment of supraspinatus tendinosis: randomized controlled trials. *Physiotherapy*. 2003;6:365–373.

[19] Stergioulas A. Effects of low-level laser and plyometric exercise in the treatment of lateral epicondylitis. *Photomed Laser Surg*. 2007;25:205–213.

[20] Takas D, Tellefsen G, Johannsen G. Pain relief after scaling and rootplaning by monochromatic phototherapy (Biolight). *Swed Dent J*. 2006;30:69–75.

[21] Tascioglu F, Armagan O, Tabak Y, et al. Low power laser treatment in patients with knee osteoarthritis. *Swiss Med Wkly*. 2004;134:254–258.

[22] Zinman L, Ngo M, Ng E, et al. Low-intensity laser therapy for painful symptoms of diabetic sensorimotor polyneuropathy. *Diabetes Care*. 2004;27:921–924.

