Photomedicine and Laser Surgery
Volume X, Number X, 2011

Pp. 1–17
DOI: 10.1089/pho.2010.2928

Inhibitory Effects of Laser Irradiation on Peripheral Mammalian Nerves and Relevance to Analgesic Effects: A Systematic Review

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Abstract

Objective: The objective of this review was to systematically identify experimental studies of non-ablative laser irradiation (LI) on peripheral nerve morphology, physiology, and function. The findings were then evaluated with special reference to the neurophysiology of pain and implications for the analgesic effects of low-level laser therapy (LLLT). ***Background:*** LLLT is used in the treatment of pain, and laser-induced neural inhibition has been proposed as a mechanism. To date, no study has systematically evaluated the effects of LI on peripheral nerve, other than those related to nerve repair, despite the fact that experimental studies of LI on nerves have been conducted over the past 25 years. ***Methods:*** We searched computerized databases and reference lists for studies of LI effects on animal and human nerves using *a priori* inclusion and exclusion criteria. ***Results:*** We identified 44 studies suitable for inclusion. In 13 of 18 human studies, pulsed or continuous wave visible and continuous wave infrared (IR) LI slowed conduction velocity (CV) and/or reduced the amplitude of compound action potentials (CAPs). In 26 animal experiments, IR LI suppressed electrically and noxiously evoked action potentials including pro-inflammatory mediators. Disruption of microtubule arrays and fast axonal flow may underpin neural inhibition. ***Conclusions:*** This review has identified a range of laser-induced inhibitory effects in diverse peripheral nerve models, which may reduce acute pain by direct inhibition of peripheral nociceptors. In chronic pain, spinal cord changes induced by LI may result in long-term depression of pain. Incomplete reporting of parameters limited aggregation of data.

Introduction

The rising incidence of chronic pain, which is predicted to reach epidemic proportions in the developed world over the next 30 years, is a major medical and economic challenge for clinicians and researchers.[1] The cost of chronic musculoskeletal pain in European countries is estimated to be €240 million per year,[2] and in the United States, lost productivity from chronic musculoskeletal pain was $61.2 billion in 2003,[3] and from arthritis alone, $7.11 billion.[4] Drugs are widely used for pain management, however they are expensive to individuals and health budgets, have limited efficacy[5,6] and potentially serious adverse effects, especially when taken long-term[7]. There is, therefore, an imperative to develop safe non-drug options for the treatment of pain, and low-level laser therapy (LLLT) is increasingly recognized as one such option.[8]

Several reviews have demonstrated the effectiveness of LLLT in numerous common, chronic conditions such as neck pain,[9,10] osteoarthritis,[11] tendinitis,[12] and lateral epicondylitis.[13] Responding to the increasing levels of evidence, the World Health Organization's Committee of the Decade of the Bone and Joint has also recently incorporated LLLT into guidelines for treatment of neck pain.[14] Mechanisms for pain-relieving effects are, however, not clearly understood although several have been proposed,[15] including the gate theory,[16] modulation of ß-endorphin production,[17–19] and anti-inflammatory effects,.[20,21] Direct inhibition of neural activity has also been identified as a plausible mechanism, based on human and animal studies in which laser irradiation (LI) slowed conduction velocity (CV) in peripheral nerves.[22–26]

The only other review of the effects of LI on mammalian nerves focused on LI-stimulated repair in experimentally

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injured nerves.[27] Our review, however, systematically evaluated effects of LI on peripheral mammalian nerve function including electrophysiology and morphology, outside the context of nerve repair. In particular, we sought to identify such laser-induced effects directly relevant to pain physiology and clinical pain relief.

Methods

Search strategy

We searched the following computerized databases from their inception to May 2010: Medline, Cochrane Database of Systematic Reviews, Allied and Complementary Medicine (AMED), Cinahl, Biological Abstracts, and Biosis, using the following key words: neuron/neural effects/peripheral nerve/nerve conduction/compound action potential/CAP/electrophysiology, combined with a broad range of synonyms to capture the diversity of terms for LI used clinically and experimentally (laser therapy; low-level/low power/low intensity/low reactive level laser therapy; LI/inhibition/stimulation/ effects; photoradiation; phototherapy; photobiostimulation; photobiomodulation; LILT/LLLT/LTLT/LPLI; 632.8 nm; 670 nm; 830 nm; 904 nm; GaAs; GaAlAs; HeNe; infrared (IR)/visible laser). We also hand-searched reference lists of retrieved articles and textbooks. The search strategy was limited to English.

Inclusion criteria

We included studies in which LI of any wavelength, in pulsed or continuous wave (cw) mode, was applied transcutaneously or directly to exposed peripheral mammalian nerves or neurons, *in vivo* or *in vitro*, in animals or human subjects. Studies were included if there were a control group or set of observations with which to compare pre and post-LI effects. We evaluated functional responses, spontaneous or evoked or morphological changes in peripheral nerves or neurons.

Exclusion criteria

We excluded studies of non-mammalian nerves, studies evaluating nerve repair in experimentally injured nerves, those that used wavelengths and power densities with ablative potential, and studies in which LI was used as a noxious or sensory stimulus. We also excluded studies where non-laser light sources were used.

Responses evaluated

We evaluated pre- and post-LI effects in nerves or neurons, specifically (a) morphological changes, (b) effects on enzymes or neurotransmitters, (c) electrophysiology, including CV, latency, compound action potentials (CAP), somatosensory evoked potentials (SSEP), and/or noxiously evoked potentials. Where studies reported only changes in latency, we reported change in CV, as latency is inversely proportional to CV. Where individual studies included two or more separate experiments using different parameters, doses or wavelengths, each experiment was evaluated separately.

Results

Forty-four of 381 studies initially identified by our search, of which 18 were human studies and 26 were animal studies, fit our inclusion criteria.

Human studies

Eighteen human studies included a total of 630 participants, with the number in individual trials ranging from 9 to 90 [22,28–44] (Table 1).

Participant selection

Five studies reported recruitment of "healthy" or "normal" participants,[28,30–32,44] and 12 studies excluded participants with underlying neurological problems.[22,29,33–42] Both male and female participants were selected in seven studies;[22,29,37–41] one study recruited only female subjects,[36] and another only males.[43]

Neurophysiological methodologies

Nine studies[22,29,36,39–42,44,45] used standardized protocols for assessment of electrophysiology.[46–55]

Ten studies used maximal or supramaximal electrical stimuli, to ensure all axons were stimulated prior to LI and to establish consistent baseline responses for each participant.[22,29,33–39,42] CAP response to LI was recorded in six studies,[29–31,40,43,44] of which four studies recorded CV and CAP simultaneously.[29,40,43,44] Cambier used "mild discomfort" as the upper limit of intensity of electrical stimulation (ES).[41]

LI application

LI was applied transcutaneously in all human studies, to between four and ten points to the arm or leg, at 1-cm intervals along or medial to the course of the median nerve in seven studies;[30,33–35,37–39] of the superficial radial nerve in six studies;[22,28,29,31,36,42] and of the sural nerve in two studies.[41,43] In three studies, LI was applied to a single point or area of skin overlying a nerve, specifically: the median nerve at the wrist or forearm;[40] one point on the skin of the palm, supplied by the median nerve;[32] and the apex of a tooth, supplied by the trigeminal nerve.[44] Electrophysiological responses were recorded for up to 30 min, 1–5 min intervals.

Laser parameters

Wavelength (λ) and beam mode of LI, either cw or pulsed, were reported in all studies. Output power ranging from 1 to 400 mW was reported in all but two studies.[29,32] Pulsed laser parameters, such as duration of pulse, and pulsation frequency (Hz) were not consistently reported. Duration of LI at each point ranged from 10 sec to 30 min; energy densities (ED) ranged from 0.019 to 138.4 J/cm^2; and power densities (PD) ranged from 300 to 1,730 mW/cm^2 but were inconsistently reported. Beam spot size was reported in 10 human studies[22,28,30,32,36–38,40,41,44] and in 14 animal studies.[23,25,56–67] Only parameters that were reported in each study were listed in the tables. In general however, in most studies parameters were not fully reported, limiting aggregation of data (Table 1).

Human studies

Fifteen studies reported CV response to LI[22,28,29,33–44] and six studies reported CAP response,[29–31,40,43,44], four of which recorded CV and CAP simultaneously.[29,40,43,44]

LI effects on CV

Visible LI. Continuous 632.8–633 nm (1 mW) and 670 nm (cw,3 mW) LI slowed CV in four studies.[22,28,36,43] However, pulsed 632.8 nm (1.7mW, 50 Hz) LI (for 120 sec) to the apex of a tooth did not.[44]

IR LI. Continuous wave 820–830 nm (30 or 40 mW), applied from 4 to 24 sec and 780 nm (cw, 3 or12 mW) applied from 25 to 835 sec, slowed CV in seven studies when applied transcutaneously overlying the course of median, sural, or radial nerves.[33–37,39,43] Continuous wave 830 nm (90 mW) LI did not slow CV when applied for 33 sec in four cycles to a single area of median nerve,[40] nor did 830 nm (40 mW) applied for 30 sec, when applied 4 cm medial to the course of the median nerve.[39]

Pulsed, 830 nm LI, 140 mW (1,500 Hz; ED: 5.1 J/cm^2) slowed CV in the sural nerve; however 30 mW (1,500 Hz; ED: 2.55 J/ cm^2) or 400 mW (1,500 Hz; ED: 7.65 J/ cm^2) did not.[41] Pulsed 820–830 nm (12Hz, 73Hz, 5kHz; 9 or 73 Hz) LI at any ED did not slow CV in median or sural nerves.[38,42] Pulsed 904 nm, (73 Hz) LI slowed CV of the superficial radial nerve with 120 sec irradiation per point but not with 20 sec.[29]

LI effects on CAP amplitude

Visible LI. Continuous wave LI, 670 nm (3 mW), at three different EDs, decreased the sural nerve CAP amplitude.[43] Pulsed 632.8 nm (1 mW, 3.1 Hz) LI, delivered continuously for 20 min to the superficial radial nerve, decreased CAP amplitude by 90%,[30] although Wu et al. could not replicate the findings of Walker et al. (1985)[30] using apparently identical experimental methodology.[31] Pulsed, 632.8nm LI (1.75 mW, 50 Hz) for 120 sec, delivered fiberoptically to the apex of the third molar, decreased SSEP amplitude by 72%[44] (Table 1).

IR LI. Continuous wave 780 nm LI (3 mW), at three different EDs, decreased CAP amplitude.[43] However, 830 nm (CW, 90 mW) LI applied to a single area of the median nerve at the wrist or forearm,[40] or when applied 4 cm medial to the course of the median nerve,[39] did not change CAP amplitude. Pulsed 904 nm (73 Hz) LI applied transcutaneously over the superficial radial nerve, decreased CAP amplitude after 120 sec, but not after 20 sec.[29]

LI can initiate SSEPs de novo

Visible, pulsed 632.8 nm (1 mW, 3.1 Hz) LI evoked SSEPs at Erb's point when applied over the median nerve at the wrist,[30] however, Wu et al. could not replicate this study.[31] Pulsed 332.2 nm LI (power or pulse rate not reported) elicited SSEPs at the scalp when applied to the palm, also innervated by the median nerve.[32] Six of the 11 subjects reported awareness of the stimulus but the recorded response was identical whether or not the subject perceived any stimulation.[31]

Animal studies

Twenty-six studies of LI on guinea pig, rat, mouse, cat, ferret, rabbit, or dog nerve met our inclusion criteria.

Methodology. Electrophysiological studies assessed electrically evoked CAPs, SSEPs or noxiously evoked potentials. CAPs[26,56–58,60,61,63,68–70] and SSEPs[59] were measured following supramaximal stimuli after baseline potentials had been established (Table 2).

Noxiously evoked potentials were elicited by mechanical, thermal, or chemical stimulation,[45,60,65,71,72] or by formalin, turpentine, or bradykinin injection[25,62,64–66] (Table 3).

LI-induced morphological and other functional changes related to nerve impairment were assessed by electron microscopy,[23] immunohistochemistry,[67,73–75] biochemical assay,[73] patch clamping,[63] confocal microscopy, or live imaging.[67]

LI application

Visible or IR LI in pulsed or cw mode was applied transcutaneously, or to exposed nerves *in situ*, to isolated nerves, or to nerve cell cultures, for 5 sec to 30 min. One study assessed repeated LI, applied twice daily for 7 days, to bradykinin-injected rat facial skin.[23]

Reporting of output power, beam mode, ED, PD, total energy, duration of exposure, and site of exposure of LI parameters was inconsistent, with only Chow et al. reporting all relevant parameters.[67]

Studies of CV and CAP recorded simultaneously

Visible LI. Continuous wave 632.8 nm (5.5 mW) LI for 3, 5, or 10 min decreased CAP amplitude, but did not slow CV, at all exposures, for up to 150 min in excised preparations of rat cervical sympathetic ganglion neurons, and the pre- and post-ganglionic fibers.[61] This outcome followed supramaximal stimuli to the pre-ganglionic fibers for 30 min recorded at the post-ganglionic fibers. Continuous wave 632.8 nm (1 or 4 mW) LI to exposed dog sciatic nerve did not slow CV or alter CAP amplitude of SSEPs recorded at the scalp,[59] nor in Aδ and C fibers of excised rabbit cornea.[60] Importantly, the study by Kao et al. did not report the power output or other parameters,[59] and the study by Jarvis[60] has been challenged as an inappropriate model.[76]

IR LI. Continuous wave 830 nm (40 mW) LI to exposed rat saphenous nerve reduced CV in the slow component of CAPs at exposures of 180 and 60 sec, but not at 30 sec.[69] The fast component, representing the large-diameter myelinated fibres, remained unchanged. LI for 60 and 180 sec also reduced CAP amplitude with the effect lasting up to 4 h but 30-sec irradiation had no effect on CAP amplitude.

Following electrical stimulation of exposed dog sciatic nerve, Gallium diode-based LI (8 mW, λ not reported) did not change CV of SSEPs.[59] However, the amplitude of the SSEPs was reduced, which later returned to normal after cessation of LI, although duration of stimulation was not reported.

LI effects on CV and CAP amplitude

Visible LI. CW, 632.8 nm LI did not slow CV in excised rat sciatic nerve at five EDs ranging from 0.1 to 1 J/cm^2.[68] Parameters, including output power, were not reported. Pulsed, 632.8 nm (1 mW, 100 Hz) LI to exposed rabbit sural nerve in the popliteal fossa slowed CV by 9–19%, persisting for 20 min.[70]

Continuous wave 632.8 nm (16 mW) LI to rat sciatic nerve delivered transcutaneously and continuously for 30 min, did not alter CAP amplitude with a cumulative dose of 3 J at 6 min. However, CAP amplitude increased during the period 6–15 min as the dose increased to 8 J, with the increase lasting $\sim$7 min.[57] When total cumulative dose of 8–15 J was reached

Table 1. Human Studies of Transcutaneous or Dental Laser Irradiation on Conduction Velocity (CV) and Compound Action Potential (CAP) Amplitude

Author and year	*Nerve*	*λ (nm) & beam mode*	*Power and Rx parameters*	*Sites treated*	*Effect on conduction velocity*	*Effect on compound action potential*
Greathouse et al.[29]	Superficial radial $n=20$	904, 73 Hz	exp: 1 20 sec exp: 2 120 sec (power not reported)	5 points at 1 mm above skin surface; observed at 1, 3, 5, 10, and 15 min post-LI	exp 1: no change exp 2: decreased $p<0.05$	exp 1: no change exp 2: no change
Snyder-Mackler et al.[28]	Superficial radial $n=20$	632.8, cw	1 mW	$6\times1\,cm^2$ points along course of nerve; 0.5 mm from skin surface	Decreased $p<0.05$	NR
Walker & Akhanjee[30]	Superficial radial & median $n=10$	632.5, 3.1 Hz	1 mW exp 1: 800 pulses exp 2: 4,800 pulses duration of exposure: 20 min	$4\,mm^2$ area at each nerve spot size: $4\,mm^2$	NR	exp 1: decreased exp 2: decreased (more prolonged exposure dec. by 20–90%)
Wu et al.[31]	Median $n=9$	632.5, 3.1 Hz	1 mW; fiberoptic probe	$4\,mm^2$ area; 2 mm above skin	NR	No light-evoked response
Snyder-Mackler & Bork[22]	Superficial radial $n=40$	632.8, cw	1 mW, 20 sec 0.02 J ED: $19\,mJ/cm^2$	$6\times1\,cm^2$ points over nerve; 0.5 mm from skin	Decreased by 14.2% $p<0.001$	NR
Czopf et al.[32]	Median $n=20$	337.1, pulsed (power NR)	300 μJ per pulse pulse duration: 1.0 nsec (power not reported)	Palm of hand (acupuncture points: PC6 and LI10) beam area: $0.3\,mm^2$	Not applicable	Evoked potential measured at the scalp
Baxter et al.[33]	Median $n=27$	830, cw	40 mW, ED: $1.2\,J/cm^2$ 30s per pt	10 points over nerve in contact with skin	Decreased $p<0.05$	NR
Baxter et al.[34]	Median $n=48$	830, cw	40 mW, ED: $1.2\,J/cm^2$ 30 sec/pt	10 points over nerve	Decreased (>1 h post-LI) $p<0.05$	NR
Baxter et al.[35]	Median $n=24$	830, cw	40 mW, ED: $1.2\,J/cm^2$, 30 sec per pt	10 points over nerve	Decreased 0, 1, 2, and 5 min post-LI	NR
Kramer & Sandrin[36]	Radial $n=40$	exp 1: 780, cw exp 2: 632.8, cw	exp 1:12 mW, 15sec 0.18 J exp 2: 10 mW, 18 sec 0.10 J ED: $10\,J/cm^2$	$6\times1\,cm^2$; 1 mm from surface; spot size diam: 0.15 cm 0 and 1 min post-LI	Exp 1: no change exp 2: decreased $p<0.03$	NR

Baxter et al.[39]	Median $n = 51$	830, cw	40 mW, 30 sec per pt, 1.2J per pt ED: 9.6J/cm^2	exp 1: 30 sec, 10 points along course of nerve exp 2: as above but 4 cm medial to nerve exp 3: 4 points along palm	exp 1: decreased obs 1 h at 5 min intervals; p 0.05 exp 2: no change exp 3: decreased p 0.05	NR
Lowe et al.[37]	Median $n = 80$	830, cw	30 mW, PD: 300 mW/cm^2 exp 1: 1.5 J, 5 sec exp 2: 3 J, 10 sec exp 3: 6 J, 20 sec exp 4: 9 J, 30 sec exp 5: 12 J, 40 sc	10 points over nerve 20 min obs at 2 min intervals spot size: 0.1 cm^2,	exp 1–3: decreased $p < 0.05$ exp 4 and 5 no effect	NR
Lowe et al.[38]	Median $n = 90$	820, pulsed, 12 Hz and 73 Hz and 5 kHz	46 mW (av power) ED 1.5 J/cm^2 or ED 9.0 J/ cm^2 Spot size: 0.125 cm^2, 368 mW/cm^2 Exp 1: 0.18 J, 4 sec Exp 2: 0.18 J, 4 sec Exp 3: 0.18 J, 4 sec Exp 4: 1.1 J, 24 sec Exp 5: 1.1 J, 24 sec Exp 6: 1.1 J, 24 sec	10 points over nerve in contact with skin	exp 1–6: no significant change at any pulse rate or ED	NR
Bartlett et al.[40]	Median $n = 42$ (4 groups)	830, cw	90 mW, ED: 33 J/cm^2 PD: 1 W/cm^2 33 sec x 4, 12 J	X 3 multi-head; spot size: 0.09 cm^2 single area; 2 areas treated separately exp 1: LI at wrist exp 2: LI at fore-arm	exp 1: LI at wrist–no change exp 2: LI at forearm–no change	No change 0 and 10 min
Cambier et al.[41]	Sural $n = 15$	830, pulsed 1-500 mW freq: 0-1500 Hz; pw: 500 μs	exp 1: 400 mW; 3.8 sec per pt, 1.5 J ED: 7.65 J/ cm^2 exp 2: 140 mW; 5 sec, 1 J per pt, ED: 5.1 J/ cm^2 exp 3: 30 mW; 16.6 sec per pt; ED: 2.55 J/cm^2; 0.5 J	6 points over nerve spot size: 0.196 cm^2	exp 1: no change exp 2: decreased $p < 0.05$ exp 3: no change	NR

(continued)

Table 1. (Continued)

Author and year	*Nerve*	*λ (nm) and beam mode*	*Power and Rx parameters*	*Sites treated*	*Effect on conduction velocity*	*Effect on compound action potential*
Walsh et al.[42]	Superficial radial $n = 32$	820, pulsed, 9.12 Hz &73 Hz	46 mW, 0.125 cm^2, ED: 9.55 J/cm^2 368 mW/cm^2 1. J per pt, exp 1: 24 sec exp 2: 24 sec	3 points over nerve; 5, 10, and 15 min	exp 1: no change exp 2: no change	NR
Nelson and Friedman[44]	Trigem. nerve, maxil. branch $n = 24$	632.5, pulsed 50 Hz	1.7mW, spot size: 0.001 cm^2, PD:1.73 W/cm^2,ED:138.4 J/cm^2 120s/pt, 0.2 J	1 point at left maxillary 3rd molar apical area	No change	Decreased to 65% at 10 min and 72% at 20 min $p < 0.001$
Hadian and Moghada[43]	Sural $n = 38$	exp 1–3: 670, cw exp 4–6: 780, cw	3 mW exp 1: ED:0.5J/cm^2 5 J, 167 sec exp 2: ED:1.5J/cm^2 15 J, 501 sec exp 3: ED: 2.5 J/cm^2 25 J, 835 sec exp 4: ED: 0.5 J/cm^2 0.075 J, 25 sec exp 5: ED:1.5 J/cm^2 0.150 J, 75 sec exp 6: ED: 2.5 J/cm^2 0.325 J, 125 sec	Along course of nerve (number of points unspecified)	exp 1–6 all decreased $p < 0.01$ $p < 0.001$	exp 1–6 all decreased $p < 0.01$ $p < 0.001$

exp, experiment; pt, point; λ, wavelength; PD, power density; ED, energy density; cw, continuous wave; NR, not reported.

after 15 min, the CAP amplitude decreased to baseline levels. With continuing LI, CAP amplitude was decreased to below baseline levels after ~30 min. A similar biphasic response was reported by Nissan et al. using the same model and parameters.[56] In contrast, in a third study using the same model and LI parameters, CAP amplitude increased by 43% after 20 min with no decline.[58] Shimoyama et al. also demonstrated an increase in CAP amplitude following 632.8 nm (5.5 mW) LI to rat superior cervical ganglion neurons.[61] Pulsed, 632.8 nm (1 mW) LI to exposed cat sural nerve decreased CAP amplitude by 25%.[26]

There were no studies of IR LI on electrically evoked CAPs.

LI reduces noxiously evoked SSEPS

LI applied before, during, or after noxious stimuli decreased amplitudes of noxiously evoked SSEPs (Table 3).

Visible LI. Continuous wave, 632.8 nm (8.5 mW) LI for 30 min prior to formalin injection to rat hind paw, innervated by peroneal nerve, inhibited SSEPs measured at the ipsilateral, lumbosacral dorsal horn neurons.[62] Pulsed, 632.8 nm (1 mW, 100 Hz) LI for 10 min to exposed sural nerve inhibited SSEPs elicited by pinch of skin of rabbit hind paws.[72]

However 632.8 nm (cw, ~1 mW), LI used as an aiming beam for Nd:YAG laser, did not inhibit SSEPs when ferret tooth pulp was mechanically stimulated.[45] Similarly, pulsed 632.8 nm (5 mW, pulse rate not reported) LI for 5 min failed to inhibit the nociceptor Aδ and C fiber response in excised rabbit cornea following mechanical, thermal, or chemical noxious stimuli.[60]

IR LI. Laser irradiation at 830 nm (cw, 350 mW) for 2 min to the surface of rat incisor, inhibited SSEPs evoked by noxious ES, in the ipsilateral trigeminal subnuclear caudal neurons;[25] and 830 nm (40 mW) LI for 3 min to exposed rat saphenous nerve, inhibited noxiously induced SSEPs in the ipsilateral L4 dorsal root following turpentine injection to the paw,[64,65] and heat, pinch, and cold to the paw, but did not inhibit response to brush stimulation,[65] indicating the specificity of the effect on the nociceptive Aδ and C fibers but not the Aβ fibres. In a parallel experiment, neonatal rats treated with capsaicin at birth, thereby specifically destroying the nociceptor Aδ and C fibers, showed no response to noxious stimuli or LI. As in the previous experiment, these rats continued to respond normally to light touch.

LI of 830 nm (cw, 16.2 mW) applied to axons in the outer chamber of a two-chamber culture preparation of murine dorsal root ganglion (DRG) neurons <25 μm diameter, characteristically nociceptors, inhibited bradykinin-evoked potentials in cell bodies in the inner chamber as demonstrated by patch clamping techniques.[66]

Another study showing nociceptor specificity was seen in a study of pulsed, 904 nm (2 W, 3040 Hz) LI to cat tongue, in which LI for 1 min inhibited noxious heat stimulation in 60% of nociceptors.[71] Further LI for 3–10 min inhibited firing frequency in 100% of cases.

IR LI depolarizes sensory neurons

Continuous wave, 830 nm (2.5–150 mW) LI at ED between 2.5 and 30 J/cm^2, caused a dose-dependent reduction in mitochondrial membrane potential (MMP) in 67% of neurons, measured by patch clamping, in rat sensory nodose ganglion neurons.[63] Depolarization persisted for 3–8 min; however, in 35% of these neurons remained depolarised for a further 40 min. Tetrodotoxin (TTX, 7.5 μM), a sodium channel blocker, abolished the LI-induced depolarization, suggesting LI-
induced inhibition of voltage-gated sodium channels. As reported earlier, the diameters of these neurons were consistent with their being nociceptors.

Visible LI hyperpolarizes sympathetic neurons

Intracellular recording of individual fibers of superior rat cervical sympathetic ganglionic nerve following 632.8 nm (cw, 5.5 mW), LI for 3, 5, or 10 min, showed hyperpolarization with an increase in CAP amplitude.[61] However, decreased CAP amplitudes recorded extracellularly in the post-ganglionic nerve were observed, indicating that LI-induced hyperpolarization reduced the number of neurons capable of responding to ES.

IR LI induces neuronal morphological and functional changes

Continuous wave, 830 nm (20 mW) LI induced varicosity formation and inhibited outgrowth of the nociceptive neuropeptide substance P and CRGP-stained positive neurites by 30% in cultured murine neurons.[74] The effect was reversed after 5 h. LI of 830 nm (cw, 300 mW) at 5, 30, 60, or 120 sec was also found to induce varicosity formation in cultured, rat DRG neurons, indicating microtubule disruption.[67] Varicosities were β-tubulin positive and contained clusters of mitochondria. Real-time confocal microscopy with JC-1, a radiometric dye, showed statistically significant decreased axonal and cell body MMP, and blocked fast axonal flow, which was reversed within 24 h.

Bradykinin injected into rat facial skin, innervated by the maxillary branch of the trigeminal nerve, showed increased mitochondrial density in the related trigeminal nucleus.[23] LI of 830 nm (cw, 60 mW) for 15 sec per point, to 12 points over the dermatome twice daily for 7 days, reduced the mitochondrial density to control levels at day 12.

LI of 830 nm (cw, 60 mW) for 1 min to exposed, electrically stimulated, rat sciatic nerve inhibited production of substance P in the ipsilateral lumbar DRG.[75]

Pulsed, ruby LI ($\lambda = 694$ nm, power or pulse frequency not reported) for 10 min increased acetylcholine release from the Auerbach plexus of isolated guinea pig ileum, after 3 min, lasting up to 30 min.[77]

IR LI affects enzyme activity

LI of 830 nm (cw, 60 mW) applied transcutaneously over rat saphenous nerve for 6–15 sec (0.9 J) increased activity of Na^+ $K+$-ATPase, essential for maintenance and restoration of resting membrane potential. The enzyme activity levels then declined with a further 30 sec of LI, decreasing to below-normal levels following 60 and 120 sec.[73] LI for <6 sec had no effect.

Discussion

This review demonstrates a range of LI-induced functional neural impairment in human and animal peripheral nerve,

Table 2. Animal Studies of Laser Irradiation on Conduction Velocity, Electrically Evoked Compound Action Potentials, Somatosensory Evoked Potentials, Morphology, or Enzyme Activity

Study	*Animal and nerve irradiated*	*λ (nm), beam mode, power,*	*Site treated and duration of LI*	*Conduction velocity*	*Electrically evoked CAP or SSEP*	*Morphological or functional change*
Vizi et al.[77]	Guinea pig Auerbach's plexus (*in vitro*)	694, P (Hz and power NR)	Isolated Auerbach's plexus	NR	NR	Increased production of acetylcholine-commenced after 3–10 min and lasted 25–30 min
Rochkind et al.[57]	Rat sciatic (*in vivo*) $n=4$	632.8, cw 16 mW 4 mm diameter	Cumulative exposure: 30 min transcutaneous	NR	Phase 1: <3 J: no change Phase 2: >3J <8 J increased Phase 3: >8J decreased	NR
Nissan et al.[56]	Rat sciatic (*in vivo*) $n=4$	632.8, cw 16 mW 4 mm diameter	Cumulative exposure; 30 min Transcutaneous	NR	Phase1: increased after 6 min (<3 J) Phase 2: high/stable for 7 min; (>3.5–7.5J J) Phase 3: decreased next 7 min (8–15 J)	NR
Rochkind et al.[58]	Rat sciatic (*in vivo*) $n=13$	632.8, cw 16 mW 4 mm diameter, TE = 5 J ED $\sim 10\,J/cm^2$	Cumulative exposure; 30 min transcutaneous	NR	Increased by 43% 20 min after LI	NR
Kao et al.[59]	Dog sciatic (*in vivo*)	632.8 P and cw 100-1000Hz exp 1: 1 mW exp 2: 4 mW beam diameter: 1.47mm Ga IR exp 3: 8 mW	Exposed nerve; 10 min cortical SSEP measured at scalp	632.8 exp 1 no change exp 2: no change IR laser exp 3 no change	exp 1: no change exp 2: no change exp 3 decreased (reversible)	NR
Kudoh et al.[73]	Rat saphenous nerve	830, cw 60 mW	Isolated nerve 6–120 sec exposure	NR	NR	Na^+ K^+-ATPase activity • 6–15 sec increased activity • 30 sec declined • 60 and 120 sec decreasing below normal levels

Maeda[23]	Rat trigeminal nerve (*in vivo*)	830, cw 60 mW PD: 1.9 W/cm^2 12 pts 2×/day for 7 days; spot size 2 mm	Skin of face innervated by maxillary branch of trigeminal nerve 15 sec per pt	NR	NR	Inhibition of increased mitochondrial density in trigeminal nucleus after bradykinin stimulation (12th day after LI) $p < 0.001$
Arber et al.[68]	Rat sciatic (*in vitro*)	633, (?cw and power NR) ED: 0.1–1 J/cm^2 PD: 0.6–10 W/cm^2	Isolated segment exp 1 10 sec exp 2 1 min exp 3 5 min exp 4 10 min exp 5 20 min	exp 1–5 no change	NR	NR
Jarvis et al.[60]	Rabbit $n = 20$ corneal nociceptors in excised cornea	632.5, cw 4 mW beam diameter 4 mm 0–1,800 sec	(a) Spontaneous spike activity Aδ and C fibers; (b) electrically evoked single fiber discharges; 5 min	No change after 120 min	No change after 120 min	NR
Shimoyama et al.[61]	Rat superior cervical sympathetic ganglia (*in vitro*)	632.8, cw 5.5 mW spot size 1.4 mm, PD: 350 mW/cm^2	Intra- and extracellular recordings from isolated nerves; 3, 5, or 10 min	exp 1 (3 min): no change exp 2 (5 min): no change exp 3 (10 min): no change	exp 1 (3 min) : decreased $p < 0.05$ exp 2 (5 min): decreased $p < 0.01$ exp 3 (10 min): decreased $p < 0.05$	NR
Chen et al.[74]	Murine nerve cultures	830, cw 20 mW	DRG neurons in culture; 5 or 15 min	NR	NR	Varicosity formation and suppression of growth of nociceptors at 0 and 5 h post-LI – $p < 0.001$
Kono et al.[26]	Cat sural $n = 3$ (*in vivo*)	632.8, cw power NR 1 mW, 100 Hz fiberoptic delivery 20–25 mm above nerve	Exposed nerve in popliteal fossa, measuring evoked dorsal horn responses; 10 min	NR	Decreased by an average of 25.6% $p < 0.01$	NR
Tsuchiya et al.[69]	Rat saphenous nerve $n = 25$ (*in vivo*)	830, cw 40 mW PD 1 W/cm^2 exposed nerve; 0.5–1.5 mm from nerve spot size: 2 mm	Exposed nerve; response to LI measured in L5 dorsal roots 30, 60, and 180 sec	exp 1 (30 sec): no change (fast component) exp 2 (60 sec): decreased (slow component)	exp 1 (30 sec): no change exp 2 (60 sec): decreased $p < 0.01$ exp 3 (180 sec): decreased 12-67% $p < 0.01$ effects lasted up to 4 h	NR

(continued)

Table 2. (Continued)

Study	*Animal and nerve irradiated*	*λ (nm), beam mode, power,*	*Site treated and duration of LI*	*Conduction velocity*	*Electrically evoked CAP or SSEP*	*Morphological or functional change*
Kasai et al.[70]	Rabbit sural $n = 7$ (*in vivo*)	632.8, P 1 mW 100 Hz fiberoptic delivery 20–25 mm above nerve	Exposed in popliteal fossa; 10 min	Aδ fiber CV decreased by 9–19%; persisted 20 min $p < 0.05$	NR	NR
Miura and Kawatani[63]	Rat cultured nodose ganglion cells	830, cw 2.5–150 mW beam diameter: 0.4 mm ED: 5–20 J/cm^2	Direct LI to cultures	NR	(a) depolarization of neurons (b) increase in Na^+ current (c) TTX abolished laser-induced depolarization	NR
Ohno[75]	Rat sciatic nerve $n = 41$ (*in vivo*)	830, cw 60 mW	LI to exposed nerve	Substance P synthesis L4-6 DRGs	Suppression of substance P at DRGs $p < 0.05$	NR
Chow et al.[78]	Rat DRG cultures ($n = 10$)	830, cw 400 mW PD: 300 mW/cm^2 ED: 1.4 J/cm^2–33.3 J/cm^2 spot size: 1.4 cm^2	Direct LI to cultures; 5–30 sec	NR	NR	Exp 1–5: varicosity formation; decreased MMP disrupted FAF; $p < 0.05$ $p < 0.01$

λ, wavelength; cw, continuous wave; DRG, dorsal root ganglion neurons; ES, electrical stimulation; FAF, fast axonal flow; MMP, mitochondrial membrane potential; P, pulsed; NR, not reported; PD, power density; ED, energy density; CAP, compound action potential; SSEP, somatosensory evoked potential.

isolated nerve, and primary nerve cell cultures. This is the first review to examine such a range of neurological effects. Neural impairment included CV slowing, decreased CAP and SSEP amplitudes, suppression of response to noxious stimuli, suppression of pain-related neurotransmitters release, inhibition of enzyme activity, and morphological changes related to nerve conduction.

The human studies were methodologically uniform with transcutaneous visible and IR LI, applied at several points along the course of peripheral nerves, causing CV slowing and decreased amplitudes of CAPs or SSEPs. What is important is that these findings establish the principle that photons delivered transcutaneously can inhibit or at least slow or partially block nerve conduction. Furthermore, these studies demonstrate that LI is most effective when applied at several points over the nerve causing an additive effect, rather than to a single point. These findings are of direct relevance to the clinical application of LLLT showing its effectiveness in painful conditions such as neck or back pain. Clinically, LI is applied transcutaneously to multiple points, such as tender points,[78] trigger points,[79] or acupuncture points,[80] in the region of injury or pathology. The neural network of nociceptor fibers within the epidermis would be most affected by the transmitted photons, as photon density is maximal in the epidermis and decreases exponentially.

The human studies also point to an important difference in the clinical effects of pulsed, IR LI compared with cw mode. In the majority of studies, pulsed 820–830-nm LI had no effect on CV, although CW LI of the same wavelengths did. Pulsed LI (either "chopped" or intrinsically pulsed) delivers lower total energy (Joules) to the nerve than does cw mode, supporting the hypothesis that CV slowing requires "high" dose LI. A study showing that 904-nm LI slowed CV with 120 sec exposure but not with 20 sec exposure, which demonstrates a dose-dependent response,[29] adds weight to the proposition that inhibition of nerve conduction requires comparatively higher doses of LI.

Visible LI in pulsed or cw modes did slow CV, which occurred at a lower output power range (1–10 mW) compared with IR LI (30–400 mW). However, direct comparisons between visible and IR studies were not possible as many studies did not report all relevant parameters, such as power density (irradiance) and energy density (radiant exposure). We propose that intrinsic differences between visible and IR LI may account for the apparent effectiveness of visible LI occurring at much lower output powers than IR. Red photons have greater electron voltage than IR, and visible LI has greater coherence than IR, with the possibility of more intense intra-tissue "speckle" formation, with the "speckles" being points of higher intensity caused by interference effects. [81,82] Countering this rationale is the lower penetration depth of visible LI (2–5 mm for visible LI compared with 3–5 cm for IR LI), although epidermal nociceptor terminals will be well within the depth of penetration in the first 2 mm of skin.[83] Differences in mechanisms of action between visible and IR LI have been described,[84] which include the formation of greater levels of reactive oxygen species (ROS) with visible LI[85–87] than with IR LI. Such differences may also account for the variation in biological responses between wavelengths, although not all authorities agree with this assertion and therefore it remains an area for debate and further resolution. We propose that all of these factors may be relevant to the inhibition of nerve activity at lower energy outputs with visible LI.

Although transcutaneous LI can slow CV in human nerves, these studies do not provide evidence that LI-induced neural inhibition is causal in the pain-relieving effects of LLLT. The animal studies, however, evaluated a diverse range of effects, which have particular relevance to the analgesic effects of LI. In particular, specific inhibition of Aδ and C fibers, which transmit nociceptive stimuli, provide the strongest evidence that functional impairment of these fibers mediates clinical pain relief. In these experiments, pulsed and cw, visible and IR LI, reduced response in nociceptors to a variety of noxious stimuli, including proinflammatory substances.[64,65] What is important is that in rats in which nociceptors were ablated by capsaicin application at birth, there was no response to noxious stimuli or to LI, although non-noxious stimuli were transmitted normally and were not inhibited by LI.

LI-suppression of bradykinin activity, a pro-inflammatory neuropeptide that sensitiszes nociceptors and is a key element in clinical pain and the associated inflammation,[23,66,88] is directly relevant to pain relief. Continuous wave, 830 nm, (16.2 mW) LI to isolated neurons blocked the stimulatory effects of bradykinin activity on nociceptors,[66] and in the trigeminal nucleus of rats, induced by bradykinin injection to facial skin, following 830 nm, (cw, 60 mW) LI over the injection site.[23] The latter study is consistent with 830 nm, (cw, 350 mW) LI-induced inhibition of SSEPs in the trigeminal nucleus of rats induced by noxious electrical stimulation of the related tooth pulp.[25] Further evidence for neurally-mediated suppression of bradykinin, was the downregulation of B1 and B 2 kinin receptors,[89] which are expressed on nociceptors,[88] by visible LI ($\lambda = 660$ or 684 nm), following injection of the pro-inflammatory polysaccharide, carrageenan, into rat paw. As bradykinin is associated with neural inflammation and peripheral sensitisation of nerves, which occur at an injury site, these studies also provide evidence for a direct link between local LI and reduced inflammation, again by direct suppression of nociceptor response.

Substance P, another neuropeptide associated with nociception, was decreased in lumbar DRG neurons when the electrically-stimulated ipsilateral rat sciatic nerve was irradiated with 830 nm (cw, 60 mW) LI.[75] Such suppression distally demonstrated that visible or IR LI to peripheral nerve, conveying nociceptive stimuli, could cause upstream inhibition of synaptic activity, via synaptic plasticity, in second-order neurons, in the dorsal horn and to the pain matrix, with potential importance in long-term pain modulation.[90]

How LI causes functional neural impairment remains unclear. Changes in neuronal morphology, in particular axonal varicosity formation, seen after LI, are an example of a specific structural change, which is a likely substrate for electrophysiological changes. Axonal varicosities are identified as multiple swellings or "beading" occurring at regular intervals along an affected axon. Confocal microscopy of varicosities shows disruption of the cytoskeleton with clustering of mitochondria, blockade of fast axonal flow (FAF), and decreased MMP, which have been described.[67,74] Varicosity formation occurs following various stimuli to nerves including mechanical stress, hypoxia, and, most relevant to LI, application of reactive oxygen species such as hydrogen

Table 3. Animal Studies of Effects of All Wavelengths of Laser Irradiation on Noxiously Evoked Stimuli

Study	*Animal and nerve*	*λ (nm), beam mode, power, LI duration*	*Noxious stimulus*	*Site of measurement*	*CAP/SSEP response*
Mezawa et al.[71]	Cat lingual nerve (*in vivo*) $n = 11$	904, P 2 W 3040 Hz; pulse width 200 ns	Heat 30 sec to tongue exp 1: 1 min exp 2: 3 min exp 3: 5 min exp 4: 10 min	Single fiber discharge in nociceptors in tongue	Exp 1: minimal change exp 2: inhibition exp 3: inhibition exp 4: inhibition
Jarvis et al.[60]	Rabbit corneal nociceptors $n = 20$	632.5, P 5 mW; 5 min pulse width 0–1,800 sec 4 mm diam.	Mechanical, chemical heat	Single fiber discharge in excised cornea Aδ fibers and mechano-receptors	No change after 120 min
Shimoyama et al.[62]	Rat dorsal horn neurons $n = 14$ (*in vivo*)	632.8, cw 8.5 mW 30 min transcutaneous LI	Subcutaneous injection of formalin to skin of hind paw - innervated by peroneal nerve	Extra-cellularly recorded single fiber discharge in neurons of the associated lumbosacral spinal cord, recorded	Inhibition
Wakabayashi et al.[25]	Rat mandibular branch of trigeminal nerve $n = 12$ (*in vivo*)	830, cw 350 mW 2 min LI, to lower incisor 10 mm above surface beam diam: 3 mm	Electrical stimulation of tooth pulp of incisor	Ipsilateral trigeminal nucleus caudal neurons, recorded extracellularly	Inhibition of C fiber EP spike activity; no change in Aδ fibre (persisted for 15 min after LI) $p < 0.005$
Kasai et al.[72]	Rabbit sural nerve $n = 7$ (*in vivo*)	632.8, P 1 mW nerve 100 Hz	Pinch to hind paw	Exposed sural nerve proximal to LI	Inhibition of evoked and spontaneous neural discharge $p < 0.01$

Sato et al.[64]	Rat saphenous nerve (*in vivo*)	830, cw 40 mW LI to exposed nerve or skin overlying nerve	Turpentine injection to paw	L4 nerve root	Exp 1: 30 sec no change exp 2: 60 sec no change exp 3: 180 sec inhibition slow component, $p < 0.05$; no change in Aβ fibers inhibition
Tsuchiya et al.[65]	Rat saphenous nerve (*in vivo*) $n = 12$ $n = 7$ (Rx'd with capsaicin)	830, cw 40 mW LI to exposed saphenous nerve PD: 1 W/cm^2 3 min beam diam: 2 mm	Pinch heat cold turpentine injection to paw	Neuronal discharge in ipsilateral dorsal horn	Decreased discharge of nociceptors (by ~30%) exp 1: pinch; $p < 0.01$ exp 2: heat; $p < 0.01$ exp 3: cold; $p < 0.01$ exp 4: inj. turpentine $p < 0.01$ exp 5: brush; no change exp 6. In capsaicin Rx'd rats – no change
Jimbo et al.[66]	Mouse DRG neurons	830, cw 16.2 mW ED: 1 J/cm^2 1 min LI to cultured DRG to cell process before BK application area irrad: 75 μm	Bradykinin – topical application to axon	Cell body of neuron	Inhibition 2 min after LI
Orchardson et al.[45]	Ferret lingual nerve (*in vivo*)	632.8 ~1 mW 60 s LI to exposed dentine in canine teeth	Mechanical	Intradental nerve responses	No inhibition

cw, continuous wave; ED, energy density; EPs, evoked potentials; P, pulsed; PD, power density; BK, bradykinin.

peroxide. Such changes would have a profound effect on nerve conduction and, because they appear to be specific for small diameter fibers, Aδ and C nociceptors, are directly relevant to pain relief.

Support for the relationship between varicosity formation and functional neural impairment and establishing a model for LI effects, is provided by the study by Tanelian and Markin, in which application of substance P induced varicosity formation in DRG neurons.[91] The authors proposed a biomathematical model of conduction block in the presence of varicosity formation to explain the biophysical consequences of such morphological changes in DRG neurons. They also proposed that varicosity formation was important in physiological nociceptive signalling and in the development of pain "memory". Similar neuritic varicosities in central nervous system (CNS) neurons following H_2O_2 exposure have been demonstrated in an "oxidative stress" model.[92] As LI-induced ROS formation in mitochondria is postulated to be a mechanism of laser energy transduction in cells,[93] which would have a similar effect as H_2O_2 did in the Roediger and Armati study,[92] this provides a mechanism by which LI results in conduction block. Varicosity formation also occurs following local anaesthetic application to DRG neurons,[94,95] and may have relevance in understanding LI-induced pain relief.

It is significant that varicosities result from blockade of FAF, which is associated with disruption of microtubules and the resulting block of anterograde transport of ATP-rich mitochondria. Interruption of FAF reduces the availability of ATP necessary for microtubule polymerization and maintenance, and maintenance of the resting potential. The ATPase, Na^+-K^+-ATPase, the enzyme responsible for the generation of action potentials, which requires ATP for function, is inhibited by high-dose LI.[73] Hence reduced availability of ATP following LI would result in failure of generation of action potentials and disruption of nerve conduction. The report by Miura and Kawatani, showing that 83-nm LI causes depolarization of rat nodose ganglion neurons by disruption of sodium channels, in a dose-dependent manner,[63] provides additional evidence of the importance of Na^+-K^+-ATPase in nerve function and its potential role in LI-induced inhibition of nerve conduction. In addition, as peripheral nervous system neurons have axons up to one meter in length in humans, they may be uniquely vulnerable to disruption of FAF compared with compact cells, such as fibroblasts, as their function relies on FAF along the cytoskeleton for transport of ATP-rich mitochondria from the neuronal cell body where synthesis of ATP activity occurs. Therefore, reduced axonal ATP provides a mechanism for LI-induced pleiomorphic, inhibitory effects, particularly on nociceptor responses.

Release of serotonin in the CNS is also postulated as a mechanism for pain relief. This was demonstrated by increased levels of urinary excretion of the serotonin byproduct, 5 hydroxyindoleacetic acid (5HIAA), following LI to peripheral nerves.[96] As low serotonin levels are associated with chronic pain,[97] increase in excretion of 5HIAA, following LLLT for chronic pain, suggests a significant CNS response mediated by LI to nerves, although whether this is a cause or effect is not clear.

Although this review identified a large number of studies reporting decreased neural function, there were a small number of animal studies using visible LI, which demonstrated increased CAP amplitude.[57,58,61] In two studies, LI was applied transcutaneously to rat sciatic nerve *in vivo* and in the third, to rat sympathetic ganglion neurons *in vitro*. The authors postulated that LI caused an increase in ATP with subsequent hyperpolarization of the nerve, which in turn led to increased amplitude of the action potential. In light of the remainder of the literature, the effects noted by Nissan et al.,[56] Rochkind et al.,[57] and Shimoyama et al. [61] need to be reconciled, but may be the result of parameters or methodologies not originally reported, including a biphasic response, not yet identified in peripheral nerve models.[98]

The inhibitory findings in this review represent an alternate perspective on the effects of LI in biological systems. Previous research has been oriented to laser-induced stimulation, rather than inhibition, as the intended and desirable outcome, and the biphasic response of biological systems to LI is widely recognized.[98] Although inhibitory effects in compact cells such as fibroblasts are well documented,[99,100] these are undesirable, especially in wound healing, which dominated early laser research.[101] In the context of pain relief, we propose a causal relationship between LI-induced impairment of neural function and pain relief, suggesting a positive aspect to inhibition.[15,26,74,102]

Poor reporting of parameters and the small number of studies using different experimental models makes pooling of data to guide clinical application unhelpful and potentially misleading. Although this limits extrapolation of the data to clinical settings, this review does establish potential lines of investigation to further explore the role of laser therapy in neural inhibition and pain relief.

Conclusion

This systematic review provides evidence that visible and IR LI cause neural impairment, in particular in small diameter Aδ and C fibers, which convey nociceptive stimuli, so relevant to pain. Disruption of the cytoskeleton, decreased ATP availability, and impaired conduction in nociceptors, may therefore underpin the pleiomorphic inhibitory effects of LI in a diverse range of nerve functions. Lack of complete reporting of the parameters limited comparison of studies and aggregation of data. Nevertheless, the evidence supports the view that neural inhibition is a plausible mechanism for the relief of acute and chronic pain with LLLT.

Acknowledgments

We acknowledge the contribution of Brigid Ryan, the Centre for Physiotherapy Research, School of Physiotherapy, University of Otago, for assistance with research and proofreading the manuscript.

Author Disclosure Statement

No competing financial interests exist

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