

# Therapeutic Laser in Veterinary Medicine



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## KEYWORDS

- Laser therapy • Therapeutic laser • Photobiomodulation • Veterinary laser treatment

## KEY POINTS

- Laser therapy is an increasingly studied modality that can be a valuable tool for veterinary practitioners to successfully treat conditions whether in a rehabilitation clinic or in a general practice.
- Understanding the basics of light penetration into tissue allows evaluation of the correct dosage to deliver for the appropriate condition, as well as for a particular patient, based on physical properties.
- Photobiomodulation has several potential benefits and using this technology in a systematic way may allow for the discovery of other applications.
- New applications are currently being studied for some of the most challenging health conditions and this field will continue to grow as we learn more.
- Additional clinical studies are still needed and collaboration is highly encouraged for all practitioners using this technology.

Laser therapy is rapidly becoming a modality that is used in a variety of conditions in veterinary medicine. It is estimated that close to 20% of veterinary hospitals in North America are using a therapeutic laser in their practice. Although lasers have been used for many years, it has been only in the past 5 or 6 years that use of laser therapy has become so widespread. The main reasons for this recent change are as follows: an increased awareness and deployment of veterinary rehabilitation services, availability of educational resources on therapy lasers, and the development of products and protocols that have resulted in more consistent clinical outcomes. Because laser therapy is a noninvasive, drug-free treatment option, many clients are happy with a nonpharmacologic treatment option.

Research in the area of photobiomodulation is continuing to increase. Many studies are now focused on particular conditions with translational studies from the laboratory to the clinic. Understanding the basics will allow the therapist to

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accurately prescribe this modality for appropriate conditions in the practice whether it be the main treatment option or as an important adjunctive to other treatments.

## THE BASICS

When laser light is absorbed by a chromophore, a biochemical change can occur. There are several examples in nature where this happens, including photosynthesis or the production of vitamin D via conversion by sunlight. Laser therapy or photobiomodulation, the scientific term for this phenomenon is an example of a photochemical process in which light from a laser, or other light source, interacts with cells and causes stimulation or other biochemical change. The term photobiomodulation is most appropriate, as some biochemical events are upregulated and others can be downregulated. Other terms that have been used are cold laser therapy (not accurate, as there is often heat produced during clinical treatments), low-level laser therapy, low light therapy, or nonablative laser therapy, which separates this treatment from more invasive laser surgical procedures. There are many published studies regarding photobiomodulation. A large number of these studies have been performed on cells in vitro. There are excellent published studies on light's effects on various types of cells. Increases in angiogenesis,<sup>1,2</sup> neurite extension,<sup>3</sup> normalization of ion channels,<sup>4</sup> stabilization of the cellular membrane,<sup>5</sup> and a host of other cellular changes have been investigated and published.

The mechanism of action associated with photobiomodulation is often still questioned among scientists in the field. There are most likely several mechanisms of action depending on the target and the type of cell being modulated. The most published and recognized mechanism is that of the cytochrome c system, which is found in the inner cell membrane in the mitochondria and acts as a photoreceptor. Cytochrome c absorbs light from 500 to 1100 nm due to specific properties of this large molecule.<sup>6</sup> After laser light is absorbed by cytochrome c, it is excited and breaks bonds with nitric oxide (NO). This action allows bonding with oxygen to become more prevalent and cytochrome c oxidase to be produced at an optimal rate. Cytochrome c oxidase is critical to the formation of ATP. ATP is essential for energy production in the cell and results in many favorable biologic responses or secondary mechanisms, including reduction of pain and inflammation, and tissue healing.

## REDUCING PAIN

There have been extensive studies evaluating various mechanisms of photobiomodulation that may result in pain relief.<sup>7,8</sup> On laser interaction with cells, the following processes may occur:

- Increase in serotonin (5-HT) levels<sup>9-11</sup>
- Increase in beta endorphins,<sup>12-14</sup> whose reception reduces the sensation of pain.
- Increase in NO,<sup>15</sup> which has an effect on vasodilatation and may enhance oxygen delivery.
- Decreases bradykinins<sup>16</sup>; bradykinins normally induce pain sensation by stimulating nociceptive afferent nerves
- Normalization of ion channels<sup>4,17</sup>
- Block depolarization of C-fiber afferent nerves<sup>18</sup>
- Increase nerve cell action potential<sup>19</sup>
- Improve axonal sprouting and nerve cell regeneration<sup>3,20-22</sup>

## REDUCING INFLAMMATION

In addition to the previously described mechanisms for reducing pain, laser treatments may reduce inflammation. The following actions may produce key elements that aid in the reduction of edema and inflammation. The following processes may be enhanced:

- ATP production<sup>23,24</sup>
- Stimulation of vasodilatation by induction of NO<sup>25</sup>
- Reduction of interleukin-1<sup>26</sup>
- Stabilization of cellular membranes<sup>5</sup>
- Acceleration of leukocyte activity<sup>27</sup>
- Decrease in prostaglandin, synthesis<sup>28,29</sup>
- Lymphocyte response<sup>30</sup>
- Angiogenesis<sup>1,2</sup>
- Superoxide dismutase (SOD) levels<sup>31,32</sup>

## PROMOTING HEALING

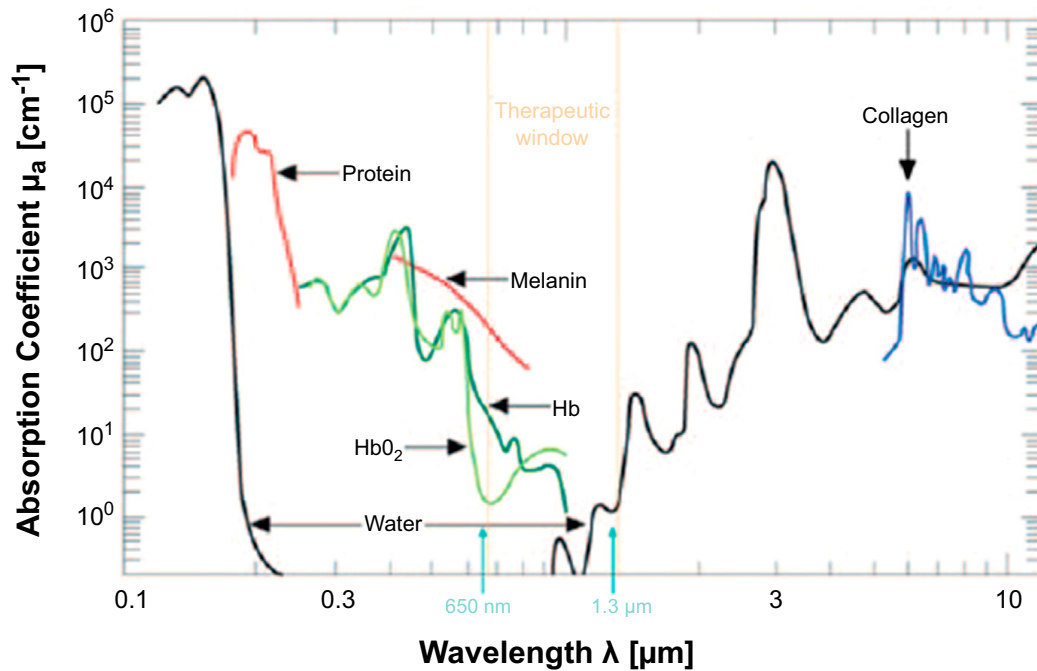
Wound healing is the area in which most of the traditional laser therapeutic studies have been completed. The results of these studies have been very encouraging and the mechanisms of tissue healing are important for other injuries, such as tears and contusions of muscles, tendons, and ligaments, as many of the same mechanisms are needed to promote healing in all tissues. The following is a list of important physiologic changes with laser treatment:

- Enhanced leukocyte infiltration<sup>30</sup>
- Increased macrophage activity<sup>33-35</sup>
- Increased neovascularization<sup>36</sup>
- Increased fibroblast proliferation<sup>37,38</sup>
- Keratinocyte proliferation<sup>39</sup>
- Early epithelialization<sup>40</sup>
- Increased growth factors<sup>41,42</sup>
- Greater wound tensile strength<sup>43</sup>

## HOW DOES LIGHT PENETRATE? WHAT DOSAGES ARE NEEDED?

Wavelengths in the range from the blue (400 nm) to the mid infrared (1100 nm) can result in a photochemical change in cells.<sup>6</sup> Light-tissue interaction is critical to understand how light penetrates biologic tissue to deliver the appropriate amount of light to the target tissue. When reviewing published studies, you should note whether the study was done in vivo or in vitro. Also notice the type and size of the animal used in the study. Dosages used in culture will be vastly different from those used to treat a laboratory rodent. Dosages needed in a clinical environment also differ regarding patient size, with much greater doses needed for treating a Siberian husky compared to a feline patient.

Depth of penetration is one of the most critical elements of laser treatment. When light interacts with biological tissue, it is absorbed, scattered (including reflection), and/or transmitted. Wavelengths from 600 nm (red end of the spectrum) to 1100 nm (near infrared end of the spectrum) are in the optimal range for penetrating into tissue (**Fig. 1**). This range of wavelengths is often referred to as the “therapeutic window” for light and laser applications. Although these wavelengths are able to penetrate, each wavelength has unique properties and each will penetrate to different depths. When white light is placed on tissue, like a flashlight in your mouth, we will see red light



**Fig. 1.** The wavelength of the photons is important in laser therapy. Various substances preferentially absorb laser light at different wavelengths. (From Millis DL, Gross Saunders D. Laser therapy in canine rehabilitation. In: Millis DL, Levine D, editors. Canine rehabilitation and physical therapy. Philadelphia: Elsevier; 2014. p. 361 with permission.)

coming through because the blue and, to some extent, the red components are absorbed, mostly by hemoglobin. A general rule is that longer wavelengths penetrate deeper into tissue.

The major chromophores that absorb light and prevent light penetration to target tissues are melanin, hemoglobin, and water. Melanin has a very high absorption, so dark skin absorbs more light, especially for wavelengths less than 830 nm. Wavelengths longer than 1300 nm absorb strongly in water and therefore penetration is difficult. Light from longer-wavelength lasers, such as the CO<sub>2</sub> laser that operates at 10,600 nm, is absorbed strongly by water and is consequently used for surgical applications.<sup>44</sup>

The important parameter for a therapy laser system is to have the appropriate wavelength to allow penetration to deep tissue. Wavelengths longer than 800 nm can typically achieve appropriate depths to treat most musculoskeletal conditions. When dealing with wounds or more superficial conditions, shorter wavelengths, such as 635 nm, can be used effectively, because penetration is less important.

A recent nerve repair study demonstrated that 2.45% of the initial light at 980 nm penetrated to the peroneal nerve on an anesthetized large New Zealand white rabbit, through approximately 3 cm of tissue. The laser was delivered directly to the skin and a specialty power meter was inserted under the muscle directly on top of the nerve. The percentage of light penetrating to the nerve was constant with increased laser power. This experiment also yielded a similar percentage of transmitted light when using 810-nm or 980-nm light.<sup>22</sup>

Because light from all wavelengths has a measurable amount of scatter, absorption, or transmission, the more power, or the greater number of photons delivered, the greater depth of penetration will be achieved as a function of time. For example, assume that 2.5% of the initial light delivered to the skin reaches the hip of a small dog. Using a 300-mW output laser, 7.5 mW of light will reach the joint space, or just

0.0075 J per second of treatment time. Using a higher-power laser will result in proportionally higher energy delivered to the joint. Lower-powered lasers must be used for longer times to achieve a large enough dose to be effective. It has been shown that extremely low exposures, less than  $0.100 \text{ mW/cm}^2$ , even when exposed for a long period of time, have no measurable results.<sup>45</sup>

Dosage can be expressed only as the amount of energy delivered to a certain area on the surface. Penetration work using cadavers and laboratory animals, as well as extrapolation from tissue studies has increased our understanding of the amount of light delivered to various target tissue depths. Dosages from  $2$  to  $20 \text{ J/cm}^2$  applied to the surface appear to be an appropriate range for photobiomodulation. The patient's size, body type, coat color, skin color, coat length, and the depth of the condition are the important parameters needed to calculate the correct dosage. The larger the dog, the larger the dosage needed.

The treatment of most deep musculoskeletal conditions for a medium-size dog requires  $4$  to  $8 \text{ J/cm}^2$ . If the dog is thin, clipped, and has a light-colored coat and skin, the dosage may be at the lower end at  $4 \text{ J/cm}^2$ . Larger body types require higher dosages because there is more tissue to penetrate through. When treating a surface contusion,  $2$  to  $3 \text{ J/cm}^2$  is an adequate dose because penetration is not as essential due to the superficial nature of the injury.

## APPLICATIONS FOR LASER THERAPY

### *Rehabilitation Applications*

Lasers are very commonly found in many rehabilitation practices. They are used as an integral part of rehabilitation protocols. It is important to use laser therapy appropriately in conjunction with surgical interventions, other modalities, exercise, massage, and pharmacologic options. Often the laser gives patients enough comfort to allow patients to initiate or increase certain exercise protocols, such as increasing range of motion of a stiff joint. Here are some common rehabilitation applications:

- Postsurgical treatment: edema control and healing
- Nonoperative muscle, ligament, tendon injury: pain management and reducing inflammation, potential improved healing depending on the size and nature of the injury (Fig. 2)
- Muscle, ligament, tendon strains and sprains: reduction of pain and inflammation, improved healing times
- Nerve damage: nerve regrowth, pain management
- Arthritis: reduction of pain and inflammation



**Fig. 2.** Laser treatment of a dog with early fibrotic myopathy of the inner thigh muscles.

### ***General Practice Applications***

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- Otitis: an adjunctive therapy used for reducing inflammation in the ear, possibly allowing for better penetration of medication and better compliance
- Lick granulomas: treatment may improve healing rates, as well as remove the irritation leading to less self-trauma. Treat with higher dosages than a standard wound. The suggested dosage should be 15 to 20 J/cm<sup>2</sup>
- Postsurgical incisions: treatment for pain as well as healing, less scarring of incisions
- Wounds: improved healing times and less scarring
- Arthritis: management of pain and reduce inflammation, routine maintenance is required
- Inflammatory conditions: lessen pain, and reduce edema

### **TREATMENT TECHNIQUES**

Treatment techniques vary depending on the condition being treated and the type of laser being used. As previously discussed regarding dosing, when treating a condition in deeper tissues, a greater dose will be required.

Prepare the surface. Make sure the hair/skin is clean. Clipping the hair is optimal for the best penetration of light into the tissue. If the hair is not clipped, be sure to increase the dosage to allow enough light to penetrate into the tissue, although studies are needed to determine the amount of increased dose. Hair and skin color are important because light of shorter wavelengths is absorbed more by melanin. Some commercially available therapeutic lasers vary wavelengths based on coat and skin color. If wavelengths less than 900 nm are used, be cautious not to overheat the coat or skin if higher power (Watts) is used. Lower the output power and treat with a greater dosage to deliver enough energy to the targeted tissue. If an overweight patient is being treated in an area with increased tissue thickness, be sure to increase the dosage because more light will be absorbed by tissues.

It is often difficult to isolate a very specific afflicted area, and often conditions will have multiple involved muscles or joints contributing to the pain. It is wise to have a broad area of treatment. Cover a large comprehensive area with the appropriate dosage. This enables the affected area and satellite areas of pain to be effectively treated. Treating a comprehensive area will ensure more consistent outcomes, as well as easier protocols for technicians to follow.

When treating there are 2 treatment techniques. Lower-power laser systems, less than 1 Watt, generally use a point-to-point method of treatment. Multiple discrete points are treated in the desired area. The dosage at each spot is delivered in approximately 30 seconds depending on the power and spot size. This method can be very time consuming when treating a large area and does not lend itself well to efficient treatment of multiple areas.

The second technique is to move the laser in a scanning fashion while treating. This method is used when using a higher-output powered laser. The dosage is delivered over a very large area by scanning the laser over the area. This technique allows for comprehensive coverage allowing for multiple areas to be treated. Most higher-power lasers have larger spot sizes, making the power density safer. Caution should always be exercised by realizing the power density and ensure the laser handpiece is moving during treatment.

When treating, the laser can also be applied in a contact or an off-contact mode. By using on-contact mode, the soft tissues may be manipulated while delivering the treatment. This allows deeper treatment because of tissue compression, and, if desired, a

gentle massage is administered while delivering the light. Patients seem to enjoy this contact method. When touching the surface is undesirable because of excessive pain, a bony prominence, or a wound, use an off-contact method. In this case, the laser handpiece is kept above the surface during treatment.

Positioning the patient is important before administration of the therapy. Make sure the patient is comfortable and that you have access to the treatment area. When possible, it is also good technique to try to put the body part being treated through some limited, passive range of motion. Be as comprehensive as possible, treating from as many sides as possible.

The frequency of the treatments somewhat depends on the nature of the condition and access to the patient. It is acceptable to treat every day. When treating an acute injury, treatment every day is ideal. If you cannot have access to the patient every day, treat as often as you can see the patient. For more chronic conditions, initial treatments can be administered every other day. The initial phase of treatments should be done until a noticeable result is seen. This change is typically achieved earlier for acute conditions (2 or 3 treatments) than with more chronic conditions (4–6 treatments). The next treatment phase can space treatments out to 2 or 3 treatments per week until healing or the desired effect is achieved. Treatment is then given on an as-needed maintenance schedule depending on the condition of the patient.

### **PRACTICE INTEGRATION**

Adding any new treatment option into a practice can be an exciting and rewarding experience, but also may cause reservations among some staff members. Staff members should be educated that there is scientific evidence behind the use of therapeutic lasers. Getting the staff to confidently use and prescribe laser therapy is key to fully integrating this modality into the practice. After each person has treated a few cases, confidence increases and it may be one of the most popular treatment options.

An easy way to start integrating laser therapy into your practice is to treat all post-surgical incisions. Laser therapy is indicated for pain relief and wound healing. Because of the superficial nature of this wound, the dosage will be low (typically 2–4 J/cm<sup>2</sup>), so the treatment times will be only a few minutes. The treatments can be done while in the operating room or shortly after the surgery. Scheduling is easy because it can be included after every surgery performed in the practice. The typical fee for this service commonly ranges from \$10 to \$25, but generally the surgical fees are increased by this amount to integrate this new high technology for healing and pain management.

This integration into surgical procedures allows the staff to become familiar with the operation of the laser and increase their confidence level. The next step is to incorporate it into everyday treatments for conditions requiring the reduction of pain and inflammation, as well as healing. Education of all the veterinarians in the practice is key so they are aware of the large number of conditions in which the laser is a treatment option.

Many practices have designated 1 or 2 as laser specialists in the practice. These staff members, usually skilled technicians, can be the primary operators of the therapeutic laser in the clinic. The veterinarians can prescribe laser therapy treatments and the laser technicians can consult and perform the therapy for conditions seen in the general practice. This approach makes scheduling easy and the procedures are efficient for the entire practice.

In a rehabilitation practice, laser therapy is generally used in conjunction with other rehabilitation modalities, such as electrical stimulation. It is used postoperatively not

only for pain and wound healing, but also for reducing edema and increasing range of motion. Laser therapy allows the physical therapist to start exercise earlier if the pain level is decreased and the patient is comfortable. Almost every rehabilitation case may be a candidate for using the laser in some manner. Pricing is usually incorporated into a rehabilitation visit. If laser is an add-on modality, prices may range from \$30 to \$60 per visit. If multiple body parts are treated, a nominal charge may be added on a per-area basis.

In general, an arthritis management program is an excellent addition to any practice. When incorporating physical rehabilitation into an arthritis management program, including laser therapy, results are generally enhanced. Laser may be especially useful to reduce inflammation and manage the pain associated with osteoarthritis.

### CLIENT CONSULTS

Laser therapy can often be a difficult treatment modality to explain to a client. Many people have experience themselves with a laser treatment, either for a cosmetic procedure, such as hair removal, or for a surgical procedure, such as corrective eye surgery. It is important to explain the difference that therapeutic laser treatments are nonablative, unlike some of the more invasive laser procedures available in human medicine. During a therapeutic laser treatment, there may be some mild heating but when used appropriately, it does not cause any pain and often can be quite soothing to the animal when used correctly. The Food and Drug Administration has cleared laser therapeutic devices for the indications of wound healing, pain reduction, reduction of inflammation, and increased microcirculation. It is also good to explain that this modality is being used worldwide for many conditions and most professional sports teams are using laser therapy in the locker room, keeping players in the game.

The following is a good layman's explanation of how therapeutic lasers work: The light generated by the laser is activating the body's cells to produce energy. When the cells are injured the energy production in a cell is impaired and often cannot make energy at an optimal rate, which is necessary for tissue to heal. The laser light stimulates this process, which causes the cell to produce more energy leading to faster healing.

Setting expectations of the outcomes is important. For acute conditions, the pain and inflammation may be reduced even after the initial treatment; however, more treatments are usually needed for the best outcomes. For more chronic conditions, such as arthritis, prepare the owner that improvements in their pet's condition may not be noticed until the third or fourth treatment and 10 or more treatment sessions may be needed. In a case like arthritis, the laser is only helping to control inflammation. It will not resolve the condition, but it can be a part of the long-term treatment plan in managing the disease. It is important to explain to clients that routine treatments may be needed to control inflammation and pain. The frequency of these maintenance treatments depends on the pain level and activity level of the animal. Typically treatments may be required every 6 to 8 weeks.

### PRECAUTIONS

1. Use protective eye wear (**Fig. 3**). Laser goggles should be matched with the particular laser equipment. Because the eye wear is wavelength-dependent, be sure to use the goggles provided with the laser being used. Specific laser protective eyewear for animals also is available. The patient's eyes can also be directed away from the treatment area or shielded with a dark cloth.





**Fig. 3.** Protective eyewear for laser use should be specific for the laser used. (From Millis DL, Gross Saunders D. Laser therapy in canine rehabilitation. In: Millis DL, Levine D, editors. Canine rehabilitation and physical therapy. Philadelphia: Elsevier; 2014. p. 359–80; with permission.)

2. Use caution when treating dark-colored skin and/or hair, or over tattoos, because more light will be absorbed and potentially heat the tissues more. Use your hand to monitor the skin temperature throughout the treatment, move the laser when using a high-power laser, and if the patient seems uncomfortable, pause the treatment.
3. Do not direct the laser into the eye.
4. Treatment is not recommended over open fontanelles, a pregnant uterus, malignancies, or for patients on photosensitive medications.
5. Remove any jewelry, leashes, and so forth.
6. Use caution around metal surfaces because light will reflect. Cover metal examination tables or other shiny objects.

## SUMMARY

Laser therapy is an increasingly studied modality that can be a valuable tool for veterinary practitioners to successfully treat conditions, whether in a rehabilitation clinic or in a general practice. Mechanisms of action have been studied and identified for the reduction of pain and inflammation, as well as the healing of tissue. Understanding the basics of light penetration into tissue allows evaluation of the correct dosage to deliver for the appropriate condition, as well as for a particular patient based on physical properties. Photobiomodulation has several potential benefits and using this technology in a systematic way may allow for the discovery of other applications. New applications are currently being studied for some of the most challenging health conditions and this field will continue to grow as we learn more. Additional clinical studies are needed and collaboration is highly encouraged for all practitioners using this technology. There are a growing number of educational resources about therapeutic lasers and recent advances.

## REFERENCES

1. Mirsky N, Krispel Y, Shoshany Y, et al. Promotion of angiogenesis by low energy laser irradiation. *Antioxid Redox Signal* 2002;4(5):785–90.
2. Bibikova A, Belkin V, Oron U. Enhancement of angiogenesis in regenerating gastrocnemius muscle of the toad (*Bufo viridis*) by low-energy laser irradiation. *Anat Embryol (Berl)* 1994;190:597–602.

3. Anders JJ, Borke RC, Woolery SK, et al. Low power laser irradiation alters the rate of regeneration of the rat facial nerve. *Lasers Surg Med* 1993;13(1):72–82.
4. Granados-Soto V, Arguelles CF, Alvarez-Leefmans FJ. Peripheral and central antinociceptive action of Na<sup>+</sup>-K<sup>+</sup>-2Cl<sup>-</sup> co-transporter blockers on formalin-induced nociception in rats. *Pain* 2005;114(1–2):231–8.
5. Greco M, Vacca RA, Moro L, et al. Helium-neon laser irradiation of hepatocytes can trigger increase of the mitochondrial membrane potential and can stimulate c-fos expression in a Ca<sup>2+</sup>-dependent manner. *Lasers Surg Med* 2001;29(5):433–41.
6. Karu T. Mechanisms of interaction of monochromatic visible light with cells. *Proc SPIE* 1995;2630:2–9.
7. Tuner J, Hode L. The laser therapy handbook. Grangeberg (Sweden): Prima Books AB; 2007. p. 68.
8. Pozza D, Fregapani P, Weber J, et al. Analgesic action of laser therapy (LLLT) in an animal model. *Med Oral Patol Oral Cir Bucal* 2008;13(10):E648–52.
9. Cassone MC, Lombard A, Rossetti V, et al. Effect of in vivo HeNe laser irradiation on biogenic amine levels in rat brains. *J Photochem Photobiol B, Biol* 1993;18(2–3):291–4.
10. Walker JB. Relief from chronic pain by low-power laser irradiation. *Neurosci Lett* 1983;43:339–44.
11. Lombard A, Rossetti V, Cassone MC. Neurotransmitter content and enzyme activity variations in rat brain following in vivo HeNe laser irradiation. Proceedings, round table on basic and applied research on photobiology and photomedicine. Bari, Italy, November 10–11, 1990.
12. Montesinos M. Experimental effects of low power laser in enkephalin and endorphin synthesis. *LASER J Eur Med Laser Assoc* 1988;1(3):2–7.
13. Labajos M. Beta-endorphin levels modification after GaAs and HeNe laser irradiation on the rabbit. Comparative study. *Invest Clin* 1988;1-2:6–8.
14. Laakso EL, Cramond T, Richardson C, et al. ACTH and beta-endorphin levels in response to low level laser therapy for myofascial trigger points. *Laser Ther* 1994;6(3):133–42.
15. Mrowiec J. Analgesic effect of low-power infrared laser radiation in rats. *Proc SPIE* 1997;3198:83–9.
16. Jimbo K, Noda K, Suzuki K, et al. Suppressive effects of low-power laser irradiation on bradykinin evoked action potentials in cultured murine dorsal root ganglion cells. *Neurosci Lett* 1998;240(2):93–6.
17. Friedman H, Lubart R. Nonlinear photobiostimulation: the mechanism of visible and infrared laser-induced stimulation and reduction of neural excitability and growth. *Laser Ther* 1911;3(1):15–8.
18. Wakabayashi H. Effect of irradiation by semiconductor laser on responses evoked in trigeminal caudal neurons by tooth pulp stimulation. *Lasers Surg Med* 1993;13(6):605–10.
19. Cambier D, Blom K, Witvrouw E, et al. The influence of low intensity infrared laser irradiation on conduction characteristics of peripheral nerve: a randomised, controlled, double blind study on the sural nerve. *Lasers Med Sci* 2000;15(3):195–200.
20. Rochkind S, El-Ani D, Nevo Z, et al. Increase of neuronal sprouting and migration using 780nm laser phototherapy as procedure for cell therapy. *Lasers Surg Med* 2009;41:277–81.
21. Byrnes K, Wu X, Waynant R, et al. Low power laser irradiation alters gene expression of olfactory ensheathing cells in vitro. *Lasers Surg Med* 2005;37:161–71.

22. Anders JJ, Moges H, Wu X, et al. In vitro and in vivo optimization of infrared laser treatment for injured peripheral nerves. *Lasers Surg Med* 2014;46:34–5.
23. Mochizuki ON, Kataoka Y, Cui Y. Effects of near-infra-red laser irradiation on adenosine triphosphate and adenosine diphosphate contents in rat brain tissue. *Neurosci Lett* 2002;323(3):207–10.
24. Passarella S, Casamassima E, Molinari S, et al. Increase of proton electrochemical potential and ATP synthesis in rat liver mitochondria irradiated in vitro by helium-neon laser. *FEBS Lett* 1984;175:95–9.
25. Shiva S, Gladwin MT. Shining a light on tissue NO stores: near infrared release of NO from nitrite and nitrosylated hemes. *J Mol Cell Cardiol* 2009;46:1–3.
26. Lopes-Martins RA, Albertini R, Martins PS, et al. Spontaneous effects of low-level laser therapy (650 nm) in acute inflammatory mouse pleurisy induced by carrageenan. *Photomed Laser Surg* 2005;23:377–81.
27. Mester E, Nagylucskay S, Waidelich W, et al. Effects of direct laser radiation on human lymphocytes. *Arch Dermatol Res* 1978;263:241–5.
28. 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(1):29–34.
29. Mizutani K, Musya Y, Wakae K, et al. A clinical study on serum prostaglandin E2 with low-level laser therapy. *Photomed Laser Surg* 2004;22(6):537–9.
30. Karu T. Low-intensity laser light action upon fibroblasts and lymphocytes. In: Ohshiro T, Calderhead RG, editors. *Progress in laser therapy*. Hoboken, NJ: J. Wiley and Sons; 1991. p. 175–80.
31. Lavi R, Shainberg A, Friedmann H, et al. Low energy visible light induces reactive oxygen species generation and stimulates an increase of intracellular calcium concentration in cardiac cells. *J Biol Chem* 2003;278:40917–22.
32. Lubart R, Eichler M, Lavi R, et al. Low-energy laser irradiation promotes cellular redox activity. *Photomed Laser Surg* 2005;23:3–9.
33. Dube A, Bansal H, Gupta PK. Modulation of macrophage structure and function by low level He–Ne laser irradiation. *Photochem Photobiol Sci* 2003;2:851–5.
34. Zeng H, Qin JZ, Xin H, et al. The activating action of low level helium-neon laser irradiation on macrophages in mouse model. *Laser Ther* 1992;4:55–8.
35. Young SR, Dyson M, Bolton P. Effect of light on calcium uptake by macrophages. *Laser Ther* 1990;5:53–7.
36. Maeda T. Histological, thermographic and thermometric study in vivo and excised 830 nm diode laser irradiated rat skin. *Laser Ther* 1990;2(1):32.
37. Vinck EM, Cagnie BJ, Cornelissen MJ, et al. Increased fibroblast proliferation induced by light emitting diode and low power laser irradiation. *Lasers Med Sci* 2003;18:95–9.
38. Hawkins D, Abrahamse H. Effect of multiple exposure of low-level laser therapy on the cellular responses of wounded human skin fibroblasts. *Photomed Laser Surg* 2006;24:705–14.
39. Haas AF, Isseroff RR, Wheeland RG, et al. Low-energy helium-neon laser irradiation increases the motility of cultured human keratinocytes. *J Invest Dermatol* 1990;94:822–6.
40. Bayat M, Vasheghani M, Razavi N, et al. Effect of low-level laser therapy on the healing of second-degree burns in rats: a histological and microbiological study. *J Photochem Photobiol B, Biol* 2005;78(2):171–7.
41. Stein A, Benayahu D, Maltz L, et al. Low-level laser irradiation promotes proliferation and differentiation of human osteoblasts in vitro. *Photomed Laser Surg* 2005;23(2):161–6.

42. Mvula B, Mathope T, Moore T, et al. The effect of low level laser therapy on adult human adipose derived stem cells. *Lasers Med Sci* 2008;23:277–82.
43. Parizotto NA, Baranauskas V. Structural analysis of collagen fibrils after HeNe laser photostimulated regenerating rat tendon. In: 2nd Congress World Association for laser therapy. Proceedings. Kansas City, September 2–5, 1998. p. 66.
44. Hale GM, Querry MR. Optical constants of water in the 200nm to 200 $\mu$ m wavelength region. *Appl Opt* 1973;12:555–63.
45. Karu T, Andreichuck T, Ryabykh T. Suppression of human blood chemiluminescence by diode laser irradiation at wavelengths 660, 820, 880 or 950 nm. *Laser Ther* 1993;5:103.