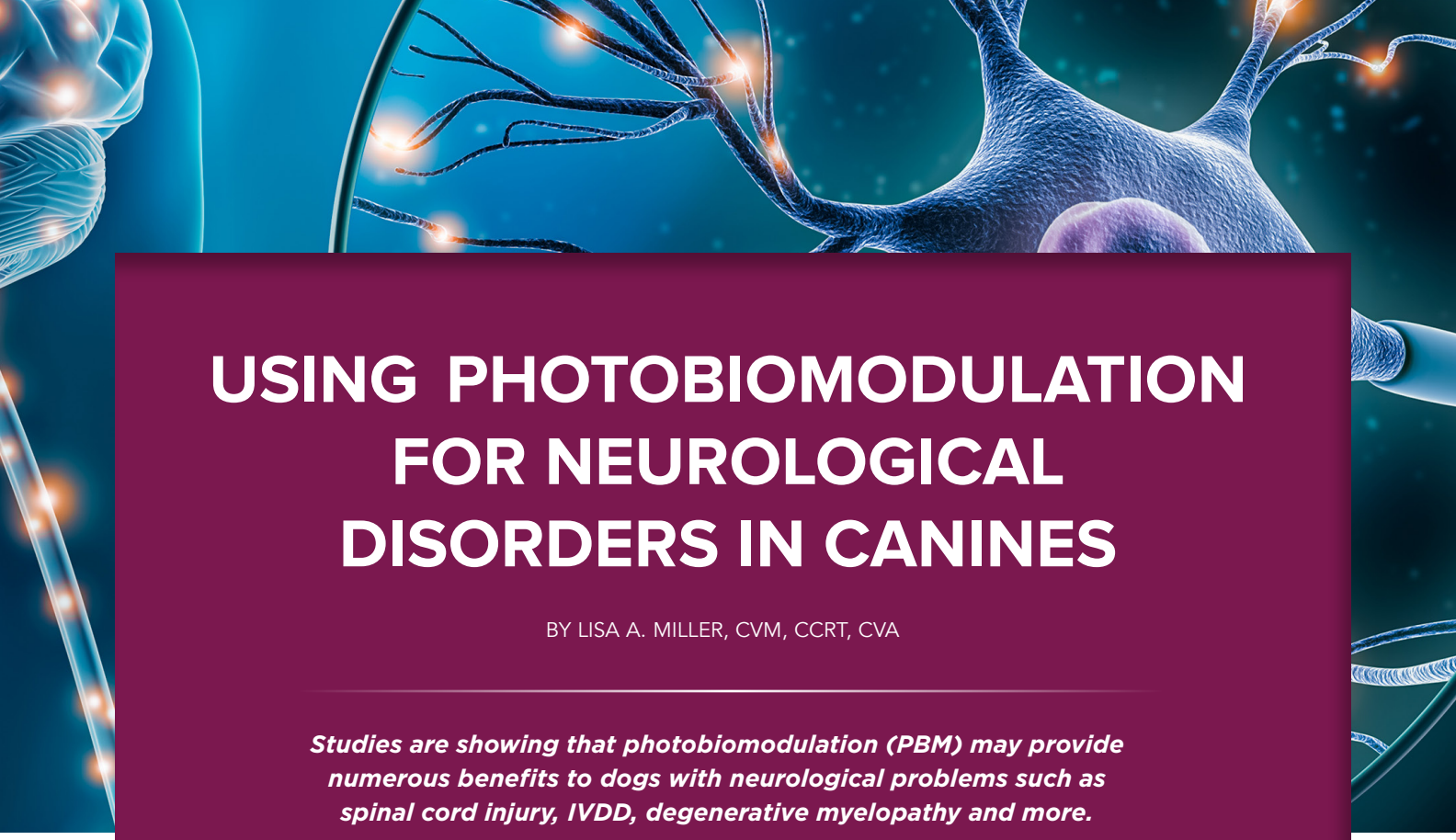


USING PHOTOBIOMODULATION FOR NEUROLOGICAL DISORDERS IN CANINES

BY LISA A. MILLER, CVM, CCRT, CVA

Studies are showing that photobiomodulation (PBM) may provide numerous benefits to dogs with neurological problems such as spinal cord injury, IVDD, degenerative myelopathy and more.

Photobiomodulation (PBM) offers a novel and beneficial approach to treating various neurological disorders in the canine. Preclinical studies indicate that PBM reduces oxidative stress and neuroinflammation, and promotes cellular regeneration. It also modulates pain while optimizing mitochondrial function, oxygen consumption, and blood flow in various injuries and diseases of the peripheral and central nervous systems. Tissues rich in mitochondria, such as the brain, spinal cord, and neurons in peripheral nerve ganglia, respond readily to PBM. This is because the principal chromophore for absorbing the wavelengths of light used in this modality is located within the mitochondrial membrane, resulting in repair and regeneration.[1] This article looks at a range of neurological conditions in the canine, and how PBM can help with treatment.

PERIPHERAL NERVE AND SPINAL CORD INJURY

Peripheral nerve injury results in the loss of associated sensory and motor function. Ensuing degeneration of the axons, and retrograde degeneration of the corresponding neurons of the spinal cord, may be followed by a very slow regeneration. However, total regeneration of the peripheral nerve, even when surgically repaired, does not occur, leading to muscle atrophy. The function of the repaired nerve almost never recovers completely.

The first pioneering report on the use of light for peripheral nerve repair was published by Rochkind,[2] and in the last 20 years, many PBM papers have reported positive effects on peripheral nerve regeneration.[3-9] These studies demonstrated that PBM can accelerate functional recovery, and improve the quality of nerve regeneration after autograft repair of severely injured peripheral nerves.

- One study on the effects of the transected and end-to-end sutured peroneal nerve demonstrated that treatment parameters initially determined using in vitro models should then be translated to in vivo research for clinical practice, taking into account the loss of light as it travels through tissue layers.

- As an example, in vivo transmission of the near infrared light measured in anesthetized rabbits showed that, on average, 2.45% of the light applied to the skin reached the depth of the peroneal nerve. This demonstrates that

much higher output powers are needed at the surface to deliver the appropriate therapeutic dose to the depth of the nerve(s) being treated. An in vivo pilot study was performed to determine the optimal parameters for applying PBM to the skin over the injury/repair site. The investigators demonstrated that PBM at various wavelengths with optimized parameters accelerated nerve regeneration and improved functional recovery.[9]

- Veterinary research offers clinical evidence for the use of PBM in cats, showing that it has analgesic effects on peripheral nerves via the decrease of ascending signals from the spinal cord to the higher central nervous system.[10] Other publications have also documented the use of PBM therapy for peripheral nerve injuries in veterinary patients.[11]

- A study in dogs with severe spinal cord injury (see sidebar on page 12) involved implantation of a segment of peripheral nerve into the injured area, followed by laser irradiation applied to the spinal cord. The results demonstrated diminished glial scar formation, induced axonal sprouting in the injured area, improved weight bearing, and improved locomotion in comparison to transplantation alone.[17] Since this publication, several research groups have demonstrated that transcutaneous PBM improves locomotor function in SCI. Transcutaneously applied PBM, used daily for two weeks to treat the transected or contused spinal cords of rats, promoted regeneration and functional recovery, and suppressed immune cell activation (a potential mediator of secondary injury) and cytokine/chemokine expression.[18]

- Both peripheral nerve and spinal cord injuries can result in neuropathic pain symptoms that may become chronic. Neuropathic pain evolves through various fundamental mechanisms, including abnormal nerve activity, heightened sensitivity in both peripheral nerves and in the central nervous system (CNS), diminished inhibitory control, and abnormal activation of microglia.[19] Evidence suggests that PBM can be effective in decreasing neuropathic pain behavior, and altering the inflammatory process associated with peripheral nerve and spinal cord injuries in animals.

- Studies focusing on various nerve injury models in rats, and treating them with PBM daily to every other day, demonstrated both decreased mechanical allodynia and improved functional recovery.[20-23] One of these studies also examined the activation of macrophages and microglia along ascending somatosensory pathways related to neuropathic pain. Immunohistochemical analysis of macrophage and microglial inflammatory markers showed a shift towards the M1 (pro-inflammatory) phenotype of microglia in injured spinal cord dorsal horn, though not in the PBM treated group, which received treatment in the hind paw, dorsal root ganglia, and the spinal cord regions. In dorsal root ganglion samples, macrophages expressing M2 markers (anti-inflammatory) were significantly increased in the PBM group, but not in the injury or sham groups, indicating that PBM may contribute to resolution of inflammation.

INTERVERTEBRAL DISC DISEASE

One of the most common causes of neuropathic pain and SCI in veterinary medicine is intervertebral disc disease (IVDD). Most of us are familiar with the differences and pathophysiology of Type I versus Type II IVDD; however, either disc extrusion or protrusion can cause varying degrees of SCI and pain. After initial injury, pathologic changes progress, and the ensuing neurodegenerative process contributes to the development of inflammation. This occurs along with a complex cascade of vascular and biochemical events that contribute to secondary SCI and neuronal damage. Even after any sources of spinal cord compression may have been surgically removed, it is important to remember that decreased perfusion and ischemia, as well as secondary oxidative damage, will contribute to the severity of spinal cord injury in these patients. Modalities that promote tissue perfusion[24] are of upmost importance in patients with these injuries.

- Canine models have shown that PBM improved neurologic function after experimentally-induced disc disease, with treated dogs being able to walk within nine to 12 weeks after spinal cord transection and sciatic nerve autograft insertion, compared to a still-paralyzed untreated control group. Histologic analysis of treated dogs revealed that new axons and blood vessels had migrated into the graft.[17]

- Another study examined the use of PBM therapy in non-ambulatory dogs with thoracolumbar IVDD following decompressive surgery, compared to a control group that received hemilaminectomy alone. A significant difference in the median time to ambulation was observed between the two groups.[25] Even though this study demonstrated a positive effect, more information needs to be gathered to optimize the parameters used to treat this condition.

TREATING PERIPHERAL NERVE CONDITIONS AND SPINAL CORD INJURY/IVDD

Recommended parameters for PBM in peripheral nerve injuries and spinal cord injury/IVDD are comparable to those recommended for deep-tissue musculoskeletal dosing (10-20 J/cm^2), scaling up with the size of the patient and depth of target tissues/nerves. Treatment surface areas used for calculating dose should encompass the suspected site(s) of injury as well as the entire nerve tract(s) of the traumatized nerve(s), along with adjacent muscles experiencing associated myofascial pain or spasms.

For the spinal cord specifically, treatment surface areas used for calculating dose should take into consideration a few spinal segments both cranial and caudal to the suspected area of intervertebral disc extrusion or protrusion. If neurological deficits are present in the limbs, treating the remainder of the spine caudally, as well as the descending nerve tracts, is recommended. For lesions in the thoracic or lumbar spine, treatment should be applied on contact directly over the spine, as well as a few inches to either side, aiming toward the spine through the paraspinal musculature. In the neck area, a lateral and ventral approach is recommended to effectively treat the caudal cervical area (***Figure 1***).

Power settings of 3-7W for small to medium patients, 5-11W for medium to large patients, and 7-15W for large to extra-large patients are likely appropriate for most neurological applications involving the peripheral nerves and spinal cord. These doses should be effective and safe for most commercially available laser units, but the practitioner should always confirm the safety specifications with the manufacturer, depending on the optics of their handpiece and the power output of the laser device.

For peripheral nerve injury, treatment should be administered daily for three to five days and then two to three times weekly, if possible, until resolution. Recovery from peripheral nerve injuries is a long, slow process, and treatment with PBM should continue until acceptable function has returned.

For patients with IVDD in which conservative management has been elected, PBM therapy should begin immediately and continue daily, if possible, until significant improvement is seen. At that time, weaning to a transition phase of less-frequent treatment sessions is recommended, to continue until clinical signs resolve. Some patients with chronic IVDD may benefit from continued maintenance therapy once every two to four weeks, as in patients with osteoarthritis.

For patients that have undergone surgery for IVDD, PBM therapy should be started immediately afterwards. Ideally, it should be performed daily for three to five days, if possible, then continued at least two to three times weekly until significant improvement is seen, when the frequency of treatment can be reduced as described previously. As always, an excellent physical rehabilitation program and other supportive care is recommended for neurologic patients.

FIGURE 1 : Applying PBM to the neck area of a canine patient.

- Two more recent studies showed contrasting results. One found no difference in recovery-related variables among dogs that received PBM and physical rehabilitation, compared to those receiving physical rehabilitation with sham PBM.[26] The second report described how including PBM in the rehabilitation protocol during the post-operative period improved patients' neurological status; there was also a shorter mean time to the return of ambulatory ability.[27]

- The three studies above used vastly different parameters, and some were incorrectly or incompletely reported, emphasizing the importance of these factors in the design and interpretation of clinical research involving PBM. While there is a need for further studies in veterinary patients, in both conservative-management and post-surgical-application models, there is certainly enough evidence in the present body of literature to support the use of PBM as an adjunct to current treatment plans for patients with IVDD. It should be noted that whether or not PBM is available, current best practices for both surgical and conservative management should be communicated to owners after examination of the patient.

DEGENERATIVE MYELOPATHY

Canine degenerative myelopathy (DM) shares similarities in cause, clinical signs, and disease progression to some forms of ALS in humans. It is characterized by progressive generalized proprioceptive ataxia of the pelvic limbs, asymmetric upper motor neuron (UMN) paraparesis (Stage I disease), and a lack of paraspinal hyperesthesia. This progresses to lower motor neuron (LMN) and paralysis of the pelvic limbs (Stage II), and eventually the thoracic limbs (Stage III) and brain stem (Stage IV).[36-37]

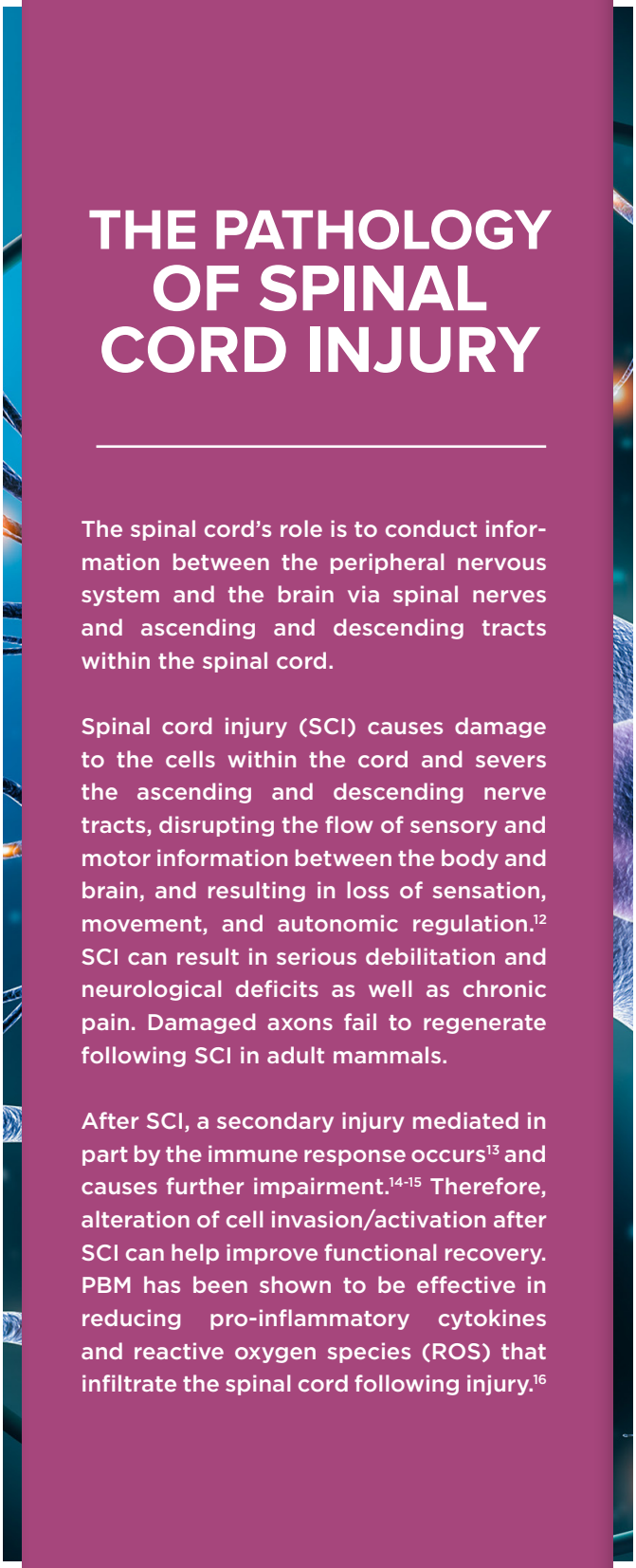
As DM is progressive, incurable, and fatal, the veterinary community looks to novel clinical interventions to improve the overall quality of life of affected patients. Dogs with DM are usually euthanized when they become non-ambulatory and/or incontinent, both of which present challenges to pet owners. Time of progression from Stage I to Stage II is generally six to nine months.[37] Various therapeutic protocols attempt to slow DM's clinical symptom progression, but none have been significantly successful.[38-39] Only daily intensive physiotherapy has demonstrated some benefit as a supportive therapy for DM.[40]

The literature discussed above provides evidence that light can confer specific beneficial effects on the response of cells in the CNS, leading to alteration of both the progression of the injury process and the secondary injury response(s). Numerous studies have suggested that astrocytes and the astrocyte glutamate transporter (GLT-1) may play a role in modifying disease progression and motor neuron (MN) loss in neurodegenerative disease progression.[28-32] Astrocytes can induce MN degeneration through secretion of inflammatory mediators, including nitric oxide and prostaglandin E2.[33-34]

- One published study specifically examined the use of PBM in an SOD1 transgenic mouse model of ALS.[35] This study reported a statistically significant yet short-lived improvement in the group that received laser therapy, suggesting a delay in the onset of motor deficits. However, this beneficial effect was seen in only the early stage of the disease. Other study findings contributed to the authors' conclusion that PBM may have conferred a protective effect by suppressing astrocytes surrounding MNs in the spinal cord.

- Recently, a retrospective study was published that examined the impact on the pathology of canine DM by adding two different doses of PBM to rehabilitation therapy.[41] The authors examined the records of dogs referred for presumed DM to a specialty rehabilitation facility, and screened for patients meeting the study criteria. Qualifying patients were divided into two groups: a lower-dose group and a higher-dose group, based on the PBM protocol used. The time between symptom onset and non-ambulatory paresis or paralysis of dogs in the higher-dose group (31.76±12.53 months) was significantly longer than those of dogs in the lower-dose group (8.79±1.60 months). Similar findings were reported relative to the time between symptom onset and euthanasia. The data showed significantly slower disease progression and longer survival times for patients in the higher-dose group than those in the lower-dose group, or for dogs in published historical data.[38] The authors suggested that the potential beneficial mechanisms of PBM observed in these findings might include a protective effect on the MNs in the spinal cord through astrocyte-neuronal interactions, similar to the studies mentioned above. In addition, they suggested that PBM may act as an aid to therapeutic exercise and the prevention of exercise-induced muscle fatigue and/or damage.

When treating DM, the author strongly recommends all dogs receive weekly to twice-weekly in-clinic rehabilitation therapy, including PBM and other therapeutic exercises as outlined



THE PATHOLOGY OF SPINAL CORD INJURY

The spinal cord's role is to conduct information between the peripheral nervous system and the brain via spinal nerves and ascending and descending tracts within the spinal cord.

Spinal cord injury (SCI) causes damage to the cells within the cord and severs the ascending and descending nerve tracts, disrupting the flow of sensory and motor information between the body and brain, and resulting in loss of sensation, movement, and autonomic regulation.[12] SCI can result in serious debilitation and neurological deficits as well as chronic pain. Damaged axons fail to regenerate following SCI in adult mammals.

After SCI, a secondary injury mediated in part by the immune response occurs[13] and causes further impairment.[14-15] Therefore, alteration of cell invasion/activation after SCI can help improve functional recovery. PBM has been shown to be effective in reducing pro-inflammatory cytokines and reactive oxygen species (ROS) that infiltrate the spinal cord following injury.[16]

by a rehabilitation therapist or practitioner. Supportive care, including the use of assistive devices (such as slings for walking support, and protective foot coverings) are also strongly recommended. If in-clinic rehabilitation is not possible, the primary veterinarian should consult with a rehabilitation-certified practitioner, since DM dogs have extremely finite exercise tolerance. If this tolerance is exceeded, it may take several days to recover and/or the dog may become temporarily worse. Similarly, a rehabilitation practitioner may outline a suitable home exercise program for pet owners.

PBM treatment should be applied with the laser treatment head in contact with the dog's skin, directly over the spinal column, as well as several inches lateral to the right and left sides of the spinal column in the paraspinal musculature, thereby treating the entire thoracic and lumbar spine. For dosimetry consistent with the higher-dose group in the aforementioned retrospective study, the area to be treated as described above should be measured in square centimeters, calculating a target energy density of 15-25 J/cm^2 to obtain the total dose (in Joules) desired (e.g. 500 cm^2 x 20 J/cm^2= 10,000 total Joules). Once the total dose is calculated for the patient, an appropriate treatment power in watts (W) may be selected based on the size of the patient, and the corresponding depth of tissue, scaling up with the patient's body mass. Power should always be adjusted down if the patient is uncomfortable, or if the laser operator feels any excessive thermal buildup in the dog's coat or on the skin.

For any chronic degenerative condition such as DM, treatment should begin with an "induction phase" of initial, more frequent treatment sessions (as described for IVDD). The author recognizes that colleagues will be presented with patients in various stages of disease progression. Subjectively, better results are seen in dogs whose intervention starts earlier. Each patient must be evaluated and treated as an individual. The practitioner is encouraged to set expectations with pet owners that immediate results may not be appreciated, and that a cure is not possible. Once improvement in clinical signs is noted, a "transition phase" of treatment sessions is initiated in which they are decreased to twice weekly, then once weekly, at which a "maintenance phase" is established. These maintenance sessions are more frequent than for pain-related chronic conditions due to the neurodegenerative nature of the disease.

TRANSCRANIAL PBM AND CANINE COGNITIVE DYSFUNCTION SYNDROME (CCDS)

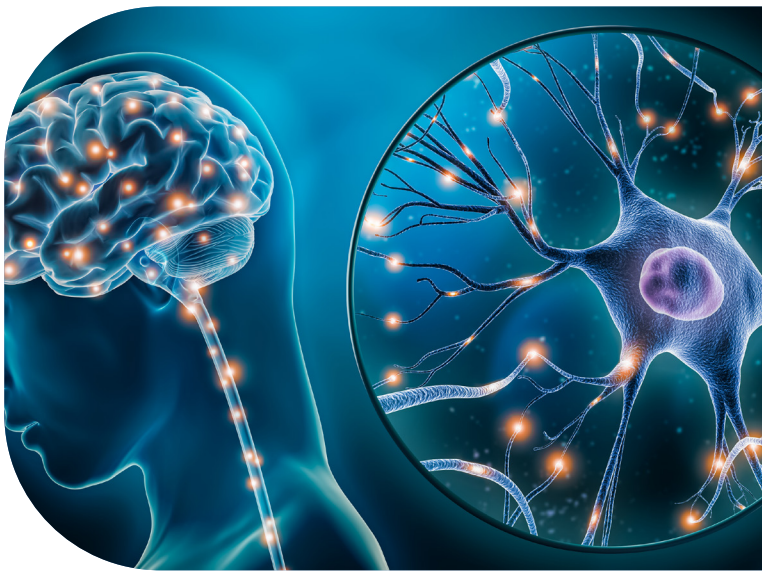
In 2004, PBM was first applied to the human brain to treat acute ischemic stroke using transcranial near-infrared light (Oron et al, 2006). In the last 20 years, transcranial PBM (tPBM) has undergone extensive trials as a therapeutic intervention for various neurological conditions, and has been found to be safe. More recently, with an improved understanding of dosing, several recent tPBM trials have demonstrated both safety and efficacy in treating Alzheimer's disease (AD)[42] and Parkinson's disease,[43] traumatic brain injuries,[44] and in improving cognitive performance in healthy young adults.[45]

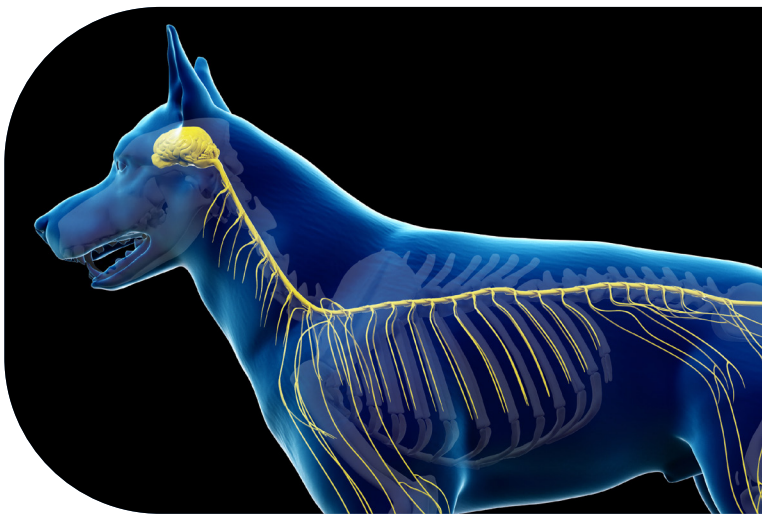
Canine cognitive dysfunction syndrome (CCDS) is becoming more common in veterinary practice as we lengthen pets' lives through better nutrition and medical care. It is a naturally-occurring degenerative brain disorder with gradual onset and insidious progression,[46-47] analogous to human Alzheimer's disease.[46,48] CCDS is often characterized by confusion, disorientation, excessive panting, pacing, agitation, separation anxiety, and other clinical signs. The pathophysiology of AD and CCDS is multifactorial, involving vascular compromise, neuronal mitochondrial dysfunction, inflammation, oxidative brain damage, and deposition of β-amyloid (Aβ) around blood vessels and neurons. Over time, these factors lead to progressive loss of dendrites, synapses, and neurons, followed by cognitive decline.[48-50] There is no cure, although a variety of supplements, pharmacological agents, special diets, and environmental strategies have been used to treat CCDS.[46]

Compromised blood flow, mitochondrial dysfunction, and subsequent oxidative stress and inflammation are at the core of this disease process, and these all happen to be where PBM may be especially helpful as a treatment modality.

- Studies have demonstrated the ability of tPBM to cause disaggregation of Aβ via suppression of β-secretase activity and the stimulation of enzymes responsible for degrading Aβ peptides.[51-55]

- Rodent studies have shown that tPBM decreased brain levels of Aβ, improved cognitive test scores, and increased cerebral vascular density.[56,53]





- While no veterinary studies have been published on the efficacy of tPBMT for treating CCDS, one publication discussed the pathophysiology and previously mentioned mechanisms by which PBMT may be beneficial.[57]

The ideal parameters for the use of tPBMT for CCDS are not well established. However, data extrapolated from rodent and human studies involving AD45[58-62] may be used as a basis of where to start. Different pulse structures have also been examined in some of these studies. The potential reasoning behind the use of pulsed delivery is that neural oscillations measured by electroencephalography recordings have been linked to different mental processes.[63] Some authors suggest that pulsing with certain frequencies might add extra benefit to tPBM against AD.[64] While it has been demonstrated that pulsing affects the biology of the brain differently than continuous wave (CW), the true benefits remain to be elucidated and should be investigated further.

For treating CCDS, the authors recommend the handpiece be held in contact with the dorsal surface of the skull, treating both hemispheres (***Figure 2***). As with any treatment on the head and neck area, laser-safe eyewear is recommended for the patient. When treating with a higher-power laser (or at the higher end of the irradiance range discussed below), the laser operator is encouraged to keep the treatment head in continuous motion at all times.

An irradiance between 250 mW/cm^2 and 1.5 W/cm^2 at the skin surface is recommended. The resultant irradiances at the cortical surface in dogs should replicate dosing shown to be safe and effective in humans,[65] and tested in other species. Therefore, the laser operator must know the spot area of their laser handpiece, as well as the power setting and duty cycle (if pulsed) for the laser to adequately calculate dose. As an example, a 50% duty cycle when pulsing would necessitate a doubling of the calculated treatment time to achieve the same dose as with CW light.

For a medium to large dog being treated over the dorsal calvarium, the size of the area may be between 50-70 cm^2, which would result in a total dose of 1,000-1,400 Joules delivered over the entire area if using a fluence of 20 J/cm^2. As with most chronic degenerative conditions, PBM therapy should be started with two to three sessions the first week, if possible, weaning to a transition phase of less-frequent treatments

FIGURE 2: Using PBM to treat canine cognitive dysfunction syndrome.

Photo courtesy of Lisa A. Miller

(twice weekly, then once weekly), and continued once every two to three weeks as needed to keep clinical signs at a minimum. The author and colleagues have observed that, in most cases, the use of transcranial PBM therapy seems very effective for improving the symptoms of CCDS within four to six weeks.

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