

# Beyond the Laboratory, Into the Clinic: What Dogs with Disk Disease Have Taught Us About Photobiomodulation for Spinal Cord Injury

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## Abstract

**Background:** For spinal-cord-injured (SCI) patients, integrative medicine approaches such as photomedicine and acupuncture can renew hope and offer previously unrecognized ways to help regain function and improve quality of life. **Objective:** By understanding the mechanisms of action that these two modalities share, practitioners can better target specific attributes of spinal cord pathophysiology that are limiting recovery. Naturally occurring intervertebral disk disease (IVDD) in dogs affords unparalleled translational opportunities to develop treatment strategies involving photobiomodulation and acupuncture. **Conclusions:** Insights derived through clinical trials of dogs with IVDD have the potential to raise the standard of care for both human and canine SCI patients.

**Keywords:** photobiomodulation, cellular processes, outcomes research, neuromodulation, acupuncture, spinal cord injury

## Introduction

RUDOLF VIRCHOW STATED over a century ago, “Between animal and human medicine there is no dividing line—nor should there be. The object is different but the experience obtained constitutes the basis of all medicine.”<sup>1</sup> The saying stands true today. In particular, the study of naturally occurring or spontaneous spinal cord injury in dogs may yield relevant and meaningful clues into the cause and treatment of persistent paralysis and related disease states in humans.

Over the past 20,000–30,000 years, dogs and humans have travelled parallel courses and experienced similar environmental factors, leading to not only mutually evolving lifestyles but also extended life expectancies.<sup>2</sup> On the downside, both species are showing higher incidence of obesity, osteoarthritis, and degenerative conditions. On the upside, the fact that dogs are facing similar spontaneous diseases as humans allows them to serve as uniquely suited translational animal models for their human counterparts.

The study of heritable and spontaneous medical disorders in dogs deepens our understanding of diseases that also plague humans, such as cancer. Finding successful treatments in dogs that target disease processes, which share cellular, molecular, and biologic parallels with humans, opens doors to clinical advancements in human healthcare. Dogs present a readily replenished study population; many veterinary clients welcome the chance to try new treatments

that might help their dog, save money, and reduce human suffering.

Clients whose dogs have become paraplegic or paraparetic due to spinal cord injury (SCI) are similarly motivated to enroll their animals in research projects; this ideally offers the chance for a “win-win” outcome that ultimately benefits both dogs and humans. Veterinary teaching hospitals have large caseloads of dogs with naturally occurring intervertebral disk disease (IVDD), many of whom also have SCI. The clinical case accrual rate can reach 90%.<sup>3</sup>

## Translational Value of Studying Spinal Cord Injury in Dogs in the Clinic Setting

Certain breeds of dogs such as Dachshunds have a high incidence of traumatic disk herniation either in the thoracolumbar spine (most commonly) or the cervical region. As indicated above, IVDD in dogs bears several similarities to acute, traumatic SCI in humans. This allows IVDD-affected dogs that participate in clinical trials to inform human preclinical research.<sup>3</sup> As it stands now, despite the high number of treatment trials performed in humans, “none has produced a major improvement in neurologic recovery or a meaningful increase in function.”<sup>4</sup>

Canine IVDD bears several similarities to human SCI. Most of the individuals affected tend to be young to middle-aged males. The gross and histopathologic lesions in dogs resemble

those recognized in some humans with traumatic myelopathies. These lesions span the gamut of a grossly normal cord with lesions visible only on histopathologic examination to cords having a normal surface with intraparenchymal hemorrhage and necrosis, and to, in the worst cases, those that exhibit extensive compression, gross anatomic distortion, and necrosis.

In both species, injuries may include axonal disruption and demyelination, neuronal necrosis, and early neutrophil infiltration. Cystic lesions may appear at the site of necrosis; neovascularization follows, weeks or months later.

In terms of treatment, the medical management of human SCI resembles that of canine IVDD; both treatment populations experience delay before arriving at a medical facility and receiving care. Current standards of care may involve anesthesia, decompressive surgery, postoperative analgesia, and rehabilitation.

### Dogs and Rodent Models, Compared

What makes naturally occurring IVDD in dogs a better translational model than experimental spinal cord injury in rodents? Dogs with IVDD are not anesthetized when the spinal cord compression and contusion occur. They are, therefore, not exposed to neuroprotective processes that may result from anesthesia-associated changes in body temperature and central nervous system metabolism. This differs from rodent models of SCI, in which rats undergo spinal cord injury while receiving anesthesia.

The direction of injury in a purposefully induced crush and contusion model occurs from the dorsal approach on a surgically exposed cord. In naturally occurring disease, the disk damages the cord from its ventral aspect. Destructive forces in dogs with IVDD arise from blunt force, not surgical excision (at least until surgery for the IVDD, if that is a treatment choice).

Dogs' spinal cords more closely resemble humans' than do those in rodent species. This larger sized cord mimics the changes taking place in human injuries, specifically with respect to axonal sprouting across glial scars. Their greater body mass also facilitates acquisition of cerebrospinal fluid specimens, the local and regional delivery of cellular therapeutics, and the withdrawal of serial blood samples for pharmacokinetic analysis. Furthermore, research suggests that certain surrogate markers of injury severity, such as matrix metalloproteinase-9, may overlap between people and dogs. Comorbidities in humans and dogs with SCI include urinary and/or fecal incontinence, acute and/or chronic abdominal complications, cardiopulmonary compromise, and decubitus ulcers for nonambulatory individuals.

Certainly, challenges exist when recruiting client-owned dogs with spontaneous disease as animal models. The variability in injury severity, time of presentation, and mechanism of injury in dogs make the study population more heterogeneous than that of an intentionally injured rodent. Not all dogs receive methylprednisolone on admission; this differs from the standard approach for humans. Dogs may live for years after the injury; they may move away or in some other way become lost to follow-up. Costs per dog for surgery and/or rehabilitation may range into thousands; this far exceeds the amount per rodent involved in experimental research.

Neuroanatomically, humans rely more on their corticospinal tracts for ambulatory function than do dogs, which

depend on other pathways more strongly. This may help to explain why spinal shock after SCI resolves more quickly in dogs. Finally, traumatic myelopathy in humans most often affects the cervical cord, whereas in dogs, the damage usually lands between T11 and L3.

### Why Surgery Alone Is Insufficient for Dogs

In dogs, a slow or incomplete resolution of the injuries stemming from SCI, addressed with or without surgery, may prompt consideration of euthanasia; caring for a handicapped dog that may also be incontinent and painful can become overwhelming to clients. As such, the return of conscious proprioception, voluntary motor movement, return of pain perception, and control over micturition and defecation are key to optimizing a more complete recovery.

Surgical decompression of the spinal cord remains, for many veterinarians, the treatment of choice for dogs with IVDD.<sup>5</sup> Surgery, however, causes additional pain and tissue trauma. It may precipitate a complex humoral and neuronal response in the cord and surrounding tissue that complicates recovery. It can also cause clinically significant spinal instability, especially when a hemilaminectomy extends beyond more than one intervertebral segment.<sup>6</sup>

Surgical interventions for IVDD typically cost thousands of dollars and there is no guarantee of a complete or speedy resolution of the damage with a surgical "fix." Recurrence of disk injury or neurologic signs, not unusual for those breeds of dogs at higher risk of IVDD, may prompt consideration of euthanasia. Studies show that clients may become unwilling to have their dog undergo another surgery due to the associated pain, trauma, and/or expense.<sup>7</sup>

Fortunately, more veterinary clinics now offer rehabilitation programs that include not only photomedicine but also acupuncture, electrical stimulation, massage, and therapeutic exercise. Results from clinical experience and growing research attest to the benefits that these approaches can offer, prompting the nervous system to recover by means of cellular repair, neuronal regeneration and reintegration, and functional restoration.

The relief and joy shared by clients and their veterinarians in seeing a paralyzed dog walk again raises the question—can these benefits extend to humans with similar disease processes? If so, why aren't spinal cord injury centers instituting treatments such as photomedicine and acupuncture that confer the benefits of photobiomodulation (PBM) and neuromodulation, respectively, as soon as possible after the impact and continue during the course of recovery? One reason may be that conventional medical facilities accustomed to providing limited options are slow to integrate new modalities unless and until they learn how the treatments work and about the evidence that supports their usage for patients with SCI. As such, if providers of photomedicine and acupuncture can communicate specific ways in which these procedures improve cord physiology and functional outcomes, perhaps more rehabilitation centers will introduce these valuable tools of recovery.

### Mechanisms of Injury—The Primary and Secondary Phases of SCI

The pathophysiology resulting from compressive SCI occurs in two parts, the primary and secondary injury phases. This twofold complex process may explain why finding

an effective and suitable therapy has posed so many challenges to conventional treatments. For example, endogenous responses to SCI may involve a highly orchestrated interplay of pro- and anti-inflammatory phases as well as specifically timed signaling pathways and cellular “clean-up, repair, and reorganize” systems. While some medications can reduce long-term damage, those that inhibit widespread receptor pools or tightly regulated biochemical responses may interfere with autoregulatory processes that might otherwise contribute to recovery. In contrast, integrative physical medicine measures tend to support the body’s endogenous recovery apparatuses in a modulatory (i.e., normalizing) manner, thereby maximizing the capacity for self-healing.

The primary phase of SCI arises from the mechanical event that produced the initial trauma of contusion and/or compression. Secondary injury begins 1–2 days after the inciting event; its effects include vascular changes, cellular manifestations, and biochemical responses that typify this stage. Consequences include biochemically mediated neuronal death, spinal cord inflammation, and long-term scarring within the cord that impede functional recovery.<sup>8</sup>

Significant issues that arise acutely after SCI may include systemic hypotension, vasospasm, spinal shock, ischemia, edema, and cell death from the direct impact. These changes extend into the subacute period, which lasts days to weeks after the inciting event, along with glutamatergic excitotoxicity affecting the neuronal pool. Soon thereafter, biochemical alterations begin manifesting as free radical production, release of excessive amounts of nitric oxide and norepinephrine, reduced ATP availability, invasion of immune cells, and proinflammatory cytokine production. Depending on the nature of the injury, vertebral compression and spinal column instability could produce ongoing tissue damage and exacerbation of the problems.

As the subacute process proceeds, surviving axons may undergo demyelination and eventually die. Cavitation within the cord may begin, damaging its delicate cytoarchitecture, and the beginnings of an astroglial scar may appear.

Once the chronic phase begins, demyelination, apoptosis, and central cavitation are well underway and the glial scar may give way to syrinx formation. The activity of ion channels and receptors has been modified and regenerative processes with neuron sprouting are occurring. These changes in structure and function produce altered neurocircuits and dysfunctional outputs.

### Challenges to Successful Outcomes

Clearly, the injured cord needs help in many ways. A successful intervention would stimulate axonal regrowth and regeneration to counter neuronal apoptosis. It would also supply new neurons and glia to repopulate the area where die-off has occurred. Surviving cells need protection from the degenerative changes that take hold during the secondary injury phase. Finally, functional restoration requires new neurons to work in concert with those that survived the impact.

Unfortunately, the spinal cord must surmount a variety of hurdles to successfully restore compromised function.<sup>9</sup> Challenges to axonal regrowth include uncontrolled, reactive astrogliosis and the release of inhibitory factors that limit regeneration. Scar formation around the lesion pro-

duces a physical barrier of astrocytic processes. Cystic cavitation alters the architectural framework of the cord and further blocks axonal regrowth.

Oligodendroglial apoptosis and minimal proliferation of oligodendrocyte precursor cells cause axonal demyelination, whereas remyelination is required. When axons lose their myelin, they are unable to accomplish normal and rapid saltatory conduction. This then makes the cord vulnerable to nonfunctional electrical signaling.

### Limitations of Conventional Care

While standard SCI treatment strategies potentially limit the impact of SCI in the primary phase, they often cannot surmount challenges associated with the secondary phase. In other words, surgical decompression reduces mechanical pressure on the cord, but it offers little in the way of functional regeneration of the neuronal pool.

Methylprednisolone succinate may mitigate oxidative stress, reduce inflammation, and enhance both oligodendrocyte and motor neuron survival, but is most effective when administered within 8 h of the injury.

Maintaining mean arterial blood pressure above 85–90 mmHg offsets spinal shock; other novel neuroprotective strategies under investigation include (1) minocycline, which inhibits activation of microglia—immune cells that foster neurodegenerative changes following SCI—and down-regulates inflammatory cytokines, and (2) sodium-channel blockers that indirectly inhibit presynaptic glutamate release and potentiate its uptake. Studies are also looking at other measures that reduce apoptosis along with the expression of proinflammatory cytokines.

### PBM and Electroacupuncture for Neuronal Support and Functional Recovery

Both PBM and electroacupuncture (EA) confer neuroprotection through overlapping mechanisms, including neuronal stimulation, neuromodulation, and regeneration.<sup>10–13</sup> In addition, both approaches reduce inflammation, support tissue repair, and provide local and regional analgesia. Table 1 contrasts and compares the mechanisms of each modality on these facets of recovery from SCI. Specific details relating to treatment parameters used (e.g., energy density, exposure time, wavelength, frequency) are available by accessing the references provided.

### Canine Clinical Studies for IVDD

Working in concert, the healing processes outlined in Table 1 serve to preserve function and restore tissue. Clinically, research studies in dogs with IVDD have demonstrated the value of both EA and PBM. In one study, EA combined with a conventional medical approach shortened the time to recover deep pain perception (an indicator of disease severity) and ambulation compared to standard of care alone in dogs with thoraco-lumbar (TL) IVDD.<sup>32</sup> Another canine study found EA offered alone or in combination with surgery more effective than surgery alone in improving neurologic outcomes.<sup>33</sup>

Preclinical work in dogs suggests that PBM improved neurologic function after experimentally induced SCI.<sup>34</sup> Dogs who received low level laser therapy (LLLT) were walking within 9–12 weeks after spinal cord transection

TABLE 1. COMPARISON OF BENEFITS OF PHOTOBIO-MODULATION AND ACUPUNCTURE FOR PATIENTS WITH SPINAL CORD INJURY

<i>Mechanism of action</i>	<i>Photobiomodulation (PBM)</i>	<i>Electroacupuncture (EA) and manual acupuncture (MA)</i>
Neuronal stimulation and neuromodulation	<ul style="list-style-type: none"> <li>• Activates photoacceptors</li> <li>• Upregulates ATP production</li> <li>• Supports cellular proliferation and cytoprotection<sup>14</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Stimulates mechanoreceptors</li> <li>• Neuromodulates</li> <li>• Improves motor control</li> </ul>
Neuroprotection	<ul style="list-style-type: none"> <li>• Preserves motor neurons</li> <li>• Supports cellular metabolism of neurons</li> <li>• Stimulates proliferation of astrocytes and oligodendrocytes</li> <li>• Promotes remyelination and axonal regeneration<sup>15</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Upregulates reparative signaling pathways<sup>24</sup></li> <li>• Modulates neurotrophin expression<sup>25</sup></li> <li>• Promotes remyelination</li> </ul>
Neuronal repair and functional restoration	<ul style="list-style-type: none"> <li>• Hastens recovery from peripheral nerve injury<sup>16</sup></li> <li>• Supports muscle tissue preservation as nerves heal<sup>17</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Improves microcirculation and neuronal morphology<sup>26</sup></li> <li>• Benefits the microenvironment of the injured spinal cord</li> <li>• Alters genetic and protein expression in ways that facilitate locomotor functional recovery<sup>27</sup></li> </ul>
Local and regional analgesia	<ul style="list-style-type: none"> <li>• Reversibly blocks fast axonal flow and mitochondrial transport along nociceptive axons, blunting transmission of nociceptive impulses to the cord<sup>18</sup></li> <li>• Induces mRNA expression of the opioid precursor molecules pro-opiomelanocortin and corticotrophin releasing factor within inflammatory tissue</li> <li>• Increases beta-endorphin concentration at the site of damage<sup>19</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Blocks pain through several mechanisms, including opioidergic, anti-inflammatory, and modulated receptor activation<sup>28</sup></li> </ul>
Tissue repair and preservation	<ul style="list-style-type: none"> <li>• Stimulates fibroblast proliferation, collagen production, growth factor release, and microvascularization of injured tissue<sup>14,20</sup></li> <li>• Improves immune function</li> <li>• Alters expression of genes involved in wound healing<sup>14</sup></li> <li>• Fosters resolution of inflammation by modulating inducible nitric oxide synthase (iNOS) expression</li> <li>• Reduces edema</li> <li>• Speeds normalization of tissue architecture<sup>21,22</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Promotes mechanical signaling through connective tissue</li> <li>• Facilitates cytoskeletal remodeling in fibroblasts<sup>29</sup></li> <li>• Supports healing of soft tissue (wound and muscular) defects</li> </ul>
Anti-inflammatory benefits	<ul style="list-style-type: none"> <li>• Reduces the expression of proinflammatory cytokines<sup>23</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Reduces the expression of proinflammatory cytokines<sup>30,31</sup></li> </ul>

and sciatic nerve autograft insertion; control dogs that did not receive PBM remained paralyzed. Histologic analysis of treated dogs revealed that new axons and blood vessels had migrated into the graft; scar tissue in the cord was minimal to absent. These changes were not evident in control animals.<sup>35</sup>

One published prospective study in the United States evaluated dogs that had received PBM following hemilaminectomy for IVDD.<sup>36</sup> Treatments involved postoperative therapy applied once daily for 5 days after surgery (810 nm wavelength, 5 × 200 mW, pulsed mode). Dogs receiving PBM support regained the ability to walk more quickly after surgery than those that did not. The findings from this research comport with the vast and growing experience of veterinary practitioners who are changing the standard of care for SCI in dogs.<sup>37</sup>

More recently, researchers in Europe studied the effects of PBM and physical rehabilitation on early recovery vari-

ables in 32 nonambulatory dogs with IVDD.<sup>38</sup> They compared the outcomes of dogs in three groups: standard postoperative care with PBM, physical rehabilitation with sham PBM, or sham PBM only after surgery. The study found no differences in recovery-related parameters (neurologic score, opioid requirements, and recovery grades) between groups. The PBM approach resembled the U.S. trial described above, although the authors provided more details regarding treatment as follows: 810 nm wavelength; 1 W laser cluster probe with five 200 mW laser diodes; peak power, 227 mW; duty cycle, 88%; beam area, 0.0364 cm<sup>2</sup>; irradiance, 5.5 W/cm<sup>2</sup>; energy, 12 J; and fluence, 329.7 J/cm<sup>2</sup>. Researchers applied the light transcutaneously over the site of the affected segment as well as one segment cranial and one caudal. The laser probe was applied with pressure to each area for 60 sec with a frequency of 2.5 Hz. Hair had been clipped already for surgical site antisepsis. Treatments

were provided immediately after surgical wound closure and then once daily for 5 days. The authors did not indicate the number of joules applied to each locus treated or whether the treatment was performed on the midline only, or lateral to the midline. No mention was made about how much heat the laser probe generated.

The sham PBM treatment utilized four “guide” light-emitting diodes. Each diode supplied light with a wavelength of 660 nm. Power was reported as “4×6 mW” and “approximately 30 mW/cm<sup>2</sup>.” This treatment was applied to the same regions as the active intervention described previously. The authors stated that “the body of the probe was heated to simulate the heat generated by the laser diodes during normal operation.” However, no thermal measurements were provided for either verum or sham application, whether for the body of the probe or the amount of heating (if any) of the surface of the patient. Length of time of sham probe application and the total fluence were similarly omitted from the report.

Physical rehabilitation included cryotherapy, range-of-motion exercises, assisted standing, hydrotherapy, and neuromuscular electrostimulation along with assisted weight shifting at a later point.

Although the authors reported no differences between groups, the methodology and outcomes require further scrutiny. First, the sham intervention was not truly inert, but involved light and heat. As with sham acupuncture needling approaches, methodological flaws arise when the supposed “placebo” approach also confers physiologic effects.<sup>39,40</sup> As such, dogs in each of the three groups received active interventions, meaning that this study was also not suitably controlled, in contrast to the authors’ claims. The authors of this small study may have concluded, correctly, that outcomes of the dogs in each group did not differ, but that does not mean that the dogs in each group did not benefit from the interventions, all of which likely had physiologic effects.

## Conclusions

Worldwide, ~2.5 million humans live with spinal cord injury; many are younger than 30 years. The cost to society per patient over a lifetime may reach millions of dollars.<sup>3</sup>

As stated by Elizei and Kwon, “Acute traumatic spinal cord injury is one of the most physically and psychologically devastating injuries; it affects tens of thousands of people of all ages around the world with incalculable personal and massive societal costs... Despite many novel therapeutic interventions showing great promise in the laboratory using animal models of SCI, translating these into clinical treatments with convincing efficacy in human SCI patients has been challenging....”<sup>41</sup>

The time is right to move beyond the laboratory and study the application of PBM and EA in human clinical trials, based on outcomes observed in dogs. Both PBM and EA are safe, well-tolerated, relatively inexpensive, and straightforward to learn and practice. Used early after injury would give the best chance at limiting injury and maximizing recovery, including reducing reliance on addictive, ineffective medications such as prescription opioids.<sup>42</sup>

## Author Disclosure Statement

No competing financial interests exist.

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