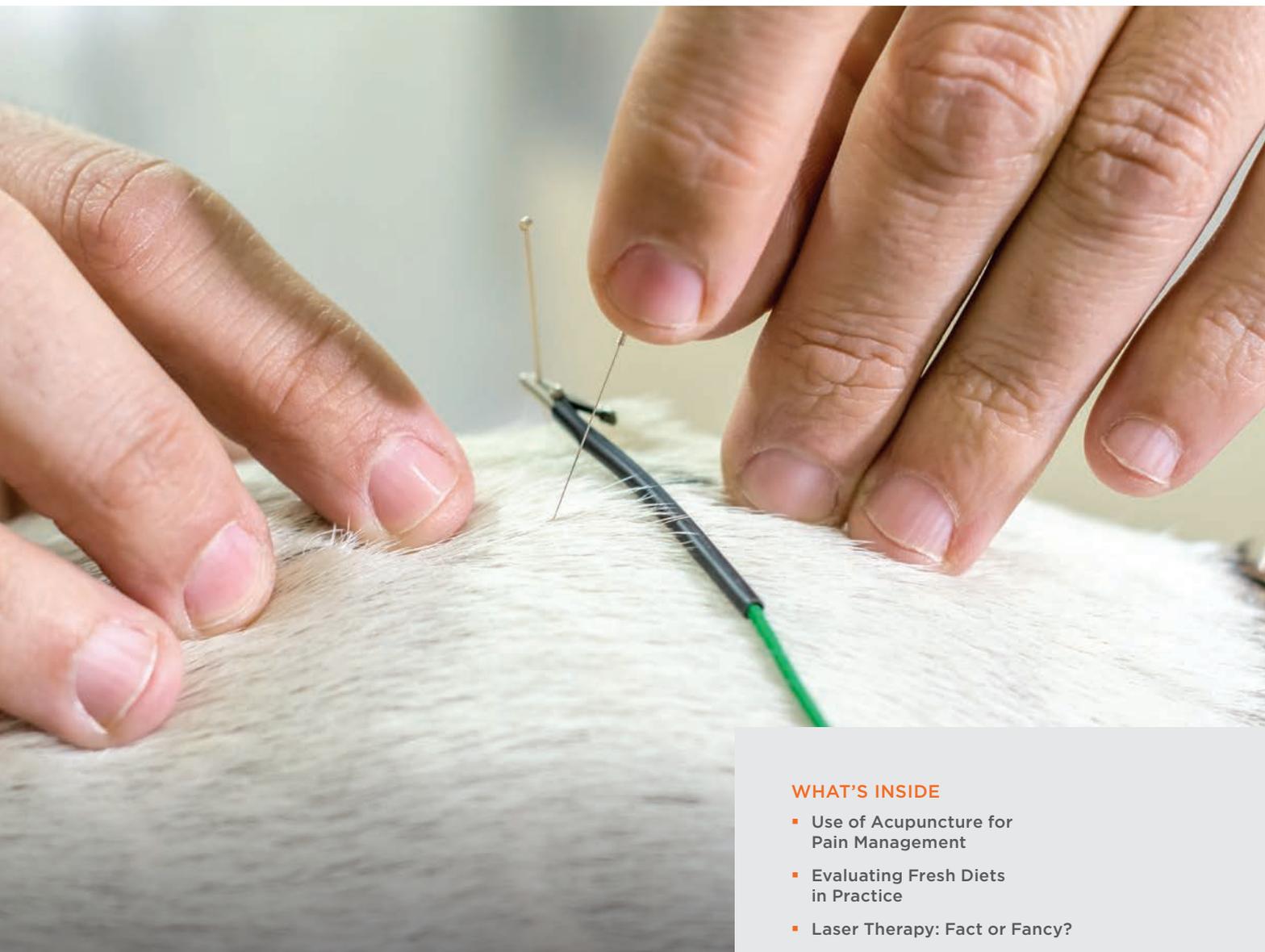


# Issues in Integrative Medicine



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- Laser Therapy: Fact or Fancy?
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A SUPPLEMENT TO

**TVP**

TODAY'S VETERINARY PRACTICE



# Use of Acupuncture for Pain Management

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Successful pain management encompasses pharmacologic and nonpharmacologic interventions. This is especially true for chronic, neuropathic, or persistent pain.<sup>1</sup> While pharmacologic options remain the mainstays, nonpharmacologic interventions are an important part of a comprehensive pain management plan.

Acupuncture is a safe, nonpharmacologic intervention with minimal adverse effects that most animals tolerate well.<sup>2,3</sup> It has become more accepted for pain relief in veterinary medicine. In fact, the pain management guidelines published by the American Animal Hospital Association, American Association of Feline Practitioners, and World Small Animal Veterinary Association endorse acupuncture as a safe adjunct treatment for pain management in dogs and cats that should be strongly considered as a part of a multimodal pain management regimen.<sup>4,5</sup>

Acupuncture can be used independently or integrated into conventional analgesia protocols. It has significant analgesic effects on inflammatory, neuropathic, cancer, and visceral pain states.<sup>6</sup> It can help ease acute pain from neuromusculoskeletal injuries and surgery, as well as chronic spinal and osteoarthritic pain. Veterinary clinical trials also provide evidence for its effectiveness.<sup>2,7-20</sup>

## HOW DOES ACUPUNCTURE WORK?

Acupuncture is the stimulation of certain points on the body that correspond to neurovascular bundles, blood plexuses, sites of nerve branching, and motor endplate zones (**TABLE 1**).<sup>21</sup> Recent evidence suggests that the effects of acupuncture are likely mediated by the nervous system at peripheral, spinal, and supraspinal levels.<sup>6,22</sup> Neurophysiologic effects of analgesia in response to acupoint stimulation include release of endogenous opioids and neurotransmitters (e.g., endorphin/endomorphin, enkephalin, 5-hydroxytryptamine), activation of the descending pain inhibitory pathway, and inhibition of inflammatory mediators (e.g., cyclooxygenase-2, interleukin-1 $\beta$ , interleukin-6).<sup>6,22</sup> Acupuncture also causes micro-trauma and vasodilation to improve local circulation and catalyze healing.<sup>23</sup> Recent evidence suggests inhibition of microglial activation by acupuncture may play a key role in neuropathic pain diseases.<sup>24</sup>

## CLINICAL EFFICACY

In 1 noncontrolled study, acupuncture alone or combined with analgesics reduced chronic pain and improved quality of life in dogs with neurologic and musculoskeletal diseases.<sup>8</sup> Results were similar for acupuncture plus manual therapy in dogs with musculoskeletal pain; the authors found immediate

short-term improvement in comfort level and mobility compared with before treatment.<sup>9</sup>

In 2 controlled studies in dogs with hip dysplasia, a gold bead implanted at acupoints significantly reduced osteoarthritic pain.<sup>10,11</sup> A 2-year follow-up study revealed that gold-bead acupuncture provided long-term pain relief, an effect not observed in dogs receiving placebo.<sup>12</sup>

In another controlled study, neither acupuncture nor carprofen significantly differed from placebo on gait analysis of dogs with hip dysplasia, but only acupuncture was associated with a decrease in validated chronic pain scores.<sup>13</sup> A controlled, blinded study in

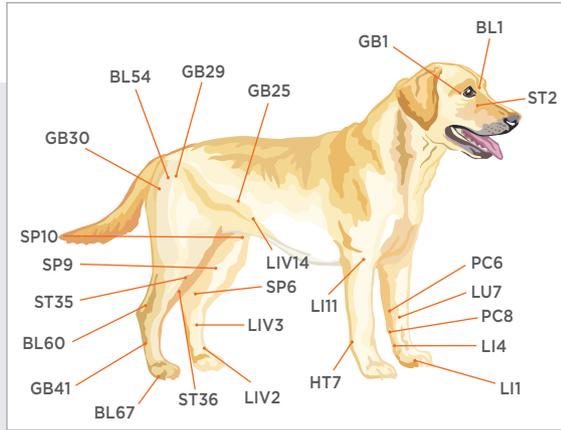
dogs undergoing hemilaminectomy found significantly lower postoperative pain scores in the acupuncture than the control group.<sup>14</sup>

Two studies showed that among cats undergoing ovariectomy, the need for rescue analgesia after surgery was lower in the acupuncture than the control group.<sup>15,16</sup> Similar results were found in dogs undergoing mastectomy.<sup>17</sup>

In horses, 2 controlled studies found acupuncture was effective in treating back pain.<sup>18,19</sup> A recent study showed horses with chronic laminitis were improved by acupuncture after receiving 2 acupuncture treatments 1 week apart.<sup>20</sup>

**TABLE 1 Common Acupuncture Points Used for Variable Pain States and Locations**

AFFECTED AREA OR CONDITION	COMMON ACUPOINTS
General pain	LI-4, LIV-3, ST-36, BL-60
Inflammation	LI-4, LI-11, ST-36, GV-14, <i>Er-jian</i>
Calming effect	GV-20, GV-21, <i>An-shen</i> , <i>Bai-hui</i>
Bone and arthritic pain	BL-11, BL-23, KID-3 (combined with local acupoints)
Dental pain	ST-6, ST-7, LI-4, LIV-3, ST-36 EA: LI-4 bilateral, ST-36 bilateral
Otitis and ear pain	TH-21, SI-19, GB-2, ST-36, <i>An-shen</i> EA: ST-36 bilateral, SI-19 to <i>An-Shen</i>
Abdominal or visceral pain	ST-36, LIV-8, BL-24, ST-25, LI-10 EA: ST-36 bilateral, LI-10 bilateral
Neck	GB-20, GB-21, GV-14, SI-3, LU-7, BL-60, <i>Jing-jia-ji</i> EA: GB-20 to GB-21, <i>Jing-jia-ji</i> bilateral
Shoulder	LI-15, TH-14, SI-9, BL-11 EA: LI-15 to SI-9, BL-11 bilateral
Elbow	LI-10, LI-11, LU-5, HT-3, TH-10, SI-9 EA: LI-10 to SI-9, LI-11 to HT-3
Carpus	LI-4, TH-5, HT-7, SI-9 EA: LI-4 to SI-9, TH-5 to HT-7
Coxofemoral	GB-29, GB-30, BL-54, BL-40, ST-41 EA: BL-54 bilateral, GB-29 to GB-30, ST-41 bilateral
Stifle	ST-35a, ST-35b, ST-36, GB-34, BL-40, BL-54 EA: ST-36 bilateral, ST-35a/b to BL-40, BL-54 bilateral
Tarsus	BL-60, KID-3, LIV-3, ST-41, BL-54 EA: ST-41 to KID-3, BL-54 bilateral
Vertebral column (intervertebral disk disease)	GV-14, LI-4, ST-36, LIV-3, <i>Bai-hui</i> , <i>Hua-tuo-jia-ji</i> , <i>Liu-feng</i> (front or hind limbs), PC-8, KID-1 EA: GV-14 to <i>Bai-hui</i> , <i>Hua-tuo-jia-ji</i> bilateral, ST-36 bilateral, KID-1 or PC-8 bilateral
Treatment settings	1. DN: 20 to 30 min 2. EA: 2 to 20 Hz (dense-disperse waves) for 20 to 30 min



**FIGURE 1.** Location of common acupoints on a dog. Acupoints are where nerves and blood vessels converge.

## METHODS OF STIMULATION

Acupoints can be stimulated by dry needle (DN), electroacupuncture (EA), aqua-acupuncture (AQ), laser acupuncture (LA), moxibustion, and material implantation (FIGURE 1).<sup>2,7</sup> Each method traditionally serves a different purpose. DN involves the insertion of fine, sterile needles into acupoints. These needles vary in size (28- to 36-gauge) and length (0.25 to 1.5 inches). The needles are typically left in place for approximately 10 to 30 minutes.

In EA, acupoints are stimulated by applying electricity through needles for 10 to 30 minutes. EA has more profound and prolonged analgesic effects than other techniques.<sup>6</sup> It is useful for neuralgia, nervous system injury, and persistent pain.<sup>6,7</sup> Low-frequency EA (2 to 10 Hz) produces longer-lasting alleviation of inflammatory pain and inhibits nerve injury–related allodynia/hyperalgesia more potently than do higher frequencies (100 Hz).<sup>6</sup>

With AA, 0.1 to 0.5 mL of sterile fluid (e.g., saline, vitamin B<sub>12</sub>) is injected into acupoints. It is commonly used after DN or EA to prolong the effect of acupoint stimulation.

LA, the modern practice of stimulating acupoints using low-level energy of wavelengths (630 to 960 nm), may provide anti-inflammatory and antinociceptive effects.<sup>15</sup>

## HOW IS ACUPUNCTURE INTEGRATED?

Veterinarians who have received formal training can incorporate acupuncture into conventional practice

settings. Basic or advanced veterinary acupuncture courses are available at the Chi Institute of Traditional Chinese Veterinary Medicine, or through the International Veterinary Acupuncture Society.

Before acupuncture, underlying pain or medical conditions are always diagnosed as part of conventional care. Once standard treatment measures are underway, acupuncture can be used as an integrative modality to reduce acute or chronic pain. For outpatients, it can be offered at the clinic, once or twice a week. For inpatients, it can be performed in the hospital, once a day before discharge. Practices that do not offer acupuncture can refer patients to veterinarians with CVA (certified veterinary acupuncturist) credentials.

Veterinarians who perform acupuncture must obtain informed consent beforehand. The discussion of acupuncture in the context of conventional medicine must focus not only on the efficacy of acupuncture but also expectations and potential adverse effects. A multimodal approach with acupuncture may allow for a reduction in dose of conventional analgesics and therefore a decrease in their adverse effects.<sup>6</sup> For patients that are resistant to pain medications or cannot tolerate their side effects, acupuncture can be a reasonable alternative treatment.

As with any therapy, not every patient responds to acupuncture; therefore, realistic expectations need to be set for clients. The author often requires clients to commit to sessions once or twice a week for at least 4 to 6 treatments, especially for chronic conditions. Although many patients may not need even 4 treatments to experience benefits, shorter durations and lower intensities of treatment may result in suboptimal outcomes. Acupuncture has both immediate and cumulative analgesic effects following repeated treatments.<sup>25</sup>

## SAFETY AND CONTRAINDICATIONS

Acupuncture is safe when performed correctly by licensed veterinarians certified in veterinary acupuncture. Common minor adverse effects after acupuncture include tiredness, increased water intake, soreness, muscle spasm, and minor bleeding, which typically resolve quickly.<sup>2,3</sup> Other rare complications include infection, dermatitis, and broken needle fragments. Acupuncture needles should not be placed on infected or inflamed skin, open wounds, or sites of tumor and fractures; around the abdomen of a

pregnant animal; or in specific points that may contribute to premature parturition (i.e., ST-36, SP-6, BL-40, BL-60, and BL-67).<sup>2</sup> Deep needle insertion into acupoints around the lung fields (e.g., SP-21, LIV-13, LIV-14, GB-24, BL-12 to BL-19) is contraindicated. Acupuncture should be used cautiously or avoided in patients with clotting abnormalities. Do not apply EA across the thorax area (heart position) in animals with heart disease or pacemakers.<sup>2</sup> Be cautious when using acupoints around the eyes.

## CASE EXAMPLES

### Case 1: Chronic Pain Associated With Polyarticular Osteoarthritis

A 13-year-old female spayed Weimaraner had osteoarthritis in multiple joints (elbows, carpi, hips, and stifles) and back pain. Despite the combination of firocoxib, gabapentin, tramadol, and glucosamine-chondroitin, her pain was worsening and her mobility was deteriorating. She developed urinary incontinence and was awoken more often during the night.

An internist suggested acupuncture as a last resort before euthanasia. The dog received acupuncture twice weekly for 4 weeks initially, then every 2 to 4 weeks. After 3 treatments, the dog could rise up and walk without assistance and sleep normally. Her urination incontinence was resolved after 6 treatments. She continued to receive acupuncture monthly for pain management. She died at home at age 16.

Her acupuncture treatment consisted of the following:

- 1. DN:** GV-20, TH-5, SI-9, GB-34, BL-40, LIV-3, Bai-hui
- 2. EA:** LI-4 to LI-11, ST-36 to ST-41, BL-11 bilaterally, BL-23 to *Shen-shu* (crossing), BL-54 bilaterally; 2 to 20 Hz for 20 minutes
- 3. AA:** TH-4, LU-5, LI-10, SI-9, BL-23, BL-54, ST-36, BL-39, KID-3; 0.1 to 0.2 mL per acupoint

### Case 2: Pain and Neurologic Deficits Associated With Meningoencephalitis of Unknown Cause

A 4-year-old male neutered Yorkshire terrier was diagnosed with meningoencephalitis of unknown cause at the cervical region. He had nonambulatory tetraparesis with severe cervical pain and was hospitalized. He received IV fluids, immunosuppressive



## Glossary

<b>BL</b>	bladder
<b>GB</b>	gallbladder
<b>GV</b>	governing vessel
<b>HT</b>	heart
<b>KID</b>	kidney
<b>LI</b>	large intestine
<b>LIV</b>	liver
<b>LU</b>	lung
<b>PC</b>	pericardium
<b>SI</b>	small intestine
<b>SP</b>	spleen
<b>ST</b>	stomach
<b>TH</b>	triple heater

doses of dexamethasone, fentanyl constant rate infusion, cytosine arabinoside, and gabapentin. On day 4 of hospitalization, he was referred for acupuncture treatment. Despite medications, his neck was still severely painful on manipulation and he continued to have nonambulatory tetraparesis.

Shortly after his first acupuncture treatment, he could stand on his own unassisted and his cervical pain was markedly improved—he could move his neck without yelping. His fentanyl was discontinued the next day because of an improved pain level. The next day, after his second acupuncture, he became ambulatory on 4 limbs with minimal assistance. He continued to make significant progress over the next 3 days with daily acupuncture. On day 7, he had full range of motion of his neck and was ambulatory with mild ataxia.

His acupuncture treatment consisted of the following:

- 1. DN:** GV-20, LU-7, SI-3, LI-4, LIV-3, ST-36, *Jing-jia-ji*
- 2. EA:** GV-16 to *Bai-hui*, GB-20 to GB-21 (crossing), BL-23 bilaterally, PC-8 bilaterally, KID-1 bilaterally; 2 to 20 Hz for 20 minutes
- 3. AA:** *Jing-jia-ji*, GV-14, *Liu-feng*; 0.1-0.2cc per acupoint

## SUMMARY

Given the low risk for adverse effects and observed benefits for acute and chronic pain, acupuncture can

For patients that are resistant to pain medications or cannot tolerate their side effects, acupuncture can be a reasonable alternative treatment.

play a large role in pain management and can be incorporated into veterinary practice as part of a multimodal approach. With the increasing number of clinical trials and laboratory research, we better understand the mechanism of action and therapeutic effects of acupuncture. Nonetheless, larger randomized controlled trials are needed to verify its efficacy in veterinary medicine. **TVP**

## ACUPUNCTURE RESOURCES

- World Association of Traditional Chinese Veterinary Medicine (AATCVM): [watcvm.org](http://watcvm.org)
- American Academy of Veterinary Acupuncture (AAVA): [aava.org](http://aava.org)
- American Holistic Veterinary Medical Association (AHVMA): [ahvma.org](http://ahvma.org)
- National Center for Complementary and Integrative Health (NCCIH): [nccih.nih.gov](http://nccih.nih.gov)
- *Xie's Veterinary Acupuncture*, 1<sup>st</sup> ed.
- *Veterinary Acupuncture: Ancient Art to Modern Medicine*, 2<sup>nd</sup> ed.

### Ronald Koh

An assistant professor and section chief of the Integrative Medicine and Rehabilitation Service at the Louisiana State University School of Veterinary Medicine, Ronald Koh received his veterinary degree in Taiwan and completed a specialty internship and master's program in acupuncture at University of Florida College of Veterinary Medicine in 2010 and 2012, respectively. He will be finishing his residency in Veterinary Sports Medicine and Rehabilitation in 2019. His clinical interests include using acupuncture, integrative therapies, rehabilitation, nutrition, and supplements for pain management, neurological disorders, geriatric conditions, and palliative and hospice care.



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# Evaluating Fresh Diets in Practice

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Dietary trends for dogs and cats closely mirror those of their owners, and it is no surprise that home-prepared meals and their commercialized derivatives are now encountered in practice. These diets pose potential benefits as well as challenges, and clients increasingly expect veterinarians to demonstrate knowledge of them.

## WHAT IS A FRESH DIET?

Fresh diets are broadly defined as diets that are not shelf-stable at room temperature, such as:

- Home-prepared cooked diets
- Home-prepared raw diets
- Commercial made-to-order diets (generally cooked and provided refrigerated)

Some owners consider fresh diets to be only those prepared in a certain window of time before feeding. The following diets therefore may or may not be considered “fresh”:

- Commercial premixes (cooked or raw ingredients are added by the owner)
- Commercial refrigerated diets (raw or cooked)
- Commercial frozen diets (raw or cooked)

## WHY DO OWNERS FEED FRESH DIETS?

Pet owners increasingly select diets based on an assessment of ingredient quality and sourcing, safety and transparency, and customization and variety.<sup>1,2</sup> Fresh diets, especially home-prepared diets, are uniquely positioned to allow this assessment and permit owner choice. Other motivations for feeding these diets are diverse, including the factors below.<sup>3-8</sup>

### Distrust of Commercial Pet Foods

Consumer distrust is primarily driven by recalls, of which there were more than 40 in 2018<sup>9</sup> for issues such as elevated vitamin D levels, low thiamine (vitamin B1), and contamination with *Salmonella* or *Listeria* bacteria. Many owners cite the melamine recalls after significant numbers of dogs and cats developed acute kidney injury.<sup>10,11</sup> This distrust in commercial options was identified in 51% of dog owners in an oncology service, and 67% of raw-feeding owners displayed similar sentiment.<sup>12,13</sup>

### Ingredient Quality

Owners now evaluate ingredients on a number of potential metrics, such as sustainability, animal welfare, organic standards, and growing region. Visual



assessment of ingredients remains important to consumers, and extruded kibble or homogenized canned food does not readily permit this. Some owners cite reports of unlabeled ingredients.<sup>14</sup> Others distrust synthetically derived vitamins and minerals, which are exempted from Association of American Feed Control Officials (AAFCO) regulations for natural foods and may be sourced from outside the United States.<sup>15</sup>

## Skepticism Regarding Current Nutritional Guidelines

The basis for “complete and balanced” pet foods is the available nutritional literature, which is limited for some nutrients and was often gathered under experimental conditions with extruded or purified diets.<sup>15,16</sup> Owners feel that dogs fed unbalanced fresh diets—that is, diets not conforming to current recommendations—show no outward signs of disease and that present knowledge is incomplete to set thresholds for some nutrients. It is true that some nutrient minima may be inaccurate and some deficiencies or excesses affect health more than others.<sup>16,17</sup>

## Palatability

Many owners report that their dogs only eat (or strongly prefer) fresh foods. This anecdotally appears more prevalent in small dogs. Improved palatability is likely influenced by a combination of factors, such as increased moisture, protein, fat, aroma, and even the owner’s perception.<sup>18,19</sup>

## Preservative Avoidance

Synthetic preservatives such as ethoxyquin, BHA, BHT, and TBHQ were historically used in commercial pet foods given their effectiveness, but controversies still surround their safety.<sup>7,20</sup> Natural preservatives, such as tocopherols, rosemary extract, and citric acid, are now commonly used, but fresh diets may reduce or eliminate the need for preservatives.

## Customization or Rotation

Home-prepared diets allow owners to change protein and carbohydrate sources readily. Many commercial fresh diets provide diets with similar nutrient composition but different ingredients. Dietary rotation of any type certainly allows for greater nutrient variability, which may confer health benefits and may mitigate suboptimal nutrient levels for a particular animal.

## Specific Health Conditions or Concerns

Fresh diets are commonly used in the management of hyporexic pets with renal disease, gastrointestinal disease, or cancer.<sup>12,21–23</sup> Home-prepared fresh diets have been recommended for the diagnosis and management of adverse food reactions.<sup>24</sup> Such diets may also be used by owners of sporting or working dogs with the thought of improving performance or providing supplemental protein, fat, or calories; sled dogs are commonly fed a hybrid diet of commercial foods and raw meat, and racing greyhounds may be fed raw foods.<sup>25,26</sup> Fresh diets may affect the microbiome differently than extruded diets, which could influence gastrointestinal or overall health, and they are often highly digestible.<sup>27,28</sup> Clients may choose fresh diets in the hopes of preventing disease by promoting health.<sup>2</sup>

Pet owners increasingly select diets based on an assessment of ingredient quality and sourcing, safety and transparency, and customization and variety.<sup>1,2</sup>

## Raw Food Claims

A number of specific claims about raw food are discussed in greater detail elsewhere.<sup>28,29</sup> There is insufficient evidence that a raw diet is superior to the same diet when cooked.

## HOW COMMON ARE HOME-PREPARED AND COMMERCIAL FRESH DIETS?

The overall prevalence of home-prepared diet use among pet owners remains unclear, but 3 studies have provided limited data:

- In one study, home-prepared diets were fed as the sole source of nutrition to 2% to 3% of dogs and 0% of cats in the general population, but noncommercial foods provided at least 25% of the diet for 17% of dogs and 6% of cats.<sup>30</sup>
- In another study, breeders fed home-prepared diets to 11% of dogs across all life stages, and the practice was more common in giant-breed dogs.<sup>31</sup>



- In the third study, 7% percent of owners with dogs presenting to an oncology service fed home-prepared cooked diets, 4% fed prepared raw diets, and 18% fed a combination of diets, including a home-prepared diet.<sup>12</sup>

Commercial fresh diets represent millions in annual sales, with most companies targeting healthy animals.<sup>32</sup> Some fresh food companies now offer therapeutic diet lines (both cooked and raw) intended for veterinary supervision and sold through established retail channels or, increasingly, shipped directly to the owner.<sup>2</sup> The market share of fresh diets is expected to increase.

## PROBLEMS WITH HOME-PREPARED DIETS?

When severely unbalanced, home-prepared diets have been implicated in clinically significant pathology, including:

- Nutritional secondary hyperparathyroidism. The absence of calcium in the diet of growing puppies has caused fibrous osteodystrophy and other skeletal abnormalities.<sup>33-35</sup> Low dietary vitamin D is often concurrently identified. The condition is rare in adult dogs but has been documented.<sup>36,37</sup>
- Thiamine deficiency<sup>38</sup>
- Electrolyte abnormalities<sup>34</sup>
- Taurine deficiency, a cause of dilated cardiomyopathy<sup>34,36,39</sup>

Adverse effects are likely underreported, as dietary change frequently corrects discovered abnormalities.

Owners appear to infrequently consult recipes for their home-prepared diets, but recipes are available on the internet and in print from veterinary and non-veterinary sources.<sup>30,40,41</sup> Such recipes often lack specificity, which could affect nutrient composition, and owners often change recipes without guidance.<sup>21,22,41</sup> A few evaluations have compared recipes to nutritional recommendations, with the following findings:

- 95% of maintenance diets did not meet recommendations for at least one essential nutrient, diets from non-veterinary sources were more deficient, and rotational strategies were unlikely to balance diets.<sup>41</sup>
- 90% of tested home-prepared diet recipes provided by veterinarians for food allergy did not meet nutrient recommendations.<sup>24</sup>

- 100% of renal diets and diets suggested for cancer failed to meet recommendations.<sup>21,42</sup>

The impact of the deficiencies identified in the above studies would be expected to range in severity. Nutrients that were commonly identified as being below established recommendations included:

- Amino acids, specifically methionine, tryptophan, and phenylalanine<sup>21,42</sup>
- Calcium<sup>21,41,43</sup>
- Zinc<sup>21,41</sup>
- Vitamin D<sup>41-43</sup>
- Choline<sup>21,41,42</sup>

Insufficient amino acids could adversely affect muscle mass, produce taurine deficiency, or contribute to poor coat quality. Inadequate vitamin D and calcium could influence bone development in growing animals, and zinc plays a role in skin and immune function. Choline may be spared by other nutrients in the diet but plays a role in lipid handling and methyl group donation.<sup>16</sup> Clinical signs of nutrient deficiency are often present only when severe, making assessment in the clinic difficult. Some deficiencies require special screening laboratory tests (ionized calcium, parathyroid hormone levels, vitamin D testing, amino acid levels).

## HOW CAN HOME-PREPARED FRESH DIETS BE IMPROVED?

Two important recommendations should be made to owners committed to preparing their own diets:

1. Offer referral to a board-certified veterinary nutritionist for evaluation and reformulation of the diet. A list of diplomates available for consultation is available at [acvn.org](http://acvn.org), and the estimated cost of diet formulation ranges from \$150 to \$500. An alternative is a computer-generated recipe conforming to nutrient guidelines (e.g., [balanceit.com](http://balanceit.com)).
2. Advise the owner to consider a commercially available fresh diet with an AAFCO statement for the appropriate life stage.

If an owner declines the above options, the following questions can help screen diets for the most commonly encountered sources of dietary deficiencies. Owners should be counseled that most diets from internet sources and other recipes fail to meet established nutrient recommendations, and puppies and kittens should always have a referral or be fed a commercial food given their more critical nutrient tolerances.

1. **Is the diet composed primarily of meat (50% or**



**more by weight)?** Dogs and cats have no requirement for dietary carbohydrate but do have requirements for amino acids and fatty acids that are often lower in vegetable sources. Contraindications to such a diet should be considered (e.g., renal disease, canine pancreatitis).

**2. Is supplemental calcium added to the food?** Most meats are high in dietary phosphorus but low in calcium. The following doses can be used as general guidelines:

- **Adult cats:** 0.4 g calcium daily =  $\frac{1}{3}$  teaspoon of calcium carbonate
- **Adult dogs:** 2 g calcium per 1000 calories (the amount of food consumed by an average 50-pound pet dog) =  $1\frac{2}{3}$  teaspoon of calcium carbonate

Diets containing bones or bone meal likely contain both calcium and phosphorus, but the amounts may be excessive, especially for large-breed puppies. These minerals and other macronutrients can be measured in a sample of the food by a commercial feed laboratory.

**3. Is there a multivitamin product in the recipe?**

Once-daily human multivitamins are preferred over pet multivitamins, unless the latter is specifically designed, evaluated, or endorsed by a nutritionist for use in balancing home-prepared diets. Many common pet vitamins contain minimal quantities of essential nutrients. Once-daily human multivitamins are typically dosed at about  $\frac{1}{4}$  tablet per 25 pounds of patient body weight.

Organ meats are used in some diets to provide trace vitamins and minerals, but their adequacy in fulfilling the nutrient needs of a dog or cat can be difficult to evaluate based on weight of inclusion or percentage of the recipe without specific analysis.

**4. Are there supplemental fatty acids in the diet?**

Most diets benefit from supplemental EPA and DHA (omega-3 fatty acids) unless the diet contains large amounts of fish (e.g., tuna, salmon). A dose of 300 mg of EPA and DHA combined (1 standard fish oil capsule) per 25 pounds of body weight is generally sufficient for maintenance purposes. Most prepared diets naturally contain adequate amounts of linoleic acid, an essential omega-6 fatty acid.

The above recommendations do not ensure nutritional adequacy for every condition or every animal, but do help to prevent the most significant deficiencies identified in diets. If owners elect to use a commercial premix, the product should be evaluated for sources of vitamins and minerals, such as calcium or bone meal,

individually named vitamins and trace minerals, and/or dried organ meats.

## HOW SHOULD COMMERCIAL FRESH DIETS BE EVALUATED?

Fresh diets should be evaluated similarly to all commercial pet foods.<sup>3,28,44</sup> Suggested metrics for evaluation include:

- **Does the product provide an AAFCO statement for the appropriate life stage of the patient?** Products labeled for intermittent or supplemental feeding should not be fed long-term without veterinary guidance, nor should products without an AAFCO statement.
- **Has the diet been analyzed to confirm the nutrient levels provided, and is a detailed nutrient profile on a caloric basis available?** Ideally, foods that are formulated to meet requirements are also tested for confirmation of expected values, which is not a statutory requirement. Feeding trials may be performed, but such trials typically only identify major deficiencies. Foods should always be compared on a caloric basis.<sup>45</sup>
- **Who formulated the diet, and what are their qualifications?** Ideally, diets would be formulated or reviewed by a nutritionist (PhD or board-certified DVM) with experience in the type of food being produced.
- **Does the company operate its own manufacturing facility?** Companies producing their own food are expected to maintain more control over the process, but this has not been objectively evaluated.

Fresh foods, by nature, are more perishable than extruded or canned diets. Therefore, owners should be encouraged to ask additional questions regarding food quality and safety:

- **How is the food best stored, and how is temperature controlled during storage and shipping?** Fresh foods are susceptible to increased bacterial growth and oxidation if exposed to temperature fluctuations.
- **How are the ingredients sourced?** Owners may have additional questions relating to their preferred evaluation rubric for ingredients.
- **What safety and quality measures are present in the manufacturing facility?** A comprehensive food safety protocol should be followed to reduce the potential for contamination. This should include routine testing for pathogens such as *Salmonella* and *Listeria*, the latter of which can reproduce under



refrigerated conditions.<sup>46</sup>

- **What strategies are used to control bacterial growth and pathogens?** Raw foods contain higher bacterial concentrations than extruded diets if untreated, but so do many fresh cooked products. Pasteurization and pH-adjusting inclusions (such as acetic and citric acids) can reduce bacterial numbers.<sup>28,47</sup> Bacteriophages appear to be in use by at least one company, but there is controversy over the regulatory status of this approach.<sup>48</sup>

## FRESH DIETS ARE THE NEW REALITY

Current recommendations are that all patients should receive a screening nutritional assessment.<sup>49</sup> Consumer demand and market forces indicate that home-prepared and commercial fresh diets will be increasingly encountered during this assessment. Knowledge of the diversity of options in this group of diets, as well as their merits, will help practitioners provide the best evidence-based guidelines to clients, match recommendations to the motivations of the owner, and support the specific nutritional needs of the patient. **TVP**

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# Laser Therapy: Fact or Fancy?

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## THE SCIENCE OF LASER THERAPY: PHOTOBIO-MODULATION

Laser therapy is the result of electromagnetic energy interacting chemically and biologically with tissue, causing “photobiomodulation.” Electromagnetic energy affecting biologic processes is not a novel concept—it fills our environment as photosynthesis occurs in plants and literally surrounds us as vitamin D is formed in our skin cells.

Lasers produce a single wavelength (monochromatic) beam of light, which is collimated as it is generated. Laser light has the property of being coherent, or in phase, which in simple terms means it is uniform and very orderly light. Laser therapy uses a simple beam of light—monochromatic, coherent, collimated light—to penetrate deeply into tissues and produce positive tissue changes.

Laser therapy has had many contradictory and confusing names. The terms cold laser therapy, low-level laser therapy, class III laser therapy, and class IV laser therapy have all been used. Unfortunately, these terms describe the devices being used rather than the effect they have on tissue. Terminology based on the tissue effect is more descriptive and accurate.

The term most descriptive of the complex mechanisms and the cascade of physiologic events that follow laser therapy is *photobiomodulation*. Photobiomodulation describes the way photons interact with target tissues. It accurately describes a nonthermal interaction within the tissue, dependent on endogenous chromophores that absorb the energy in photons and elicit photophysical and photochemical events.

## THE RESULTS OF PHOTOBIO-MODULATION

The effects of photobiomodulation are a result of photons—packets of electromagnetic energy—interacting with cells.

In the clinical setting, therapy lasers that emit near infrared light are most often used. Different from LEDs (light-emitting diodes), therapeutic diode lasers emit invisible light in the 800- to 1000-nanometer (nm) range. These therapeutic wavelengths are less absorbed by water and other nontarget chromophores within the tissue and therefore achieve greater depth of penetration. They also interact with target chromophores to produce photochemical changes within the tissue.

Key to photobiomodulation is the absorption of photonic energy by chromophores within cells. The chromophore cytochrome oxidase is concentrated within mitochondria; it absorbs the energy in photons and delivers it into metabolic processes, including the Krebs cycle. This results in increased ATP production, as well as increased levels of nitric oxide and reactive oxygen species, important in cellular signaling. Metabolic activity increases, and cell growth and reproduction are accelerated.

Other complex mechanisms occur at the same time. There is an increased release of endogenous opioids; beta-endorphin levels rise. There is a direct effect on nerve tissue producing suppression of nociceptors and an increase in stimulation threshold. Neuron impulses are reduced, reducing pain. Researchers describe a “neural blockade” that results from the slowing of mitochondrial transport along axonal fibers.

A marked and rapid effect on inflammation is due to modulation of chemical mediators, with a decreased release of proinflammatory substances such as prostaglandins. A transient vasodilation results in increased circulation and oxygenation of the tissue. In addition, there is a similar effect on lymph vessels, activating the lymph drainage system and reducing edema.

Significant stimulatory effects on the healing process are induced. As with the anti-inflammatory effect, chemical mediators are involved, with an increased release of pro-healing cytokines such as transforming growth factor and platelet-derived growth factor. Angiogenesis is stimulated, fibroblast replication and migration increase, collagen production increases, and wound contraction is accelerated by the conversion of fibroblasts into myofibroblasts.

There is a similar stimulatory effect on bone healing. Angiogenesis is stimulated at the fracture site, accompanied by an elevation of osteogenic factors in the damaged tissue, resulting in accelerated development of new bone and faster fracture healing.

## LASERS FOR PHOTOBIMODULATION

Regulatory agencies classify lasers based on their ability to do harm if used improperly. Different agencies use somewhat different systems, but in general, lasers are classed into 1 of 4 broad hazard classes (I, II, III, IV) depending on their potential

In the clinical setting, therapy lasers that emit near infrared light are most often used. Different from LEDs (light-emitting diodes), therapeutic diode lasers emit invisible light in the 800- to 1000-nanometer range.

for causing biologic damage. Classification is based on wavelength, power, and exposure time.

Therapy lasers, like most medical lasers, are usually class III or class IV. Class III therapy lasers have a maximum power of 500 mW (0.5 W). Class IV therapy lasers are those over 500 mW in power.

Class III therapy lasers are applicable for treatment of superficial lesions and wounds. These lasers can be used for treatment of deeper tissue and musculoskeletal conditions, but due to their lower power level, longer treatment times are needed to achieve effective target doses.

Class IV therapy lasers are usually diode lasers emitting light in the 800- to 1000-nm wavelength range. The longer wavelengths in this spectrum have the deepest tissue penetration and produce excellent photobiomodulation. With these devices, effective treatments can be delivered in an acceptable amount of time, even when treating deep tissue conditions in large patients.

## TREATING ANIMALS WITH LASER THERAPY

Incorporation of laser therapy into routine pain control protocols is appropriate. As an adjunct to medical protocols, laser therapy is helpful after surgery and dental procedures. Most postprocedure patients require a single treatment immediately after the procedure. Examples are patients undergoing elective surgeries, minor dental procedures, and closure of minor wounds. Postprocedure patients with more extensive tissue disruption should receive additional treatments (2 to 6) daily or every other day.

Patients with a wide variety of acute problems benefit from laser therapy. Acute conditions are treated once or multiple times, until resolution of the condition. Patients with acute conditions that include pain, inflammation, a healing process, or a combination of any of these are candidates for laser therapy.

Chronic conditions involving pain, inflammation, and healing may also be helped, although the treatments have to extend over a longer time and are frequently followed by ongoing treatments to maintain effect. Patients with chronic conditions that include pain, inflammation, a healing process, or a combination of any of these are candidates for laser therapy.

Successful treatment design for chronic conditions follows accurate diagnosis and assessment of chronicity. Practitioners must avoid having a “one-size-fits-all” treatment design for chronic condition patients. Patients with chronic conditions are treated in 3 phases: induction, transition, and maintenance. Evaluation of an acceptable response to treatment depends on the patient signalment, the condition, and the expectations of the clinician and the owner.

Eye protection is critical when using class IIIB or class IV therapeutic lasers. All persons in the treatment area should wear appropriate safety glasses and pay strict attention to avoiding direct exposure of their eyes.

## EVIDENCE-BASED DATA

When first introduced to laser therapy, most veterinarians ask for evidence-based data. Initially, much of the knowledge practitioners had about laser therapy was experience-based information shared within the profession. Now veterinarians can find supporting evidence-based data in peer-reviewed publications and scientific literature. The results of in vitro and in vivo studies and clinical trials are readily available in publications like *Lasers in Surgery and*

*Medicine; Photobiomodulation, Photomedicine, and Laser Surgery; Journal of Photochemistry and Photobiology B: Biology; Journal of Clinical Laser Medicine & Surgery; and Lasers in Medical Science.*

## HEALING WITHOUT HARM

Virtually any medical laser has potential to do damage if used improperly. Proper training about a device, and how to use it safely, gives practitioners and staff the confidence that patients can be treated without harm.

In 2011, the American National Standards Institute revised guidelines for the safe use of lasers in healthcare. *ANSI Z136.3 – 2011 Safe Use of Lasers in Health Care* is the foundation of laser safety in veterinary medicine. Practices are encouraged to be familiar with ANSI Z136.3 and to have a designated, trained, and certified laser safety officer responsible for their laser safety program.

Eye protection is critical when using class IIIB or class IV therapeutic lasers. All persons in the treatment area should wear appropriate safety glasses and pay strict attention to avoiding direct exposure of their eyes.

The eyes of patients should also be protected with safety glasses (clients love this) or goggles made specifically for animals, or by covering their eyes with a dark cloth, a hand, or any material that the patient will tolerate. Some patients will not tolerate any covering of the eyes. For these patients, sedation is recommended, or if the patient is still and not moving, treatment can be administered with the therapist instantly ready to divert the laser beam in a safe direction if the patient moves.

## CONTRAINDICATIONS

For over 40 years, a list of contraindications has accumulated and been passed down, often repeated in publications and in device manuals, without consideration of whether it is valid. Currently, the one absolute contraindication is exposure of the retina by a direct or reflected beam transmitted through the pupil. Scattered photons reaching the retina through adjacent tissue treatment are not the concern; penetration through the pupil is.

Since there is no knowledge about how different wavelengths of light interact chemically with medications, and one does not want to alter the rate of absorption of medications, do not treat over areas into

which medication or vaccines have been injected. Apply laser therapy to tissue before injecting; then, do not treat the area again until the injection has been absorbed.

It is contraindicated to treat over a malignancy, or the surgical site from which a malignancy has been removed. There is contradictory data from the laboratory indicating that some malignant cell lines are stimulated, some are inhibited, and photobiomodulation has no effect on others. There is no contraindication for treating a site distant to a malignancy, and it is valid to treat areas of malignancy, with informed owner consent, for pain management in hospice care.

Historically, treating over a gravid uterus has been contraindicated. This was based on studies done decades ago in which chicken embryos showed cellular changes when exposed to high doses of visible red light through an eggshell window. This has no practical application to the clinical treatment of patients. Near infrared light is neither mutagenic nor teratogenic, and an embryo or fetus within a gravid uterus is well protected from photons that are readily absorbed by multiple layers of chromophores in the surrounding tissues.

Do not treat areas of active hemorrhage since a transient vasodilation is induced. Once hemorrhage has stopped, laser therapy will not reactivate the hemorrhage.

Treatment over active epiphyses, the testicles, or the thyroid glands all require similar consideration. Treatment with high doses for a prolonged time has been demonstrated to produce change in these tissues. However, negative effects are not reported with lower dose treatment over shorter periods.

Several historical contraindications are false. Treatment over areas of hyperpigmentation and over tattoos is safe with appropriate monitoring of skin temperature and delivery technique.

Treatment over implants is safe and indicated. Near infrared photons have no effect on metal implants. Photobiomodulation improves the health of the soft tissue around implants, contributing to implant success. Do exercise care when treating over very superficial metal implants because of the very small amount of overlying soft tissue.

Finally, the historical contraindication of treating patients on photosensitizing medications is invalid. In

Do not treat areas of active hemorrhage since a transient vasodilation is induced.

2014, a review of publications over the last 40 years found photosensitization and laser therapy linked only 4 times and no adverse effects ever reported. **TVP**

### Suggested Readings

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# Rehabilitation Modalities for Pain Management and Healing

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Physical rehabilitation is an emerging area of veterinary medicine. Multiple training programs offer certification in canine rehabilitation, board certification with the American College of Veterinary Sports Medicine and Rehabilitation, and credentialing with the Academy of Physical Rehabilitation Veterinary Technicians. Rehabilitation modalities can be particularly useful as part of a multimodal pain management program. Rehabilitative methods can improve patient comfort and quality of life, especially in cases where pharmaceutical pain relievers are contraindicated. This article reviews some of the more common modalities

that can be used to help reduce pain, enhance tissue healing, and improve patient function, as well as highlights associated evidence of efficacy (TABLE 1).

Which modality to choose depends largely on specific patient needs and the condition being treated. Although modalities can sometimes be used simultaneously, the synergistic or countereffects they may have on each other remain unknown. For this reason, you should consider the main goal of therapy and choose the most appropriate modality for addressing that goal.

**TABLE 1 Summary of Clinical Evidence of Efficacy of Rehabilitation Modalities for Treating Various Conditions in Dogs, 2012-2019**

EFFECT	LASER	PEMF	ECSW
Improved ambulation after hemilaminectomy	+/-		
Reduction of pain/pain medication administration	+	++	
Improved pelvic limb function after TPLO	+/-		
Alleviation of patellar desmitis			+
Improved wound healing	--	+	
Improved bone healing	-		+
Reduced lameness in dogs with osteoarthritis	+		+
Reduced lameness in dogs with shoulder tendinopathies			++

*+ indicates number of studies with results supporting efficacy; - indicates number of studies with results showing lack of efficacy. ECSW=extracorporeal shockwave; PEMF=pulsed electromagnetic field; TPLO=tibial plateau-leveling osteotomy.*



**FIGURE 1.** Class 4 laser and targeted pulsed electromagnetic field therapy being administered to a canine athlete with myofascial trigger points. This particular laser is ideal for providing massage and heat therapy simultaneously with the laser. Combined heat, laser, and massage can help relieve tense muscles.

## LASER THERAPY/ PHOTOBIO-MODULATION

Perhaps the most commonly used rehabilitative modality is laser therapy, which stands for light amplification by stimulated emission of radiation (**FIGURE 1**). This modality has more recently been called photobiomodulation, primarily because therapeutic lasers modulate biological cellular activity as opposed to other nontherapeutic lasers (e.g., grocery store scanners or laser pointers) that do not have a biological effect.

One proposed mode of action for therapeutic laser is stimulation of the respiratory chain in the mitochondria. The respiratory chain is a complex of genes that provide instructions for proteins involved in oxidative phosphorylation. As light enters the cell, it is absorbed by cytochrome c oxidase (the next-to-last step in the mitochondrial respiratory chain process) leading to increased production of adenosine triphosphate. Cells also release low levels of ROS (reactive oxygen species), resulting in endogenous anti-oxidant production by the cell and release of nitrous oxide, which leads to vasodilation and increased perfusion.

Lasers are classified according to risk for eye injury. The higher the class of laser, the greater the risk for eye injury and thermal damage to eyes and/or other tissue. Class 4 lasers are defined as those with power output of 500 mW and above. In general, therapeutic lasers with potential for photobiomodulation are Class 3 and above and require protective eyewear. Lower-class lasers can have photobiomodulation potential when tissues

are exposed for a longer time at specific wavelengths. In general, lower wavelengths are more effective for superficial tissues (~600 nm) and higher wavelengths, for deeper tissues (up to 3 to 5 cm, or 800 to 900 nm).

Several recently published studies evaluated the efficacy of using photobiomodulation in veterinary medicine.<sup>1-10</sup> The results can be difficult to interpret because of the large number of different products on the market and variations in protocols and outcome measures. Thus, we should be cautious when making conclusions. Some authors question whether photobiomodulation can help improve recovery after hemilaminectomy in dogs. Draper et al. found that dogs receiving a low-level Class 3B laser (810-nm wavelength for 1 minute daily for 5 days) regained the ability to ambulate significantly faster than untreated dogs (3.5 vs 14 days).<sup>1</sup> In contrast, using the same laser and protocol, Bennaim et al. found no difference in outcome between laser and placebo groups.<sup>2</sup> In another prospective study evaluating wound healing, Kurach et al. found no apparent beneficial effects for dogs with experimentally induced incisions and subsequent exposure to a Class 2 laser (635-nm wavelength laser for 5 minutes for a total dose of approximately 1 J/cm<sup>2</sup>).<sup>3</sup> When Kennedy et al. evaluated this same laser in a prospective study, they found no beneficial effects on pain, radiographic healing, or pelvic limb function in dogs who received this Class 2 laser before and 10 times after tibial plateau-leveling osteotomy (TPLO) for the first 96 hours at 2.5 J/cm<sup>2</sup> and then weekly at home for 4 weeks (at 1.5 J/cm<sup>2</sup>).<sup>4</sup> However, those studies may have failed to demonstrate lack of efficacy because they used a lower class of laser. Usually, rehabilitation practitioners use Class 3B lasers and above. A small study demonstrated improved scores in incisional scars in 4 dogs who received postoperative

Lasers are classified according to risk for eye injury. The higher the class of laser, the greater the risk for eye injury and thermal damage to eyes and/or other tissue.

The most notable benefits of PEMF include pain relief, increased wound healing, and reduced soft tissue pain and edema.

photobiomodulation daily for 7 days at 8 J/cm<sup>2</sup> with a Class 3B laser compared with 5 dogs who did not receive photobiomodulation.<sup>10</sup>

Another study that evaluated the effects of laser on dogs after TPLO found improved pelvic limb function (determined by measuring peak vertical force with a pressure mat system).<sup>5</sup> Those dogs received a single Class 4 laser dose with dual 800- and 970-nm wavelengths, at 6 W for a unified dose of 3.5 J/cm<sup>2</sup> over a 100-cm<sup>2</sup> area.<sup>5</sup> In another recent prospective blinded study, dogs with naturally occurring elbow osteoarthritis demonstrated reduced lameness, pain scores, and nonsteroidal anti-inflammatory drug dosages compared with placebo-treated dogs.<sup>6</sup> The treated dogs received photobiomodulation therapy with a Class 4 laser twice weekly for 3 weeks and then weekly for 3 weeks at a dose of 10 to 20 J/cm<sup>2</sup> per joint.<sup>6</sup>

As previously stated, use of wide-ranging doses and various laser devices make it difficult to base conclusions on these limited data. Larger prospective, randomized, controlled clinical trials are needed before any conclusions about the therapeutic benefits of laser use in companion animals can be reached.

In human medicine, data are also not conclusive. A systematic review of the treatment of plantar fasciitis in people showed reduced pain and improved function; however, laser doses varied widely among studies, making it difficult to determine best treatment parameters.<sup>7</sup> Another recent systematic review and meta-analysis of photobiomodulation effects on bone healing in humans showed improvement in pain and function; however, the level of evidence is considered low to very low, and no effect on radiographic healing of the fracture line was found.<sup>8</sup> Similarly, results of a systematic review of low-level laser on pressure ulcers in humans were conflicting and not conclusive.<sup>9</sup>

## PULSED ELECTROMAGNETIC FIELD THERAPY

Another rehabilitation modality that has recently gained popularity and become widely available to rehabilitation and general practitioners is pulsed electromagnetic field (PEMF) therapy (**FIGURE 1**). This technology has been available for over a century; however, it became more popularized in the 1980s when the Food and Drug Administration approved low-powered PEMF devices as bone growth stimulators. Since then, the technology has been further developed and targeted. There are many devices on the market, including PEMF beds and devices that provide more targeted therapy, such as a loop device. Of note, the particular signal of the device affects its therapeutic potential. Variations exist in pulse width, pulse frequency, size and geometry of the antenna, and duration of the signal. The targeted shortwave forms (27 mHz, 2-ms pulse width, 2-Hz pulse frequency) are thought to be more effective. Practitioners are advised to ask PEMF manufacturers what specific signal is used by their product and what evidence they have to support their dosage recommendations. In general, acute conditions should be treated 3 to 4 times daily for 5 to 10 days until pain resolves. Chronic conditions can be treated once or twice daily or even less frequently, depending on response. The postulated mode of action for the signal emitted by the loop device is upregulation of the voltage-dependent binding of calcium to calmodulin. This binding enhances release of constitutive nitrous oxide synthase, leading to vasodilation and an anti-inflammatory cascade.

The most notable benefits of PEMF include pain relief, increased wound healing, and reduced soft tissue pain and edema (**TABLE 1**). Two recent randomized and controlled clinical trials demonstrated benefits of PEMF use on recovery of dogs after hemilaminectomy.<sup>11,12</sup> In particular, Alvarez et al. demonstrated reduced client administration of opioid medications during the initial 7-day postoperative period for dogs who received PEMF therapy compared with those who received placebo.<sup>11</sup> In addition, 6-week postoperative wound scores were better for treated than control dogs.<sup>11</sup>

With regard to potential side effects, PEMF is perhaps one of the most benign of the rehabilitation modalities. However, its use is contraindicated for patients with pacemakers or arrhythmias and those with active hemorrhage.



## EXTRACORPOREAL SHOCKWAVE THERAPY

Shockwave therapy was first introduced as a method for breaking up urinary calculi (lithotripsy). Since then, the technology has advanced and is widely used in human and veterinary medicine for treatment of nonunion or delayed union fractures, wound healing, tendinopathies, arthritis, and other conditions. Among rehabilitation modalities in the veterinary field, the level of evidence for efficacy is perhaps highest for extracorporeal shockwave (ECSW) therapy (TABLE 1). The mode of action is emission of acoustic waves at high velocity and pressure. A large amount of energy is deposited in the tissues, creating cavitation bubbles that subsequently collapse and lead to increased cellular permeability and expression of cytokines and growth factors. Because the pressure waves of ECSW are emitted at lower frequency than those of therapeutic ultrasonography, they cause no thermal effect. The analgesic effects most likely result from nociceptor stimulation and endorphin release.

A variety of ECSW devices, with varying effectiveness, are available. In particular, devices can vary by depth of penetration and focal area. Therefore, devices should be chosen according to the condition being treated and



**FIGURE 2.** High-energy extracorporeal shockwave therapy being administered to a dog with chronic supraspinatus and biceps tendinopathy.

available evidence to support that use. Focal superficial signal devices may be more effective for treating myofascial trigger points, whereas electrohydraulic devices with higher energy and deeper penetration may be more appropriate for treating nonunion fractures, osteoarthritis, or other deeper tissue disorders. Several prospective studies that used higher energy and deeper signal devices demonstrated efficacy for treating patellar desmitis after TPLO,<sup>13</sup> acceleration of bone healing,<sup>14</sup> and osteoarthritis<sup>15</sup>; retrospective studies demonstrated efficacy for treating shoulder tendinopathies (FIGURE 2).<sup>16,17</sup> Contraindications include use on patients with immune-mediated joint disease, septic arthritis, neoplasia, diskospondylitis, unstable fractures, and neurologic deficits.

## TAKE-HOME POINTS

- Rehabilitation modalities are used to help reduce pain and enhance tissue healing.
- Choice of rehabilitation modality should be based on the patient's needs, the condition being treated, and level of evidence.
  - **Laser:** Prospective clinical trials in veterinary medicine are reported for hemilaminectomy, TPLO, and elbow osteoarthritis. Results are not conclusive enough to use for clinical decision making.
  - **PEMF:** Most notable published veterinary benefits include pain relief, increased wound healing, and improved recovery after hemilaminectomy.
  - **ECSW:** Sufficient evidence in dogs exists to warrant use for nonunion or delayed union fractures, tendinopathies, and arthritis.
- Overall, rehabilitation modalities can be part of a multimodal pain management program and can improve patient comfort and function in a noninvasive manner. **TVP**

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# Laser Therapy for Treatment of Joint Disease in Dogs and Cats

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Photobiomodulation (PBMT), or laser therapy, is a rapidly growing treatment modality used for a variety of medical conditions in companion animals. PBMT is painless, noninvasive, and easily administered in a primary care setting.<sup>1</sup> Therapeutic laser devices are estimated to be used by 20% of all companion animal practices in North America.<sup>1</sup>

PBMT accelerates healing in a number of tissues, provides analgesia, and decreases inflammation through

modulation of immune and inflammatory responses.<sup>2</sup> PBMT has been used in human and veterinary medicine to improve wound healing, treat snake bites, decrease pain and inflammation resulting from musculoskeletal conditions, improve neurologic function after trauma or injury, treat stomatitis and other oral inflammatory conditions, treat intraoperative and postoperative inflammation, and enhance healing of sport-related injuries.<sup>1</sup> The focus of this article, however, is on treatment of joint conditions in companion animals.

**TABLE 1 PBMT Glossary\***

TERM	DEFINITION
Coherent	Photons travel in the same phase in time and space
Collimated	Light divergence is minimized over a distance
Duty cycle	Percentage of total emission time to total treatment time in a pulsed laser
Fluence, J/cm <sup>2</sup>	Energy absorbed per area treated
Frequency, Hz	Number of waveforms in a defined time interval
Irradiance, W/cm <sup>2</sup>	Power intensity
Joule	Energy unit used to measure dose or rate of energy delivery
Monochromatic	Light of 1 wavelength
Spot size	Radius of the laser beam
Watt	Unit of power measured as 1 J/second
Wavelength, nm	Distance between crests of electromagnetic waves

\*Hz=hertz; J=joule; nm=nanometer; PBMT=photobiomodulation therapy; W=watt.

Adapted from a table published in "Photobiomodulation Therapy in Veterinary Medicine: A Review" in Topics in Companion Animal Medicine.<sup>7</sup>



## WHAT IS PHOTOBIO-MODULATION THERAPY?

Since its development, PBMT has been referred to by many names; terms such as cold laser, low-level laser therapy, phototherapy, and low-level light therapy appear in the literature and have caused confusion. Participants at a nomenclature consensus meeting recommended that the term photobiomodulation be adopted to mean “a form of light therapy that utilizes nonionizing forms of light sources, including lasers, light-emitting diodes (LEDs), and broadband light, in the visible and infrared spectrum.”<sup>3</sup> PBMT is defined as a “therapeutic use of light, absorbed by the chromophores found in the body, to stimulate nonharmful and nonthermal reactions within the cell that result in a beneficial therapeutic outcome.”<sup>3</sup> Although PBMT describes the effects of the therapeutic modality, the term LASER (commonly lowercased) is an acronym for light amplification by stimulated emission of radiation. Veterinary lasers can be used for either therapeutic or surgical applications, depending on the laser.

## HOW DOES PBMT WORK?

Studies have shown that PBMT alters the inflammatory response and affects cell signaling.<sup>4,5</sup> The main factors underlying the laser’s therapeutic effects are increased reactive oxygen species (ROS), adenosine triphosphate (ATP), and nitric oxide (NO). Increased ROS activates the endogenous anti-oxidant enzyme systems; increased ATP supplies cells with energy for repair; increased NO promotes angiogenesis, modulates the inflammatory and immune responses, and mediates

vasodilation.<sup>4,5</sup> The fundamental step that eventually results in the production of increased ATP is photostimulation of the enzyme cytochrome c in the mitochondrial respiratory chain. Cytochrome c absorbs light in the spectrum of 500 to 1000 nm (therapeutic window) and breaks the bond with NO, which allows bonding with oxygen and production of cytochrome c oxidase at an optimal rate. Cytochrome c oxidase is responsible for the formation of ATP. Additional electrons are accepted by oxygen to produce ROS.

PBMT reduces the pain and inflammation of osteoarthritis and joint disease through several mechanisms of action. PBMT has been shown to reduce cyclooxygenase 2 and bradykinin production (bradykinins induce pain by stimulating afferent nociceptors).<sup>6</sup> Cytokines and growth factors that have anti-inflammatory, anti-oxidative, and anti-apoptotic properties are increased. PBMT reduces the production of inflammatory markers such as interleukin 1 beta, tumor necrosis factor alpha, and prostaglandin E2.<sup>6</sup> PBMT decreases neutrophils in joint fluid, relieves pain, and increases joint mobility and function.<sup>6</sup> PBMT decreases inflammation in tendons and ligaments while increasing tensile strength, collagen fibril size, and fibroblast production.<sup>7</sup> Research has shown that after cruciate transection and subsequent tibial plateau-leveling osteotomies, PBMT reduces cartilage degeneration and synovial inflammation and improves peak vertical force.<sup>7</sup> It has also been shown to accelerate bone healing and promote recovery of atrophied muscles.<sup>7</sup> All these PBMT effects can be amplified when combined with multimodal therapy for the treatment of joint disease.

**TABLE 2 Laser Classification\***

CLASS	DESCRIPTION
1	<ul style="list-style-type: none"> <li>Not hazardous to the eyes and requires no eye protection.</li> <li>Examples: laser printers and CD players.</li> </ul>
1M	<ul style="list-style-type: none"> <li>Not hazardous to the eyes unless using optical instruments such as binoculars or microscopes.</li> </ul>
2/2M	<ul style="list-style-type: none"> <li>Limited to 1 mW of power.</li> <li>No protective eyewear is needed, but extended viewing is not recommended.</li> <li>This class includes point-of-sale scanners.</li> </ul>
3R	<ul style="list-style-type: none"> <li>Have output of up to 5 mW.</li> <li>Are not a fire hazard.</li> <li>Only an optical hazard if focused or viewed for an extended period of time. This class includes laser pointers.</li> </ul>
3B	<ul style="list-style-type: none"> <li>Have output of up to 500 mW and wavelengths from 300 nm up to the far infrared.</li> <li>Requires protective eyewear.</li> <li>This class includes therapy lasers from 5 to 500 mW.</li> </ul>
4	<ul style="list-style-type: none"> <li>Have output greater than 500 mW.</li> <li>Can burn skin or cause permanent eye damage.</li> <li>Protective eyewear must be worn when operating these devices.</li> </ul>

*\*Adapted from a table published in “Fundamental Information” in Veterinary Medicine: Photobiomodulation.<sup>8</sup>*



### BOX 1 Benefits of Laser Therapy for Joint Disease

- Pain reduction
- Reduced markers of inflammation in the joint
- Reduced swelling and edema
- Increased joint mobility and function
- Stimulation of collagen synthesis
- Decreased dosage or frequency of pharmaceutical use for patients with chronic disease

Adapted from "Musculoskeletal Disorders and Osteoarthritis" in Laser Therapy in Veterinary Medicine: Photobiomodulation.<sup>6</sup>

## LASER FUNDAMENTALS AND CLASSIFICATIONS

Fundamental PBMT terms and definitions are summarized in **TABLE 1**.<sup>7</sup> All lasers are classified according to potential to cause optical damage by wavelength, power, and exposure duration. Classes 3B and 4 can be used safely; however, classes 1, 1M, 2/2M, and 3R are not appropriate for any use in veterinary rehabilitation. **TABLE 2** describes laser classifications.<sup>8</sup>

### Tissue Penetration

One of the most critical elements of laser therapy is depth of penetration. Laser light is monochromatic, collimated, and coherent, enabling it to penetrate through tissues to a cellular level. When light interacts with biological tissue, it is either absorbed, scattered, or reflected.

### Wavelength

A therapy laser will emit light in the 620- to 1200-nm range, often called the therapeutic window. Wavelengths that minimize scattering and reflection as well as absorption by unwanted chromophores will provide optimal penetration into the tissue and ensure a better therapeutic result.<sup>1</sup> Melanin, hemoglobin, and oxyhemoglobin chromophores absorb shorter wavelengths (600 to 800 nm), making these wavelengths better for superficial areas. Wavelengths above 1000 nm are primarily absorbed by water, making tissue penetration difficult. Surgical lasers, such as the CO<sub>2</sub> laser, produce wavelengths around 10,600 nm, which are strongly absorbed by water and therefore

can be used for surgical applications.<sup>1,6</sup> Wavelengths of 800 to 1000 nm can achieve appropriate depth of penetration to treat most musculoskeletal conditions.

### Power and Duration

Penetration depends on wavelength and tissue type, not laser power (watts [W]) or laser intensity (irradiance) at the tissue surface (W/cm<sup>2</sup>). Using a higher-powered laser delivers more photons to the penetration depth and also determines the time needed to deliver the energy. Lower-powered lasers must be used for a longer time to achieve the same dose. Very low-powered lasers will have no measurable results even when used for long periods of exposure.<sup>1,6</sup>

## Dosage

### Manual

Another consideration with regard to PBMT is dosage applied to the tissue. Dosage is expressed as the amount of energy (joules [J]) delivered to a certain surface area (cm<sup>2</sup>). When calculating the correct dose, the therapist must consider the size of the patient, body type, coat length and color, skin color, and depth of the condition to be treated. When joint conditions are being treated, the dose can be influenced by the size of the patient, whether the fur is clipped, and the joint involved.<sup>1,6,7</sup> In general, the larger the patient, the larger the dose required for a therapeutic effect. For most joints, 8 to 12 J/cm<sup>2</sup> will work well; however, for some joints (e.g., the elbow), a higher dose may be required.<sup>9</sup> **TABLE 3** lists commonly used doses for joints<sup>1</sup> and **BOX 1** summarizes the benefits of PBMT for joint disease.

### Preset

Many of the newer laser units have preset protocols for treating various conditions. The operator inputs parameters such as size, coat length and color, and area and condition treated, and the machine uses this input to calculate the fluence required. Settings can be manually changed if the therapist wishes to adapt or change the dose. Protocols vary with the manufacturer, and it is in the best interest of the patient for the practitioner to understand laser dosimetry. However, the presets on newer machines have increased safety features and enable veterinarians to confidently delegate delivery of the therapy to well-trained persons.<sup>6</sup>



## TREATMENT TECHNIQUES

Before beginning treatment, ensure that the patient is wearing protective eyewear and is comfortable and appropriately positioned, providing good access to the area being treated. If that area is a joint, ensure access to all sides of the joint. Passive range of motion therapy before and after PBMT is a good idea to ensure improved function.

Treatment techniques will vary according to the condition treated, the joint treated, and the type of laser used. In general, clipping the area will allow the best penetration of light to the underlying tissues; however, if clipping is not possible then the dosage needs to be adjusted. Be cautious not to overheat the coat or skin if using lasers with higher wattage or wavelengths less than 900 nm.

When treating joints, treat a broad area. For example, treat the specific joint and surrounding muscles and tendons as well as satellite areas of pain. Treating a comprehensive area will ensure a more consistent outcome.<sup>1</sup>

Treatment technique will vary with the laser used. Lower-powered lasers (less than 1 W) can use a point-to-point method in which a dose is delivered for up to 30 seconds in 1 location before the probe is moved. This method can be more time-consuming, depending on which joint is being treated and whether multiple joints are involved. Higher-powered lasers use a scanning method that delivers the dose over a large area, ensuring that the handpiece is moving during treatment. The therapy can be delivered with a contact or off-contact method, depending on the unit. The contact method allows for tissue compression and can cause deeper penetration. The off-contact method is frequently used over bony prominences or excessively painful areas.<sup>1</sup>



**FIGURE 1.** Patient undergoing laser therapy. Note the protective eyewear, soft surfaces, and minimal restraint.

For acute or chronic painful joint conditions, it is useful to begin with an induction phase of treatment, followed by more frequent treatment sessions until a significant effect is noticed. For patients with acute joint injury or a flare-up of chronic arthritis, daily treatment is recommended. After clinical signs have improved significantly, then treatments can be reduced to twice weekly for 2 to 3 weeks and then further reduced to maintenance according to the patient's response. It is not unusual for patients with osteoarthritis to receive treatment every 3 to 6 weeks, depending on response. In general, 4 to 6 treatments are needed to see improvement, although 8 to 10 sessions may be needed for patients with multiple joint involvement or severe disease. Be sure that clients are aware that each patient responds differently to PBMT.<sup>6</sup>

## USE OF PBMT WITH METAL SUTURES AND IMPLANTS

Smooth metal implants and staples will primarily reflect diffuse near-infrared light; thus, heating of the implants is not a concern. However, with small patients (e.g., cats and small dogs) the implant will be covered

**TABLE 3** Common Laser Doses for Small Animal Joints\*

JOINT	DOSE
Carpus	1-4 J/cm <sup>2</sup>
Elbow	4-8 J/cm <sup>2</sup> but may be up to 20 J/cm <sup>2</sup> for chronic conditions
Shoulder	8-10 J/cm <sup>2</sup>
Hip	10-12 J/cm <sup>2</sup> or higher for large breed dogs
Stifle	4-8 J/cm <sup>2</sup> for small dogs; 10-12 J/cm <sup>2</sup> for large breed dogs
Tarsus	1-4 J/cm <sup>2</sup>

\*Adapted from a table published in "Therapeutic Laser in Veterinary Medicine" in Veterinary Clinics of North America: Small Animal Practice.<sup>7</sup>



by superficial tissue only. Because of the light reflection, these areas will need an increased dose; therefore, to ensure patient comfort, adjustments need to be made to decrease the power or time of treatment. Because the light does not penetrate the hardware, apply the laser 360 degrees around the limb. Do not hover the laser over sutures; instead, apply the laser to both sides of the suture line.<sup>6</sup>

## PRECAUTIONS FOR PBMT USE

Keep in mind the following safety precautions when using PBMT:<sup>1</sup>

1. Use protective eyewear (for patient and therapist), specific for the laser being used.
2. Do not treat over a pregnant uterus or open fontanelles.
3. Do not treat over malignancies.
4. Remove all metal from the patient (e.g., jewelry, leashes, collars).
5. Use caution with dark skin (melanin increases absorption by chromophores). Use your hand to monitor skin temperature while PBMT is being applied.

## SUMMARY

PBMT is a valuable modality that can be used to treat a variety of joint conditions in dogs and cats. For PBMT to be effective, the dose must be appropriate for the particular condition, joint, and patient. Additional veterinary clinical studies are required to document further benefits and determine optimal parameters for all applications. **TVP**

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# The Therapeutic Power of Monoclonal Antibody Therapy

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Although biotherapeutics have been used in human medicine for more than 30 years, they are still relatively new in veterinary medicine.<sup>1</sup> Recent advances in the veterinary arena include updated labeling and industry acquisition and collaboration to develop new biologic agents. This article reviews biologic therapy as it relates specifically to monoclonal antibodies (mAbs) and covers the only fully licensed and commercially available product, lokivetmab (CYTOPOINT™), which is made by Zoetis.

## PRINCIPLES OF BIOTHERAPY

Biotherapy differs from traditional pharmacotherapy in that it mimics the body's normal immune response to treat disease or protect against adverse events.<sup>2</sup> Biologic agents are commonly categorized into 3 groups:

1. Peptides and small proteins (hormones and cytokines)
2. Nonimmune proteins (replacement enzymes and blood factors)
3. Therapeutic antibodies and Fc receptor–like proteins

The major advantages of biotherapeutic agents over traditional drugs are the agents' specificity, which facilitates precise action (ideally with minimal unintended effects), and their long half-lives, which allow infrequent dosing.<sup>1</sup>

In human medicine, mAbs represent the area of biotherapy that offers the greatest array of potential therapies. This is also the therapeutic arena most likely to see peak growth in products brought to the veterinary marketplace for clinical use in treating arthritis, autoimmune disease, allergic conditions, infectious disease, and oncologic disorders.<sup>2</sup>

## MONOCLONAL ANTIBODIES

### Production

mAbs are essentially identical to naturally occurring antibodies produced and secreted by plasma cells in the body. However, in a normal immune response to stimulation by an infectious agent or disease, numerous plasma cells produce thousands of antibodies that recognize multiple



epitopes on a particular antigen. mAbs arise from a single plasma cell line and recognize the same target region on an antigen.

Production of mAbs was historically accomplished by immunizing mice, isolating the desired B cells, and fusing these cells with an immortal myeloma cell line (the *hybridoma technique*).<sup>3</sup> However, when these murine antibodies were injected into nonmouse subjects, they stimulated significant undesired immune reactions. To resolve this problem, genetic engineering and recombinant DNA techniques have been developed, and speciated (humanized, caninized, or felinized) mAbs that are greater than 90% similar to those of the target species' composition can now be created.<sup>3,4</sup> This level of speciation limits the use of the products to only the labeled species but also decreases the risk of adverse effects.

As of September 2018, the label indication is that lokivetmab has been shown to be effective for the treatment of allergic dermatitis and atopic dermatitis in dogs.

## Mechanism of Action

Therapeutic mAbs exert their biologic effect predominantly via one of three mechanisms. The first is through the binding or “soaking up” of soluble extracellular targets (i.e., cytokines) before these targets arrive at a cellular receptor.<sup>2</sup> This action prevents the target molecules from activating cellular receptors and is the primary mechanism by which lokivetmab exerts its effect.

The second mechanism is to simply bind a target receptor on the cell surface and block activation of signal transduction; mAbs that act through this pathway are classified as *antagonistic*.<sup>2</sup> Many currently approved human products act through this mechanism.<sup>2</sup>

The third mechanism is to bind to an infectious agent or cancer cell and either activate cell lysis (via

complement-dependent cytotoxicity or antibody-dependent cell-mediated cytotoxicity) or enhance clearance of the foreign agent by antibody-dependent phagocytosis.<sup>1,2</sup> The backbone or immunoglobulin (Ig) isotype also affects the specific mechanism of action and half-life of an individual mAb.<sup>5</sup>

Like any protein, mAbs undergo denaturation and proteolytic enzymatic breakdown in the stomach if given orally. Thus, all therapeutic mAbs are administered by intravenous, subcutaneous, or intramuscular injection. Once injected, they have long half-lives similar to those of naturally produced antibodies (roughly 20 days).<sup>2</sup>

Unlike traditional drugs, mAbs do not need to undergo biotransformation so that they can be inactivated or excreted from the body; rather, as biologic agents that mimic normal physiologic products, they are inactivated through pathways similar to that of the natural product. mAbs undergo intracellular catabolism within the lysosome, where they are broken down to amino acids that can either be recycled for the synthesis of new proteins or be renally excreted. This inactivation pathway provides mAbs a tremendous advantage over traditional drugs in that they are unlikely to result in adverse drug–drug interactions when administered to patients concurrently receiving other medications.

## Safety

As with anything new, biotherapy carries with it concern about the unknown. Many practitioners worry about a wide array of potential adverse events from mAb therapy, most of which are unlikely, as mAbs are very target specific and have unique metabolic aspects. Because mAbs do not have intracellular activity, it is easier to predict adverse events before clinical trials, based on the anticipated blockade of the target, and it is a generally accepted concept that mAbs tend to be a safer form of treatment than traditional drugs. This improved risk–benefit ratio is grounded by the fact that the likelihood of a mAb reaching the market is roughly 4 times greater than that of a newly developed pharmacologic agent.<sup>1</sup>

The overall safety of any particular mAb is largely determined by the mAb's target and level of speciation. Adverse events that have been encountered with therapeutic mAbs in human medicine are listed in **BOX 1**; these events are, for the most part, predictable based on the mechanism and target of the specific product.



## LOKIVETMAB

To date, several mAbs have received conditional or full license approval. They include biologics for cancer therapy (blontuvetmab [Blontress<sup>®</sup>] and tamtuvetmab [Tactress<sup>®</sup>] ([aratana.com](http://aratana.com)), osteoarthritis (ranevetmab and frunevetmab), and canine allergic dermatitis (lokivetmab). However, at this time, the only fully licensed commercially available product is lokivetmab.

Lokivetmab is a caninized anti–interleukin-31 (IL-31) mAb that works by neutralizing soluble IL-31 produced predominantly by lymphocytes. It was developed after IL-31 was shown to play a role in development of canine pruritus.<sup>7</sup> IL-31's potential role in the development of pruritus associated with atopic dermatitis has been further substantiated by more recent studies.<sup>8,9</sup>

### Indication and Use

Lokivetmab is approved and licensed through the U.S. Department of Agriculture. The original label indication was to aid in the reduction of clinical signs associated with atopic dermatitis. As of September 2018, the label indication is that lokivetmab has been shown to be effective for the treatment of allergic dermatitis and atopic dermatitis in dogs.

Lokivetmab is provided in 1-mL sterile, ready-to-use vials (10, 20, 30, or 40 mg/mL). Individual vials are meant for single use and should be administered to a patient in their entirety via subcutaneous injection. The current labeled target dose is 2 mg/kg, which can be repeated every 4 to 8 weeks as needed.

### Clinical Trials

Since lokivetmab's release, several published studies and research abstracts have assessed its clinical efficacy and safety in dogs. The first study was a dose-determination study using client-owned dogs to assess efficacy and safety of a single subcutaneous injection over a 56-day period.<sup>10</sup> In this study, dogs were randomly assigned to receive a dose of lokivetmab (0.125, 0.5, or 2 mg/kg) or placebo. Efficacy was evaluated by the clinician and the owner using objective scales. The study showed that clinical parameters were improved at the 2 higher doses compared with placebo and that the level and duration of response correlated with the dose given. In addition, pharmacokinetic data from this study revealed that the half-life for lokivetmab was 16 days, with peak serum concentration reached at 9.8 days after administration.

### BOX 1 Adverse Events Observed in Human Medicine With mAb Therapy<sup>1,6</sup>

- Injection site discomfort
- Lethargy
- Fever
- Gastrointestinal upset
- Production of anti-drug antibodies
- Anaphylaxis
- Reactivation of infectious diseases
- Thrombocytopenia
- Leukopenia
- Hypothyroidism
- Pulmonary events
- Autoimmune disease
- Neoplasia (tumor necrosis factor- $\alpha$  specific products)
- Pruritus
- Erythema and rash
- Cardiotoxicity
- Tumor lysis syndrome
- Cytokine release syndrome

Safety data generated in this clinical trial revealed no hypersensitivity-related reactions to the single injection immediately after dosing, no evidence of treatment-induced immunogenicity, and no specific safety concerns associated with treatment.<sup>10</sup>

A second study provided additional safety data from canine patients with atopic dermatitis receiving 2 doses of lokivetmab (1.0 to 3.3 mg/kg) compared with placebo.<sup>11</sup> This study enrolled 245 dogs, and 2 injections were given 28 days apart. Adverse events observed in greater than 2% of participants included secondary skin or ear infections, pruritus, gastrointestinal (GI) upset (anorexia, vomiting, and diarrhea), and lethargy. Both treatment groups experienced GI upset and lethargy at a similar rate, which resolved spontaneously or with supportive care; no immediate hypersensitivity or injection site reactions were reported. However, 2.5% of lokivetmab-treated dogs developed treatment-induced immunogenicity. No adverse interactions with concomitant medications were observed in this study.<sup>11</sup>

A third investigation evaluated the safety and efficacy of lokivetmab compared with cyclosporine over a



3-month period, then followed 81 dogs for an additional 6 months as part of a continuation study.<sup>12</sup> Overall, lokivetmab-treated patients compared favorably with those treated with cyclosporine. No significant differences between groups were appreciated in measured clinical outcome parameters. The continuation phase demonstrated continued efficacy, with 76.3% of animals assessed to have a normal level of pruritus after the ninth month of treatment. This study had safety results similar to those of the first 2 clinical trials, with GI upset occurring significantly less frequently in dogs treated with lokivetmab than in those treated with cyclosporine. No hypersensitivity reactions or immediate post-dosing injection site reactions were appreciated during the 9-month study. Treatment-induced immunogenicity was seen in 2% of dogs during the initial 3 months but in no new dogs during the continuation phase.<sup>12</sup>

The final published report at this time is a retrospective study that evaluated the experiences of dogs treated with lokivetmab over a 1-year period at a dermatology specialty hospital.<sup>13</sup> Treatment with lokivetmab improved pruritus scores in 87.8% of dogs, with 77% of dogs experiencing >50% reduction in pruritus. There was no association of improvement with the dosage and response, but a trend was observed that larger dogs were more likely to be classified as treatment successes, as defined by reduction in pruritus scores. The study evaluated speed of onset and found that almost 96% of dogs responded within the first 72 hours after administration, with more than half (55.9%) experiencing improvement by 24 hours. Additionally, dogs with pruritus considered “severe” or “very severe” before treatment were more likely to be classified as treatment successes. Of note, 71.4% of dogs that had an inadequate response to oclacitinib, an oral JAK inhibitor, were considered treatment successes

with lokivetmab.<sup>13</sup> Adverse events were reported in 11 of 132 dogs (8.3%) treated with lokivetmab; the most common adverse effect reported was lethargy within 72 hours of receiving the injection (8 of 11 patients).<sup>13</sup>

## CONCLUSION

Taken together, the clinical studies show that lokivetmab appears to be a safe and effective treatment option for dogs with allergic dermatitis. In addition, lokivetmab offers several advantages over traditional drugs (cyclosporine, oclacitinib, and glucocorticoids) used in the management of allergic dogs; namely, it can be given to dogs of all ages, with any concomitant medication, and with any concurrent medical condition. This therapy offers some exciting new opportunities in treating dogs with allergic dermatitis. **TVP**

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