

# Nonsteroidal, Nonimmunosuppressive Therapies for Pruritus

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## KEYWORDS

- Pruritus • Dog • Barrier dysfunction • Epidermal lipids • Atopic dermatitis
- Topical therapy • Antihistamines • Essential fatty acids

## KEY POINTS

- Pruritus is a symptom associated with a wide variety of causes and treatment options.
- There is no single therapy that is effective in every case of pruritus (no magic solution).
- Treatment frequently involves a multimodal approach.
- Atopic dermatitis is a common cause of pruritus in the dog.
- Percutaneous absorption of antigen and barrier dysfunction are now recognized as important components of pruritus associated with atopic dermatitis.
- Topical therapy is becoming the new target for the treatment of pruritus.
- Systemic therapy, other than with immunosuppressive agents, is becoming a less important treatment of pruritus.

## INTRODUCTION

Pruritus, or itch, is defined as “a sensation that, if sufficiently strong, will provoke scratching or the desire to scratch.”<sup>1,2</sup> Pruritus does serve a useful purpose. It has a self-protective mechanism that helps defend the skin against harmful external agents. Pruritus can be evoked in the skin directly by mechanical and thermal stimuli or indirectly through chemical mediators. Chemical mediators include histamine, catecholamines, acetylcholine, neuropeptides (eg, substance P, calcitonin gene-related peptide), vasoactive intestinal polypeptide, serotonin, corticotropin-releasing hormone, opioids, cannabinoids, neurotrophins (nerve growth factor, neurotrophin-4), bradykinin, proteases (chymases, tryptases, and carboxypeptidase), lipid mediators (leukotriene B<sub>4</sub>), cytokines, and interleukins (IL-2, IL-4, IL-6, IL-8, and most recently IL-31).<sup>3–7</sup>

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Dr Bloom has had lectures or meetings sponsored by Virbac; their products include Resicort, Allermyl, and Allerderm Spot On.

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Vet Clin Small Anim 43 (2013) 173–187  
<http://dx.doi.org/10.1016/j.cvs.2012.09.001>

[vetsmall.theclinics.com](http://vetsmall.theclinics.com)

0195-5616/13/\$ – see front matter © 2013 Published by Elsevier Inc.

## CAUSES OF PRURITUS

There are many different classification schemes for pruritus described in human medicine. One method divides pruritus into 4 categories.<sup>8</sup> These categories help dictate the treatment of the patient. They are as follows:

1. Dermatologic (associated with skin diseases, eg, psoriasis, atopic dermatitis [AD])
2. Systemic disease (eg, primary cholestatic liver disease, renal failure)
3. Neuropathic causes by diseases of the central or peripheral nervous system (eg, brain tumor)
4. Psychogenic

Pruritus is regulated by a large number of neurotransmitters that transmit information between the skin, nervous system, endocrine system, and immune system.<sup>9</sup> The wide array of causes, as demonstrated by the different categories of pruritus along with the numerous neurotransmitters, explains why the symptomatic treatment of pruritus can be difficult and why there is no magic solution for treating the pruritus.

## TREATMENT OVERVIEW

Treatment of pruritus involves both identifying and treating the primary cause. Although the primary cause is addressed, adjunctive supportive therapy may be needed. Symptomatic treatment of pruritus can be broken down into 2 categories: topical treatment and systemic therapy.

In human medicine, a suggested therapeutic ladder<sup>10</sup> for generalized pruritus is described:

1. Topical medications
2. Sedating antihistamines
3. Narrow-band ultraviolet B rays
4. Combination treatments
5. Mirtazapine or thalidomide
6. Butorphanol

For the purpose of this article, only therapies that have been used in dogs or cats are discussed in depth. Allergen-specific immunotherapy, sublingual immunotherapy, systemic glucocorticoid therapy, and cyclosporine therapy are beyond the scope of this article and are discussed in other articles in this issue.

## TOPICAL THERAPY OVERVIEW

A ladder approach to pruritus is appropriate in veterinary medicine. It is important that the treatment is not worse than the disease (eg, side effects being worse than the pruritus). Treatment must also take into account the owner's ability to comply with the recommended treatment and to be able to afford the prescribe treatments. Symptomatic treatment of pruritus can be similar to eating at a buffet in which you can eat whatever you want, just not everything. Our goal is to select the items that are most "palatable" for that patient.

The first step in the ladder is topical therapy. Evidence-based medicine supporting the effectiveness of any of the following topical therapies will be presented. Unfortunately, there are no controlled studies supporting the efficacy of one topical therapy over another. Until then, anecdotal evidence must suffice.

Topical therapy has a few advantages over systemic treatment. Topical therapy can access the diseased tissue directly, allowing for higher concentrations of the drug at

the site of the problem with fewer side effects. Topical therapy may also be effective enough that systemic therapy either is not needed or can be used at a lower dose.

There are some disadvantages associated with topical therapy. Topical therapy, even if limited to a localized area, may be more time-consuming and labor-intensive. It may be easier depending on the patient and the location of the lesion to administer an oral medication rather than washing, drying, and then applying a topical residual acting product to the affected area. Because shampoos are rinsed off the skin, residual ingredients that are included in shampoos are of limited effectiveness. Therefore, moisturizers, emollients, and antipruritic agents have limited to no effect when used in a shampoo formulation.

Cost can be an advantage or a disadvantage of using topical therapy. If a small area needs to be treated, topical therapy is usually less expensive than systemic treatment. However, if large areas or costly topical medication needs to be used, topical therapy may be prohibitive.

Before applying topical medication, it is important to consider what will happen to the drug once it is applied. In some cases, the goal is to obtain therapeutic blood levels ("transdermal" medication), whereas in other cases the goal is to obtain therapeutic local tissue levels ("topical" medication). In cases of pruritus, medication will be most effective when it stays locally rather than being systemically absorbed. Both chemical factors (drug's properties) and physical factors (host factors) affect whether a medication that is applied to the skin (or mucous membrane) stays on the surface of the skin or penetrates it. These same factors also determine how much of the drug remains in the epidermis and how much is absorbed into the systemic circulation. To be most effective, ingredients for residual effects should be applied as a leave-on product.

### TOPICAL THERAPY—MECHANISM OF ACTION

Five different mechanisms in which topical therapy may control pruritus are listed.<sup>7,11</sup>

1. *Mechanically substituting another sensation for pruritus.* This substitution involves cooling (baths, ice packs), heating, or counter irritation, which may be accomplished with ingredients such as menthol (0.12%–1%), camphor (0.12–5.0%), or thymol (0.5%–1%). There are a variety of products available for veterinary use. Anecdotal evidence has demonstrated that this therapy is largely ineffective in controlling pruritus in the moderately to severely pruritic patient.
2. *Anesthetizing sensory nerve endings.* Pramoxine and lidocaine work by this mechanism. Limitations with these products include unpredictability of effectiveness, short duration of activity, and the development of tachyphylaxis. A crossover study<sup>12</sup> applying a pramoxine-containing cream rinse (Relief or Dermal-Soothe) was performed. In this study, bathing with a baby shampoo was followed by one of the products, twice weekly for 2 weeks. After 2 weeks, the treatment with the cream rinse was reversed between the 2 groups. Based on the owner's evaluation, a good reduction (51%–75%) in pruritus in 41% of the dogs was reported. This antipruritic effect remained for approximately 48 hours. Be aware that in human beings allergic sensitization or contact dermatitis may occur with lidocaine or pramoxine.<sup>8</sup> Anecdotal clinical response to this therapy is ineffective in the moderately to severely pruritic patient.
3. *Blocking pruritogenic mediators.* Because of the diversity of mediators involved in pruritus, this therapy is of limited value. Capsaicin has been used in human medicine and canine medicine.<sup>9,13</sup> Capsaicin is the active component derived from the fruit of capsicum (cayenne pepper). It is thought that capsaicin works by temporarily depleting substance P, a neurotransmitter involved in transmitting pruritus

to the brain. However, it has been reported to be frequently ineffective for pruritus associated with AD in humans.<sup>9</sup> In dogs, a blinded randomized placebo-controlled crossover study evaluating the efficacy of 0.025% capsaicin treatment was reported.<sup>13</sup> There was a significant decrease in pruritus (>50%) in 25% of the dogs as reported by the owners. This observation was reported in only 8% of the dogs by the investigators. In addition, 8% of the dog owners reported a 90% decrease in their dog's pruritus by the end of the study (6 weeks). A meta-analysis report concluded there was fair evidence of low-to-medium efficacy of topical capsaicin in the treatment of pruritus in dogs.<sup>14</sup> Human patients frequently report a burning sensation associated with capsaicin application. It has been suggested to minimize this effect by gradually increasing the capsaicin concentration from 0.025 to 0.05, 0.075, and finally 0.1% or to the highest concentration that is tolerated.<sup>15</sup> It was noted, in the previously mentioned dog study, that owners observed an increase in pruritus in the first week of treatment; however, this worsening was not statistically significant.

- a. Topical over-the-counter antipruritic products containing antihistamines have been used for many years in human medicine with the goal of avoiding the sedation associated with orally administered agents. Despite being one of the most commonly used topical antihistamines, there has only been one study performed evaluating the antipruritic effectiveness in human patients. In this study, topical diphenylhydramine failed to demonstrate any effective antipruritic activity.<sup>16</sup> In canine patients, a study evaluating interferon-gamma in the treatment of atopic dogs used diphenhydramine spray in the control group. The spray was applied every 12 hours for 4 weeks in 1 group and for 8 weeks in the other group of dogs. A good-to-excellent response for reduction of skin lesions or pruritus was reported in 23% (6/26) to 39% (10/26) of treated dogs depending on the clinical signs or symptoms assessed.<sup>17</sup> This therapy is relatively ineffective in treating the moderately to severely pruritic canine patient.
4. *The fourth method is reducing inflammation of the skin.* Topical glucocorticoids are currently the "best in class" in regards to effectiveness of topical therapies for treating pruritic dogs. Topical steroids are divided based on their strengths into 4 groups/7 classes, ranging from class I/high potency to class VII/low potency. The strength of a steroid is determined by measuring vasoconstriction of vessels in the upper dermis. The most potent steroids are in group I and the least potent steroids are in group VII.<sup>18</sup> The quickest and most effective way to get positive results with topical steroids is to start with one of the more potent steroid-containing products when clinical improvement is noted: either discontinue the use of topical glucocorticoids altogether or switch to one with lower potency. The use of low-potency steroids decreases the likelihood of cutaneous reactions such as cutaneous atrophy, ulceration, telangiectasia, alopecia, comedones, and calcinosis cutis. Topical steroids can cause systemic effects, such as adrenal suppression, polyuria and polydipsia, elevated liver enzymes, and suppression of thyroid levels.<sup>19,20</sup> To help combat this problem, newly developed topical steroids have been introduced that are metabolized in the skin. These metabolites are largely inactive molecules that tend to limit the systemic or topical side effects of topical steroids. Hydrocortisone aceponate (Cortavance) is one such glucocorticoid. It is available in many parts of the world including Europe as a veterinary spray product. Unfortunately, it is not currently available in the United States. Hydrocortisone aceponate is a diester, which because of its lipophilic properties readily penetrates an intact stratum corneum. It accumulates in the skin while obtaining a low plasma concentration, providing for local effectiveness with

minimal systemic effects. It is a prodrug, which after absorption is deesterified by esterases present in the skin into hydrocortisone 17 (HC 17) propionate. This latter molecule's potency is equivalent to dexamethasone. While in the skin, HC 17 propionate is converted to HC 21 propionate and then to HC. HC is conjugated with glucuronic acid and excreted primarily in the feces. This therapy is extremely effective at decreasing pruritus and inflammation except when microbial infection or ectoparasites are present. In those cases, antimicrobial/parasitocidal therapy is more effective. A recommended protocol may include the application of a moderately potent topical steroid (containing triamcinolone, 0.1%; dexamethasone, 0.1%; or prednisolone, 0.5% twice a day for 7 days then every day for 7 days. Assuming the dog's symptoms are in remission, therapy is then changed to 1% hydrocortisone lotion (ResiCort Leave-On Lotion). This product is selected because a study<sup>21</sup> showed that applying it twice weekly over the entire body of dogs for 6 weeks did not result in clinically evident adverse effects and only minor, clinically insignificant changes in blood parameters. Personal experience with this product has demonstrated that there are limited cutaneous long-term side effects with the application of this lotion if applied to limited areas of the body. Calcinosis cutis has been observed from the chronic use of low-dose (0.015%) triamcinolone spray (Genesis) and, therefore, as with the more potent steroid-containing products, should not be used long term.

Other topical anti-inflammatories/immunomodulators that are sometimes effective for treating pruritus in human patients and dogs belong to the family of calcineurin inhibitors.<sup>22-25</sup> In human medicine, it has been reported that drugs such as tacrolimus and other calcineurin inhibitors block sensory nerve fibers that may have direct antipruritic activity in addition to its anti-inflammatory activity.<sup>22</sup> Because of the delay in effectiveness associated with topical tacrolimus, it may be best reserved for proactive applications as part of a preventive maintenance. Because of the high cost and the availability of other effective, less costly topical therapies, it is not a commonly prescribed treatment. The fifth mechanism of treating pruritus includes addressing any microbial overgrowth/infection or ectoparasite infestation. Bacterial (most commonly *Staphylococcus pseudintermedius*) and *Malassezia pachydermatis* overgrowth can contribute significantly to pruritus in dogs or humans.<sup>26-28</sup> It has been shown that dogs and human beings with AD have an increased incidence of cutaneous bacterial and/or *Malassezia* overgrowth/infection.<sup>26,29</sup> In humans this may be partially explained by the observation that *Staphylococcus aureus* colonizes 80% to 100% of patients with AD as opposed to 5% to 30% of healthy controls.<sup>30</sup> In dogs, there are studies that demonstrate that *Staphylococcus intermedius* (now recognized as *S. pseudintermedius*) adheres more readily to canine corneocytes of dogs with AD than healthy dogs. Treating these secondary bacterial or fungal infections and/or ectoparasite infestation is an important part of treating pruritus. The response to this treatment varies from partial to complete, depending on how much the organism is contributing to the pruritus. Topical antibiotics (mupricin, fusidic acid, and chloroxyleneol), antiseptics (chlorhexidine, benzoyl peroxide, acetic acid/boric acid), and antifungal agents (3% or higher chlorhexidine, azoles) are effective antimicrobials that will decrease pruritus associated with bacterial pyoderma or *Malassezia* dermatitis. It is generally recommended to treat the secondary infections with both topical and systemic therapy. Because many dogs will at some point develop a bacterial infection or *Malassezia* dermatitis, a common recommendation is to dispense a product that contains both an antibacterial and an antifungal agent. Systemic antibacterial or antifungal therapy and antiparasitic therapy are beyond the scope of this article.

## PRURITUS AND ATOPIC DERMATITIS

In addition to topical or systemic medication, good skin care may help control pruritus. There are a number of studies demonstrating the persistence of antigens on the skin and its involvement in cutaneous pathologic abnormalities. These studies help support the importance of good skin care (clipping, bathing, and topical therapy) in regard to managing pruritus in dogs. In 1 study,<sup>31</sup> a group of house dust mite (HDM) allergic research beagles were exposed to house dust mites by 3 different methods—oral, percutaneous, and inhalation. In the percutaneous group clinical signs peaked at 72 hours after the first exposure to the HDM, even though no new exposure occurred after 48 hours. This peak was suspected to be caused by continued exposure to HDM antigen that persisted on the skin of the beagle dogs. This persistence of antigen on the skin and coat of the dogs was also documented in a study of 29 pet dogs of various breeds. In this study, skin and coat dust samples were obtained via vacuuming. HDM antigen (Der f 1) was then measured in the collected samples. Der f 1 was detected in skin and coat dust samples from 6 of 29 (21%) dogs.<sup>32</sup> In 2 subsequent studies HDM antigen was found on 11.7% and 35.5% of the hair coat samples, respectively.<sup>33,34</sup> It stands to reason that good skin care includes bathing that mechanically removes irritants and antigens. Removing these substances will decrease the load of allergens that the skin is exposed to and thereby help control pruritus.

## BATHING

Bathing is routinely used as a part of the management of pruritic dogs. The frequency of bathing needs to be individualized for each case. Factors that should be taken into consideration include the owners' ability and desire to bathe the dog, the dog's acceptance of the baths, and the effectiveness (or lack thereof) of the baths in that individual dog. It is usually recommended to initially bathe the dog semiweekly to weekly. This recommendation is based on a couple of different studies. In 1 study, a double-blinded randomized controlled trial (RCT), dogs were bathed weekly with a shampoo containing lipids, complex sugars, and antiseptics (Allermyl). This bathing led to a 50% decrease in pruritus for 24 hours in 25% of the dogs and >90% decrease in pruritus in 6.3% of the bathed dogs.<sup>35</sup> In a separate study published as an abstract, 35 dogs with AD were treated with Allermyl shampoo or lotion. One of the products was applied, alternating every 3 days. They evaluated the response to therapy based on lesional score and pruritus scores. Within 3 weeks, both the lesional and the pruritus scores had decreased significantly (55% and 58%, respectively). More than 48% of the dogs had a >50% improvement and 75.9% had obvious clinical improvement (defined as 30% reduction).<sup>36</sup> Even though these studies support the effectiveness of bathing based on an analysis of all available published reports, selection of ingredients for the treatment of pruritus has not been performed. The American College of Veterinary Dermatology task force on AD stated that, "There is currently no evidence of any benefit from using other shampoos or conditioners containing ingredients such as oatmeal, pramoxine, antihistamine, lipids or glucocorticoids." Please note that lack of evidence does not mean that the benefits are not present, only that the studies could not support that statement.<sup>37</sup>

## COMPONENTS OF GOOD SKIN CARE

In addition to bathing, clipping medium-haired to long-haired dogs is also a component of good skin care. It has been shown that dogs with long hair have more HDM

antigen on their skin/hair coat than short-coated dogs. By clipping the hair, there is a decrease in the amount of antigen present on the surface of the skin that can cause an increase in antigen contact. It also allows for more effective drying of the hair, coat, and skin. Excessive moisture or drying can lead to an increase in clinical signs. Water evaporating off the skin dries it out and can lead to an increase in pruritus. This evaporation has been demonstrated in people<sup>38</sup> and probably occurs in dogs as well. Maintaining a shorter hair coat will help to ensure that the skin and coat will be thoroughly dried after each bath. It has been suggested that all atopic dogs have their coats clipped to less than 5 cm.

## EPIDERMAL BARRIER DYSFUNCTION

Epidermal barrier dysfunction has been recognized as a key component of the pathogenesis of pruritus in cases of human AD.<sup>39</sup> Recently, barrier dysfunction has been reported to be involved with the pathogenesis of AD in dogs.<sup>40</sup>

In people, there are many different causes of barrier dysfunction associated with AD.<sup>41</sup> These defects include deficiencies of intercellular lipids, especially ceramides, such as ceramide-1 (in dogs ceramides-1 and ceramides-9 are deficient),<sup>42</sup> loss-of-function mutations in the flaggrin gene, mutations in the genes encoding for proteases (gain of function) and protease inhibitors (loss of function), and impaired expression of cornified cell envelope proteins.<sup>40,41</sup> Decreased ceramides may be due to a decrease in epidermal sphingomyelinase activity, a decrease in the biosynthesis of free glucosylceramides and ceramides in the skin, or an excess of sphingomyelin glucosylceramide deacylase (a sphingolipid-metabolizing enzyme).<sup>40</sup> A decrease in ceramides, an important water-retaining intercellular lipid, is one of the defects that has been identified in the skin of dogs with AD.<sup>42,43</sup>

## CONSEQUENCES OF BARRIER DYSFUNCTION

When epidermal barrier dysfunction occurs, regardless as to the cause, there is an increase in percutaneous absorption of antigen. If this occurs in a genetically predisposed individual, an abnormal immunologic response (production of antigen-specific Immunoglobulin E [IgE]) occurs. On subsequent exposure, crosslinking of 2 IgE molecules on the surface of the mast cells is followed by the degranulation of the mast cell and the release of preformed inflammatory chemical mediators, such as histamine and proteases, de novo production, and release of eicosanoids and cytokines.<sup>44,45</sup> In addition, in atopic individuals, Langerhan cells in the epidermis will capture and then present, via their high-affinity IgE receptor (Fc epsilonR1), antigens to allergen-specific T cells inducing an immunologic response.<sup>41,46,47</sup> Emollients and moisturizers help restore skin hydration and barrier function. By repairing/restoring the barrier function, this cascading of events will become less frequent.<sup>48,49</sup> There are a variety of barrier repair products available; some are general moisturizers, whereas others are specific lipid replacement therapy. Topical emollient and moisturizers containing ceramides have been reported to be more effective at repairing the barrier than those without such lipids.<sup>50,51</sup> Children with AD improve clinically and need less topical steroids when an emollient is a component of their treatment.<sup>52,53</sup> In fact, even when asymptomatic, continued emollient application to the previously affected areas can be beneficial in delaying recurrence of the pruritic lesions.<sup>54</sup>

In contrast to allergic contact dermatitis, irritant contact dermatitis may occur when the skin comes in contact with a substance that directly damages the skin. Human patients with AD are at risk because of the barrier dysfunction. Whether this occurs in dogs with AD has not been investigated. It is reasonable to assume that this occurs



because of the many similarities between humans with AD and dogs with AD. To help address this potential contributor to pruritus, it is recommended to the owners that they wipe the dog off with a wet cloth after coming in from outdoors. Another recommendation is to purchase breathable socks (Power paws dog socks) to apply to the patient's feet before going outdoors. The breathable socks may help to decrease contact with allergens. Another option is to use clothing to protect the skin. The author has owners use t-shirts or a dog body suit (Medical Pet Shirt [Fig. 1] or K9 TOP COAT Lycra bodysuit). These t-shirts or dog body suits are left on the dog all the time, other than when they are being bathed.

### TREATMENT OF BARRIER DYSFUNCTION AND PRURITUS

Because of all the evidence in human medicine and the evolving evidence in veterinary medicine that treatment of the epidermal barrier dysfunction is critical in the successful management of pruritus in atopic patients, it is rational to consider topical moisturizers/emollients as adjunct therapy. Because bathing, in addition to cleansing, also hydrates the stratum corneum, it is valuable to retain some of this moisturizer. It is important in people to obey the 3-minute rule. The rule states that after bathing/showering, the skin should be patted dry. Patting dry should be followed by the application of a moisturizer. By applying the moisturizer within 3 minutes of exiting the bath, the water has not had a chance to evaporate and thus prevents drying out of the skin. There are numerous veterinary products that claim to moisturize the skin. There are currently no quality studies suggesting which products might be more efficacious for an atopic canine patient. It may be prudent to try several products to see which might work best for the individual dog.

### LIPID REPLACEMENT LOTIONS

There are now lipid replacement lotions available for dogs and cats. They are Dermoscent Essential 6 Spot-on Skin Care, Douxo Calm Micro-emulsion Spray, and Allerderm Spot-On. They may contain essential fatty acids (EFA), essential oils, and/or complex lipid mixtures. Only 3 studies evaluating their effectiveness in repairing barrier function have been published to date.<sup>55-57</sup>

The study using Dermoscent Essential 6 Spot-on involved 5 normal dogs and 14 dogs with AD. They used either the spot-on or a spray that had similar but different ingredients than the spot-on. The spot-on was applied weekly, whereas the spray



Fig. 1. Medical pet shirt.



was used daily. The results did demonstrate a decrease in scale and odor along with improvement in the quality of the hair coat. The effects on pruritus and barrier repair were inconsistent.

The next study investigated phytosphingosine, which is a pro-ceramide included in Douxo Calm Micro-emulsion Spray. In this study, 47 dogs were assigned to 1 of 3 groups: a control group, a group that was bathed with a phytosphingosine-containing shampoo, and a group that would have phytosphingosine shampoo used initially but then the last 4 baths were replaced by a phytosphingosine spray. The dogs were bathed every 3 days. None of the dogs had more than a 50% decrease in pruritus. As a point of reference, most clinical studies use a threshold of 50% improvement or more to define effectiveness.

The last study investigated Allerderm Spot-On. This lotion contains ceramides, free fatty acids, and cholesterol that mimic the composition and structure of the lipids in the canine epidermal barrier. It was demonstrated that treatment stimulated the production and secretion of endogenous stratum corneum lipids, improved the quality and quantity of epidermal intercellular lipids, and helped to repair the lipid layer of the stratum corneum. Improvement in clinical signs (pruritus, excoriation, etc) was not evaluated in this study.

## CLINICAL APPLICATION OF LOTIONS

Many dogs have their “favorite” spots to itch when symptoms occur. Of the 3 lipid replacement products, only the Allerderm Spot-On evaluated how far its product diffuses (10 cm halo) when applied to the back of a dog. None diffused to the ventrum of the extremities, which are common problem areas. Based on the concern that the products do not diffuse as extensively as desired, these products are best reserved for treating focal lesions. It is currently recommended to have the owners apply the lotions to the affected areas once daily, even though the instructions recommend less frequent application. This daily application of lotion is based on the recommendation for these types of lotions in human patients with AD, where daily applications of barrier repair products are recommended.<sup>58</sup> When using the spot-on product for dogs, any remaining product can be capped and refrigerated for use the next day. This spot-on treatment is administered for 30 days and then the dog is reevaluated. If the symptoms have not improved or have recurred, then one of the other products is tried. A key point is that these products should be used for prevention or maintenance of the pruritic atopic dog.

## SYSTEMIC TREATMENT OF PRURITUS

Various systemic treatments for pruritus associated with canine AD have been reported. A review of all published RCTs was published in 2010.<sup>59</sup> These RCTs will be summarized by category.

## ANTIHISTAMINES THERAPY

Effectiveness of antihistamine therapy in dogs was recently reviewed.<sup>59</sup> Based on 6 RCTs, there was inadequate conclusive evidence to demonstrate the efficacy of oral antihistamines in reducing clinical signs. This conclusion is consistent with the reports in human medicine. In fact, although antihistamines are often used in the treatment of human AD, there is limited objective evidence to demonstrate relief of pruritus.<sup>60</sup> The American College of Veterinary Dermatology AD task force states that first-generation and second-generation type 1 antihistamines are unlikely to be

of clinical benefit in dogs with chronic AD-associated skin lesions.<sup>37</sup> There is anecdotal evidence that first-generation antihistamines are effective at decreasing pruritus in canine atopic patients. Perhaps this discrepancy can be explained by the fact that pruritic dogs are a heterogeneous group. Those without chronic skin changes may respond better to antihistamines compared with those with chronic changes. Antihistamines can be effective in dogs that are mildly pruritic and without chronic changes. They seem to work better if given consistently and prophylactically rather than after the dog has become moderately pruritic. They also seem to be synergistic with EFA. Unfortunately, there is no antihistamine clinically proven to be the most effective. Recommended products and the dosages are listed in **Table 1**. Each antihistamine should be tried for at least 2 weeks before evaluating their effectiveness. Interestingly, there is clinical evidence of steroid sparing when using a combination of the antihistamine trimeprazine and prednisolone (Temaril-P).<sup>61</sup> Other antihistamines do not seem to be synergistic with glucocorticoid medications.

### TRICYCLIC ANTIDEPRESSANTS AND MISCELLANEOUS OTHER MEDICATIONS

Tricyclic antidepressants are used to treat behavioral diseases (eg, obsessive/compulsive disorder) of dogs and people. They have also been used to treat pruritus even though studies show that they are ineffective.<sup>14</sup> Anecdotal reports have shown that these drugs will occasionally be effective at reducing pruritus in canine atopic patients. It is unclear whether the response is due to the behavioral effects, sedating properties, or the antihistamine effects (eg, doxepin is 800 times more potent than diphenhydramine as a histamine receptor antagonist).<sup>62</sup> These drugs may be synergistic with EFA in a manner similar to the antihistamines. Doxepin or amitriptyline should be considered in an antihistamine trial. Both are dosed for dogs at 0.5 to 1 mg/lb every 12 hours. They should be used for at least 21 days before evaluating their effectiveness. Sedation is a common side effect. In the review article, it was stated that leukotriene inhibitors or a phosphodiesterase inhibitor (pentoxifylline) had poor efficacy in controlling pruritus. In contrast, others report that oral pentoxifylline<sup>63</sup> or misoprostol (Cytotec)<sup>64</sup> may have some effect

<b>Drug</b>	<b>Dose</b>	<b>Frequency</b>
Amitriptyline <sup>a,b</sup>	0.5–1 mg/lb	q12h
Cetirizine	0.2–0.5 mg/lb	q24h
Chlorpheniramine <sup>c,d</sup>	0.2–0.25 mg/# Maximum 0.5 mg/#/d	q12h
Cyproheptadine <sup>e</sup>	0.1–0.5 mg/lb	q8–12h
Diphenhydramine	0.5–1 mg/lb	q8–12h
Doxepin <sup>a</sup>	0.5–1 mg/lb	q12h
Hydroxyzine	0.5–1 mg/lb	q8–12h
Loratadine	0.2–0.5 mg/lb	q24h

<sup>a</sup> Do not administer concurrently with amitraz or phenylpropanolamine.

<sup>b</sup> Use for 21 days.

<sup>c</sup> Bitter tasting if cut.

<sup>d</sup> Do not exceed 0.5 mg/lb/d; sudden death has occurred.

<sup>e</sup> In some dogs, agitation or restlessness may occur at higher doses.

on pruritus. These products are generally regarded as ineffective in controlling pruritus in canine atopic patients.

### FATTY ACIDS THERAPY

EFA have been used for many years in the management of canine AD. The mechanisms of action of EFAs may be due to their anti-inflammatory and immunomodulatory properties or an improvement of barrier function. The latter is evaluated by measuring the transepidermal water loss. A decrease in transepidermal water loss correlates to an improvement in barrier function. The anti-inflammatory properties of EFA include the following: production of anti-inflammatory eicosanoids (prostaglandin and leukotriene) and inhibition of inflammatory cytokine production. There are many studies evaluating the effectiveness of EFA (omega 3, omega 6) in the treatment of canine AD. From 19 RCTs there were only 2 that were rated as high quality.<sup>59</sup> In one of the studies<sup>65</sup> that used a specific EFA liquid supplement (Viacutan Plus), there was a statistically significant reduction in prednisolone dosage needed to control pruritus after approximately 2 months of administration. In the other study,<sup>66</sup> the efficacy of an EFA-containing supplement (Megaderm) combined with an antipruritic shampoo (Allermyl) was as effective in treating the pruritus as prednisolone. It is unclear whether the bathing, the specific shampoo, the EFA, or some combination of these therapies was responsible for the result. The question that needs to be answered is whether these results are product dependent. The overall conclusion from the RCTs was that there is limited improvement with EFA whether used as a supplement or fed as an EFA-enhanced diet. In addition, there was no evidence that any particular formation or ratio of omega 3 and omega 6 was effective. Because of the 2 previous studies, the low cost and the very mild side effects (diarrhea), EFA should be considered as a part of the therapy for canine AD. Omega 3 series fatty acids do not form the inflammatory eicosanoid, arachidonic acid, and therefore, a product containing only omega 3 should be used. Based on a study,<sup>67</sup> the recommended amount of EFA that is administered should be 18 mg/lb of eicosapentaenoic acid, administered for a minimum of 60 days.<sup>37</sup> Sixty days should allow enough time for the anti-inflammatory EFAs to be incorporated into the phospholipid layer of cell membranes of keratinocytes, replacing some of the inflammatory arachidonic acid. Omega 6, specifically linoleic acid, is the most important epidermal lipid in regard to barrier function. Because omega 6s are converted to arachidonic acid when administered systemically, it might be best to use them as topical agents.

### ANTIMICROBIAL THERAPY

Dogs with atopic dermatitis frequently have overcolonization and/or infection from *S pseudintermedius* and/or *M pachydermatis*. Many times the infection is generalized and therefore not amendable to topical monotherapy. Systemic antibiotics (beta-lactams, clindamycin, and potentiated sulfas) and antifungals (ketoconazole, itraconazole, or fluconazole) are frequently needed. Because infections can contribute a significant amount to the dog's pruritus, it is important to identify (via cytology and physical examination) and treat the secondary infections. If the infections are generalized, it is better to withhold glucocorticoids or cyclosporine until the infection has resolved. This will allow the evaluation of how much pruritus is due to the infection and how much is due to the underlying disease. Giving steroids concurrently will only complicate this assessment. In cases of generalized pruritus and localized infection, judicious administration of short-acting oral glucocorticoids could be considered.

## SUMMARY

The treatment of pruritus in the dog must be approached in a systematic manner and should include the search and resolution of the primary causes. Identifying and treating the primary cause of pruritus greatly increase the rate of success of any therapy for pruritus. In addition to identifying and treating the underlying cause, symptomatic therapy for pruritus is frequently needed. Successful treatment usually involves a multimodal approach that encompasses both topical and systemic therapy. Atopic dermatitis is a frequent cause of pruritus in both human beings and dogs. In recent years, the importance of barrier dysfunction as a major contributor to pruritus in atopic dermatitis has been recognized in both species. Restoration of barrier function is the foundation of treatment in those cases of human AD and is becoming recognized as an important component in the treatment of pruritus in canine atopic dermatitis. Recognizing and treating secondary bacterial and *Malassezia* overgrowth/infection is essential to treating the pruritic dog successfully.

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