

Canine Fear-Related Aggression Toward Humans

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Fear-related aggression (FRA) in dogs is a progressive emotional disorder with a physiologic response causing behavioral signs. Some cases have a hereditary component; however, traumatic incidents, learning, and a lack of socialization often contribute. The disorder is often chronic by the time the patient is presented. Aggressive behaviors negatively impact the patient's and client's quality of life. Ramifications of aggressive disorders include mistreatment, relinquishment, or euthanasia of the patient, as well as physical risk for the public, veterinary team, and owners.¹

Clinical Signs

The initial signs of FRA often go unnoticed. Early clinical signs exhibited at presentation of the stimulus (ie, the thing that provokes fear) prior to the onset of aggression may include hiding, attempting to escape, distance-increasing signals (eg, averted gaze, lip lick, stress yawn, back turn), physiologic stress signals (eg, tachycardia, tachypnea, urination, defecation, mydriasis, panting), and apathy.²

When exposure to the stimulus does not decrease in response to these social signals, overt aggression may occur in an attempt to prevent continued approach of the stimulus. At presentation, signs of FRA may include barking, lunging, growling, snarling, snapping, and biting, with accompanying fearful body language (eg, tail down, ears back, nose lifted), caudal one-quarter to half of body lowered, physiologic arousal (eg, tail 90° or less to the back, mydriasis, injected sclerae, panting) or approach-retreat (eg, moving toward the stimulus and backing or turning away) in response to the presence of the stimulus. Dogs that exhibit fear-related aggression may wag their tails while exhibiting the clinical signs. A wagging tail does not indicate friendly intent and should be interpreted as a willingness to interact with a stimulus, even if the interaction is to bite. Offensive and neurochemically aroused body language can be negatively reinforced in fearfully aggressive dogs because of repeated removal of the stimulus in response to aggressive displays.

As the disorder becomes chronic, overtly fearful body language is often replaced by offensive or aroused body language. FRA cannot be ruled out based on the lack of fearful body language alone, as the initial fearful stage may not always be observed. In addition, approach-retreat patterns and physiologic signs of fear in these patients point to fear-related aggression as a diagnosis.

HOW I RECOGNIZE

Clinical Signs of Canine Fear-Related Aggression

- Early signs are often missed.
- Animal displays disengagement, distance increasing, fearful body language in response to stimuli.
- Offensive or aroused body language can be displayed if the disorder is severe or chronic.

FRA = fear-related aggression, OA = osteoarthritis

Pain-related, irritable aggression and medical disorders affecting mentation should be ruled out with a physical examination and any other diagnostics indicated based on initial examination and history.

Diagnosis

A diagnosis of FRA can usually be confirmed through owner description of the progression of the patient's behavior, including early signs of fear; patient's behavior as a puppy, if known; viewing videos of the pet at home or in situations that elicit fearful or fear aggressive behavior (if safe to do so); identification of a list of stimuli or situations that elicit FRA (eg, reaching, cornering, petting); detailed description of clinical signs before, during, and after representative incidents; and evaluation of the dog's behavior during the appointment.

History, pictures, and videos supplied by the client are essential for proper diagnosis as observation in the hospital setting alone is not sufficient to confirm diagnosis.

Pain-related, irritable aggression—a medical condition that might not cause pain, but increase irritability and therefore increase aggression or retreat during approach and/or handling—and medical disorders affecting mentation should be ruled out with a physical examination and any other diagnostics indicated based on initial examination and history.

Situations occur in which dog trainers have made a “diagnosis” and the client requests tests or treatments based on that diagnosis. Just as a veterinarian would not blindly accept a dermatologic diagnosis from a groomer, a “diagnosis” from a trainer should not be taken at face value. Veterinarians should formulate their own diagnoses and treatment plans based on their own assessments and evaluations. Note that although legal advice cannot be given by a general

HOW I DIAGNOSE

Canine Fear-Related Aggression

1. Observe patient's body language during physical examination and in videos.
2. Collect a detailed behavioral history, including progression of clinical signs.
3. Consider changes in clinical signs caused by chronicity of disorder.
4. Rule out medical disorders (including pain-related aggression) and irritable aggression.

practitioner, clients should be reminded that aggression poses a legal concern that may result in legal action by victims.

Treatment

The treatment of FRA is similar to other medical disorders. First, stimuli that cause clinical signs should be identified so they can be avoided or addressed through behavior modification. Just as a client may be advised to avoid playing Frisbee with a dog that has osteoarthritis (OA), clients who own dogs displaying FRA should be instructed how to avoid situations that trigger a fearful or aggressive response. For example, if the dog is aggressive on the couch, advise the client to block access to the couch. These simple measures can reduce clinical signs significantly in many cases.

A veterinarian treating a patient with OA may discuss with the owner that an agility career is not a realistic expectation for the patient, but pain-free leash walks are a reasonable goal. Similarly, veterinarians should discuss reasonable goals with owners of fear-related aggressive dogs along with practical ways to achieve a positive outcome. For example, if a dog is aggressive toward

the owner's grandchildren, having the dog in the same room as the children as a form of treatment may be too dangerous or unethical to attempt. Owners should be advised that interactions between their dog and grandchildren may be an unrealistic goal, that working with the children to modify the behavior may not be an option, and that boarding or confining the dog when the grandchildren are visiting may be the safest and least stressful option for all concerned.

Continuing the analogy of a patient with OA, medication may be used to lower pain and discomfort so that physical therapy can be instituted. In the same way, psychopharmaceutical medications can be used to treat FRA by lowering neurochemical mediators of fear and arousal, altering the patient's emotional state thereby making treatment more productive. Selective serotonin reuptake inhibitors and tricyclic antidepressants can help to mediate neurochemical imbalance. Multiple types of medications can be effective in the treatment of FRA. Research on mechanisms,

continues

duration of action, latency to positive clinical effect, and interactions should always be performed before starting medical treatment.

Just as the patient with OA would be sent to physical rehabilitation, the patient with FRA begins with a behavioral therapy plan. The first behaviors to be taught are control behaviors (ie, behaviors that do not change the pet's behavioral state but control its actions), which are incompatible with the aggressive response (ie, cannot be exhibited at the same time). For example, if a dog is aggressive on the couch, it can be taught to go to a specific location away from the couch, such as a dog bed, and stay there on cue. Once control behaviors are in place and the dog is regulated neurochemically, counterconditioning techniques (eg, changing the pet's behavioral response by pairing a positive stimulus with a negative stimulus) are instituted for maximum alteration in behavioral response.

Behavioral therapy (behavior modification) plans should be made by the veterinarian and implemented by a qualified veterinary technician or a qualified dog trainer if a veterinary technician is not available. Because the dog training industry is unregulated with no legal certifications or verification of claims, cases should not be turned over to dog trainers without a plan—constructed by the veterinarian—in place to guide treatment. Each time a trainer sees the patient, the veterinarian should receive a report so medical treatment and follow-up can be altered if necessary. Cases outside of the scope of the veterinarian's knowledge should be referred to a board-certified veterinary behaviorist.

Information on how to select a qualified dog trainer is available through the American Veterinary Society of Animal Behavior (avsonline.org). ■ **cb**

References

1. Salman MD, Hutchinson J, Ruch-Gallie R. Behavioral reasons for relinquishment of dogs and cats to 12 shelters. *J Appl Anim Welf Sci*. 2000;3(2): 93-106.
2. Landsberg G, Hunthausen W, Ackerman L. Canine aggression. *Behavior Problems of the Dog and Cat*, 3rd ed. Edinburgh, Scotland: Saunders Elsevier; 2013:297-327.

Suggested Reading

Handelman B. *Canine Behavior: A Photo Illustrated Handbook*. Norwich, VT: Woof and Word Press; 2008.

FRA = fear-related aggression, OA = osteoarthritis

NexGard®
(afoxolaner) Chewables

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

Description:

NEXGARD® (afoxolaner) is available in four sizes of beef-flavored, soft chewables for oral administration to dogs and puppies according to their weight. Each chewable is formulated to provide a minimum afoxolaner dosage of 1.14 mg/lb (2.5 mg/kg). Afoxolaner has the chemical composition 1-Naphthalenecarboxamide, 4-[5-[3-chloro-5-(trifluoromethyl)-phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl].

Indications:

NEXGARD kills adult fleas and is indicated for the treatment and prevention of flea infestations (*Ctenocephalides felis*), and the treatment and control of Black-legged tick (*Ixodes scapularis*), American Dog tick (*Dermacentor variabilis*), and Lone Star tick (*Amblyomma americanum*) infestations in dogs and puppies 8 weeks of age and older, weighing 4 pounds of body weight or greater, for one month.

Dosage and Administration:

NEXGARD is given orally once a month, at the minimum dosage of 1.14 mg/lb (2.5 mg/kg).

Dosing Schedule:

Body Weight	Afoxolaner Per Chewable (mg)	Chewables Administered
4.0 to 10.0 lbs.	11.3	One
10.1 to 24.0 lbs.	28.3	One
24.1 to 60.0 lbs.	68	One
60.1 to 121.0 lbs.	136	One
Over 121.0 lbs.	Administer the appropriate combination of chewables	

NEXGARD can be administered with or without food. Care should be taken that the dog consumes the complete dose, and treated animals should be observed for a few minutes to ensure that part of the dose is not lost or refused. If it is suspected that any of the dose has been lost or if vomiting occurs within two hours of administration, redose with another full dose. If a dose is missed, administer NEXGARD and resume a monthly dosing schedule.

Flea Treatment and Prevention:

Treatment with NEXGARD may begin at any time of the year. In areas where fleas are common year-round, monthly treatment with NEXGARD should continue the entire year without interruption.

To minimize the likelihood of flea reinfestation, it is important to treat all animals within a household with an approved flea control product.

Tick Treatment and Control:

Treatment with NEXGARD may begin at any time of the year (see **Effectiveness**).

Contraindications:

There are no known contraindications for the use of NEXGARD.

Warnings:

Not for use in humans. Keep this and all drugs out of the reach of children. In case of accidental ingestion, contact a physician immediately.

Precautions:

The safe use of NEXGARD in breeding, pregnant or lactating dogs has not been evaluated. Use with caution in dogs with a history of seizures (see **Adverse Reactions**).

Adverse Reactions:

In a well-controlled US field study, which included a total of 333 households and 615 treated dogs (415 administered afoxolaner; 200 administered active control), no serious adverse reactions were observed with NEXGARD. Over the 90-day study period, all observations of potential adverse reactions were recorded. The most frequent reactions reported at an incidence of > 1% within any of the three months of observations are presented in the following table. The most frequently reported adverse reaction was vomiting. The occurrence of vomiting was generally self-limiting and of short duration and tended to decrease with subsequent doses in both groups. Five treated dogs experienced anorexia during the study, and two of those dogs experienced anorexia with the first dose but not subsequent doses.

Table 1. Dogs With Adverse Reactions.

	Treatment Group			
	Afoxolaner		Oral active control	
	N ¹	% (n=415)	N ²	% (n=200)
Vomiting (with and without blood)	17	4.1	25	12.5
Dry/Flaky Skin	13	3.1	2	1.0
Diarrhea (with and without blood)	13	3.1	7	3.5
Lethargy	7	1.7	4	2.0
Anorexia	5	1.2	9	4.5

¹Number of dogs in the afoxolaner treatment group with the identified abnormality.

²Number of dogs in the control group with the identified abnormality.

In the US field study, one dog with a history of seizures experienced a seizure on the same day after receiving the first dose and on the same day after receiving the second dose of NEXGARD. This dog experienced a third seizure one week after receiving the third dose. The dog remained enrolled and completed the study. Another dog with a history of seizures had a seizure 19 days after the third dose of NEXGARD. The dog remained enrolled and completed the study. A third dog with a history of seizures received NEXGARD and experienced no seizures throughout the study.

To report suspected adverse events, for technical assistance or to obtain a copy of the MSDS, contact Merial at 1-888-637-4251 or www.merial.com/nexgard. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VEIS or online at <http://www.fda.gov/AnimalVeterinary/SafetyHealth>.

Mode of Action:

Afoxolaner is a member of the isoxazoline family, shown to bind at a binding site to inhibit insect and acarine ligand-gated chloride channels, in particular those gated by the neurotransmitter gamma-aminobutyric acid (GABA), thereby blocking pre- and post-synaptic transfer of chloride ions across cell membranes. Prolonged afoxolaner-induced hyperexcitation results in uncontrolled activity of the central nervous system and death of insects and acarines. The selective toxicity of afoxolaner between insects and acarines and mammals may be inferred by the differential sensitivity of the insects and acarines' GABA receptors versus mammalian GABA receptors.

Effectiveness:

In a well-controlled laboratory study, NEXGARD began to kill fleas four hours after initial administration and demonstrated >99% effectiveness at eight hours. In a separate well-controlled laboratory study, NEXGARD demonstrated 100% effectiveness against adult fleas 24 hours post-infestation for 35 days, and was > 93% effective at 12 hours post-infestation through Day 21, and on Day 35. On Day 28, NEXGARD was 81.1% effective 12 hours post-infestation. Dogs in both the treated and control groups that were infested with fleas on Day 1 generated flea eggs at 12- and 24-hours post-treatment (0-11 eggs and 1-17 eggs in the NEXGARD treated dogs, and 4-90 eggs and 0-118 eggs in the control dogs, at 12- and 24-hours, respectively). At subsequent evaluations post-infestation, fleas from dogs in the treated group were essentially unable to produce any eggs (0-1 eggs) while fleas from dogs in the control group continued to produce eggs (1-141 eggs).

In a 90-day US field study conducted in households with existing flea infestations of varying severity, the effectiveness of NEXGARD against fleas on the Day 30, 60 and 90 visits compared with baseline was 98.0%, 99.7%, and 99.9%, respectively. Collectively, the data from the three studies (two laboratory and one field) demonstrate that NEXGARD kills fleas before they can lay eggs, thus preventing subsequent flea infestations after the start of treatment of existing flea infestations.

In well-controlled laboratory studies, NEXGARD demonstrated >94% effectiveness against *Dermacentor variabilis* and *Ixodes scapularis*, 48 hours post-infestation, and against *Amblyomma americanum* 72 hours post-infestation, for 30 days.

Animal Safety:

In a margin of safety study, NEXGARD was administered orally to 8- to 9-week-old Beagle puppies at 1, 3, and 5 times the maximum exposure dose (6.3 mg/kg) for three treatments every 28 days, followed by three treatments every 14 days, for a total of six treatments. Dogs in the control group were sham-dosed. There were no clinically-relevant effects related to treatment on physical examination, body weight, food consumption, clinical pathology (hematology, clinical chemistries, or coagulation tests), gross pathology, histopathology or organ weights. Vomiting occurred throughout the study, with a similar incidence in the treated and control groups, including one dog in the 5x group that vomited four hours after treatment.

In a well-controlled field study, NEXGARD was used concomitantly with other medications, such as vaccines, anthelmintics, antibiotics (including topicals), steroids, NSAIDs, anesthetics, and antihistamines. No adverse reactions were observed from the concomitant use of NEXGARD with other medications.

Storage Information:

Store at or below 30°C (86°F) with excursions permitted up to 40°C (104°F).

How Supplied:

NEXGARD is available in four sizes of beef-flavored soft chewables: 11.3, 28.3, 68 or 136 mg afoxolaner. Each chewable size is available in color-coded packages of 1, 3 or 6 beef-flavored chewables.

NADA 141-406, Approved by FDA
Marketed by: Frontline Vet Labs™, a Division of Merial Limited.
Duluth, GA 30096-4640 USA
Made in Brazil.
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