

Pet dander and perennial allergic rhinitis: Therapeutic options

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ABSTRACT

Pet allergy may now be the most common perennial allergen in the United States based on recent skin-prick testing data. This trend corresponds with the rise (from 56 to 63%) in U.S. households having indoor pets over the past 10 years. Furthermore small, suspended, particulate animal allergens may be found in 90% of all homes and most public indoor areas. Although the most important cat and dog allergens are Fel d 1 and Can f 1, respectively, there are five well-described allergens for both cats and dogs. The effects of early life domestic pet and endotoxin exposure and subsequent clinical sensitivity remain controversial. Given that only the rare pet-allergic patient is willing to give away his/her pet, it is important to take an evidence-based approach to environmental control. Unfortunately, the benefits from changes in the environment that have been shown in research studies relate more to a reduction of allergens than symptoms. The pharmacotherapy for pet allergy will vary based on whether this is episodic or perennial allergic rhinitis (PAR) and on the severity of the symptoms. A stepwise approach for management, using both mono- and combination therapy, is proposed. Allergen immunotherapy, the only disease-modifying treatment available, may be the best therapeutic recommendation for patients with moderate to severe pet-induced PAR.

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Pets, dogs specifically, have often been described as “man’s best friend,” but patients with allergic rhinitis and the allergists caring for these patients might take exception to this characterization. Up to 30% of adults and 40% of children in the United States are diagnosed with allergic rhinitis, a disease that has a significant effect on quality of life (QOL), contributes to comorbid diseases such as asthma or sinusitis, and accounts for a financial burden of direct and indirect costs totalling over \$12 billion/year.^{1–4} Pet allergy is a major contributor to this burden of allergic rhinitis. In the United States, 37 and 32% of homes have at least one dog (average 1.7/household) or one cat (average 2.2/household), respectively, resulting in a total U.S. pet population of >72 million dogs and 82 million cats.⁵ There is an increasing tendency to have indoor

pets, with a rise in households with pets from 56% in 1998 to 63% in 2007 in the United States. De Groot in 1991 published data showing that 24 and 17% of allergic patients are allergic to cats and dogs, respectively.⁶ However, more recent data show that up to 72% of atopic patients have a positive skin-prick test to cats, making cat the number one perennial allergen, higher than dust mite (61%) or ragweed (52%) and twice as high as dog (36%).⁷

INDOOR ANIMAL DANDER: LOCATION, QUANTITY, AND MEASUREMENT

Animal dander, small, suspended particulate allergens (2.5–10 μ m in size), becomes airborne with any disturbance of the environment, *e.g.*, vacuuming or even walking on carpeted floors, and can remain suspended indoors for up to several hours. Furthermore, these allergens are not limited to households with pets but are passively transferred by clothing, shoes, and even women’s hair⁸ to >90% of all homes and most public indoor areas.^{9,10} Approximately 46% of homes, both with and without resident cats, were found to have Fel d 1 levels of >2 μ g/gm of dust, a dose associated with provoking symptoms in sensitized patients.⁹

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Middle schools often have 1.5–3.0 $\mu\text{g/g}$ of Can f 1 and 0.5–1.1 $\mu\text{g/g}$ of Fel d 1,¹¹ possibly contributing to sensitization,¹² and sandboxes at daycare centers often have >8 $\mu\text{g/g}$ of Fel d 1, levels that definitely can cause sensitization.¹³ It has been shown that the measured cat allergen (Fel d 1) levels in school classrooms are correlated with the number of cat owners among the children in the class.^{14–16} Furthermore, asthmatic children who are allergic to cats develop more symptoms in classes with many cat owners, a phenomenon that is most obvious after returning from summer vacation.¹⁷

Although most research studies have measured indoor allergen presence in micrograms per gram of dust, it has been argued that with these aerodynamically smaller-sized particles, *e.g.*, Fel d 1, measuring airborne allergen concentrations may more accurately determine levels of allergen exposure. Bollinger compared settled versus airborne Fel d 1 in 37 homes with cats to 40 homes without cats.¹⁸ Homes without cats had median and high range settled (2.58 and 3.7 $\mu\text{g/g}$ of dust, respectively) and airborne (0.017 and 0.088 $\mu\text{g/g}$, respectively) levels of Fel d 1 that were ~3–10 times lower than that of homes with cats, but well above levels used in experimental cat rooms to provoke symptoms of the upper and lower airway.^{8,18} Median levels of airborne Fel d 1 correlated significantly with the number of cats (1–15) present in these homes ($r_s = 0.77$; $p < 0.01$).¹⁸

CHARACTERIZATION OF DOG AND CAT ALLERGENS

The most significant and best-studied cat allergen, Fel d 1, considered to be a major allergen, is secreted by the sebaceous glands of the skin and the salivary glands. It lies on the fur, and concentrations vary based on the anatomic site, with levels being higher on the face than on the chest.¹⁹ Although Fel d 1 has been found to a lesser degree in cats' urine, urine allergens have not been purified or characterized at a molecular level. Additional cat allergens include Fel d 2 (albumin), considered to be a minor allergen; Fel d 3 (a cystatin); Fel d 4 (a lipocalin), considered to be a major allergen; and Fel d 5 (cat IgA). This cat IgA (mainly heavy chain) allergen contains cross-reactive epitopes also present on cat IgM and has been identified in the serum of $\frac{1}{3}$ of cat-allergic patients.²⁰

Fel d 1 levels (mean levels) are significantly higher in intact male versus female cats (5.46 versus 1.53 U/g), whereas castrated male cats have similar (1.28 U/g) levels to intact or spayed female cats.²¹ Separate research confirms that castration reduces Fel d 1 levels and indicates that testosterone replacement can reverse this effect.²²

Over 28 dog allergens have been detected, and at least five are believed to be significant. In dog-allergic

patients, ~52–70% are sensitized to Can f 1 (a major allergen), 20–33% are sensitized to Can f 2 (a 19-kDa protein, a minor allergen), 35–48% are sensitized to Can f 3 (a 70-kDa protein, serum albumin), 60% are sensitized to Can f 4 (a lipocalin), and 70% are sensitized to Can f 5 (kallikrein), a major allergen.^{23–27} Most of these allergens are present in dog saliva, hair, and dander,²⁸ although Can f 1 is predominantly found in saliva.⁶ Can f 1 has been isolated from almost all breeds of dogs, but the amount can vary among individual dogs and is produced more by male than female dogs.²⁹ Although we have limited information about and are lacking molecular characterization of Can f 4, it has been detected in dog-allergic patients who are negative to Can f 1, 2, and 3. Can f 5, isolated from male dog urine and dander and noted to be dramatically reduced in castrated male dogs, is found in up to 38% of dog-allergic patients who are negative for Can f 1, 2, and 3. Almost all (85%) of the patients with specific IgE to dog dander, but who clinically are non-allergic, have Can f 5 present. Furthermore, there are no patients negative to dog dander who are positive for Can f 5.³⁰ It is perhaps reassuring to allergic patients that 87% of pet cats and 75% of owned dogs are neutered, as reported by the Humane Society.

Can f 5 allergen and human prostate-specific antigen (PSA) share substantial structural similarity (55–60% sequence identity), and it has been suggested that sensitization to Can f 5 confers an increased risk of development of an allergic reaction to human seminal fluid.³⁰ In fact, 24% of dog dander-allergic patients have serum recognition of IgE binding to human PSA found in seminal fluid.³¹ Weidinger reported a patient with vaginal hypersensitivity to semen who was sensitized to human PSA, which is present in seminal plasma.³² Furthermore, in 40% of human seminal fluid allergy, allergic symptoms develop during or just after the first sexual intercourse with a specific partner, suggesting prior cross-reactivity of allergens, possibly with Can f 5.³¹ Possible associations of the Can f 5 cross-reacting PSA antigen with the development of infertility and chronic vulvovaginitis have also been suggested.³¹

Most allergists who observe that many patients are skin test positive to both cats and dogs may very well question whether dogs and cats are distant cousins. Indeed, shared IgE epitopes of major dog and cat allergens has been suggested, and Reininger has discovered a Fel d 1-like allergen in dog dander extracts and was able to show that 25% of Fel d 1-reactive cat-allergic patients are able to cause 50% inhibition of these dog allergens.³³ When patients are positive for the Can f 5-related 28-kDa IgE to human PSA, 80% of these patients are allergic only to dogs. On the other hand, when negative for this Can f 5-related allergen, 72% are allergic to both cats and dogs.³¹

EFFECT OF LIVING WITH PETS IN EARLY LIFE

The effects of living with domestic pets in early life and early endotoxin exposure with subsequent sensitization and clinical sensitivity to pets remain controversial topics. It has been suggested that the decreased sensitization to animal allergens in those who have lived with indoor pets during early life is the result of the concomitant increase in endotoxin exposure. Platts-Mills *et al.*³⁴ concluded that endotoxin is present in almost all homes, sometimes at similar levels regardless of the presence or absence of pets. Airborne endotoxin levels are significantly lower in homes with a cat compared with homes with a dog ($p < 0.001$).³⁴ There is a significant correlation between airborne Can f 1 and airborne endotoxin ($r = 0.50$; $p < 0.01$), but not between endotoxin and Fel d 1 ($r = 0.17$; $p = 0.27$).³⁴ The researchers further concluded that the potentially beneficial effects of cat ownership on reduced development of allergy to animals could not be explained by increased endotoxin.³⁴ Campos followed 532 infants (with home cats, dogs, both, or none) for 12 months and found that neither dog and cat ownership nor endotoxin levels were related to the prevalence of wheezing. Moreover, he found that living with pets and/or having increased endotoxin exposure did not increase the number of positive skin-prick tests to foods or aeroallergens.³⁵ Although homes with more dogs had higher endotoxin levels, and having both dogs and cats was associated with the highest endotoxin levels, he could find no overall relationship between atopy and endotoxin levels. Only infants living in homes with two or more dogs and high endotoxin levels had reduced wheezing (OR = 0.4).³⁵ He concluded that, in general, no relationship between atopy and dog and cat ownership could be established.³⁵

Ingram studied the clinical consequences of living with pets in homes with low dust-mite levels on children with asthma.¹¹ A high percentage of these children with increased bronchial hyperreactivity and asthma symptoms were sensitized to dogs (67%) and cats (62%).¹¹ Ninety-five percent of homes with either dogs or cats had allergen levels that exceeded sensitizing levels (>10 and $>8 \mu\text{g/g}$, respectively) and even homes without animals had levels usually considered to be above those necessary for symptom provocation (>1 and $>2 \mu\text{g/g}$, respectively).¹¹ It should perhaps be pointed out that definitive threshold levels of dog and cat allergen for provoking symptoms have not been established. When looking at individual homes, however, no clear relationship was found between sensitization or symptoms and the current level of animal allergen.¹¹

The effect of living with indoor pets seems to be related not only to the patient's age, but also to community prevalence of pets, atopic status, and specific

disease state. Atopic patients living with cats during childhood in communities with low cat prevalence may suffer from increased asthma severity as adults.³⁶ Nonatopic children or adults living with dogs experienced increased asthma in adulthood,³⁶ whereas atopic patients living with dogs in childhood had no increased risk for asthma and reduced risk for allergic rhinitis.³⁶ Dog exposure in high-risk children may reduce the development of atopic dermatitis.³⁷ High-level exposure to cats may lead to a modified Th2 response, increased IL-1, and increased IgG4 to Fel d 1 and to the induction of a state of tolerance. Some studies have shown that children who have ever lived with a cat are less likely to have IgE antibodies to cat.³⁸ However, as with the hygiene hypotheses controversy, we are still awaiting the "real" answer as to the effects of pet ownership on atopic and nonatopic diseases affecting the upper and lower airway.

OBTAINING A PATIENT HISTORY OF PET ALLERGY

When obtaining a medical history, one of the few questions with significant, positive predictive value for diagnosing allergic rhinitis involves symptoms related to animal exposure.³⁹ Patients with animal allergies will often report severe ocular as well as nasal symptoms. Furthermore, skin itching, urticaria, and lower respiratory symptoms, *e.g.*, wheezing and coughing, may be reported to occur exclusively with animal exposure. Patients with both asthma and allergic rhinitis have more severe symptoms of allergic rhinitis and longer duration of symptoms after a single allergen exposure.⁴⁰ Although one might not expect to note any seasonal variation in animal allergies, animal dander in homes peaks in May and June.⁹ With bedrooms having the highest level of animal dander,⁹ one finds that symptoms may be more severe during the evening and early morning hours.

Given that cat and dog allergens can be measured in most public areas, particularly schools, Karlsson followed three groups of school children for 1 year. Group 1 changed into special school clothing on arrival at school each morning. Group 2 gave up having pets at home, and group 3 (control) made no changes, with pet owners (a portion of the class) keeping their pets. At the end of the study, airborne cat allergen levels in both intervention groups were reduced four- to sixfold compared with the control group. Control group children having cats at home had a threefold higher cat allergen level on their clothing than those without cats at home. It is noteworthy that the pet ownership ban was less accepted than using special school clothing as an intervention measure.⁴¹

DIAGNOSTIC TESTING TO CONFIRM PET ALLERGY

When confirming the clinical diagnosis of pet (specifically cat), allergy, skin-prick testing for allergic rhinitis is superior to intracutaneous testing, which gives a poor positive and negative predictive value.⁴² The skin-prick test can also be used to rule out allergic rhinitis triggered by cat exposure.⁴² Using an prick test response of 3.0–6.0 mm as a indicator of clinical allergy gave the highest positive (90%) and negative (87%) predictive values.⁴² When comparing cat skin-prick testing to CAP-RAST and Phadezyme RAST there is similar specificity but greater sensitivity.⁴³ However, negative serological test results can not be relied on for excluding clinical sensitivity to pet allergen.⁴²

ENVIRONMENTAL CONTROL FOR PET-ALLERGIC PATIENTS

Most allergists would not be surprised that in 2006, 49.7% of pet owners considered their pets to be “family members”.⁵ Thus, animal-allergic patients almost always seek effective interventions that will allow them to keep their animals and are not interested in hearing that avoidance is the best intervention.⁴⁴ Suggesting that allergic patients have their pets live outdoors often is countered by patients arguing that not only are they giving up a meaningful, close relationship between the pet and family members, but that they are also putting the pet at risk from outdoor dangers, depriving them of human companionship, and exposing the owners to potential health risks. Once these QOL decisions have been discussed, educational efforts need to focus on interventions in the environment that may help reduce allergic symptoms. In addition to in-office education, the Humane Society,⁴⁵ perhaps a resource that the patient would feel is less biased against animal ownership, does an excellent job, among other suggestions, of reinforcing that “Contrary to popular belief, there are no non-allergic breeds of dogs or cats; even hairless breeds may be highly allergenic.” They also agree with “The diagnosis and management of rhinitis: An updated practice parameter”¹ that it takes up to 6 months to eliminate completely allergens in a home where a pet has lived.⁴⁶

For animal-allergic patients living with their pets, there are no specific environmental interventions that have been shown to reduce symptoms of allergic rhinitis and asthma and very few that have been shown to reduce airborne animal allergen exposure significantly. In 2003, a systematic review by the *Cochrane Database*⁴⁷ looked at pet allergen control measures for allergic asthma. They examined the effects of pet removal, use of air filtration (high-efficiency particulate air [HEPA] filter and any other), and use of chemical agents. However, only 2 of the 34 references identified fulfilled sound research inclusion criteria. Both of these exam-

ined the effectiveness of an air filtration unit, and no significant differences were found. The authors of the systematic review concluded that adequately powered trials are needed for all pet allergen environmental control measures. An updating of references through September 2008 did not reveal any new data.⁴⁷

TOP EVIDENCE-BASED ENVIRONMENTAL CONTROL FINDINGS FOR PET ALLERGY PATIENTS

Keeping in mind that most environmental intervention studies have not demonstrated a reduction in symptoms and may not measure up under strict scrutiny, we will review some studies where significant allergen reduction has been shown or suggested (Table 1). These may be of value for clinical allergists to use as they make recommendations for patients with pet allergies:

1. Confining a cat to an uncarpeted room (other than the bedroom) with an HEPA may reduce up to 90% of airborne allergen dissemination to the remainder of the house.¹
2. Carpeted floors accumulate 100 times more cat allergen than polished floors.⁴⁸ In a study conducted in Swedish school classrooms, upholstered furniture and curtains contained equal amounts of cat dander and more than that found on the floor.⁴⁹
3. Increased ventilation rate and reduced furnishings decrease the level of Fel d 1 levels in a room recently vacated by a cat.⁴⁸
4. Not all studies have shown that washing dogs and cats on a frequent basis (one to two time a week) reduces airborne allergens, and even when this can be established, the reduction is for only a short time, at times returning to baseline within 3 hours.^{50–52}
5. Although the use of tannic acid on carpeting and upholstery initially reduced ($p < 0.05$) the concentration and total amount of Fel d 1 by 30% and Can f 1 by 10%, this effect waned after 1 week.⁵³
6. HEPA vacuum cleaners have not been shown to reduce animal dander exposure significantly.⁵³ HEPA filters have been shown to remove 99.97% of particles $\geq 0.3 \mu\text{m}$ in an experimental chamber. Likewise, new residential vacuum cleaners fitted with HEPA filters failed to release any cat allergen into an experimental chamber, whereas an old, non-HEPA vacuum increased the allergen 23-fold. However, when testing these same vacuums in a real-world cat resident home setting, the nasally inhaled cat allergen was increased when both the HEPA and the non-HEPA vacuum cleaners were in use (three- and fivefold increases, respectively, NS).⁵⁴ The authors felt that the disturbance of dander-containing dust reservoirs, e.g., carpet, soft fur-

Table 1 Environmental control for pet-allergic patients having pets in home: An evidenced-based approach

Environmental Change		Significant Allergen Reduction Shown or Suggested		
		Yes	No	Maybe/Unknown
1	Limit animal to uncarpeted room of house with separate HVAC with HEPA filtration	X		
2	Keep animal out of bedroom	X		
3	Replace carpeting with hard surface, preferably polished	X		
4	Use tightly woven (<4 μ m) protective coverings on all bedding	X		
5	Use MERV 12 filter on HVAC			X
6	Use HEPA vacuum		X	
7	Use HEPA free-standing air filtration unit			X
8	Provide adequate ventilation to homes, at least 6 air exchanges/hour			X
9	Limit or remove fabric upholstered furniture	X		
10	Wash bedding/curtains (a) at 60°C with one rinse, (b) at any temperature with two rinses, or (c) with a steam washing machine	X		
11	Wash pet with water $\pm$ special shampoo		X	
12	Steam clean carpeting/upholstery		X	
13	Give pet oral agents/topical sprays to reduce shedding		X	
14	Select female pet or consider neutering male pet	X		
15	Use tannic acid spray for carpeting and upholstery			X
16	Wear face mask for high animal allergen exposure activities	X		
17	After petting animal, wash hands before touching face			X
18	Require passive carriers of animal dander to change clothes before exposure to patient	X		

See text for references.

HVAC = heating, ventilation, air conditioning; HEPA = high-efficiency particulate air; MERV = minimum-efficiency reporting value.

nishings, and wall surfaces, outweighed any benefit of the HEPA vacuum. They concluded that they could not justify the recommendation of an HEPA vacuum for cat dander control. Likewise, Munir concluded that central, microfilter, and HEPA filter vacuum cleaners have not been found to reduce Fel d 1 or Can f 1 allergens from a carpeted home with resident animals.⁵³ However, because most HEPA vacuums today are competitively priced, offer a minor benefit for pet dander removal, and may assist in the removal of other

allergens such as dust mites, it seems prudent to recommend a HEPA vacuum for patients purchasing a new vacuum.⁴¹

- HEPA filtration freestanding units for reducing airborne animal dander are often recommended, but there is very limited scientific evidence for the recommendation. In a small study, Gore showed marginal reduction of inhaled cat allergen, especially if the cat is present in the room.⁵⁵ After 3 months of HEPA filtration, Wood demonstrated reduced airborne cat allergen but no improvement

in disease activity.⁵⁶ A 6-month study by Van der Heide indicated that the combined use of air cleaners and mattress covers contributed not only to a reduction in dust-mite and cat allergen exposure but to improvement of airway hyperresponsiveness in asthmatic patients.⁵⁷

8. Filters for the HVAC (heating, ventilation, and air conditioning) units are required for efficient appliance operation and preventative maintenance. The minimum-efficiency reporting value 12 disposable, pleated filter seems to be an efficient, cost-effective recommendation that could remove 91–95% (based on particle size collected) of airborne cat and dog allergens if there is adequate home ventilation. Six air changes per hour would provide particulate removal efficiency of 80%. A true HEPA filter (minimum-efficiency reporting value [MERV] 17–20) creates more air resistance than a residential HVAC unit could handle and is only used in specialized commercial settings. The patient needs to be reminded that the filter must be tightly fitted to the HVAC unit and that the fan must run continually, even if not required for cooling or heating, if filtration is to occur.
9. Commercial products widely advertised, *e.g.*, Pro-MACE (Ford Dodge Animal Health, Fort Dodge, IA) (acepromazine, a tranquilizer recommended in subsedating doses) and Allerpet-C (Allerpet, New York, NY), a topical spray, have not been shown to reduce Fel d 1 shedding.⁵⁸
10. Protective coverings for mattresses, box springs, pillows, quilts, and comforters are often recommended, but there are limited data on benefit, with few studies being completed.⁵⁹ Tightly woven fabric with 3.95- μm openings should be selected to capture the small cat allergens (2.5–10.0 μm in size).
11. Laundry techniques for dog dander removal that have been shown to be effective include (a) washing at 60°C with one rinse, (b) washing at any temperature with two rinses, and (c) using a steam washing machine.⁶⁰
12. Face masks could be considered for short-term, high animal dander exposure, *e.g.*, when vacuuming or litter box changing. The N95 face mask is inexpensive and $\geq 95\%$ efficient at filtering 0.3- μm particles. Although reported by patients to be beneficial, there are no published studies showing reduced inhalation of animal dander or symptom reduction with N95 use.
13. Washing hands after touching the pet and before touching one's face is almost always recommended and would seem to be appropriate, but has not been studied.
14. As has been shown for cockroach environmental control where multiple interventions were com-

bined to achieve success,⁶¹ it is likely that making many of the aforementioned changes concurrently will be required to achieve significant reduction in airborne dander and before any clinical benefit can be established.

TREATMENT OF EPISODIC AND PERENNIAL ALLERGIC RHINITIS (PAR), INCLUDING PET ALLERGY

Episodic Rhinitis

Pet allergy is recognized as a major cause of PAR, but the recent "The diagnosis and management of rhinitis: An updated practice parameter,"¹ compared to the prior practice parameter on rhinitis,⁶² added a new category of episodic rhinitis, which is neither seasonal nor PAR. An example of episodic rhinitis can be illustrated by the case of a patient with cat allergy who does not live with a cat and who experiences symptoms only when directly exposed to indoor cats. When unexpected encounters with a cat occur, this patient needs a quick-acting medication, *e.g.*, a topical antihistamine with onset of action within 30 minutes.⁶³ For a planned short visit to a home with a resident cat, additional medications that could be considered include an oral second-generation antihistamine, topical sodium cromolyn used before exposure, and, possibly, even a leukotriene antagonist or intranasal corticosteroid, although these latter two drugs would need to be started ~12 hours before exposure. For an extended visit to a home with a resident cat, any of the aforementioned medications could be used, and if symptoms are not well controlled, the combination of a topical antihistamine and an intranasal corticosteroid could be considered. Although combining sodium cromolyn with another medication, *e.g.*, one of the nonsedating antihistamines, has been suggested, this research has not been completed. When allergic conjunctivitis symptoms are not adequately controlled with the medication used to treat allergic rhinitis, a topical ophthalmic agent should be considered (Table 2).

PAR: Pharmacotherapy Single Agent

For perennial rhinitis due to pet allergy, there are no described differences in treatment response compared with other perennial allergens such as dust mites. A new proposed stepwise therapy for perennial allergic rhinoconjunctivitis, based to a large extent on the 2008 Rhinitis PP,¹ is presented in Table 2. In contrast to the previous rhinitis practice parameter,⁶² the 2008 Rhinitis PP does not define specific first-line agents but indicates that any of the pharmacotherapeutic agents for PAR, except systemic corticosteroids, could be considered as a first-line agent.¹ A closer review of the therapeutic options for the treatment of mild to severe PAR points out some subtle differences in risks and benefits:

Table 2 Pharmacotherapy for episodic and perennial allergic rhinoconjunctivitis

Medication Category*	Episodic Allergic Rhinoconjunctivitis		Perennial Allergic Rhinoconjunctivitis: Disease Severity			
	Episodic (unexpected or short term; one to two medications)	Episodic (planned or extended; one to two medications)	Mild (one medication)	Mild to Moderate (change medications or add second medication)	Moderate to Severe (change medications or add second medication)	Very Severe
Nasal medications						
Antihistamines (oral second generation)		X	X	X	X	X
Antihistamines (oral second generation) with decongestants		XX	XX	XX	XX	XX
Antihistamines, nasal topical	XXX	XXX	XXX	XXX	XXX	XXX
Corticosteroids, oral						XXXXX
Cromolyn, nasal			X	X		
Decongestants nasal (short-term use)#	XX	XX				
Decongestants, oral	X	X	X	X	X	X
Corticosteroids, intranasal		XXX	XXX	XXX	XXX	XXX
Ipratropium#	X	X	X	X	X	X
Montelukast		X	X	X	X	
Ocular eye gtts						
Antihistamine	X	X	X	X		
Antihistamines/ mast cell stabilizer	XX	XX	XX	XX	XX	XX
Antihistamine/ vasoconstrictor (short term use)	XX					
Corticosteroid						XXXX
Mast cell stabilizer		X	X	X	X	
NSAID	X	X	X	X	X	
Vasoconstrictor (short-term use)#	X					

Number of "Xs" gives a general comparison of the benefit and/or recommendations at the various severity levels. See text for details.

*Listed in alphabetical order within nasal and ocular sections.

#Used rarely as single agent for PAR.

NSAID = nonsteroidal anti-inflammatory drug; PAR = perennial allergic rhinitis.

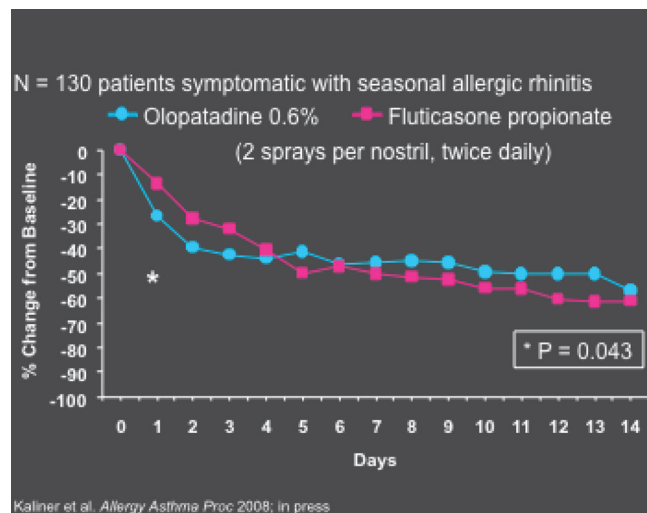


Figure 1. Olopatadine vs. fluticasone: Mean % daily change in total nasal symptom score

1. Leukotriene antagonists are considered to be equal to second-generation antihistamines if one is using loratadine as the comparator.¹ "Intermittent use" of intranasal corticosteroids (INS), as defined in the research studies, was still >55% of the time.⁶⁴⁻⁶⁶
2. Ipratropium, having benefit only for the symptom of rhinorrhea, would rarely be indicated as a single agent for PAR, as additional symptoms are usually present.
3. Topical antihistamines are equal or superior to oral antihistamines.¹
4. For mild to moderate allergic rhinitis, preliminary studies show that topical antihistamines are effective and comparable with INS (Fig. 1).⁶⁷⁻⁶⁹
5. Intranasal steroids are the most efficacious single agent for moderate to severe allergic rhinitis. When comparing the various INS agents, significant differences in efficacy have not been established.¹
6. Topical nasal decongestant use should be limited to a few days per episode, *e.g.*, severe exacerbation of PAR, to avoid the development of rebound that occurs in a high percent of patients.¹
7. Oral decongestants, with pseudoephedrine being the most and perhaps only effective agent, and topical decongestants should be used cautiously in older adults and children <6 years of age because of increased side effect profile.¹
8. Oral corticosteroids should be used only as a last resort, and then for a very short time because of their well-recognized systemic side effects, including adrenal suppression, cataract formation, osteoporosis, increased intraocular pressure, and growth suppression in children.¹

The potential side effects of pharmacotherapy for PAR should always be discussed with patients with this disease, perhaps even more so when the major and

perhaps only allergen, *e.g.*, dog or cat, is one that could, theoretically, be avoided. Second-generation antihistamines, oral or topical, have an overall excellent safety profile in both adults, including pregnant women, and children^{1,70-72} avoiding, for the most part, the sedation, performance impairment, and anticholinergic effects associated with the first-generation antihistamines. Although the α -adrenergic agonists are frequently combined with oral antihistamines, thereby enhancing the reduction of nasal congestion, their use can result in insomnia, irritability, and palpitations.¹ Caution is advised when these agents are used in patients with cardiac arrhythmia, angina pectoris, cerebrovascular disease, hypertension, bladder neck obstruction, glaucoma, or hyperthyroidism.¹ When given in recommended doses, intranasal corticosteroids are not generally associated with clinically significant systemic side effects, including bone growth in children.¹ The commonly reported local side effects include nasal irritation and bleeding. The anticholinergic agents have a low incidence of adverse events, mainly epistaxis and nasal dryness, but caution should be used in patients with narrow-angle glaucoma, prostatic hypertrophy, or bladder neck obstruction. Leukotriene antagonists, intranasal cromolyn, and saline have an excellent safety profile, with very minimal side effects reported.¹

PAR: Pharmacotherapy Combination of Agents

Combination pharmacotherapy in the management of PAR does not always add enough benefit to justify the increased cost and potential side effects. There are, however, a few combinations that should be considered. Pseudoephedrine, more effective than phenylephrine, in combination with a second-generation antihistamine shows additional efficacy but has more side effects.^{73,74} Although the combination of an oral antihistamine and a leukotriene antagonist may give added benefit over either agent used alone, INS monotherapy is more effective.¹ Although the studies are limited, the combination of an INS and a topical nasal antihistamine has shown significant clinical benefit, a benefit not adequately established when adding an oral antihistamine.⁷⁵ The benefit of INS, oral antihistamines, and nasal antihistamines on allergic conjunctival symptoms is comparable,¹ but for severe eye symptoms, topical antiallergy eye preparations give added benefit. Furthermore, the combination of an ocular antihistamine and a vasoconstrictor is more efficacious than either agent alone.¹

PAR: Immunotherapy

It is well recognized that allergy immunotherapy is the only treatment for PAR that can potentially modify the disease. Additional benefits of subcutaneous immunotherapy (SIT) include the prevention of new al-

lergen sensitization and reduction of the risk of developing asthma.⁷⁶ The most effective maintenance dose for cat SIT is 15 μ g Fel d 1 that would equate to between 2000 and 4000 BAU. Dog allergen is not standardized, and there are limited dosing studies. One acetone-precipitated dog extract study concluded that the best efficacy was obtained with 15 mg of Can f 1.⁷⁷ Nanda showed that one could predict the success of SIT for cat after 1 year of treatment by completing select studies when the maintenance level (15 μ g of Fel d 1) was reached, ~5 weeks after starting treatment. These studies included titrated nasal allergen challenge using symptom scores, titrated skin-prick test, and allergen-specific IgG4 levels. After completion of 3 years of SIT for asthmatic patients with dog and/or cat allergy, Hedlin did a 5-year follow-up study and found that patients reported no worsening of symptoms and experienced only mild asthma. There was no change in bronchial histamine sensitivity after discontinuing SIT. Although the IgG4 had declined after stopping SIT, the specific IgE remained low. Although the bronchial allergen sensitivity had increased to near pretreatment levels, this did not seem to affect asthma symptoms.⁷⁸

Sublingual immunotherapy (SLIT) has also established benefits using standardized cat dander extract in a double-blind placebo-controlled trial of 33 adult patients with PAR $\pm$ asthma. During the study there was continued cat dander exposure, as 16/17 patients lived with cats.⁷⁹ The maintenance level was reached at 35 days of treatment, and the total accumulated dose was 17.1 μ g of Fel d 1.⁷⁹ Although this level was quite low compared with other SLIT studies, a natural cat room challenge after treatment showed a 62% reduction in symptoms, a diminished decline in forced expiratory flow, and a reduced skin-test response to cat.⁷⁹ An 8-week, open-label SLIT safety study of four U.S. standardized extracts was conducted that included cat extract in 31/91 patients with AR $\pm$ asthma.⁸⁰ Using a 1-day, 7-interval dose escalation protocol, 69% were able to achieve a dose of 2090 BAU_m which is ~15 μ g of Fel d 1, with the range being 50–2090 BAU. Although 99% of the study group had adverse reactions, 95% were considered mild. However, 6/12 severe adverse reactions, 1 being anaphylaxis, occurred in those patients receiving cat SLIT. Adherence was quite good at 80%.⁸⁰ However, a high dose (total dose of 45,000 BAU) SLIT study using Food and Drug Administration-approved standardized cat over 105 days was only marginally effective.⁸¹

There have been eight Fel d 1 peptide immunotherapy studies completed between 1996 and 2005 involving >350 patients. Most have shown reduced symptoms, improved forced expiratory volume at 1 second, improved PD20, and/or reduced early and late-phase skin response. Unfortunately, these high-dose SIT

studies have shown significant adverse events in >20% of the patients. Currently, low-dose, intradermal, shorter peptide immunotherapy is being studied and holds promise for an effective and safer treatment.⁸²

USE OF QOL QUESTIONNAIRES AND AN ACTION PLAN

The clinical allergist is encouraged to review the effects of PAR on quality of life (QOL), both initially and at each follow-up visit. Consideration should be given to using one of the validated QOL questionnaires used in research studies, although additional study is needed to guarantee that these instruments give adequate sensitivity and precision for the individual patient. As introduced in the 2008 Rhinitis PP, the "Rhinitis Action Plan" will provide the patient with an individualized written plan for managing their disease.^{1,83}

In conclusion, pet allergy is and will likely continue to be a major cause of PAR. It is unlikely that allergy patients will choose to avoid these allergen-producing "members of the family." If cost-effective environmental changes can be established to reduce symptoms, patients will likely comply. However, most patients are ideally seeking a "cure" and prefer not to take daily medications that only temporarily control their allergy symptoms. Therefore, allergen immunotherapy may be the best therapeutic recommendation for patients with moderate to severe pet-induced PAR.

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