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*Short communication*

# Fluoxetine (SSRI) treatment of canine atopic dermatitis: a randomized, double-blind, placebo-controlled, crossover trial

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## Abstract

This study investigated effects of a fluoxetine (selective serotonin reuptake inhibitors; SSRI, 1 mg/kg) on pruritus in canine atopic dermatitis (CAD). After 4-weeks of base-line observation, 8 dogs with CAD entered a 2-months randomized, double-blind, placebo-controlled, crossover trial comparing fluoxetine with placebo. Clinical efficacy was evaluated using a Canine Atopic Dermatitis Extent and Severity Index (CADESI-03) and Pruritus Visual Analog Scale (PVAS). Six dogs completed the study [two out of eight dogs (both of them were Shiba Inu) dropped out from the study due to a depression]. CADESI-03 and PVAS between fluoxetine and placebo showed no significant difference statistically ( $P>0.05$  and  $P>0.05$  respectively). Fluoxetine showed no efficacy on pruritus in CAD. Further researches are needed for the treatment on pruritus of CAD.

**Key words:** canine atopic dermatitis, fluoxetine, SSRI, pruritus

## Introduction

It is now accepted that canine atopic dermatitis (CAD), similar to the human counterpart, is a multifaceted disease determined by a combination of genetic (filaggrin related gene) and environmental factors affecting both the immunologic response as well the skin barrier function (Marsella et al. 2012). A recent study focused on cytokine called IL-31 which is related to pruritus (Gonzales et al. 2013). Moreover injection of canine IL-31 into laboratory beagle dogs caused transit episodes of pruritic behavior regardless of the route of administration. So pruritus of nerve might be some factors in CAD (Marsella et al. 2012).

In the brain, reduction of itch perception and modulation of emotions may possibly be achieved through drugs acting on the anterior cingulate cortex (Tey and Yosipovitch 2011). Fluoxetine (selective serotonin reuptake inhibitor: SSRI) is widely used in human medical field as psychoactive drug. Previous study has reported an efficacy of fluoxetine on canine acral lick dermatitis (Rapoport et al. 1992, Wynchank and Berk 1998). In human study, SSRI showed high antipruritic potency in patient with chronic pruritus. Thus, the aim of this study is clinical evaluation of fluoxetine for CAD related pruritus.

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## Materials and Methods

### Animals

The investigators recruited 8 dogs from our hospital with a diagnosis of CAD and persistent pruritus despite some therapies. The age of the dogs at entry in the study was 3-12 years (mean: 5 years). The age of disease onset was 1-7 years (mean: 2.8 years). 2 females, 5 spayed females, and 1 castrated male. Breeds (Golden Retriever, Toy Poodle, West Highland White Terrier, Chihuahua, Cavalier King Charles Spaniel, French Bulldog, respectively. 2 Shiba Inu) were included in the study.

### Pretreatment Assessment

The diagnosis of CAD was based upon elimination of other causes of pruritus, compatible history, and compatible clinical signs, as well as Favrot's 2010 criteria for the diagnosis of CAD (Favrot et al. 2010). Intradermal allergy testing was performed with 24 selected antigens (Greer Pharmacy, Lenoir, NC, USA; or Torii Pharmaceutical co., Ltd., Tokyo, Japan). Six dogs had positive reactions to house dust mite mix (*Dermatophagoides farinae* and *D. pteronyssinus*) and 3 dogs had positive reactions to cotton and other antigens.

### A randomized, double-blind, placebo-controlled, crossover trial

A fluoxetine (1 mg/kg) and its placebo (sugar) were put in same kind of capsule and orally administered to patients for 4-weeks respectively.

### Concurrent Treatments

Allergen-specific immunotherapy was continued as a combination therapy for Dogs. Seven dogs were receiving allergen-specific immunotherapy for 5 to 57 months prior to inclusion in the study. Assessments were performed 4 weeks prior to starting the study to ensure that there was no improvement in clinical signs from any concurrent therapies. No other therapies (e.g., corticosteroids, cyclosporine, and antimicrobial) were allowed during the 8-week treatment period.

### CADESI-03: Canine Atopic Dermatitis Extent and Severity Index and PVAS: Pruritus Visual Analog Scale

CADESI-03 was used to assess lesion severity. The severity of erythema, lichenification, excoriations,

and alopecia was assessed at 62 body sites using a scale from 0-5 (0 = none, 1 = mild, 2-3 = moderate, and 4-5 = severe). A pruritus liners score was recorded using a scale from 0-5 (0 = absence of pruritus, 1 = almost no pruritus, 2 = mild pruritus, 3 = moderate pruritus, 4 = severe pruritus, and 5 = extremely severe pruritus). Owner of the dogs scored their own dog every week, four times for both fluoxetine and placebo. An average score was calculated for the result.

### Statistical Analysis (Wilcoxon signed-rank test)

Statistical analysis was performed by use of paired *t*-tests with SAS 8.2 software. Statistical significance was defined as  $P < 0.05$ . In this study, the mean data for total scores and subscores were pooled at each time point and compared to the other assessment periods.

## Results and Discussion

Before the trial, no variation of efficacy of allergen-specific immunotherapy was confirmed by CADESI-03 score. Average CADESI-03 score at start of the month (PRE1) was  $377.6 \pm 201.4$ , CADESI-03 score at end of the month (PRE2) was  $395.1 \pm 199.1$  respectively. It was not significant difference ( $P > 0.05$ ). Two out of 8 dogs treated with fluoxetine were dropped out by cause of depression. Both breeds were young Shiba Inu. One of the cases showed depression in day 3 and another dog showed a decrease in the activity after 2 weeks of treatment. Six out of 8 dogs completed the trial. CADESI-03 score of a fluoxetine and placebo showed no significant difference from their baseline scores ( $P > 0.05$ ). PVAS score also showed no significant differences in both test substances ( $P > 0.05$ ).

In human study, efficacy of SSRI for pruritus was evaluated in many studies. These studies assumed that SSRI show efficacy for pruritus associated with the central nervous system rather than the peripheral nervous system (Ständer et al. 2009). In this study, fluoxetine showed no efficacy for pruritus in CAD by CADESI-03 and PVAS. From the results, we assumed that the peripheral nervous system is associated more closely to pruritus in CAD rather than the central nervous system. Previous studies reported the efficacy of fluoxetine for dogs with pruritus in behavior disorder (Rapoport et al. 1992, Wynchank and Berk 1998). In human study, efficacy of fluoxetine on many kinds of pruritus including atopic dermatitis was reported (Ständer et al. 2009). However, our results did not show reduction of pruritus in CAD. In the dogs, pruritus in CAD and pruritus in behavior disorder might be different in their cause or mechanism. Moreover, unlike human, a psychological aspect might only take

a minor part in cause of pruritus for dogs. Unfortunately, fluoxetine showed no efficacy for pruritus in CAD but a control of pruritus is important for the treatment of CAD. Further investigations are needed in order to control pruritus in CAD.

### Conclusion

The present study suggests that fluoxetine was no effect on pruritus in CAD.

Further studies are needed in order to find anti-pruritus medicines which can help to control pruritus in CAD. Moreover, the cause for pruritus in CAD requires further investigations.

### Reference

Dunham SA, Fuller TE, McCall RB (2013) Interleukin-31: its role in canine pruritus and naturally occurring canine atopic dermatitis. *Vet Dermatol* 24: 48-53.

Favrot C, Steffan J, Seewald W, Picco F (2010) A prospective study on the clinical features of chronic canine atopic dermatitis and its diagnosis. *Vet Dermatol* 21: 23-31.

Gonzales AJ, Humphrey WR, Messamore JE, Fleck TJ, Fici GJ, Shelly JA, Teel JF, Bammert GF, Marsella R, Sousa CA, Gonzales AJ, Fadok VA (2012) Current understanding of the pathophysiologic mechanisms of canine atopic dermatitis. *J Am Vet Med Assoc* 241: 194-207.

Marsella R, Sousa CA, Gonzales AJ, Fadok VA (2012) Current understanding of the pathophysiologic mechanisms of canine atopic dermatitis. *J Am Vet Med Assoc* 241(2): 194-207.

Rapoport JL, Ryland DH, Kriete M (1992) Drug treatment of canine acral lick. An animal model of obsessive-compulsive disorder. *Arch Gen Psychiatry* 49: 517-521.

Roosterman D, Goerge T, Schneider SW, Bunnett NW, Steinhoff M (2006) Neuronal control of skin function: the skin as a neuroimmunoendocrine organ. *Physiol Rev* 86: 1309-1379.

Ständer S, Böckenholt B, Schürmeyer-Horst F, Weishaupt C, Heuft G, Luger TA, Schneider G (2009) Treatment of chronic pruritus with the selective serotonin re-uptake inhibitors paroxetine and fluvoxamine: results of an open-labelled, two-arm proof-of-concept study. *Acta Derm Venereol* 89: 45-51.

Tey HL, Yosipovitch G (2011) Targeted treatment of pruritus: a look into the future. *Br J Dermatol* 165: 5-17.

Wynchank D, Berk M (1998) Fluoxetine treatment of acral lick dermatitis in dogs: a placebo-controlled randomized double blind trial. *Depress Anxiety* 8: 21-23.