

# Veterinary Record

## Is there a link between treatments with exogenous corticosteroids and dog behaviour problems?

Journal:	<i>Veterinary Record</i>
Manuscript ID	vetrec-2016-103768.R1
Article Type:	Paper
Date Submitted by the Author:	20-Jun-2016
Complete List of Authors:	Notari, Lorella Burman, Oliver; University of Lincoln, School of Life Sciences Mills, Daniel; University of Lincoln, Department of Biological Sciences
Abstract:	<p>Possible side effects of exogenous corticosteroids have been described in both humans and laboratory animals with recent studies highlighting this issue in dogs. In this paper the behaviour of 345 dogs drawn from the behavioural caseload of a behaviour clinic based in the north of Italy between February 2012 and November 2014, were analysed. Possible relationships between dogs that received treatment with corticosteroids versus dogs that received a treatment with drugs other than corticosteroids and positive or negative affective states, aggression towards people, other behaviour problems apart from aggression, occurrence of severe bites and prescription of psychoactive drugs were initially assessed using a Pearson's Chi Squared test.</p> <p>Regression analysis was then performed in order to evaluate the best predictors of the investigated items. The goal of this retrospective survey was to investigate possible relationships between the affective states associated with the behavioural complaint of dogs and their previous history of treatment with corticosteroids drugs. Results showed that a history of corticosteroid treatment was a significant predictor of a range of behaviour problems associated with negative affective state, but this result may be confounded by age related effects.</p>

SCHOLARONE™  
Manuscripts

# 1 Is there a link between treatments with exogenous corticosteroids and dog 2 behaviour problems?

3 L. Notari, O. Burman and D. S. Mills

4 Author affiliation: Animal Behaviour, Cognition and Welfare Group, School of Life Sciences,  
5 Joseph Banks Laboratories, University of Lincoln, Lincoln LN6 7DL, UK

6 Corresponding author: Lorella Notari [lorellanotari@lorellanotari.it](mailto:lorellanotari@lorellanotari.it)

## 7 Abstract

8  
9 Possible side effects of exogenous corticosteroids have been described in both humans and  
10 laboratory animals with recent studies highlighting this issue in dogs. In this paper the behaviour of  
11 345 dogs drawn from the behavioural caseload of a behaviour clinic based in the north of Italy  
12 between February 2012 and November 2014, were analysed. Possible relationships between dogs  
13 that received treatment with corticosteroids versus dogs that received a treatment with drugs other  
14 than corticosteroids and positive or negative affective states, aggression towards people, other  
15 behaviour problems apart from aggression, occurrence of severe bites and prescription of  
16 psychoactive drugs were initially assessed using a Pearson's Chi Squared test.  
17 Regression analysis was then performed in order to evaluate the best predictors of the investigated  
18 items. The goal of this retrospective survey was to investigate possible relationships between the  
19 affective states associated with the behavioural complaint of dogs and their previous history of  
20 treatment with corticosteroids drugs. Results showed that a history of corticosteroid treatment was  
21 a significant predictor of a range of behaviour problems associated with negative affective state, but  
22 this result may be confounded by age related effects.

## 24 Introduction.

25  
26 Psychiatric side effects of corticosteroid drugs have been reported in humans and laboratory  
27 animals (Drozdowicz and Bostwick, 2015; Mikics et al., 2007; Warrington and Bostwick, 2006)  
28 and behavioural changes related to corticosteroid treatments have also been reported by dog owners  
29 (Notari and Mills, 2011; Notari et al., 2015). Direct testing of dogs also showed that dogs on  
30 corticosteroids were less explorative compared with control dogs (Notari et al., 2015). There is a  
31 literature to indicate that corticosteroid therapies might negatively influence the behaviour of both

1 human and non-human animals and so it is worth investigating about what proportion of dogs  
2 presented for different behaviour problems have a history of treatment with corticosteroids and  
3 whether corticosteroids appear to increase the risk of any complaints associated with sensitivity to  
4 aversion, e.g. fears and anxieties.

5 From the human psychiatric literature, we know that the negative psychological side effects of  
6 corticosteroid therapies can be more evident in patients that already have some psychiatric  
7 disturbance (Fardet et al., 2012; Kenna et al., 2011; Sirois, 2003; Ularntinon et al., 2010), But we do  
8 not know if an analogous situation occurs in non-human animals or what proportion of dogs with  
9 different types of behaviour problem previously have been given corticosteroid drugs. Such  
10 information will provide better insight into the possible behavioural side effects of these drugs, in  
11 particular in dogs predisposed to behaviour disturbance.

12 The use of corticosteroid drugs in veterinary practice has been investigated previously using a  
13 survey in three UK veterinary practices and a wide variation in prescribing patterns was detected. It  
14 was reported that 14.55% of dog consultations resulted in systemic glucocorticoid therapy  
15 (O'Neill et al., 2012). Despite the frequency of this practice and the large amount of literature in  
16 other species that indicates the possible influence of corticosteroid drugs on behaviour, no  
17 retrospective analysis has ever been done to investigate possible relationships between  
18 corticosteroid therapies and behavioural problems in dogs.

19 The retrospective analysis of cases presented in this paper, for the first time, investigates the  
20 possible implications of a history of treatment with corticosteroids in a population of dog behaviour  
21 patients. The goals were to gather information about the proportion of dogs with behaviour  
22 problems that had a history of corticosteroid therapies and to investigate possible relationships  
23 with behaviour problems and the underlying affective state associated with groups of these  
24 problems. The relationship between history of corticosteroid therapy and the prescription of  
25 psychoactive drugs was also investigated, because this might be related to the severity of behaviour  
26 problems (Dodman et al., 1996; King et al., 2000; Marder, 1991; Pineda et al., 2014).

## 27 **Material and methods**

### 29 **Sample**

30  
31 The files of 345 dogs aged between 1 and 10 years that had presented for behavioural problems  
32 were selected from the dog caseload of a veterinary behavioural clinic based in the north of Italy.  
33 This age range was selected to decrease the probability that reported behaviour problems were due

1  
2  
3 1 to management problems in puppies or health conditions due to aging in older dogs. The data were  
4 2 collected for cases seen in the period February 2012 to November 2014. .  
5  
6 3

#### 4 **Investigated items**

5  
6 Each case file was analyzed and the following items of data were extracted for the purpose of this  
7 investigation:

- 8 1. Age of dog
- 9 2. Gender and reproductive status of dog
- 10 3. Breed type divided into the number of Federation Cinologique International Group (FCI) for  
11 all the recognized breeds. Pitbull type dogs were coded as 'Pitbull', with crossbreed dogs  
12 coded as 'crossbreed'. Dog breed recognition was based on morphological features of the  
13 dogs and from owner statements.
- 14 4. Treatment and medical history of dogs treated with corticosteroid drugs
- 15 5. Treatment and medical history of dogs treated with other drugs.
- 16 6. Presence of aggression towards people
- 17 7. Types of bites (severe or not severe)
- 18 8. Behaviour problems other than aggression
- 19 9. Prescription of psychoactive drugs to address the behavioural complaint
- 20 10. Affective state (see below for details about definition of positive or negative affective state)

21  
22 The source of the above information was both the Dog Behavioural History Form used in the  
23 behaviour clinic, that was completed for every dog at the time of the first consultation, and the  
24 therapist's own diagnostic and therapeutic notes.

25 For 'history of treatment with corticosteroids' only systemic treatments that lasted more than one  
26 week were taken into consideration, in order to avoid single treatments for emergency interventions,  
27 since the effects of longer term administration were the focus of interest. Data about treatment with  
28 corticosteroid drugs was extrapolated from the Dog Behavioural History Form completed during  
29 behavioural consultation in the section concerning the medical history of patient. The exact  
30 administered dose was not always recalled by owners and an inclusion requirement for those  
31 subjects recorded as 'received treatment with corticosteroids' was that the owner could recall the  
32 name of the product, the reason why it was prescribed and the length of the therapy in terms of  
33 more than a week or less than a week. As far as the item 'history of treatment with other drugs'  
34 (Item 5) was concerned, reported treatments were considered as for treatment with corticosteroids.

1  
2  
3 1 Evidence of past medical problems and past treatments were provided by medical records given by  
4  
5 2 owners or by veterinary surgeons that referred the behavioural case.

6 3 As far as the item 'types of bites', bites that required medical intervention were considered as  
7  
8 4 'severe bites'. Negative and positive affective states were coded (see below) on the basis of the  
9  
10 5 responses of the owners to questions included in the Dog Behavioural History Form specifically in  
11  
12 6 the section entitled 'Your dog's personality' in conjunction with the evaluation of the veterinary  
13  
14 7 behaviourist who held the consultation. As far as the information extracted from the Dog  
15  
16 8 Behavioural History Form was concerned, owners had to answer 'yes' or 'no' to the following  
17  
18 9 questions:

- 10 1. Do you consider your dog as aggressive in most situations?
- 11 2. Do you think that your dog is often or always nervous or fearful in the presence of unknown  
12 situations or stimuli (sounds, new stimuli, unknown people or dogs)?
- 13 3. Do you consider your dog largely enthusiastic and excited?
- 14 4. Do you think that your dog is sociable in general?
- 15 5. Do you consider your dog confident?

16 To be coded as having a positive affective state, the owner had to answer 'No' to questions one and  
17 two and 'Yes' to at least two of the last three questions. To be coded as having a negative affective  
18 state the owner had to answer 'Yes' to at least one of the first two questions. The final definition of  
19 affective state as positive or negative in connection with the type of behaviour problem was  
20 established through the behavioural consultation and based on the description of the problem  
21 behaviour and its context as well as the direct observation of the dog's behaviour in the clinical  
22 context by the behaviour clinician.

23 Positive affective state was attributed to dogs with problem behaviours that were most likely to be  
24 related to positive emotional reactions but perceived as problematic and/or exaggerated by their  
25 owners, for example:

- 26 • excessive play behaviour
- 27 • excessive activity such as running, digging, stealing objects
- 28 • excessive attention seeking behaviours, such as jumping on people, barking for attention

29 Negative affective state was attributed to dogs presenting with behaviours that were more likely to  
30 be related to negative emotions such as fear, anxiety and frustration. For example:

- 31 • fear, phobia and anxiety
  - 32 • avoidant or assertive displays of aggressive behaviours
  - 33 • repetitive conflict behaviours
- 34

1  
2  
3 1 **Statistical analysis**

4 2  
5  
6 3 Analysis was performed using IBM SPSS Statistic 21, with summary descriptive statistics  
7 4 calculated initially.

8  
9 5 We assessed, using the Pearson's Chi Squared test, possible associations between dogs that received  
10 6 treatment with corticosteroids versus dogs that received a treatment with other drugs different from  
11 7 corticosteroids and:

- 12  
13  
14 8
  - 15 9 • positive or negative affective states
  - 16 10 • aggression towards people
  - 17 11 • other behaviour complaints besides aggression
  - 18 12 • occurrence of severe bites
  - 19 13 • prescription of psychoactive drugs

20  
21 14 Regression analysis was then performed in order to hierarchically evaluate the best predictors of the  
22 15 investigated items ( $p < 0.05$ ).

23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## Results

From the initial sample of 345 dogs selected from the author's caseload database containing completely filled in Dog Behavioural Forms, 2 dogs were excluded because of incomplete reports about medical history and treatment and a final sample of 343 was used for analysis.

Gender and reproductive state of dogs are shown in Table 1.

Gender and reproductive state	Total frequency n. (%)	Frequency (n.) (%)	
		No cortico group	On cortico group
intact male	177 (51.6)	147 (51)	30 (54.5)
intact female	56 (16.3)	49 (17)	7 (12.7)
castrated male	35 (10.2)	29 (10.1)	6 (10.9)
spayed female	75 (21.9)	63 (21.9)	12 (21.8)

**Table 1. Gender and reproductive state distribution within the sample of 343 dogs with behaviour problems. No cortico group = group of dogs without a history of corticosteroid treatment; On cortico group= group of dogs with a history of corticosteroid treatment**

Within the sample of 343 dogs, the age distribution of dogs is shown in Table 2.

Age	Total frequency n. (%)	Frequency n. (%)	
		No cortico group	On cortico group
1-2 years	195 (56.9)	179 (62.2)	16 (29.1)
3-4 years	87 (25.4)	70 (24.3)	17 (30.9)
5-6 years	34 (9.3)	24 (8.3)	8 (14.5)
7-8 years	26 (7.6)	14 (4.9)	12 (21.8)
9-10 years	3 (0.9)	1 (0.3)	2 (3.6)

**Table 2. Age distribution within the sample of 343 dogs with behaviour problems. No cortico group = group of dogs without a history of corticosteroid treatment; On cortico group= group of dogs with a history of corticosteroid treatment**

Breed distribution within the sample of 343 dogs is shown in Table 3:

Breed group/type	Frequency n. (%)	Frequency n. (%)	
		No cortico group	On cortico group
FCI Group1 - <i>Sheepdogs and Cattle dogs</i>	45 (13.1)	34 (11.8)	11 (20.0)
FCI Group 2 - <i>Pinscher and Schnauzer – Molossoid and Swiss Mountain and Cattle dogs</i>	43 (12.5)	32 (11.1)	11 (20.0)
FCI Group 3 - <i>Terrier</i>	23 (6.7)	17 (5.9)	6 (10.9)
FCI Group 4 - <i>Dachshunds</i>	8 (2.3)	6 (2.1)	2 (3.6)
FCI Group 5 - <i>Spitz and primitive types</i>	10 (2.9)	10 (3.5)	0 (0)
FCI Group 6 - <i>Scent hounds and related breeds</i>	8 (2.3)	8 (2.8)	0(0)



FCI Group 7 - <i>Pointing Dogs</i>	9 (2.6)	8 (2.8)	1 (1.8)
FCI Group 8 - <i>Retrievers – Flushing Dogs – Water Dogs</i>	18 (5.2)	13 (4.5)	5 (9.1)
FCI Group 9 - <i>Companion and Toy Dogs</i>	29 (8.5)	25 (8.7)	4 (7.3)
FCI Group 10 - <i>Sighthounds</i>	7 (2.0)	7 (2.4)	0(0)
Crossbreed	126 (36.7)	113 (39.2)	13 (23.6)
PITBULL	17 (5.0)	15 (5.2)	2 (3.6)

**Table 3. Breed distribution within the sample of 343 dogs with behaviour problems. No cortico group = group of dogs without a history of corticosteroid treatment; On cortico group= group of dogs with a history of corticosteroid treatment.**

Within the sample of 343 dogs, 209 (73.8%) had a history of treatment with drugs other than corticosteroids and 55 (16.0%) had a history of treatment with corticosteroid drugs. Forty-eight of the 55 dogs that had a history of treatment with corticosteroids also had a history of treatment with other drugs. In Table 4, the types of drug treatments other than corticosteroid in the two groups of dogs with and without a history of treatment with corticosteroid drugs are shown. Drug therapies have been divided into four main categories:

- Antibiotics and antifungal drugs
- Antacid drugs
- Non Steroidal Anti-inflammatory drugs (NSAIDs)
- Other drugs

TYPE OF DRUG	Frequency n.	Frequency n.
	(%)	(%)
	No cortico group (n.209)	On cortico Group (n.55)
antibiotics and antifungal drugs	162 (78.3)	32 (66.7)
antacid drugs	18 (8.7)	12 (25.0)
NSAIDS	17 (8.2)	3 (6.3)
others	10 (4.8)	1 (2.1)

**Table 4. Types of drug treatments other than corticosteroids used in the two groups of dogs:**

**No cortico group = group of dogs without a history of corticosteroid treatment; On cortico group= group of dogs with a history of corticosteroid treatment**

Reported medical problems were divided into 5 main groups:

- Dermatological
- Orthopaedic
- Gastroenteric
- Respiratory
- Others

Whithin 'Others' were included urinary and reproductive problems, cardiovascular and hematological diseases and neurological diseases.

Medical problems reported in dogs treated with corticosteroid drugs and dogs treated with drugs other than corticosteroids are show in Table .5.

Medical problems	Frequency n. (%)	Frequency n. (%)
	No Cortico Group (n. 288)	On Cortico Group (n.55)
Dermatological	53 (18.4)	36 (65.5)
Orthopaedic	15 (5.2)	12 (21.8)
Gastrointestinal	74 (25.7)	5 (9.1)
Respiratory	54 (18.8)	1 (1.8)
Others	33 (11.5)	1(1.8)
No medical problems with more than 1 week therapy	79 (27.2)	0

**Table 5. Medical problems in dogs a history of treatment with corticosteroids. No cortico group = group of dogs without a history of corticosteroid treatment; On cortico group= group of dogs with a history of corticosteroid treatment. The sum of percentages is not 100% because some subjects have multiple medical problems.**

The main behavioural complaints within the sample of 343 dogs are listed in Table .6. Specific conditions were pooled into broader categories to create more suitable population sizes for analysis, as described below.

All forms of aggressive behaviour towards people with the exception of that associated with play, were grouped into a single category whether this was aggression towards family members or strangers.

Aggression towards other dogs including both aggression between dogs living together in the same family and towards unfamiliar dogs formed another class.

Predation was the complaint for just one dog and related to severe predatory behaviour towards cats. This subject was not pooled with other aggressive dogs.

All problem behaviours that were associated with distress in the absence of owners/when the dog was left alone were classed as separation problems.

Both urine marking and forms of inappropriate elimination and housetraining problems were grouped into a single class 'housesoiling problems'.

Fear of specific situations (e.g. thunderstorm, wind, unknown environments), social fear (fear of people, fear of other dogs) and fear of sounds were grouped together as phobias.

1 Repetitive behaviours included compulsive licking, tail chasing and tail biting.  
 2 Excessive barking was used to refer to problematic barking in different situations.  
 3 Excessive play and play biting, excessive attention seeking behaviours, jumping on people,  
 4 destructiveness and excessive excitement in different situations were grouped as forms of  
 5 hyperactivity.  
 6 Other behaviour problems were grouped together as a single class and included cases involving a  
 7 tendency to run away from the property, digging and decreased activity levels.  
 8 Multiple behaviour problems were presented in 66.5% (228) of the total sample of dogs. Within the  
 9 sample of dogs receiving treatment with corticosteroids, 51% (28) presented with multiple  
 10 behaviour problems.

Behaviour	Total frequency n. (%)
Aggression towards people	148 (43.1)
Aggression towards other dogs	59 (17.2)
Predation	1 (0.3)
Separation problems	47 (13.7)
Housoiling problems	22 (6.4)
Phobias	91 (26.2)
Repetitive behaviours	11 (3.2)
Excessive barking	43 (12.5)
Hyperactivity	90 (25.9)
Other	37 (10.7)

11 **Table 6. Categories of presenting complaint; the sum of percentages is not 100% because of**  
 12 **some subjects presenting with multiple behaviour problems.**

14 Psychoactive drugs were prescribed to 31.2 % (107 dogs) of the sample. Among the 55 dogs with a  
 15 history of corticosteroid treatments psychoactive drugs were prescribed in 43.6 % of cases (24  
 16 dogs). Among the 290 dogs without any history of corticosteroid drugs psychoactive drugs were  
 17 prescribed in the 28.4 % of cases (83 dogs).

18 The distribution of drugs used is shown in Table 7.  
 19

1

Prescribed drug	Frequency n. (%)	Frequency n.	Frequency n. (%)
	Total n.	(%) No cortico group n.	On cortico group n.
Fluoxetine	69 (20.1)	50 (17.4)	19 (34.5)
Fluvoxamine	9 (2.6)	9 (3.1)	-
Paroxetine	11 (3.2)	10 (3.5)	1 (1.8)
Selegiline	9 (2.6)	8 (2.8)	1 (1.8)
Clomipramine	8 (2.3)	5 (1.7)	3 (5.5)
Carbamazepine	1 (0.3)	1 (0.3)	-

**Table 7. Psychoactive drugs prescribed within the whole sample (n= 343) of dogs with behaviour problems. No cortico group= dogs that did not have an history of treatment with corticosteroid drugs. On cortico group= dogs had a history of treatment with corticosteroid drugs.**

The possible relationships between corticosteroid therapies, behaviour problems, affective states, incidence of severe bites and prescription of psychoactive drugs in the whole sample of dogs are shown in Table 8. The same relationships were investigated using the same statistical approach taking into account only dogs that had a history of medical problems that required more than one week of therapy (n = 264) using Chi Square Tests.

Within this sample (n = 264), dogs with a history of corticosteroids were significantly more likely to be in negative affective states ( $X(1)= 10.970, p < 0.001$ ), to present with aggression towards people ( $X(1)= 5.527, p= 0.0014$ ) to be prescribed psychoactive drugs ( $X(1)=3.588, p= 0.043$ ), but significantly less likely to present problems coded as ‘hyperactivity’ ( $X(1) = 9.099, p< 0.001$ ).

Within dog with a history of medical problems that required more than one week of therapy (n.264) no significant relationship was found between the use of drugs other than corticosteroids and affective states, aggression towards people, prescription of psychoactive drugs and hyperactivity.

Patient factors	Cortico group	No cortico group	Pearson Chi square X(1)	p value
	n. (%)	n. (%)		
Positive affective state	0	51 (17.7)		
Negative affective state	55 (100.0)	237 (82.3)	11.441	< 0.001
Aggression towards people	31 (56.4)	117 (40.6)	4.663	0.023
Hyperactivity	4 (7.3)	85 (29.5)	11.889	< 0.001
Aggression towards other dogs	9 (16.4)	50 (17.4)	0.032	0.518
Separation problems	9 (16.4)	38 (13.2)	0.330	0.392
Phobias	13 (23.6)	77 (26.7)	0.229	0.384
Excessive barking	5 (9.1)	38 (13.2)	0.709	0.276
History of severe bites	16 (29.1)	64 (22.2)	1.218	0.175
Psychoactive drug prescription	24 (43.6)	83 (28.8)	4.724	0.024

**Table 8. Relationship between history of treatment with corticosteroids and negative affective state, reported behaviour problems, occurrence of sever bites and the prescription of psychoactive drugs in the whole sample (n. 343). No cortico group = group of dogs without a history of corticosteroid treatment; On cortico group= group of dogs with a history of corticosteroid treatment**

The predictive value of age, gender and type of medical problems in the onset of positive or negative affective states was investigated in the group of dogs without a history of corticosteroid drugs but with a history of medical problems (n = 209) by means of binary logistic regression using forward analysis. Age was found to be the only predictor, with dogs between one and two year of age 3.167 times more likely to be in positive affective states than other ages (B= 1.153; p<0.01; exp(B)= 3.167 C.I: 95% [1.44 – 6.96]). 82.8% of cases could be correctly predicted in this analysis.

The role of corticosteroid treatment history, medical condition, age and gender of dogs on the main effects of aggression towards people, hyperactivity and prescription of psychoactive drugs were investigated by means of binary logistic regression using a forward analysis .

1  
2  
3 1 The best predictor for aggression towards people was gender, with intact males 3.49 times more  
4 2 likely to be aggressive compared to other gender groups ( $B=1.250$ ;  $\text{Exp}(B)=3.489$ ;  $p<0.01$ ; C.I. :  
5 3 95% [2.10-5.79]) and castrated male dogs 2.8 times more likely to show aggression compared to  
6 4 other gender groups ( $B=1.049$ ;  $\text{Exp}(B)=2.828$ ;  $p=0.011$ ; C.I. : 95% [1.27-6.28] ). Age and  
7 5 gastrointestinal conditions showed a significant relationship with aggression towards people: dogs  
8 6 between one and two years were less likely to be aggressive towards people ( $B=-0.752$ ;  $\text{Exp}(B)=$   
9 7 0.471;  $p<0.01$ ; C.I. : 95%[0.312-0.802] as were dogs with a history of gastrointestinal conditions  
10 8 ( $B=-0.809$ ;  $\text{Exp}(B)=0.445$ ;  $p<0.01$ ; C.I. : 95%[0.250-0.792] ). 64.7 % of cases were correctly  
11 9 predicted in this analysis.

12  
13  
14  
15  
16  
17  
18  
19 10 The best predictors for hyperactivity related problems were age and corticosteroid treatment: dogs  
20 11 between one and two year of age were 4.27 times more prone to show hyperactivity related  
21 12 problems compared to other ages ( $B=1.193$ ;  $\text{Exp}(B)=3.298$ ;  $p<0.01$ ; C.I. : 95%[1.78-6.12]). By  
22 13 contrast, dogs treated with corticosteroids were less prone to hyperactivity related problems ( $B=-$   
23 14 1.455;  $\text{Exp}(B)=0.233$ ;  $p<0.01$ ; C.I. : 95%[0.08-0.68] ). 74.1% of cases were correctly predicted in  
24 15 this analysis.

25  
26  
27  
28  
29  
30 16 The best predictors for the prescription of psychoactive drugs were gender and age: castrated males  
31 17 were 2.49 times more likely to be prescribed psychoactive drugs compared with other genders  
32 18 ( $B=0.911$ ;  $\text{Exp}(B)=2.486$ ;  $p=0.014$ ; C.I.: 95%[1.20-5.14] ). Dogs between one and two years of  
33 19 age were less likely to receive prescriptions for psychoactive drugs compared with other age groups  
34 20 ( $B=-0.730$ ;  $\text{Exp}(B)=0.482$ ;  $p<0.01$ ; C.I. : 95%[0.30-0.77]). 70.6% of cases were correctly  
35 21 predicted in this analysis.

36  
37  
38  
39  
40  
41 22

42  
43  
44 23

## 45 46 24 Discussion

47  
48 25

49 26 Within the sample of 343 dogs referred for behaviour problems in this particular caseload, 16% had  
50 27 a history of previous treatments with corticosteroids and it should be noted that this investigation  
51 28 reveals only association and not necessarily causal relationships. The main finding of this  
52 29 retrospective case study was that history of corticosteroid treatment was significantly associated  
53 30 with negative affective states and a predictor of a reduced likelihood of problems of hyperactivity.  
54 31 A significant association between affective state and hyperactivity in the opposite direction was also  
55  
56  
57  
58  
59  
60



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1 found with age with dogs between one-two years of age being more likely to have problems  
2 associated with positive affective states and hyperactivity than older dogs.

3  
4 Younger dogs were less likely to show aggression towards people and to be prescribed psychoactive  
5 drugs. By contrast, intact male dogs were more likely to show aggression towards people and this  
6 result is consistent with much of the previous literature data (Fatjo et al., 2007; Guy et al., 2001;  
7 Overall and Love, 2011; Overall, 1997).

8 A history of medical problems was not a significant predictor for behaviour problems with the  
9 exception of gastrointestinal problems that were associated with a lower tendency to show  
10 aggression towards people. No link with affective states or behaviour problems was found between  
11 the administration of drugs other than corticosteroids.

12  
13 These results must be considered with some caution, but they highlight the need for further  
14 investigation of the possible links between behavioural problems related with negative affective  
15 states and the use of corticosteroids. Although it should be emphasised that a causal link has not  
16 been demonstrated, these data when considered alongside previous studies in this field (Notari and  
17 Mills, 2011; Notari et al., 2015) and the absence of data to the contrary, suggest that there might be  
18 behavioural side effects of corticosteroids. The small sample size and the differences in the two  
19 groups, with and without history of corticosteroid drug treatments, are obvious limitations as well  
20 as the possibility that the link between corticosteroid treatments and negative affects might be  
21 simply due to the fact that older dogs, who were more represented in the corticosteroid group, might  
22 also be more likely to show negatively motivated behaviours compared with younger dogs, and  
23 were over-represented in the group not receiving corticosteroids. Medical problems and age  
24 distribution of subjects in the two groups were also very different: in the group of dogs with a  
25 history of corticosteroid treatment dermatological and orthopedic problems were over-represented  
26 compared with the other group which is perhaps not surprising given the indications for these drugs;  
27 gastrointestinal conditions were more frequent within the group of dogs without a history of  
28 corticosteroid drugs, and these drugs would rarely be indicated for such problems. The effects of  
29 medical histories cannot be reliably evaluated here due to the low number of cases and although the  
30 effect of pain and discomfort on dog behaviour is an important issue  
31 (Barcelos et al., 2015, ; Camps et al., 2015) and medical problems are important sources of distress  
32 ((Mills et al., 2014; Notari, 2009), no medical problems were reliable predictors for problems  
33 relating to negative affective state. It cannot also be excluded that dogs on steroid treatment may be  
34 affected by more advanced problems that may contribute to a negative affective state.

35 As stated above, the main finding of this investigation is that dogs presented for behaviour  
36 problems with a history of corticosteroids treatment appear to suffer more from problems associated



1  
2  
3 1 with negative affect. The finding suggests that exposure to corticosteroids might increase dogs'  
4 2 sensitivity to environmental and social stressors increasing the risk of problem behaviour. Given  
5 3 that the sample of dogs with a history of corticosteroid drugs was quite small (55 dogs), random  
6 4 effects have a greater chance of biasing the results, and so this study should not be considered  
7 5 definitive. Dermatological conditions were over-represented in the group of dogs with a history of  
8 6 corticosteroid drugs (65.5%), compared with the other group of dogs (18.4%) and, even though  
9 7 dermatological condition was not found to be a predictor for affective state, a combined effect of  
10 8 drugs and disease on negative affective states cannot be excluded. A matched control study with a  
11 9 similar result would provide stronger evidence.

12 10 It has been shown that pruritus might be exacerbated by psychological disorders in humans but also  
13 11 that pruritus can worsen behaviour (Shaw et al., 2007). The issue of the influence of pruritus as a  
14 12 main sign of dermatological conditions was investigated in dogs by Klinck et al. (2008) and they  
15 13 found no relationship between pruritus and aggression or anxiety, but they did find a significant  
16 14 increase in reactivity to potentially fearful stimuli in dogs treated with corticosteroid drugs. This is  
17 15 consistent with our hypothesis of an increase in negative affective states due to corticosteroid  
18 16 treatment.

19 17 Among dogs who had a history of corticosteroids, the co-administration of other therapies further  
20 18 complicates the interpretation of the results for two main reasons: multiple drug treatments might  
21 19 indicate that the medical problems are more severe and also other kind of medication might have  
22 20 psychiatric side effects (Sternbach and State, 2009; Turjanski, 2005).

23 21 Corticosteroids and age were significantly related to problems of hyperactivity. Dogs with a history  
24 22 of corticosteroid treatment were significantly less likely to be hyperactive, and, given the definition  
25 23 of hyperactivity used in this study which included excessive play behaviours, this result might be  
26 24 consistent with the decreased tendency to play and decreased dogs' activity levels reported in  
27 25 previous studies (Notari and Mills, 2011; Notari et al., 2015) although, again, young dogs might  
28 26 just be more prone to be hyperactive compared with older ones. Dogs between one and two years  
29 27 of age were much more represented in the 'no cortico' group (62.2%) compared with those  
30 28 receiving corticosteroids (29.1%) and the effect of corticosteroid might be a concomitant effect of  
31 29 age. This also raises the possibility that, the relationship between corticosteroid and negative affect  
32 30 might also be due to such age-drug association rather than an effect of corticosteroids *per se*.

33 31 Hyperactivity problems in this study included a list of problematic behaviours like play and play  
34 32 biting, excessive attention seeking behaviours, jumping on people, destructiveness, and excessive  
35 33 excitement in different situations; all of which might be considered to reflect positive affect (reward  
36 34 seeking). The term does not imply a diagnosis of pathological hyperactivity associated with

1  
2  
3 1 impaired attention as in humans beings (Blum et al., 2008; Wright et al., 2012), and a lower level of  
4 2 activity might also be related to a lower motivation to play and seeking rewards in general.  
5  
6 3 In the caseload presented here, overall 16% of dogs had a history of treatment with corticosteroid  
7 4 drugs, this is slightly higher than that reported in general veterinary practice (14.55) (O'Neill et al.,  
8 5 2012). For dermatological conditions 20% of dogs have been reported to receive a prescription of  
9 6 corticosteroid drugs (Hill et al., 2006) and in our caseload among those dogs with a history of  
10 7 dermatological conditions, corticosteroid drug prescription was even more common (40.4%). This  
11 8 might again suggest that dogs on corticosteroid are more likely to show behaviour problems or that  
12 9 a combination of corticosteroid treatment and dermatological conditions influences problematic  
13 10 behaviour. However, as there was not a control group from general veterinary practice included in  
14 11 this study, it is not possible to establish if dogs treated with corticosteroids are over represented  
15 12 among subjects with behavioural problems; nonetheless these percentages indicate that the issue is  
16 13 an important one that requires further attention.  
17  
18 14 In this retrospective study, no specific behaviour problem was found to be linked with a history of  
19 15 corticosteroid drugs while in previous surveys owners reported behavioural changes in specific  
20 16 aspects of their dogs' behaviour (Notari and Mills, 2011; Notari et al., 2015).  
21  
22 17 Nevertheless these results deserve attention because a higher apparent tendency to be in negative  
23 18 affective states, a condition defined following the criteria described in the Material and Method  
24 19 section, might be particularly important for individual dogs that already have the propensity to  
25 20 show avoidance or aggressive behaviours.  
26  
27 21 Systemic glucocorticoid prescription in pet dogs seems to be determined more by the clinical  
28 22 experience and personal opinion of vets (O'Neill et al., 2012) and greater recognition of the  
29 23 widespread risk of the possible drawbacks from these drugs, including the conditions identified in  
30 24 this research, might contribute to improved evidence-based guidance for the therapeutic use of these  
31 25 drugs that minimize the risks .  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

## 27 **Conclusions**

28

29 In this study it was shown that a history of corticosteroid treatment is significantly associated with  
30 30 problem behaviours associated with negative affective state. Negative changes in companion dog  
31 31 behaviour impact not only the welfare of dogs but also the life of their owners and caregivers.  
32 32 Given that other studies have shown that corticosteroid drugs can bias sensitivity towards aversion  
33 33 in dogs making them more prone to react negatively to novel or mildly stressful situations, the  
34 34 current data add to the suggestion that behavioural considerations should be taken into account

1 when corticosteroid drugs are being prescribed, in particular when this relates to dogs who show or  
2 have shown behaviour problems associate with negative affect such as fear and frustration related  
3 issues.

4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Confidential: For Review Only

## References

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31
- A-M. Barcelos, D. S. Mills, H.Z., 2015. Clinical indicators of occult musculoskeletal pain in aggressive dogs. *Vet. Rec.* Open doi:10.113.
- Blum, K., Chen, A.L.-C., Braverman, E.R., Comings, D.E., Chen, T.J.H., Arcuri, V., Blum, S.H., Downs, B.W., Waite, R.L., Notaro, A., Lubar, J., Williams, L., Prihoda, T.J., Palomo, T., Oscar-Berman, M., 2008. Attention-deficit-hyperactivity disorder and reward deficiency syndrome. *Neuropsychiatr. Dis. Treat.* 4, 893–918. doi:10.2147/NDT.S2627
- Camps, T., Amat, M., Mariotti, V.M., Le Brech, S., Manteca, X., 2015. Pain-related aggression in dogs: 12 clinical cases. *J. Vet. Behav. Clin. Appl. Res.* 7, 99–102. doi:10.1016/j.jveb.2011.08.002
- Dodman, N.H., Donnelly, R., Shuster, L., Mertens, P., Rand, W., Miczek, K., 1996. Use of fluoxetine to treat dominance aggression in dogs., *Journal of the American Veterinary Medical Association.*
- Drozdowicz, L.B., Bostwick, J.M., 2015. Psychiatric Adverse Effects of Pediatric Corticosteroid Use. *Mayo Clin. Proc.* 89, 817–834. doi:10.1016/j.mayocp.2014.01.010
- Fardet, L., Petersen, I., Nazareth, I., Ph, D., 2012. Suicidal behavior and severe neuropsychiatric disorders following glucocorticoid therapy in primary care. *Am. J. Psychiatry* 169, 491–497.
- Fatjo, J., Amat, M., Mariotti, V.M., de la Torre, J.L.R., Manteca, X., 2007. Analysis of 1040 cases of canine aggression in a referral practice in Spain. *J. Vet. Behav. Clin. Appl. Res.* 2, 158–165.
- Guy, N.C., Luescher, U.A., Dohoo, S.E., Spangler, E., Miller, J.B., Dohoo, I.R., Bate, L.A., 2001. A case series of biting dogs: Characteristics of the dogs, their behaviour, and their victims. *Appl. Anim. Behav. Sci.* 74, 43–57.
- Hill, P.B., Lo, A., Eden, C.A.N., Huntley, S., Morey, V., Ramsey, S., Richardson, C., Smith, D.J., Sutton, C., Taylor, M.D., Thorpe, E., Tidmarsh, R., Williams, V., 2006. Survey of the prevalence, diagnosis and treatment of dermatological conditions in small animals in general practice. *Vet. Rec.* 158, 533–539.
- Kenna, H. a., Poon, A.W., De Los Angeles, C.P., Koran, L.M., 2011. Psychiatric complications of treatment with corticosteroids: Review with case report. *Psychiatry Clin. Neurosci.* 65, 549–560. doi:10.1111/j.1440-1819.2011.02260.x
- King, J.N., Simpson, B.S., Overall, K.L., Appleby, D., Pageat, P., Ross, C., Chaurand, J.P., Heath, S., Beata, C., Weiss, A.B., Muller, G., Paris, T., Bataille, B.G., Parker, J., Petit, S., Wren, J., 2000. Treatment of separation anxiety in dogs with clomipramine: Results from a prospective, randomized, double-blind, placebo-controlled, parallel-group, multicenter clinical trial. *Appl. Anim. Behav. Sci.* 67, 255–275.

- 1  
2  
3 1 Klinck, M.P., Shofer, F.S., Reisner, I.R., 2008. Association of pruritus with anxiety or aggression in dogs. *J.*  
4 2 *Am. Vet. Med. Assoc.* 233, 1105–1111.  
5  
6  
7 3 Marder, A.R., 1991. Psychotropic drugs and behavioral therapy. *Vet. Clin. North Am. Small Anim. Pract.*  
8 4 21, 329–342.  
9  
10 5 Mikics, É., Barsy, B., Haller, J., 2007. The effect glucocorticoids on aggressiveness in established colonies  
11 6 of rats. *Psychoneuroendocrinology* 32, 160–170.  
12  
13  
14 7 Mills, D., Karagiannis, C., Zulch, H., 2014. Stress-its effects on health and behavior: A guide for  
15 8 practitioners. *Vet. Clin. North Am. - Small Anim. Pract.*  
16  
17  
18 9 Notari, L., 2009. Stress in veterinary behavioural medicine, in: Horwitz, D.F., Mills, D.S. (Eds.), *BSAVA*  
19 10 *Manual of Canine and Feline Behavioural Medicine*. British Small Animal Veterinary Association,  
20 11 Gloucester, pp. 136–145.  
21  
22  
23 12 Notari, L., Burman, O., Mills, D., 2015. Behavioural changes in dogs treated with corticosteroids. *Physiol.*  
24 13 *Behav.* 151, 609–616. doi:10.1016/j.physbeh.2015.08.041  
25  
26  
27 14 Notari, L., Mills, D., 2011. Possible behavioral effects of exogenous corticosteroids on dog behavior: A  
28 15 preliminary investigation. *J. Vet. Behav. Clin. Appl. Res.* 6, 321–327.  
29  
30  
31 16 O'Neill, D., Hendricks, A., Summers, J., Brodbelt, D., 2012. Primary care veterinary usage of systemic  
32 17 glucocorticoids in cats and dogs in three UK practices. *J. Small Anim. Pract.* 53, 217–222.  
33 18 doi:10.1111/j.1748-5827.2011.01190.x  
34  
35  
36 19 Overall, K.L., 1997. *Clinical Behavioral Medicine For Small Animals*. Mosby, Philadelphia USA.  
37  
38  
39 20 Overall, K.L., Love, M., 2011. Special Report Dog bites to humans — demography , epidemiology , injury ,  
40 21 and risk. *Javma* 218, 1923–1934.  
41  
42  
43 22 Pineda, S., Anzola, B., Olivares, A., Ibáñez, M., 2014. Fluoxetine combined with clorazepate dipotassium  
44 23 and behaviour modification for treatment of anxiety-related disorders in dogs. *Vet. J.* 199, 387–391.  
45  
46  
47 24 Shaw, R.J., Dayal, S., Good, J., Bruckner, A.L., Joshi, S. V, 2007. Psychiatric medications for the treatment  
48 25 of pruritus. *Psychosom. Med.* 69, 970–8. doi:10.1097/PSY.0b013e3181572799  
49  
50  
51 26 Sirois, F., 2003. Steroid psychosis: A review. *Gen. Hosp. Psychiatry* 25, 27–33.  
52  
53  
54 27 Sternbach, H., State, R., 2009. *Antibiotics: Neuropsychiatric Effects and Psychotropic Interactions*.  
55  
56  
57 28 Turjanski, N., 2005. Psychiatric side-effects of medications: recent developments. *Adv. Psychiatr. Treat.*  
58 29 Ularntinon, S., Tzuang, D., Dahl, G., Shaw, R.J., 2010. Concurrent treatment of steroid-related mood and  
59 30 psychotic symptoms with risperidone. *Pediatrics* 125, e1241–e1245. doi:10.1542/peds.2009-1815  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1 Warrington, T.P., Bostwick, J.M., 2006. Psychiatric Adverse Effects of Corticosteroids. *Mayo Clin. Proc.*

2 Wright, H.F., Mills, D.S., Pollux, P.M.J., 2012. Behavioural and physiological correlates of impulsivity in  
3 the domestic dog (*Canis familiaris*). *Physiol. Behav.* 105, 676–82. doi:10.1016/j.physbeh.2011.09.019

4

5

Confidential: For Review Only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1

Confidential: For Review Only