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Trazodone as a mediator of transitional stress in a shelter: effects on illness, length of stay, and outcome.

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Abstract

Companion dogs housed in animal shelters are subject to a great number of uncontrollable and unalterable stressors. To combat these stressors and the associated immunosuppression that can result in high rates of contagious disease in sheltered dogs, a large open admission municipal animal shelter in New York City introduced trazodone hydrochloride, a serotonin receptor antagonist and reuptake inhibitor (SARI) to help reduce their transitional stress. Dogs were given low doses of trazodone at intake (5 mg/kg), one to two doses within 48 hours of arrival. Prevalence of illness was calculated two time periods at the Brooklyn and Manhattan Care Center locations (N = 1,766); November and December 2018, when trazodone was administered to the population, and a historical control in November and December 2017 and 2016, when no trazodone was administered. A statistically significant difference in the percentage of sick dogs was found when comparing the No Trazodone group (2016/2017) and Trazodone treatment group in 2018 (χ^2 (1, N = 1766) = 19.4, p <0.001). An increased percentage of sick dogs was observed in the No Trazodone group (41%) compared to the Trazodone treatment group (29%). Moreover, a significant difference in the average length of stay (LOS) in the shelter was observed when comparing the two groups (t(1764) = 2.71, p = .007). The average LOS was longer for the dogs in the No Trazodone group (M = 10.47, SD = 8.53) compared to the Trazodone treatment group (M = 9.23, SD = 6.57). Finally, a significant difference was observed in the percent of adoptions between the two groups (χ^2 (1, N = 1766) = 19.4, p < .001). A larger percentage of dogs were adopted in the Trazodone treatment group (42%) than the No Trazodone group (30%). While correlational, the preliminary results of this study suggest that trazodone may be effective in reducing illness and increasing adoptions by decreasing transitional stress in dogs living in a shelter setting.

Keywords: Dogs, Animal shelter, Trazodone, Transitional stress, Canine infectious disease respiratory complex

Introduction

Animal shelters are known to cause distress for all dogs, even the most well-adjusted, because they are subjected to new and typically uncomfortable situations (Hennessy et al., 1998). Anxiety, phobias, heightened arousal, and fear are among the most commonly-reported behavior issues for dogs, and those are all exacerbated in a shelter setting (Beerda et al., 1999; Wells, 2004; Protopopova and Gunther, 2017). Animal shelters are faced with constant welfare challenges. Dogs experience a jarring loss of control over their situations. They are separated from their attachment figures (Hennessy et al., 1997; Hennessy, 2013; Shiverdecker et al., 2013; Protopopova, 2016), experience severe social isolation and radical spatial restriction (Hennessy et al., 1997; Beerda et al., 1999; Wells, 2004; Coppola et al., 2006; Hennessy, 2013; Protopopova, 2016), and are exposed to persistent, uncontrollable, and often threatening noises and odors (Hennessy, 2013; Shiverdecker et al., 2013). Conflicts, stress, and frustration caused by the physical and social environment can lead to undesirable behaviors and stereotypies in the shelter, decreasing the likelihood of adoption (Hennessy, 2013; Shiverdecker et al., 2013; Kuhne et al., 2014).

The stressful shelter environment means dogs typically need time to adjust to their new surroundings in order to feel comfortable enough to behave in their normal manner (Bollen and Horowitz, 2008). However, shelter staff are tasked with making quick decisions about placement options, suitability for adoption, and medical conditions, sometimes with just a single interaction

before there is an opportunity to get to know a dog's personality, temperament, and full behavioral repertoire. Open admission shelters (typically municipal or animal control facilities), which must accept all animals regardless of available space, behavior, or medical concerns may be even more distressing. For dogs brought into these shelters, there is additional urgency to limit length of stay (LOS) both due to high daily intake numbers and in order to minimize environmental stress. Adjustment time needs may be unmet.

Psychogenic and physical stressors abound in a shelter setting due to novelty, routine disruption, unpredictability, and loss of control (Hennessy et al., 1997; Hennessy et al., 1998; Hennessy, 2013; Protopopova, 2016). Stressors, like those common in shelter settings, have been found to have adverse effects on health. Stressors specifically related to physical and mental suffering (Hekman et al., 2014) represent a psychological challenge to the body's homeostasis (Dhabhar, 2009; Hekman et al., 2014) and may result in suppression of the immune system (Dhabhar, 2009; Hennessy, 2013; Shiverdecker et al., 2013), increased susceptibility to and severity of infection, decreased vaccine immune response, and slow wound healing (Glaser and Kiecolt-Glaser, 2005). Infectious disease rates are consistently high in sheltered dogs (Protopopova, 2016), which places this population at increased risk of contagious illness. Plasma adrenocorticoid levels may rise within four hours in a novel environment and cortisol levels have routinely been found to be elevated in shelters (Tuber et al., 1996; Hennessy et al., 1997). During the first three days in a shelter setting, cortisol levels are three times higher than those of a dog in their own home (Hennessy et al., 1997). The findings from behavioral and physiologic assessments suggest that stress-reducing interventions in the first few days within the new shelter environment are important for a dog's successful adjustment (Hennessy et al., 1997).

Pharmacologic interventions have been suggested as a way to improve wellbeing and decrease stress, particularly when other enrichment and socialization programs have already been instituted. Studies have pointed out the need for a fast-acting oral anxiolytic that can alleviate the stress itself and protect mental wellbeing, rather than just diminishing the physical signs of stress, when dogs are hospitalized or otherwise confined (Hekman et al., 2014; Gilbert-Gregory et al., 2016). Moderating the initial stress response may help prevent the risk of chronic stress activation and system dysregulation (Hennessy, 2013). Additional investigation is needed to determine how viable such interventions may be, and which medication(s) may fill the role, but one possibility that has been used in veterinary settings is trazodone hydrochloride (from here on termed trazodone) (Gruen and Sherman, 2008; Gilbert-Gregory et al., 2016; Gruen et al., 2017).

Trazodone is an atypical antidepressant that has been used in human medicine since 1966 (Gruen and Sherman, 2008; Gruen et al., 2017). Classified as a serotonin receptor antagonist and reuptake inhibitor (SARI), trazodone is primarily a serotonin 2A postsynaptic receptor antagonist, and secondarily a presynaptic serotonin reuptake inhibitor (Gruen and Sherman, 2008). The medication has a high bioavailability with oral dosing, a wide dose range, is well tolerated, and has few side effects (Gruen and Sherman, 2008). Daily trazodone is commonly used in dogs diagnosed with generalized anxiety disorders, however it can also be administered ‘as needed’ for dogs experiencing intermittent or acute anxiety or those who have a clear anxiety trigger (eg. thunderstorm phobia) (Gruen and Sherman, 2008). Few scientific studies evaluating the effects of trazodone as a single agent have been conducted to this point, and thus far, results from studies on the efficacy of the drug in mediating stress are inconclusive (Gilbert-Gregory et al., 2016; Gruen et al., 2017).

In 2018, Animal Care Centers of NYC (ACC), a New York City animal shelter, set out to evaluate the effect of trazodone on transitional stress. Despite careful review of medical and shelter operations policies and procedures in recent years, contagious respiratory illness – specifically canine infectious respiratory disease complex (abbreviated CIRDC and commonly referred to as "kennel cough") – remains high. It has been proposed that this is likely due to increased stressors on the immune system in combination with the presence of an increased viral load and exposure to novel infectious agents. For shelters like ACC who have made great strides in addressing overall welfare practices and have attended to the clearest, easiest, and most direct sources of contagion in a shelter, pharmacological intervention is a logical next step to reduce prevalence of illness and stress levels. This study had three aims: to evaluate if the administration of trazodone would 1) reduce the prevalence of CIRDC in the shelter, 2) reduce LOS, and 3) increase the percentage of live outcomes (adoptions) while decreasing the percentage of euthanasia.

Methods

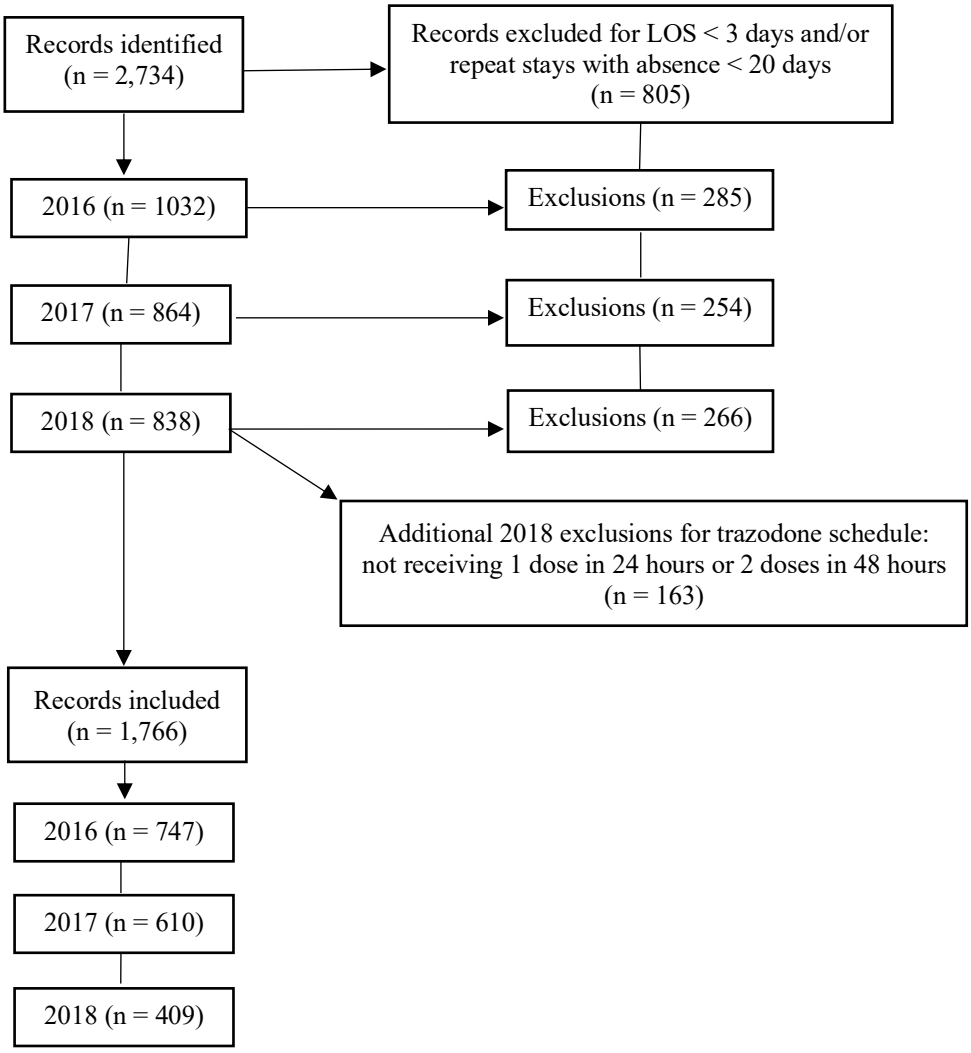
ACC is New York City's only open admission animal shelter, a combination municipal shelter with a city contract and 501(c)(3) non-profit that offers a range of community services. ACC has two large full-service care centers in Manhattan and Brooklyn. The records of all dogs coming into those two locations during the months of November and December 2016, 2017, and 2018 were reviewed. A total of 2,734 records were collected and 1,766 dogs' records were included in the final analysis.

Only dogs with lengths of stay of four or more days were included in the final data set, in order to focus on the post-transition period. November and December were selected as the

months to be evaluated each year as the shelter population tends to be more manageable in the winter than the summer months, increasing the likelihood of dogs receiving trazodone consistently. Reports included all dogs who came directly into the Brooklyn and the Manhattan Care Centers from November 1 through December 31 for each of the three years. For situations involving repeated stays in the care center, first stays were included and subsequent stays excluded if the dog was out of the care center for less than 20 full days. This amount of time allowed for the development and treatment of CIRDC should it appear and/or reappear post-adoption. Figure 1 is a flowchart of record inclusion and exclusion criteria.

Figure 1

Flowchart of Compiled Record Review Process



For all dogs meeting the inclusion criteria, demographic and descriptive data were collected for each individual, including length of stay, CIRDC diagnosis date (if applicable), outcome type, and exit date. Outcome types include public adoption ("adopted"), placement with a rescue group partner ("placed"), movement into an ACC foster home ("foster"), reunification with the owner ("reclaimed"), and euthanasia for medical and/or behavioral reasons ("euthanized"). This study did not request any changes made to any dog's housing, treatments,

enrichment, or movements through the shelter. All dogs were housed and cared for per ACC practices and policies.

For the Trazodone treatment group (2018) the protocol determined by the Senior Medical Director was to give the first dose on the day of intake, and the second dose the following morning. Not all dogs coming into the care center received doses on this schedule owing to the constraints on time and manpower in an active shelter. Exam delays caused some dogs to receive their first doses on their second or third day in the care center. Some dogs did not receive or consume a second trazodone dose. Multiple types of high-value treats and foods were used to encourage consumption, but if the dog did not eat their second dose it was recorded as a missed dose. Ultimately the decision was made to consider three different dosing scenarios: Ideal (as per protocol); dogs with a Delayed First Dose who still received two doses within 48 hours of arriving at the shelter; and dogs who received One Dose on day one in the shelter but did not ingest a second dose

Procedure

Trazodone administration began in June 2018, during which time the experimental group (hereafter termed “Trazodone”), received the medication. In years 2016 and 2017 no trazodone was administered and dogs from these periods served as a medication-free historical comparison group (hereafter termed “No Trazodone”). From mid-2018 onwards, all dogs received two doses of trazodone during the first 48 hours, the transition period, in the shelter. Trazodone was prescribed by licensed veterinarians at 5mg/kg and given by mouth. The first dose was given by the medical team as close to a dog’s arrival as possible, and the second dose was given the following morning. For November and December 2018, the dates of the first and second

trazodone doses were recorded for each dog. All breeds and breed mixes, ages, and sexes were included. Table 1 summarizes treatment group by number, month, year, and shelter, while Table 2 provides demographic information for the two treatment groups.

Table 1

Final sample sizes

Year	Month	Treatment group	Shelter location	Total records reviewed	Final sample size (all)	Final sample size (sick)
2016	November	No Trazodone	Brooklyn	186	132	65
2016	November	No Trazodone	Manhattan	289	195	80
2016	December	No Trazodone	Brooklyn	261	203	98
2016	December	No Trazodone	Manhattan	296	217	80
2017	November	No Trazodone	Brooklyn	210	147	51
2017	November	No Trazodone	Manhattan	206	144	65
2017	December	No Trazodone	Brooklyn	224	158	50
2017	December	No Trazodone	Manhattan	224	161	70
2018	November	Trazodone	Brooklyn	216	91	30
2018	November	Trazodone	Manhattan	223	111	33
2018	December	Trazodone	Brooklyn	170	86	22
2018	December	Trazodone	Manhattan	229	121	34

Table 2

Demographic data

Treatment group	Sex		Lifestage[1]			Size[2]		
	Male	Female	Junior	Adult	Senior	Small	Medium	Large
No Trazodone	76% (769)	78% (588)	84% (193)	77% (1027)	67% (137)	76% (419)	79% (478)	75% (460)
Trazodone	24% (242)	22% (167)	16% (38)	23% (304)	33% (67)	24% (132)	21% (126)	25% (151)
Total number	1011	755	231	1331	204	551	604	611

[1]- Per ACC guidelines, dogs are categorized into lifestages at intake based on a combination of age and size

[2]- Size small = 0-20 lbs, medium = 21-50 lbs, large = 51+ lbs

Data Analysis

Data sets were compiled using Microsoft Excel and data were analyzed with IBM *SPSS* 25. Pearson Chi-square tests were run for the count data and two-tailed independent samples t-tests evaluated averaged data. When homogeneity could not be assumed, Mann-Whitney tests were conducted. The alpha level was set at 0.05, but in cases of multiple comparisons a Bonferroni correction was used to reduce the risk of type 1 error. This correction decreased the alpha level to 0.01.

Results

Trazodone Dosing Schedules

A Pearson Chi-square test comparing the three schedules found no significant difference amongst the different methods of dosing, (χ^2 (2, N = 409) = 0.43, p = 0.81). Therefore, all three of these schedules were combined in the final Trazodone treatment group data set (Table 3).

Table 3

Final descriptive data for No Trazodone and Trazodone groups

Dosing Schedule	Sick	Not sick	Total	Percent sick
Ideal	69	158	227	30.40
Delayed First	16	41	57	28.07
One	34	91	125	27.20
Totals	119	290	409	28.56

Prevalence of Illness

The No Trazodone treatment group was stratified by year and shelter. These subgroups were compared to one another to evaluate differences between populations and year. A Pearson Chi-square test found no difference in the number of sick dogs between locations (χ^2 (1, N = 1357) = 0.002, p = 0.968) or the years 2016 and 2017 (χ^2 (1, N = 1357) = 2.9, p = 0.09). Therefore, data for the two shelters and years were combined.

A Pearson Chi-square test was used to determine whether the prevalence of illness differed between the No Trazodone group (2016/2017) and Trazodone treatment group (2018). A statistically significant difference in the number of sick dogs was observed when comparing the No Trazodone group and the Trazodone treatment group (χ^2 (1, N = 1766) = 19.4, p < 0.001). The percent of sick dogs in the No Trazodone group was 41.19%, while the percent of sick dogs in the Trazodone group was 29.1% (Table 4).

Table 4

Group sizes for No Trazodone and Trazodone treatment groups

Treatment group	Number sick	Number not sick	Total	Percentage sick
No Trazodone (2016/2017)	559	798	1357	41.19
Trazodone (2018)	119	290	409	29.10

Length of Stay

To evaluate changes in average LOS, the No Trazodone group was compared to the Trazodone treatment group (using the descriptive data presented in Table 3). A two-tailed independent samples t-test indicated that dogs in the shelter No Trazodone group had a longer average LOS (M = 10.47, SD = 8.53) than did those in the Trazodone treatment group (M = 9.23, SD = 6.57). In other words, dogs receiving trazodone had a significantly shorter average LOS ($t(1764) = 2.71$, $p = 0.007$). However, when separated out by illness (sick and not sick), no difference was seen in the LOS between the groups. For dogs that were not diagnosed with CIRDC, an independent samples t-test found no difference in LOS between the No Trazodone group (M = 8.26, SD = 8.13) and the Trazodone treatment group (M = 7.76, SD = 6.00) ($t(1088) = 0.97$, $p = 0.33$). For the sick dogs, an assumption of equal variance could not be assumed (F = 0.008); therefore, a Mann-Whitney test was conducted. No difference in LOS was found between the No Trazodone group (Mdn = 12.0) and the Trazodone treatment group (Mdn = 11.0) (U = 31236.0, $p = 0.296$). Thus, these findings suggest that the effect observed on LOS is likely due to physical wellness.

Outcome

When evaluating differences in dogs' outcomes between No Trazodone and Trazodone treatment groups, a Pearson Chi-square test found a statistically significant difference across the five outcome groups (χ^2 (4, N = 1766) = 24.9, $p < 0.001$) (Table 5). To determine where the significant difference occurred, each outcome group was compared individually using a Pearson Chi-square and a Bonferroni correction ($p = 0.01$). A statistically significant difference was observed in the adoption outcome type between the No Trazodone and Trazodone treatment

groups (χ^2 (1, N = 1766) = 19.4, p < 0.001). The percent of dogs adopted in the No Trazodone group was 30.4%, compared to 42.1% for the dogs in the Trazodone treatment group. No significant differences were observed across the treatment groups for any of the other four outcome types.

Table 5

Outcome data for No Trazodone and Trazodone groups

			Adopted	Placed	Reclaim	Foster	Euth	Total
No Trazodone	Sick	Number	136	314	35	11	63	559
		Percent	24.33	56.17	6.26	1.97	11.27	100
		LOS (days)	11.83	14.04	15.40	15.18	14.17	14.13
	Not sick	Number	276	331	87	24	80	798
		Percent	34.59	41.48	10.90	3.01	10.03	100
		LOS (days)	8.21	8.12	9.79	6.38	7.95	8.09
Trazodone	Sick	Number	34	70	4	1	10	119
		Percent	28.57	58.82	3.36	0.84	8.40	100
		LOS (days)	10.88	13.40	14.75	10.00	14.90	12.79
	Not sick	Number	138	104	23	1	24	290
		Percent	47.59	35.86	7.93	0.34	8.28	100
		LOS (days)	7.20	8.36	7.26	7.00	8.88	7.74
Totals	Sick	Number	170	384	39	12	73	678
		Percent	25.07	56.64	5.75	1.77	10.77	100
		LOS (days)	11.36	13.72	15.08	12.59	14.56	13.46
	Not sick	Number	414	435	110	25	104	1088
		Percent	38.05	39.98	10.11	2.30	9.56	100
		LOS (days)	7.71	8.24	8.53	6.69	8.42	7.92

Discussion

The results of this study indicate a possible practical and novel use for trazodone. Previous studies have acknowledged that stress reduction within the first days in a shelter is critical for a dog's success (Hennessy et al., 1997). The more tools available to reduce stress early in a dog's stay within a shelter, the greater the opportunity for increased quality of life. This study asked whether trazodone could help moderate stress to the point that immune system suppression was prevented and fewer dogs were diagnosed with CIRDC. While correlational, the results suggest that trazodone may be able to help mediate the prevalence of CIRDC within animal shelters. However, it is important to note that trazodone is one of many possible interventions available for shelter dogs and, therefore, may not be the best tool available. With limited empirical studies, these findings provide a promising exploration into shelter welfare improvement through psychopharmacology.

The most robust and promising result of this study is the difference in the prevalence of illness noted between the No Trazodone and Trazodone treatment groups. A smaller percentage of dogs contracted CIRDC when receiving trazodone than did dogs not receiving the pharmacological intervention. Moreover, dogs in the Trazodone treatment group left the shelter faster, on average, than did dogs in the No Treatment group. This result suggests that the effect on LOS, and hence on increased percentage of adoptions in the Trazodone group, may be due to physical wellness. Finally, of the five possible outcome types studied, a significant difference between the No Trazodone and Trazodone treatment groups was found in only one: adoption. A greater percentage of dogs were adopted in the Trazodone treatment group than the No Trazodone group. No difference between the treatment groups was observed when analyzing the outcome of euthanasia. However, euthanasia at ACC occurs for a number of reasons, both

medical and behavioral. Therefore, it is possible that euthanasia of dogs for contagious medical illness (CIRDC) decreased while euthanasia for behavioral reasons increased, keeping overall numbers fairly consistent but reducing euthanasia in behaviorally sound, medically treatable animals. Taken together, the findings regarding prevalence of illness, LOS, and outcome suggest that administration of trazodone does not affect sick dogs, but seems to decrease the likelihood that dogs will become sick. An increased population of healthy dogs may explain the increase in adoption rate seen in 2018.

The primary goal of ACC's program was to decrease the prevalence of contagious illness in the shelter. Trazodone administered during the transition period decreased the number of sick dogs and dogs' average LOS across comparable time periods. While the results here certainly do not indicate causation, they do suggest that trazodone may be a possible tool to ease dogs through a difficult transition period. We hypothesize that trazodone may have anxiolytic effects in the form of decreasing signs of physical distress and immunosuppression, which could result in more robust resistance to infectious disease in kennel environments. Future research is needed to substantiate this claim as well as to evaluate which (there may be multiple) short-acting SARIs or anxiolytic medications may be most effective in these circumstances.

Limitations. This study occurred in an active, full-service shelter. While this study was controlled to the extent possible, a number of staffing, facility, and protocol changes occurred between 2016 and 2018 that may influence average LOS, adoption percentages, and illness percentages over the three years surveyed. All diagnoses were made by licensed and practicing veterinarians, but the medical staff experienced numerous changes from the start to the end of the study, and diagnoses were made by different veterinarians both within and between the months

evaluated. In terms of facility improvement and protocol changes, the most significant of these occurred early in 2017, a time period represented within the No Trazodone group that served as a historical control. We believe any possible effects of these changes would be minimal as two years (2016 and 2017) were included in the No Trazodone group and no significant differences between years were observed.

Finally, while the aim was to give all dogs trazodone on a specified schedule, adherence to the schedule was not always possible. The lack of significant differences across the dosing schedules compared suggests that the effects observed may be due to a single trazodone dose at intake. Further study of the use, upon admission, of a range of short acting anti-anxiety medications on illness, measures of behavioral stress, adoption, LOS, and euthanasia is warranted.

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Authorship statement:

The idea for the paper was conceived by Jennifer Abrams & Sarah-Elizabeth Byosiere. The experiments were designed by Jennifer Abrams, Robin Brennen, & Sarah-Elizabeth Byosiere.

The experimental medication was prescribed and administered by Robin Brennen and the ACC veterinary team. The records were reviewed by Jennifer Abrams. The data were analyzed by Jennifer Abrams & Sarah-Elizabeth Byosiere. The paper was written by Jennifer Abrams & Sarah-Elizabeth Byosiere. All authors have approved the final article.

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References

Beerda, B., Schilder, M.B., van Hooff, J., de Vries, H.W., Mol, J.A., 1998. Behavioural, saliva cortisol and heart rate responses to different types of stimuli in dogs. Appl. Anim. Behav. Sci. 58, 365-381.

Beerda, B., Schilder, M.B., van Hooff, J., de Vries, H.W., Mol, J.A., 1999. Chronic stress in dogs subjected to social and spatial restriction. I. Behavioral responses. Physiol. Behav. 66(2), 233-242.

Bollen, K.S., Horowitz, J., 2008. Behavioral evaluation and demographic information in the assessment of aggressiveness in shelter dogs. Appl. Anim. Behav. Sci. 112, 120-135.

Coppola, C.L., Grandin, T., Enns, R.M., 2006. Human interaction and cortisol: Can human contact reduce stress for shelter dogs? Physiol. Behav. 87, 537-541.

Dhabhar, F.S., 2009. Enhancing versus suppressive effects of stress on immune function: Implications for immunoprotection and immunopathology. Neuroimmunomodulation 16, 300-317.

Gilbert-Gregory, S.E., Stull, J.W., Rice, M.R., Herron, M.E., 2016. Effects of trazodone on behavioral signs of stress in hospitalized dogs. J. Am. Vet. Med. Assoc. 249(12), 1281-1291.

Glaser, R., Kiecolt-Glaser, J.K., 2005. Stress-induced immune dysfunction: Implications for health. Immunology 5, 243-251.

Gruen, M.E., Roe, S.C., Griffith, E.H., Sherman, B.L., 2017. The use of trazodone to facilitate calm behavior after elective orthopedic surgery in dogs: Results and lessons learned from a clinical trial. J. Vet. Beh. 22, 42-45.

Gruen, M.E., Sherman, B.L., 2008. Use of trazodone as an adjunctive agent in the treatment of canine anxiety disorders: 56 cases (1995-2007). J. Am. Vet. Med. Assoc. 233(12), 1902-1907.

Hekman, J.P., Karas, A.Z., Sharp, C.R., 2014. Psychogenic stress in hospitalized dogs: Cross species comparisons, implications for health care, and the challenges of evaluation. Animals 4, 331-347.

Hennessy, M.B., 2013. Using hypothalamic-pituitary-adrenal measures for assessing and reducing the stress of dogs in shelters: A review. Appl. Anim. Behav. Sci. 149, 1-12.

Hennessy, M.B., Davis, H.N., Williams, M.T., Mellott, C., Douglas, C. W., 1997. Plasma cortisol levels of dogs at a country animal shelter. Physiol. Behav. 63(3), 485-490.

Hennessy, M.B., Williams, M.T., Miller, D.D., Douglas, C.W., Voith, V.L., 1998. Influence of male and female petters on plasma cortisol and behavior: Can human interaction reduce the stress of dogs in a public animal shelter? Appl. Anim. Behav. Sci. 61, 63-77.

Hilby, E., Rooney, N.J., Bradshaw, J.W.S., 2006. Behavioural and physiological responses of dogs entering re-homing kennels. Physiol. Behav. 89, 385-391.

Kuhne, F., Hossler, J.C., Struwe, R., 2014. Emotions in dogs being petted by a familiar or unfamiliar person: Validating behavioural indicators of emotional states using heartrate variability. Appl. Anim. Behav. Sci. 161, 113-120.

Protopopova, A., 2016. Effects of sheltering on physiology, immune function, behavior, and the welfare of dogs. Physiol. Behav. 159, 95-103.

Protopopova, A., Gunther, L.M., 2017. Adoption and relinquishment at the animal shelter: a review. Animal Welfare 26, 35-48.

Shiverdecker, M.D., Schiml, P.A., Hennessy, M.B., 2013. Human interaction moderates plasma cortisol and behavioral responses of dogs to shelter housing. Physiol. Behav. 109, 75-79.

Tuber, D.S., Hennessy, M.B., Sanders, S., Miller, J.A., 1996. Behavioral and glucocorticoid response of adult domestic dogs (Canine familiaris) to companionship and social separation. J. Comp. Psychol. 110, 103-108.

Wells, D.L., 2004. A review of environmental enrichment for kenneled dogs, Canis familiaris. Appl. Anim. Behav. Sci. 85, 307-317.