2015 Grant Proposal for the Winn Feline Foundation

1. Title of Study:

Study Name:
Assessment of Transdermal Mirtazapine as an Appetite Stimulant in Cats with Chronic Kidney Disease

2. List ALL Principal Investigator(s) Information:

**Please add additional Principal and Co-investigators below if necessary.

a. Name: Jessica Quimby
Institution:
Email:
Mailing Address:

3. Agency/Institution Information (where grant would be payable):

Agency Name:
Mailing Address:
EIN Number (US Applicants):
Check Made Payable to:
Grant Administrator Name:
Grant Administrator Email:

4. Amount Requested:

$13,856

5. Signatures

Signature of the principal investigator and appropriate grant administrator:

Signature:
Signature:

Typing your name above constitutes electronic signature.

II. Scientific Summary

Chronic kidney disease (CKD) is a common progressive disease in geriatric cats and inappetence is frequently reported as a clinical sign. Inappetence can lead to negative energy balance with associated weight loss and muscle weakness, and is perceived by owners to be a major concern for quality of life. Poor body condition is associated with a poor prognosis and maintaining nutrition is a key goal of medical management. Mirtazapine is an appetite stimulant that previously has been demonstrated to be useful in the management of appetite and weight in cats with CKD. The medication is currently available in pill form, presenting a problem for cats resistant to pill administration, and potentially interfering with the bond between owner and pet. Preliminary data has indicated that mirtazapine is amenable to transdermal application and results in increased appetite. The purpose of this study is to assess the efficacy of transdermal mirtazapine in stimulating appetite in cats suffering from inappetence associated with CKD.

III. Lay-language Abstract

Chronic kidney disease (CKD) is a common progressive disease in elderly cats and inappetence is frequently reported as a clinical sign. Inappetence can lead to negative energy balance with associated weight loss and muscle weakness, and is perceived by owners to be a major concern for quality of life. Poor body condition is associated with a poor prognosis and maintaining nutrition is a key goal of medical management. Mirtazapine is an appetite stimulant that previously has been demonstrated to be useful in the management of appetite and weight in cats with CKD. The medication is currently available in pill form, which presents a problem for cats resistant to pill administration, and potentially interferes with the bond between owner and pet. Preliminary data in normal cats has demonstrated that mirtazapine is amenable to transdermal application and results in increased appetite. The purpose of this study is to assess the efficacy of transdermal mirtazapine in stimulating appetite in cats suffering from inappetence associated with CKD.

IV. Continuing Study; not applicable

V. Study Proposal

Background

CKD is a common disease in geriatric cats. Clinical signs include polyuria, polydipsia, decreased appetite, weight loss and vomiting. There are several factors leading to lethargy and inappetence in these patients, including azotemia, hypokalemia, metabolic acidosis, anemia, and renal secondary hyperparathyroidism.[1] Inappetence can lead to negative energy balance with associated weight loss, muscle weakness, and poor quality of life. In addition, several recent studies have documented the therapeutic value of specially formulated diets in the management of CKD.[2,3] The failure of the patient to eat the diet negates the benefit of dietary management, and therefore a key therapeutic target for these patients is the maintenance of appetite and food intake. Metabolic complications of CKD should be corrected to enhance appetite and nutrition should be actively managed.[1] Feeding tubes are encouraged, but are not an acceptable option for many pet owners.

Mirtazapine is a tetra-cyclic antidepressant that has become popular as an appetite stimulant in cats for both acute and chronic causes of inappetence. A recent study demonstrated benefit of using mirtazapine in the nutritional management of feline CKD.[4] However, one of the biggest quality of life concerns that owners face with managing CKD is administering multiple recommended medications and not having it interfere with the bond between them and their cat. Alternative administration forms are continuously sought for feline patients. Transdermal administration is a very attractive concept. However, the efficacy of very few transdermal medications has been studied, despite the fact that compounding pharmacies are willing to manufacture just about any medication as a transdermal gel. There are certain characteristics to a drug that will make it amenable to application in transdermal form. The drug needs to be administered at a small dose, have a small molecular size (< 500 Daltons) and be moderately lipophilic with a log p between 1-3.[5] Mirtazapine is a candidate for assessment as a transdermal medication because a common dose is just 1.87 mg, it is 265 Daltons in size and has a log p of approximately 2.9. Delivery of mirtazapine in this form would be of great advantage to owners who struggle with medication administration.

Preliminary Data

Preliminary data in normal research cats and normal client-owned cats demonstrates that mirtazapine adequately crosses the skin barrier to provide therapeutic serum levels resulting in stimulation of appetite. However dose titration studies in research cats revealed that a higher dose (7.5 mg) was needed to achieve similar serum drug concentrations to 1.87 mg orally.

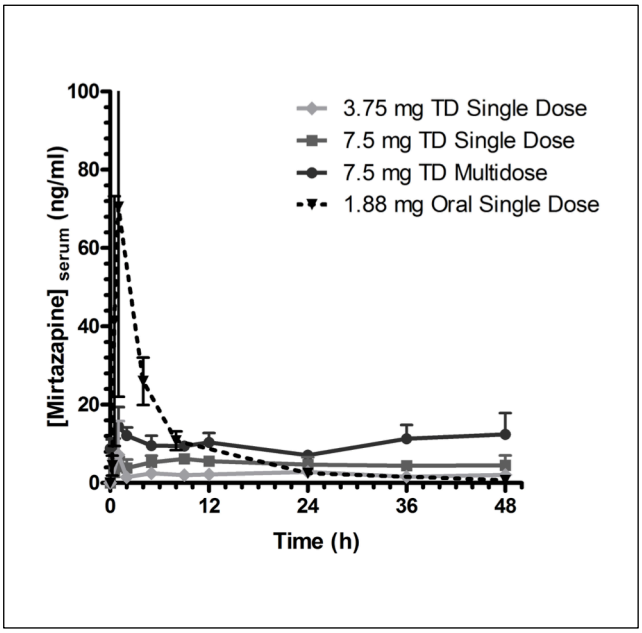

Figure 1: Three 1.5 year old healthy purpose-bred research cats participated in a series of pharmacokinetic studies to determine relative serum concentration curves for 3.75 mg mirtazapine gel administered once, 7.5 mg mirtazapine gel administered once, and 7.5 mg mirtazapine gel administered daily for 5 days. This was compared to previous data collected in research cats when 1.87 mg oral mirtazapine was administered once.[6] When administered at a higher dose than the typical oral dose of 1.87 mg, transdermal mirtazapine was able to achieve serum concentrations within a potentially therapeutic range. It was also noted that the serum concentration peak typically associated with side effects that occurs with oral administration was not present with transdermal administration.

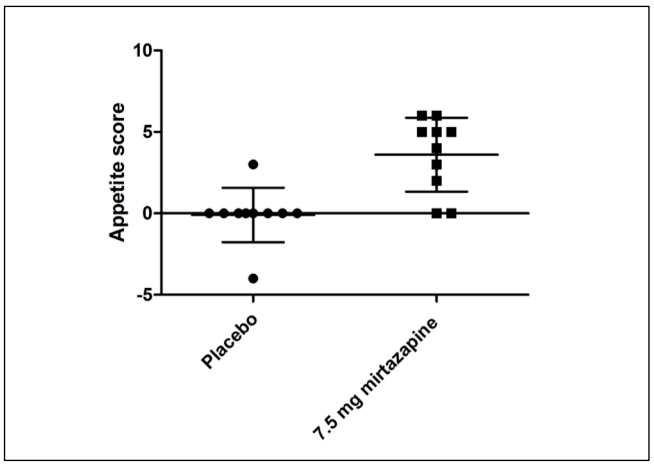

Figure 2: In a double-blind placebo-controlled cross over study client-owned healthy cats < 7 years of age received transdermal mirtazapine 7.5 mg/dose daily for 6 days. Their appetite was scored daily as 0= no change, 1= increased or -1= decreased and summed for the 6 day period. A statistically significant difference in appetite score was seen between placebo and mirtazapine (p=0.0139). No changes in serum ALT were appreciated after 6 days of transdermal mirtazapine administration.

In summary, based on the preliminary data, mirtazapine does achieve therapeutic serum concentrations and result in appetite stimulating effects when given in transdermal form. Transdermal application appears to maintain relatively steady serum concentrations for at least 48 hours which makes it amenable to every other day administration once multi-dosing blood concentrations are obtained.

Study Aim

The aim of the proposed study is to assess efficacy of transdermal mirtazapine in stimulating appetite in cats suffering from inappetence associated with CKD.

Hypothesis:

Transdermal mirtazapine will result in an increased appetite and subsequent weight gain in cats with CKD.

Study Design

Animals: This is a double blind placebo-controlled crossover prospective study. 20 client-owned cats with stable Stage II or III CKD (serum creatinine of 2.0 – 5.0 mg/dl) and history of decreased appetite will be enrolled. Diagnostic tests required before enrollment include a serum biochemistry profile, complete blood count, urinalysis, urine culture, blood pressure, and serum total thyroxine measurement. Exclusion criteria include other systemic illnesses, complications of CKD such as pyelonephritis or ureteral obstruction, or decompensation of CKD requiring hospitalization and intravenous fluid therapy. Other concurrent therapies such as dietary management, famotidine, potassium supplementation, anti-hypertensive medications and subcutaneous fluids are acceptable if they are given consistently throughout the study period.

Recruitment: Study participants will be enrolled from Colorado State University (which sees an average of 60 cats with CKD per year) as well as feline-specific veterinary clinics in the community.

Experimental Procedures: Pharmaceutical grade mirtazapine powder will be compounded into a 75mg/ml (7.5 mg/0.1 ml dose) transdermal Lipoderm gel by the CSU Veterinary Medical Center pharmacy. An aliquot of each cat's gel will be saved for drug concentration analysis. An identical placebo will be manufactured. The lots will be coded A and B. The pharmacy staff will keep the key to the code. A preset randomization for order of distribution (AB or BA) will be determined and as cats are enrolled they will be assigned consecutively to a treatment regime. The clinician and owner will be masked as to the treatment order. The randomly predetermined gel (A or B) will be administered to the inner ear pinna daily for three days, and then every other day for three weeks and then the animal will switch treatment groups. Owners will be asked to fill out a daily log sheet regarding their cats' behavior (this information will later be converted to a clinical score). At the end of each treatment phase cats will have an office visit at which a physical exam and serum biochemistry will be performed as well as trough (the time the gel is normally administered) blood sampling for serum mirtazapine levels.

Serum mirtazapine and gel concentration analysis: Mirtazapine will be measured in trough and peak serum samples and gel samples by the use of liquid chromatography (LC) coupled to tandem mass spectrometry (MS/MS). All analyses will be carried out in the Pharmacology Core at the Colorado State University Veterinary Medical Center (VMC) using a matrix-validated assay as previously described (Q)

Power calculation: In cats with kidney disease, an increase in body weight is a readily obtained objective measure of increased food intake. A previous study looking at oral mirtazapine in cats indicated that a mean difference in weight between placebo and mirtazapine was 0.3 kg with a standard deviation of 0.2 kg.[4] Using Lenth's online power calculator for calculating power: http://homepage.stat.uiowa.edu/~rlenth/Power/ this resulted in a power of 95% with an n of 15 cats. Based on previous clinical trials experience it is expected that 2-5 cats might be enrolled but not successfully complete the trial. Therefore the budget is calculated for 20 cats to ensure 15 cats complete the trial for adequate power.

Statistical analysis: Appetite and activity data will be converted to clinical scores; decreased appetite or activity scored as -1, unchanged appetite or activity scored as 0 and increased appetite or activity scored as 1. Scores will be summed for the three week treatment period. Number of vomiting episodes over 21 days and summed clinical scores for appetite and activity will be compared between placebo and mirtazapine treatment phases using a Wilcoxon matched pairs test. Body weight, body condition score, serum creatinine, BUN, potassium, and phosphorus will be compared individually using linear mixed model analysis (SAS 9.3). Specifically, a two period crossover model will be used which includes period, randomization (AB or BA) and treatment as fixed effects, cat within randomization as a random effect.

Expectations for Results

Based on our previous experience with oral mirtazapine, and the preliminary data for transdermal mirtazapine in research cats, we expect that transdermal mirtazapine will be well tolerated and easy to administer and result in increased appetite and weight in comparison to placebo.

Possible Pitfalls

Adequate enrollment is the most common pitfall associated with a clinical trial like the proposed project, particularly when elderly cats with no concurrent disease are sought (many cats in this age group have other medical problems). Given the number of cats with CKD seen at Colorado State University and the attractive nature of the study from the owner's perspective, we do not anticipate a problem with enrollment. However to actively address this issue we have already planned to collaborate with two feline clinics who have clinical trial experience. If enrollment is an issue despite these efforts then additional clinics can be recruited.

In the event that an undesirable amount or degree of side effects (hyperactivity, vocalization) were noted with the dose proposed for the study, the dose would be titrated down and resume as previously planned. Previous studies have indicated that side effects are dose related.[6]

VI. Timeline

0-3 months: Advertising and press release for study

3-18 months: Recruitment of patients from CSU patient population as well as two feline-exclusive primary care veterinary clinics.

12 months: If enrollment is not proceeding as desired, an additional press release and encorporation of another enrollment site to boost study entry.

18-24 months: Analysis of study results, preparation for abstract presentation, manuscript writing and publication.

VII. Itemized Budget with justification:

Personnel

Jessica Quimby: As PI, Dr. Quimby will be responsible for oversight of patient recruitment, enrollment, and randomization. She will spend 5% effort on this project which will be paid by her department.

Andrea Herndon: Andrea is a veterinary student who will be responsible for helping to coordinate study enrollment and manage the data produced. She will spend 5% effort on this project.

Year 1: 104 hours x $12.48: plus fringe (1%) = $1,311
Year 2: 104 hours x $12.48: plus fringe (1%) = $1, 311

Materials and Supplies

Mirtazapine Compounding: transdermal gel (20 x 2 @ $8.33/syringes)	$334
Shipping: shipping of supplies and drug to participating clinics ($15 x 20 x 3)	$900

Total Year 1: $617; Total Year 2:$617

Patient Procedures and Monitoring

Costs are estimated for 10 cats each year:	Year 1
Initial assessment for enrollment: Office visit, CBC, Chemistry, UA, BP, T4, urine culture	$2,500
3 week visit: Office visit, Chemistry	$750
6 week visit: Office visit, Chemistry	$750
Veterinarian incentive: $100 per cat enrolled	$1,000

Total year 1: $5,000

	Year 2
Initial assessment for enrollment: Office visit, CBC, Chemistry, UA, BP, T4, urine culture	$2,500
3 week visit: Office visit, CBC, Chemistry	$750
6 week visit: Office visit, CBC, Chemistry	$750
Veterinarian incentive: $100 per cat enrolled	$1,000

Total for year 2: $5,000

Serum mirtazapine and gel concentrations:
Analysis costs will be covered by the Angelo Fund for Feline Therapeutics and no funds are requested.

Total Personnel	**Year 1: $1,311; Year 2: $1,311**
Total Materials and Supplies	**Year 1: $617; Year 2: $617**
Total Procedures and Monitoring	**Year 1: $5,000; Year 2: $5,000**
Total Project Costs	**Total: $13,856**

VIII. Animal Justification

Colorado State University evaluates an average of 60 cats with CKD per year, and in addition has several feline clinics that collaborate with study enrollment. Based on previous enrollment rates we do not anticipate that there will be a problem enrolling 20 cats for this pilot study within the allotted time. The animals in this study are client-owned and will live with their owners for the duration of the study. IACUC approval will be obtained once funding is acquired.

IX. References

1. Polzin DJ. Chronic kidney disease in small animals. Vet Clin North Am Small Anim Pract 2011;41:15-30.
2. Ross SJ, Osborne CA, Kirk CA, et al. Clinical evaluation of dietary modification for treatment of spontaneous chronic kidney disease in cats. J Am Vet Med Assoc 2006;229:949-957.
3. Geddes RF, Elliott J, Syme HM. The effect of feeding a renal diet on plasma fibroblast growth factor 23 concentrations in cats with stable azotemic chronic kidney disease. J Vet Intern Med 2013;27:1354-1361.
4. Quimby JM, Lunn KF. Mirtazapine as an appetite stimulant and anti-emetic in cats with chronic kidney disease: A masked placebo-controlled crossover clinical trial. Veterinary journal 2013;197:651-655.
5. Hill K. Transdermal Medications in Cats: A review of the literature and evidence. ACVIM 2014 proceedings 2014.
6. Quimby JM, Gustafson DL, Samber BJ, et al. Studies on the pharmacokinetics and pharmacodynamics of mirtazapine in healthy young cats. J Vet Pharmacol Ther 2011;34:388-396.

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Jessica M. Quimby (previously Czederpiltz)	Assistant Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
University of Wisconsin	B.A.	1997	Zoology and Anthropology
University of Wisconsin	D.V.M.	2003	Veterinary Medicine
Colorado State University	DAVCIM	2009	Small Animal Internal Medicine
Colorado State University	PhD	2012	Clinical Sciences

Positions

OCCUPATION	BEGIN (mm/yy)	END (mm/yy)	FIELD	INSTITUTION	SUPERVISOR/ EMPLOYER
Veterinarian	9/2004	6/2006	Veterinary	Kentwood Cat Clinic	Tammy P. Sadek
Intern	9/2003	9/2004	Veterinary	Sacramento Animal Medical Group	Steve Crow
Resident/PhD	7/2006	7/2012	Veterinary	Colorado State University	M. Lappin/S. Dow
Clinical Instructor	7/2012	present	Veterinary	Colorado State University	Christopher Orton

A. Role

Primary Investigator

B. Academic and Professional Honors

American Association of Veterinary Clinicians Resident Award - 2011
Small Animal Resident of the Year Award – Colorado State University – 2008
Phi Zeta National Veterinary Honor Society – University of Wisconsin - 2003
American Association of Feline Practitioners Senior Award – University of Wisconsin – 2003
University Book Store Award for excellence in undergraduate research – University of Wisconsin - 1997
Phi Beta Kappa National Honor Society – University of Wisconsin - 1996
Academic Excellence Scholar awarded from the State of Wisconsin; full tuition at any state college – 1993

B. Selected Peer-Reviewed Publications (from 25 total)

1. McLeland SM, Cianciolo R, Duncan C, Quimby JM. A comparison of biochemical and histopathologic staging in cats with chronic kidney disease. Vet Path 2014: accepted for publication (11/2/2014).
2. Quimby JM, Brock WT, Moses K, Bolotin D, Patricelli K. Maropitant for the management of vomiting and inappetence associated with chronic kidney disease in cats. J Fel Med Surg: 2014: pii: 1098612X14555441.[epub ahead of print].
3. Trzil JE, Masseau I, Webb TL, Chang CH, Dodam JR, Liu H, Quimby JM, Dow SW and Reinero CR. Longitudinal evaluation of effects of intravenous mesenschymal stem cells in a feline model after establishment of chronic asthma. Clin Exp Allergy 2014: doi: 10.1111/cea.12411.[epub ahead of print].
4. Quimby JM, Lappin MR. Evaluating sucralfate as a phosphate binder in normal cats and cats with chronic kidney disease. JAAHA: 2014: accepted for publication (1/27/2014)
5. McLeland SM, Lunn KF, Duncan CG, Refsal KR, Quimby JM. Relationship between serum creatinine, serum gastrin, calcium-phosphorus product and uremic gastropathy in cats with chronic kidney disease. J Vet Int Med 2014; 28: 827-837
6. J.M. Quimby, R.C. Lake, R.J. Hansen, P.J. Lunghofer, D.L. Gustafson. Oral, subcutaneous and intravenous pharmacokinetics of ondansetron in healthy cats. J Vet Pharmacol Ther 2014; 37: 348-353.
7. J.M. Quimby, D.G. Maranon, S.M. McLeland; W.T. Brock; S.M. Bailey. Feline chronic kidney disease is associated with shortened telomeres and increases cellular senescence. Am J Physiol Renal Physiol. 2013 Aug; 305(3): F295-303.
8. J.M. Quimby, T. L. Webb, L.M. Habenicht, S. W. Dow. Safety and efficacy of intravenous infusion of allogeneic cryopreserved mesenchymal stem cells for treatment of chronic kidney disease in cats: Results of three sequential pilot studies. Stem Cell Res Ther, 2013; 4: 48.
9. J.M Quimby and K.F. Lunn. Mirtazapine as an appetite stimulant and anti-emetic in cats with chronic kidney disease: A masked placebo-controlled crossover clinical trial. Vet J 2013; 197: 651-654.
10. S.M McLeland, D.J. Imhoff, M. Thomas, B.E. Powers, J.M. Quimby. Subcutaneous fluid port-associated soft tissue sarcoma in a cat. J Fel Med Surg 2013; 15: 917-920.
11. L.M. Habenicht, T.L. Webb, L.A. Clauss, S.W. Dow, J.M. Quimby. Urinary cytokine levels in apparently healthy cats and cats with chronic kidney disease. J Fel Med Surg 2013; 15: 99-104.

12. T.L. Webb, J.M. Quimby and S.W. Dow. In Vitro Comparison of Feline Bone-Marrow-derived and Adipose Tissue derived Mesenchymal Stem Cells J Fel Med Surg 2011; 14: 165-168.
13. J.M. Quimby, D.L. Gustafson, K.F. Lunn. The Pharmacokinetics of Mirtazapine in Cats with Chronic Kidney Disease and In Age-Matched Control Cats. J Vet Int Med 2011; 25: 985-988.
14. J. M. Quimby, T. L. Webb, D. Gibbons, S. W. Dow. Evaluation Of Intrarenal Mesenchymal Stem Cell Injection For Treatment Of Chronic Kidney Disease In Cats: a Pilot Study. J Fel Med Surg 2011; 13(6):418-26.
15. J.M. Quimby, M.L. Smith and K.F. Lunn. Evaluation of effects of hospital visit stress on physiologic parameters in the cat. J Fel Med Surg 2011; 13:733-737.
16. D. Catbagan, J.M. Quimby, J. Bratley, C. Sonius, P. Mich, P. Vogel, K. Mama. Comparison of the efficacy of an oral transmucosal buprenorphine and sustained release subcutaneous buprenorphine in cats post-surgical ovariohysterectomy. Am J Vet Res 2011; 72: 461-466.
17. J.M. Quimby, D.L. Gustafson, B.J. Samber, K.F. Lunn. Studies on the pharmacokinetics and pharmacodynamics of mirtazapine in healthy cats. J Vet Pharmacol Ther 2010: 34: 388-396.
18. J.M. Quimby, S Hoffman, J Duke and M.R. Lappin. Adverse neurologic events associated with voriconazole use in three cats. Manuscript accepted for publication. J Vet Int Med 2010; 24: 647-649.
19. J.M. Quimby, F Olea-Popelka, M.R. Lappin. Comparison of rectal and microchip transponder thermometry in cats. J Am Assoc Lab Anim Sci 2009; 48(4):402-4.
20. J.M. Quimby, T Elston, J Hawley, M Brewer, A. Miller, M.R. Lappin. Evaluation of the association of Bartonella species, feline herpesvirus 1, feline calicivirus, feline leukemia virus, feline immunodeficiency virus with chronic feline gingivostomatitis. J Fel Med Surg. 2008; 10: 66-72.
21. J.M.C. Czederpiltz, N.C. La Croix, A. van der Woerdt, E. Bentley, R.R. Dubielzig, C.J. Murphy, P.E. Miller. Putative Aqueous Humor Misdirection Syndrome as a Cause of Glaucoma in Cats: 32 cases (1997-2003). J Am Vet Med Assoc 2005; 207 (9): 1434-1441.

Selected Abstracts (from 29 total)

1. Felumlee A, Marolf A, Randall R, Bachand A, Quimby JM. Intra and Interobserver Variability of GFR Rate Determination in Cats with Chronic Kidney Disease via Gamma Camera Uptake of Tc-99M DTPA. American College of Veterinary Radiology Annual Scientific Meeting, St Louis, MO, 2014.
2. Fitzpatrick RL, Wittenburg LA, Hansen RJ, Lunghofer P, Gustafson DL, Quimby JM**.** Pharmacokinetics of Subcutaneous Ondansetron in Healthy Geriatric Cats, Cats with Chronic Kidney Disease and Cats with Liver Disease. J Vet Int Med 2014; 28: 1096.
3. Ferguson LE, McLean MK, Quimby JM. Mirtazapine Toxicity in Cats: Retrospective Study of 104 Cases (2006-2011). J Vet Int Med 2014; 28: 1097
Quimby JM, Dowers K, Randall E. Renal Pelvic and Ureteral Ultrasonogranphic Characteristics of Normal Cats, and Cats with Stable Chronic Kidney Disease, Pyelonephritis and Ureteral Obstruction. *J Vet Int Med* 2014; 28: 1076.
4. S.M. McLeland, J.M. Quimby, M.R. Lappin. Renal Expression of Enolase in Cats with Chronic Kidney Disease. ACVP, Montreal, Canada, 2013.
5. M.C Seward, J.M. Quimby, E.Randall. Ultrasound Measurement of Cortiomedullary Ratios to Determine Progression of Chronic Kidney Disease in Cats ACVR, Savannah, GA, 2013.
6. S.M. McLeland, C.G. Duncan, J.M. Quimby. A Comparison of Biochemical and Histopathological Staging in Cats with Renal Disease. American Association of Veterinary Laboratory Diagnosticians Annual Conference. Buffalo, NY, 2011.

C. Current Research Support

Winn Feline Foundation: PI: Dr. Jessica Quimby (2014-2016; $24,777)
Assessment of Renal Intra-arterial Administration of Allogeneic Mesenchymal Stem Cells for the Treatment of Feline Chronic Kidney Disease

College Research Council: PIs Dr. Jessica Quimby and Dr. Susan Bailey (2013-2014; $20,881)
Telomere Length, Cellular Senescence and Renal Aging in Feline Chronic Kidney Disease

Angelo Foundation for Feline Therapeutics: PI: Dr. Jessica Quimby (2014-2016; $14,099)
Pharmacokinetics and Pharmacodynamics of of Transdermal Mirtazapine in Normal Cats

Assessment of Transdermal Mirtazapine as an Appetite Stimulant in Cats with Chronic Kidney Disease

Client Consent Form

Client ID

What is the study about?

Mirtazapine is a medication that has been used in human medicine as an antidepressant. The drug widely used in veterinary medicine due to the presence of several desirable effects, namely its significant anti-nausea, anti-vomiting and appetite stimulating properties. It has been shown to be effective in increasing weight and appetite and decreasing vomiting in cats with chronic kidney disease. However, many owners have difficulty administering pills to their cat. We believe that mirtazapine, like many other medications, could be effective when formulated as a transdermal gel that can be applied to the skin of the ear. The purpose of this study is to perform a study to document the appetite stimulation properties of the transdermal form of the drug in cats with kidney disease.

Is your cat eligible to participate?

Cats with stable chronic kidney disease (creatinine 2-5 mg/dL) are potentially eligible for entry into the study. Diagnostic tests required before enrollment include a serum biochemistry profile, complete blood count, urinalysis, urine culture, blood pressure, and thyroid level. Exclusion criteria include other systemic illnesses, complications of CKD such as pyelonephritis or ureteral obstruction, or decompensation of CKD requiring hospitalization and intravenous fluid therapy. Other concurrent therapies such as dietary management, famotidine, potassium supplementation, anti-hypertensive medications and subcutaneous fluids are acceptable if they are given consistently throughout the study period.

What does the study involve?

The study involves bringing your cat into the hospital for three visits and administering a gel to the ear for a total of 6 weeks. There are two treatment periods (placebo transdermal gel, mirtazapine transdermal gel) and your cat will receive both in a randomly determined order. During the two transdermal treatment periods (placebo or mirtazapine) you will administer the gel daily for 3 days then every other day for three weeks, fill out a daily log sheet, and then bring your cat in for the hospital visit on the last day of gel administration. During this day, your cat will receive its last transdermal gel dose or oral mirtazapine (administered by the researchers) and will get a physical exam and weight, and have a blood sample drawn to check kidney values and to measure how much mirtazapine is in your cat's body.

What are the risks?

The risks involve side effects of the drug including hyperactivity, vocalization, increased affection and appetite. Side effects are transient and are minimal at the dose that will be administered. Mild discomfort during blood draws is possible.

Is there compensation for your participation?

If your cat is eligible, you will receive a complementary CBC, chemistry, urinalysis, urine culture and thyroid level to confirm your cat's health prior to participation. All costs of the visits and the gel medication are covered by the study.

Owner Consent

I have read the explanations of the study provided above and I understand the above stated conditions and I agree to allow my cat to undergo the procedures described above. If I have any concerns or questions related to this study I should contact Dr. Jessica Quimby at (970) 297-5000 or jquimby@colostate.edu.

Signed: _____

Date:_____

Witness:_____

Colorado State University
James L. Voss Veterinary Medical Center
300 W. Drake Road
Fort Collins, CO 80523

Mirtazapine CKD Trial Daily Log Sheet

Cat's Name:_____

Date: _____ Treatment Phase: _____

Did you apply the transdermal gel today?

Yes No

Which ear was the gel applied to?

Right ear Left ear

Did your cat tolerate receiving the medication?

Yes No

Did you notice any redness or irritation of the ears?

Yes No

Describe your cat's appetite today:

Decreased Unchanged Increased

How quickly did your cat eat his/her food today?

Slower than normal Unchanged Faster than normal

Describe your cat's activity level today:

Decreased Unchanged Increased

Described your cat's begging/food seeking behavior today:

Decreased Unchanged Increased

Described your cat's vocalization behavior today:

Decreased Unchanged Increased

Did you notice any unusual behavior today?

Yes No