UNIVERSIDADE DE LISBOA

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OWNER'S PERSPECTIVE ABOUT THE USE OF MIRTAZAPINE TRANSDERMAL OINTMENT IN CATS – A SURVEY-BASED STUDY

SOFIA ISABEL FERNANDES DE CARVALHO

ORIENTADOR:
Doutor Rodolfo Assis Oliveira Leal

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Resumo

“Perspetiva do detentor sobre o uso da pomada transdérmica de mirtazapina em gatos – estudo baseado em questionário”

A mirtazapina é um antidepressivo tetracíclico utilizado como estimulante do apetite em gatos. Historicamente, estava apenas disponível sob a forma de comprimidos para uso humano, mas, em 2019, foi autorizada como medicamento veterinário na forma de pomada transdérmica para gatos. O objetivo do estudo é avaliar a perspetiva do detentor sobre a utilização da mirtazapina transdérmica, nomeadamente, a sua perceção sobre a facilidade de administração, eficácia e efeitos secundários.

Foi desenvolvido um questionário com 15 perguntas que, posteriormente, foi enviado, via *email,* para os detentores dos gatos seguidos em dois Hospitais Veterinários aos quais a mirtazapina transdérmica tinha sido prescrita entre janeiro de 2021 e março de 2023. No final, foi realizada estatística descritiva e a associação entre variáveis foi avaliada estatisticamente (qui-quadrado, teste exato de Fisher e *odds ratio)*.

De um total de 108 questionários enviados, foram obtidas 70 respostas. A aplicação tópica foi considerada fácil por 68/70 (97%) dos inquiridos. Seguindo o RCM (Resumo das Características do Medicamento), 64/70 (91%) dos detentores confirmaram a aplicação alternadamente em cada uma das orelhas, ao contrário de 6/70 (9%) que admitiram aplicar a pomada sempre na mesma orelha. Considerando que a duração de tratamento recomendada é de 14 dias, as respostas foram divididas em dois grupos: terapêutica '<14 dias' (33/64; 51.6%) e terapêutica '≥14 dias' (31/64; 48.,4%). Os efeitos secundários foram identificados por 14/70 (20%) dos inquiridos, sendo os mais comuns: vocalização (5/14), eritema (4/14) e agitação (4/14). A maioria dos detentores (54/70; 77%) considerou a pomada eficaz na estimulação do apetite. As razões para a prescrição foram detalhadas em 57 respostas, sendo as mais comuns: doença renal crónica (18/57; 32%) e enteropatia crónica (10/57; 18%). Um total de 9/70 (13%) dos inquiridos já tinham administrado mirtazapina por via oral ao seu gato antes de utilizar a pomada. Enquanto 7/9 (78%) consideraram a pomada mais vantajosa devido à facilidade de administração, os restantes (2/9, 22%) deram vantagem aos comprimidos devido ao seu menor custo. Foi demonstrada uma associação estatisticamente significativa entre eficácia e duração do tratamento (p=0.015), com terapêuticas ‘<14 dias’ associadas a uma menor eficácia e terapêuticas ‘≥14 dias’ associadas a uma maior eficácia.

Este estudo realça a perceção dos detentores acerca do uso da mirtazapina transdérmica em gatos, reforçando a sua aplicabilidade, eficácia e segurança.

PALAVRAS-CHAVE: Mirtazapina; Estimulante do apetite; Pomada transdérmica; Perspetiva dos detentores; Questionário.

Abstract

“Owner’s perspective about the use of mirtazapine transdermal ointment in cats – a survey-based study”

Mirtazapine is a tetracyclic antidepressant used as an appetite stimulant in cats. Despite its historical off-labelled oral administration in cats, it was licensed in 2019 for use as a transdermal ointment. Being a topical product, its efficacy relies on good compliance. The aim of this study is to assess the owner's perspective on the use of transdermal mirtazapine, specifically their perception of ease of administration, efficacy and side effects.

A cross-sectional survey-based study was conducted, utilising a questionnaire with 15 questions. The electronic medical records of two European Veterinary Teaching Hospitals were searched for cats for whom transdermal mirtazapine was prescribed from March 2021 to January 2023. These cat owners were contacted by email and invited to complete the survey. Descriptive statistics and statistical tests (Chi-square, Fisher’s Exact Test, and Odds Ratio) were performed.

From the 108 contacted owners, 70 answers were obtained. The topical application was found easy by 68/70 (97%) of the owners. Following the manufacturer instructions, 64/70 (91%) owners confirmed the daily application in alternating ears, contrasting with 6/70 (9%) who admitted applying the ointment always in the same ear. Recognizing that the recommended treatment duration is 14 days, the responses were divided into two groups: '<14 days' (33/64; 51.6%) and '≥14 days' (31/64; 48.,4%). Side effects were reported by 14/70 (20%), being the most common vocalisation (5/14), erythema (4/14), and agitation (4/14). Most of the respondents (54/70; 77%) considered that transdermal mirtazapine efficiently stimulates the appetite. Reasons for mirtazapine prescriptions were detailed in 57 answers, with the most common being chronic kidney disease (18/57; 32%) and chronic enteropathy (10/57; 18%). A total of 9/70 (13%) owners had previously administered mirtazapine by oral route to their cats before trying the transdermal administration. While 7/9 (78%) considered transdermal more beneficial due to an easier administration, the remaining (2/9, 22%) preferred oral mirtazapine due to its lower cost. A significant statistical association between efficacy and treatment duration was demonstrated (p=0.015), with durations '<14 days' linked to lower efficacy and durations '≥14 days' associated with higher efficacy.

This study highlights the owners’ perception of transdermal mirtazapine use, reinforcing its applicability, effectiveness, and safety as an appetite stimulant in cats.

KEYWORDS: Mirtazapine; Appetite stimulant; Transdermal ointment; Owners’ perspective; Survey.

Resumo alargado

“Perspetiva do detentor sobre o uso da pomada transdérmica de mirtazapina em gatos – um estudo baseado em questionário”

A inapetência e a anorexia, definidas como uma diminuição/paragem da ingestão voluntária por parte do animal, são sinais clínicos não específicos muito comuns em medicina veterinária, sendo frequentemente o primeiro sinal de alerta identificado pelos detentores. A inapetência e a anorexia podem ser causadas por diversas doenças (como por exemplo, doença renal crónica, doença hepatobiliar ou neoplasia) e alguns fatores (como stress, náusea, dor ou medo). A ingestão alimentar inadequada pode ter um impacto extremamente negativo na saúde do animal, aumentando a sua morbilidade e mortalidade, prolongando a recuperação da doença subjacente, diminuindo a cicatrização de feridas, aumentando o risco de sépsis, etc. A abordagem médica a gatos com anorexia deve ser multimodal, sistemática e personalizada a cada paciente. É importante identificar e tratar a doença subjacente à anorexia e controlar fatores como o stress, a dor e a náusea. Simultaneamente, é crucial garantir uma nutrição adequada, por exemplo, através da colocação atempada de sondas de alimentação e administração de fármacos estimulantes do apetite.

A estimulação farmacológica do apetite pode ser útil em algumas circunstâncias, mas nunca deve substituir ou atrasar a implementação de outras formas de maneio nutricional (por exemplo, sondas de alimentação). Historicamente, vários medicamentos têm sido usados para a estimulação do apetite, incluindo a ciproheptadina e vitaminas do complexo B, entre outros. No entanto, atualmente, apenas dois medicamentos estão autorizados para uso em gatos: capromorelina (Elura®; Elanco, disponível nos EUA) e mirtazapina (Mirataz®; Dechra, disponível nos EUA, Canadá e Europa).

A mirtazapina é um antidepressivo tetracíclico utilizado como estimulante do apetite em gatos. Historicamente, estava apenas disponível sob a forma de comprimidos para uso humano, mas, em 2019, foi autorizada como medicamento veterinário na forma de pomada transdérmica para gatos (Mirataz®). No Resumo das Características do Medicamento do Mirataz®, a dose recomendada para gatos é de 2 mg de mirtazapina por gato, o que corresponde a uma linha de 3,8 cm de pomada, administrada uma vez por dia durante 14 dias consecutivos. O medicamento deve ser aplicado na parte interna da orelha do gato e a aplicação deve feita alternadamente em cada uma das orelhas, por exemplo, aplicar na orelha direita num dia e na a orelha esquerda no dia seguinte.

O principal objetivo deste estudo é investigar e analisar o *feedback* dos detentores de gatos sobre a utilização da pomada de mirtazapina transdérmica, nomeadamente, sobre a facilidade de aplicação e cumprimento das recomendações de aplicação, nomeadamente, aplicação diária alternamente em cada orelha e duração de

tratamento. Os objetivos secundários incluem a avaliação das razões para a prescrição, os efeitos secundários descritos, a preferência em relação aos comprimidos de mirtazapina (aprovados apenas para uso humano), a avaliação da eficácia e o intervalo de tempo até os detentores notarem melhorias a nível do apetite do seu gato. Não tendo conhecimento da existência de estudos sobre a perspetiva do detentor acerca desta pomada, este estudo pretende trazer novas informações com vista à otimização do tratamento.

Foi desenvolvido um questionário com 15 perguntas. Inicialmente, foram consultados os registos eletrónicos de dois Hospitais Veterinários (HEV-FMV e Hospital Veterinário de Pádua) relativos a gatos aos quais a mirtazapina transdérmica foi prescrita entre março de 2021 e janeiro de 2023. Os detentores destes gatos foram contactados por *email*/telefone, entre fevereiro e março de 2023, para responderem ao questionário. No final, foi realizada estatística descritiva e a associação entre variáveis foi avaliada estatisticamente (qui-quadrado, teste exato de Fisher e *odds ratio)*.

O questionário foi enviado para 108 detentores, obtendo-se um total de 70 respostas. A aplicação tópica foi considerada fácil por 68/70 (97%) dos inquiridos. Seguindo as recomendações, 64/70 (91%) dos detentores confirmaram alternar diariamente a orelha em que aplicaram a pomada, ao contrário de 6/70 (9%) que admitiram aplicá-la sempre na mesma orelha.

Os efeitos secundários foram identificados por 14/70 (20%) dos inquiridos, sendo os mais comuns: vocalização (5/14), eritema (4/14) e agitação (4/14). As razões para a prescrição foram detalhadas em 57 respostas, sendo as mais comuns: doença renal crónica (18/57; 32%) e enteropatia crónica (10/57; 18%).

A maioria dos detentores (54/70; 77%) considerou a pomada eficaz na estimulação do apetite. Aos detentores que responderam que a mirtazapina transdérmica tinha sido eficaz foi perguntado quanto tempo após a primeira aplicação de pomada notaram efeitos positivos no apetite do seu gato, sendo que 51.9% (28/54) referiu um intervalo '≤1 semana' e 44.4% (24/54) referiu '≤24 horas'.

Um total de 9/70 (13%) dos inquiridos já tinham administrado mirtazapina por via oral ao seu gato antes de utilizar a pomada. Enquanto 7/9 (78%) consideraram a pomada mais vantajosa devido à facilidade de administração, os restantes (2/9, 22%) deram vantagem aos comprimidos devido ao seu menor custo.

Considerando que a duração de tratamento recomendada é de 14 dias, as respostas foram divididas em dois grupos: terapêutica '<14 dias' (33/64; 51.6%) e terapêutica '≥14 dias' (31/64; 48.,4%). Foi demonstrada uma associação estatisticamente significativa entre eficácia e duração do tratamento (p=0.015), com

terapêuticas ‘<14 dias’ associadas a uma menor eficácia e terapêuticas ‘≥14 dias’ associadas a uma maior eficácia.

O presente estudo mostrou que os detentores, em geral, consideram a pomada fácil de aplicar, mostrando algumas vantagens sobre a administração de medicamentos por via oral, que pode ser bastante desafiante tendo em conta a suscetibilidade dos gatos ao stress. Sendo um produto tópico frequentemente administrado em casa, a sua eficácia está diretamente ligada à adesão à terapêutica e à vontade e habilidade dos detentores para procederem à sua correta aplicação.

Este estudo mostrou também versatilidade deste medicamento, aplicado em situações mais cronicas (por exemplo, doença renal crónica) e também em situações mais agudas (por exemplo, recuperação pós-cirúrgica). Adicionalmente, este estudo sugere que durações de tratamento mais curtas (‘<14 dias’) podem estar associadas a uma eficácia reduzida, enquanto durações iguais ou mais longas do que as recomendadas (‘≥14 dias’) podem estar ligadas mais eficácia. Estes achados enfatizam a importância de aderir à duração recomendada.

O presente estudo tem algumas limitações que devem ser tidas em consideração. É importante referir a possibilidade de viés associados à memória, uma vez que alguns dos inquiridos já tinham utilizado a pomada transdérmica no ano 2021, tendo respondido ao questionário apenas no ano 2023. Este intervalo de tempo significativo entre o momento do uso do medicamento e a resposta ao questionário induz dificuldades em relembrar com precisão detalhes sobre as suas experiências/opiniões. Para mitigar essa limitação, estudos futuros poderiam beneficiar de um desenho de estudo prospetivo, com recolha de respostas em tempo real ou logo após o uso do medicamento. Adicionalmente, existe a possibilidade de variações na interpretação das perguntas do questionário por parte dos inquiridos, reforçando a importância de colocar as questões de forma clara e percetível.

No geral, este estudo realça as vantagens práticas da pomada transdérmica de mirtazapina, reafirmando o seu potencial como uma ferramenta a considerar no maneio de gatos anoréticos. Adicionalmente, seria interessante a realização de investigações futuras em maior escala e em diferentes locais geográficos, de modo a generalizar estes resultados e proporcionar uma compreensão mais abrangente das experiências dos detentores com o Mirataz®.

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List of abbreviations

5-HT – Serotonin or 5-hydroxytryptamine

ALT – Alanine Aminotransferase

AUC – Area Under the Curve

BCS – Body Condition Score

BW – Body Weight

CKD – Chronic Kidney Disease

Cmax – Maximum Concentration

CNS – Central Nervous System

CT – Computed Tomography

CTM – Compounded Transdermal Mirtazapine

CTZ – Chemoreceptor Trigger Zone

CYP – Cytochrome P450

EMA – European Medicines Agency

FDA – United States Food and Drug Administration

FeLV – Feline Leukaemia Virus

FIP – Feline Infectious Peritonitis

FIV – Feline Immunodeficiency Virus

FLUTD – Feline Lower Urinary Tract Disease

GABA – Gamma-aminobutyric Acid

H1 – Histamine type 1 receptors

IMHA – Immune-Mediated Haemolytic Anaemia

MRI – Magnetic Resonance Imaging

NE – Norepinephrine

NSAID's – Non-Steroidal Anti-Inflammatory Drugs.

OR – Odds Ratio

PEG - Polyethylene Glycol

PK – Pharmacokinetics

PO – *per os*

RER – Resting Energy Requirement

Tmax – The time it takes for a drug to reach the maximum concentration (Cmax)

TNF – Tumour Necrosis Factor

List of symbols

® – Registered Trademark

1. INTRODUCTION

This document represents a master's thesis conducted within the framework of the MIMV (Integrated Master's Degree in Veterinary Medicine) by the Faculty of Veterinary Medicine at the University of Lisbon. The primary objective of this dissertation was to analyse the opinions of cat owners regarding mirtazapine transdermal ointment, an appetite stimulant that has been recently used in veterinary medicine. The introduction of this research begins with an account of my curricular traineeship at the Hospital Escolar Veterinário from FMV-ULisboa (HEV-FMV). Following this, the document delves into a literature review of the subject, encompassing the medical approach to inappetence/anorexia in cats, an introduction to appetite stimulants, and a summary of the pharmacokinetics and pharmacodynamics of mirtazapine.

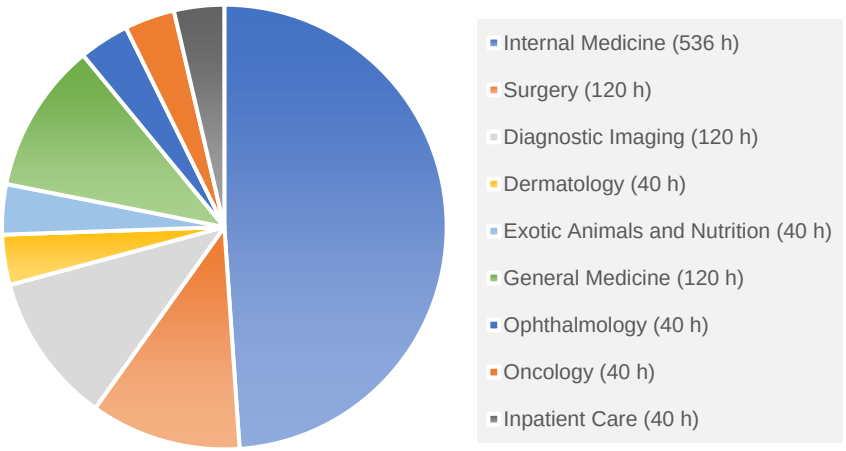
The significance of this study lies in its potential to shed light on the use of mirtazapine transdermal ointment, Mirataz®, from the perspective of cat owners, thereby contributing to feline healthcare and providing valuable insights for veterinarians.

1.1. Traineeship report

My curricular traineeship took place at the Hospital Escolar Veterinário of the Faculty of Veterinary Medicine, University of Lisbon (HEV-FMV). It had a duration of six months, from September 2022 to March 2023, with approximately 1096 hours.

My trainee period was divided into two different parts. In the first three months, I was scheduled on a rotation across almost all the departments of the hospital. During these months, I was able to develop my skills in a variety of areas of small animal practice. In the second trimester, I was assigned to the department of Internal Medicine and joined the Referral Internal Medicine Service (SMIR) team, attending to their consultations and procedures. The time spent in each department is depicted in Graph 1.

Graph 1 – Distribution of time I spent in each department.



Legend: h – hours.

1.1.1. Surgery

I joined the surgery and anaesthesia team for three weeks, during which I assisted on several soft tissue, orthopaedic, ophthalmic, and oral surgeries. During this rotation, there was the possibility to perform some technical procedures, such as peripheral venous catheterization, pre-anaesthetic drug preparation and administration, endotracheal intubations, trichotomy and surgical asepsis, anaesthetic induction, positioning of the animal onto the surgery table, monitoring anaesthesia, and post-surgery care. Additionally, I was a surgeon assistant for one or two surgeries a day, where I had the opportunity to learn about different surgical techniques.

1.1.2. Diagnostic Imaging

1.1.2.1. X-ray and CT-scan

During this week, I assisted on x-rays, admission, contention, sedation, and positioning of the animals, and had the opportunity to interpret the images and learn how to identify certain abnormalities, including orthopaedic, thoracic, and abdominal. I also had the opportunity to assist with myelographies and cerebrospinal fluid collection. Furthermore, I assisted with at least two computed tomographies (CT) a day, helping with intravenous catheter placement, administration of medication, endotracheal intubation, and monitoring of anaesthesia. I also participated in the interpretation of images and the elaboration of reports.

1.1.2.2. Ultrasound

In this rotation, I spent two weeks attending ultrasonography exams. My responsibilities included trichotomy and positioning of the patients. During this time, I gained experience in

identifying various abdominal organs on ultrasound and recognizing the most prevalent abnormal findings. I assisted in the performance of ultrasound-guided percutaneous needle biopsies, fine needle aspirations, and subcutaneous ureteral bypass lavages. Additionally, I participated in eye ultrasounds and ultrasonography exams for exotic animals.

1.1.3. Dermatology

The rotation in dermatology lasted one week with 8-hour shifts, during which I had the opportunity to improve my anamnesis skills and discuss the most common skin diseases. Under doctor's guidance, I performed dermatological examinations and diagnostic tests, such as skin cytology, skin scrapings, ear cytology, trichograms, fine-needle aspiration, and assisted in skin biopsies and videotoscopies. Additionally, I learned how to collect and send skin, hair, and ear samples for bacteriological and mycological cultures. We also discussed differential diagnoses and treatment protocols.

1.1.4. Exotic Animals and Nutrition

During this week, I had the opportunity to attend two different departments: exotic animals and nutrition. I joined consultations and surgeries for exotic animals, assisting with procedures such as mastectomy, dental care, and ovario-hysterectomies/orchiectomies, and gained knowledge about the most common diseases of rodents and reptiles.

Furthermore, I attended nutrition consultations in which I had the opportunity to participate in a weight-loss programme for patients. This experience provided me with further knowledge about how to evaluate the body condition of a patient and calculate their food consumption needs. Additionally, I received valuable insights into the nutritional requirements of dogs and cats and their respective diets.

1.1.5. General Practice Service

In this rotation, I had the opportunity to attend primarily first-opinion preventive care consultations and emergencies, providing valuable experience in communication skills, anamnesis practice, clinical examinations, and supervised medical procedures. These procedures included blood sampling, cystocentesis, intravenous catheter placement, fluid system preparation and placement, glycaemia measurement, blood pressure assessment, urethral catheterization, thoracocentesis, abdominocentesis, and electrocardiography, among others. These clinical cases facilitated discussions on medical approaches, different diagnoses for each case, and the best available treatment options. I actively participated in conversations with owners, addressing euthanasia concerns and assisting in its execution. Additionally, I

attended emergency consultations, further enhancing my ability to handle urgent situations such as seizures, trauma, sepsis, dyspnoea, and more.

1.1.6. Ophthalmology

The week I spent in the ophthalmology department provided me with a deeper knowledge of the major diseases affecting the eyes of dogs and cats. I attended consultations where I conducted several diagnostic tests, including reflex testing, tonometry, ocular examination, biomicroscopy, the Schirmer tear test, and the fluorescein stain test. Throughout these weeks, I acquired knowledge of the most common medications used in ophthalmological treatment.

1.1.7. Oncology

In the week spent in the oncology department I was able to learn more about the diagnosis and treatment modalities of the most common malignancies in small animals and to participate in the preparation and execution of chemotherapy plans. Furthermore, I was given the opportunity to discuss more challenging cases and innovative approaches to cancer in small animals. I took part in first-time referral consultations and follow-ups and performed blood sample collections and fine-needle aspirations when needed. There was also the possibility of discussing chemotherapy protocols and their administration with the assigned oncology nurse.

1.1.8. Inpatient Care

I was assigned one night per month and two 12-hour day shifts in inpatient care. Each shift started with a medical round in which the clinical cases were discussed in group. During this period, I followed inpatient cases and their evolution. Along with the nurse, I was responsible for feeding the patients, doing their clinical examinations, and administering drugs. In this service, I was able to perform several procedures, including intravenous catheter placement, fluid system preparation and placement, glycaemia measurement, blood pressure assessment, urethral catheterization, and nasogastric tube feeding placement, among others. I witnessed life-threatening situations that required prompt measures such as fluid supplementation, blood transfusion, oxygen supplementation, and cardiopulmonary resuscitation. The evolution of the clinical case was discussed with the clinician, as well as the discharge plans and prognosis for each animal.

1.1.9. Internal Medicine

Within small animal practice, internal medicine, especially endocrinology, has always been the area that most captivates me. During the months I spent on the Internal Medicine Service, I acquired knowledge in the diagnostics and treatment of many diseases, including hepatobiliary, endocrine, urinary, hematologic, digestive, and respiratory.

Throughout these months, the morning started with a medical round where the clinical cases of hospitalised animals were discussed with doctors and nurses from different departments. Then, I accompanied Prof. Rodolfo in his consultations, where I was allowed to collect the anamnesis of the patient, and then we discussed which complementary exams and treatment options were suitable for each case. Posteriorly, I collected the blood and urine samples and did the appropriate shipment of samples for internal and external laboratories. During the afternoon, we discussed all the clinical cases of the day, the list of differential diagnoses, the adequate complementary exams to perform, the most appropriate treatment plan, relevant follow-up tests, and the prognosis.

Once a week, I assisted in endoscopies (gastroscopies, colonoscopies, rhinoscopies, laryngoscopies, tracheobronchoscopies, and cystoscopies), observing different diseases and participating in the consultations and in the elaboration of endoscopy reports. We also performed many endoscopy-guided biopsies and then discussed the histopathological results. I also had the opportunity to assist with bronchoalveolar lavages, foreign body removal, and joint and bone marrow punctures, among other procedures.

I also participated in a weekly journal club, where each one of us presented two recent articles. These presentations were followed by discussions and a summary of the most important conclusions of each article.

Furthermore, a poster with the title “Owner’s perspective about the use of mirtazapine transdermal ointment – a survey-based study” was presented in ECVIM-CA – European College of Veterinary Internal Medicine (Annexe 4 and 5). Congress which took place in Barcelona in September, 2023.

Apart from the study conducted in the scope of this master project, I was involved as primary researcher in a project titled “The use of transdermal mirtazapine in hospitalised cats with feeding tubes and hepatobiliary disease” in partnership with the Centro de Investigação Interdisciplinar em Sanidade Animal (CIISA). The objective of this study was to assess the effect of Mirataz® on cats hospitalized for hepatobiliary disease in which a naso or oesophagostomy tube was placed. Additionally, an abstract with the title “The effect of transdermal mirtazapine in hospitalized cats with hepatobiliary disease: a prospective study” was submitted for oral or poster presentation in the congress of ACVIM-CA – American College of Veterinary Internal Medicine in 2024 (Annexe 6).

2. LITERATURE REVIEW

2.1. Inappetence in cats

Inappetence is a nonspecific clinical sign very common in feline medicine, being associated with a variety of underlying diseases such as upper respiratory tract disease, chronic kidney disease (CKD), hepatobiliary disorders or neoplasia (Little 2020). Inappetence is sometimes also termed ‘hyporexia’, describing reduced nutritional intake (Taylor et al. 2022), while anorexia is defined as a complete lack of appetite for food and no food intake (Batchelor and German 2019). Adequate nutrition is required to provide energy for cellular function, substrates for protein synthesis, vitamins and minerals for metabolic processes, and maintenance of homeostasis (Harvey 2015).

Inappetence or anorexia may be the first sign noted by caregivers and may require a prompt veterinary assessment. Robinson et al. (2015) conducted a study on clinical signs that led owners to seek first-opinion small animal consultations (n = 1901) and concluded that skin lumps, vomiting, and inappetence were the most common presenting signs. Additionally, owners believe their cat's appetite and food intake are reliable indicators of the cat's quality of life and health status (Michel 2001).

To understand if a cat or kitten is consuming adequate diet, guidelines for daily caloric intake should be noted. For adult cats, the starting point for daily resting energy requirement (RER) is calculated by the equation: $[70 \times BW\ (kg)^{0.75}]$. The RER should be calculated according to current body weight (even if overweight or underweight). Body weight should be monitored daily, and total calories fed should be adjusted by a maximum of 10% every 48-72 hours according to weight gain or loss (Taylor et al. 2022).

Body condition score (BCS) has been related to survival, and Teng et al. (2018) analysed the BCS records of more than 2600 cats, concluding that a BCS of 6/9 had the highest survival probability. Lifespan decreased when cats had a BCS less than 5/9 or a BCS of 9/9, according to WSAVA’s scale of BCS (Figure 1).

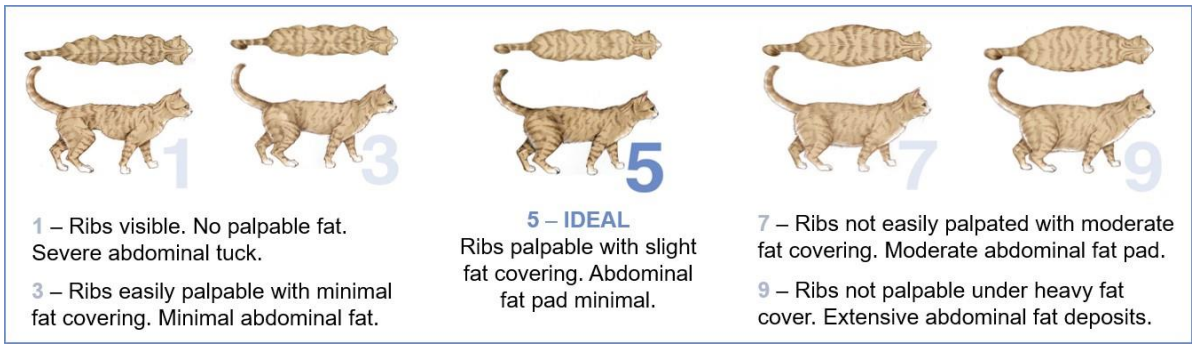


Figure 1 – Cat Body Condition Scoring (Adapted from WSAVA 2017).

Inadequate food intake may have a significant negative impact on the feline patient, and the deleterious effects of anorexia on almost all body systems are well-known. Prolonged inadequate nutrition may be more detrimental to the patient than the primary disease (Agnew and Korman 2014); for instance, hepatic lipidosis can have worse consequences than the inciting disease or event that led to anorexia (Miller 2016). Anorexia is also known to extend illness, delay recovery, slow wound healing, and affect immune and gut health (Taylor et al. 2022). Increased risk of sepsis, altered drug metabolism (Harvey 2015), hepatic dysfunction, and intestinal alterations are also known consequences.

Critical illness induces unique metabolic changes in cats that predispose them to malnutrition and its deleterious effects. An important distinction in the body's response to inadequate nutrition intake occurs in disease or stressed starvation compared with healthy starvation (Michel 2001; Chan et al. 2006). In sick cats undergoing starvation, there is a risk of malnutrition because of what can be described as "stressed" starvation. Initially, when there is insufficient energy intake, endogenous sources become the prime source of energy, and glycogen stores are used as the initial energy source (Saar 2022). Normally, in a healthy animal undergoing starvation, this process shifts to the preferential utilisation of fat stores for energy so that the lean body mass is conserved. However, in the case of sick and anorexic animals, these physiological adaptations do not take place, and there is a preferential loss of muscle tissue even when there are sufficient adipose stores available. This derangement is believed to occur due to changes in the profiles of hormones, metabolites, and cytokines (Gajanayate 2014). There are a few metabolic changes that take place in anorexia (Gajanayake 2014), including low concentrations of circulating insulin and elevated levels of glucose, lactate, cortisol, glucagon, and norepinephrine (Chan et al. 2006) as well as protein-energy malnutrition, increased metabolic rate, protein catabolism, and alterations in fat metabolism (Miller 2016).

The mechanisms underlying decreased food intake are complex and not completely understood (Michel 2001), although, they can be divided into psychological, pathophysiological, the influence of neurotransmitters, hormones, and gastrointestinal factors, drugs (that cause nausea or delayed gastric emptying), and environmental conditions. Psychological reasons include stress, fear, and pain. Pathophysiological conditions include degenerative, anatomic (oropharyngeal diseases and foreign bodies), metabolic, neurologic (for example, alterations in mentation), neoplasia, infection, or inflammation. Taking into account neurotransmitters, serotonin decreases appetite, and gamma-aminobutyric acid (GABA) stimulates the hunger centre or inhibits the satiety centre. Considering hormones, insulin decreases appetite, and cortisol increases appetite (Miller 2016). Environmental and sensory factors like taste, smell, format, etc. of food (Little 2020) may also affect a cat's appetite.

Another way to think about the differential diagnosis of anorexia is to divide it into primary and secondary anorexia. Primary anorexia includes affections such as neurological dysfunction, psychological disorders, or loss of smell. Secondary anorexia includes pain, abdominal organ disorders, toxic agents, endocrine diseases, neoplasia, infectious diseases, etc. We can also include a third group named pseudo-anorexia, which includes problems in the mouth that inhibit the ability to pick up, chew, or swallow food (for example, retrobulbar disease, mandibular paralysis, or disorders of the oral cavity) (Miller 2016).

Some of the more common underlying diseases that lead to anorexia or weight loss could be hyperthyroidism, chronic kidney disease (CKD), chronic enteropathy, neoplasia, pancreatitis, and liver disease (Laflamme 2005; Baez et al. 2007; Pittari et al. 2009). Taylor et al. (2022) present us with a list of common causes of inappetence in cats (Table 1).

Table 1 – Common causes of inappetence in cats (Adapted from Taylor et al. 2022).

- **Pyrexia** (eg, infection or inflammatory disease)
- **Anosmia or reduced sense of smell** (eg, nasal/neurological disease)
- **Gastrointestinal disease** (eg, inflammatory enteropathy, oesophagitis)
- **Pancreatic disease** (eg, acute/chronic pancreatitis, neoplasia)
- **Liver disease** (eg, neutrophilic/lymphocytic cholangitis)
- **Urinary disease** (eg, acute/CKD, ureteral obstruction, FLUTD)
- **Respiratory/cardiac disease** (eg, congestive heart failure)
- **Endocrine disease** (eg, diabetic ketoacidosis, hyperaldosteronism)
- **Neurological disease** (eg, intracranial disease)
- **Orthopaedic disease** (eg, pain due to degenerative joint disease)
- **Immune-mediated disease** (eg, IMHA)
- **Haematological conditions** (eg, anaemia)
- **Neoplasia**
- **Medication effects** (eg, some antibiotics or NSAID's)
- **Food aversion or dietary factors** (eg, food type/texture/smell)
- **Constipation**
- **Dehydration and electrolyte abnormalities** (eg, CKD)
- **Stress and pain**

Legend: FLUTD – Feline Lower Urinary Tract Disease; IMHA – Immune-Mediated Haemolytic Anaemia; NSAID's – Non-Steroidal Anti-Inflammatory Drugs.

In his work, Gajanayake (2014) categorises common diseases that lead to anorexia in cats into groups based on body systems and provides a list of clinical signs associated with each disease.

Table 2 – Common causes of anorexia in cats and possible associated clinical signs (Adapted from Gajanayake 2014).

Body system	Common disease processes	Clinical signs
Oropharyngeal	Dental disease, stomatitis, oral or nasal neoplasia	Dysphagia, salivation, halitosis, nasal discharge, sneezing, stertor
Cardiorespiratory	Pleural effusion, cranial mediastinal mass, airway disease, congestive heart failure	Lethargy, dyspnoea, tachypnoea, orthopnoea, coughing, retching, syncope
Gastrointestinal	Chronic enteropathy, gastrointestinal neoplasia, pancreatitis	Weight loss, diarrhoea, vomiting, salivation
Hepatobiliary	Cholangitis/cholangiohepatitis	Lethargy, vomiting, weight loss, jaundice
Renal	Acute renal failure, CKD	Polydipsia, polyuria, weight loss, salivation
Neurological	Inflammatory CNS disease, neoplasia	Obtundation, seizures, ataxia
Systemic	Lymphoma, FIP, FIV, FeLV	Lethargy, weight loss

Legend: CNS – Central Nervous System; FeLV – Feline Leukaemia Virus; FIP – Feline Infectious Peritonitis; FIV – Feline Immunodeficiency Virus.

2.1.1. Medical approach to inappetence

Medical approach to anorexia in cats is multimodal. This approach needs a systematic, step-by-step investigation to identify and address the causes of anorexia. The primary objectives are to diagnose and treat the underlying diseases while simultaneously restoring proper nutrition (Agnew and Korman 2014). Gajanayake (2014) underscores the importance of accurately pinpointing the underlying cause of anorexia and applying tailored management techniques accordingly.

The clinical approach to the anorexic cat starts with a detailed medical history. A complete anamnesis and description of clinical signs can give important clues to make the correct diagnosis (Miller 2016). Likewise, the importance of a thorough physical exam cannot be underestimated. Disorders of the mouth (pseudo-anorexia) can often be ruled in or out on the basis of a physical exam. Additionally, it may aid in the identification of secondary causes of anorexia, such as abdominal masses.

Diagnostic tests should be carried out to support the historical and examination findings rather than be performed instead of these (Gajanayake 2014). A complete blood count (CBC), chemistry panel, and urinalysis will allow the clinician to evaluate systemic diseases. Liver disease, renal failure, and diabetes are just a few of the causes of anorexia that can be evaluated with bloodwork. Radiography, ultrasonography, exploratory surgery, endoscopy, CT-scanning, or magnetic resonance imaging (MRI) are other diagnostic modalities that should be considered when appropriate (Miller 2016). Close monitoring of BW, BCS, liver enzymes, and total bilirubin is also really important in the management of anorexic cats, since these cats are at risk of developing hepatic lipidosis (Miller 2016).

To manage anorexia in cats, reduction of stress, medication (such as antiemetics or appetite stimulants), and assisted nutrition in the form of tube feeding or parenteral nutrition are crucial but must be assessed on a case-by-case basis. Basic supportive care may be required for inappetent cats and can include hydration, vitamin B12 supplementation, and treatment of fever, pain, or nausea, if present. Dehydration can contribute to anorexia and, if detected, should be early treated (Miller 2016). Clinicians should be mindful of signs of nausea in cats, for example, ptyalism, lip licking, drooling, dropping food from the mouth, and turning away from food (Little 2020; Hill 2019).

Other strategies that can be helpful are encouraging eating (warming the food, small meals, treats, and baby food are often used to tempt cats to eat) and alternative therapies (pheromones, acupuncture, etc.) (Little 2020).

The approach to managing an anorexic cat depends on multiple factors, which encompass the duration of anorexia, the underlying disease and its prognosis, any concurrent illnesses, the necessity for and potential risks associated with sedation or anaesthesia, the

availability of equipment and technical expertise, financial considerations, and the potential need for at-home assisted feeding (Gajanayake 2014).

2.1.1.1. Assisted nutrition

Assisted nutrition should be implemented no later than 3 days after the cessation of eating (Taylor et al. 2022). Nutritional support can be categorised as either enteral (feeding tubes) or parenteral (Miller 2016).

Enteral nutrition involves using feeding tubes to deliver food directly to the gastrointestinal tract. It is advisable to place feeding tubes as soon as possible, instead of waiting until the patient has end-stage disease or is extremely debilitated (Little 2020). The duration of tube usage depends on the specific case. Once the cat is voluntarily eating about 60% of its daily nutritional requirements, tube feeding can be gradually decreased as its appetite improves. The tube should not be removed until the cat is consistently maintaining adequate nutritional intake on its own (Little 2020).

There are different types of tubes that should be chosen based on the clinical situation. Nasoesophageal or nasogastric tubes (small-bore) are easy to place and considered safe for short-term support (3-5 days) (Davidson 2016). Oesophagostomy tubes (large bore) are generally well tolerated (Little 2020) and are typically indicated for short- to mid-term use, specifically one to four weeks (Gajanayake 2014). Their placement requires general anaesthesia, but they can be managed by caregivers at home. Gastrostomy tubes (large-bore) are generally reserved for cases where oesophagostomy tubes are contraindicated. They are placed surgically or via endoscopy and are appropriate for long-term use (Gajanayake 2014). These tubes cannot be removed within 10–14 days (Taylor et al. 2022). Jejunostomy or nasojejunal tubes (small-bore) bypass the stomach and duodenum and are less common and only used for specific cases (Taylor et al. 2022).

Parenteral nutrition involves the administration of essential nutrients via intravenous infusion and can be used as an alternative in patients unable to tolerate enteral feeding; for example, those with intractable vomiting and diarrhoea, a lack of gag reflex, presenting a high anaesthetic risk, coagulopathy, or recovering from severe gastric or intestinal disease. Parenteral nutrition may be associated with a higher rate of complications than tube feeding (Perea 2012), detailing: infection from the catheter site and villous atrophy of the small intestine, which may increase the risk of bacterial translocation and sepsis. Moreover, it tends to be more expensive and less widely available (Elliott 2004). Therefore, enteral feeding is preferred whenever possible, as it helps maintaining gastrointestinal health and is safe, convenient, and cost-effective (Taylor et al. 2022).

2.1.1.2. Appetite stimulants

Pharmacological appetite stimulation can be useful in some circumstances and is generally effective at increasing food consumption, but it should never take the place of monitoring and ensuring adequate caloric intake. It is important to note that these drugs do not work reliably in every patient and might not be suitable in some situations, such as patients who are critically ill or severely malnourished (Agnew and Korman 2014) or for whom a diagnostic effort is not being made (Reinhart 2019). Some conditions, like dehydration, anaemia, nausea, pain, fever, etc., can affect appetite and should be addressed. Appetite stimulants must only be used in inappetent hospitalised cats when nausea, pain, and stress are being managed (Taylor et al. 2022).

Historically, several drugs have been used for appetite stimulation, including cyproheptadine, an antihistamine and anti-serotonergic drug with anecdotal efficacy at the dosage of 1–4 mg/cat q12–24h (Agnew and Korman 2014). However, currently, only two drugs are approved for use in cats: capromorelin (Elura®; Elanco, available in the USA) and mirtazapine (Mirataz®; Dechra, available in the USA, Canada, and Europe). Other substances thought to stimulate appetite, such as steroids (anabolic or corticosteroids), megestrol acetate, propofol, diazepam, and B vitamins, have not been assessed for efficacy or are associated with significant adverse effects that likely outweigh their potential benefits (Taylor et al. 2022).

Capromorelin, approved by the United States Food and Drug Administration (FDA), is a ghrelin receptor agonist and thus acts directly as an orexigenic compound, stimulating appetite in a similar way as ghrelin while also acting to stimulate growth hormone and insulin-like growth factor-1 (Zollers et al. 2016). A clinical trial performed in 112 cats with CKD (71 capromorelin, 41 placebo) with >5% unintended weight loss demonstrated that 2 mg/kg PO q24h for 56 days resulted in significant weight gain (FOI Elura® 2020). The most common adverse effects were vomiting, hypersalivation, and lethargy (Wofford et al. 2017; FOI Elura® 2020). Use in cats with acromegaly is contraindicated, and caution should be exercised in patients with diabetes as hyperglycaemia has been documented (Pires et al. 2020). Transient bradycardia and hypotension have also been reported in feline patients. Therefore, it is advisable to avoid using this medication in patients with significant systemic compromise, making it unlikely to be suitable for hospitalised patients (FOI Elura® 2020).

Mirtazapine, in its transdermal ointment form, is approved by both the European Medicines Agency (EMA) and the FDA. It is used as an appetite stimulant and weight-gain drug, and for the management of nausea, vomiting, and anorexia in cats. Additionally, in humans, it exhibits antidepressant and anxiolytic properties.

In conclusion, appetite stimulants are a helpful addition to the veterinarian's toolkit for the management of inappetent cats, although they must be administered properly and only

after nausea, pain, and stress have been managed. The efficacy of appetite stimulants must be monitored closely in hospitalised patients to avoid underfeeding or a delay in the implementation of more direct and reliable forms of nutritional support, such as feeding tubes (Taylor et al. 2022).

2.2. Mirtazapine

Mirtazapine is a benzazepine, tetracyclic, noradrenergic, and specific serotonergic antidepressant. In humans, it was originally developed for the treatment of moderate to severe depression. Moreover, in advanced cancer-related cachexia, mirtazapine increases appetite and demonstrates anti-nausea effects (Kast and Foley 2007).

In veterinary medicine, mirtazapine is mostly used as an appetite stimulant, making it a valuable tool for addressing anorexia in animals. Furthermore, mirtazapine may possess antiemetic and anti-nauseant properties. Giorgi and Owen (2012) have suggested that mirtazapine may be useful in the management of chronic and cancer-related pain, as well as anxiety-related conditions in cats. These potential applications in pain and anxiety are attributed to its impact on both the noradrenergic and serotonergic systems, but it is important to note that further research is necessary before considering its clinical implementation in these specific cases.

A medication that addresses all these positive effects has the potential to become important in the treatment of many medical conditions. Mirtazapine is commonly recommended for hospitalised cats, who are often at risk of anorexia due to stress and underlying diseases. Additionally, it is useful in the management of chronic diseases that diminish appetite, such as CKD, chronic enteropathy or neoplasia. Commonly, the hospitalised patients are sent home with appetite stimulant therapy to ease the transition to the home environment and promote caloric intake during the recovery period (Taylor et al. 2022).

In veterinary medicine, mirtazapine is available as a transdermal ointment for cats known as Mirataz®, that will be further discussed.

2.2.1. Transdermal mirtazapine

This topical medication received approval in 2019 from the EMA and the FDA, being the first and only transdermal medication designed for the management of weight loss in cats.

While not approved by the EMA and FDA for veterinary use, human and compounded versions of mirtazapine have been used off-label in cats. However, this practice may not be optimal due to challenges associated with splitting or breaking human tablets, leading to potential inaccuracies in dosing. Studies, such as one conducted by Fergunson et al. (2016), have indicated that this approach can result in accidental overdose and toxicity. Furthermore,

the safety of humans handling cut or broken pills remains uncertain, as does the uniform distribution of the drug in the pill fragments.

Transdermal drug administration is a very appealing strategy and has some advantages: elimination of first-pass hepatic metabolism, stable delivery and blood levels, better compliance by owners, decreased systemic drug interactions, avoidance of medically assisted drug administration, shorter drug administration times, and overall improved therapeutic efficacy (Murthy 2012).

A study by Mirataz® Pricing Research in 2017 (Mirataz® - veterinary detailer 2020), which involved 204 small animal veterinarians, concluded that 74% of veterinarians considered ease of administration as one of the most important factors when selecting a medication for managing weight loss in cats. Accordingly, Mirataz® can offer veterinarians a safe, effective, and convenient alternative when prescribing appetite stimulants.

This area is suitable for transdermal administration because it is non-hairy, highly vascularized, and cannot be easily licked or rubbed, thereby allowing for good absorption of mirtazapine through the skin (Buhles et al. 2018; Hill 2019).

In the Mirataz® Summary of Product Characteristics (2020), the recommended dose for cats is 2 mg of mirtazapine per cat (0.1g of ointment per cat, equivalent to a 3.8 cm line, as illustrated in Figure 2), administered once a day for 14 consecutive days. The product is used daily, with the application alternating between the ears each day, for example, the right ear one day and the left ear the next day. Owners should exercise caution during application, wearing gloves, washing their hands afterward, and avoiding direct contact with the cat for 2 hours after applying the product to ensure complete absorption through the skin and prevent unintentional exposure. The safety of this product has not been tested in cats under 2 kg BW, kittens under six months old, or pregnant or lactating females.

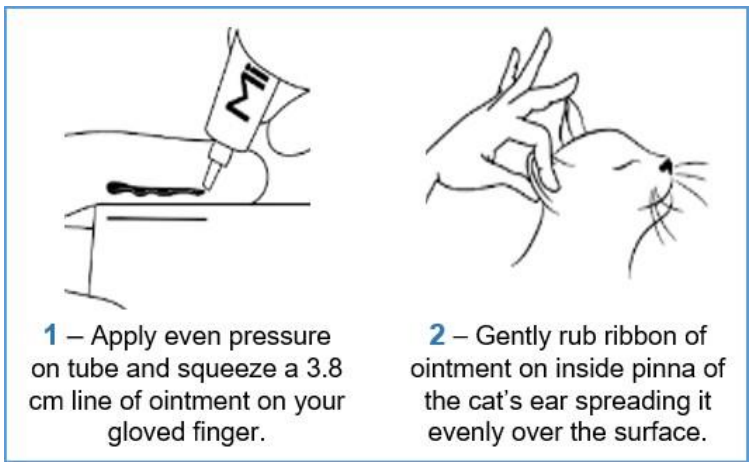


Figure 2 – Representation of the correct way of applying Mirataz® (Adapted from Mirataz® - Summary of Product Characteristics 2020).

2.2.2. Pharmacokinetics

In humans, when given orally, the absorption of mirtazapine from the gastrointestinal system is rapid and complete, with peak plasma concentrations reaching within 2 hours. Mirtazapine binds non-specifically and reversibly to plasma proteins (85%). The absolute bioavailability is approximately 50%, and its absorption is not affected by food. The half-life is long and variable, between 20 and 40 hours, and the steady state is reached in 4 to 6 days (Timmer et al. 2000, Daves et al. 2001). The pharmacokinetics of mirtazapine are dependent on gender and age: females and elderly people show higher plasma concentrations than males and young adults (Timmer et al. 2000).

Delbressine et al. (1998) studied the biotransformation of mirtazapine in humans and found out that the major pathways were demethylation and oxidation, mainly mediated by the Cytochrome P450 (CYP)'s CYP2D6 and CYP3A4 isoenzymes, followed by conjugation.

Quimby et al. (2010) studied mirtazapine's pharmacokinetics after oral administration in healthy young cats and concluded that the mean half-life of mirtazapine is 10.3 ± 2.3 hours after a low dose (1.88 mg per cat) and 15.3 ± 4.7 hours after a high dose (3.75 mg per cat). When a 1.88 mg dose was given daily to these cats, no significant drug accumulation occurred. Mirtazapine's pharmacokinetics in cats are not linear, and with higher doses, the metabolism seems to slow down, presumably as a result of overburned enzyme systems.

Multiple studies have demonstrated that mirtazapine is suitable for transdermal administration. Before Mirataz® was officially authorised (2019), several studies investigated compounded versions of transdermal mirtazapine (CTM). Transdermal mirtazapine achieves therapeutic serum concentrations, resulting in appetite stimulation, weight gain, and improvement in body condition score in cats (Quimby et al. 2020; Buhles et al. 2018; Benson et al. 2017; Poole et al. 2018). Single and repeat topical doses of CTM achieve measurable plasma concentrations in cats (Buhles et al. 2018). Transdermal mirtazapine exhibits certain pharmacokinetics differences compared to oral pills in cats. In a crossover study involving the administration of the product at 0.5 mg/kg to eight cats to determine the relative bioavailability of oral and transdermal mirtazapine administration (MedVet RCM Mirataz®), the mean terminal half-life was significantly longer with topical administration (25.6 ± 5.5 hours) compared to oral administration (8.63 ± 3.9 hours). Additionally, transdermal mirtazapine demonstrates a lower maximum concentration (Cmax), a reduced AUC (area under the curve), and an extended Tmax (time to reach maximum concentration). Topical administration, characterised by a flatter drug concentration curve and lower peak serum concentrations, results in a more subdued appetite effect in some patients compared to oral mirtazapine. This characteristic also contributes to fewer adverse effects when administered transdermally (Buhles et al. 2018; Benson et al. 2017).

In hospitalised patients, perfusion status and body temperature should be taken into account when determining whether transdermal mirtazapine is appropriate, as poor peripheral perfusion may have an unknown effect on absorption (Taylor et al. 2022).

Mirtazapine elimination is dependent on both hepatic metabolism and renal clearance. Thus, when liver or renal failure is present, dose reductions may be necessary (Anttila and Leìnonen 2001; Daves et al. 2001).

In humans, liver diasease delays the clearance of oral mirtazapine because of its hepatic metabolism (Verbeeck 2008). A study by Fitzpatrick et al. (2018) demonstrated similar results in cats with liver diasease (alanine aminotransferase [ALT] >200 IU/l or total bilirubin >1 mg/dl), in which the half-life (13.8 hours) is significantly (p<0,002) prolonged compared to age-matched controls (7.4 hours); these facts can be explained due to reduced hepatic metabolism in these cases. Tmax is also longer in cats with liver diasease, probably due to poor intestinal perfusion and reduced absorption in these animals. This study also demonstrates a positive correlation between mirtazapine half-life, alkaline phosphatase, ALT, and total bilirubin concentrations. Nevertheless, the alterations in metabolism appear to be variable, making it difficult to predict which cats would be most affected.

In a study by Quimby et al. (2011), mirtazapine's blood concentrations were compared in 2 groups - 6 cats with CKD vs 6 age-matched controls - after administration of a single PO dose of 1.88 mg of mirtazapine. The mean half-life of mirtazapine in cats with CKD (15.2 ± 4.2 hours) was prolonged compared with age-matched controls (12.1 ± 1.1 hours). There were statistically significant differences in AUC (p=0.01) and in clearance/bioavailability (p=0.04) between groups, concluding that CKD may delay the clearance/bioavailability of mirtazapine. In healthy young cats with no pre-existing liver or kidney disease, daily administration of oral mirtazapine is feasible due to its short half-life. However, in cats with CKD, it is widely recommended a 1.88 mg dose of oral mirtazapine every 48 hours.

In summary, underlying diseases and medical status should be taken into account when prescribing mirtazapine. Nowadays, there is no information that indicates that oral mirtazapine is contraindicated in liver disease or CKD, but the dose and dosing interval should be carefully considered for each patient. Considering transdermal mirtazapine, a study by Poole et al. (2018) concluded cats with CKD experienced similar therapeutic efficacy without an increase in behavioural side effects (vocalisation, hyperexcitability). Therefore, for most patients with CKD or liver disease, daily dosing of transdermal mirtazapine appears appropriate.

2.2.3. Pharmacodynamics

2.2.3.1. Mechanism of action

Mirtazapine's mechanism of action is complex. Centrally, mirtazapine blocks presynaptic alpha-2-adrenergic on both noradrenergic and serotonergic neurons, thus facilitating the release of norepinephrine (NE) and serotonin (5-HT) into the synapse. Additionally, it directly blocks postsynaptic serotonergic receptors type two and three (5-HT2 and 5-HT3). The net effect is that only serotonergic receptor type one (5-HT1) is stimulated, which is the primary antidepressant mechanism of this drug (Davis and Wilde 1996; Timmer et al. 1997; Delbessine et al. 1998; Gordman 1999; Anttila and Leìnonen 2001). Mirtazapine has no effect on monoamine reuptake (Boer 1995). In addition, mirtazapine is a potent inhibitor of histamine H1 receptors (Kast and Foley 2007).

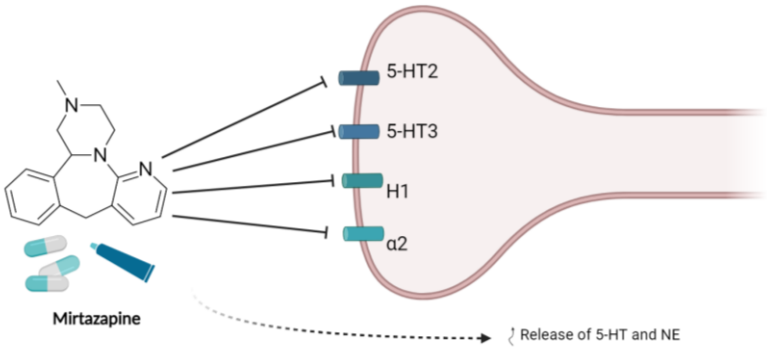


Figure 3 – Representation of the mechanism of action of mirtazapine. Legend: Mirtazapine is an antagonist of 5-HT2A, 5-HT2C, 5-HT3, H1, and α2 receptors. Created with BioRender.

Antagonism of presynaptic α-2 receptors, serotonin receptors (5-HT2A, 5-HT2C, and 5-HT3), and H1 receptors by mirtazapine has been demonstrated to result in an orexigenic effect via interaction with nuclei within the hypothalamus (Riechelmann et al. 2010). The mechanism of action by which mirtazapine stimulates appetite is not fully described, but it is probably due to suppression of 5-HT2 and H1. The receptor 5-HT2 is known for its appetite inhibition activity (Bickerdike 2003; Miller 2005). H1 receptors regulate energy metabolism, and H1-antagonists cause an increase in food intake (Masaki and Yoshimatsu 2007).

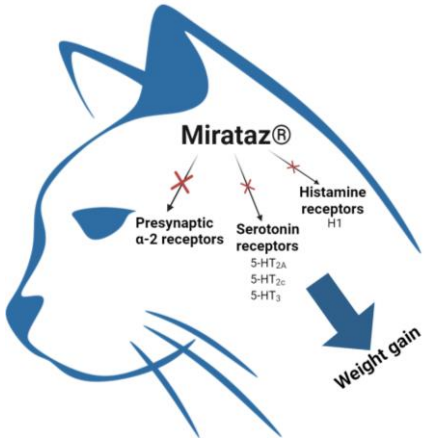


Figure 4 – Mechanism of action of Mirataz® (Adapted from Mirataz® - mechanism of action 2020. Created with BioRender).

The weight gain induced by mirtazapine may result from alterations in leptin and tumour necrosis factor (TNF) (MedVet RCM Mirataz®). Leptin, a hormone released by adipose tissue, plays a crucial role in signalling the body's energy status and regulating appetite, neuroendocrine function, and overall energy homeostasis (Grinspoon et al. 1996). Studies have shown that blocking H1 receptors can reduce the response to leptin in rats (Morimoto et al. 1999). In humans, Schilling et al. (2013) found that treatment with mirtazapine is associated with increased leptin secretion. However, despite higher leptin levels, people usually tend to gain weight, indicating the presence of leptin resistance. This resistance may be mediated by mirtazapine's anti-histaminergic effect on hypothalamic nuclei that integrate signals relevant to energy balance.

Mirtazapine also exhibits antiemetic effects in humans and cats. This is likely a result of antagonism of the 5-HT3 receptor, which plays a significant role in the physiology of emesis (Kast and Foley 2007; Quimby and Lunn 2013). The 5-HT3 receptor antagonists inhibit serotonin from binding to these receptors, reducing nausea and vomiting. The solitary tract nucleus and the chemoreceptor trigger zone (CTZ) of the CNS have the highest concentration of 5-HT3 receptors, and it is thought that 5-HT3 receptor antagonists act in both areas (Smith et al. 2012).

Because of mirtazapine’s complex actions on neurotransmitter physiology, specific care should be taken to avoid potential drug interactions. Mirtazapine should not be combined with other drugs that either directly or indirectly affect serotoninergic systems, including monoamine oxidase inhibitors, tricyclic antidepressants, and selective serotonin reuptake inhibitors. Examples of such drugs commonly used in veterinary medicine include fluoxetine, selegiline, tramadol, and amitriptyline. Combining mirtazapine with these medications may increase the risk of serotonin syndrome (Reinhart 2019).

2.2.3.2. Therapeutic efficacy

Several studies have demonstrated mirtazapine's efficacy (Quimby et al. 2010; Quimby et al. 2011; Quimby and Lunn 2013, Benson et al. 2017; Poole et al. 2018; Quimby et al. 2019).

The appetite-stimulating effect of oral mirtazapine was demonstrated by Quimby et al. (2010) in a blinded trial showing that cats receiving oral mirtazapine at 1.88 mg q24h and 3.75 mg q24h ingested significantly more food than did cats given a placebo. The amount of food ingested did not differ between the dose groups. On the basis of this research, 1.88 mg is recommended as the initial starting dose for oral mirtazapine and can be given daily to young healthy cats.

In cats with CKD, oral mirtazapine has shown a significant increase in weight, appetite, and rate of food consumption, as well as a decrease in vomiting (Quimby and Lunn 2013). Consequently, mirtazapine is an effective appetite stimulant and anti-emetic for cats with CKD that could be a useful adjunct to their therapeutic role (Quimby et al. 2011; Quimby and Lunn 2013).

A study by Benson et al. (2017) measured drug exposure and clinical effects after administration of CTM in healthy cats and concluded CTM achieved clinically appropriate serum concentrations in young healthy cats without the need for higher doses. Transdermal mirtazapine proved successful in increasing appetite and the rate of food ingestion when compared to placebo gel.

Quimby et al. (2019) studied CTM appetite stimulation properties in cats with CKD. Two different doses were studied: 3.75 mg and 1.88 mg. Both doses of CTM resulted in a statistically significant increase in weight, an increase in appetite, and an increase in the rate of food consumption. Improvement in body condition score was seen in five of the nine cats (5/9) in the 3.75 mg dose and six of the ten cats (6/10) in the 1.88 mg dose.

Poole et al. (2018) studied the effect of Mirataz® in a double-blind, randomised, and placebo-controlled study. Cats with greater than 5% unintended weight loss were included and were treated once daily with either 2 mg/cat mirtazapine ointment (n=83) or placebo ointment (n=94) for 14 days. They concluded that cats on mirtazapine gained significantly more weight compared with their baseline (3.9% weight gain) than those in the placebo group (0.4% weight gain). Transdermal administration appeared well tolerated locally and systemically, and daily topical application of Mirataz® effectively increased body weight in cats experiencing unintended weight loss associated with various underlying diseases.

2.2.3.3. Side effects

Mirtazapine is generally well tolerated, but side effects can occur. In humans, the most commonly reported side effects include somnolence, dry mouth, increased appetite, and

weight gain (Ware 2022). Mirtazapine can also lead to signs of serotonin toxicity, sometimes referred to as serotonin syndrome (Ubogu and Katirji 2003). These signs range from very mild signs (nausea, low-grade fever, tachycardia, diarrhoea, and agitation) to life-threatening conditions (extreme hyperthermia and rigidity) (Kast and Foley 2007).

In cats, the most common side effects associated with mirtazapine use are vocalisation, agitation, vomiting, incoordination while walking, restlessness, muscle tremors, increased salivation, and sleepiness. Depending on the severity, these signs may indicate serotonin syndrome and suggest the need for dose reduction (Fergunson et al. 2016). Taylor et al. (2022) suggest a 50% dose decrease when behavioural side effects are observed.

Adverse effects associated with oral mirtazapine administration in cats are not extensively documented, but a few studies have been conducted. Quimby et al. (2010) investigated the effects of two different doses of oral mirtazapine in healthy young cats - 1.88 mg q24h and 3.75 mg q24h -, and observed significantly more side effects (increased vocalisation, activity, and socialisation) with the higher dose. Ferguson (2016) reported the most common adverse effects in 84 cats exposed to oral mirtazapine. Among these cases, 59 (70.2%) were considered accidental ingestions, while 25 (29.8%) were given mirtazapine as prescribed. The ten most common side effects reported included vocalisation (observed in 56% of cats), agitation (31%), vomiting (26.2%), abnormal gait/ataxia (16.7%), restlessness (14.3%), tremors/trembling (14.3%), hypersalivation (13%), tachypnea (11.9%), tachycardia (10.7%), and lethargy (10.7%). The doses associated with signs of toxicity were 15.00 mg (40 cats), 3.75 mg (25 cats), 7.50 mg (4 cats), 30.00 mg (one cat), 18.75 mg (1 cat), 11.25 mg (1 cat), 5.80 mg (1 cat) and 1.88 mg (1 cat). A greater number of adverse effects were reported at the dose of 3.75 mg rather than 1.88 mg, which, as Quimby et al. (2010) suggested, makes the latter a more appropriate starting dose for stimulating appetite while limiting toxicity. Brooks (2007) reported that mirtazapine, in rare cases, can lead to abnormalities in blood cell lines developing in the bone marrow. In rare instances, hypersensitivity reactions may occur and manifest as breathing difficulties, hives, or swelling of the lips, tongue, or face (Ware 2022).

The side effects associated with transdermal administration are similar to those observed with oral mirtazapine. However, local reactions, such as erythema, dryness, or pruritus at the site of application, may occur (Reinhart 2019).

Mirataz® contains macrogol 3350 as an excipient (Mirataz® Summary of Product Characteristics (2020)). This excipient, also known as polyethylene glycol (PEG) 3350, has been identified as a potential allergen, as highlighted by Stone et al. (2018). High-molecular-weight PEGs, including PEG 3350, are commonly found in various medications, household products, and industrial items, and they may serve as a vehicle for sensitisation in susceptible individuals. It's essential for allergists to be aware of the possibility of immediate hypersensitivity reactions to these substances.

The product information of Mirataz® (MedVet RCM Mirataz®) indicates local application reactions (erythema, scabs, dryness, peeling, and itching) and behavioural changes (increased vocalisation, hyperactivity/agitation, disorientation, lethargy, and aggressiveness) occurred very frequently in both safety and clinical studies. Cases of vomiting, polyuria associated with reduced urine specific gravity, elevated blood urea levels (BUN), and dehydration were frequently observed in safety and clinical studies. Depending on the severity of vomiting, dehydration, or behavioural changes, the administration of Mirataz® may be interrupted according to the benefit-risk assessment conducted by the veterinarian. These side effects, including local reactions, were resolved at the end of the treatment period without any specific treatment.

Some studies have assessed the side effects of the compounded transdermal mirtazapine. In a study by Benson et al. (2017), drug exposure and clinical effects after administration of CTM in healthy cats were measured. The authors concluded that CTM increased activity, begging, and vocalisation at home. Moreover, in a study by Quimby et al. (2019) evaluating two different doses of CTM in cats with CKD - 3.75 mg and 1.88 mg-, no significant difference between the two doses was observed in terms of activity or vocalisation. However, individual cats experienced excessive meowing. Brooks (2007) reported that hyperactivity was observed in 11% of cats using Mirataz®, along with increased affectionate behaviour and vocalisation.

The Mirataz® Summary of Product Characteristics (2020) includes a field study by Poole et al. (2018) that examined the effect of Mirataz® in a double-blind, randomised, and placebo-controlled trial. The most commonly reported adverse effect were mild erythema at the application site, noted in 17.4% of placebo-treated cats and 10.4% of cats treated with mirtazapine. A comparison of adverse reactions between a group treated with Mirataz® (n=115) and a control group treated with a placebo ointment (n=115) is provided in Annexe 1. The most frequent adverse reactions included application site reactions, behavioural abnormalities (such as vocalisation and hyperactivity), and vomiting. Behavioural disorders were more prevalent in the Mirataz® group, with vocalisation being the most common (11.3% in the Mirataz® group).

3. OWNERS' PRESPECTIVE ABOUT THE USE OF MIRTAZAPINE TRANSDERMAL OINTMENT IN CATS – A SURVEY-BASED STUDY

3.1. Introduction

Topical products offer several advantages, including ease of application and reduced systemic side effects (Murthy 2012). However, the success of these treatments heavily relies on owner compliance. As far as we know, there have been no studies investigating and analyzing the perspectives of owners who have administered Mirataz® to their cats. Therefore, this study aims to bridge this critical gap by assisting veterinarians in better understanding owner experiences and optimizing treatment outcomes.

3.2. Objectives

This survey-based study aims to evaluate cat owners' perspectives on the use of transdermal mirtazapine, as there are currently no studies in this particular field. The primary objective of this research is to investigate and analyse the feedback from cat owners regarding the use of transdermal mirtazapine ointment (Mirataz®). This includes assessing the ease of application and correct application (applying daily it to alternating ears and adhering to the recommended treatment duration). The secondary objectives are to explore common prescription patterns, common side effects reported, whether owners prefer it over mirtazapine pills for human use, assess if they found transdermal mirtazapine effective in stimulating appetite, and evaluate the time until efficacy.

3.3. Materials and methods

3.3.1. Survey development and distribution

A cross-sectional survey-based study was conducted online using the electronic platform Google Forms®. The questionnaire, consisting of 15 questions (13 multiple-choice and 2 free-opened), was distributed in two countries, Portugal and Italy, with translations provided in Portuguese and Italian respectively (Annexes 2 and 3). The survey development process involved careful consideration of the questions to ensure comprehensive coverage of various aspects of Mirataz®'s use, including its efficacy, side effects, and overall perception.

Electronic medical records of two veterinary teaching hospitals, Hospital Escolar Veterinário from FMV-ULisboa and University Veterinary Teaching Hospital of Padova, were searched for cats in which mirtazapine ointment was prescribed during the period from March 2021 to January 2023.

The questionnaire was distributed through the mailing list of the two hospitals involved between February and March 2023, and owners were contacted by email and/or telephone

calls to encourage participation. Participation in the survey was entirely voluntary, with no incentives offered. Prior to engaging in data collection, each respondent had the option to agree or disagree with the following affirmation: "My participation in this survey is free and voluntary. I authorise the data to be used exclusively for statistical purposes, and my identity will not be disclosed".

The Summary of Product Characteristics (MedVet RCM Mirataz®) recommends a treatment duration of 14 days. For statistical analysis, we categorised responses into two groups: less than 14 days ('<14 days') and 14 or more days ('≥ 14 days'). The group '<14 days' included owners who applied only once, less than once a week, a week, and owners who admitted applying only when necessary. The group '≥14 days' includes owners who administered it for 2 weeks, 3 weeks, 1 month, more than 1 month, and continuously.

The 'reasons for the prescription of Mirataz®' were obtained using a comprehensive database with the patient's medical history and/or a free-opened question where owners recalled the grounds for the prescription. The reason 'liver disease' encompasses hepatobiliary diseases such as triaditis, cholangitis, cholecystitis, acute hepatitis, and chronic hepatitis.

3.3.2. Data processing and statistical analysis

All data were collected using Google Forms® and imported into a Microsoft Excel® 2016 database. Descriptive statistics were generated in Microsoft Excel® 2016 to summarise the data. Statistical analysis was conducted using IBM SPSS® Statistics for Windows, version 28.0.1.0, with a significance level set at $p<0.05$ for a 95% confidence interval in all tests.

For the statistical analysis, when appropriate, tests such as Chi-square and Fisher's Exact test were used to evaluate owner's responses and identify potential correlations between variables. Examined relationships included efficacy versus alternating ears, efficacy versus treatment duration, efficacy versus reason for prescription, side effects versus alternating ears, side effects versus treatment duration, and side effects versus reason for prescription. Additionally, odds ratios were calculated to investigate the relationship between efficacy and treatment duration, which was the only one demonstrating statistical significance ($p<0.05$).

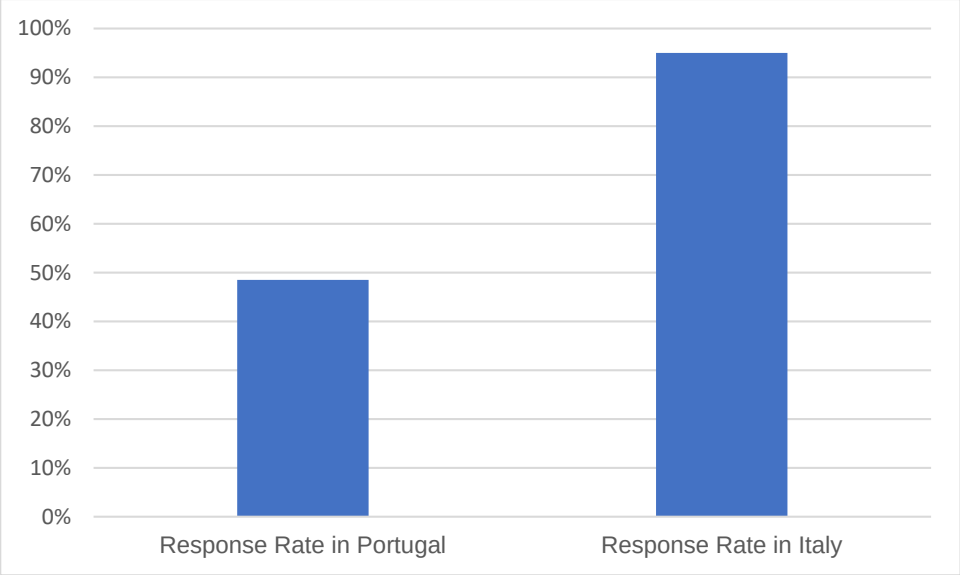
Several variables were excluded from statistical relationship analysis due to their distinct characteristics. The variable 'time until efficacy' was not included because of its wide range of responses, presenting substantial diversity and subjectivity that precluded meaningful statistical analysis. Similarly, the variables assessing the 'ease of application,' 'current use of Mirataz®,' and 'comparison between mirtazapine pills and ointment' were excluded from statistical analysis as they were considered independent variables.

3.4. Results

From the HEV-FMV mailing list, 68 owners were contacted by email, and 33 answers were obtained. From Padova Hospital, 40 owners were contacted by email and telephone call, and 38 answers were obtained. In total, the survey was distributed to 108 owners, and 71 answers were obtained.

3.4.1. Rate of replies

Out of the 108 contacted owners (68 Portuguese and 40 Italians), 71 responses were received, resulting in an overall response rate of 65.7% (71/108). In Portugal, the response rate was 48.5% (33/68), while in Italy, it was significantly higher ($p<0.001$) at 95% (38/40) (Graph 2 and Annexe 7).



Graph 2 – Response Rates (%) of Portugal and Italy (n=108).

The first question in the questionnaire addresses the owner's recall of using Mirataz®, with one respondent indicating he did not remember using the ointment. For the purpose of statistical analysis, we included the 70 responses from owners who confirmed their use of Mirataz®.

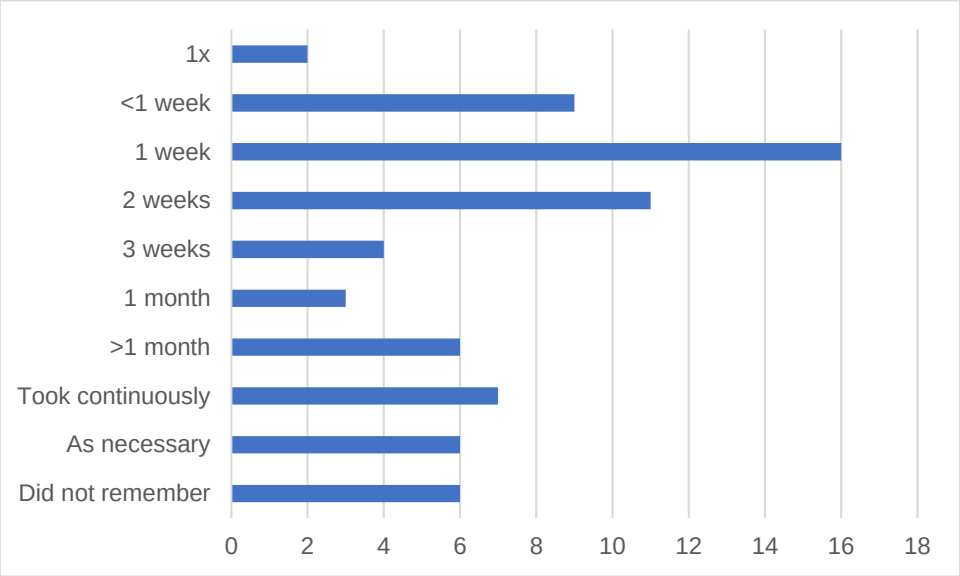
3.4.2. Application

The topical application on the inner ear was found easy by 68/70 (97.1%) of the respondents. The two owners who found it difficult to apply the ointment mentioned the cat's behaviour (2/2) and ear debris (1/2) as the main causes.

Adhering to the manufacturer's instructions, 64/70 (91.4%) owners confirmed the daily application in alternating ears, contrasting with 6/70 (8.6%), who admitted applying always in the same ear. Among these six owners, one was Italian, and five were Portuguese.

3.4.3. Duration of treatment

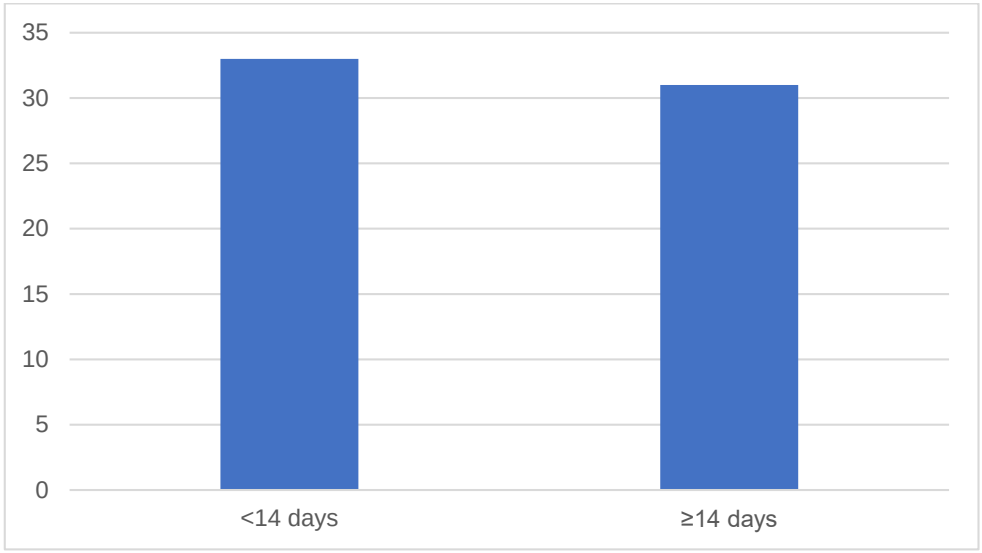
Concerning duration of treatment, responses from cat owners revealed a range of practices (Graph 3). The most frequently selected treatment durations were one week, chosen by 22.9% (16/70) of the participants, and two weeks, selected by 15.7% (11/70) of owners. Notably, a small proportion of owners (9/70) reported applying the transdermal ointment for less than one week. A few respondents (6/70) stated that they did not remember the exact duration of therapy, while another six owners (6/70) admitted to using Mirataz® when it was necessary, particularly when their cats' appetite was reduced. In contrast, seven owners (7/70) mentioned using the ointment continuously for a longer period of time. Furthermore, a range of other treatment durations, such as three weeks, one month, and more than one month, were reported by 4/70, 3/70, and 6/70 owners, respectively. This diverse range of responses underscores the variable nature of treatment duration practices among cat owners.



Graph 3 – Distribution of treatment duration practices among cat owners (n=70).

Graph 4 illustrates the distribution of responses across two groups of treatment duration, excluding owners who did not remember the time of use of Mirataz® (n=64), with

'<14 days' receiving 33 responses (51.6%, 33/64), and '≥14 days' garnering 31 responses (48.4%, 31/64).

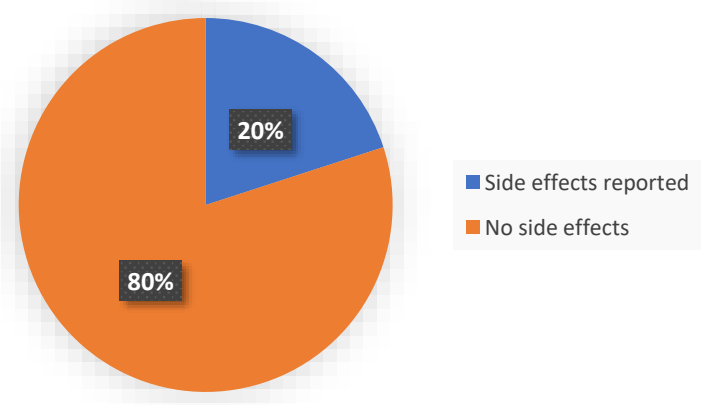


Graph 4 – Distribution of responses by the 2 groups of treatment duration (n=64).

Out of the 70 respondents, ten (10/70) reported currently using Mirataz®, while sixty (60/70) stated they were not.

3.4.4. Side effects

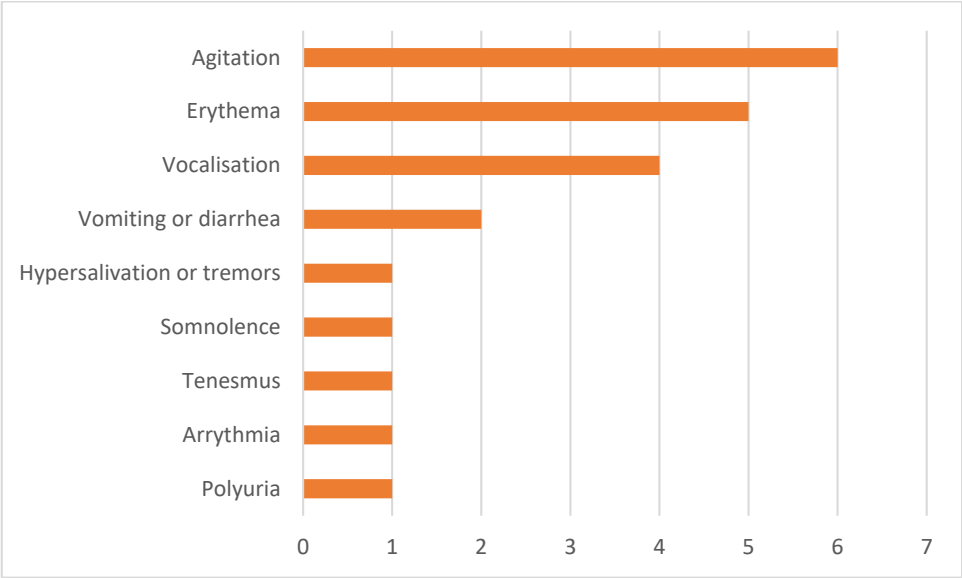
Side effects were reported by 14/70 (20%) owners, and 56/70 (80%) noticed no side effects (Graph 5).



Graph 5 – Percentage of owners reporting side effects (n=70).

The most common reported side effects were agitation (6/14), erythema (5/14), and vocalisation (4/14), followed by vomiting/diarrhoea (2/14). Hypersalivation/tremors, somnolence, tenesmus, arrhythmia, and polyuria were each reported by 1 out of 14 owners.

Each owner could select more than one side effect, resulting in a total of 22 side effects being chosen. Graph 6 details the frequency of reported side effects.



Graph 6 – Frequency of reported side effects (n=22) among cat owners.

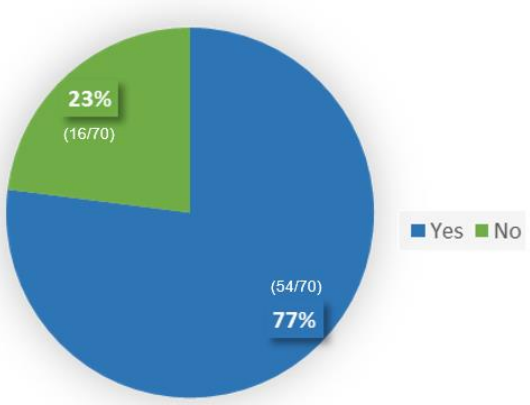
Table 3 illustrates the disparities in the reported percentages of side effects between our study and the data from a study by Poole et al. (2018), included on the Mirataz® Summary of Product Characteristics (2020).

Table 3 – Comparison of side effects reported in our study and in a study by Poole et al. (2018).

	Our results (n=70)	Poole et. al (2018) (n=115)
Agitation/hyperactivity	8.6% (n=6)	7.0% (n=8)
Erythema	7.1% (n=5)	10.4% (n=12)
Vocalisation	5.7% (n=4)	11.3% (n=13)
Vomiting	1.4% (n=1)	11.3% (n=13)

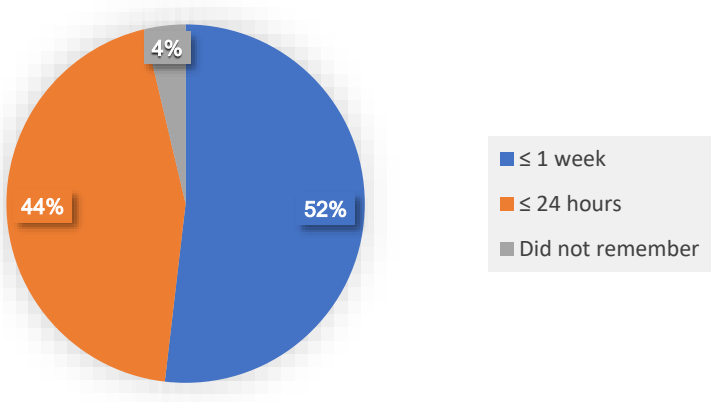
3.4.5. Efficacy

Most of the respondents (54/70; 77%) considered that mirtazapine ointment efficiently stimulates the appetite, while 16 owners (16/70, 23%) did not find Mirataz® effective (Graph 7).



Graph 7 – Perception of Mirataz®'s efficacy among cat owners (%) (n=70).

The 54 owners who considered mirtazapine effective were requested to answer an open-ended question regarding the time it took for the medication to take effect, i.e., they were asked how long it took for them to notice an increase in their cat's appetite after the first ointment application. Most respondents (25/54, 46.3%) reported observing an increase in their cat's appetite within a few days following the first application of Mirataz®. Additionally, a significant proportion (10/54, 18.5%) reported noticing positive effects as early as the first day. Some owners (8/54, 14.8%) reported rapid effects within a few minutes, while a few (6/54, 11.1%) indicated results within a few hours. A smaller number mentioned effects after a week (3 owners), and 2 owners (2/54, 3.7%) could not recall the exact time until efficacy. To facilitate interpretation, the answers 'a few days' and '1 week' were categorised into a group '≤1 week' (28/54, 51.9%). The answers 'a few minutes', 'a few hours', and '1 day' were included in a group '≤ 24 hours' (24/54, 44.4%). Graph 9 displays these proportions.



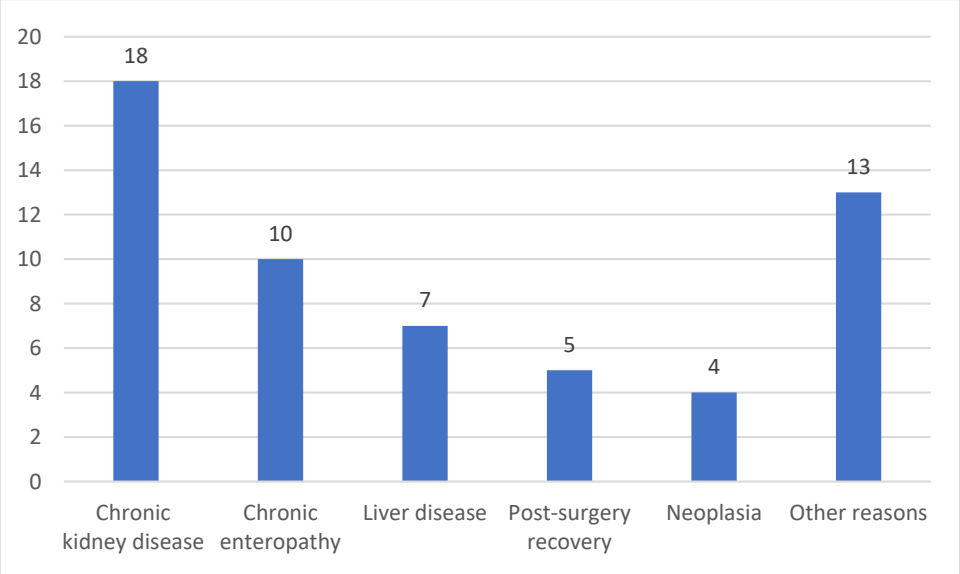
Graph 8 – Distribution of cat owners (%) in groups of time until efficacy (n=54).

3.4.6. Reasons for prescription

Regarding the reasons for prescription, it is crucial to acknowledge the different approaches taken in gathering this information. Concerning responses from Italy, owners were

directly asked to specify the reasons for prescribing Mirataz® in the survey. A total of 38 responses were collected; however, 7 of these were excluded as they cited 'inappetence' as a reason, impairing the right identification of the underlying disease. In contrast, for the Portuguese respondents, the survey did not directly query them about the reasons for the prescription and data was assessed based on the medical information available. Out of 32 Portuguese responses, 26 answers were obtained, as six cats either lacked sufficient historical data in the database or did not have a definitive diagnosis.

Among the 57 answers (31 Italians and 26 Portuguese) about the reasons for prescribing Mirataz®, the most common were CKD (18/57), chronic enteropathy (10/57), liver disease (7/57), post-surgical recovery (5/57) and neoplasia (4/57). Other reasons included chronic pancreatitis (3/57), gastroenteritis (2/57), respiratory diseases (2/57), cystitis (1/57), feline leukaemia virus (FeLV) (1/57), hypercalcemia (1/57), intestinal malformation (1/57), leukocytosis (1/57), and lymphadenopathy (1/57) (Graph 9).



Graph 9 – Distribution of cats by reason for prescription of Mirataz® (n=57).

3.4.7. Comparison with oral mirtazapine

Out of the 70 respondents, 9 owners had previous experience using mirtazapine pills with their cats, while 61 owners had not. Among those who have experience with both formulations of mirtazapine (ointment and pills) 9/70 (13%), 7/9 (78%) found the transdermal ointment more beneficial. This preference was attributed to its easier administration (7/7). Other owners confirmed oral pill administration to their cats is challenging (3/7), and some respondents (2/7) considered transdermal more efficient in stimulating appetite. Conversely, the remaining two respondents (2/9, 22%) preferred oral mirtazapine. They mentioned factors such as low cost (2/2), considering oral mirtazapine to be more effective (1/2), admitting not to adapt to the topical application (1/2), and one owner claimed that topical application required

daily use while oral mirtazapine only needed to be administered every other day (1/2). Table 4 displays this comparison.

Table 4 – Owner's responses: comparison between oral and transdermal mirtazapine (n=9).

Preference	Number of Respondents	Reasons for preference
Transdermal ointment	7	• Easier administration (7/7)
		• Difficulty administering pills (3/7)
		• More efficient (2/7)
Oral pills	2	• Lower cost (2/2)
		• Not adapting to topical application (1/2)
		• Daily vs every other day application (1/2)
		• More efficient (1/2)

3.4.8. Statistical analysis of variable relationships

In the statistical analysis of variable relationships, we examined cat owners' responses to identify potential correlations. The explored relationships included efficacy versus alternating ears, efficacy versus treatment duration, efficacy versus reason for prescription, side effects versus alternating ears, side effects versus treatment duration, and side effects versus reason for prescription (Annexe 7).

For instance, the assessment of efficacy versus alternating ears aimed to elucidate whether the correct application might impact the medication's efficacy, potentially influencing absorption rates. Examining efficacy in relation to the reason for prescription sought to unveil potential variations in treatment outcomes based on underlying diseases, providing valuable insights into Mirataz®'s efficacy across different feline diseases. The exploration of efficacy versus treatment duration aims to investigate whether adhering to the manufacturer-recommended treatment duration of 14 days or more correlates with improved efficacy. Additionally, analysing side effects in relation to reasons for prescription and treatment durations aimed to uncover patterns that could contribute to our understanding of the mirtazapine's safety profile and tolerability in distinct clinical scenarios.

Using statistical tests such as Chi-square or Fisher's test, we observed that, among these relationships, only one demonstrated statistical significance ($p<0.05$)—specifically, the association between efficacy and treatment duration.

3.4.8.1. Erythema vs alternating ears

Data revealed no association between the presence of erythema and not alternating the ear of application ($p=0.370$). Among the five owners who did not alternate the ear of application, only one cat reported experiencing erythema in the ear (Annexe 7).

3.4.8.2. Efficacy vs treatment duration

There was a statistically significant association (p=0.015) between the two groups of treatment duration ('≥14 days' and '<14 days') and efficacy (Table 5 and Annexe 7). This suggests that the observed distribution of treatment duration and efficacy is unlikely to be due to random chance alone, indicating a meaningful relationship between these variables. This finding suggests that the efficacy of the treatment, as measured by efficacy outcomes, is not uniform across different durations of treatment.

Table 5 – Cross-tabulation: Efficacy vs treatment duration (2 groups).

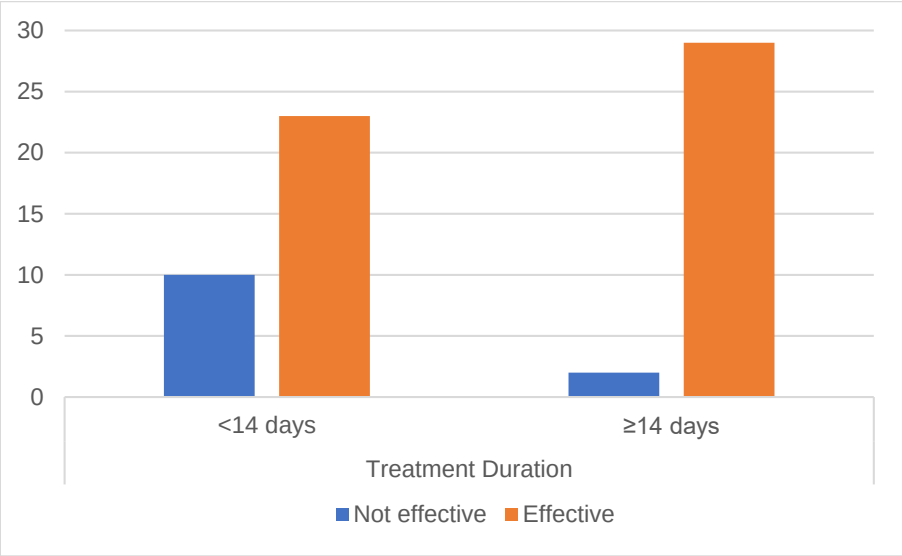
		EFFICACY			
		NO	YES		Total
DURATION	≥14 days	2	29		31
	<14 days	10	23		33
Total		12	52		64

Given the observed association between efficacy and treatment duration, a detailed examination was conducted through odds ratio (OR) analysis (Table 6). The overall odds ratio revealed a statistically significant negative association between treatment duration and the likelihood of achieving efficacy across the entire dataset (OR 0.159, 95% CI: 0.032 to 0.797). However, subgroup analyses indicated different associations. Odds ratio analysis of the '<14 days' group hinted at a statistical significant negative association with durations '<14 days' demonstrating approximately 0.531 times the odds of achieving efficacy compared to the '≥14 days' group (OR 0.531, 95% CI: 0.357 to 0.789). Conversely, in the '≥14 days' group, there was a positive association, suggesting increased efficacy for longer treatment durations. Cats undergoing treatment for '≥14 days' exhibited approximately 3.346 times the odds of achieving efficacy compared to the '<14 days' group. However, this association did not reach statistical significance (OR 3.346, 95% CI: 0.923 to 12.133). These findings suggest that the duration of treatment may influence the likelihood of positive efficacy outcomes, with shorter durations potentially associated with reduced efficacy and longer durations potentially linked to increased efficacy.

Table 6 – Odds ratio: Efficacy vs treatment duration (2 groups).

		Confidence Interval of 95%	
	Value	Inferior	Superior
Odds ratio for EFFICACY (Yes/No)	**,159**	,032	,797
DURATION <14 days	**,531**	,357	,789
DURATION ≥14 days	**3,346**	,923	12,133
N Valid Cases	64		

Analysing Graph 10, the group with a longer treatment duration ('≥14 days') showed a striking 93.5% positive efficacy outcome. In contrast, the group with a shorter treatment duration ('<14 days') demonstrated a slightly lower efficacy rate of 69.7%. These findings align with the odds ratio results, suggesting that a longer treatment duration may be associated with a higher likelihood of positive outcomes, while a shorter duration exhibits a noteworthy but slightly lower efficacy rate.



Graph 10 – Efficacy vs treatment duration (2 groups) (n=64).

3.5. Discussion

This study provides new insights about the owner's perception of the use of transdermal mirtazapine (Mirataz®) in cats.

In this study, a significant difference in response rates ($p<0.001$) was observed between the surveyed countries, Portugal and Italy. This disparity can be attributed to variations in survey distribution methods. While owners in Portugal were exclusively contacted via email, in Italy, low email response rates prompted the inclusion of telephone calls to request survey participation. The dual communication strategy, involving both email and telephone calls in Italy, resulted in a higher response rate. This highlights the potential benefits of such an approach in enhancing survey engagement, with oral communication with owners allowing better understanding of the importance of participating in the survey.

Our study found that owners generally find the ointment easy to apply, highlighting its advantages over traditional pills. Administering oral medications to cats can be challenging due to their susceptibility to stress. Therefore, the simplicity of ointment application not only improves compliance but also reduces feline stress levels during treatment. This emphasises the importance of versatile and stress-minimising treatment options for the well-being of feline

patients. Incorporating a question about whether owners experienced challenges in accurately measuring the prescribed dose (using the 3.8 cm line) would have been an interesting addition to the survey.

The correct application of topical treatments is paramount to their efficacy, especially in cases where owners are responsible for administering the product at home. Our study revealed variations in the way the ointment was applied in the two countries. In Italy, it was noted that only one owner consistently applied the product to the same ear, neglecting the recommended practice of alternating ears (applying it to the right ear on one day and the left on the next). Similarly, in Portugal, five owners applied the ointment always in the same ear. These findings emphasise the critical role of veterinarians in clearly communicating product details and proper application techniques to cat owners. Enhancing communication between veterinarians and cat owners is crucial for ensuring the accurate administration of treatments.

The observed distribution of treatment durations offers valuable insights into the practical application of Mirataz®. In contrast with the recommended 14-day duration outlined in the official product information (MedVet RCM Mirataz®), our study unveils a noteworthy disparity in the treatment duration among cat owners. Approximately 51.6% of owners applied Mirataz® for a shorter duration than the recommended 14 days, suggesting potential deviations from clinical guidelines. Conversely, in the group '≥14 days,' we find that 48.4% followed or exceeded the recommended duration. This underscores the necessity for a deeper exploration of the factors influencing treatment duration practices among cat owners.

In our study, side effects were reported by 14 out of 70 (20%) cat owners being the most frequent agitation/hyperactivity. Comparing our results with those from Poole et al. (2018) (included in the Summary of Product Characteristics (2020)) we can draw some conclusions. The latter indicate that in the Mirataz® group, agitation/hyperactivity was reported in 7%, erythema in 10.4%, and vocalisation and vomiting in 11.3%. Our study observed a slightly higher percentage of agitation, a lower percentage of erythema, and a lower percentage of vocalisation compared to the product documentation. The major difference was in vomiting, with our study reporting 1.4% and Poole et al. (2018) reporting 11.3%. By comparing the observed side effects in our study with those documented on the Summary of Product Characteristics (2020), we gain insights into the practical implications and real-world experiences of using Mirataz® in a clinical context.

The assessment of Mirataz® efficacy in stimulating appetite revealed a predominantly positive perception among respondents. About ¾ of the respondents expressed satisfaction with the appetite-stimulating effects of mirtazapine ointment. This positive answer highlights the perceived efficacy of Mirataz® in addressing appetite increase in feline patients. However, it is noteworthy that still a notable proportion of owners did not find Mirataz® effective. Investigating the reasons behind this divergence in perceived efficacy could provide valuable

insights into factors influencing owner experiences with this medication. Understanding components such as individual cat behaviour, underlying health conditions, and adherence to the prescribed regimen, may contribute to optimizing the use of Mirataz® and improving overall patient outcomes.

Considering the time until efficacy, there were some variations in the responses. It's important to consider the possibility of a placebo effect, particularly for owners who reported noticing effects within the first 24 hours of ointment use (44.4%). The rapid response observed in these cases may be influenced by owner expectations or other factors unrelated to the medication's pharmacological action. These variations in perceived efficacy timelines underscore the individualised nature of feline responses to Mirataz® and the variability in owners' perceptions. While pharmacokinetic parameters such as Tmax provide valuable data on drug concentration dynamics, the time until perceived efficacy reported by owners reflects the broader clinical impact and aligns with the dynamic nature of feline responses to appetite stimulants and owners' interpretations.

To determine the reasons for prescribing Mirataz® in cats, there were differences in the methods employed by the two countries involved in this study. Italian respondents were directly asked to specify these reasons in the survey. While this approach seems straightforward, it is crucial to acknowledge the potential for human error and bias. Respondents may lack the medical expertise to differentiate between underlying diseases and clinical signs or laboratory findings, introducing potential inaccuracies in the data. For example, some owners might attribute a cat's reduced appetite ('inappetence') as a reason for prescribing, which is, in fact, a clinical sign rather than an underlying disease. On the other hand, concerning Portuguese respondents, we relied on the examination of medical records from the Hospital Escolar Veterinário to gather information about underlying diseases. This method may decrease classification errors in terms of categorising diseases. However, some cats lacked sufficient historical data, or a definitive diagnosis was not available impairing a right characterization of the whole sample. Consequently, when interpreting our results related to the reasons for prescription, it is important to acknowledge these methodological differences that might introduce variation and potential limitations in the data.

Mirataz® is recognised as a medication designed to promote an increase in body weight in cats experiencing long-term conditions associated with poor appetite and weight loss. The responses from our survey highlighted chronic kidney disease as the predominant reason for prescribing transdermal mirtazapine, followed by chronic enteropathy, liver disease, post-surgical recovery, and neoplasia. In our study, the most prevalent reasons for prescription included chronic situations (chronic kidney disease, chronic enteropathy, liver disease, and neoplasia). Furthermore, our results also highlight the versatility of Mirataz®, extending its application in more acute scenarios such as post-surgical recovery. The absence of

comparative data makes it challenging to draw direct parallels. However, the available information, indicating transdermal mirtazapine is recommended for increasing body mass in cats with loss of appetite and weight resulting from chronic diseases, aligns with our study's emphasis on its role in managing chronic situations.

The comparison of owners who had previous experience using both formulations of mirtazapine (ointment and pills) revealed interesting insights into their preferences. Among the 70 respondents, nine had prior experience with mirtazapine pills. Within the subset of owners who had experience with both formulations (9/70; 13%), a substantial majority (7/9; 78%) expressed a preference for the transdermal ointment. Contrasting to a minority of respondents (2/9, 22%) who preferred oral mirtazapine. These preferences underscore the individualised nature of cat responses and owner perceptions, reflecting the multifaceted considerations that influence the choice between oral and transdermal mirtazapine administration.

Statistical analyses revealed only one significant relationship: efficacy vs duration of treatment. The lack of more statistical patterns may be attributed to the intricate nature of feline responses to transdermal mirtazapine, influenced by individual variations, diverse owner practices, and underlying diseases within our surveyed population. Additionally, it is important to note that the relatively small sample size in our study could contribute to the absence of more statistically significant findings.

The investigation into a potential association between the side effect of erythema in the inner ear and owners not alternating the ear of application yielded insightful findings. Employing the Fisher’s exact test, our analysis did not reveal a significant correlation between these variables. Among the small subset of six owners who did not alternate the ear of application, only one cat reported experiencing erythema in the ear.

This study suggests that, according to owner’s perceptions, shorter durations of treatment (<14 days) may be associated with reduced efficacy, while durations equal to or longer than the recommended could be linked to a more evident clinical effect. These findings emphasise the importance of adhering to the recommended duration. The overall analysis suggests a negative trend, but subgroup analyses reveal variability in the association within the two specific treatment duration groups, indicating a nuanced association between treatment duration and efficacy. It is crucial to acknowledge the multifaceted nature of this relationship and the potential variations in treatment efficacy among distinct treatment durations. Further research, incorporating larger sample sizes and detailed treatment protocols, may provide a more comprehensive understanding of these dynamics.

3.5.1. Limitations

Although this study provides valuable insights into cat owners' perspectives on the use of transdermal mirtazapine, it is essential to acknowledge certain limitations.

The analysis is based on a relatively small sample of 70 responses, which may restrict the extent of conclusions that can be drawn from the data. The use of telephone calls in Portugal, similar to Italy, could have increased the sample size and potentially addressed this limitation. This constraint may impact the generalizability of the findings, as the experiences and opinions of the participating cat owners may not fully represent the broader population using Mirataz®. Moreover, the study was conducted in specific geographical areas (Portugal and Italy) and focused on the responses of cat owners in these regions. These findings might not apply universally to all cat owners globally.

It's worth noting that some owners who participated in the survey had used the transdermal ointment as far back as 2021 and were responding to the survey in 2023. This significant gap between the time of medication use and the survey response introduces the possibility of recall bias, where owners may struggle to accurately remember details about their experiences with the medication. Such gaps in memory can lead to variability and inaccuracies in their responses, potentially affecting the reliability of the data collected. To mitigate this limitation, future research could benefit from a prospective study design, which involves collecting data in real-time or shortly after the medication's use.

Furthermore, there is a possibility for variations in the interpretation of survey questions. The clarity and wording of these questions could influence the accuracy of responses. Additionally, there is potential for response bias, as owners who experienced significant effects, whether positive or negative, with mirtazapine may have been more motivated to participate, thereby introducing selection bias.

One limitation of our study pertains to the question regarding the time until efficacy of transdermal mirtazapine. Presenting this question in a free-response format may have inadvertently resulted in a wide variety of responses. In retrospect, providing predefined options could have facilitated subsequent statistical analysis.

Additionally, variations in collecting reasons for prescription between Portugal and Italy introduce challenges, such as classification errors and the absence of direct owner input in Portugal, along with variability in historical data availability. In Italy, direct inquiries with owners were made, but the drawback was the lack of access to detailed medical histories. These methodological differences emphasise the need for cautious interpretation and recognition of potential biases when comparing data between the two countries, introducing potential limitations and uncertainty into our findings.

One notable limitation of this study pertains to the assessment of side effects. Side effects were solely evaluated based on owners' recollection. To enhance the objectivity and precision of side effect reporting, future research could benefit from the incorporation of a standardized scale. This would allow for the systematic assessment of side effects and provide insights into their frequency and severity, thus offering a more robust and metric-based evaluation of treatment outcomes.

The study did not thoroughly investigate variations in medication dosage, regimens prescribed by veterinarians, or other medications that cats may be taking, as well as the severity of the underlying disease or the medical status of the cat. These factors could potentially influence treatment outcomes. Additionally, a comparison group of cats not receiving mirtazapine but receiving, for example, a placebo ointment was not included, making it challenging to isolate the specific effects of this medication. Another valuable aspect for future research would be measuring the cat's weight at the beginning and end of Mirataz® therapy. Understanding weight gain or loss during treatment could provide a more comprehensive assessment of this medication's efficacy on the cat's health.

Furthermore, the survey could have been enhanced by including questions related to owners' self-assessment of their compliance with treatment regimens and the reasons for any reported non-compliance. It would have been beneficial to include questions addressing owners' adherence to specific precautions during the application of the product, such as wearing gloves, washing their hands post-application, and avoiding direct contact with their cats for a recommended period. Additionally, the study did not incorporate a scale for cat owners to indicate their overall satisfaction levels with the use of transdermal mirtazapine. These additions could have provided a more comprehensive understanding of owner experiences and satisfaction with this treatment.

3.6. Conclusion

This survey-based study highlights the owner's perceptions of transdermal mirtazapine usage, reinforcing its accessible applicability, efficacy, and safety as an appetite stimulant in cats.

Overall, this study emphasises the practical advantages of transdermal mirtazapine in veterinary medicine, affirming its potential as a valuable option for both veterinarians and cat owners. Moreover, effective communication between veterinarians and cat owners is crucial, and future research could delve deeper into its role in optimising the therapeutic experience for both the cat and its owner. Additionally, to enhance the generalizability of these findings, future research on a larger scale and in diverse geographical locations would be valuable, offering a more comprehensive understanding of owner experiences with Mirataz®.

In conclusion, this work has provided valuable insights into the owner's perspectives on the use of Mirataz® transdermal ointment in cats. Chronic kidney disease was the most frequent cause of its prescription. Side effects were reported by a minor percentage of owners and were mild, supporting the safety of this formulation. Additionally, this study identified a significant association between efficacy and treatment duration, emphasising the potential impact of treatment duration on positive outcomes.

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5. ANNEXES

Annexe 1 - Adverse reactions reported during a field study (Mirataz® - Summary of Product Characteristics (2020)).

Adverse Reaction	Mirataz N=115 (%)	Vehicle Control N=115 (%)
Application site (Ear pinna)		
Erythema	12 (10.4%)	20 (17.4%)
Crust/Scab	3 (2.6%)	6 (5.2%)
Residue	3 (2.6%)	8 (7.0%)
Scaling/Dryness	3 (2.6%)	3 (2.6%)
Dermatitis or irritation	1 (0.9%)	9 (7.8%)
Alopecia	1 (0.9%)	2 (1.7%)
Pruritus	1 (0.9%)	4 (3.5%)
Behavioral		
Vocalization	13 (11.3%)	2 (1.7%)
Hyperactivity	8 (7.0%)	1 (0.9%)
Disoriented state or ataxia	4 (3.5%)	2 (1.7%)
Lethargy/weakness	4 (3.5%)	9 (7.8%)
Attention Seeking	3 (2.6%)	0
Aggression	2 (1.7%)	0
Physical Examination or Observational		
Vomiting	13 (11.3%)	15 (13.0%)
Dehydration	6 (5.2%)	5 (4.3%)
Diarrhea or soft stool	6 (5.2%)	7 (6.1%)
Heart murmur	5 (4.3%)	7 (6.1%)
Inappetence	5 (4.3%)	5 (4.3%)
Renal insufficiency*	4 (3.5%)	0
Ear infection	3 (2.6%)	0
Urinary tract infection	3 (2.6%)	0
Clinical Pathology		
Hematuria	7 (6.1%)	1 (0.9%)
Elevated BUN (without creatinine)**	6 (5.2%)	0
Elevated creatinine and BUN	5 (4.3%)	1 (0.9%)
Hyperphosphatemia	5 (4.3%)	0
Hypokalemia	5 (4.3%)	2 (1.7%)
Pyuria	5 (4.3%)	0
Anemia	3 (2.6%)	8 (7.0%)
Low urine specific gravity	3 (2.6%)	1 (0.9%)
Monocytosis	3 (2.6%)	2 (1.7%)
Neutrophilia	3 (2.6%)	2 (1.7%)

Annexe 2 - Questionnaire provided online – Portuguese (original) version

Uso de Miratаz® no Hospital Escolar Veterinário

O Miratаz® é uma pomada, aplicada na orelha, que tem como objetivo estimular o apetite dos gatos.

Além de contribuir para o avanço da ciência, a sua resposta é essencial para avaliar a perceção dos detentores sobre o Miratаz® e será certamente importante para otimizar este tratamento em casos futuros.

Este questionário demora cerca de 2 minutos a ser respondido. Agradecemos muito a sua participação.

Responsável pelo estudo: Sofia Carvalho (estudante do 6º ano do Mestrado Integrado em Medicina Veterinária)

Orientador do estudo: Professor Rodolfo Oliveira Leal

Se tiver alguma dúvida ou pretender algum esclarecimento, pode contactar-me através do meu email: sofiaicarvalho@campus.ul.pt.

1. □ A minha participação é livre e voluntária. Autorizo que os dados sejam utilizados exclusivamente para fins estatísticos, não sendo revelada a minha identidade.
2. Indique por favor o seu endereço de email:_____

3. **Lembra-se de utilizar a pomada Miratаz®?**
   □Sim □ Não

4. **A aplicação da pomada foi fácil?**
   □Sim □ Não

5. **Por que razão? (**Se respondeu *Não* à pergunta anterior)
   □ Sujidade na orelha
   □ Foi difícil dosear a quantidade
   □ Não consegui aplicar a pomada por causa do comportamento do meu gato
   □ Outra razão:_____

6. **Foi alternando a orelha em que colocou a pomada?** (num dia colocou na orelha esquerda, no dia seguinte na orelha direita, etc.)
   □Sim □ Não, coloquei sempre na mesma orelha

7. **Quantos dias aplicou a pomada?**
   □ 1 semana
   □ 2 semanas
   □ 3 semanas
   □ 1 mês
   □ Mais de um mês
   □ O meu gato toma Miratаz® de forma contínua
   □ Não me lembro
   □ Outra:_____

8. **O seu animal ainda está a utilizar a pomada Miratаz® de momento?**
   □Sim □ Não

9. **Identificou algum efeito secundário associado ao Miratаz®?**
   □Sim □ Não

10. **Se sim, selecione quais.**
    - □ Vocalização
    - □ Agitação
    - □ Vómitos
    - □ Diarreia
    - □ Vermelhidão no local de aplicação
    - □ Urinar mais
    - □ Salivação/tremores
    - □ Outros:_____

11. **Considera que a pomada fez efeito, estimulando o apetite?**
    □Sim □ Não

12. **Quanto tempo após o começo das aplicações notou melhorias a nível do apetite?** (se respondeu *sim* à pergunta 11): _____

13. **O seu animal alguma vez tomou mirtazapina por via oral (comprimido)?**
    □Sim □ Não

14. **Considera que a formulação em pomada é vantajosa em relação aos comprimidos?** (se respondeu *sim* à pergunta 13)
    □Sim □ Não

15. **Na sua ótica, quais as principais vantagens da pomada em relação aos comprimidos?** (se respondeu *sim* à pergunta 14)
    - □ Não gosto de dar comprimidos ao meu gato
    - □ A pomada é fácil de aplicar
    - □ Acho que a pomada fez mais efeito (recuperação mais rápida do apetite)
    - □ Outra razão: _____

16. **Na sua ótica, qual/quais as principais desvantagens da pomada em relação aos comprimidos?** (se respondeu *não* à pergunta 14)
    - □ A pomada é mais cara
    - □ Acho que não fez tanto efeito como os comprimidos
    - □ Não me adaptei à aplicação da pomada na pele da orelha
    - □ Outra razão: _____

17. Muito obrigada pela sua participação!

Annexe 3 - Questionnaire provided online – Italian version

Uso di Mirataz® – la prospettiva del proprietario

Mirataz® è un unguento, applicato a livello di padiglione auricolare, che mira a stimolare l'appetito nel gatto.

La sua risposta contribuirà al progresso della scienza, permettendoci di valutare la percezione dei proprietari riguardo la terapia con Mirataz® e di ottimizzare questo trattamento in casi futuri.

Per rispondere a questo questionario occorrono circa 2 minuti.
Vi ringraziamo molto per la vostra partecipazione.

Responsabile dello studio: Sofia Carvalho (studentessa del 6° anno del Master Integrato in Medicina Veterinaria presso l'Università di Lisbona)

Supervisore dello studio: Professor Rodolfo Oliveira Leal

In collaborazione con: Dott. Andrea Corsini, Dipartimento di Scienze Medico-Veterinarie dell'Università di Parma

Se dovesse avere domande o dubbi, è possibile contattare il responsabile dello studio al seguente indirizzo: sofiaicarvalho@campus.ul.pt.

1. □ La mia partecipazione è gratuita e volontaria. Accetto che i dati vengano utilizzati esclusivamente per fini statistici e la mia identità non verrà divulgata.
2. Indirizzo mail (facoltativo):_____

3. **Ricorda di aver utilizzato Mirataz®?**
   □ Sì □No

4. **L'applicazione dell'unguento è risultata facile?**
   □ Sì □No

5. **Per quale ragione?**
   □ L'orecchio era troppo sporco
   □ Era difficile dosare l'unguento
   □Il comportamento del mio gatto non mi ha permesso di utilizzare l'unguento
   □Un'altra ragione:_____

6. **Ha cambiato orecchio su cui andava ad applicare l'unguento?** (Un giorno sull'orecchio sinistro, il giorno sucessivo sull'orecchio destro e così via)
   □ Sì □No, l'ho sempre applicato sullo stesso orecchio

7. **Per quanti giorni ha applicato Mirataz®?**
   □ 1 settimana
   □ 2 settimane
   □ 3 settimane
   □ 1 mese
   □ Più di un mese
   □ Il mio gatto sta continuando a ricevere Mirataz®
   □ Non ricordo
   □ Altro:_____

8. **Sta ancora utilizzando attualmente Mirataz®?**

□ Sì □No

9. **Ha notato effetti collaterali associati alla somministrazione di Mirataz®?**
□ Sì □No

10. **Quali?**
□ Vocalizzazioni
□ Agitazione
□ Vomito
□ Diarrea
□ Irritazione a livello auricolare
□ Urinazione eccessiva
□ Ipersalivazione o tremori
□ Altro:_____

11. **Ritiene che l'unguento utilizzato abbia funzionato, stimolando quindi l'appetito del gatto?**
□ Sì □No

12. **Dopo quanto tempo rispetto all'inizio della terapia ha notato miglioramenti nell'appetito?**_____

13. **I suo gatto ha mai assunto Mirtazapina per via orale (in compresse)?**
□ Sì □No

14. **Ritiene che l'unguento sia migliore rispetto alle compresse?**
□ Sì □No

15. **Secondo il suo punto di vista, quali sono i principali vantaggi dell'utilizzo di un unguento rispetto alle compresse?**
□ Non è semplice somministrare compresse al mio gatto
□ L'unguento è facile da applicare
□ Ritengo che il mio gatto abbia ricominciato a presentare appetito più velocemente con l'utilizzo dell'unguento
□ Altro: _____

16. **Secondo il suo punto di vista, quali sono i principal svantaggi dell'utilizzo di un unguento rispetto alle compresse?**
□ L'unguento è più costoso
□ Ritengo che il mio gatto abbia ricominciato a presentare appetito più velocemente con l'utilizzo delle compresse
□ Ho trovato difficile l'applicazione dell'unguento a livello auricolare
□ Altro: _____

17. **Per quale patologia è stato prescritto Mirataz® dal suo veterinário?** _____

18. Grazie per la sua partecipazione!

Annexe 4 - Poster presented at the Congress of the European College of Veterinary Internal Medicine (ECVIM) – Companion Animals (21-23 September 2023)

Owners' perspective about the use of mirtazapine transdermal ointment in cats – a survey-based study

Carvalho, S.[1], Mendoza, B.[1,2], Dias, M. J.[1,3,4], Tirelli, I.[5], Corsini, A.[5], Leal, R.O.[1,3,4]

[1] Veterinary Teaching Hospital; Faculty of Veterinary Medicine – University of Lisbon; Av. Universidade Técnica, 1300-171 Lisbon, Portugal; [2] IVC Evidensia, Bom Jesus Veterinary Hospital, 4715-380 Braga, Portugal; [3] CIISA – Centro de Investigação Interdisciplinar em Sanidade Animal – Faculty of Veterinary Medicine – University of Lisbon; Av. Universidade Técnica, 1300-171 Lisbon, Portugal; [4] Associate Laboratory for Animal and Veterinary Sciences (AL4AnimalS), 1300-477 Lisbon, Portugal; [5] Department of Veterinary Medical Sciences, University of Parma, Parma, Italy.

Introduction

- Mirtazapine is a tetracyclic, noradrenergic and specific serotonergic antidepressant used as an appetite stimulant in cats.
- It was recently licensed for use as a transdermal ointment in Europe.
- The aim of this study is to evaluate the owners' perspective about the use of transdermal mirtazapine in cats, since little is known about this topic.

Materials and methods

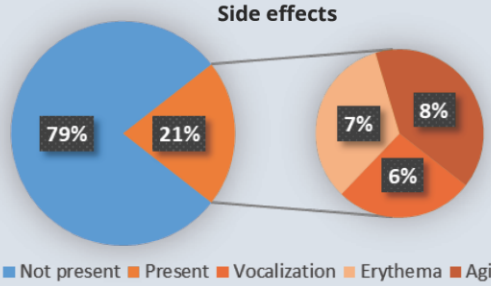
- Cross-sectional study.
- Online survey with 15 questions was uploaded on Google Forms® and sent to owners with cats to which mirtazapine ointment was precribed, in two European Veterinary Teaching Hospitals.
- Data was analysed using descriptive statistics.

Results

69 answers were obtained (out of 100 owners that received the survey).

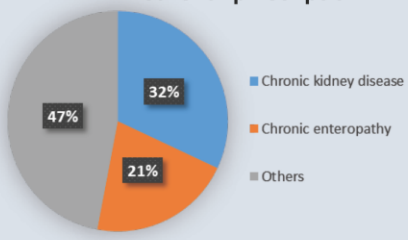
- 97% (67/69) of the owners found the topical application easy.
- Those that considered it difficult mentioned **cat's behaviour** and **ears debris** as the main causes.
- 91% (63/69) of the survey respondents confirmed the daily application in alternating ears, contrasting to 6/69 (9%) which admitted applying always in the same ear.

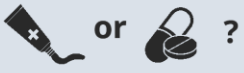
Side effects



- Most of the respondents (53/69; 77%) considered that transdermal mirtazapine efficiently stimulates the appetite.
- Reasons for mirtazapine prescription were detailed in 56 answers.

Reasons for prescription





- 13% (9/69) of the owners have already administered oral and transdermal mirtazapine:
  - 7/9 preferred the transdermal option due to easier administration;
  - 2/9 decided on oral mirtazapine because of its lower cost.

- **This study highlights the applicability and effectiveness of transdermal mirtazaptine ointment.**
- **Chronic kidney disease was the most frequent cause for its prescription.**
- **Mild side effects were reported by a minor percentage of owners, supporting this formulation's safety.**

Acknowledgments

This work was supported by FCT - Fundação para a Ciência e Tecnologia IP, grant UIDB/00276/2020 and by LA/P/0059/2020 - AL4AnimalS.

Annexe 5 - Abstract submitted for poster presentation at the ECVIM 2023 Congress

Owners' perspective about the use of mirtazapine transdermal ointment in cats – a survey-based study

Carvalho, S.[1], Mendoza, B.[1,2], Dias, M. J.[1,3,4],Tirelli, I.[5], Corsini, A.[5], Leal, R.O.[1,3,4]

[1] Veterinary Teaching Hospital; Faculty of Veterinary Medicine – University of Lisbon; Av. Universidade Técnica, 1300-171 Lisbon, Portugal.
[2] IVC Evidensia, Bom Jesus Veterinary Hospital . 4715-380 Braga, Portugal.
[3] CIISA – Centro de Investigação Interdisciplinar em Sanidade Animal – Faculty of Veterinary Medicine – University of Lisbon; Av. Universidade Técnica, 1300-171 Lisbon, Portugal.
[4] Associate Laboratory for Animal and Veterinary Sciences (AL4AnimalS), 1300-477 Lisbon, Portugal.
[5] Department of Veterinary Medical Sciences, University of Parma, Parma, Italy.

Mirtazapine is a tetracyclic, noradrenergic and specific serotonergic antidepressant used as an appetite stimulant in cats. Despite its historical off-labeled oral administration in cats, it was recently licensed for use as a transdermal ointment in this species. Being a topical product, it requires a good compliance for success. To the authors knowledge, little is known about owners' feedback on this therapeutic option.

This study aims to evaluate the owners' perspective about the use of mirtazapine transdermal ointment in cats.

A cross-sectional survey-based study was conducted. An online survey with 15 multiple-choice and open-ended questions was developed and uploaded on an electronic platform (Google Forms). Questions focused on efficacy feedback, side-effects and overall perception of mirtazapine ointment. Electronic medical records of two European Veterinary Teaching Hospitals were searched for cats in which mirtazapine ointment was prescribed from March 2021 to January 2023. Owners were contacted by email, asking to fulfill the survey. Results were detailed with descriptive statistics.

From 100 contacted owners, 69 answers were obtained. The topical application was found easy by 67/69 (97%) of the owners. Those that considered it difficult mentioned cat's behaviour and ears debris as the main causes. Following the manufacturer instructions, 63/69 (91%) owners confirmed the daily application in alternating ears, contrasting to 6/69 (9%) which admitted applying always in the same ear. Side effects were reported by 14/69 (20%), being the most common: vocalisation (5/14), erythema (4/14) and agitation (4/14). Most of the respondents (53/69; 77%) considered that transdermal mirtazapine efficiently stimulates the appetite. A total of 9/69 (13%) owners had previously administered oral mirtazapine formulation to their cats before trying transdermal option. While 7/9 (78%) considered transdermal more beneficial due to an easier administration, the remaining (2/9, 22%) preferred oral mirtazapine due to its lower cost. Reasons for mirtazapine prescription were detailed in 56 answers, being the most common: chronic kidney disease (18/56; 32%) and chronic enteropathy (12/56; 21%). Length of therapy was variably described by owners, being mirtazapine most frequently applied during 7 days (18/69, 26%) or 14 days (12/69, 17%).

This study highlights the owners' perception on transdermal mirtazapine use, reinforcing its applicability and effectiveness as an appetite stimulant in cats. Chronic kidney disease was the most frequent cause for its prescription. Side effects were reported by a minor percentage of owners and were mild, supporting the safeness of this formulation.

Annexe 6 - Abstract submitted for poster presentation at the ACVIM 2024 Congress

The effect of transdermal mirtazapine in hospitalized cats with hepatobiliary disease: a prospective study

Carvalho, S., Marques, P.L., Mendoza, B., Leal, R.O.

Background

Transdermal mirtazapine ointment (Mirataz®) is a commonly prescribed appetite stimulant. Its effect on cats with hepatobiliary disease is scarcely studied.

Hypothesis/Objectives

We aim to evaluate the effect of Mirataz® on cats hospitalized for hepatobiliary disease in which a feeding tube was placed.

Animals

Thirteen anorectic client-owned cats hospitalized with hepatobiliary disease were enrolled. Cats were included if there were clinicopathological and ultrasound-features compatible with hepatobiliary disease and had a nasal or esophagostomy tube placed. Cats were excluded in case of concurrent systemic diseases or previous history of appetite stimulants in the last four weeks.

Methods

A randomized controlled trial was conducted. All cats received standard medical care for hepatobiliary disease. After placing the feeding tube, cats were randomized into one of two groups: G1 – cats treated with Mirataz® (0.1g ointment/cat, once a day) and G2 –control group. Data concerning clinical signs, appetite recovery and length of hospitalization was analyzed. Nonparametric tests were performed.

Results

Seven cats were included in G1 and six cats in G2. No side effects were reported in G1. Median days until spontaneous appetite recovery were 3+/-7.25 and 11+/-4 for G1 and G2, respectively (p=0.4). Length of hospitalization was shorter in G1 (3+/-1 versus 12 +/- 3 for G2; p=0.057).

Conclusions and clinical importance

Although no significant differences were found, this study suggests that Mirataz® seems to be safe and might contribute to a faster appetite recovery alongside a shorter hospitalization in cats with hepatobiliary disease and a feeding tube.

Annexe 7 – Results of the statistical analysis

Response rate between countries

Tabulação cruzada Country * Participated

		Participated		
		No	Yes	Total
Country	Portugal	35	33	68
	Italy	2	38	40
Total		37	71	108

Testes qui-quadrado

	Valor	df	Significância Assintótica (Bilateral)	Sig exata (2 lados)	Sig exata (1 lado)
Qui-quadrado de Pearson	24,148[a]	1	**<,001**		
Correção de continuidade[b]	22,129	1	<,001		
Razão de verossimilhança	28,741	1	<,001		
Teste Exato de Fisher				**<,001**	<,001
N de Casos Válidos	108				

a. 0 células (0,0%) esperavam uma contagem menor que 5. A contagem mínima esperada é 13,70.

b. Computado apenas para uma tabela 2x2

Erythema vs alternating ears

Tabulação cruzada: ERYTHEMA vs ALTERNATING EARS

		ALTERNATING EARS		
		YES	NO	Total
ERYTHEMA	NO	60	5	65
	YES	4	1	5
Total		64	6	70

Testes qui-quadrado

	Valor	Sig exata (2 lados)
Teste Exato de Fisher		**,370**
N de Casos Válidos	70	

Erythema vs alternating ears

Chi-square test: Efficacy vs treatment duration (2 groups).

	Valor	df	Significância Assintótica (Bilateral)	Sig exata (2 lados)	Sig exata (1 lado)
Qui-quadrado de Pearson	5,969[a]	1	**,015**	,023	,015
Correção de continuidade[b]	4,506	1	,034		
Razão de verossimilhança	6,453	1	,011	,023	,015
Teste Exato de Fisher				,023	,015

N de Casos Válidos	64					

a. 0 células (0,0%) esperavam uma contagem menor que 5. A contagem mínima esperada é 5,81.
b. Computado apenas para uma tabela 2x2

Efficacy vs alternating ears

Tabulação cruzada EFFICACY * ALTERNATING EARS

		ALTERNATING EARS		
		YES	NO	Total
EFFICACY	NO	14	2	16
	YES	50	4	54
Total		64	6	70

Testes qui-quadrado

	Valor	df	Significância Assintótica (Bilateral)	Sig exata (2 lados)	Sig exata (1 lado)
Qui-quadrado de Pearson	,408[a]	1	,523		
Correção de continuidade[b]	,017	1	,896		
Razão de verossimilhança	,377	1	,539		
Teste Exato de Fisher				**,614**	,417
N de Casos Válidos	70				

a. 2 células (50,0%) esperavam uma contagem menor que 5. A contagem mínima esperada é 1,37.
b. Computado apenas para uma tabela 2x2

Efficacy vs reason for prescription

- Efficacy vs chronic kidney disease

Tabulação cruzada EFFICACY * CKD

		CKD		
		NO	YES	Total
EFFICACY	NO	10	2	12
	YES	29	16	45
Total		39	18	57

Testes qui-quadrado

	Valor	df	Significância Assintótica (Bilateral)	Sig exata (2 lados)	Sig exata (1 lado)
Qui-quadrado de Pearson	1,564[a]	1	,211		
Correção de continuidade[b]	,812	1	,367		
Razão de verossimilhança	1,710	1	,191		
Teste Exato de Fisher				**,303**	,186
N de Casos Válidos	57				

a. 1 células (25,0%) esperavam uma contagem menor que 5. A contagem mínima esperada é 3,79.
b. Computado apenas para uma tabela 2x2

- Efficacy vs chronic enteropathy

Tabulação cruzada EFFICACY * Chronic enteropathy

		CE		
		NO	YES	Total
EFFICACY	NO	8	4	12
	YES	39	6	45
Total		47	10	57

Testes qui-quadrado

	Valor	df	Significância Assintótica (Bilateral)	Sig exata (2 lados)	Sig exata (1 lado)
Qui-quadrado de Pearson	2,620[a]	1	,106		
Correção de continuidade[b]	1,419	1	,233		
Razão de verossimilhança	2,325	1	,127		

Teste Exato de Fisher					**,193**	,119
N de Casos Válidos		57				

a. 1 células (25,0%) esperavam uma contagem menor que 5. A contagem mínima esperada é 2,11.
b. Computado apenas para uma tabela 2x2

- Efficacy vs liver disease

Tabulação cruzada EFFICACY * Liver disease

		Liver disease		
		NO	YES	Total
EFFICACY	NO	11	1	12
	YES	39	6	45
Total		50	7	57

Testes qui-quadrado

	Valor	df	Significância Assintótica (Bilateral)	Sig exata (2 lados)	Sig exata (1 lado)
Qui-quadrado de Pearson	,220[a]	1	,639		
Correção de continuidade[b]	,000	1	1,000		
Razão de verossimilhança	,238	1	,626		
Teste Exato de Fisher				**1,000**	,541
N de Casos Válidos	57				

a. 1 células (25,0%) esperavam uma contagem menor que 5. A contagem mínima esperada é 1,47.
b. Computado apenas para uma tabela 2x2

- Efficacy vs post-surgical recovery

Tabulação cruzada EFFICACY * POSTCX

		POSTCX		
		NO	YES	Total
EFFICACY	NO	11	1	12
	YES	41	4	45
Total		52	5	57

Testes qui-quadrado

	Valor	df	Significância Assintótica (Bilateral)	Sig exata (2 lados)	Sig exata (1 lado)
Qui-quadrado de Pearson	,004[a]	1	,952		
Correção de continuidade[b]	,000	1	1,000		
Razão de verossimilhança	,004	1	,952		
Teste Exato de Fisher				**1,000**	,719
N de Casos Válidos	57				

a. 2 células (50,0%) esperavam uma contagem menor que 5. A contagem mínima esperada é 1,05.
b. Computado apenas para uma tabela 2x2

- Efficacy vs neoplasia

Tabulação cruzada EFFICACY * NEOPLASIA

		NEOPLASIA		
		NO	YES	Total
EFFICACY	NO	10	2	12
	YES	43	2	45
Total		53	4	57

Testes qui-quadrado

	Valor	df	Significância Assintótica (Bilateral)	Sig exata (2 lados)	Sig exata (1 lado)
Qui-quadrado de Pearson	2,169[a]	1	,141		
Correção de continuidade[b]	,700	1	,403		
Razão de verossimilhança	1,789	1	,181		
Teste Exato de Fisher				**,192**	,192

N de Casos Válidos		57				

a. 2 células (50,0%) esperavam uma contagem menor que 5. A contagem mínima esperada é ,84.
b. Computado apenas para uma tabela 2x2

Side effects vs alternating ears

Tabulação cruzada SIDE EFFECTS * ALTERNATING EARS

		ALTERNATING EARS		
		YES	NO	Total
SIDE EFFECTS	NO	53	3	56
	YES	11	3	14
Total		64	6	70

Testes qui-quadrado

	Valor	df	Significância Assintótica (Bilateral)	Sig exata (2 lados)	Sig exata (1 lado)
Qui-quadrado de Pearson	3,691[a]	1	,055		
Correção de continuidade[b]	1,925	1	,165		
Razão de verossimilhança	3,006	1	,083		
Teste Exato de Fisher				**,090**	,090
N de Casos Válidos	70				

a. 2 células (50,0%) esperavam uma contagem menor que 5. A contagem mínima esperada é 1,20.
b. Computado apenas para uma tabela 2x2

Side effects vs treatment duration

Tabulação cruzada SIDE EFFECTS * DURATION

		DURATION		
		NO	YES	Total
SIDE EFFECTS	NO	27	24	51
	YES	4	9	13
Total		31	33	64

Testes qui-quadrado

	Valor	df	Significância Assintótica (Bilateral)	Sig exata (2 lados)	Sig exata (1 lado)
Qui-quadrado de Pearson	2,039[a]	1	,153		
Correção de continuidade[b]	1,248	1	,264		
Razão de verossimilhança	2,088	1	,148		
Teste Exato de Fisher				**,217**	,132
N de Casos Válidos	64				

a. 0 células (0,0%) esperavam uma contagem menor que 5. A contagem mínima esperada é 6,30.
b. Computado apenas para uma tabela 2x2

Side effects vs reasons for prescription

- Side effects vs chronic kidney disease

Tabulação cruzada SIDEEFFECTS * CKD

		CKD		
		NO	YES	Total
SIDE EFFECTS	NO	33	14	47
	YES	6	4	10
Total		39	18	57

Testes qui-quadrado

	Valor	df	Significância Assintótica (Bilateral)	Sig exata (2 lados)	Sig exata (1 lado)
Qui-quadrado de Pearson	,398[a]	1	,528		
Correção de continuidade[b]	,066	1	,798		
Razão de verossimilhança	,386	1	,535		

Teste Exato de Fisher					**,709**	,388
N de Casos Válidos		57				

a. 1 células (25,0%) esperavam uma contagem menor que 5. A contagem mínima esperada é 3,16.
b. Computado apenas para uma tabela 2x2

- Side effects vs chronic enteropathy

Tabulação cruzada SIDE EFFECTS * Chronic Enteropathy

		CE		
		NO	YES	Total
SIDE EFFECTS	NO	39	8	47
	YES	8	2	10
Total		47	10	57

Testes qui-quadrado

	Valor	df	Significância Assintótica (Bilateral)	Sig exata (2 lados)	Sig exata (1 lado)
Qui-quadrado de Pearson	,051[a]	1	,822		
Correção de continuidade[b]	,000	1	1,000		
Razão de verossimilhança	,049	1	,824		
Teste Exato de Fisher				**1,000**	,565
N de Casos Válidos	57				

a. 1 células (25,0%) esperavam uma contagem menor que 5. A contagem mínima esperada é 1,75.
b. Computado apenas para uma tabela 2x2

- Side effects vs liver disease

Tabulação cruzada SIDE EFFECTS * LIVERDISEASE

		Liver disease		
		NO	YES	Total
SIDE EFFECTS	NO	40	7	47
	YES	10	0	10
Total		50	7	57

Testes qui-quadrado

	Valor	df	Significância Assintótica (Bilateral)	Sig exata (2 lados)	Sig exata (1 lado)
Qui-quadrado de Pearson	1,698[a]	1	,193		
Correção de continuidade[b]	,597	1	,440		
Razão de verossimilhança	2,902	1	,088		
Teste Exato de Fisher				**,333**	,238
N de Casos Válidos	57				

a. 1 células (25,0%) esperavam uma contagem menor que 5. A contagem mínima esperada é 1,23.
b. Computado apenas para uma tabela 2x2

- Side effects vs post-surgical recovery

Tabulação cruzada SIDE EFFECTS * POSTCX

		POSTCX		
		NO	YES	Total
SIDE EFFECTS	NO	43	4	47
	YES	9	1	10
Total		52	5	57

Testes qui-quadrado

	Valor	df	Significância Assintótica (Bilateral)	Sig exata (2 lados)	Sig exata (1 lado)
Qui-quadrado de Pearson	,023[a]	1	,880		
Correção de continuidade[b]	,000	1	1,000		
Razão de verossimilhança	,022	1	,882		
Teste Exato de Fisher				**1,000**	,634
N de Casos Válidos	57				

a. 2 células (50,0%) esperavam uma contagem menor que 5. A contagem mínima esperada é ,88.
b. Computado apenas para uma tabela 2x2

- Side effects vs neoplasia

Tabulação cruzada SIDE EFFECTS * neoplasia

		neoplasia		
		NO	YES	Total
SIDE EFFECTS	NO	43	4	47
	YES	10	0	10
Total		53	4	57

Testes qui-quadrado

	Valor	df	Significância Assintótica (Bilateral)	Sig exata (2 lados)	Sig exata (1 lado)
Qui-quadrado de Pearson	,915[a]	1	,339		
Correção de continuidade[b]	,076	1	,783		
Razão de verossimilhança	1,606	1	,205		
Teste Exato de Fisher				**1,000**	,452
N de Casos Válidos	57				

a. 2 células (50,0%) esperavam uma contagem menor que 5. A contagem mínima esperada é ,70.
b. Computado apenas para uma tabela 2x2