UNIVERSIDADE DE LISBOA

FACULDADE DE MEDICINA VETERINÁRIA

THE EFFECT OF TRANSDERMAL MIRTAZAPINE ON THE APPETITE RECOVERY TIME IN HOSPITALIZED CATS WITH HEPATOBILIARY DISEASE: AN AMBISPECTIVE STUDY

CARLOTA MACHADO PIRES GUEDES PINTO

ORIENTADOR:

Professor Doutor Rodolfo Assis Oliveira Leal

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Faculdade de Medicina Veterinária da Universidade de Lisboa, 21 de Abril de 2026

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Durante a minha primeira semana de faculdade, uma frase que ouvi constantemente foi “aproveita bem a faculdade, que vão ser os melhores anos da tua vida”. E, apesar de não ter sido sempre fácil, o tempo voou e agora que posso olhar para trás e ver todo o caminho que percorri até aqui, só me resta agradecer às pessoas que permitiram que estes 6 anos fossem dos melhores da minha vida.

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EFEITO DA MIRTAZAPINA TRANSDÉRMICA NO TEMPO DE RECUPERAÇÃO DE APETITE DE GATOS HOSPITALIZADOS POR DOENÇA HEPATOBILIAR: UM ESTUDO AMBISPETIVO

Resumo

A mirtazapina é um antidepressivo tetracíclico, utilizado em medicina veterinária como estimulante do apetite. Na Europa, o Mirataz® (Dechra), pomada transdérmica que contém mirtazapina e cujo uso está aprovado em gatos, é frequentemente utilizado em hospitais veterinários no combate à anorexia. Uma vez que este fármaco é metabolizado pelo fígado (tendo maior tempo de semivida de eliminação em gatos com disfunção hepática) e que a anorexia é um sinal clínico que aparece com regularidade associado à doença hepatobiliar, o presente estudo foi realizado de forma a explorar a eficácia da mirtazapina transdérmica em pacientes hospitalizados por doença hepatobiliar.

Este estudo ambispetivo dividiu-se em duas fases. Numa primeira abordagem, foi realizado um ensaio clínico randomizado, de forma prospetiva, em gatos que se apresentaram no hospital veterinário com doença hepatobiliar e anorexia. Além do tratamento padrão da doença hepatobiliar instaurado em hospitalização, estes gatos foram divididos em dois grupos: o grupo MT: gatos que receberam tratamento com mirtazapina (Mirataz®), numa dose de 2 mg por gato, a cada 24 horas; e grupo C: gatos que receberam apenas tratamento sintomático. Gatos que morreram antes de retomarem o apetite foram excluídos. Na segunda fase, adicionaram-se dados retrospectivos de gatos hospitalizados por doença hepatobiliar. Destes, os que receberam tratamento sintomático adjuvante com mirtazapina foram adicionados ao grupo MT e os que não receberam tratamento foram alocados ao grupo C.

No total foram incluídos 29 gatos: 15 do grupo de controlo e 14 no grupo da mirtazapina. Os gatos do grupo da mirtazapina recomeçaram a comer significativamente mais cedo do que os do grupo de controlo ($p = 0.007$) e passaram tipicamente menos tempo hospitalizados ($p = 0.018$). Apesar da diferença não ter sido significativa ($p = 0.087$), os gatos do grupo da mirtazapina tendencialmente ganharam peso durante a hospitalização, enquanto os do grupo de controlo perderam peso. Não se observaram reações adversas graves nos gatos tratados com mirtazapina.

Estes resultados apoiam o uso da mirtazapina transdérmica em gatos hospitalizados por doença hepatobiliar, reforçando que, quando associado ao tratamento sintomático individualizado, aparenta reduzir o período de anorexia e o tempo de hospitalização, não estando associado a reações adversas graves.

Palavras-chave: doença hepatobiliar; mirtazapina; anorexia; gatos.

THE EFFECT OF TRANSDERMAL MIRTAZAPINE ON THE APPETITE RECOVERY TIME IN HOSPITALIZED CATS WITH HEPATOBILIARY DISEASE: AN AMBISPECTIVE STUDY

Abstract

Mirtazapine is a tetracyclic antidepressant used in veterinary medicine as an appetite stimulant. In Europe, Mirataz® (Dechra) – a transdermal ointment containing mirtazapine approved for use in cats – has been frequently used in veterinary hospitals to manage anorexia. Since this drug is metabolized by the liver, with cats with hepatic dysfunction showing a longer elimination half-life, and anorexia is a well-known clinical sign of hepatobiliary disease, this study was designed to explore the efficacy of transdermal mirtazapine in hospitalized cats with hepatobiliary conditions.

This ambispective study was divided into two phases. On a first approach, a prospective, randomized clinical trial was conducted on client-owned cats presenting at the hospital with hepatobiliary disease and anorexia. Beside the standard treatment for hepatobiliary disease, which all cats received, these cats were divided into two groups: the MT group: cats who received treatment with Mirataz transdermal ointment at 2 mg/cat once daily; and the C group: cats who received only the standard treatment. Cats that died before they restarted eating were excluded. Afterwards, retrospectively collected cases of cats with hepatobiliary disease were added to the dataset; from these, cats whose treatment plan included transdermal mirtazapine were added to the MT group, whereas those who did not were added to the C group.

In total, 29 cats were included: 15 part of the control group and 14 part of the mirtazapine group. Cats in the mirtazapine group restarted eating voluntarily significantly earlier than those in the control group ($p = 0.007$), and spent less time hospitalized ($p = 0.018$). Although the difference was not significant ($p = 0.087$), cats in the mirtazapine group also showed a tendency towards weight gain during hospitalization, whereas those in the control group typically lost weight. No severe adverse effects were observed.

These results support the use of transdermal mirtazapine in hospitalized cats with hepatobiliary disease, showing that, when associated with individualized symptomatic treatment, it seems to lower the anorexia period and hospitalization duration, while also not being associated with severe adverse reactions.

Key words: hepatobiliary disease; mirtazapine; anorexia; cats.

EFEITO DA MIRTAZAPINA TRANSDÉRMICA NO TEMPO DE RECUPERAÇÃO DE APETITE DE GATOS HOSPITALIZADOS POR DOENÇA HEPATOBILIAR: UM ESTUDO AMBISPETIVO

Resumo Alargado

A mirtazapina é um antidepressivo tetracíclico, utilizado em medicina veterinária como estimulante do apetite. A sua eficácia no aumento do apetite e no ganho de peso em gatos já foi comprovada por diversos estudos, particularmente em gatos saudáveis e com doença renal crónica. Durante anos, este fármaco foi utilizado fora das indicações (“off-label”) por médicos veterinários, no entanto, em 2019, o primeiro medicamento com mirtazapina como substância ativa foi aprovado na Europa: o Mirataz® (Dechra). Este medicamento está disponível para uso em gatos sob a forma de uma pomada transdérmica, e é comercializado como uma solução médica para promover o apetite e estimular o ganho de peso em gatos com doença crónica.

Para além do seu uso em pacientes crónicos, a mirtazapina é também regularmente utilizada em gatos hospitalizados para combater a anorexia, sendo o seu uso recomendado em normas orientadoras atuais. A anorexia, definida como a ausência total de apetite e de alimentação voluntária, é um sinal clínico frequentemente observado em animais hospitalizados. Esta alteração tem um impacto significativo na saúde e no bem-estar dos pacientes, tendo a capacidade de perpetuar doenças, atrasar a recuperação e aumentar a mortalidade. Em gatos, pode ser particularmente perigosa devido ao risco acrescido de desenvolvimento de lipidose hepática. Tendo isto em conta, é importante que a abordagem médica à anorexia seja rápida; esta deve incluir o tratamento da causa primária bem como medidas para combater diretamente a falta de apetite, como intervenções nutricionais (por exemplo, a colocação de tubo de alimentação) e estimulantes de apetite como a mirtazapina.

As alterações hepatobiliares podem ocorrer com alguma frequência em gatos, sendo, na maioria, casos agudos. A anorexia é um sinal clínico frequentemente observado nestes animais, pelo que a mirtazapina pode ser uma solução útil. No entanto, este fármaco é metabolizado pelo fígado e aparenta ter maior tempo de semivida de eliminação em gatos com disfunção hepática.

Tendo isto em conta, o presente estudo foi realizado de forma a determinar a eficácia da mirtazapina transdérmica em pacientes hospitalizados por doença hepatobiliar.

Este estudo ambispetivo dividiu-se em duas partes. Numa primeira fase, foi realizado um ensaio clínico prospetivo randomizado, em gatos que se apresentaram no hospital veterinário com doença hepatobiliar e anorexia. Os critérios de exclusão incluíram a presença

de doença sistémica grave capaz de afetar o apetite, diagnóstico de neoplasia ou historial de utilização de estimulantes de apetite nas últimas 4 semanas. Além do tratamento padrão da doença hepatobiliar instaurado em hospitalização, estes gatos foram divididos em dois grupos: grupo MT: gatos que receberam tratamento com a pomada transdérmica Mirataz, numa dose de 2 mg de mirtazapina por gato, a cada 24 horas; e grupo C: gatos que receberam apenas tratamento sintomático. Os gatos que morreram antes de retomarem o apetite foram excluídos. Na segunda fase, adicionaram-se dados retrospectivos de gatos com doença hepatobiliar hospitalizados; destes, os que receberam tratamento sintomático adjuvante com mirtazapina, foram adicionados ao grupo MT e os que não receberam tratamento, foram alocados ao grupo C.

Os dados obtidos durante o estudo incluíram características do animal (idade, sexo, estado reprodutivo (inteiro/castrado), raça), sinais clínicos, tempo (em dias) de anorexia pré-admissão, diagnóstico (presuntivo ou definitivo), colocação de tubo de alimentação, tempo (em dias) até ao retorno do apetite, duração (em dias) da hospitalização, aparecimento de efeitos adversos e desfecho clínico (morte ou alta médica; alta antes ou depois de retomar a alimentação voluntária). As alterações de valores bioquímicos (alanina aminotransferase, fosfatase alcalina e bilirrubina total) e de peso foram contabilizadas.

Os dados foram analisados estatisticamente utilizando testes não paramétricos e a significância estatística foi definida como $p < 0.05$.

O estudo incluiu nove gatos do ensaio clínico prospetivo e 20 gatos cujos dados foram obtidos retrospetivamente. No total, a análise estatística incluiu 29 gatos: 14 pertencentes ao grupo da mirtazapina e 15 ao grupo de controlo.

Os gatos não apresentaram diferenças entre grupos no que toca à idade, sexo, estado reprodutivo, raça, tempo de anorexia pré-admissão ou colocação de tubo de alimentação. Os sinais clínicos (exceto anorexia, presente em todos os gatos) mais frequentemente observados foram icterícia (75.9%), desidratação (62.1%), vómito (55.2%), dor abdominal (44.8%), perda de peso (44.8%) e letargia (44.8%). Na maioria dos gatos não foi obtido um diagnóstico definitivo, e os diagnósticos presuntivos mais comuns foram lipidose hepática e/ou colangite/colangiohepatite.

Os gatos do grupo da mirtazapina resolveram a anorexia numa mediana de 3,5 dias após a admissão hospitalar, enquanto, no grupo de controlo, a mediana foi de 11 dias ($p = 0.007$). Estes resultados estão de acordo com estudos anteriores que apontam para a eficácia da mirtazapina como estimulante de apetite e sugerem que o uso deste fármaco pode ser útil em gatos hospitalizados por doença hepatobiliar.

O grupo da mirtazapina também passou menos tempo hospitalizado (p = 0.018). Tendo em conta a redução do tempo de anorexia, estes resultados são expectáveis, já que este sinal clínico aparenta ter um efeito negativo na recuperação.

Os valores bioquímicos (ALT, ALP e TBil) de admissão, alta e e a respectiva variação (estabelecida como: valor do parâmetro bioquímico aquando da alta – valor na admissão) não apresentaram diferenças significativas entre grupos. No entanto, estes valores mostraram tendência a diminuir entre a admissão e a alta em todos os grupos, o que demonstra uma melhoria clínica.

Para além disso, os gatos do grupo da mirtazapina tendencialmente ganharam peso durante a hospitalização, enquanto os do grupo de controlo tipicamente perderam peso. No entanto, a diferença não foi significativa (p = 0.087). Em teoria, o aumento de peso é um sinal associado à administração do Mirataz, tendo sido reportado em estudos em gatos com doença crónica. No entanto, é importante notar que o ganho de peso em gatos hospitalizados pode depender de diversos fatores, e pode não representar aumentos reais na massa corporal, mas sim apenas alterações no balanço hídrico.

Não se observaram reações adversas durante a realização do ensaio clínico prospetivo. No entanto, tal pode ter ocorrido apenas devido ao número reduzido de animais submetidos a tratamento com mirtazapina. Nos dados retrospetivos, um gato desenvolveu picacismo e o tratamento com mirtazapina foi descontinuado.

As análises da mortalidade foram realizadas apenas com os animais que participaram no ensaio clínico prospetivo. Neste, 38,9% dos gatos não sobreviveram à hospitalização, sendo que os resultados foram similares entre grupos (p = 1). No entanto, é importante notar que apenas foram incluídos no estudo gatos com anorexia, um fator que pode aumentar a mortalidade, e estes resultados podem não ser transpostos para toda a população de gatos com doença hepatobiliar.

Este estudo apresenta algumas limitações, como, por exemplo, o reduzido tamanho amostral ou o facto de não ter sido possível realizar uma medição objetiva da alimentação voluntária dos gatos (uma vez que o hospital não media a comida oferecida aos animais na altura da realização do estudo).

Apesar das limitações, os resultados obtidos apoiam o uso da mirtazapina transdérmica em gatos hospitalizados por doença hepatobiliar. Estudos futuros devem ser direcionados a confirmar estes resultados, em ensaios clínicos com maior tamanho amostral, e aferir se esta recuperação mais rápida do apetite se reflete em melhores desfechos a longo prazo.

Palavras-chave: doença hepatobiliar; mirtazapina; anorexia; gatos.

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HE – Hepatic Encephalopathy

FHL – Feline Hepatic Lipidosis

ALT – Alanine Aminotransferase

AST – Aspartate Aminotransferase

ALP – Alkaline Phosphatase

GGT – Gamma-Glutamyl Transferase

FNA – Fine-Needle Aspiration

CCHC – Cholangitis/Cholangiohepatitis Complex

CC – Cholecystitis

RER – Resting Energy Requirements

CKD – Chronic Kidney Disease

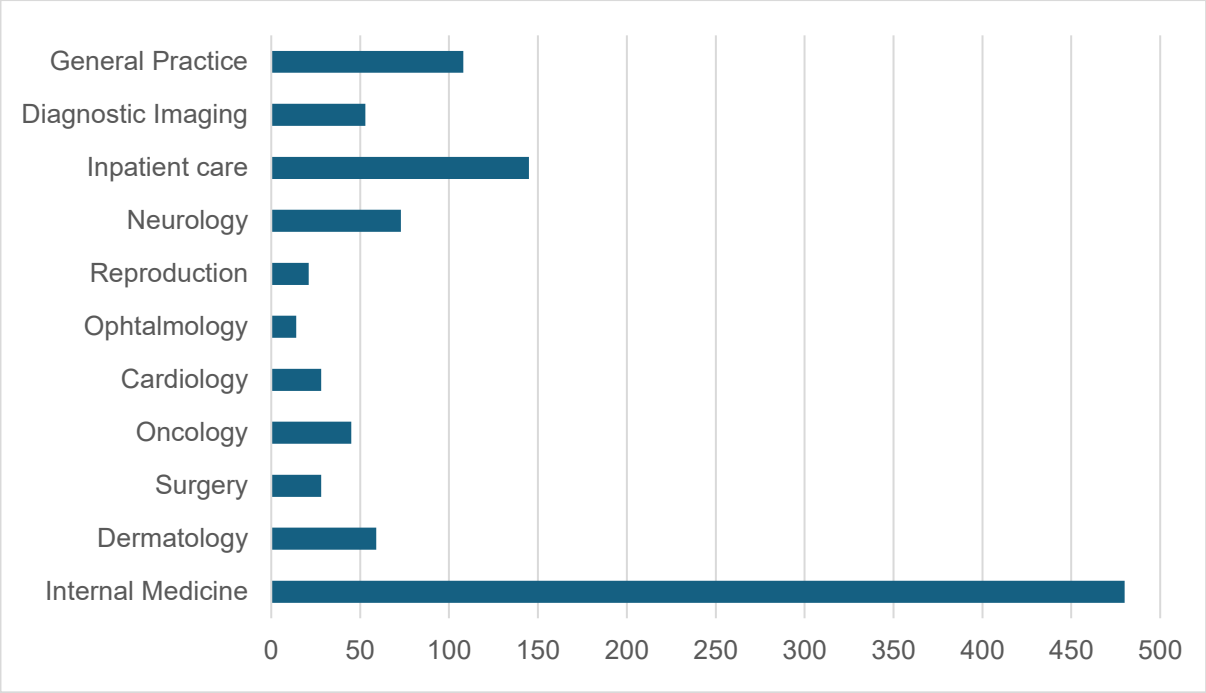
TBil – Total Bilirubin

1. EXTERNSHIP REPORT

The following report describes the activities I performed during my curricular externship at the Veterinary Teaching Hospital ("HEV – Hospital Escolar Veterinário") of the Faculty of Veterinary Medicine, University of Lisbon. The externship lasted from the 10th of March, 2025, to the 5th of September, 2025, spanning about 26 weeks. I spent the first trimester in the internal medicine department and the second trimester rotating through the remaining veterinary specialties available at the hospital: dermatology, surgery, oncology, cardiology, ophthalmology, reproduction, neurology, diagnostic imaging, inpatient care, and general practice.

The externship resulted in a little over 1000 hours of clinical training, distributed across the different rotations mentioned before. The shifts varied by department but, on average, lasted 7 hours a day, 5 days a week. Additionally, I did a 12-hour night shift in the inpatient care facility every 3 weeks. The total amount of time, in hours, I spent in each department is shown in Graph 1.

Graph 1 - Distribution of the time (in hours) spent in each department



1.1. Internal Medicine

I spent approximately half of my externship time in this department, under the direct supervision of two internal medicine board-certified specialists and an internal medicine resident.

My shifts started at 08:30 with medical rounds for hospitalized patients, where I witnessed discussions about possible diagnoses, diagnostic tests, and treatments.

Following that, I attended various appointments, including first-opinion, referral, and follow-up appointments of cases related to endocrinology, gastroenterology, nephrology, respiratory medicine, and hematology. I initiated some of these appointments by performing the initial anamnesis. Afterwards, I presented the information I collected and discussed possible diagnostic tests and disease management with the internal medicine team. This gave me a chance to improve my communication skills with both pet owners and the veterinary team. I improved practical skills such as physical exams, blood draws, urine collection with ultrasound-guided cystocentesis, and sample management. One or two days a week, I also witnessed and assisted in procedures such as upper and lower gastrointestinal endoscopies, bronchoscopies, bronchoalveolar lavages, cystoscopies, rhinoscopies, and bone marrow aspiration and biopsies.

Later in the day, I was present and part of clinical case discussions focused on interpreting the results from complementary exams, establishing differential diagnosis, managing treatment plans, and planning possible follow-up tests.

Once a week, I was part of a journal club with the internal medicine team, where I read one or two articles from well-known scientific journals in the field, presented the results, and discussed them with the team.

During this rotation, I encountered a wide variety of cases, including hyper- and hypothyroidism, hyper- and hypoadrenocorticism, diabetes mellitus, diabetes insipidus, chronic enteropathies, chronic kidney disease, immune-mediated polyarthritis, chronic and acute hepatopathies, and exocrine pancreatic insufficiency, among many others.

1.2. Dermatology

Over the week I spent in the dermatology rotation (plus some extra hours, totalling approximately 60 hours), I witnessed first-opinion, referral, and follow-up appointments, as well as some procedures such as skin biopsies and otoscopies. In some cases, I did the initial patient anamnesis and the dermatological examination. I also performed trichograms and ear

and skin cytologies, followed by the observation under the microscope and interpretation of the results.

This rotation improved my knowledge of some skin conditions, important diagnostic tests to do, and results interpretation. I encountered many cases, including those more common, such as atopic dermatitis, otitis externa, and skin infections (pyoderma and Malassezia overgrowth), as well as some less common cases, such as immune-mediated skin conditions and cutaneous manifestations of systemic disease (e.g. calcinosis cutis in a dog with hyperadrenocorticism).

1.3. Surgery

I spent approximately 35 hours (1 week) in this department. The 7-hour shifts started at 8 am, when I admitted the patients. This included an anamnesis, with questions focused on the animals' medical conditions, ongoing medications, known allergies, and fasting duration. Following this, I helped the team perform physical exams, place intravenous catheters, intubate animals, and prepare and administer pre-anesthetic drugs.

In some surgeries, I scrubbed in as an assistant surgeon and helped with some of the surgical procedures. In other surgeries, I helped with the anesthesia and vital signs monitoring as well as with post-operative monitoring.

During my time in this rotation, I attended a wide variety of surgeries, including but not limited to ovariohysterectomies and castrations, nodulectomies, mastectomies, SUB placement surgeries, enucleations, and mandibulectomies.

1.4. Oncology

Over the course of my week in this rotation, I attended first-opinion and referral appointments, as well as follow-ups. In almost every appointment, I was charged with performing a complete physical exam and exposing my findings to the clinicians to ensure I could detect any possible abnormalities. I did the anamnesis for some of the patients, trained my blood draws when blood collection was required, and helped with fine needle aspiration and sample accommodation of cytologies.

On one of the days I spent in oncology, I also had the chance to watch and help in chemotherapy procedures. Here, I learned more about how to safely handle chemotherapy drugs, how to check if an animal could safely undergo chemotherapy, and the possible side effects of these procedures.

This rotation gave me some crucial knowledge on how to manage some common and uncommon neoplasms in small animal practice and gave me insight into how to approach the discussion of complex topics with pet owners. In this department, I witnessed cases of mast cell tumors, mammary carcinomas, lymphomas, and soft-tissue sarcomas, as well as many other common and uncommon small animal neoplasms.

1.5. Cardiology

The cardiology rotation lasted a week, where I did shifts of 5 to 9 hours, totaling about 26 hours. In this department, I assisted in echocardiographies and electrocardiograms, learned more about common and uncommon cardiac diseases, and enhanced my cardiopulmonary auscultation skills.

I followed cases such as degenerative mitral valve disease, hypertrophic cardiomyopathy, dilated cardiomyopathy, and systemic and pulmonary hypertension, all of them at various stages of development.

1.6. Ophthalmology

During my week in the ophthalmology rotation, I attended first-opinion and follow-up appointments. Under supervision, I performed complete ophthalmological examinations, which included reflex evaluations, Schirmer tear tests, fluorescein tests, tonometry, fundoscopy, and eye examination under a biomicroscope.

I discussed the cases with the team, familiarized myself with common ocular medication, and learned how to manage common ophthalmological conditions. Here, I witnessed cases such as corneal ulceration, glaucoma, and keratoconjunctivitis sicca.

1.7. Reproduction

Over my week in the reproduction department, I was able to witness several consultations, from pre-surgery appointments to reproductive ultrasounds. I watched and assisted in procedures such as vaginal cytologies, spermograms, artificial inseminations, and pregnancy confirmation procedures.

In this rotation, I refreshed my knowledge of small animal reproductive health. I also watched some more complicated cases, such as cryptorchidism and pyometra.

1.8. Neurology

I was assigned to do two 7-hour shifts in this specialty, but due to my interest, I ended up doing some extra hours with the neurology team. In total, I spent about 70 hours in this department. Here I witnessed some first-appointment consultations as well as some follow-ups, and I also assisted in cerebrospinal fluid collection procedures.

I started some of the appointments by making the initial anamnesis and the physical exam. Under supervision, I was encouraged to attempt to diagnose the problems in some patients, and I helped with the management of several neurological diseases. I also practiced my soft skills by calling owners and explaining the results of diagnostic tests performed.

In this department, I learned how to handle some neurological diseases and signs, how to perform a full neurological exam correctly and localize lesions, and how to differentiate between common neurological disorders (such as full and partial seizures and paroxysmal dyskinesias). I encountered cases such as idiopathic epilepsy, intervertebral disc disease, trigeminal neuritis, vestibular disease, and syringomyelia.

1.9. Diagnostic Imaging

Radiology and Advanced Imaging

During this week, I witnessed imaging procedures such as X-rays, CT scans, MRIs, and myelographies. I assisted in patient admission, restraint, and positioning for the exams. Later, I learned how to interpret the images collected and how to identify some common and uncommon abnormalities.

Ultrasound

I spent one week in this department, where I witnessed abdominal, eye, and cervical ultrasounds, as well as some ultrasound-guided fine needle aspirations and cystocentesis. I assisted with patient positioning and trichotomies, gained experience identifying abdominal organs and their pathologic variations, and helped complete ultrasound exam reports. In some cases, I was allowed to perform the exam under supervision.

1.10. Inpatient care

I was assigned one week in the hospitalization facilities, as well as multiple 12-hour night shifts. Each shift started with a medical round, where cases were discussed. These discussions included whether the patients were recovering or not, possible needed diagnostic

tests, treatment plans, and prognosis. Afterwards, I followed the team and helped in the daily tasks, including: blood, urine, or free fluid collection; intravenous catheter placement; fluid therapy preparation; blood pressure and glycemia measurement; and patient feeding. I also witnessed emergency situations such as cardiopulmonary resuscitation, blood transfusions, and dyspnoea management.

This rotation gave me the opportunity to follow inpatient cases closely (sometimes from the moment they were hospitalized up until their discharge) and gave me a better understanding of the procedures necessary to ensure the patient's swift recovery.

1.11. General Practice

I was assigned two weeks in this department and completed additional hours, bringing my total to about 100 hours in this rotation. Here, I shadowed in first-opinion consultations, follow-ups, and emergencies.

My time in this rotation gave me valuable information on the role of a first-opinion veterinarian. It also allowed me the opportunity to practice not only my clinical skills but also soft skills like organization, record keeping, and communication. In some cases, I collected the initial anamnesis, performed the physical exam, and later discussed my findings and proposed the following course of action with the clinicians. Afterwards, they gave me valuable feedback, allowing me the chance to learn from my mistakes.

I also enhanced practical skills, such as blood draws, urine collection, blood pressure and glycemia measurements, and intravenous catheter placement, among others. The cases I witnessed in this rotation varied, from vaccinations to emergencies, and sometimes included first-opinion cases that would later be referred to specific specialties.

1.12. 2026 ACVIM Forum abstract submission

Following the writing of the present dissertation, an abstract of this study was submitted and accepted for oral presentation at the 2026 ACVIM Forum. The abstract is included in Appendix 3.

2. LITERATURE REVIEW

2.1. Feline Hepatobiliary Disease

The liver is a vital organ that carries out a vast range of essential physiological functions. It is involved in processes such as metabolism, detoxification, and maintenance of nutrient balance. As a result, disorders of the hepatobiliary system – which includes the liver, gallbladder, and bile ducts – can have a significant impact on overall health (Gow 2024).

Moreover, the liver is actively involved in the activation, metabolism, and excretion of many compounds. This can make the effect of hepatic disease on a drug's pharmacokinetics unpredictable, and the therapeutic approach to these patients should be evaluated carefully (Gow 2024).

2.1.1. Presentation and Clinical Signs

The clinical signs of liver disease may vary according to the type of liver injury and its severity. These can include icterus, hepatic encephalopathy (HE), ascites, coagulation disorders, and portal hypertension (Gow 2024). However, these clinical signs may not be present until the final stages of a hepatobiliary disease process, due to the liver's remarkable regeneration capacity (Cocker and Richter 2017; Hall and Hall 2021). Consequently, signs of liver disease, especially those seen in early stages, are mostly nonspecific and can include vomiting, diarrhea, weight loss, and polyuria/polydipsia (Johnson and Sherding 2006; Cocker and Richter 2017; Nelson and Couto 2020). Another common sign of these disorders is anorexia (Johnson and Sherding 2006; Cocker and Richter 2017; Nelson and Couto 2020) (further discussed in chapter 2.2.), which explains why an appetite-stimulant drug like mirtazapine could prove helpful in these patients.

In cats, hepatobiliary disease is relatively common, but it is typically an acute disorder and rarely progresses into chronicity. Clinical signs are generally nonspecific, with feline hepatic lipidosis (FHL) presenting with the more classic signs of hepatic disorders, such as jaundice or HE (Nelson and Couto 2020).

2.1.2. Diagnosis and Clinical Findings

Diagnosing hepatobiliary diseases can be challenging, especially in early stages. A thorough history and physical exam are crucial steps that may point clinicians towards the right direction (Johnson and Sherding 2006).

In addition, a biochemical profile can be a valuable tool, and interpreting liver enzyme values is an essential step towards diagnosis. These liver enzymes include hepatocellular leakage enzymes and inducible enzymes. However, these rarely provide enough information on the etiology of the liver disease in process, and further diagnostic tests are usually needed (Kam et al. 2025).

Hepatocellular leakage enzymes, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), are indicative of hepatocellular damage. Since ALT is predominantly present in the liver, it is usually considered the most specific of the two (Center 2007). These enzymes have a much shorter half-life in cats than in dogs, meaning that even small changes are considered more clinically relevant in feline patients than in their canine counterparts (Cocker and Richter 2017; Lawrence and Steiner 2017; Little 2020; AST [date unknown]). The inducible enzymes alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) are found in the hepatocyte cell membrane and are used as a marker of cholestasis (Cocker and Richter 2017; Lawrence and Steiner 2017). Both of these enzymes are present in other organs (Kidney and Jackson 1988; Hall and German 2016; Cocker and Richter 2017), with the particularity that an increase in ALP can be induced by corticosteroids in dogs, but not in cats (Kidney and Jackson 1988; Center 2007). In feline patients, ALP is usually considered more specific (Hall and German 2016), while GGT is considered more sensitive. An exception to this is cases of FHL, where a marked increase in ALP is usually identified, while GGT may remain normal (Center 2007; Kam et al. 2025).

Some additional biochemical parameters can be used to evaluate liver function. These include glucose, blood urea nitrogen, albumin, cholesterol, bilirubin, bile acids, ammonia, and coagulation proteins (Cocker and Richter 2017).

Routine hematology and urinalysis can also provide clues for hepatobiliary diagnosis, although the abnormalities found are usually not specific for liver disease (Center 2007; Rothuizen 2009; Webster and Cooper 2014; Cocker and Richter 2017). One particularly important finding (although still not specific) is the presence of bilirubin in the urine of feline patients, since this species has a higher renal threshold for bilirubin (Rothuizen 2009).

Imaging can provide valuable information, with ultrasound being the most common test used to diagnose hepatobiliary disease (Rothuizen and Twedt 2009; Cocker and Richter 2017). Radiography and other, more complex, imaging tests can also be helpful in some situations (Cocker and Richter 2017).

Liver sampling may be necessary for definitive diagnosis and can be performed via fine-needle aspiration (FNA) or biopsy. FNA is less invasive, has fewer risks, yields faster results, and is less expensive. However, this methodology has a higher rate of inaccurate

results (Willard et al. 1999; Sharkey et al. 2007; Cocker and Richter 2017), with the agreement between cytologic and histologic diagnoses reported to be between 30-61% (Roth 2001; Wang et al. 2004; Bahr et al. 2013; Cocker and Richter 2017). Moreover, in some cases – particularly those where infectious cholecystitis is suspected – an ultrasound-guided percutaneous cholecystocenthesis may be indicated in order to perform cytologic and microbiologic analysis of bile (Brain et al. 2006; O'Neil 2024).

2.1.3. Prevalence, Common Diseases, and Prognosis

The prevalence of liver disease in cats was reported to be 7.02% in a study conducted in Brazil (Melchert et al. 2016). Prevalence rates for specific diagnoses are not always consistently documented and seem to differ across geographical locations. Nevertheless, FHL and cholangitis/cholangiohepatitis complex (CCHC) are usually considered the most common diseases (Nelson and Couto 2020).

As examples of these differences, FHL has been recognized as the number one cause of liver disease in cats in the United States and Brazil (Gagne et al. 1996; Melchert et al. 2016). On the other hand, research findings from Japan, New Zealand, and the UK point to cholangiohepatitis as the most common diagnosis (Hirose et al. 2014; Bayton et al. 2018; Fluen et al. 2019). These differences may result from regional variations, such as variances in cats' lifestyles and habits.

Feline Hepatic Lipidosis (FHL)

FHL is defined by excessive accumulation of triglycerides in the hepatocytes, leading to loss of liver function. The primary metabolic abnormalities involved in this event are complex and not completely understood, but most likely entail changes in free fatty acid metabolism (Valtolina and Favier 2017; Kuzi and Watson 2024).

FHL can be classified as a primary or secondary disease (Webb 2018; Nelson and Couto 2020). The primary, idiopathic form occurs spontaneously and usually affects obese cats. On the other hand, secondary lipidosis occurs as a consequence of anorexia and may develop in any patient presenting with this clinical sign (Center 2005; Webb 2018; Nelson and Couto 2020).

Prognosis is very dependent on the treatment and possible concurrent diseases. Typically, cats with idiopathic FHL are younger and more likely to survive than cats with secondary FHL (Center et al. 1993). In general, prognosis is good (reported survival rate of

55%-80%) when cats are given nutritional support intensively and early (Nelson and Couto 2020). However, survival can go down to 20% in some cases of secondary FHL, such as patients with concomitant acute pancreatitis (Akol et al. 1993; Kuzi and Watson 2024).

Cholangitis/Cholangiohepatitis Complex (CCHC)

Cholangitis is the term used to describe the inflammation of the bile tract. Whenever this inflammation also involves the liver parenchyma, it is called cholangiohepatitis (Magne and Shell 2004; Nelson and Couto 2020; Jaffey 2022). Current guidelines by the World Small Animal Veterinary Association (WSAVA) divide these biliary disorders into four categories: neutrophilic cholangitis, lymphocytic cholangitis, destructive cholangitis, and chronic cholangitis associated with liver fluke infestation (Van Den Ingh et al. 2006).

Neutrophilic cholangitis, which can also be called suppurative cholangitis, is characterized by the infiltration of neutrophils in the bile tract (Nelson and Couto 2020). It is speculated to result from ascending bacterial infection, and most bacteria isolated from bile and liver tissue are of enteric origin, such as E. coli and the Enterococcus species (Wagner et al. 2007; Jaffey 2022; Schlachet et al. 2025). Prognosis is good, and cats are likely to make a full recovery if given the right treatment (Nelson and Couto 2020).

Lymphocytic cholangitis is an indolent chronic disorder marked by infiltration of the liver portal tracts with small lymphocytes. The chance of cure is slim, but very few cats die directly from this condition, as the disease rarely progresses to end-stage cirrhosis in this species (Nelson and Couto 2020).

The diagnosis of these disorders can be challenging due to the relatively high occurrence of concomitant diseases (Jaffey 2022). Chronic enteropathy and pancreatitis are commonly found in cats with cholangitis, and FHL is present in about one third of these cats (Clark et al. 2011).

Other diseases

Other, less common, hepatobiliary diseases in feline patients include cholecystitis (CC), extrahepatic bile duct obstruction, cholelithiasis, portosystemic shunts, and toxic hepatopathies, among others (Nelson and Couto 2020).

Hepatic neoplasms are uncommon in cats, representing 1-2.9% of all neoplasms in this species. Primary hepatobiliary tumors are more common than metastatic neoplasia, and benign tumors are more common than malignant ones (Liptak 2020; Nelson and Couto 2020).

2.1.4. Treatment

Treatment for hepatobiliary disease should include supportive therapy, treatment of the disease in progress, and control of complications. Additionally, the potential impact of liver malfunction on drug metabolism should always be taken into account to avoid drug toxicity or lack of efficacy (Johnson and Sherding 2006).

Supportive care can include fluid therapy to sustain hydration, maintain electrolyte and acid-base balance, and prevent or treat hypoglycemia. Pharmacological supportive treatment can include hepatoprotectants, antiemetics, appetite stimulants, and pain management (Johnson and Sherding 2006; Ridgway 2020; Taylor et al. 2022). Additionally, the treatment plan should be based on the confirmed or presumptive diagnosis and may consist of antibiotics, antidotes, immunosuppressive therapy, and even surgery (Nelson and Couto 2020).

Nutritional support is also important, especially in patients presenting with appetite disturbances. A high-fat diet can be helpful, since it increases both energy density and palatability (Biourge 2024; Stockman 2025), but it may exacerbate clinical signs in patients presenting with hypertriglyceridemia, gallbladder mucocele, or concurrent diseases such as pancreatitis and chronic enteritis (Stockman 2025). Glucose intolerance is common, and carbohydrates should account for no more than 35% of total caloric intake. Ideally, daily food intake should be divided into three or more meals (Biourge 2024). Protein levels need to be tailored to the specific hepatobiliary diagnosis: animals with hepatic lipidosis require a high-protein diet, whereas animals presenting with severe HE may benefit from some degree of protein restriction (or the use of non-meat, highly digestible proteins such as soy isolate). Moderate amounts of dietary fiber can be beneficial, and vitamin and mineral deficits should be corrected (Biourge 2024; Stockman 2025).

As mentioned, treatment should also be adapted to address possible complications. In cats with HE, warm-water enemas, antibiotics, non-absorbable disaccharides (such as lactulose), anticonvulsants for seizures, and mannitol in case of cerebral oedema may be beneficial (Shell and Rishniw 2005; Lidbury et al. 2016; Gow 2024). Ascites treatment should be directed towards the cause, with spironolactone recommended for chronic or refractory cases (Gow 2024). Sodium restriction has also been advised in these cases (Johnson and Sherding 2006), but it has been shown to reduce caloric intake and promote malnutrition in

people (Haberl et al. 2018). For animals presenting with coagulopathies, administration of vitamin K1 can be helpful, and administration of fresh frozen plasma can provide coagulation factors to animals actively bleeding (Johnson and Sherding 2006; Gow 2024). Finally, gastrointestinal protectants such as omeprazole can be used in cases of gastrointestinal hemorrhage (Shell and Rishniw 2005).

2.2. Anorexia in Cats

As mentioned in the previous chapter, anorexia is a clinical sign commonly observed in patients presenting with hepatobiliary disease. However, it is not specific to these conditions. Decreased appetite and reduced food intake are commonly observed in veterinary medicine and can be caused by a wide range of acute or chronic conditions (Delaney 2006; Agnew and Korman 2014; Alenza 2024). A clinical survey published by Robinson et al. (2015) showed that inappetence was the third most common clinical sign recorded at a veterinary hospital (3.9%), with cats exhibiting the sign more often than dogs (5.8% vs 2.2%).

Assessment of appetite in small animal practice can pose some challenges. In particular, appetite in and of itself cannot be objectively measured, so more objective, quantifiable factors (such as food intake or body weight) need to be employed (Johnson and Freeman 2017).

Another problem when dealing with appetite changes, especially in older literature, is the lack of consistent terms. To address this, Johnson and Freeman (2017) proposed the following definitions: *adequate food intake*, when an animal voluntarily consumes the number of calories necessary to meet caloric requirements; *hyporexia*, when voluntary food intake is decreased and does not provide enough calories to meet caloric requirements; *anorexia*, when there is a complete absence of voluntary food intake; and *dysrexia*, to describe abnormal food intake patterns (such as cyclic appetites or altered food preferences).

2.2.1. Impact on the Hospitalized Patient

A decrease in appetite can be commonly found in hospitalized feline patients (Delaney 2006). In these cats, it can have a significant impact, perpetuating diseases and delaying recovery. In some cases, anorexia and weight loss can even increase morbidity and mortality rates (Finn et al. 2010; Taylor et al. 2022), with a study by Molina et al. (2018) showing that anorexia at admission is associated with a higher risk of death in hospitalized dogs.

In cats in particular, prolonged anorexia can have an especially negative impact due to the species' particular metabolic adaptations (including higher protein and certain amino acid requirements) (MacDonald et al. 1984; Chan 2009; Taylor et al. 2022). Moreover, in this species, anorexia may lead to the development of FHL, which may in turn worsen anorexia (Center 2005; Miller 2016; Valtolina and Favier 2017).

2.2.2. Physiology of Appetite and Pathophysiology of Anorexia

Regulation of appetite and food intake is influenced by complex, multifactorial mechanisms that depend on metabolic, gastrointestinal, and sensory signals, as well as several neurotransmitters (Agnew and Korman 2014).

The hypothalamus is the central region of the brain involved in the regulation of appetite, with adipose tissue, the gastrointestinal tract, and nutrients also playing important roles. In a healthy animal, there is a balance between orexigenic (e.g. ghrelin) and anorexigenic (e.g. cholecystokinin) signals. After a meal, there is an increase in anorexigenic signals, accompanied by a decrease in orexigenic ones. As time passes, the former decreases while the latter increases, leading to a feeling of hunger that pushes the animal to feed (Michel 2001; Johnson and Freeman 2017).

Additionally, "adiposity" hormones such as leptin are secreted in proportion to body fat, helping regulate appetite to maintain ideal body weight. A healthy animal that loses weight (due to insufficient caloric intake) produces less of these anorexigenic hormones, which in turn increases food intake (Woods and D'Alessio 2008; Guyenet and Schwartz 2012; Fantinati et al. 2020).

This balance between orexigenic and anorexigenic factors can be lost in healthy animals, leading to a shift in favor of weight gain. This may happen, for example, due to highly palatable foods (Johnson and Freeman 2017).

At the other end of the spectrum, this balance can be lost in sick animals, leading to a shift in favor of weight loss. While, in theory, diseased patients have increased orexigenic and decreased anorexigenic factors – as a consequence of their reduced caloric intake and possible weight loss – this can be countered (Johnson and Freeman 2017). Inflammatory cytokines (such as interleukin-1 and tumor necrosis factor-α), for example, have potent anorexigenic effects and can be increased in many acute or chronic diseases (Plata-Salamán 1999; Michel 2001; Iwakura et al. 2017; Johnson and Freeman 2017). Moreover, conditions such as nausea, pain, or ileus, all relatively common in hospitalized patients, can further decrease appetite (Chan 2009).

Furthermore, sick and anorectic animals can be predisposed to weight loss. In a healthy patient, periods of fasting and nutrient deprivation lead to the use of glycogen and fat stores as energy sources – a process called simple starvation. On the other hand, in sick patients, there are metabolic changes that lead the organism towards a catabolic state. In these situations, glycogen stores are quickly depleted. When anorexia causes animals to stop eating, the predominant energy source starts coming from proteolysis, leading to a decrease in lean body mass – a process called stressed starvation (Chan 2020; Taylor et al. 2022).

2.2.3. Causes of Anorexia

Anorexia can be divided into primary anorexia, secondary anorexia, and pseudoanorexia. In primary anorexia, there is a direct loss of appetite, caused by problems such as neurological dysfunction, psychological disorders, or loss of smell. On the other hand, secondary anorexia can happen whenever a disease causes loss of appetite as a side effect. This includes conditions associated with nausea, pain, and inflammation, among others. Pseudoanorexia is the term used when appetite itself is maintained, but an existing condition inhibits the ability to pick up, chew, or swallow food. Causes of pseudoanorexia include oral cavity diseases or hypoglossal paralysis. (Miller 2016).

Aside from these pathological causes of anorexia, other factors may lead a hospitalized feline patient to decrease or even cease its food intake, with stress being an important one. Cats are particularly vulnerable to stress, and the novelty of the hospital environment can be an impactful factor leading to anorexia (Mills et al. 2014; Fantinati et al. 2020; Alenza 2024).

2.2.4. Medical Approach to Anorexia

Managing anorexia in the hospital setting can prove challenging and, at times, frustrating. Taking the time to gather a detailed medical history is essential, both to diagnose the primary problem and to better deal with appetite disturbances. History should include the duration and severity of the reduced appetite, previous and current body weight to assess changes, and a report of the patient's dietary history and habits (Taylor et al. 2022; Alenza 2024).

A careful evaluation of the patient's medication is needed, and nausea-inducing drugs should be avoided. Parenteral methods of drug administration are preferred over oral in the anorectic patient, and bitter-tasting drugs should be avoided if possible (Taylor et al. 2022).

The clinical environment and human-cat interactions should be optimized to avoid stress and encourage voluntary food intake (Johnson and Freeman 2017; Taylor et al. 2022).

Food aversions should also be avoided, as these can keep causing reduced food intake even after the pathological factors have been managed. Forced feeding should never be employed, and it is important to address nausea, pain, or other negative feelings that may accompany the patient's attempt to feed (Agnew and Korman 2014; Chan 2020; Quimby 2023). Additionally, other situations that may lead to a negative association with food, such as administering drugs during feeding, should be avoided (Agnew and Korman 2014; Johnson and Freeman 2017; Alenza 2024). Physical barriers to eating, such as the Elizabethan collar, need to be removed when offering food to patients (Johnson and Freeman 2017; Alenza 2024).

It is crucial not to forget to address the cause of anorexia, and efforts towards the diagnosis and treatment of any underlying disease should be made (Gajanayake 2014; Miller 2016; Johnson and Freeman 2017).

2.2.4.1. Appetite Stimulants

Appetite stimulants can be a valuable tool when it comes to fighting anorexia (Taylor et al. 2022). Their use is common in veterinary hospitals and can be employed both before and after a specific diagnosis is established (Alenza 2024). However, these drugs should not be used as diagnostic tools in and of themselves, and over-reliance on them should be avoided, as it may delay nutritional intervention and the diagnosis of the underlying problem (Chan 2009; Johnson and Freeman 2017). Appetite stimulants' use is recommended only after other anorexia factors like pain, nausea, pyrexia, or ileus are correctly managed (Agnew and Korman 2014).

Appetite-stimulating drugs used in veterinary medicine include: oral and transdermal mirtazapine (which will be talked about in further detail in chapter 2.3.); capromorelin, a ghrelin receptor agonist; or cyproheptadine, a serotonin antagonist and antihistamine (Taylor et al. 2022; Quimby 2023). Out of these, only two are licensed for use in cats: transdermal mirtazapine (Mirataz®, Dechra) and capromorelin (Elura®/Eluracat®, Elanco) (Taylor et al. 2022).

Other drugs like anabolic steroids, benzodiazepines, glucocorticoids, and megesterol acetate have historically been used to manage anorexia in cats. These are currently not recommended for that purpose due to possible adverse effects (Agnew and Korman 2014).

2.2.4.2. Nutritional Support

Nutritional support plays a significant role in successful patient management (Quimby et al. 2010). A nutritional assessment should be done for all hospitalized patients, including a determination of the number of calories needed. This can be achieved by calculating resting energy requirements (RER): “RER = 70 x body weight in $kg^{0.75}$” for pets of any weight; or “RER = (30 x body weight in kg) + 70” if body weight is between 3 and 25 kg (Johnson and Freeman 2017; Taylor et al. 2022; Alenza 2024). Body weight should be monitored daily, if possible, and total calories fed should be adjusted by up to 10% every 48-72 hours based on weight changes (Taylor et al. 2022).

It is important to note, however, that in hospitalized patients, the immediate goal is not to achieve weight gain but rather to minimize further loss of lean body mass (Chan 2014).

Food preferences should be assessed, as cats can be picky eaters, and understanding the patient’s favored food textures and flavors can be a significant help in achieving voluntary feeding (Johnson and Freeman 2017; Taylor et al. 2022; Alenza 2024). Dividing the food into small meals and giving the patient treats and baby food may also tempt the feline patient to eat (Miller 2016). Warming the food is also a trick that may be helpful, as higher food temperature can enhance aroma; however, this practice may be counterproductive, as increasing food smell may also increase nausea in some patients (Michel 2001).

While these tips may prove useful, in some animals, more drastic measures should be taken. The impact of early nutritional intervention has been studied mostly in dogs, and evidence shows that it greatly improves patient outcome (Serón-Arbeloa et al. 2011; Liu et al. 2012; Chan 2020). Current guidelines state that nutritional interventions (such as placement of a feeding tube or parenteral nutrition) in cats should be implemented if the patient: has been consuming less than 80% RER for three or more days; is physically unable to consume an adequate amount of food (e.g. disorders of the oral cavity); is anticipated not to be able to consume an adequate amount of food (e.g. following a major surgery); is considered at a high risk of malnutrition; or if there is a need to facilitate medication compliance (Taylor et al. 2022).

Placing a feeding tube can be a valuable tool for nutritional support. Common types of feeding tubes include nasoesophageal, esophagostomy, and gastrotomy tubes, each with its own benefits and problems (Gajanayake 2014; Chan 2020; Taylor et al. 2022; Lopez 2024). Jejunostomy tubes are also a possibility, but they are rarely placed in feline patients (Taylor et al. 2022). Diet choice depends on the patient's specific needs and diagnosis, and food intake in patients with a feeding tube should be increased slowly to avoid the development of refeeding syndrome (Chan 2020; Taylor et al. 2022).

Parenteral nutrition involves the administration of nutrients via intravenous infusion. It can be considered in patients unable to tolerate enteral feeding, but this method is associated with a higher complication rate, making enteral nutrition preferred when possible (Taylor et al. 2022).

2.3. Mirtazapine

Mirtazapine is a tetracyclic antidepressant that was first commercialized in the 1990s. It was originally used to treat moderate to severe depression in human patients, as well as some of the symptoms associated with it. It has been shown to have the potential to improve appetite and decrease nausea in cancer patients (Kast and Foley 2007) and, in women, was shown to increase body weight and body fat mass (Laimer et al. 2006).

In veterinary medicine, the drug has gained some popularity, primarily for its orexigenic potential (Quimby and Lunn 2013; Agnew and Korman 2014; Ferguson et al. 2016; Quimby et al. 2020). Mirtazapine quickly became a powerful tool in the arsenal of veterinarians when it came to tackling anorexia in cats, being used “off-label” in a tablet or capsule format up until recently. This practice came with some challenges, including the problems associated with splitting human tablets, potentially leading to imprecise or incorrect dosages and, occasionally, overdoses (Ferguson et al. 2016).

Moreover, not all feline patients are easy to medicate orally, especially those who aren’t eating to begin with. Forcing oral medication in these patients, who are already reluctant to eat, could increase nausea and anorexia and may decrease patient well-being both in the hospital and at home. Oral medication in some cats may even go so far as to create a rift in the owner-cat relationship and represent a source of frustration for owners, decreasing their compliance (Benson et al. 2017; Sivén et al. 2017).

2.3.1. Transdermal mirtazapine

Transdermal medications bypass some of the constraints of oral medications and have gained popularity recently for their ease of administration, improving compliance and patient well-being (Hill et al. 2011).

However, not all medications can be given transdermally. To predict the absorption, distribution, metabolism, and excretion of a drug, Lipinski’s “Rule of Five” describes four physicochemical parameters that predict the likelihood of poor oral absorption and permeability (Lipinski 2000). More recently, investigators have adapted this system to apply more strictly to

transdermal drugs, since the skin barrier is much more restrictive than the intestinal one. So, ideally, drugs that can be administered transdermally fall under these categories: 1) < 2 hydrogen donors; 2) molecular weight < 335 Daltons; 3) log p (n-octanol/water partition coefficient) < 5; 4) < 5 hydrogen acceptors (Choy and Prausnitz 2011). Mirtazapine has no hydrogen donors, a molecular weight of 265 Daltons, a log P coefficient of 2.9–3.2, and only three hydrogen acceptors. Because of this, transdermal administration of mirtazapine was deemed suitable, and the drug was developed for transdermal use (Mirtazapine 2005; Benson et al. 2017).

In 2019, the first mirtazapine-containing veterinary medicine in Europe received approval from the European Medicines Agency. Mirataz®, a transdermal ointment containing mirtazapine as its active ingredient, is marketed by Dechra Veterinary Products as a medical solution to increase appetite and promote weight gain in cats with chronic illnesses (Mirataz 2020).

In the Mirataz Summary of Product Characteristics (2020), the recommended dosage is 2 mg of mirtazapine – corresponding to a 3.8cm line of ointment – per cat once daily for 14 days. The ointment should be applied in the ear's inner pinna, alternating between ears each day. The product is not advised for pregnant or lactating cats, cats less than 7.5 months old, or cats weighing less than 2 kg.

The inner pinna of the cat's ears is commonly chosen as the preferred application site for transdermal drug studies. Due to its less hairy, highly vascular nature, this area shows the most promise for the absorption of transdermal drugs (Sartor et al. 2004; Helms 2007; Hill et al. 2015). Moreover, cats cannot directly lick this area, allowing the drug to stay in contact with the skin for longer, most likely improving absorption and reducing oral ingestion.

Since the drug is absorbed through the skin, the Mirataz Summary of Product Characteristics (2020) encourages owners and veterinary staff applying the product to take safety measures. These include using gloves when applying the ointment, washing their hands thoroughly, and avoiding contact with the cat for the first 12 hours after each application. Despite its many benefits, this last point can put a strain on the owner-cat relationship. However, a study by Williams et al. (2017) showed that, for body petting, residues from mirtazapine ointment were very low after the 0.5-hour mark (although ear petting showed more significant residues in the first few hours). This could mean that petting the cat after that time frame is unlikely to result in substantial human exposure, so long as the ears are avoided, and the 12-hour mark may be somewhat conservative.

In any case, owners seem to prefer the transdermal ointment over oral mirtazapine, according to a study by Carvalho et al. (2025). In this survey, 78% of owners claimed to like

the transdermal form better due to its ease of administration, while 22% preferred oral mirtazapine due to its lower cost.

2.3.2. Pharmacodynamics and Pharmacokinetics

Mirtazapine's mechanism of action is complex and not completely understood. The drug acts as an antagonist at central presynaptic α2 receptors of noradrenergic and serotonergic neurons. These receptors usually inhibit further neurotransmitter release, meaning that the antagonism provided by mirtazapine results in an increased release of norepinephrine and serotonin to the synaptic cleft. Mirtazapine also inhibits histamine H1 receptors and has a potent serotonergic antagonist activity by blocking 5-HT2A, 5-HT2C, and 5-HT3 receptors, while not significantly affecting 5-HT1 receptors. This process means that only 5-HT1 receptors are stimulated, which is the primary mechanism of the drug's antidepressant effect. Antagonism of 5-HT3 receptors explains the anti-nausea and anti-emetic effect, while mirtazapine's action on 5-HT2C and H1 receptors may be responsible for the drug's orexigenic effect. The increase in norepinephrine could also explain its appetite-enhancing impact, since it can act on other α receptors to increase appetite. Effects on H1 receptors may also contribute to sedating effects. Additionally, the drug appears to affect leptin and tumor necrosis factor-α, potentially explaining its weight-gain effects (Anttila and Leinonen 2001; Mirtazapine 2017; Mirataz 2020; Budde and McCluskey 2023).

Mirtazapine is metabolized in the liver in a process that involves multiple pathways and can vary by species. It is metabolized via 8-hydroxylation followed by conjugation, N-oxidation, and demethylation. In humans and guinea pigs, this process is followed by conjugation to glucuronic acid (Timmer et al. 2000; Budde and McCluskey 2023). In cats, the exact metabolic process has not been studied, but it is probably similar.

In human patients, mirtazapine displays linear pharmacokinetics (Timmer et al. 2000). However, in cats, reality is different: oral mirtazapine does not seem to show linear pharmacokinetics, with the elimination half-life of about 9 hours when using the lowest effective dose of 1.88 mg, but this number goes up to 16 hours if the dose is 3.75 mg (Quimby et al. 2020). Considering mirtazapine's metabolism and cats' deficient glucuronidation, caused by a deficiency of UDP-glucuronosyltransferase enzymes (Court 2013), there's a strong possibility that the increased elimination half-life at higher dosages is due to saturation of the glucuronidation system.

In humans, elimination occurs via urine (75%) and feces (25%). Liver and moderate kidney impairment seem to decrease mirtazapine clearance by 30%, with that number going

up to 50% in cases of severe kidney disease (Timmer et al. 2000). Similarly, the elimination half-life of oral mirtazapine is prolonged in cats with liver disease (13.8 hours with an oral dose of 1.88 mg) (Fitzpatrick et al. 2018), and chronic kidney disease (CKD) seems to delay clearance (Quimby et al. 2011).

Transdermal mirtazapine appears capable of achieving therapeutic levels and can maintain a steady serum concentration for longer than its oral counterpart (at least 48 hours after administration) (Benson et al. 2017). Compared to an oral dose, a single dose of transdermal mirtazapine has a relative bioavailability of around 65%, slower absorption, and lower maximum concentration. However, after 4-7 days of once-daily treatment, plasma levels of mirtazapine seem to reach a steady state, with differences from the oral dosage decreasing (Buhles et al. 2018). The elimination half-life is longer, at about 25.6 hours, after administration of 0.5 mg/kg (Mirataz Summary of Product Characteristics 2020).

2.3.3. Therapeutic efficacy

In feline patients, mirtazapine – in both its oral and transdermal form – has been shown to increase food intake and weight gain (Quimby et al. 2010; Quimby and Lunn 2013; Benson et al. 2017; Poole et al. 2019; Fantinati et al. 2020; Quimby et al. 2020). When it comes to its use in diseased cats, its efficacy has been particularly demonstrated in those with CKD (Quimby and Lunn 2013; Quimby et al. 2020). It could, additionally, be considered an option to combat anorexia and weight loss in cats undergoing chemotherapy, according to a study by Ferro et al. (2022), but further studies are needed.

There seem to be no significant differences in therapeutic efficacy between administering the drug at a high dose (over 3.75 mg) or a low dose (1.88 mg) (Quimby et al. 2010; Quimby et al. 2020).

Mirtazapine also appears to have antiemetic effects in cats with CKD (Quimby and Lunn 2013), which could represent an additional benefit of the medication. One study by Giorgi and Owen (2012) hypothesized that mirtazapine could even be used as an analgesic in a multidrug approach to chronic pain, but such an application needs further study.

It is, however, important to note that while many studies support the use of mirtazapine, as well as its clinical efficacy, data regarding the long-term safety of the drug is limited.

2.3.4. Adverse effects

Mirtazapine is known to cause some adverse effects. Oral mirtazapine has been reported to cause adverse effects such as vomiting, hyperactivity, and vocalization, among others. These signs are more often seen in cats following an accidental overdose, with that reason accounting for up to 70% of cases (Ferguson et al. 2016).

Mirataz seems to cause similar side effects, with the additional possibility of application site reactions (Mirataz Summary of Product Characteristics 2020). In a study by Carvalho et al. (2025), 20% of owners reported side effects after using Mirataz. A study by Poole et al. (2019) showed that after transdermal mirtazapine application, hyperactivity was present in 7% of cats, vocalizing in 11.3%, vomiting in 11.3% and application site erythema in 10.4%; however, there were no significant differences in these last two side effects between the test and control (placebo-controlled) groups.

Higher doses of mirtazapine are associated with a higher incidence of adverse effects (Quimby et al. 2010; Ferguson et al. 2016; Benson et al. 2017). However, adverse effects appear unrelated to a cat's body weight or the presence of CKD (Poole et al. 2019).

A dose-dependent increase in liver enzymes has been reported in a human patient receiving mirtazapine (Adetunji et al. 2007). Similarly, an increase in ALT is listed as a possible adverse effect of Mirataz treatment by the manufacturer (Mirataz Summary of Product Characteristics 2020) and was reported in one cat in a study by Quimby and Lunn (2013) after the use of oral mirtazapine. This increase in ALT resolved after discontinuation of mirtazapine, and the mechanism behind it is unclear. Additionally, mirtazapine may cause an increase in blood urea nitrogen levels, unaccompanied by an increase in serum creatinine (Poole et al. 2019).

In humans, mirtazapine has been reported as a possible (albeit rare) cause of serotonin syndrome (Hernández et al. 2002; Wagner 2024), especially when used in conjunction with other serotonergic drugs (Wu et al. 2015). Serotonin syndrome is a potentially life-threatening condition caused by excessive serotonergic stimulation. Signs tend to fit into three categories: autonomic hyperactivity, neuromuscular signs, and altered mental status (Indrawirawan and McAlees 2014; Coleman 2023). Serotonin syndrome is also a possible but rare adverse effect of mirtazapine in cats, although the occurrence is not well studied in feline patients (Ferguson et al. 2016).

Finally, mirtazapine has been associated with blood dyscrasias in human patients, although this situation seems extremely rare and, to the best of the author's knowledge, hasn't been reported in animals (Hutchison 2001; Kawano et al. 2022; Budde and McCluskey 2023).

If cats experience minor adverse effects from the use of mirtazapine, discontinuation of the drug or a reduction of 50% in drug dose is advised (Taylor et al. 2022).

3. THE EFFECT OF TRANSDERMAL MIRTAZAPINE ON THE APPETITE RECOVERY TIME IN HOSPITALIZED CATS WITH HEPATOBILIARY DISEASE: AN AMBISPECTIVE STUDY

3.1. INTRODUCTION

Anorexia is a common and important clinical sign often observed in feline patients (Delaney 2006; Agnew and Korman 2014; Robinson et al. 2015; Alenza 2024), particularly in those suffering from hepatobiliary conditions (Cocker and Richter 2017; Nelson and Couto 2020). The lack, or decrease, of voluntary food intake, as well as the loss of lean body mass seen as a consequence, can have a significant negative impact in wound healing and the immune system (Remillard 2002). Cats are especially vulnerable due to their particular metabolic adaptations (MacDonald et al. 1984; Chan 2009; Taylor et al. 2022), and the possibility of anorexia leading to the development of hepatic lipidosis in this species (Center 2005; Miller 2016; Valtolina and Favier 2017).

As a way to combat anorexia, certain appetite-simulating drugs have gained popularity. Mirtazapine, one such drug, is a tetracyclic antidepressant, with a well-documented orexigenic effect on feline patients (Quimby et al. 2010; Quimby and Lunn 2013; Benson et al. 2017; Fitzpatrick et al. 2018; Poole et al. 2019; Fantinati et al. 2020; Quimby et al. 2020). Its efficacy has been shown in both healthy and disease cats (particularly those with CKD). While historically administered to feline patients in an oral form, a transdermal ointment cointaining mirtazapine as its active ingredient, Mirataz® (Dechra Veterinary Products), received approval in 2020 for use in cats with chronic illnesses. However, it has also been widely used off-label in hospitalized, acutely ill patients, and is included in current guidelines for management of anorexia (Agnew and Korman 2014; Taylor et al. 2022).

Despite this, evidence on the use of transdermal mirtazapine on acutely ill, hospitalized patients remains limited. Aditionally, mirtazapine is metabolized by the liver, but there is very little literature accounting for its efficacy in cats with hepatobiliary disease, especially when considering the transdermal ointment application.

3.2. OBJECTIVES

This study was designed to explore the therapeutic effects of transdermal mirtazapine in cats hospitalized with hepatobiliary disease. It was hypothesized that the appetite recovery time in hospitalized cats with hepatobiliary disease would be significantly shorter in the cats receiving mirtazapine treatment, and that this treatment would not result in significant adverse effects.

3.3. MATERIALS AND METHODS

3.3.1. Study design and sample population

The present study consists of an ambispective study, which included data from a randomized prospective clinical trial as well as retrospective cases.

For the randomized prospective clinical trial, client-owned cats were recruited at the Veterinary Teaching Hospital of the Faculty of Veterinary Medicine, University of Lisbon (HEV FMV-ULisboa), during two time periods: from November 2022 to July 2023, and from March 2025 to October 2025.

Cats were considered eligible for this study if they were hospitalized, presenting with anorexia, and had a confirmed or presumptive diagnosis of hepatobiliary disease. Inclusion criteria were: ultrasound features compatible with hepatobiliary disease; increased liver enzyme activity (ALT, ALP, and/or Total Bilirubin (TBil)); and a recent history of anorexia for at least 24 hours prior to hospital admission.

Cats were excluded if they: showed evidence of severe systemic disease that could affect appetite recovery (including but not limited to: exacerbation of CKD, uncontrolled hyperthyroidism, or diabetes ketoacidosis); had a diagnosis of neoplasia; or had history of recent use of appetite-stimulating drugs (within the previous 4 weeks).

Being an ambispective study, cats enrolled were collected either retrospectively or prospectively.

The retrospective cases were acquired from the database of the same veterinary hospital (HEV FMV-ULisboa) from January 2024 to February 2025.

The study was previously evaluated and approved by the Ethical Committee and owners formerly agreed with the use of data for retrospective and prospective studies.

Concerning cases enrolled in the prospective cohort, the cats considered eligible were randomly assigned to one of two groups: a control group (receiving standard supportive

treatment) and a mirtazapine group (receiving standard supportive treatment plus mirtazapine transdermal ointment (Mirataz)). Simple randomization was performed using an online tool (random.org).

Due to the nature of the retrospective data, in that cohort treatment with mirtazapine (or lack thereof) was decided by the medical team at the time of hospitalization. For the inclusion in this study, these cats were assigned to the mirtazapine group if they had received Mirataz treatment (at a dosage of 2mg of mirtazapine per cat, once daily), starting within the first 48 hours of hospitalization, and to the control group if they had not received Mirataz until hospital discharge. Cats that died before achieving voluntary feeding were excluded.

All cats in the prospective clinical trial received supportive therapy, which could include fluid therapy, nutritional care, and treatment for hepatobiliary disease and any underlying conditions. Feeding tubes were placed if needed. Therapy for nausea, pain, pyrexia, ileus, and other clinical signs capable of influencing anorexia was performed when needed to try and minimize the effect of these conditions on the appetite recovery time. All these medical decisions were made by the medical team in charge of the inpatient facility, taking into consideration each cat's particular needs. Decisions regarding treatment for the cats (with the exception of mirtazapine use) were made independently from the study.

Cats in the mirtazapine group received an additional treatment with mirtazapine transdermal ointment (Mirataz), at a dosage of 2 mg/cat, applied in the ear pinna once daily. Mirtazapine treatment started 24 hours after admission to the hospital. Whenever possible, the application site was alternated between the left and right ears each day to try to minimize local irritation.

3.3.2. Data collection

Data collection included signalment information (age, breed, sex, neutered status), clinical signs present at hospital admittance, appetite or anorexia progression, length of hospitalization (days from admittance until discharge), placement of feeding tube, and outcome (death or discharge; discharge before or after appetite was recovered).

Presumptive hepatobiliary diagnoses (hepatic lipidosis, cholangitis, etc.) were assessed for all cats, and definitive diagnoses were recorded whenever achieved. Whenever available, results from liver or gallbladder biopsy, FNA, or bile cytology were also included.

Changes in body weight and laboratory findings (ALT, ALP, and TBil) were recorded whenever possible. Changes in biochemistry parameters were defined as "ΔParameter =

[parameter] value at discharge – [parameter] value at admission" (e.g.: ΔALT = ALT at discharge – ALT at admission). The same formula was used to calculate weight change during hospitalization.

The period, in days, before hospital admission when anorexia was present was defined as pre-admission anorexia duration.

Appetite recovery time was evaluated for each cat. It was defined as the period (in days) from the start of the hospitalization until a cat achieved and maintained an adequate food intake. Adequate food intake was defined as consistent, voluntary feeding that persisted until hospital discharge. When patients were discharged before achieving voluntary feeding, it was defined as consistent and voluntary feeding for at least 3 days and lasting until the next hospital follow-up. The first day on which this criterion was met was recorded as the day of appetite recovery.

Finally, in the mirtazapine group, an evaluation of the medical records was made to scan for the presence of adverse effects.

3.3.3. Statistical analysis

Normality of continuous data was assessed using histograms, Q-Q plots, and the Shapiro-Wilk test. Due to a lack of normality and/or a small sample size, nonparametric tests were used for statistical comparisons. For quantitative data, the median and interquartile range (IQR; first and third quartiles) were reported, and comparison between groups was made using the Mann-Whitney U test. For qualitative data, counts and percentages were reported, and comparison between groups was performed using Fisher's exact test or Pearson's chi-square test. For biochemistry values and weight change during hospitalization, the Wilcoxon signed-rank test was used to compare admission and discharge values within each group.

A comparison between the retrospective and prospective samples was conducted for each variable (except clinical signs and diagnosis) prior to merging to ensure sample homogeneity. The Mann-Whitney U test was used for quantitative data, and Fisher's exact test or the Pearson chi-square test was used for qualitative data. Since a pre-analysis showed that the two datasets did not show a significant difference in any of the variables, they were deemed acceptable to merged and analyzed as a whole.

Missing data were handled using pairwise deletion. Statistical significance was set at $p < 0.05$. All analyses were performed using IBM SPSS version 29.0.0.0.

3.3.4. Ethical considerations

This study was conducted in accordance with institutional ethical standards and approved by the Comissão de Ética para a Investigação e Ensino. Dechra Veterinary Products provided the transdermal mirtazapine (Mirataz®) used in the prospective clinical trial, but the company was not involved in study design, case selection, or statistical analysis.

Written or oral informed consent was obtained from all cat owners prior to their inclusion in the prospective trial. No identifying information was used anywhere in the study, and no photos of participating animals were taken.

3.4. RESULTS

3.4.1. Sample characterization

A flowchart describing enrolment, allocation, and analysis of the cats participating in the study is presented in Figure 1.

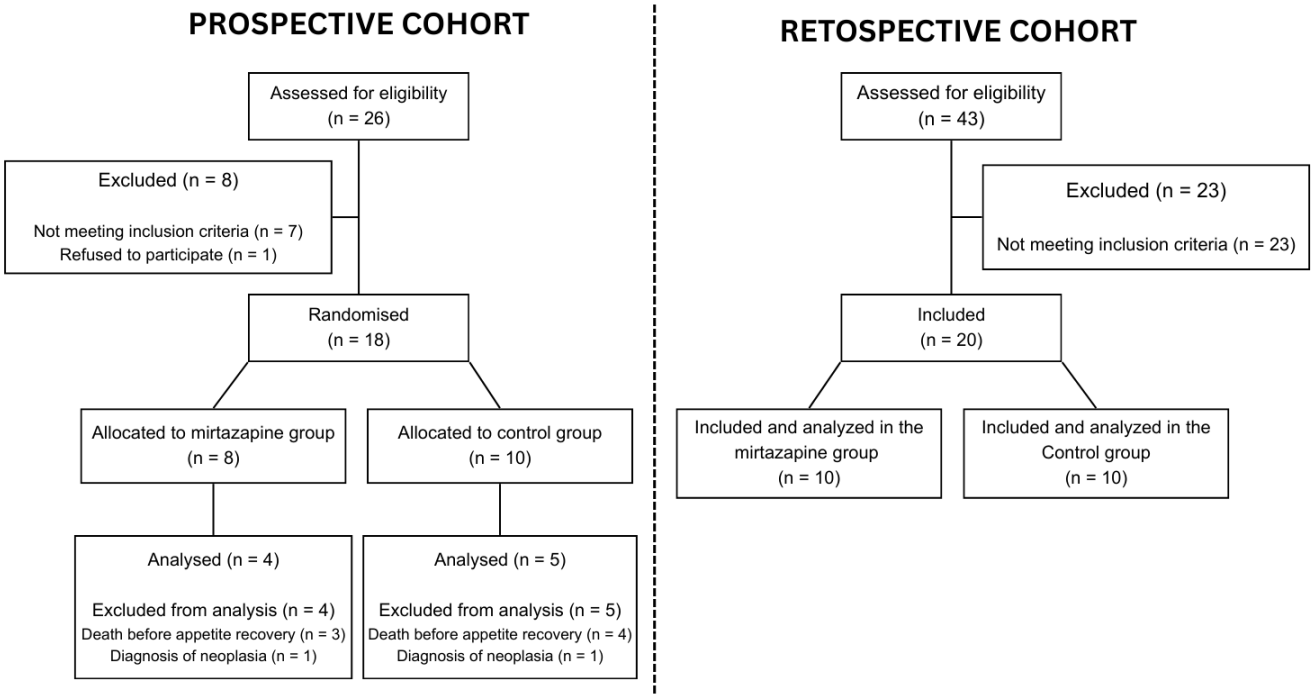


Figure 1 - Consort diagram describing the number of cases participating in this study

A total of nine cats from the prospective clinical trial were part of the ambispective study. To these, 20 cases screened retrospectively were added. In total, 29 cases were included: 14 in the mirtazapine group, and 15 in the control group.

Cats in the mirtazapine group were generally older than those in the control group, but this difference was not significant (p = 0.400). Similarly, no significant differences were found in the sex/neuter status of the cats (p = 0.290). Signalment information is summarized in Table 1.

Table 1 - Sample population baseline characteristics comparison between groups

	All (n = 29)	**Control (n = 15)**	**Mirtazapine (n = 14)**	***p value***
Age, years				0.400
Median (IQR)	7 (4.6 - 12.9)	6.8 (3.7 - 13)	8.1 (6.0 - 12.2)	
Sex/Neuter Status, n (%)				0.290
Female (intact)	3 (10.3)	0 (0)	3 (21.4)	
Female (neutered)	11 (37.9)	6 (40)	5 (35.7)	
Male (intact)	1 (3.4)	1 (6.7)	0 (0)	
Male (neutered)	14 (48.3)	8 (53.3)	6 (42.9)	

Note: IQR: Interquartile range (first and third quartiles).

Three cats had a recorded breed (Maine Coon (n = 1), Sphynx (n = 1), and Siamese (n = 1)), all of which were part of the control group. The remaining were classified as European/Domestic Shorthair. All cats were neutered with the exception of four cats (three from the mirtazapine group and one from the control group).

3.4.2. Clinical Presentation

Clinical signs recorded at hospital admittance are presented in Table 2. All cats (100%) presented with anorexia, since this was one of the inclusion criteria. Other common signs included icterus, dehydration, vomiting, abdominal pain, lethargy, and weight loss (Table 2).

Table 2 - Clinical signs present at hospital admission

	All (n = 29) n (%)	Control (n =15) n (%)	Mirtazapine (n = 14) n (%)
Anorexia	29 (100)	15 (100)	14 (100)
Icterus	22 (75.9)	12 (80)	10 (71.4)
Dehydration	18 (62.1)	9 (60)	9 (64.3)
Vomiting	16 (55.2)	6 (40)	10 (71.4)
Abdominal pain	13 (44.8)	4 (26.7)	9 (64.3)
Weight loss	13 (44.8)	7 (46.7)	6 (42.9)
Lethargy	13 (44.8)	9 (60)	4 (28.6)
Fever	4 (13.8)	2 (13.3)	2 (14.3)
Heart murmur	5 (17.2)	5 (33.3)	0 (0)
Adipsia	3 (10.3)	3 (20)	0 (0)
Drooling	3 (10.3)	1 (6.7)	2 (14.3)
Hypothermia	3 (10.3)	1 (6.7)	2 (14.3)
Panting	2 (6.9)	2 (13.3)	0 (0)
Polyuria/Polydipsia	2 (6.9)	1 (6.7)	1 (7.1)
Vocalizing	1 (3.4)	0 (0)	1 (7.1)
Dysphonia	1 (3.4)	0 (0)	1 (7.1)
Hematemesis	1 (3.4)	1 (6.7)	0 (0)
Cough	1 (3.4)	0 (0)	1 (7.1)

In most cats, a definitive diagnosis was not possible, so a presumptive diagnosis was made. Overall, the most common hepatobiliary diagnoses (presumptive or confirmed) were CCHC and FHL, diagnosed independently or together. In some cases, it was not possible to differentiate between CCHC and FHL, or to determine whether the two entities were present together. For clarity, these cats were classified as “CCHC and/or FHL”. CC by itself was present in only two cats (prospective cohort n=1, retrospective cohort n=1), but it was concurrently present in other cases. The frequency of each diagnosis can be seen in Table 3.

Table 3 - Presumptive or definitive diagnoses attributed to the cats

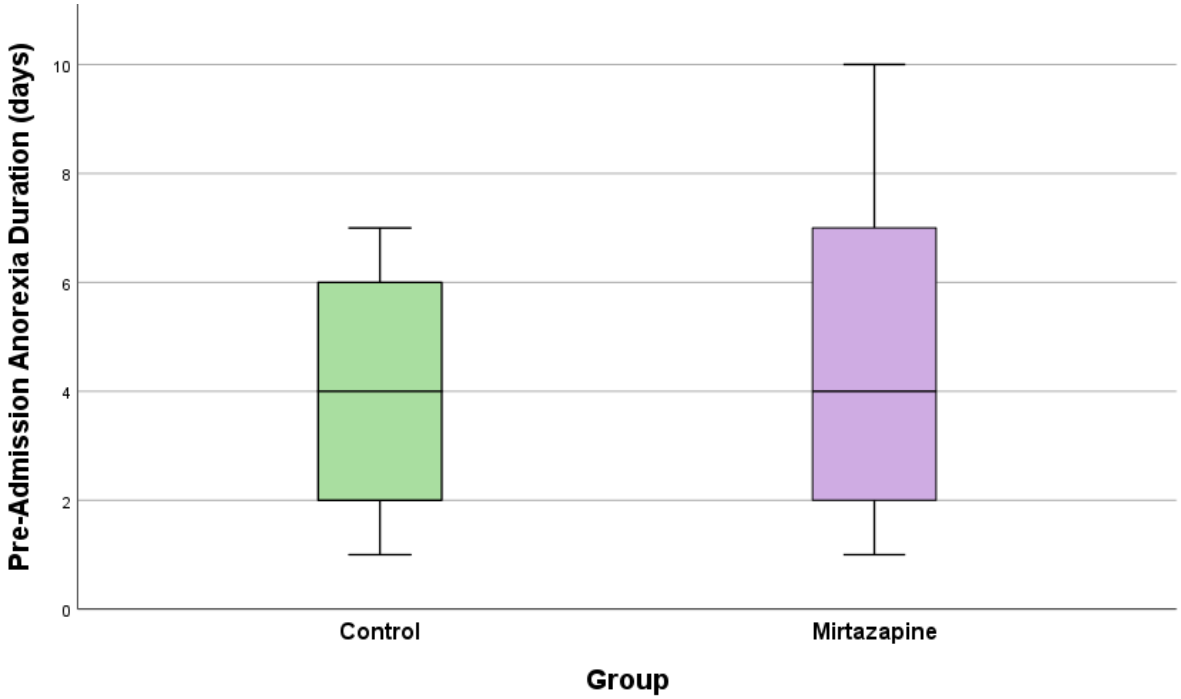
	All (n = 29) n (%)	Control (n = 15) n (%)	Mirtazapine (n = 14) n (%)
CCHC and/or FHL	8 (27.6)	2 (13.3)	6 (42.9)
CCHC and/or FHL + CC	3 (10.3)	1 (6.7)	2 (14.3)
CCHC	2 (6.9)	1 (6.7)	1 (7.1)
CCHC + CC	1 (3.4)	1 (6.7)	0 (0)
CCHC + CC + EHBO	2 (6.9)	1 (6.7)	1 (7.1)
FHL	6 (20.7)	2 (13.3)	4 (28.6)
FHL + CC	2 (6.9)	2 (13.3)	0 (0)
Suppurative CC	2 (6.9)	2 (13.3)	0 (0)
CC + Cholelithiasis	1 (3.4)	1 (6.7)	0 (0)
Toxic Hepatopathy	1 (3.4)	1 (6.7)	0 (0)
EHBO	1 (3.4)	1 (6.7)	0 (0)

Note: CCHC: Cholangitis/cholangiohepatitis complex; FHL: Feline hepatic lipidosis; CC: Cholecystitis; EHBO: Extrahepatic bile duct obstruction.

In 10/29 cats (all from the retrospective group), an ultrasound-guided FNA of the liver was performed. Cytology results were compatible with FHL in nine cats and neutrophilic cholangitis in one cat. A liver biopsy was performed in one cat (part of the prospective clinical trial), with results compatible with both FHL and lymphocytic cholangitis. In eight cats, bile culture and cytology were performed; five had normal results, and three showed signs of suppurative/neutrophilic cholecystitis.

Pre-admission anorexia duration was obtained for all cats in the prospective clinical trial, but information was missing in three cats (control n = 2, mirtazapine n = 1) from the retrospective cohort. Median pre-admission anorexia duration was the same for both groups, and the difference was not significant ($p = 0.762$; Graph 2).

Graph 2 - Pre-admission anorexia duration (in days) distribution in each group. Bars represent median, first and third quartiles, and minimum and maximum values.



A feeding tube was placed in 79.3% of cats (86.7% of the control group; 71.5% of the mirtazapine group), with 44.8% of these occurring within the first 24 hours of hospitalization (40% of the control group; 50% of the mirtazapine group). This means that more cats in the control group had a feeding tube placed, but more cats in the mirtazapine group had it placed early. However, these differences between groups were not significant ($p>0.05$ for both the overall tube placement and the placement within the first 24 hours).

3.4.3. Appetite Recovery Time and Hospitalization Length

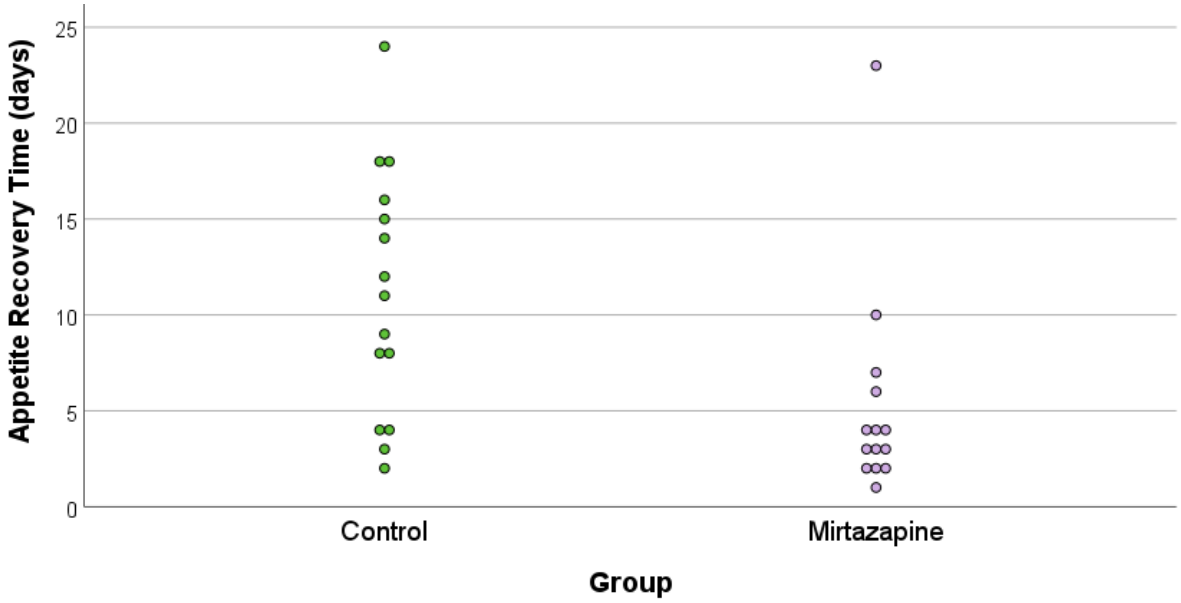
Cats under mirtazapine treatment recovered appetite and restarted voluntary feeding significantly earlier than those in the control group (Table 4; Graph 3). Patients treated with mirtazapine also had a shorter median hospitalization length, with a significant difference between groups (Table 4).

Table 4 - Appetite recovery time and hospitalization length (in days) comparison between groups

	All (n = 29)	Control (n = 15)	Mirtazapine (n = 14)	*p value*
Appetite recovery time, days				0.007
Median (IQR)	6 (3-13)	11 (4-16)	3.5 (2-6.25)	
Hospitalisation length, days				0.018
Median (IQR)	7 (4.5-9)	7 (7-10)	5 (3-8)	

Note: IQR: Interquartile range (first and third quartiles).

Graph 3 - Appetite recovery time (in days) in each group. Each dot represents one cat.



3.4.4. ALT, ALP, and TBil

Admission and discharge values for ALT, ALP, and TBil did not differ significantly between groups (all $p > 0.05$). In general, ALT and TBil changes (Δ) showed greater decreases in the mirtazapine groups, but the differences between groups were not significant ($p = 1$ and $p = 0.841$, respectively).

Within-group comparisons showed that ALT and ALP values decreased significantly from admission to discharge in the mirtazapine group ($p=0.003$ and $p=0.008$, respectively) and

in the control group (p=0.005 and p=0.002, respectively). TBil showed a decreasing trend, but the results did not reach significance.

One cat in the mirtazapine group showed an increase only in ALT values (from 253 to 338 U/L). Additionally, one cat (from the control group) showed an increase only in ALP, five cats (mirtazapine group n=2, control group n=3) showed an increase only in TBil, and one cat (control group) showed an increase in all three values.

Complete descriptive statistics are available in Appendix Table 1. Additionally, information on missing data is presented in Appendix Table 2.

3.4.5. Body Weight Changes

All cats were weighed at admission. One cat from the mirtazapine group and three cats from the control group were not weighed at discharge.

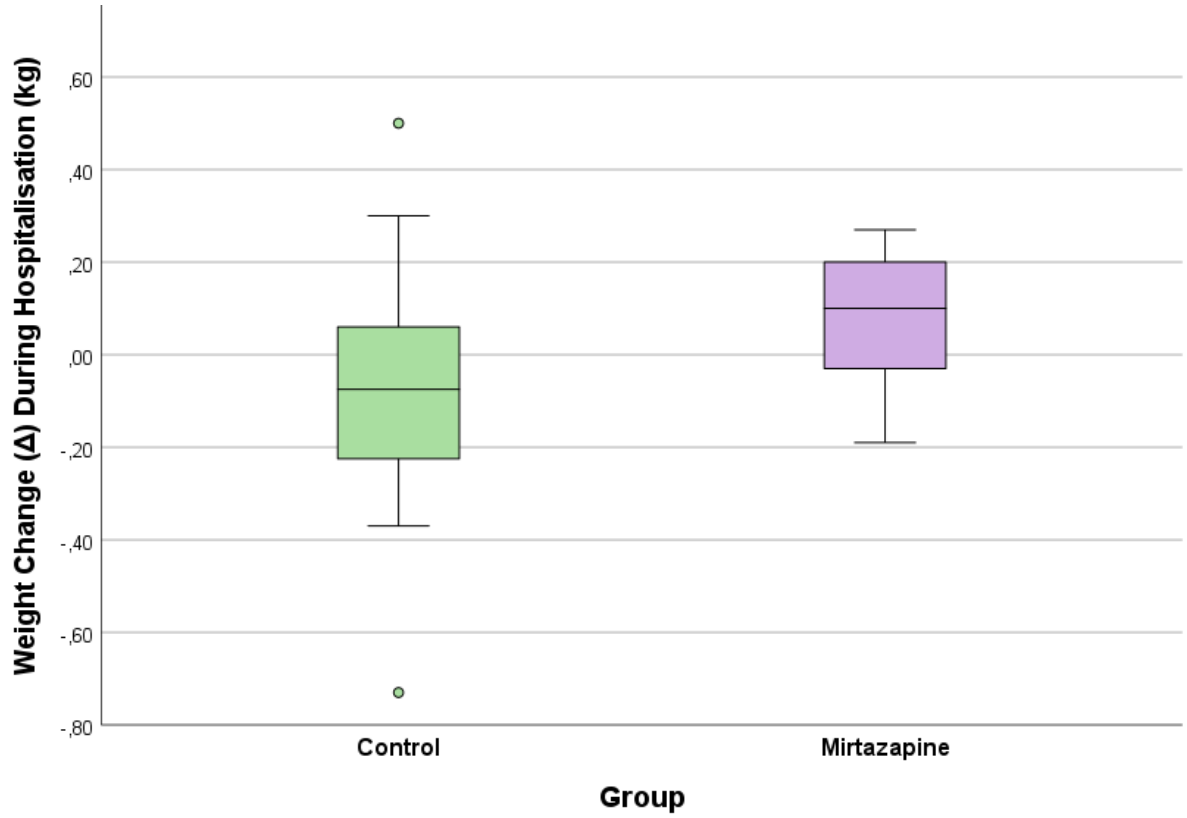
In general, cats in the mirtazapine group weighed more at admission and discharge, but differences between groups were not significant (p = 0.847 for admission values, p = 0.470 for discharge values). Cats in the mirtazapine group more often gained weight during hospitalization, whereas cats from the control group typically lost weight (Graph 4). However, while the comparison of weight change (Δ) between groups approached significance, it did not reach it (p = 0.087). Within-group comparisons of values between admission and discharge were not significant.

3.4.6. Adverse effects

No adverse effects were reported in the cats in the mirtazapine group during the conduction of the prospective clinical trial.

One cat in the retrospective cohort developed pica after 4 days of mirtazapine treatment, and the drug was discontinued. No further mention of the behavioral issue was made after the Mirataz treatment was discontinued, and the cat continued to eat voluntarily.

Graph 3 - Changes in weight during hospitalization in each group. Bars represent median, first and third quartiles, and minimum and maximum values. Outliers are shown using dots.



3.4.7. Outcome

In this study, 46.7% of the cats in the control group and 21.4% in the mirtazapine group were discharged before appetite was recovered. Differences between groups were not considered statistically significant (p = 0.245).

Death rates were analysed using only the prospective sample. In this dataset, 61.1% of the cats survived the hospitalization period and were discharged, while 38.9% died. In the control group, 40% of cats died, and in the mirtazapine group, this percentage was similar at 37.5%. There was no significant difference between groups (p = 1). This study does not account for possible deaths after hospital discharge.

3.5. DISCUSSION

The present study tested the effect of transdermal mirtazapine (Miratazaz) on the appetite recovery time of cats hospitalized with anorexia and hepatobiliary disease. Overall, findings

point towards a positive outcome from the use of the transdermal drug, with Mirataz significantly decreasing the time until the cats started eating voluntarily: the patients in the mirtazapine group started eating about 3.5 (2 - 6.25) days after admission (median values), whereas in the control group the median was 11 (4-16) days. This seems to align with previous data supporting mirtazapine's orexigenic properties in feline patients (Quimby et al. 2010; Quimby and Lunn 2013; Benson et al. 2017; Poole et al. 2019; Fantinati et al. 2020; Quimby et al. 2020) and suggests that its use may prove beneficial in hospitalized patients with hepatobiliary disease.

While mirtazapine as Mirataz is commercialized for use in chronically ill cats (Mirataz 2020), the drug has been used by clinicians in hospitalized, acutely ill patients and is included in current guidelines for anorexia management in hospitalized cats (Taylor et al. 2022). Anorexia can have a serious impact on these patients, and so restoring caloric intake early can be crucial for recovery (Stockman 2025). However, data regarding mirtazapine's efficacy in acutely ill patients remains limited, and even more so in hospitalized patients with hepatobiliary disease, despite mirtazapine's liver metabolism. In this study, the majority of the cats showed no increases in liver enzymes after the use of mirtazapine, supporting that a biochemical increase of liver parameters due to a potential toxic hepatopathy is unlikely in these patients (further discussed below). The present study was designed to help bridge this knowledge gap, and these results provide preliminary evidence for the use of transdermal mirtazapine in these patients. Further studies are needed to determine whether these findings can be replicated in all acutely ill patients, rather than only in those suffering from hepatobiliary conditions.

The use of Mirataz was also associated with shorter hospitalization periods in these cats. This result makes sense in theory, seeing as anorexia has a well-known (previously mentioned) impact on overall health and is often a decisional parameter for hospital discharge.

While there were no significant differences between the control and test groups for age, sex/neutered status, and pre-admission anorexia duration, some imbalances were present (e.g. cats in the mirtazapine group were typically older than those in the control group). To the best of the author's knowledge, there is no evidence linking these variables to appetite recovery in cats with hepatobiliary disease. Regardless, due to the small sample size, the clinical relevance of the observed differences remains uncertain. Feeding tube placement occurred similarly across groups and is unlikely to have influenced the results of this study. On a first approach to this research, Carvalho et al. 2024 studied the appetite recovery time in cats with hepatobiliary disease in which a feeding tube was placed. This showed similar (albeit non-significant due to their lower sample size) results.

Information on clinical signs and diagnosis was included only to help in characterizing the population, and conclusions should be taken with care. Notably, a higher proportion of cats presented with icterus in this study than was typically reported (Sherding 2000; Rothuizen 2009). This may reflect that the presence of anorexia involves a worse disease, and such can be accompanied by high TBil and the presence of clinical icterus. Regarding diagnostic data, most cats in this study did not receive a definitive diagnosis, and only one cat underwent a liver biopsy, the current gold standard for liver disease diagnosis (Campbell and Reddy 2004; Center 2023). Additionally, frequent use of FNA in the retrospective dataset may have led to an overdiagnosis of FHL, consistent with the known limitations of this technique (Willard et al. 1999; Nelson and Couto 2020).

Biochemical markers (ALT, ALP, TBil) showed a decreasing tendency over the course of hospitalization in both groups, reflecting a clinical improvement over time. No significant differences were found between groups at any time point. Interpretation of these results is limited due to variable hospitalization lengths, small sample size, and heterogeneity of diagnoses. Regardless, in almost all cats treated with mirtazapine, liver values decreased – a point in favor of the safety of mirtazapine use in these cats, since it would be expected to see an increase in these values if the drug were to worsen the existing liver disease or cause a drug-induced injury.

Although most mirtazapine treated cats did not show an increase in liver enzymes, in a small number of cats, increases in one or more parameters were observed. In one of these cases, a cat receiving mirtazapine displayed an increase in ALT while ALP and TBil decreased. An increase in ALT levels has been reported after mirtazapine use in a human patient (Adetunji et al. 2007) and in a cat (Quimby and Lunn 2013), and is commented as a possible side effect in the Mirataz Summary of Product Characteristics (2020). While disease progression cannot be ruled out, it could be argued that, given the decrease in the other parameters, this situation could have been caused by transdermal mirtazapine. Mirataz use continued after discharge, and ALT values normalized about two weeks after, but it is unclear from hospital records whether the drug had been discontinued by that point. In any case, this normalization of the values suggests that even if the ALT increase was caused by mirtazapine use, this change is most likely not permanent. The cat may still have benefited of the use of the drug during hospitalization, ensuring a quicker recovery.

Weight changes in this study also followed expected patterns: cats in the mirtazapine group tended to gain weight during hospitalization, while those in the control group tended to lose weight. These results align with those previously published by Poole et al. (2019) in chronically ill cats. However, while these results approached significance, they did not reach

it, and their interpretation should remain cautious: discharge occurred at variable times, and other factors, such as fluid therapy, different medications, and feeding tube placement, may have influenced body weight. Additionally, weight gain in hospitalized cats does not necessarily mean a gain of lean body mass and can just as likely be due to shifts in water balance (Chan 2014).

In the prospective arm of this study, no cats showed adverse reactions to the use of Mirataz. This could be due to the small sample size, which may have allowed eventual side effects to go undetected. Additionally, some of the clinical signs more associated with Mirataz use are behavioral, such as increased agitation or vocalization (Poole et al. 2019; Mirataz Summary of Product Characteristics 2020; Carvalho et al. 2025), which could be masked in acutely ill, hospitalized patients. In the retrospective sample, one cat had the Mirataz treatment discontinued after exhibiting pica behaviors (particularly, eating the litter). There was no further mention of this behavior after medication discontinuation, and no mention of whether the cat had a history of such a behavior. Because of the inherent nature of retrospective data, it was harder to evaluate for side effects in this sample, and the fact that there were no other mentions of side effects does not necessarily mean they were not present. Overall, as was seen in reports of the general population (Benson et al. 2017; Poole et al. 2019; Quimby et al. 2020; Ferro et al. 2022), mirtazapine transdermal ointment seems to be safe and well tolerated in patients hospitalized with hepatobiliary disease, but further studies, more directed at the drug's safety and side effects, are needed in order to expand these preliminary data.

Mortality for the cats recruited in the prospective clinical trial was relatively high (38.9%). This number likely reflect the mortality rates associated with hepatobiliary disease, particularly that of hepatic lipidosis cases, where mortality can be high (Kuzi et al. 2017; Kuzi and Watson 2024) . Mortality was similar across groups, suggesting that while mirtazapine may help with faster recovery, it does not appear to decrease mortality rates in these cats.

This study comes with its own set of limitations. Importantly, the use of both prospective and retrospective data could be a strong limitation. The small sample size of the prospective clinical trial is by itself a limitation, and the introduction of retrospective data into the study brings biases (including incomplete records and a lack of standardized monitoring) that should be acknowledged. It is important to note, however, that the combination of the prospective and retrospective datasets for the combined cohort was done in order to increase the number of animals enrolled. Furthermore, this study was made only after statistical tests showing no significant differences between them, to ensure sample homogeneity.

A major limitation was that, at the time the study was conducted, the hospital did not weigh the food offered to the animals. This made it impossible to reliably measure food intake

and calculate the percentage of RER the cats consumed, meaning that appetite recovery was not an objective measure but rather a more subjective one. Moreover, the absence of clinician blinding to treatment group assignment could create subconscious bias that might have influenced decision-making.

Because the appetite recovery time could only be measured in cats who survived long enough to restart voluntary feeding, cats who died earlier were excluded. This exclusion could potentially have introduced a survivor bias into the analysis, with the results representing only the surviving population. Still, if present, this effect was most likely small, since the mortality rate was similar across groups. In any case, the interpretation of the results must take this limitation into account.

Another limitation was the fact that information on the total length of mirtazapine treatment was very limited. In most cases, information on mirtazapine use after discharge was scarce and in most cases, it was impossible to assume if the 14-day treatment advised by the manufacturer was completed.

Finally, due to the wide range of possible hepatobiliary diseases in this study, cats received different, personalized treatments. This introduces a degree of heterogeneity that limits the results.

Further research should aim to confirm these preliminary findings in larger, multicenter trials and determine if early appetite recovery reflects better long-term outcomes. It would be interesting to see if mirtazapine's therapeutic effect changes with gravity and type of hepatobiliary disease, and so a stratification by disease type or severity may give valuable information. Additionally, further clinical trials should be made to test whether these results may apply to other diseases and the general acutely ill hospitalized population, rather than just the cats diagnosed with hepatobiliary diseases.

3.6. CONCLUSION

In this study, cats who received transdermal mirtazapine treatment (Mirataz) restarted eating significantly earlier than those who did not. Moreover, these cats had shorter hospital stays, supporting that Mirataz can be an effective appetite stimulant in cats with hepatobiliary disease. Cats in the mirtazapine group also tended to gain weight during hospitalization, while those in the control group tended to lose weight, but these results did not reach significance. Furthermore, no major adverse effects were observed, and Mirataz seems to be safe and well-tolerated in this population.

Regardless of the assumed limitations that influence the presented results, this study opens new insights in favor of the use of Mirataz in anorectic patients hospitalized with hepatobiliary disease.

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5. APPENDICES

Appendix Table 1 – Complete comparison of biochemical values in both cohorts

	Control	Mirtazapine	p value[1]
ALT			
admission	501 (310 - 1000)	485 (239 - 688)	0.652
discharge	202 (122 - 414)	172 (75-287)	0.392
change (Δ)	(-210) [(-449) - (-118)]	(-363) [(-420) - (-89)]	1
p value[2]	0.005	0.003	
ALP			
admission	259 (193 - 679)	340 (65 - 569)	0.719
discharge	232 (67 - 345)	208 (81 - 394)	0.975
change (Δ)	(-131) [(-266) - (-18)]	(-152) [(-392) - (-63)]	0.477
p value[2]	0.002	0.008	
Tbil			
admission	7,3 (4.4 – 11.3)	3.6 (1.1 – 9.4)	0.201
discharge	3,3 (1.2 – 9.4)	3,0 (0.6 – 7.5)	0.709
change (Δ)	-0.9 [(-6.9) – 1.5]	(-1.8) [(-5.9) – 0.1]	0.841
p value[2]	0.139	0.084	

Note: ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; TBil: Total Bilirubin. Values presented are median (first quartile-third quartile)

[1] - p value obtained from the statistical comparison between the control and mirtazapine groups

[2] - p value obtained from the statistical comparison of admission and discharge values within each group

Appendix Table 2 – Number of cats missing data on biochemical parameters

	Control	Mirtazapine	Total
ALT, n			
admission	1	0	1
discharge	2	3	5
change	3	3	6
ALP, n			
admission	0	2	2
discharge	1	5	6
change	1	5	6
Tbil, n			
admission	0	1	1
discharge	1	4	5
change	1	4	5

Note: ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; TBil: Total Bilirubin.

Apendix 3 – Abstract submitted for presentation at the 2026 ACVIM Forum

Title: Effect of transdermal mirtazapine on appetite recovery in hospitalized cats with hepatobiliary disease

Background – Anorexia is a well-known clinical sign associated with hepatobiliary disease in cats. Mirtazapine is widely used as an appetite stimulant, but data regarding its efficacy and safety in acutely ill feline patients with hepatobiliary disease remains limited.

Hypothesis/Objectives – This study aims to explore the effect of transdermal mirtazapine in cats hospitalized with hepatobiliary disease. It was hypothesized that cats receiving mirtazapine treatment would resolve anorexia sooner, and that the treatment would not result in clinically relevant side effects.

Animals – Twenty-nine client-owned cats hospitalized with hepatobiliary disease and showing signs of anorexia were included: 15 in the control group and 14 in the mirtazapine group.

Methods – An ambispective study was performed, combining a prospective randomized clinical trial with a retrospective cohort study. All cats received standard and individualized treatment for hepatobiliary disease, with cats in the mirtazapine group receiving concurrent treatment with mirtazapine transdermal ointment (2mg/cat q24h) (Mirataz®).

Results – Cats receiving adjunctive mirtazapine treatment resumed voluntarily eating a median of 7.5 days earlier than controls ($p = 0.007$) and had shorter hospitalization periods ($p = 0.018$). Although the difference was not significant ($p = 0.087$), cats receiving mirtazapine also showed a trend toward weight gain during hospitalization, in opposition to controls, which tended to lose weight. No clinically relevant side effects were observed.

Conclusions and Clinical Importance – When used in conjunction with individualized symptomatic treatment, the use of transdermal mirtazapine seems to be a safe adjunctive therapy that may facilitate a faster recovery from anorexia in cats with hepatobiliary disease.