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Retrospective study on the use of venlafaxine in 176 cats diagnosed with behavioral disorders

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ABSTRACT

Behavioral disorders in cats can severely affect their well-being and the owner-pet relationship, sometimes resulting in relinquishment or euthanasia. While selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) have been routinely used, venlafaxine, a serotonin norepinephrine reuptake inhibitor (SNRI) that has been effective in treating various human psychiatric conditions, offers potential for veterinary use in addressing feline behavioral disorders.

This retrospective study evaluates the use of venlafaxine in 176 cats diagnosed with a variety of behavioral disorders to assess its efficacy, safety, and ease of administration within privately owned-cats. Cats were from multiple veterinary practices which collected data on dosage, administration, adverse effects, and overall treatment outcomes. Both quantitative and qualitative data were gathered through veterinary records and owner surveys, allowing for a comprehensive analysis of venlafaxine's effect on cat behavior and wellbeing.

Findings from this study highlight venlafaxine as an effective treatment for a broad spectrum of behavioral disorders in cats, with a noteworthy rate of owner compliance in administering the drug, facilitated by its convenient formulation. Adverse effects were reported in 35.4% of the cats (N=61), they were primarily minor and of short duration. Dosage adjustments based on individual responses and specific behavioral diagnoses improved treatment outcomes and minimized adverse effects. A significant portion of the treated population exhibited substantial behavioral improvement, with 20% (N=35) of cats successfully weaned off the medication without a relapse of clinical signs.

Venlafaxine represents a promising pharmacological intervention for behavioral disorders in cats, meriting further investigation in prospective studies.

Introduction

Venlafaxine is a dual serotonin (5-HT) and noradrenaline reuptake inhibitor (NRI). Venlaxine was the sixth most prescribed antidepressant in humans in the USA in 2007, with 17.2 million prescriptions, and the second-most prescribed in 2008 (Pugh et al., 2013).

Venlafaxine is available in different formulations depending on the country. In some regions, only the extended-release (XR) version is available, while in others, only the immediate-release formulation can be accessed.

Venlafaxine is an alternative psychopharmacological treatment to the SSRIs in human patients in many disorders, and it has been proven effective in the treatment of major depression (Aldosary et al., 2022; Coutens et al., 2022; Fagiolini et al., 2023), attention-deficit hyperactivity disorder (ADHD) (Zarinara et al., 2010; Amiri et al., 2012), social phobia (Glue, 2012), generalized anxiety disorder (Rynn et al., 2007), treating panic disorder (Pollack et al., 2007). It has also been used to treat conditions with a comorbid psychological/behavioral components such as fibromyalgia (VanderWeide et al., 2015), psoriasis (Tzeng et al., 2021), and intestinal bowel disease (Sharbafchi et al., 2020).

Venlafaxine comprises a racemic mixture of two enantiomers (Nichols et al., 2011). Its plasma concentration is similar for both enantiomers in humans and dogs (Howell et al., 1993, 1994). Venlafaxine is absorbed by the gastrointestinal tract and bio transformed in the liver

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by cytochrome 2D6 (CYP2D6) to generate two main metabolites: an active metabolite called *O*-desmethylvenlafaxine (desvenlafaxine) and a secondary metabolite called *N*-desmethylvenlafaxine. Other metabolites seem to play a minor role in the mechanism of action of venlafaxine (Lin et al., 2019). The serotonergic effects of venlafaxine occur at low doses, while its noradrenergic effects are progressively enhanced as the dose is increased (Berridge and Waterhouse, 2003; Ross and Van Bockstaele, 2021). It is also a weak inhibitor of dopamine reuptake but the clinical effect of this action is unclear (Coutens et al., 2022). Like venlafaxine, desvenlafaxine inhibits reuptake of 5-HT (serotonin reuptake inhibitor [SRI]) and NRI, but its NRI actions are greater than its SRI actions (Stahl, 2013). In plasma, desvenlafaxine is usually twice as concentrated as venlafaxine, depending on the genetic profile of the patient with regard to the expression of CYP2D6 (Lin et al., 2019). Because its action is more noradrenaline-based, desvenlafaxine has been purified to produce a selective NRI (SNRI) that is more noradrenaline-oriented than the venlafaxine one (Stahl, 2013).

In humans, several genetic variants of the enzyme CYP2D6 have been identified, leading to different effects of venlafaxine (Preskorn et al., 2009; Nichols et al., 2011) These different profiles might explain the failure of some treatments and the variation of the dose needed from one individual to another, as well as the possible adverse effects observed in some patients and not others (Lin et al., 2019).

Behavioral problems in companion animals affect the quality of life of both pets and their owners (Buller and Ballantyne, 2020; Truffert et al., 2024) to an extend that behavioral disorders are by far the most commonly reported reason for relinquishment (Jensen et al., 2020). Veterinarians have a possible role to play to reduce dogs and cats relinquishments and euthanasia by actively identifying behavioral problems and treating them early (Scarlett et al., 2002).

In dogs, venalafaxine has been proposed as a treatment for cataplexy-narcolepsy (Tonokura et al., 2007), neuropathic pain (Delucchi et al., 2010; KuKanich, 2013), and to treat behavioral disorders such as fear and anxiety (Overall, 2013; Maffeo et al., 2023).

In cats, many behavioural disorders cannot be treated without the help of psychotropic drugs given daily for long periods and combined with behavioural modification. Selective serotonin reuptake inhibitors (SSRIs) (e.g., fluoxetine, Reconcile™) and tricyclic antidepressants (TCAs) (e.g., clomipramine, Clomicalm™) have been the first-line treatment for most behavioral disorders and are licensed for dogs. In Australia Clomicalm™ is licenced for cats.

In cats, venlafaxine has been compared with the simultaneous use of an SSRI (norfluoxetine) and an NRI (thionisoxetine) to increase bladder capacity and urethral sphincter electromyographic activity (Katofiasc et al., 2002). It was concluded that there are unexplained pharmacological differences between the effects of individual compounds that inhibit both noradrenaline (NE) and 5-HT reuptake, and those of a combination of compounds that selectively inhibit either NE or 5-HT reuptake. Venlafaxine's efficacy has also been compared with that of tricyclic antidepressants (TCA). SNRI molecules are likely to have fewer adverse effects than do TCAs since they do not block α1-noradrenergic, histaminic or cholinergic receptors (Bjorvatn et al., 2000).

Venlafaxine toxicity appears limited in cats. Bjorvatn et al showed that full inhibition of the neurons of the dorsal raphe only occurs at doses of at least 5 mg/kg IV (Bjorvatn et al., 2000). Pugh et al. (2013) showed that for 12 cats that ingested their owners' venlafaxine at doses ranging from 5 to 30 mg/kg, six were asymptomatic, while the other six recovered from sedation, depression, arousal, gastrointestinal disorders, tachycardia, and hypertension with fluid therapy (Pugh et al., 2013).

In cats, venlafaxine has been suggested to be useful for the treatment of idiopathic cystitis at doses ranging from 1 to 2 mg/kg PO (Hopfensperger, 2016; Sinn, 2018), and refractory misdirected play and impulse control aggression at a dose of 1.1 mg/kg PO (Pflaum and Bennett, 2020); however dose-determination studies are lacking.

Cats are reluctant to take medications (Sivén et al., 2017) which often leads to a lack of compliance with the veterinary prescription (Taylor et al., 2022) and a possible failure of the cat care. The brand name of venlafaxine, is marketed as Effexor® in the formulation capsular form, containing small granules that are easily taken by cats (Metz et al., 2021).

For all of these reasons, we assessed the possible efficacy and ease of administration of venlafaxine in cats presenting with aggression, house-soiling, and fear in a pilot study (Metz et al., 2021). In this pilot study, all cats included took the medication during the 60 days trial without major difficulties.

The goal of this retrospective study was to further document the use of venlafaxine in cats as a part of the treatment plan in privately owned cats diagnosed by the authors with a variety of behavioral conditions. In some countries, including France, only the extended-release (XR) version is available, while in other countries, only the immediate-release formulation can be accessed.

Most cases in this retrospective study were treated with venlafaxine because the state diagnosis (e.g. phobia, anxiety *sensu* Masson et al., 2024a) was in line with the primary use of this medication, but many cases were treated with venlafaxine after the owners declined the first-choice drug (e.g., fluoxetine, clomipramine) or because its lack of efficacy.

All owners whose cats were in the study were instructed to implement an individual behavioral treatment plan, including environmental modification and behavioral modification, tailored to treat each patient.

We sought to assess the efficacy and ease of administration of venlafaxine across all patients in our pilot study, regardless of treatment outcome. Additionally, we evaluated the occurrence and timing of any adverse effects, possible reasons for treatment interruption, and the dosage of venlafaxine with respect to breed, age, sex, and behavioral diagnoses. We hypothesized that the use of venlafaxine combined with environmental and behavioral modification would lead to a significant improvement of the cat's behavioral condition, as reported by the owner and acknowledged by the veterinarian using standardized assessment tools. We suspected that the main adverse effects would be rare and short-lasting. We hypothesized that the efficacious dosage would vary depending on the behavioral diagnosis.

Material and methods

Inclusion criteria

Cats were included if their first consultation occurred between January 1st, 2019 and June 30th, 2023, were diagnosed with a pathological psychological state (i.e. phobic, anxious, depressive, manic, senile, impulsive, compulsive or dissociated state) (Masson et al., 2024b) by one of the four authors, and were prescribed venlafaxine since the first consultation. A pathological psychological state in animals refers to a condition where neurophysiological processes are misbalanced, leading to maladaptive behavioral responses that are spontaneously irreversible and cause suffering. These states result from the dysfunction of neurophysiological loops that normally help regulate behavior in response to environmental stimuli. When these loops—such as the cortico-striato-thalamo-cortical (CSTC) loop or the amygdala circuit—are excessively activated or dysregulated, they contribute to chronic stress and abnormal behaviors. This dysfunction can manifest in various forms, such as phobic, anxious, depressive, and compulsive states, each linked to specific brain circuits and neurotransmitters (Masson et al., 2024a).

Two of the authors are European specialists in behavioral medicine (ECAWBM diplomates), and the two others have a French diploma in behavioral medicine (respectively DIE de vétérinaire comportementaliste and DU de psychiatrie vétérinaire). All the clinicians collecting the case have an exclusively referral practice in behavioral medicine.

For all treated cats, treatment was implemented according to the patients' presenting problem using an individual environmental modification and behavioral modification plan.

Environmental modifications included ethological advice concerning litter box, food and environmental enrichment in general in order to ensure that the cat needs were met. Depending on the specific case, the veterinarian required a specific part of these environmental modifications and often provided handouts to have a written record of what was explained to the owner.

Behavioral modification was conducted using different techniques such as classical and operant conditioning, especially primary positive reinforcement training (Landsberg et al., 2003; Overall, 2013; Willson et al., 2017). Positive punishment was discouraged in all cases (Grigg and Kogan, 2019) since it leads to poor welfare and more risks of misbehaviors from their cat. To address specific problematic behaviors of the cats, a classical desensitization and counterconditioning with response substitution protocol (DS-CC protocol) was implemented. Depending on the targeted behavior an initial learning was necessary (e.g., teach sit or teach the cat to go on a specific spot). This learning was done in calm and easy contexts without external stimuli or stressful contexts and the DS-CC protocol was only started after this initial learning phase was mastered. Each practitioner provided a specific behavioral prescription and, if needed, handouts to guide the owners in implementing the behavioral modification techniques effectively, ensuring they had the necessary tools and instructions for success.

Venlafaxine was usually prescribed at the starting dose of 1 mg/kg, which corresponds to 4 granules per kg extracted from a capsule of Effexor-XR®. This dosage was administered once daily.

Effexor-XR® capsules contain granules of relatively uniform size, ensuring consistency in dosing. However, practitioners should be aware that in some generic versions the capsules may contain granules of varying sizes or even small tablets, which can complicate accurate dosing. It is advisable for practitioners to ensure they know the number of granules per capsule of the product they are using. A lower starting dose between 0.5 mg/kg and 1 mg/kg was used if the patient previously has adverse effects with another SSRI or TCA or to any other serotoninergic or adrenergic drug, or if the cat was over 8 of age or treated for a concomitant disease (e.g., chronic renal failure). The cat's response to treatment was evaluated by email as needed, until an effective dosage was achieved (i.e., signs improve, and the cat exhibits no adverse effects.). The dose was increased or lowered depending on the results. If the efficacy was considered insufficient by the veterinarian in charge of the case, the dose was increased and if the cat experienced adverse effects, the dose was lowered for at least 2 weeks. The maximum dose used on the cats in our study was 2.5 mg/kg.

During the initial consultation, owners were informed that the drug was used off-labeled and that the main possible adverse effects included sedation, sleepiness, lethargy, pupil dilatation, change in appetite (most likely decrease appetite), and lowering of urine frequency.

Retrospective review of the medical files

All medical records were reviewed to extract the following information: age, sex and reproductive status, breed, weight, date of the first consultation, reason for consultation, number of follow-up consultations (restricted to in-person, only), behavioral diagnoses (including psychological state diagnosis and nosographic diagnoses) (Masson et al., 2024a), other medical diagnoses, additional over-the-counter or psychotropic drugs tried before venlafaxine, starting dosage of venlafaxine, last dosage of venlafaxine in the file (i.e., the effective optimal dosage), concomitant medication (including time and duration), reported adverse effects. The effective dosage of venlafaxine was the lowest dose at which the condition stabilized or that dose to which the patient was weaned, if weaning was possible. This resulted in the identification of 242 cats treated with venlafaxine for which these data were complete.

Email and phone survey

Owners of all 242 cats were first contacted by electronic mail (email) for the survey. They could choose between answering the electronic mail or having a phone call to answer to the veterinarian's questions. There was no difference in response between groups. Venlafaxine dosage over time and actual weight of the cat were checked to be consistent with the medical record. Details of each question asked to owners are presented in Table 1.

All owners were informed that the data were needed for a scientific retrospective study on venlafaxine and that their name would stay anonymous. They were given the chance to withdraw without penalty at any time.

One month after the initial electronic mailing, a second electronic mailing was sent to the owners that did not answer the first email and three months later a phone call was given to those that did not respond to the first 2 emails. Three attempts to contact the owners of cats treated with venlafaxine in an attempt to avoid a bias of having only satisfied owners answering the veterinarian.

Using this procedure, 176 cats were included in the study out of 242 contacted initially by email leading to a 72.7% response rate, and 27.3% (N=66) non-response rate.

Raw data collection and collation

Each clinician entered their data in an Excel file containing the following variables: subject number, name of the clinician, name of the cat, breed, age of the cat when the first consultation happened (in months), weight at first consultation (in kilograms), reasons for consultation, psychological state diagnoses, nosographic diagnoses, total number of consultations at the clinic, initial dosage of venlafaxine (in number of granules), actual weight, actual dosage of venlafaxine (in granules) or if weaning was achieved last dosage of venlafaxine before weaning, duration of the venlafaxine treatment (in months), adverse effects, easiness of administering the treatment (i.e., no difficulty, mild difficulties or impossible to give), possibility to wean the treatment (using the 0–3 points scale of Table 2), other medications (before and concomitantly to the venlafaxine treatment), owner score (using the 0–3 points scale of Table 3), veterinarian score (using the 0–3 points scale of Table 3).

Table 1
Questions asked to the owners during the email or phone survey.

Question	Type of response
What is the current weight of your cat	A number in kilograms
Is your cat still under venlafaxine medication?	Yes/No
If yes, at what dosage (in number of granules)	Number
If no, when did you stop it?	Date
If no, at what dosage was your cat before stopping the treatment?	Number
Did you notice any possible adverse effects during the treatment? These adverse effects can for example include lethargy, sedation, vomiting, diarrhea, … Please specify when it happened and for how long.	Yes/No Open ended question
Did you encounter any difficulty giving your cat its treatment? Choices: not at all, mild difficulty (e.g., I had to use a special treat to put the granules inside), impossible (e.g., I gave up because it was really hard to have my cat take the medication).	1) Not at all 2) Mild difficulties 3) Impossible Open ended comments were possible, and most owners explained how they were giving the granules.
Concerning the possibility to wean the cat from the treatment, would you say that:	See Table 2 to answer 0, 1, 2 or 3 + open-ended comments
Concerning the efficacy of treatment, combined with the environmental and behavioral modifications prescribed by, you would say that:	See Table 3 to answer 0, 1, 2 or 3 + open-ended comments

Table 2
Scores used to rate the possibility of weaning the cat from venlafaxine. The number of each score, including 0, was tallied.

Score	Statement
0	Yes, we stopped the treatment, because it was not satisfactory (precise why)
1	We didn't try to wean the cat because it still seems impossible (e.g., some signs persist despite the treatment, so we don't want to risk it to worsen)
2	We tried to wean the cat, but it was not satisfactory (e.g., some signs reappeared), so we maintained it and our cat is still under venlafaxine treatment
3	The venlafaxine treatment has been withdrawn and this is satisfactory, i.e., the initial signs did not reappear

Table 3
Scores used to rate the efficacy of the venlafaxine treatment combined with an environmental and behavioral modifications according to the owner. The number of each score, including 0, was tallied.

Score	Statement
0	The treatment did not improve any of my cat's annoying behaviors
1	The treatment improved only a small part of my cat's problematic behaviors (less than half)
2	The treatment improved a large part of my cat's problematic behaviors but not all of them (more than half)
3	The treatment improved all of my cat's annoying behaviors

To establish the veterinarian score, the authors were asked to use the same criteria as owners did (i.e., Table 3), but they were asked to focus on the clinical objective signs and to quantify them (i.e., quantify the frequency of an undesired behavior like urine marking, or quantify the number of signs that improved when several undesired behaviors occurred)

The main author collected all the Excel files and collated them to assure consistency. Comments added by the clinicians in all the scoring tables were removed and put in a comment column. Reasons for consultation were lumped into broad categories to ensure consistency. For example: aggressivity towards owners, or aggression to the daughter of the owner, or aggression against familiar people, were all labelled aggression toward familiar people. In the same way, aggression toward unfamiliar people, familiar cats, unfamiliar cats were created.

Data were similarly collated for other conditions to ensure that a minimal number of variables were present and that identical variables named differently were transformed in a unique variable (e.g., productive generalized anxiety and generalized productive anxiety became only one label (Masson et al., 2024c).

The dosage of venlafaxine was converted in mg/kg using the initial and final weight data, combined with the initial and final dosages of venlafaxine in granules.

Statistical analyses

The data for the 176 cats whose owners could be contacted were analyzed using descriptive statistics. Continuous variables were described as follows: number of non-missing observations, arithmetic mean, standard deviation, median, minimum and maximum. Categorical variables were presented using the number of non-missing observations and percentages.

The overall population was classified by subgroups of disease status. For each subgroup, pairwise comparisons were performed using an analysis of variance (ANOVA) or a non-parametric Wilcoxon rank-sum test depending on the distribution of the variable. Normality of the distribution was tested using a Shapiro-Wilk's test at the level of significance of 0.01. If significant, the variable was analyzed using the Wilcoxon rank-sum test.

The final dosage of venlafaxine was used to test if different variables would influence this dosage, especially the cats age and the different diagnoses.

A priori, p-values < 0.05 were considered statistically significant. Statistical analysis were conducted using SAS software (version 9.4).

Results

Cats

One hundred and seventy-six cats (84 males and 92 females) of various breeds were included in the study. One male and one female were not neutered, and each was less than 6 months at the first consultation. Both were neutered while being treated with venlafaxine.

Ages ranged from 3 months to 16.5 years old at first consultation (mean = 5.58 years old; [SD] = 46 months; median = 4.95 years old).

The initial weight of the cats ranged from 1.45 to 10 kg (mean = 4.97 kg; [SD] = 1.42 kg; median = 5.00 kg). The final weight of the cats (i.e., age when data were collected for the study) ranged from 2.50 to 10 kg (mean = 5.03 kg; [SD] =1.29 kg; median = 5.00 kg).

The treatments length recorded ranged from 3 to 48 months. For the cats who could be weaned (N=36), treatment length ranged from 6 to 41 months (mean = 13.61 months; [SD] = 11.16 months; median = 11 months), whereas for the cats who were still under treatment at the end of the study (N=128) treatments length ranged from 3 to 48 months (mean = 16.53 months; [SD] = 12.17 months; median = 13 months). The cats that did not take the treatment, or stopped because the owner was not satisfied (N=12) were treated 0–3 months (mean = 1.54 months; [SD] = 1.08 months; median = 2 months).

The number of consultations at the veterinary clinic ranged from 1 to 4 (mean = 1.55; [SD] = 0.8; median = 1). The exchanges by email or phone with the owners of the cats were not counted in these data. All the cats that discontinued or stopped the treatment only had one visit in-person.

The weight variations between treatment onset and end of the study (final weight minus initial weight) of the cats ranged from −2.50–5.20 kg (mean = 0.07 kg;[SD] = 0.74 kg; median = 0.00 kg). This result occurred despite reports of appetites lowering, but many cats in this study matured during the course of the study.

Eighty-two percent of the cats (145) were mixed breeds. The 31 remaining cats were from 10 different breeds (Table 4). No further statistical analysis was done with respect to breed.

Investigators effect

Four investigators participated in the data collection. They gathered respectively 67 (38.1%), 65 (36.9%), 31 (17.6%), and 13 (7.4%) cases. Statistical analyses conducted to check for differences between investigators showed no differences across investigators.

Table 4
Breeds of the cats in the study.

Breed	Number of cats	Percentage
Mixed	145	82.4
Main coon	8	4.5
Birman	6	3.4
Siamese	4	2.3
Ragdoll	3	1.7
Bengal	2	1.1
Persian	2	1.1
Crossbred	2	1.1
British shorthair	1	0.6
Exotic shorthair	1	0.6
Himalayan	1	0.6
Sphynx	1	0.6
TOTAL	**176**	**100**

Reasons for consultation

The reasons for consultation are presented in Table 5. The categories are not exclusive.

138 cats presented with only one reason for consultation, 32 with two reasons, and 6 with three reasons.

The most common reasons for consulting were aggression towards familiar people (20.5%), aggression towards unfamiliar cats (16.5%), urine soiling (15.3%) aggression towards unfamiliar people (10.8%), and phobia of humans (8.5%).

Behavioral diagnosis

Behavioral diagnosis contain two different levels of diagnosis: psychological state diagnosis are presented in Table 6 and reflect the type of brain dysfunction that needs to be treated (Masson et al., 2024c), whereas nosographic diagnosis are presented in Table 7 and describe the disease itself, providing expected evolution, i.e., prognosis and behavioral therapy options.

127 cats were diagnosed with only one state diagnosis, 49 cats with comorbidity of two. Note that for the anxious state, clinicians outlined if the anxiety state was inhibited or productive and if it was intermittent or generalized. These categories are mutually exclusive.

124 cats were diagnosed with only one nosographic diagnosis, 47 cats with a comorbidity of two and 5 cats with a comorbidity of three, as presented in Table 7. Because there were not many cats diagnosed with dysthymia and dissociative syndrome, and because these terms are not used commonly in the scientific literature for cats, these diagnoses were coopted into "other" for further analyses.

Venlafaxine doses

Initial venlafaxine dose ranged from 0.38 to 1.92 mg/kg (mean = 1.02 mg/kg; [SD] = 0.24 mg/kg; median = 0.99 mg/kg).

The final venlafaxine dosage was administered to only 175 cats, as one cat, according to its owner, declined the treatment despite attempts with various types of treats to conceal it. Final venlafaxine doses ranged from 0.11 to 2.5 mg/kg (mean = 1.09 mg/kg; [SD] = 0.43 mg/kg; median = 1.01 mg/kg).

Table 5
Number and percentage of cats per reason for consulting as reported by the owner.

Reason for consultation	Number of cats	Percentage
Excitement	7	4.0
Obesity, bulimia (rapid ingestion of food, often followed by immediate regurgitation)	2	1.1
Vocalizations	6	3.4
Harassment towards a cat of the same household	4	2.3
Aggression towards unfamiliar cats (biting or scratching)	29	**16.5**
Aggression towards unfamiliar people	19	**10.8**
Aggression towards familiar people	36	**20.5**
Tail chasing or attacks	2	1.1
Excessive licking	10	5.7
Feline extensive alopecia (widespread hair loss due to excessive grooming or stress)	8	4.5
Phobia of humans (excessive fear reaction)	15	**8.5**
Phobia of cats	4	2.3
Phobia of the household dog	1	0.6
Phobia of noises	3	1.7
Idiopathic cystitis (referred by the general veterinarian)	10	5.7
Urine marking (only spraying)	7	4.0
Urine soiling	27	**15.3**
Fecal soiling (feces outside of the litterbox)	7	4.0
TOTAL	197	111.93

Table 6
Number and percentage of cats per state diagnosis category.

Psychological state diagnosis	Definition (adapted from Masson et al., 2024b)	Number of cats	Percentage
Normal	Shows typical, adaptive behavior	2	1.1
Phobic	Displays intense, persistent fear triggered by specific stimuli	14	8.0
Anxious	Exhibits ongoing tension, anticipation and hypervigilance in addition of phobic behaviours	124	70.4
Intermittent/ Generalized	*Intermittent: irregular behaviour episodes; Generalized: pervasive, consistent symptoms.*	*95/29*	*76.6/23.4*
Productive/ Inhibited	*Productive: agitation, with restlessness or excessive activities; Inhibited: withdrawal or reduced activity, with avoidance behaviors and inhibition.*	*84/40*	*67.7/32.3*
Impulsive	Acts quickly without forethought, often in response to sudden stimuli	59	33.5
Compulsive	Engages in repetitive actions, unable to stop them in addition of impulsive behaviours	11	6.2
Depressive	Shows signs of low motivation, withdrawal, and lack of interest, caused by the lowered mood	7	4.0
Manic	Characterized by high energy, rapid movements, caused by the heightened mood	7	4.0
Dissociative	Experiences disconnection from reality or altered perception	1	0.6

Table 7
Number and percentage of cats per nosographic diagnosis.

Nosographic diagnosis	Number of cats	Percentage
Organic disease causing the behavioral disorder	9	5.1
Deprivation syndrome	38	21.6
HSHA syndrome (feline ADHD)	64	36.4
Social post-traumatic phobia	6	3.4
Interspecific social phobia (human phobia)	5	2.8
Interspecific relational disorder	34	19.3
Intraspecific relational disorder (altered relationship between cats living together causing one of them at least to exhibit a psychological state, i.e. phobic or anxious)	40	22.7
Environmental disorder by excess of stimuli	10	5.7
Environmental disorder by lack of stimuli	9	5.1
Separation related disorder	8	4.5
Dysthymia disorder[a]	7	4.0
Dissociative syndrome[b]	1	0.6
Emotional dysregulation of the old cat	1	0.6

[a] Dysthymia disorder (equivalent to bipolar disorder in humans) is a chronic mood disorder characterized by alternating periods of depression and mania, leading to fluctuating behavior and mood in cats

[b] Dissociative syndrome (equivalent to schizophrenia in humans) is a disorder characterized by a disruption in the normal integration of consciousness, identity, or perception, leading to behaviors indicative of a disconnection from the environment or self.

Adverse effects

Most adverse effects, as reported by the owners, occurred within the first week of treatment and typically lasted less than two weeks. Only one sign (blood in feces) was reported after three months of treatment, potentially attributable to the medication, but resolved after reducing the dosage for a few weeks and then increasing it slowly. In instances of

reported adverse effects, clinicians typically adjusted the venlafaxine dosage until the adverse effects subsided and reverted to the initial dosage if necessary. In such cases, no new adverse effects were reported.

Adverse effects were reported in 35.4% (62/175) of cats and consisted of transient and mostly minor effects lasting less than two weeks as described in Table 8. The most common adverse effect reported was a decrease in energy level (51/175; 29.1%), which caused one cat owner to stop the treatment three days after starting. Decreased appetite was reported by 8 owners (8/175; 4.6%). Instances of more severe adverse effects prompting a temporary reduction or cessation of venlafaxine treatment for a few days were infrequent (10 out of 175; 5.7%), including signs such as vomiting, diarrhea, anuria, or absence of defecation.

Ease of administration and compliance

Owner compliance for giving the venlafaxine was excellent. One owner reported that their cat consistently refused the treatment despite multiple attempts with various treats to conceal it. The remaining owners successfully administered venlafaxine to their cats, as indicated in Table 9.

Nearly all the owners (165/176; 94.3%) reported no difficulty in giving the granules to their cat. A few owners (9/176; 5.1%) reported mild difficulties giving the medication. For all but one owner, the reason for successful administration was attributed to the necessity of changing the treat periodically to maintain the cat's acceptance of the medication. However, one owner encountered difficulty due to their cat occasionally not returning home, resulting in missed treatments on certain days.

Most owners reported no difficulty to implement the behavioral modification, but there was no investigation done during the data collection to quantify the time they spent doing the therapy.

Previous and concomitant treatments

During the first consultation, a few owners reported having already tried other medications that did not resolve their cat's disorder (18/176; 10.2%). Previously tried medication are in Table 10.

During the time of the study several cats received concomitant treatments either because they were required for another medical condition (e.g., dermatitis, musculoskeletal pain, intestinal chronic disease) (9/175; 5.2%), or because the venlafaxine treatment was not sufficient to result in cessation of the behavioral condition (13/175; 7.3%). This small number of cats was analyzed separately but was not different than the overall population. See Table 11.

Treatment effects

Based on owners' assessment

Response to treatment with venlafaxine combined with behavioral and environmental modifications based on the scores reported in Table 3 is presented in Fig. 1.

Table 8
Adverse effects of venlafaxine reported by owners.

Adverse effects	Number of cats	Percentage
Apathy, tiredness, lethargy, sleepiness	51	29.1
Loss of appetite	8	4.6
Pupillary dilatation	3	1.7
Vomiting	3	1.7
Anuria (up to 24 h long)	3	1.7
Diarrhea	2	1.1
No defecation (up to 24 h long)	2	1.1
Blood in feces	2	1.1
Polydipsia	1	0.6
Salivation	1	0.6
Muscular movements when sleeping	1	0.6
Excitement	1	0.6

Table 9
Ease of administration of the treatment according to owners.

Ease of administration	Number of cats	Percentage
No problem with the cat taking the medication	165	94.3
Partial difficulties (need to change of treat regularly)	9	5.1
Impossible	1	0.6

Table 10
Medications tried previously and that did not resolve the cat case before starting venlafaxine.

Previous treatment	Number of cats	Percentage
Feliway	6	3.4
Fluoxetine	7	4.0
Clomipramine	4	2.3
Phytotherapy	3	1.7
Alpha casozepine	2	1.1
Gabapentin	2	1.1
Selegiline	1	0.6
Sertraline	1	0.6
Clonazepam	1	0.6
Buspirone	1	0.6

Table 11
Concomitant treatments used during the venlafaxine treatment.

Concomitant treatments	Number of cats	Percentage
Behavioral treatments		
Gabapentin	9	5.1
Feline pheromones	4	2.3
Other medical conditions		
NSAID	5	2.9
Cortisone	4	2.3

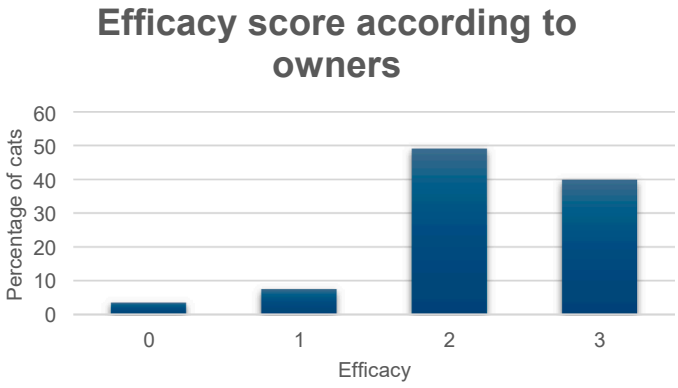

Fig. 1. Efficacy score according to owners scored using the following criteria: score: 0 = no improvement; score 1= improvement of less than half of the behavioral signs; score 2 = improvement of more than half of the behavioral signs; score 3 = improvement of all behavioral signs.

Based on veterinarian's assessment

Response to treatment was also evaluated by the behavioral veterinarian and the results are presented in Fig. 2.

Weaning

In addition to the efficacy score, we assessed length of treatment, especially if a weaning was possible without relapse as shown in Table 12. Twenty percent of the cats (36/176) could be weaned without having any signs that reappear, as shown in Fig. 3. The mean length of

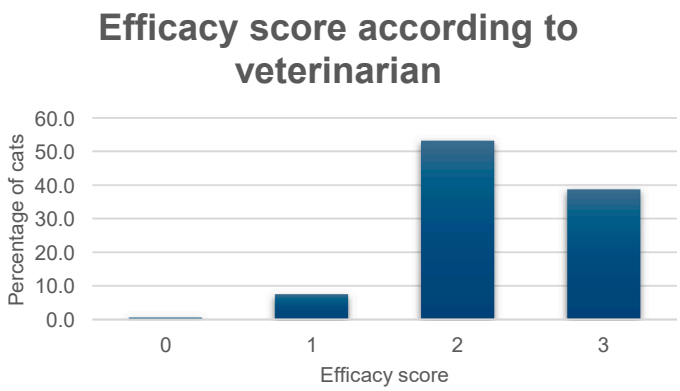

Fig. 2. Efficacy score according to veterinarian scored using the following criteria: score: 0 = no improvement; score 1= improvement of less than half of the behavioral signs; score 2 = improvement of more than half of the behavioral signs; score 3 = improvement of all behavioral signs.

treatment for these cats was 13.6 months ([SD] = 11.16 months; median = 11 months).

In addition, 25% tried a weaning (44/176) but the cat behavior worsened so the treatment was continued. Nearly half of the cat owners did not try to wean the cat because some signs persisted, and they would not risk having it worsening (84/176; 47.7%). A small percentage of the owners stopped the treatment because they were not satisfied with the improvement of their cat's behavior (12/176; 6.8). The reasons for stopping were adverse effects of the treatment (2/12), impossible to give the treatment (1/12), not enough efficacy (2/12) and fluoxetine was prescribed instead with more success, and no clear reason (7/12).

Dosage variations during the treatment

Data regarding the effect of dosage were not normally distributed according to Shapiro-Wilks test. Wilcoxon tests were used to test if different psychological state diagnoses influenced whether the initial and final dosages differed. Initial venlafaxine dosages ranged from 0.38 to 1.92 mg/kg (mean = 1.02 mg/kg; [SD] = 0.24 mg/kg; median = 0.99 mg/kg). Final venlafaxine dosages ranged from 0.11 to 2.5 mg/kg (mean = 1.09 mg/kg; [SD] = 0.43 mg/kg; median = 1.01 mg/kg). Hence, the difference between final and initial dosage was considered to represent the dosage adjustment to obtain efficacy. The results are presented in Table 13.

The initial dosage for most cats was approximately 1 mg/kg, equivalent to 4 granules per kilogram, following the recommended dosage from our prior study (Metz et al., 2021). The final dosage was significantly adjusted based on diagnosis or the cat's age.

Cats older than 8 years received a reduced dosage with a mean of 4 granules per cat, i.e., 0.25 mg/kg less than cats < 8 years old (p=0.007). Similarly, dosage reduction was observed in depressive states, with 9 granules, i.e. 0.5 mg/kg less than non-depressive cats (p=0.009). However, the proportion of cats in the depressive and manic state categories represented only 4% (7/176) of the total so these results are not possible to extrapolate into a larger context.

Cats diagnosed with an impulsive state received a significantly higher final dosage compared to cats with other pathological states, with an average increase of 3 granules, i.e. 0.2 mg/kg more than non-impulsive cats (p=0.003).

Weight changes during the treatment

Data regarding the effect of treatment on weight were not normally distributed according to Shapiro-Wilks test. Wilcoxon tests were used to test if different psychological state diagnosis would influence the weight during the treatment. In humans, venlafaxine is not reported to have a noticeable effect on weight gain (Vanina et al., 2002). In our study the effects of the treatment on weight not significant for any state diagnosis but was significant for cats over 8 years (N=?) as shown in Table 14.

Cats over 8 years of age (p<0.03) lost weight during the treatment with a mean weight loss of 0.3 kg, despite the lower dosage. However, cats aged during this study.

Discussion

The most remarkable point of the study is the fact that nearly all owners reported an ease of administration of venlafaxine treatment,

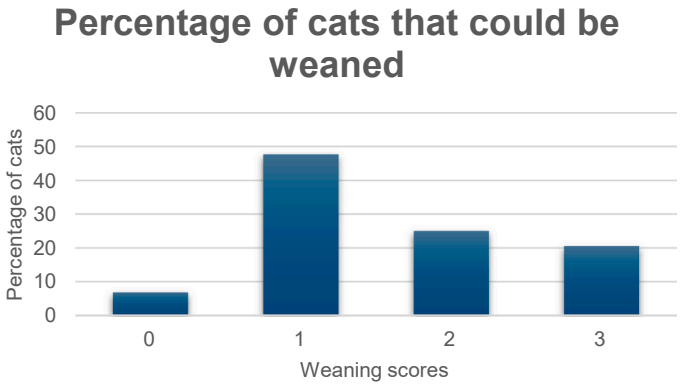

Fig. 3. Percentage of cats that could be weaned scored using the following criteria: score: 0 = treatment stopped because not satisfying; score 1= no weaning tried yet because improvement is not sufficient yet; score 2 = weaning was tried but behavioral signs reappeared and treatment with venlafaxine was maintained; score 3 = venlafaxine could be weaned without relapse.

Table 13
Influence of variables on the dose of venlafaxine needed to treat the cat.

Variables	Wilcoxon test p-values (final dose – initial dose)
Phobic state	0.206
Anxious state	0.555
Impulsive state	0.003*
Compulsive state	0.940
Depressive state	0.009*
Manic state	0.892
Age (>8 years old)	0.007*

Table 12
Distribution of cats by weaning score with associated treatment duration and statistical analysis.

Weaning score	Number of cats	Percentage	Mean time of treatment (in months)	Median time of treatment (in months)	Standard deviation (in months)
0 = stopped early	12	6.8	1.5	2	1.1
1= did not attempt	84	47.7	16.1	13	12.1
2= attempted but fail	44	25	17.4	13	12.4
3=weaned successfully	36	20.5	13.6	11	11.6
TOTAL	**176**	**100**			

Table 14
Influence of the treatment on weight of the cats.

Variables	p-values (final weight – initial weight)
Phobic state	0.794
Anxious state	0.069
Impulsive state	0.056
Compulsive state	0.617
Depressive state	0.758
Manic state	0.430
Age (>8 years old)	0.027*

because of the particular formulation of the small granules contained in the capsule. This finding is concordant with our previous work (Metz et al., 2021).

In this retrospective study, outcomes were rated good to excellent (i.e., weaning is possible) for over 80% of the cats. Of course, behavioral and environmental modifications were implemented with venlafaxine treatment, and it is not possible to know to which extent it played a role in the improvement of the cats' behavior. However, several cats were referred after failing to treat them with other medications or options treatments, which is in favor of venlafaxine efficacy.

This retrospective study indicated that adverse effects of venlafaxine in cats were reported for only 35.4% (62/175) of the cats and were transient in virtually all cases. Because of the nature of a retrospective study, owners were not probed about potential adverse effects as treatment was ongoing so it is possible that adverse effects were underreported. Additionally, the retrospective nature of the study might contribute to recall bias, where owners might not accurately remember or notice all adverse effects, especially if they were mild or transient.

The most common adverse effect reported was a decrease in energy level, observed in 29.1% of cases, which lead, in one instance, to the discontinuation of treatment. Other adverse effects, such as decreased appetite, vomiting, diarrhea, and anuria, were less common.

The dosage of venlafaxine needed to be adjusted in some cases to achieve a treatment effect, while minimizing adverse effects. This adjustment underscores the importance of providing individualized treatment plans based on the cat's response to medication, its age, and specific behavioral diagnoses. Cats older than 8 years required lowered dosages and still lost, on average, 0.3 kg. We'd recommend that cats older than 8 years could be started at a 3 granules/kg of Effexor® XL (i.e., 0.75 mg/kg) dose rather than 4 granules/kg (i.e., 1 mg/kg) as initially recommended (Metz et al., 2021). The tendency for weight loss among cats over 8 years old could be attributed to several factors including a possible undiagnosed physical disorder. In both humans and animals, anxiety and depression are often associated with changes in appetite and eating behaviors (Fava, 2000; Vanina et al., 2002). The action of venlafaxine, which increases serotonin and noradrenaline levels, might play a role in these changes. While these neurotransmitters are targeted to alleviate signs of anxiety and depression, they can also influence satiety signals and metabolic processes, potentially contributing to a change in appetite. However, in this study, no effect in the long term on the weight of the treated cats was noted, except in cats > 8 years.

Treating behavior cases is difficult and complex because of the numerous social and environmental factors that influence them, and the fact that most medications used to treat them lack dose-determination studies, so frequent follow-up is recommended.

Twenty percent of the cats (N= 35) could be successfully weaned without a relapse of clinical signs. However, a notable portion of owners chose not to attempt weaning due to the persistence of signs or fear of worsening conditions. This decision reflects a cautious approach to discontinuing medication, prioritizing the maintenance of behavioral improvements achieved through treatment.

While venlafaxine is generally effective for treating behavioral disorders in cats, it is important to note that this medication is palatable to cats, which increases the risk of accidental ingestion and potential toxicity. Hence, it is crucial for practitioners to advise pet owners on the secure storage of the medication. Furthermore, although serotonin syndrome was not reported in this study, it remains a possible risk with venlafaxine, particularly at high doses or in cases of unwanted ingestion. Serotonin syndrome can present with clinical signs such as agitation, hyperthermia, and tremors, and immediate veterinary intervention is required if these clinical signs are observed (Indrawirawan and McAlees, 2014). Therefore, while venlafaxine can be a valuable tool in managing feline behavioral disorders, its use must be carefully monitored to mitigate these risks.

It is important to note that the availability of venlafaxine formulations varies internationally, with some countries only offering the extended-release (XR) version, while others may only have the immediate-release formulation. This distinction is crucial for clinicians to consider when applying these findings in different international contexts, as the formulation can significantly influence dosing strategies and therapeutic outcomes. In this study we used the extended-release (XR) formulation.

While this study marks an important step forward in the application of venlafaxine for feline behavioral disorders, it also illuminates areas requiring further exploration. The implications of potential underreporting of adverse effects, the long-term effect of venlafaxine on feline patients, and determination of the range of favorable dosages on individual responses highlight the complexity of treating behavioral conditions in cats.

These findings advocate for the initiation of more comprehensive, prospective studies for the use of venlafaxine in the treatment of cats with behavioral conditions. By continuing to refine our approach to veterinary behavioral medicine, we can better meet the nuanced needs of our feline patients and their caregivers, paving the way for more effective and tailored treatments in the future.

Conclusion

Venlafaxine can be a highly manageable and effective treatment option for a variety of behavioral disorders in cats, thanks to its excellent ease of administration. The findings affirm the drug's efficacy across multiple types of behavioral diagnoses while reporting a relatively low prevalence of adverse effects. Nevertheless, the possibility of adverse effects being underreported necessitates vigilant monitoring and open communication between veterinarians and owners. It's imperative that practitioners discuss the potential adverse effects with owners thoroughly prior to initiating treatment, setting realistic expectations, and ensuring a well-informed consent.

Ethical considerations

After evaluating the project prior to the study, no ethical certificate seemed necessary because of the retrospective nature of the study. However, all the owners were informed during the data collection that their veterinarian intended to use their cat's medical file for a retrospective study and their informed consent was collected. 176 out of 242 contacted owners agreed to answer our questions.

Authorship statement

The original idea was conceived by Sylvia Masson and Françoise Schwobthaler. The experiment was designed by Sylvia Masson, Delphine Metz, Stéphane Bleuer-Elsner and Françoise Schwobthaler.The data were collected by Sylvia Masson, Delphine Metz, Stéphane Bleuer-Elsner and Françoise Schwobthaler and analyzed by Sylvia Masson and Eric Guemas. The paper was written by Sylvia Masson.

CRediT authorship contribution statement

Françoise Schwobthaler: Validation, Project administration, Investigation, Data curation, Conceptualization. **Delphine Metz:**

Validation, Methodology, Data curation. **Stéphane Bleuer-Elsner:** Validation, Project administration, Methodology, Data curation. **Sylvia MASSON:** Writing – original draft, Supervision, Methodology, Formal analysis, Data curation, Conceptualization.

Conflict of Interest

No conflict of interest to disclose.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jveb.2024.11.004.

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