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ORIGINAL RESEARCH

Use of mirtazapine in the treatment of canine behaviour problems: A review of 32 cases

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Abstract

Background: Canine behaviour problems seen by speciality behavioural medicine services often involve chronic anxiety disorders that have resulted in maladaptation of the individual to its environment. Common stressors include the presence of other individuals (other dogs or people), noise and being alone. The treatment of these behavioural problems usually includes a combination of behaviour modification, environmental modification and biological therapies. Within the latter, anxiolytic drugs such as clomipramine or fluoxetine have proven useful.

Methods: Here, we present a retrospectively analysed series of 32 cases that were treated with the anxiolytic drug mirtazapine, which is widely used in human medicine but has not previously been reported for the treatment of behavioural problems in dogs (although it is marketed as an appetite stimulant in cats). Cases included dogs with a range of anxiety-related behavioural problems.

Results: Eighty-one percent of dogs that presented with a behavioural problem showed improvement and suspected adverse effects were mild and tolerable.

Limitations: Further studies are required to isolate this result from the other therapeutic measures and to compare its efficacy with other drugs.

Conclusion: Mirtazapine appears to be a suitable and safe option for the treatment of anxiety-related behavioural problems in dogs.

INTRODUCTION

Canine behaviour problems seen by specialist behavioural medicine services often involve chronic anxiety disorders that have resulted in maladaptation of the individual to its environment.[1] Common stressors include the presence of other individuals (other dogs or people), noise and being alone.[2] The treatment of these behavioural problems usually includes a combination of behaviour modification, environmental modification and biological therapies. Biological therapies are very valuable in helping to regulate motivational states, emotions (such as anxiety and fear) and the neurological mechanisms that control behaviour, which underlie most behavioural disorders.

Commonly prescribed and well-documented biological therapies in veterinary behavioural medicine include tricyclic antidepressants (TCAs),[3] selective serotonin reuptake inhibitors (SSRIs),[4] serotonin 2A antagonist/reuptake inhibitors (SARIs)[5] and monoamine oxidase A inhibitors (MAOIs).[6]

In this retrospective case series, we explore the use of the tetracyclic antidepressant and anxiolytic drug mirtazapine in the treatment of behavioural problems. It has a unique mechanism of action, different from that of classical TCAs, SSRIs and monoamine oxidase inhibitors, and is described as a noradrenergic and specific serotonergic antidepressant.

Mirtazapine has alpha-2-adrenoceptor antagonist properties (both auto- and heteroreceptors), but unlike TCA/SARI/SSRI or MAOI drugs, it has no effect on monoamine reuptake. Mirtazapine increases noradrenergic and serotonergic transmission[7] and shows similar effects to 5-HT1a agonists despite having

a low affinity for 5-HT1a receptors.[8] Moreover, it specifically blocks 5-HT2 and 5-HT3 receptors.[9] Blocking 5-HT2 and 5-HT3 receptors prevents the side effects associated with nonselective activation of 5-HT receptors and contributes to the anxiolytic and sleep-enhancing properties of mirtazapine. Mirtazapine has been shown in laboratory rodents to act as an anxiolytic through its effect on 5-HT1a and α-1 receptors.[10] Its action mainly affects the median raphe nucleus.[11] This nucleus is formed by abundant serotonergic cells that project to the forebrain, mainly to limbic areas of the prosencephalon that control emotional behaviour. It also projects extensively to the hippocampus, regulating memory and regulating dopaminergic activity in the forebrain. Enhancement of both noradrenergic and serotonergic transmission underlies the therapeutic activity of mirtazapine.

Mirtazapine has shown efficacy in the treatment of major depression in humans. It also has quicker action in the first weeks of treatment than proven antidepressants such as fluoxetine (SSRI) or venlafaxine (SNRI).[12] In addition to its main use in psychiatry as an antidepressant, it has also been used in various anxiety-based psychiatric problems, such as social phobia, general anxiety disorder, obsessive compulsive disorder and panic disorders.[13,14] In terms of safety and toxicity, mirtazapine also outperforms other drugs such as SSRIs, as it has far fewer side effects related to sleep disorders, gastrointestinal disorders and sexual dysfunction. The only notable side effect is increased appetite, which can lead to weight gain, but in most cases does not represent a long-term problem.[15]

In veterinary behavioural medicine, the cases we treat often involve severe fear and anxiety. These emotional states can generate deficit signs (inhibition, inactivity and reduced motivation) or productive signs (excitement, agitation and hypervigilance). The majority are treated with TCAs (clomipramine) or SSRIs (fluoxetine), as those drugs have the greatest scientific support.

However, when first-line treatments fail, or their adverse effect profile includes common adverse effects that could present issues for a particular patient, we should look for effective alternatives. This may include drug substitution or augmentation. Ideally, we want our selected drug to have no deleterious effects on motivation, memory, learning or appetite, because these could affect the response to behavioural therapy. Unfortunately, many of the first-line options commonly fail in at least one of these areas. Common adverse effects that are associated with TCAs include sedation, hyporexia/anorexia, restlessness, nausea and anticholinergic signs. The same is true with SSRIs, albeit to a lesser extent. However, most of the SSRIs cause hyporexia/anorexia.[16] This reduction in appetite and interest in food can interfere with behaviour modification programmes that are based on positive reinforcement using food. Anxiolytics such as benzodiazepines can induce anterograde amnesia and therefore impair or delay the effects of behaviour modification programmes.[17] In view of these drawbacks, finding an alternative that can reduce fear and anxiety without any impact on memory or appetite can be of great help in improving treatment programmes in behavioural medicine, and according to previous literature in humans and other experimental species, mirtazapine offers this possibility.

Mirtazapine has been used as an appetite stimulant in veterinary patients, for example, to treat hyporexia in chronic renal failure.[18] A veterinary formulation licensed for cats has recently become available for this indication (Mirataz). In behavioural medicine, this positive effect on appetite can help to increase food motivation and facilitate behaviour modification programmes. It could also be of help in improving motivation in food-based environmental enrichment programmes that are used for patients with separation-related problems (SRPs). However, despite its apparent advantages, mirtazapine has only recently received attention as an anxiolytic in veterinary behavioural medicine.

Here, we report a retrospective case series evaluating the tolerability and efficacy of mirtazapine for the treatment of behavioural problems in dogs. Our findings suggest possible indications, and we present information about observed adverse effects.

MATERIALS AND METHODS

The case records for Ethoclinic Valencia were searched between July 2016 and December 2022 to identify all dogs that received mirtazapine for behavioural problems. Only those for which mirtazapine was the monotherapy from the beginning to the end of treatment were included in the case population ($n = 32$); this was done to simplify the interpretation of the response to therapy and outcome.

The clinical decision to prescribe mirtazapine instead of other anxiolytics was based on patients meeting at least one of the following three criteria:

1. Failure of response to a previous treatment with a first-line therapy (a drug indicated as first-line according to the current literature).
2. Cases previously treated with TCA/SARI/SSRI drugs, for which loss of appetite substantially impaired the behaviour modification programme. For example, in separation-related disorders, environmental enrichment is often based on chewing or foraging games.
3. Cases for which increased food motivation was essential to the behaviour modification plan (including when the patient is alone at home). For example, in a case of compulsive disorder, the patient engaged in uncontrolled destructive behaviour and did not respond to behaviour modification because she was not food motivated.[19]

Patients were excluded from mirtazapine treatment if they had a high motivation for food and in cases of offensive aggressiveness based on learning and protection of resources. After an exhaustive review of the clinical histories, all cases for which no follow-up was recorded were also excluded from the analysis.

Finally, 32 cases that met the inclusion criteria were analysed to establish the possible efficacy of mirtazapine in the resolution of behavioural problems and its possible limitations and side effects.

The staff involved in the cases were as follows:

Veterinary behaviourist: one of the two veterinarians working at Ethoclinic Valencia who have a higher qualification in behaviour (Master's degree).

Dog trainer: only one person worked as a dog trainer at Ethoclinic Valencia, and he was in charge of training interventions for all the cases presented.

Information about breed, sex, reproductive status, age at the time of prescription and the diagnoses for which medication was prescribed, the progression of the case and the final outcome was collected from the clinical records. As with any behaviour case requiring medication, prior to starting mirtazapine, all dogs underwent a physical exam, routine haematology and biochemistry at their referring veterinary clinic.

The prescribed dose range of mirtazapine was 1.0–1.5 mg/kg once daily, with this range being chosen based on a previous pharmacokinetic study performed with Beagle dogs.[20] Each dog's clinical records were reviewed to identify any potential short- or medium-term adverse effects that had occurred. The duration to the first onset of improvements, as reported by the dog's caregiver, was also recorded. That recorded improvement does not correspond to the ultimate improvement of the case but to the first appearance of notable behavioural improvements that occurred during that initial time period. Follow-up information was collected by the veterinary behaviourist during follow-up appointments and from the information provided by the dog trainer in charge of the behaviour modification sessions (always the same person). This included the amount of follow-up that the case had required and the final result of the treatment.

Five contextual diagnostic categories (CDCs) were applied to the cases:

1. Interspecific social problems: problems based on fear and anxiety in the presence of strangers, especially if the dog anticipated physical contact or manipulation. Most dogs showed avoidant reactions, but some showed aggression.
2. Intraspecific social problems: problems based on fear and anxiety in the presence of other dogs. Most dogs showed avoidant reactions, but some showed aggression, especially if they were tethered.
3. Noise-related problems: problems of fear, anxiety and phobia of loud noises, especially firecrackers and thunderstorms, but also urban noises (dogs that were confident to go on walks outside in busy areas but were frightened by some of the specific noises they encountered, such as a sudden loud motorbike passing by) and even household noises (such as household appliances or neighbourhood noises).
4. SRPs: problems related to separation from the attachment figure and motivated by anxiety or frustration.
5. Compulsive problems: repetitive behaviour disorders with a negative effect on wellbeing, based on chronic anxiety and frustration. In this category, we included only one case, with uncontrolled destructive behaviour, which had not responded to behaviour modification because she was not food motivated.

Categorisation was not exclusive, so some dogs had multiple CDCs. In all cases, the recommended treatment consisted of a combination of:

1. Environmental modifications.
2. Improvement of owner management to decrease the patient's overall stress.
3. Behavioural modification to achieve better response to, and adaptability in the presence of, problematic environments and stressors.
4. Psychopharmaceuticals to improve a negative emotional state: fear, anxiety and frustration.

All cases were followed up to ensure the implementation of the environmental changes and behavioural modification necessary for the treatment of the case. Between 10 and 15 days after the first visit by the veterinary behaviourist, the dog trainer contacted the family to implement and supervise the behaviour modification programme prescribed by the veterinary behaviourist in charge of the case. If, after two telephone contacts and one email contact, separated by 15 days each, the treatment could not be monitored, the veterinary behaviourist would again try to contact the family directly 1 month after the dog trainer's last contact. If no response was received after these contacts, the referring veterinarian was informed of the situation and the follow-up was abandoned.

Planned follow-up included visits every 7–30 days by the dog trainer, depending on the case. The design and objective of the specific learning exercises were explained in the initial consultation. Implementation of the exercises was supervised by the dog trainer working within Ethoclinic Valencia. Follow-up visits with the dog trainer implemented the exercises and monitored progress. The veterinary behaviourist in charge of the case also checked progress or implemented any necessary changes if results were unsatisfactory. Follow-up visits with the veterinarian in charge of the case were recommended if the problem did not improve substantially within 3 months or if the problem had improved sufficiently for at least 8 weeks for evaluation of the withdrawal of the medication. The number of follow-up visits was counted as an additional measure of the success of the treatment (Figure 1).

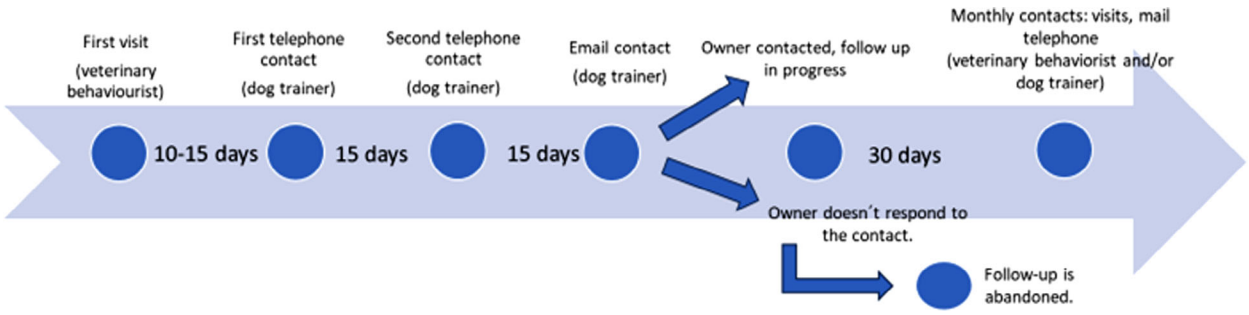

FIGURE 1 Follow-up timeline

The recommended environmental guidelines were generic in terms of avoiding contact with the stressor until behaviour modification had been implemented, promoting walks with physical exercise and games, and improving unsupervised activities with games based on food searching.

After the first visit, the family was contacted to check management and environmental measures, compliance with the medication and its possible effects, and to set an appointment to start behaviour modification. Each behaviour modification visit was reported to the veterinarian in charge of the case during at least weekly meetings. If for any reason the dog trainer's help was rejected, the veterinarian was informed and became responsible for the follow-up of the case. In this case, the caregiver was asked for a monthly report via email and a follow-up visit was scheduled every 3 months. With this system, it was possible to, in most cases, record efficacy onset and adverse effects and monitor environmental changes and proposed behavioural modification.

Cases were considered finished if the treatment had been completed, the caregiver was sufficiently satisfied with the results, treatment had been abandoned due to lack of caregiver interest or for economic reasons, or the dog had been euthanased for any reason (behavioural or health). We recorded the patient's status at that endpoint time and cases were allocated to the following categories:

1. Complete improvement: resolution of symptoms was complete, allowing the patient to fully adapt to its environment.
2. Sufficient improvement: some symptoms persisted, but adaptation in most daily situations was adequate, allowing a good quality of life.
3. Partial improvement: some symptoms improved, but the patient's adaptation to its environment remained problematic and there was a diminished quality of life.
4. No improvement: despite treatment, symptoms did not improve appreciably, and the problem persisted at a similar level as at the time of initial consultation.

Treatment was considered successful when the case fell into either of the two first categories, which both provided a useful improvement in behaviour and the dog's quality of life.

TABLE 1 Distribution of contextual diagnostic categories (CDCs) in the cases followed

CDC	Number (%)
Social interspecific	12 (33%)
Social intraspecific	12 (25%)
Separation-related problems	8 (17%)
Noise-related problems	11 (23%)
Compulsive disorder	1 (2%)

Due to the retrospective nature of the case series and the lack of a control group, we present the results using only descriptive statistics. The number of cases in the outcome groups was insufficient to make a valid statistical comparison with respect to the duration of treatment or number of follow-ups.

RESULTS

Forty-seven percent of cases were female (15/32) and 53% were male (17/32), of which 56% (18/32) were neutered (13 females and five males). In terms of breed, eight were mixed-breed dogs and 24 were purebreds, with five cases being German Shepherd dogs. Age at the time of prescription ranged from 0.6 to 10.2 years, with a mean of 3.7 years. Weight ranged from 4.0 to 46.3 kg, with a mean of 17.9 kg.

Comorbidity of more than one CDC was observed in 10 of the 32 cases followed, resulting in 48 CDCs distributed as shown in Table 1.

It was possible to record the onset of favourable changes in behavioural signs in 28 of the 32 cases. The mean time to some type of improvement was 39 days (range 14–120 days), with 35% (10/28) responding during the first 3 weeks of treatment and 64% (18/28) responding during the first 6 weeks of treatment (Figure 2).

The cases were followed up for a mean of 265 days, with a range of 90–1005 days. During this follow-up period, some type of visit (behaviour modification or veterinary) was made in 90% of the cases (45/50), with an average of 2.3 visits per case.

To evaluate the effect of mirtazapine in the cases studied, the overall treatment outcome was categorised into the four categories previously described (complete improvement, sufficient improvement,

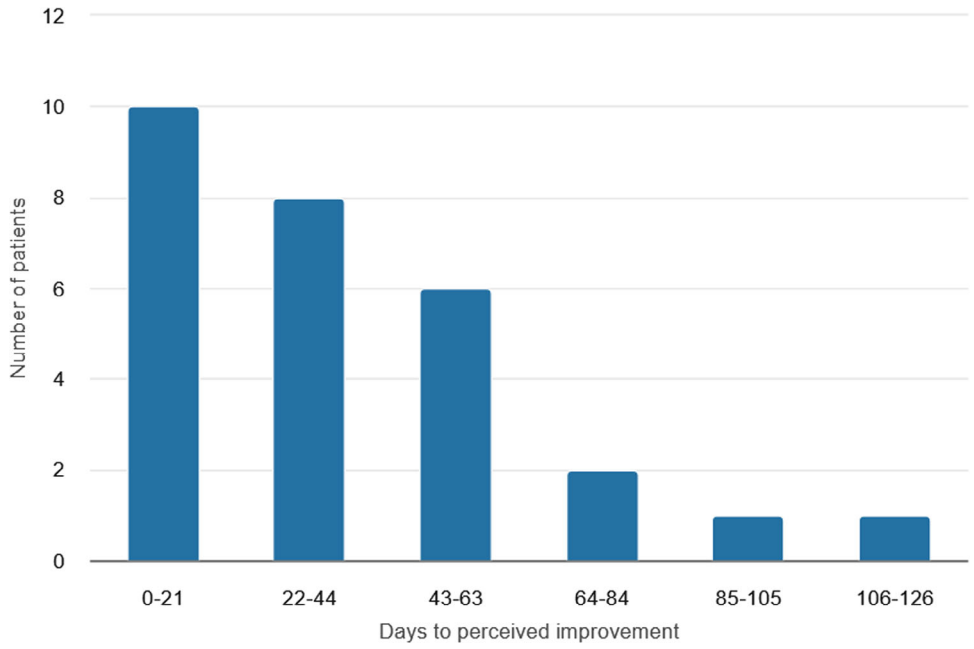

FIGURE 2 Distribution of cases according to the first record of improvement after initiation of mirtazapine treatment

TABLE 2 Summary of the final outcomes of the cases

Final outcome	No. of cases (%)	Outcome
Complete improvement	5 (15.6%)	Successful outcome: 81.2%
Sufficient improvement	21 (65.6%)	
Partial improvement	6 (18.7%)	Unsuccessful outcome: 18.8%
No improvement	0 (0%)	

partial improvement and no improvement). The final outcome for the 32 cases is presented in Table 2. There was some level of improvement in all cases, but we only considered treatment to be successful if there was a complete or sufficient improvement. An overall success rate of 81.2% was noted.

Table 3 shows the outcome for each of the types of CDC (i.e., presenting problems). There were 48 CDCs due to comorbidity in 10 cases (Table 3).

Suspected adverse effects that might be attributable to mirtazapine were detected in four cases:

1. Case no. 11: mirtazapine had to be withdrawn after 12 months of treatment with sufficient improvement, due to ingestion of a foreign body that required endoscopy for its removal. It was not replaced by another drug.
2. Case no. 13: mirtazapine was withdrawn at 7 months with sufficient improvement, without veterinary control, due to apparent polyuria. It was not replaced by another drug.
3. Case no. 15: mirtazapine had to be withdrawn after 4 months with partial improvement due to increased appetite that worsened the dog's scavenging of rubbish that was already present occasionally before the treatment. It was replaced by fluoxetine.
4. Case no. 26: mirtazapine had to be withdrawn after 23 months of treatment with sufficient improvement due to excess weight gain. It was replaced by fluoxetine.

DISCUSSION

The study population was extracted from the database of the behavioural medicine referral service at Ethoclinic Valencia, which receives cases from this province in Spain. In terms of population, the only noteworthy finding is the over-representation of the German Shepherd breed, which in our series represented 15.6% of the cases (five out of 32), compared with 5.27% of the clinic's overall caseload (192 out of 1898) and 0.25% of the dogs registered in Valencia.[21]

Overall, we obtained 81% of cases with complete or sufficient improvement in the patient's adaptation to the environment and 100% of patients with some kind of positive response during follow-up. In people, the main explanation for the therapeutic effect of mirtazapine is the increase in noradrenaline (NA) by antagonism of the alpha-2-adrenergic auto-receptor and the increase in serotonin in the synaptic space by antagonism of the alpha-2-adrenergic heteroreceptor that regulates serotonin release (not by reuptake inhibition). In addition, once more NA is released it interacts with postsynaptic alpha-1-adrenergic receptors on serotonergic raphe neurons, further increasing serotonin release. It is also described to have a high antihistamine H1 activity that promotes sleep without disturbing the rapid eye movement phase. In addition, its antagonism with 5-HT3 receptors, located in the chemoreceptor zone of the brainstem, prevents nausea and vomiting and its 5-HT2C antagonism would cause (together with the H1 antihistamine effect) increased appetite and potential weight gain.[22] This complicated mechanism of action has not been

TABLE 3 Final outcomes related to contextual diagnostic category (CDC)

Final outcome	Social intraspecific ($n = 12$)	Social interspecific ($n = 16$)	SRP ($n = 8$)	Noises ($n = 11$)	Compulsive Disorders ($n = 1$)
Complete improvement	2	2	3	2	
Sufficient improvement	7	12	4	8	1
Partial improvement	3	2	1	1	
No improvement	0	0	0	0	
Specific CDC outcome (%)	75	87.5	87.5	91	100

Abbreviation: SRP, separation-related problem.

corroborated in the dog. We do find many similar effects in the dog (anxiolytic effect, increased appetite, no adverse digestive effects) but also some differences (lack of effect on sleep). With this previous information in humans and without previous data in veterinary literature, the main author expected, a priori, that it could be a useful drug in highly inhibited patients in which negative signs predominate (lack of motivation, lack of social interaction, lack of playfulness, lack of exploratory behaviour). In contrast, it was considered that it could be a poor drug for highly excitable patients with a predominance of positive signs (hyperexcitability, lack of impulse control, offensive aggressiveness). This is reflected in the treatment protocols, in which 50% of the prescriptions were for social problems.

We started this case series with case no. 1, a female crossbreed Ibizan hound, rescued after a traffic accident, which presented a severe interspecific phobia that made her remain immobile inside the house and prevented her from going outside. After initial therapy with fluoxetine/trazodone and despite behavioural improvement, the medication caused anorexia that did not subside until the drugs were withdrawn. This led us to look for an alternative anxiolytic drug that did not cause loss of appetite, a common side effect of SSRIs. To propose the clinical use of mirtazapine, only one pharmacokinetic study in Beagle dogs[20] was found in the peer-reviewed literature, from which the dose used in the cases described (from 1 to 1.5 mg/kg/24 h) was taken.

However, there are many occasions when a social problem can involve aggression, and indeed, in 10 of the 32 cases, aggression was present in some form. Initially, mirtazapine's prescription was closely monitored in cases in which aggression was present. The positive initial results[23] led to us prescribing it in cases with aggression that were especially well controlled, and we soon felt comfortable prescribing it in patients with defensive fear aggression and avoiding it in offensive frustration/rage aggression. However, the safety of this drug in cases of aggression should be properly investigated before it is considered for use in such cases.

With regard to time to onset of effect, the initial impression is that mirtazapine is faster than other serotonergic drugs. One-third of patients responded within the first 3 weeks and up to two-thirds responded before the sixth week. This initial improvement continued in most cases until 81% overall success was achieved; however, it is difficult to establish when the maximum effect appears and whether this is due to the drug, behaviour modification or the synergy between the two treatments.

Side effects in our study were few and mild. Of the four cases in which side effects were detected, the main one attributable to mirtazapine was undoubtedly increased appetite, which was detected in three cases. One of them required endoscopic intervention due to foreign body ingestion, and the other two cases involved weight gain and eating rubbish in the street. Also, there was one case of urine leakage. This side effect, also described in humans, seems difficult to explain but could be related to an alteration in the secretion of antidiuretic hormone. In all cases, the side effects subsided when the drug was withdrawn.

No other problems were found, such as excessive sedation, widely described in humans, and even prescribed for this purpose in some sleep disorders. This leads us to suspect that the H1 antihistamine effect is different in the canine species, either due to the action of the drug or more likely due to the distribution of these receptors in the central nervous system (CNS) of canids. However, despite a specific reference search, we were not able to find specific references about the distribution of H1 receptors in the CNS of dogs.

Other side effects described as common in human patients (incidence up to 10%) in the summary of product characteristics (SPC) for mirtazapine products,[24] such as lethargy, vomiting, diarrhoea, constipation, urticaria, nausea, myalgia or arthralgia, were not found in our patients. Some other side effects described in humans, such as headache, memory problems or reliving dreams, are very difficult to evaluate in veterinary patients and we do not know if they occurred in our patients, but during the behaviour modification training our subjective impression is that there were no learning problems and the patients progressed as expected.

The main drawback of mirtazapine use in humans may be the weight gain associated with increased appetite. However, generally speaking in veterinary medicine and specifically in behavioural medicine, this effect can be considered an advantage in most cases. There is now a commercial preparation of mirtazapine (Miratax) registered for appetite enhancement in cats. This transcutaneous formulation is used to increase appetite in chronically ill cats,

especially those with chronic kidney disease.[17] The drug's SPC describes behavioural changes such as increased vocalization, hyperactivity and attention seeking as common side effects. While these effects can be undesirable in certain cases, they are usually desired when treating behavioural problems with negative signs.

In our patients, the need to stimulate appetite was the primary reason for choosing mirtazapine as an alternative to SSRIs, which frequently cause anorexia or hyporexia as common side effects. This increase was reflected in case no. 2, the only one with a diagnosis of compulsive disorder,[18] in which a patient with compulsive disorder associated with destructiveness changed her preference from biting and crushing plastic objects to searching for food treats and so could be treated with behaviour modification. This effect of increased appetite was not constant or of the same magnitude in all cases. The fear and anxiety that patients sometimes suffer mean that lack of motivation for food may remain despite treatment, but the subjective impression in behaviour modification sessions suggests that it does not affect reinforcement programmes with food and in most cases increases this motivation.

This study faces several limitations. The first is that the results are based on the observations and opinions of the owners and veterinarians in charge of the case. We also do not have a control group with similar characteristics treated only with environmental and behavioural modifications or even with another drug. So, it is not possible to isolate the effect of mirtazapine from the other therapeutic measures (environmental enrichment and behaviour modification). The implementation of environmental and training measures varied enormously in each case, and despite being insistently recommended, follow-up of each case was irregular and random due to owner compliance. The only way to homogenise the treatment and avoid bias was for all handlers to receive the same instructions from the veterinary behaviourist team and be treated by the same dog trainer. Although this limitation will undoubtedly be present in any retrospective clinical study on psychotropic drugs, we attempt to approximate the effect of behaviour modification by relating the number of follow-up visits to the final outcome. It would be logical to think that the more visits by the therapist, the better the results should be, always using the same drug. However, we failed to confirm this association in our series of 32 cases because we had insufficient cases in all of the outcome groups to make a statistical comparison.

Another bias of this case series might be that we selected only cases in which mirtazapine was prescribed alone from the beginning to the end of treatment, as more problematic cases would more likely be treated with a combination of drugs rather than a monotherapy.

Intraspecific social problems appear to have had a worse overall outcome than other problems. However, the result is still good, and the difference may simply be related to practical difficulties that are common in dealing with intraspecific problems (i.e., the behaviour of other dogs is often an uncontrollable factor). The effects of mirtazapine on compulsive disorder cannot be evaluated as we had only one case.

The main limitation in evaluating the efficacy of mirtazapine is probably the lack of similar studies with other drugs, or even comparative studies with a larger number of cases, as is usually done in human studies. This makes further studies necessary to solve the common problem of lack of unification of diagnostic criteria and the difficulty in obtaining a series of many cases.

CONCLUSIONS

In view of these follow-up results of cases treated with mirtazapine, we can conclude that the use of mirtazapine as a monotherapy appears to be safe in dogs. The final results obtained are satisfactory, and it can thus be considered a useful drug in the treatment of behavioural problems in dogs. However, comparative studies with other treatments, following a similar systematic approach and with a larger number of cases, are needed to confirm these results.

AUTHOR CONTRIBUTIONS

Idea of the paper, acquisition and interpretation data and article draft: Juan Argüelles. *Acquisition and interpretation data*: Marina Miralles and Blanca Duque. *Article draft, critical revision and final approval*: Jaume Fatjo and Jonathan Bowen.

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

After being consulted, the ethics committee of the Cardenal Herrera-CEU University considers that the study is exempt from ethical approval, as it does not include any activity considered as a procedure on animals according to Royal Decree RD 53/2013.

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