



TOOLS FOR MANAGING FELINE PROBLEM BEHAVIOURS

Psychoactive medications

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Practical relevance: When a cat is presented for evaluation of a problem behaviour, it is likely that the cat's wellbeing is negatively affected by the condition. In addition, the owners and any other animals around the cat may also be experiencing negative consequences.

When managing these cases, it is important to consider all options (including behaviour modification, environmental changes, medications) that can help to reach an optimal solution. Medication cannot teach the cat how to behave or change a particular behaviour; it can, however, reduce arousal, excitability, reactivity and anxiety.

Rationale: The rationale for using psychoactive medications in behavioural medicine, or veterinary psychiatry, is to increase the wellbeing of the animal and to aid the owner and practitioner in managing problem behaviours. Medications should always be used as an adjunct to behavioural and environmental modification.

Clinical challenges: Many psychoactive medications cannot be used in the face of certain physical illnesses or concurrently with other medications. Some medications may also have side effects, not be effective at the recommended dose or have a paradoxical effect. Furthermore, success is reliant on the owner being able to administer the medication.

Aims: This article aims to guide practitioners by discussing questions such as how to choose the appropriate medication, how to dose it and how long to use it. The psychoactive medications most commonly used in feline medicine are reviewed, as well as some that are newer or less common.

Evidence base: Data for the use of medications in cats is limited, with just a small number of clinical-, species- and problem-directed studies available, and a few more case series and case reports. Where feline-specific research is not available, the authors have drawn upon research published in other species, such as humans, dogs and rats, as well as anecdotal reports and expert opinions.

Keywords: Anxiety; arousal; dopamine; emotion; fear; gamma-aminobutyric acid; GABA; noradrenaline; psychoactive medication; reactivity; serotonin

USING PSYCHOACTIVE MEDICATIONS

As in other areas of veterinary medicine, when deciding to use medication for behavioural purposes, several questions arise. These may include:

- ❖ What is the diagnosis?
- ❖ What is the aim of using medication?
- ❖ How do I choose the appropriate medication?
- ❖ How do I dose the medication?
- ❖ How do I know whether I made the right choice?
- ❖ How long should I use the medication?

What is the diagnosis?

Before deciding which medication to use, the clinician must establish an accurate diagnosis. While this is beyond the scope of this article, a few guidelines should be considered. A common tendency is to give a descriptive diagnosis such as 'house-soiling', 'urine spraying' or 'inter-cat aggression'. While these terms succinctly define the situation, they are not actual diagnoses, but a description of a clinical sign. A cat may soil outside of its litter box for a variety of underlying reasons, such as anxiety or simply due to an owner's inappropriate cleaning routine.¹ While the former may require medication, the latter does not.

As in any individual, a cat's behaviour is driven by one or more underlying motivations. These motivations include primary physiological drives, such as hunger or pain, emotions (psychological drives), such as fear, anxiety or frustration, and cognitive drives, such as mental stimulation.²

The clinician must establish the underlying motivations for a problem behaviour before choosing a psychoactive medication.



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The expression of a particular behaviour depends on many internal factors including genetics, previous experience and learning, and external factors including the owners and other pets in the household.^{3,4} For example, a cat that is afraid of other cats may attack if it has learned that doing so eliminates the threat. Also, a cat may choose to attack a second cat in the home simply because there is no escape route. Medication cannot teach the cat how to behave or change a particular behaviour; ie, no medication eliminates house-soiling or specifically decreases aggression towards other cats. Medication can, however, reduce arousal, excitability, reactivity and anxiety.⁵ Therefore, the underlying emotional motivation must be determined and addressed before implementing behavioural modification, environmental adaptations and medication (see article in Part 1 on [understanding feline emotions](#)).

Furthermore, since many physical illnesses (eg, hyperthyroidism, diabetes mellitus, food hypersensitivity) and pain can alter a cat's behaviour, a full physical examination and necessary laboratory tests should be carried out to rule out medical options.¹ Finally, many psychoactive medications cannot be used in cats with certain physical illnesses or concurrently with other medications (see 'Medications used in feline psychiatry', page 1038, for more information).

What is the aim of using medication?

The rationale for using medications in behavioural medicine is to increase the wellbeing of the animal and to aid the owner and practitioner in managing the situation. The intended purpose is to reduce anxiety, fear, arousal and intensity of the behaviour and, hence, in many cases, also improve welfare. Psychoactive medications should always be used as an adjunct to behavioural and environmental modification (see accompanying article in this issue on [environmental and behavioural modification](#)).^{5,6}

In complex situations in which the cat suffers from behavioural pathology or is subjected to multiple triggers and stimuli that cannot be adequately controlled, eliminated or reduced, the use of medication can be highly valuable. This is the case, for example, with cats that suffer from separation distress or noise phobia. Owners of such cats cannot always effectively eliminate all of the triggers or control the situation, and the use of medications is crucial.

Psychoactive medications and behavioural modification

There are many cases in which a cat's high level of arousal (due to fear or anxiety) limits the response to behavioural modification. In these situations, the use of medication can help to reduce the cat's threshold and allow the owner to institute a behavioural modification programme. Similarly, there are cases where the owner can initiate behavioural modification, but progress is slow and the success rate is low. In these cases, the use of medication can help to improve the effectiveness of behavioural modification.

One intended purpose for the use of psychoactive medications is restoring normal patterns of feline behaviour.



Psychoactive medications should always be used as an adjunct to behavioural and environmental modification.

An additional intended purpose for the use of psychoactive medications is restoring normal patterns of feline behaviour. Many cats that suffer from anxiety, fear, compulsive behaviour or cognitive decline do not have normal baseline behaviours. For example, many of these cats do not sleep sufficiently, are highly reactive to benign stimuli, are easily overstimulated by the environment, and have reduced appetite and abnormal responses. Psychoactive medications can help to restore normal patterns by balancing levels of neurotransmitters, enhancing neuronal signals and promoting gene translation in the brain. In turn, this can, for example, reduce arousal, anxiety and/or reactivity, and improve learning, the sleep-wake cycle and appetite.

How do I choose the appropriate medication?

When deciding which medication to use, three practical considerations arise:

- ✦ Availability
- ✦ Administration
- ✦ Frequency (of the problem)

For a discussion on specific indications, doses and side effects see 'Medications used in feline psychiatry'.

Availability

With the exception of clomipramine (Clomicalm; Novartis Animal Health) no psychoactive medications are currently licensed for use in cats. Clomicalm (licensed in Australia) is indicated for cats that are urine spraying.⁷ Clomicalm is available in several sizes (5 mg, 20 mg and 80 mg), of which only the 5 mg tablet might be suitable for the average cat. However, even this tablet size might be too large for some cats.

Other medications might be available in the right presentation but are not licensed for cats. Compounding medications or using a liquid form may help to achieve the desired dose; however, the two options raise other concerns such as quality of compounding and rejection or spillage of part of the liquid.

Desired effects

Psychoactive medications have a broad range of effects, depending on which neurotransmitters they influence. For example, serotonergic medications can reduce arousal, intensity and motivation to perform undesired behaviours, and can be used in a wide variety of problems. Dopaminergic medications can improve learning and memory. Gabaergic medications can reduce fear and anxiety.



Administration

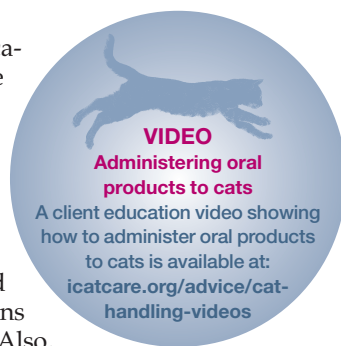
The success of using psychoactive medications depends not only on the appropriate selection of medication, its dose and frequency of administration, but also on the owner administering it successfully. The administration process itself must be considered, and an open discussion with the owner about the possible difficulties of administering medications to cats should precede their use. Most human medications are bitter, a taste that cats naturally avoid. Also, many owners struggle to administer medications to their cats. Some cats with fear and aggression problems may bite or scratch (accidentally at times) the person who administers the medications. Therefore, using a single medication might be preferable to the use of several medications.

Owners might report side effects that may not be a direct result of the medication, but rather reflect difficulties in administering the medication. Some cats may hide, show aggression or refuse their food due to aversive administration techniques or the taste of medication in their food rather than the actual (side) effect of the medication.

Transdermal preparations may appeal to owners and clinicians. However, several studies indicate very poor absorption and bioavailability.^{8,9} Increasing the dose or concentration is not a reliable method to increase bioavailability and can carry the risk of overdosing should the cat lick the medication. Transdermal preparations may cause local irritation and lead to dermatitis.⁸ As with medicating orally, there is likewise a risk to an owner when trying to apply transdermal medications to aggressive or defensive cats. Moreover, there is a risk of a second animal at home licking the preparation from the patient or the cat bunting against the owner, furniture or another animal and removing or transferring the medication. Finally, the transdermal absorption rate is heat- and moisture-dependent. In a warmer environment, a higher dose may be absorbed than initially desired.

Frequency

Another consideration when selecting medications is the frequency of the problem. Some medications can be used for cats presented with situational problems (eg, travel anxiety, fear at the vet's or firework phobia). Whereas other medications must be used daily (eg, fluoxetine or clomipramine), rather than on an 'as needed' basis. Most medications that are used for situational problems can also be used daily (eg, gabapentin, trazodone or benzodiazepines). For specific indications, the frequency of administration and potential benefits, refer to 'Medications used in feline psychiatry'.



When choosing a medication, a low dose should be used to start with to reduce the likelihood of side effects and to allow the cat's body to adapt to the changes.



When prescribing medications for situational use, the authors always recommend testing the medication in the owner's presence before the actual intended use; for example, to give a dose a few days before a scheduled visit to the vet's and observe the effects the medication has on the cat. Some medications may have a side effect, not be effective in the recommended dose or have a paradoxical effect (eg, stimulating the cat, rather than calming it).

How do I dose the medication?

Once the medication has been chosen, a low dose (the lowest dose within the therapeutic range) should be used to start with. The main reasons for this are to reduce the likelihood of side effects and to allow the cat's body to adapt to the changes. In selected cases (eg, senior cats, cats with concurrent health problems or cats on other medications) it might be prudent to start on a dose below the recommended therapeutic range. Side effects may appear within minutes of administration, or days later, depending on the medication, while beneficial effects may take up to several weeks to be seen. Side effects may be distressing to the cat and the owners, hence avoiding them may increase compliance and improve the outcome. The clinician must advise owners to seek veterinary advice if they notice side effects.

When evaluating the effect of the medication, the veterinarian must be confident that the dose is correct and that sufficient time is allowed for the medication to take effect. For example, 0.25 mg/kg of fluoxetine is an insufficient dose regardless of the duration. Equally, using 1 mg/kg for 2 weeks is not long enough to evaluate the effect. (For more detailed information, refer to 'Selective serotonin reuptake inhibitors', page 1040). When no beneficial effects are observed, despite using an appropriate dose for a sufficient timeframe, one question to consider is whether the diagnosis is correct. A second question is whether the owner was able to implement the prescribed management, including behavioural and environmental modifications, successfully.

Mode of action

Psychoactive medications exert their effect by influencing the levels and activity of different neurotransmitters and their receptors in the brain. Most medications act at pre- and post-synaptic receptors, on enzymes that either produce or degrade neurotransmitters or on reuptake processes (see 'Medications used in feline psychiatry' for modes of action of different medications). The neurotransmitters that are targeted most commonly in the management of problem behaviour are the monoamines (eg, serotonin, dopamine and noradrenaline) and gamma-aminobutyric acid (GABA). To a lesser degree, the following neurotransmitters are targeted as well: glutamate, substance P and acetylcholine, among others. Therefore, knowledge of these neurotransmitters, and their receptors, target centres and functions, is paramount. Note that most psychoactive medications may affect more than one neurotransmitter, especially at higher doses. Affecting other neurotransmitters is one of the reasons for their side effects.¹⁰



The prescribing veterinarian should advise owners what to expect (both desired effects and side effects), and in which timeframes. If no desired effect is seen following the initial course the dose should be increased (see 'Medications used in feline psychiatry' for specific indications and timeframes based on the type of medication). Once the dose is changed, it is likely to take the same timeframe (medication dependent) before the effect is noted. As long as there are no side effects, the dose can be increased while attempting to achieve the desired effects. The higher the dose, the more likely it is that side effects will be seen.¹⁰

Most psychoactive medications used for cats are off-label human medications with presentation (eg, tablets or capsules) adapted to human body weight. Thus, correct dosing of a cat with commercially available medication may prove difficult. The authors dose cats based on 2.5 kg for small cats, 5 kg for average-sized cats and 7.5 kg for obese or very large cats. Moreover, the authors dose based on the size of the available medication. For example, when choosing to use Clomicalm 5 mg tablets, the authors will dose at 2.5 mg increments. Using medications compounded for a specific cat, or liquid formulation, allows the dose to be adjusted more accurately.

If no-to-minimal desired effects are seen at the highest dose, a change of medication must be considered. It cannot be assumed that when one medication is not effective the same would be true for another, even from the same class (ie, paroxetine may be helpful where fluoxetine failed).¹¹

How do I know whether I made the right choice?

Monitoring the effects of medications

Once the psychoactive medication has been prescribed, the cat must be monitored to evaluate the effects. Most serotonergic medications require approximately 4 weeks or more to exert their desired effect, while other medication may be active in a matter of hours (see 'Medications used in feline psychiatry' for specific medications and their pharmacokinetics). Depending on the medication chosen and the cat, owners may see side effects initially. At times, the cat may experience side effects that owners may interpret as beneficial. For example, clomipramine has an anticholinergic effect that can reduce micturition, which may be desired in a cat that urinates in the home.⁵ Thus, changes in, or cessation of, undesired behaviours should not be the only parameter indicating the usefulness of a particular psychoactive medication.

Evaluating the effect of medication

Measuring behaviour and comparing with baseline

The owner should be instructed to measure the cat's behaviour in different situations and compare it with a baseline (ie, before starting the medication). For example, owners might be asked to monitor how often the cat soils in the house each week. They then chart this on a graph and see if there is a noticeable and sustained reduction. Similarly, owners can observe the cat during problem situations and see if the cat shows a lesser intensity of the behaviour. It can be helpful to develop a numerical scale with the owners: 0 representing situations in which the cat is completely relaxed, possibly sleeping; 10 indicating situations in which the cat is highly aroused and showing abnormal behaviours. Even if the scale is not accurate, owners may be able to see a trend developing. Maintaining a daily diary is also very important to track progress. Of course, the medication is given as part of a wider behaviour management programme and, therefore, some of the changes might be due to the other components.

Measuring the recovery period

Another way to evaluate the effect of a medication is the recovery period. Owners are asked to measure how long it takes their cat to recover from a given situation. For example, a cat may start showing signs of arousal and possible aggression when it sees the second cat in the house, or hides when visitors arrive (T0). The owner then measures how long it takes the cat to settle down or come out when the second cat has left the room, or the visitors have departed (T1). The recovery time (duration of T0 until T1) should decrease if the medication is effective.

Changing medication

When considering a change of medication, there are two options:

- ✦ Replacing the medication in use by switching to another medication;
- ✦ Adding a new medication to the existing one.

When switching from one medication to another, the clinician must wean the cat off the first medication and allow a washout period before introducing the new medication. The length of weaning and washout times depends on the specific medications.

Medication interactions and precautions

Cats generally tolerate psychoactive medications well. Most medications can be used throughout the cat's life; however, some precaution is necessary. Certain common medications may interact with psychoactive medications, and the metabolism of each might be affected. Also various antibiotics (eg, metronidazole), antiemetics (eg, metoclopramide) or analgesics (eg, tramadol) may increase levels of serotonin, which warrants caution when using these medications concurrently with serotonergic medications.^{5,12}

Serotonergic medications such as fluoxetine, paroxetine and sertraline are known (in humans and to a lesser degree in dogs) to inhibit subtypes of the cytochrome P450 enzyme system.¹² While similar information in feline medicine is lacking, it is prudent to consider these data from humans and dogs.

Cats generally tolerate psychoactive medications well.



In some situations, the use of one medication provides a degree of the desired effect that is not sufficient. However, increasing the dose may not be an option. In these cases, adding a second medication may augment or complement already existing effects. For example, a cat in which urine spraying frequency has decreased from several times daily to a few times weekly on 1.5 mg/kg fluoxetine q24h may further benefit from an additional benzodiazepine.

'Rules of thumb' when combining psychoactive medications

- ❖ Serotonergic medications can be used with gabapentin or benzodiazepines.
- ❖ Caution must be taken to avoid serotonin syndrome (see box, below right). Primarily, monoamine oxidase inhibitors (MAOIs) should not be used with other serotonergic medications.
- ❖ When combining medications, the clinician should start introducing the second medication with a dose at the lower end of the therapeutic range.

How long should I use the medication?

Medications should be used for as long as necessary. The goal of treatment involving medications is to improve the situation and possibly solve the problem. This may entail lifelong use of medications. Once the owner reports that the cat is acting normally, and the problem is no longer present or has been reduced to an acceptable level for a few months, the clinician may consider weaning the cat off the medication.

Having made the decision to withdraw the medication, the process must be conducted with care. Ideally, the medication is tapered off gradually over time. If the cat has been on the medication for several months, a good rule of thumb is to decrease the medication by 25% per month. Gradual reduction allows the brain chemistry to adjust, reduces the likelihood of side effects or withdrawal signs, and makes it possible for the owners to monitor changes in behaviour. In the authors' experience, if the cat starts showing signs of previous undesired behaviours during the weaning off process, the dose should be gradually increased again. Moreover, if the cat shows a similar pattern the second or third time the owner begins to taper off the medication, despite adequate behavioural and environmental management, the authors suggest maintaining the medication for life.

When weaning a cat off long-term medication this should ideally be done gradually over time. A good rule of thumb is to decrease the medication by 25% per month.



MEDICATIONS USED IN FELINE PSYCHIATRY

Once a decision has been made to use psychoactive medications, the clinician must choose which agent to use – the goal being to improve the behaviours (and thereby well-being) and avoid side effects.¹⁵ Aside from an accurate diagnosis and ruling out physical illness, good knowledge of the available options, pharmacological and pharmacokinetic properties, and possible side effects is required.

Table 1 lists class, indications, dosage and pertinent comments for a range of psychoactive medications.

Serotonergic medications

These medications are intended primarily to enhance the beneficial effects of the serotonergic pathways in the brain. Different serotonergic medications have a variety of mechanisms of action including affinity to different serotonin receptors (eg, pre-synaptic 5HT1A, and postsynaptic 5HT2A, 5HT2C and 5HT3) and effects on other neurotransmitters (eg, noradrenaline, dopamine and acetylcholine). This explains the diverse range of effects. Hence serotonergic medications can be used for many different problems including anxiety, fear, compulsive behaviours (abnormal repetitive behaviours), hypersensitivity–hyperactivity and high arousal. (Refer to the specific medications discussed in the following sections for more details.)

Serotonin syndrome

A serious potential side effect that is common to all serotonergic medications is serotonin syndrome. It is a potentially fatal condition caused by an excessive amount of serotonin in the brain that can lead to abnormally high neuronal activity. This condition is very uncommon in cats; however, it can result from an accidental overdose, whether through giving too high a dose of a single medication or by combining several products (medication and nutraceuticals) that act on serotonin. Signs can include mental changes (eg, agitation, restlessness, aggression), and neurological (eg, tremors, ataxia, seizures, coma), gastrointestinal (eg, diarrhoea, vomiting, anorexia) and autonomic signs (eg, tachycardia, tachypnoea, hypertension, pyrexia).^{13,14} Treatment should include decontamination of gastric content (if early enough), intravenous fluid therapy and supportive care, such as thermoregulation, and use of anticonvulsants and antiemetics.

Table 1 Psychoactive medications for consideration in cats: indications and dosage chart

Medication*	Class	Indications	Dosage (oral)	Comments
Alprazolam	Benzodiazepine	Fear, panic attack	0.125–0.25 mg/cat q8–12h	Can be used on an 'as needed' basis
Amitriptyline	TCA	Anxiety, fear; may also be useful as an adjunct in self-harm behaviours	0.5–1.5 mg/kg q24h	Data are lacking on efficacy Mild sedative
Buspirone [†]	Azapirone	Anxiety, fear (including increasing confidence in victim cats)	0.5–1 mg/kg q12–24h Up to 7.5 mg/cat q12h	10–14 days to take effect
Carbamazepine	Sodium channel blocker	Hyperaesthesia, impulsivity, seizures	2–5 mg/kg q12h	Possible serotonin reuptake inhibitor
Citalopram	SSRI	Anxiety, fear, compulsive behaviour	0.5–1.5 mg/kg q24h	4 weeks for full effect
Clomipramine [†]	TCA	Anxiety, fear, compulsive behaviour	1–3 mg/kg q24h	4 weeks for full effect
Clonazepam	Benzodiazepine	Anxiety, hyperaesthesia, panic attack, seizures	0.1–0.25 mg/kg q8–24h	Long-acting (6–8 h)
Diazepam [†]	Benzodiazepine	Anxiety, fear, seizures	0.25–0.5 mg/kg q12–24h	Monitor closely; avoid when hepatic disease is present and consider alternatives
Doxepin	TCA	Anxiety, fear, compulsive behaviour	0.5–1 mg/kg q24h	Mild sedative, no proof of efficacy
Fluoxetine [†]	SSRI	Anxiety, fear, impulsivity, compulsive behaviour	0.5–1.5 mg/kg q24h	Most commonly used SSRI
Fluvoxamine	SSRI	Anxiety, fear, impulsivity, compulsive behaviour	0.5–1 mg/kg q24h	–
Gabapentin [†]	Anticonvulsant	Anxiety, fear, compulsive behaviour, seizures	5–20 mg/kg q8–24h 50 mg/cat as needed	Can be given for situational fear or as an adjunct to SSRI and TCA
Imepitoin	Partial GABA-A receptor agonist Weak calcium channel blocker	Anxiety, fear, seizures (anecdotal use by one of the authors [MBD])	10–30 mg/kg q12h	Takes 5–10 days to take effect; start with a lower dose range
Lorazepam	Benzodiazepine	Anxiety, fear, panic attack	0.125–0.25 mg/cat q12–24h	Can be used on an 'as needed' basis
Mirtazapine [†]	Alpha-2 antagonist/ 5HT _{2A} , 5HT _{2C} and 5HT ₃ antagonist	Anxiety, appetite stimulant	1.88 mg/cat q24–48h	Quarter of the 7.5 mg tablet
Oxazepam	Benzodiazepine	Anxiety, fear	0.2–0.5 mg/kg q12–24h	Not an anticonvulsant
Paroxetine [†]	SSRI	Anxiety, fear, compulsive behaviour	0.5–1.5 mg/kg q24h	No active intermediate metabolites
Selegiline [†]	MAOI-B	Cognitive decline, chronic emotional disorder, HSHA	0.5–1 mg/kg q24h	Avoid if using serotonergic medication; should be given in the morning due to its stimulant effect
Sertraline	SSRI	Anxiety, fear, impulsivity	0.5–1.5 mg/kg q24h	Avoid if using serotonergic medication
Trazodone [†]	5HT _{2A} antagonist/ reuptake inhibitor SARI	Fear (situational), panic attack	25–50 mg/cat	Must be given 1–2 h before fear-eliciting event
Venlafaxine	SNRI	Anxiety, fear	1–2 mg/kg q24h	Avoid if using serotonergic medication

*See text for more information on each specific medication

[†]Medications for which published studies or case reports are available documenting use in cats. All other medications are used based on anecdotal data
TCA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitor; MAOI = monoamine oxidase inhibitor; SNRI = serotonin–noradrenaline reuptake inhibitor; HSHA = hypersensitivity–hyperactivity; SARI = serotonin antagonist reuptake inhibitor; GABA = gamma-aminobutyric acid

Azapirones

Mode of action and metabolism

These medications are serotonergic and, to a lesser degree, dopaminergic agonists. Buspirone is the most commonly used medication in this class. It is a 5HT_{1A} (serotonin 1A receptor) partial agonist and partial dopamine (D₂) receptor agonist.^{16,17}



Buspirone – indicated to reduce fear and anxiety and to increase confidence – is well tolerated in cats.

The bioavailability of buspirone in cats, when administered transdermally, is weak.⁹ However, oral administration leads to very high bioavailability.^{9,18} Buspirone is well tolerated in cats, with minimal side effects.¹⁹

Indications

Buspirone is indicated to reduce fear and anxiety and to increase confidence.⁶ A common presentation for which buspirone may be useful is urine spraying.¹⁹ One of the authors (SD) has also used it successfully in cases of inter-cat aggression (for the victim cat). It can be administered as a first-choice medication, although it is not as potent as some of the other serotonergic medications.

Side effects

In the experience of one of the authors (SD), side effects are infrequent, with gastrointestinal signs the most likely to occur. Also, sedation has been reported in some cats.¹⁹ Based on information in other species, caution is advised in cats with chronic renal or hepatic disease.⁵

Combination with other psychoactive medications

Bupirone can be administered concurrently with other serotonergic medications such as tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs), but careful monitoring is recommended due to the risk of serotonin syndrome. This medication should not be combined with any MAOI, such as selegiline.¹⁶

Selective serotonin reuptake inhibitors**Mode of action and metabolism**

SSRIs increase the level of serotonin in the synaptic cleft by inhibiting the reuptake pump (serotonin transporter [SERT]) at the presynaptic neuron.¹¹ Additionally, SSRIs lead to a decrease in a number of different serotonergic receptors, both on the pre- and post-synaptic cells. They have a lesser effect on other neurotransmitters in the brain (eg, dopamine, noradrenaline, acetylcholine and histamine) compared with TCAs. This explains the lower incidence and profile of side effects compared with TCAs.⁵

Following absorption, SSRIs are metabolised by the liver and excreted by the kidneys.⁵ Caution is required in senior cats or those with hepatic or renal failure. Transdermal administration of fluoxetine has been proven to produce approximately 10% of the bioavailability of oral administration, and is therefore not recommended.⁸ SSRIs lead to increased levels of serotonin at the somatodendritic synapse (at the median raphe) within hours, but not in other brain centres. This pharmacological sequence explains why cats may experience side effects within the first few days of treatment. After this time, the presynaptic receptors become desensitised and decrease in number (downregulation). This leads to increased activation of the serotonin neuron, thus releasing more serotonin at the axon terminal synapses in the target centres. A higher level of serotonin at the axon synapses ultimately leads to downregulation of the post-synaptic receptors. The whole process takes approximately 3–4 weeks and correlates with the decrease in side effects and the appearance of desired effects.¹¹ Furthermore, SSRIs stimulate gene translation that leads to an increase in neurotrophic substances (eg, brain-derived neurotrophic factor), which are crucial for learning and memory.

Cats may experience side effects of SSRIs within the first few days of treatment, and it can take approximately 3–4 weeks for the appearance of desired effects.

**Indications**

Common indications include anxiety, fear, compulsive disorders, impulsivity and high arousal. Typical presentations include aggression, separation-related problems and urine spraying.^{20–22} Based on available data, the most commonly used SSRI in cats is fluoxetine,^{8,20–22} which is well tolerated with a wide safety margin.²³ Other options include paroxetine, fluvoxamine, sertraline and citalopram.

Side effects

The most common side effects reported are gastrointestinal signs (anorexia, nausea, diarrhoea), as serotonin receptors are also found in the digestive system.²⁴ An important side effect to note is urinary retention, which owners can keep track of by recording, for example, the number of urine marks in the litter box. In the authors' experience, this side effect is uncommon, but in the rare cases where urinary retention does occur, it may be life-threatening if it goes unnoticed. Serotonin is involved in the control of urination by affecting different centres in the brain including the central micturition nucleus.^{25–27} Starting with a low dose and increasing incrementally over 3–4 weeks may help to avoid these side effects.

Interactions with other medications

Based on data in humans and dogs, SSRIs are known to be competitive inhibitors of the cytochrome P450 liver enzyme systems.^{5,12} It is not known to what extent this applies to cats; however, general caution is advised. Most SSRIs inhibit CYP2D6, which also metabolises most TCAs. Therefore, it is not recommended to combine TCAs and SSRIs.²⁸ Cats should be weaned off SSRIs slowly to reduce the risk of clinical signs due to withdrawal.^{29,30}

TCAs should not be combined with SSRIs and MAOIs.

**Tricyclic antidepressants****Mode of action and metabolism**

Similar to SSRIs (see above), TCAs inhibit the reuptake of serotonin by blocking SERT. However, these medications are less selective than SSRIs and have a more profound effect on other neurotransmitters, such as noradrenaline, acetylcholine and histamine.²⁴ As a result, they have a greater propensity for side effects and are less potent than SSRIs. Efficacy and side effect profiles of each medication differ based on the medication's pharmacological profile.

Indications

Clomipramine is the most serotonin-selective TCA and the only one that is licensed – for urine spraying – in cats (Clomicalm in Australia). It also has noradrenergic and mild antihistaminic and anticholinergic effects. The main indications for the use of clomipramine include anxiety and compulsive behaviours.^{22,31} Amitriptyline is still commonly used by veterinarians; however, the evidence is anecdotal and no scientific data exist.⁶

Side effects

Common side effects can be categorised based on which neurotransmitter is affected. Strong antihistaminic (H1 and H2 receptors) TCAs, such as amitriptyline and doxepin, can cause sedation. However, they can be useful in cases where pruritus is also suspected.⁶ Anticholinergic (mostly muscarinic) side effects can lead to a dry mouth, reduced gastrointestinal motility, urine retention, keratoconjunctivitis sicca and mydriasis.²⁴

TCAs are contraindicated in cats that have cardiac disease or glaucoma, and should be used cautiously in cats with seizures.⁵ As a result of an extensive side effect profile and low potency compared with SSRIs, apart from clomipramine TCAs should not be considered first-choice medications.

Combination with other psychoactive medications

TCAs should not be combined with SSRIs and MAOIs. Furthermore, TCAs should be combined cautiously with other antihistaminic or anticholinergic medications.

Serotonin–noradrenaline reuptake inhibitors

Mode of action and metabolism

Serotonin–noradrenaline reuptake inhibitors (SNRIs) block the reuptake of serotonin and noradrenaline at the presynaptic level; at higher doses they also block dopamine reuptake inhibition but to a lower degree.¹¹ Not much data exist on the use of these medications in cats.

Indications

Venlafaxine appears to be well tolerated in cats, with a wide safety margin.³² In human psychiatry, SNRIs are used for mood disorders such as depression and anxiety, and for chronic pain. Venlafaxine appears to have similar indications in cats, including treatment of urine spraying when anxiety and idiopathic cystitis are present.³³

Side effects

Side effects of SNRIs are similar to those seen with SSRIs and TCAs.

A low dose of trazodone can lead to increased sleeping and may be useful for treating night-time waking in cats.



Serotonin antagonist reuptake inhibitors

Mode of action and metabolism

Serotonin antagonist reuptake inhibitors (SARIs) block the 5HT_{2A} and 5HT_{2C} serotonin receptors when used at a low dose. At higher doses, these medications also block serotonin reuptake (SERT) at the presynaptic neuron.¹¹

Indications

Trazodone is the most commonly used SARI. A low dose can lead to increased sleeping and may be useful for treating night-time waking in cats. At high doses, trazodone is also helpful in treating anxiety, fear and impulsivity, but can lead to sedation.³⁴ The combination of possible sedative effects at high dose and a relatively short half-life leads to trazodone being a second- or third-option medication. More recently, trazodone has been used on an as-needed basis for situational fears and phobias, such as trips to the vet's or travel-related problems.³⁴

Combination with other psychoactive medications

Trazodone can be combined with SSRIs or TCAs. However, caution should be taken to avoid serotonin syndrome.

Alpha-2 (α_2) antagonist

Mode of action and metabolism

Noradrenaline can bind to the presynaptic α_2 heteroreceptor on serotonergic neurons and inhibit serotonin release.¹¹ Medications from this class block this effect, leading to disinhibition and thereby an increased release of serotonin. Moreover, these medications can bind to the α_1 postsynaptic receptors on serotonergic neurons in the locus coeruleus, preventing noradrenaline from binding. Blocking these receptors leads to increased secretion of serotonin from these neurons downstream in the cortex.

Mirtazapine is a commonly used α_2 antagonist. It is also a potent 5HT_{2A}, 5HT_{2C} and 5HT₃ antagonist, and has mild antihistaminic activity.^{11,35} These properties provide both an anxiolytic effect and appetite stimulation. Moreover, blocking 5HT₃ receptors centrally also provides antiemetic effects.³⁶

Indications and combination with other psychoactive medications

Mirtazapine is most commonly used as an appetite stimulant in cats, primarily those suffering from chronic renal failure.^{35–37} Based on experience with other species, such as dogs³⁸ and rats,³⁹ mirtazapine is also used alone or as an adjunct to SSRIs or TCAs in the management of high arousal in cats due to fear or anxiety.

Monoamine oxidase inhibitors

Mode of action and metabolism

Medications from this class have effects in addition to inhibiting the enzymes monoamine oxidases A and B. They also enhance the activity of the enzymes superoxide dismutase and catalase that decrease toxic oxygen-free radical species in the brain, thus reducing oxidative damage to the brain tissue.⁴⁰ Furthermore, MAOIs can inhibit reuptake of catecholamines, stimulate the release of catecholamines and stimulate action potential–transmitter release coupling. Monoamine oxidase B is mostly active in the central nervous system and catabolises catecholamines (dopamine, noradrenaline, serotonin and beta-phenylethylamine). Monoamine oxidase A is primarily active in the intestine and catabolises exogenous amines such as tyramine (found in some foods such as cheese).

The medication most frequently used in animals is selegiline. Most MAOIs are selective for type A or B oxidase. Selegiline is a preferential, irreversible MAOI-B, but with minor MAOI-A effect (in high doses).⁴¹ It inhibits the enzymes in two steps: first a reversible inhibition, and then an irreversible inhibition.⁴² Its effect varies between species: it increases dopamine levels in dogs, humans and possibly cats, but not in rats.⁵ It also blocks the reuptake of serotonin and noradrenaline.

Indications

The main indications for the use of selegiline include cognitive decline and chronic emotional disorders.^{41,43} Selegiline should be given in the morning due to its stimulant effect.⁶

Side effects

Selegiline has proven to be safe in cats at doses up to 10 times the recommended dose.⁴⁴ Side effects may include restlessness, agitation, lethargy, vomiting, diarrhoea and reduced hearing.⁴¹ Although it is a weak MAOI-A at therapeutic doses, it may be prudent to caution owners to avoid feeding tyramine-containing foods such as cheese.⁵

Combination with other psychoactive medications

Selegiline should not be used concurrently with other serotonergic medications, such as SSRIs or TCAs, due to a high risk of serotonin syndrome. Also it should not be given for at least 2 weeks after the discontinuation of a TCA, or 5 weeks following an SSRI.⁵

Interactions with other medications

In dogs, selegiline may interact with metronidazole, prednisone and trimethoprim-sulfa; therefore, caution is advised in cats as well.⁵

Benzodiazepines

Mode of action and metabolism

Benzodiazepines facilitate GABA activity by binding to GABA-A receptors in the central nervous system.¹¹ When the hypothalamic and limbic system receptors are activated, the effect is anxiolytic.⁵

These medications have a rapid onset of action, and the effect lasts between 2 and 12 h depending on the medication.¹¹ The most commonly used benzodiazepines are diazepam, alprazolam, clonazepam, lorazepam and oxazepam. Most medications from this class are metabolised by the liver's glucuronidation pathway, except for alprazolam.⁴⁵ Therefore, alprazolam is considered a safe option for cats. Moreover, lorazepam, oxazepam and clonazepam do not have active intermediate metabolites and may be safe for use in cats.

Diazepam has been shown to be effective in cats for anxiety and fear that lead to urine spraying.⁴⁶ However, due to potentially fatal hepatic necrosis, and lower efficacy compared with SSRIs, it should not be considered as a first- or second-choice medication for cats.⁴⁵

Selection between the different benzodiazepines is based on the duration of action. As there is a lack of research into the pharmacokinetics of benzodiazepines in cats, most of this information is extrapolated from other species. Alprazolam is a short-acting medication with an effect of 2–3 h, lorazepam has a duration of 4–6 h, while oxazepam and clonazepam may last up to 10 h.⁵

Indications

Given the rapid onset of action, benzodiazepines can be considered as situational medications for problems such as noise phobia and travel phobia, as well as for veterinary visits.²⁴ Furthermore, in low doses benzodiazepines may stimulate appetite, which can be beneficial in fearful or anxious cats.

When deciding to use a benzodiazepine for a particular fear-eliciting event, it is prudent to prescribe it ahead of time and advise the owner to give a test dose to evaluate its effect on the cat when the owner is present.

Side effects

Common side effects of benzodiazepines include sedation, ataxia, muscle relaxation, increased appetite and paradoxical excitation.²⁴

Combination with other psychoactive medications

Benzodiazepines can be administered as an adjunct to SSRIs and TCAs. When combining a benzodiazepine with other sedatives, gaba-nergic medications or trazodone, profound sedation or ataxia may occur.

Due to potentially fatal hepatic necrosis, and lower efficacy compared with SSRIs, diazepam should not be considered as a first or second choice for cats.



Gabapentin

Mode of action and metabolism

Gabapentin is structurally related to GABA. However, it does not mimic GABA's effect or metabolism.⁴⁷ The most likely mode of action is inhibition of calcium influx through the pre-synaptic voltage-gated calcium channels, thus inhibiting release of excitatory neurotransmitters such as glutamate and noradrenaline.⁴⁸

Gabapentin has approximately 90% bioavailability in cats, and it takes around 10 days to reach full therapeutic effect.⁴⁷ It is eliminated fully by the kidneys; therefore, caution is required for cats with renal failure.

Indications

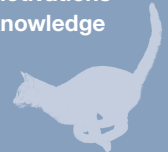
Common indications include chronic pain,⁴⁹ seizures⁵⁰ and anxiety.⁵¹ Gabapentin may be useful as an adjunct to SSRIs and TCAs for refractory anxiety as well as for compulsive behaviours such as psychogenic alopecia or feline hyperaesthesia; the latter often have a physical pain-related component that can additionally be decreased by this medication. Gabapentin can also be used for situational fears, such as travel-related problems or visits to the vet's.⁵²

Side effects

Common side effects include sedation, ataxia and gastrointestinal signs such as vomiting and diarrhoea.⁵²

KEY POINTS

- ❖ The rationale for using medications in behavioural medicine is to increase the wellbeing of the animal and to aid the owner and practitioner in managing problem behaviours.
- ❖ Medication cannot teach the cat how to behave or change a particular behaviour; it can, however, reduce arousal, excitability, reactivity and anxiety.
- ❖ Psychoactive medications should always be used as an adjunct to behavioural and environmental modification.
- ❖ Many psychoactive medications cannot be used for cats with certain physical illnesses or concurrently with other medications.
- ❖ The success of psychoactive medications depends on appropriate selection, dose, frequency of administration and duration of use, as well as the owner being able to successfully administer the medication.
- ❖ Having chosen a medication, a low dose should be used to start with. When weaning off a medication this should ideally be gradual.
- ❖ Changing medication or combining medications can help to increase the desired effect; caution is required, however, to avoid serotonin syndrome.
- ❖ Accurate diagnosis and recognition of underlying motivations leading to the problem behaviour, as well as good knowledge of the available medications, their pharmacological and pharmacokinetic properties, and possible side effects, is necessary when deciding to use a psychoactive medication.



Gabapentin has approximately 90%

bioavailability in cats, and it takes around 10 days to reach full therapeutic effect.



Miscellaneous medications

The below medications are used in other species (eg, humans and dogs) for behavioural purposes. No scientific data exist for behavioural indications in cats; hence, their use in this species is based on anecdotal information.

❖ **Imepitoin** (Pexion; Boehringer Ingelheim) is a low-affinity partial GABA-A receptor agonist and a weak calcium channel blocker that is licensed (in some countries) as an antiepileptic for dogs. It has recently been shown to have anxiolytic properties in dogs as well.⁵³ It is used in and well tolerated by cats as an antiepileptic drug.⁵⁴ One of the authors (MBD) has successfully used imepitoin in a few cats showing excessive vocalisation and urine spraying.

❖ **Carbamazepine** is a sodium channel blocker that is used for seizures in humans, impulsivity in dogs and head shaking in horses.⁵⁵⁻⁵⁷ One of the authors (SD) has used it as an adjunct to SSRIs for cats with high impulsivity leading to unprovoked aggression towards people and other animals.

Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

SERIES OUTLINE

This article forms part of a series of evidence-based reviews on feline behaviour, independently written by key opinion leaders, spanning three Special Issues of *JFMS*. Part 1 was published in May 2018. An outline of the full series is included as supplementary material alongside the article at: cpsj.jfms.com



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