

A Review of Pharmacologic Agents Used to Treat Feline Behavioral Disorders

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The use of pharmacologic agents to treat feline behavioral disorders has become a widely accepted practice in modern veterinary medicine. It is the responsibility of the veterinarian to be aware of the appropriate uses, mechanisms of action, and side effects of these agents.

Pharmacological therapy needs to be part of an integrated program which considers the physical, behavioral, and social environments of the pet. Client compliance is critical as therapy is more often successful when combined with environmental changes.

It is important to obtain a thorough history, perform a complete physical exam, and evaluate biochemical and hematologic profiles prior to initiating treatment. This is done to rule out medical causes for abnormal behavior and to alert the veterinarian to possible therapeutic contraindications. Felines are prone to toxicities since they have impaired hepatic drug metabolism. This is caused by a limited ability to conjugate glucuronic acid due to a relative absence of UDP-glucuronyl transferase.¹ All long-term pharmacologic therapy requires continued monitoring of biochemical and hematologic profiles to assume adequate organ function.

This article is intended to provide a review of the various drug groups available for treating feline behavioral disorders; specific drug dosages will not be included.

Progestins

Progestins are drugs which mimic the actions of the hormone progesterone.

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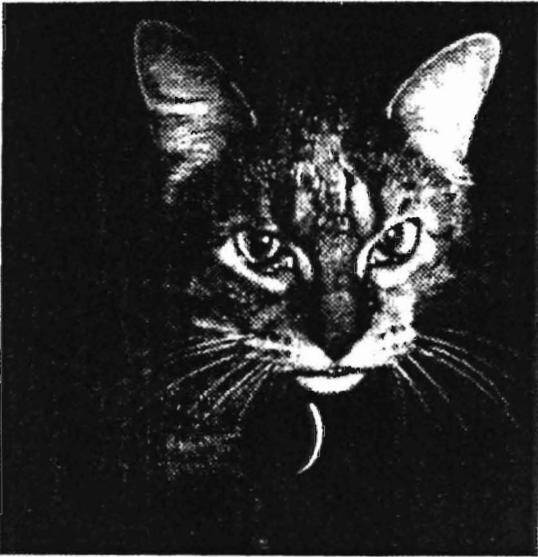
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Progestins bind to cytosolic receptors which are translocated into the cell nucleus to bring about RNA and protein synthesis.²

Progestins have progestational and glucocorticoid-like activities.³ They have been useful in the past for treating behavioral disorders because of their calming effects and suppression of male stereotypic behaviors.⁴ Progestins have been specifically used to treat feline inappropriate elimination (urine spraying or marking), in which progestins have been found to be effective one third of the time, with males responding more favorably than females (48% vs. 13%).⁵ Progestins have also been used to treat aggression (intermale and sex-related).^{6,7}

Progestins are now used as a choice of last resort due to the severity of the potential side effects. Baseline CBCs and serum biochemical panels should be run, with repeated blood work every six to eight weeks to monitor for possible side effects. The side effects of progestins include gynecomastia, endometrial hyperplasia, pyometra, and possible mammary gland neoplasia.^{4,8} Glucocorticoid-like effects include adrenocortical suppression and atrophy, diabetogenesis, and weight gain.^{4,8} Sedation can be produced at high doses because of a nonspecific CNS depression.⁶ Occasional hair loss or change in hair pigmentation has been found at the injection site when progestins are administered SC.⁹ Progestins are contraindicated in breeding animals, animals currently receiving corticosteroid therapy, or in cases of diabetes mellitus.⁴

The two most widely used compounds include medroxyprogesterone acetate (MPA, injectable) and megestrol acetate (MA, oral), both of which are derivatives of 17-alpha-acetoxyprogesterone.⁵ MPA and MA have been found to be equally effective, but it has been suggested that MPA be used first since it causes a decreased frequency of depres-



Savek, a 5-year-old spayed female DSH cat, does not enjoy long car rides. Her owner must sedate her with Acepromazine, a phenothiazine derivative, to make the trip more relaxing for both of them. Note the elevated nictitating membranes, a common occurrence with sedation.

sion and appetite suppression than does MA.⁵ Treatment with MPA or MA may be effective after initial treatment when the other was ineffective.^{5,11}

Benzodiazepines

Benzodiazepines act on an inhibitory supramolecular receptor complex that consists of a gamma-aminobutyric acid (GABA) receptor, a benzodiazepine receptor, and a chloride channel.¹² These drugs act to potentiate GABA, an inhibitory CNS neurotransmitter, with calming effects attributed to action on the limbic system and reticular formation.⁴ Benzodiazepines have global/nonspecific anxiolytic effects which are in part due to sedation.⁴

Specific benzodiazepines include diazepam, alprazolam, clorazepate dipotassium, oxazepam, clonazepam, and chlordiazepoxide. These various compounds vary in their kinetics, but have similar efficacies because of a common intermediate metabolite, desmethyldiazepam.^{4,13}

Benzodiazepines can be used for short-term management of acute fear (car rides, thunderstorms),¹⁴ fear-induced aggression,^{7,15} urine spraying/markings,^{15,16} and may be effective during early stages of ste-

reotypy.¹⁷ Diazepam has been shown to produce favorable responses in feline urine spraying/markings (55%,¹⁶ 74%¹⁵) with no evidence of gender difference.¹⁶ A high recurrence rate (90%) was found after treatment was discontinued.¹⁶

Ataxia, sedation, and impaired depth perception are common side effects seen after initial dosage and usually resolve spontaneously after three to four days.^{4,13} This is correlated with the attainment of steady-state blood concentrations of desmethyldiazepam.^{4,13} Paradoxical increases in aggression due to disinhibition have been observed.¹⁴ Induction of physiologic and behavioral dependency can occur after long-term use¹⁴ and may contribute to the high rate of abnormal behavior recurrence following discontinuation of treatment.¹⁶ It has been suggested that benzodiazepines be gradually withdrawn to prevent withdrawal reactions.¹⁵

Other side effects seen with benzodiazepines include an increased appetite (and weight gain) and increased affection toward owners.^{15,16} These drugs should be used cautiously in patients with impaired liver function since the primary metabolic route is hepatic biotransformation.¹⁵ A more recent concern is that on occasion a cat may develop hepatic failure when exposed to this group of drugs.⁸ All benzodiazepines interfere with learning ability and short-term memory which may affect the progress of behavioral training programs.^{4,13}

Benzodiazepines have short half-lives and must be administered frequently in order to be effective.⁴ Longer acting, sustained-release formulations of diazepam and clorazepate are available and may be easier for clients to administer.⁶

Benzodiazepines have gained favor because they have fewer and less serious side effects than progestins, and because they are more effective than progestins when treating urine spraying/markings.⁹

Azapirones

Azapirones are termed anxiolytic agents since they have specific anxiolytic actions and minimal side effects.⁶ Buspirone HCl is the compound that has been used to treat feline behavioral disorders. It is a nonspe-

cific anxiolytic which acts as a partial serotonin agonist, pre- and postsynaptically.¹³

Buspirone has been used to treat feline urine spraying/markings,¹⁸ feline ritualistic or stereotypic behaviors,⁴ and some cases of aggression.⁶ A study done by Hart¹⁸ found that buspirone markedly reduced urine spraying/markings in 55% of cats and only 50% resumed the behavior once therapy was discontinued. In addition, no significant gender difference was found. Cats from single-cat households responded favorably less frequently than did those from multi-cat households.¹⁸

The onset of action for buspirone is gradual and full effect may not be seen for up to four weeks.⁶ Long-term use of buspirone does not present a problem because of the lack of dependence and minimal side effects.¹⁴ Possible side effects include increased affection toward owners and minor incidences of inter-cat aggression.¹⁴ Other side effects are inappetance, lethargy, and possible interference with thyroid medication.⁸ Gastrointestinal symptoms may also occur.^{4,15}

Buspirone, benzodiazepines, and progestins each have different side effects and mechanisms of action in the CNS, so that a feline may respond favorably to one drug and not another. With regard to the treatment of urine spraying/markings, a sequential trial is recommended starting first with buspirone, then diazepam, and finally progestins in order to minimize complications.¹⁸

Phenothiazines

Phenothiazines are low potency neuroleptics which cause dopamine antagonism.¹⁴ They include such agents as acetylpromazine maleate, chlorpromazine HCl, and promazine.¹⁵

Phenothiazines have occasionally been used to treat short-term anxiety in cats (car rides), but are not often used in continuous, long-term behavioral therapy.⁴ These tranquilizers are accompanied by marked sedation⁶ and as such are generally inappropriate as a treatment for aggression since they suppress both normal and abnormal behavior.⁴ Side effects of these drugs are initial vasodilation and possible hypotension. Phe-

nothiazines also act to lower seizure thresholds. Major side effects of long-term use include cardiovascular abnormalities (primarily hypertension), and extrapyramidal signs such as ataxia, muscle tremors, and incoordination.^{4,10}

These agents are biotransformed by hepatic mechanisms and should be used cautiously (or avoided) in patients with hepatic insufficiency.

Butyrophenones

Butyrophenones are high potency neuroleptics which cause dopamine antagonism.¹⁴ This group includes drugs such as haloperidol and droperidol. Side effects are similar to those of the phenothiazines except butyrophenones produce less sedation and a higher frequency of extrapyramidal signs.⁸ They also do not lower the seizure threshold.

Butyrophenones have recently been used to treat stereotypic behaviors. These behaviors are thought to originate from a stressor that causes the release of endorphins, which in turn activates dopaminergic (nigrostriatal) neurons leading to the stereotypic motor activity.⁶ Butyrophenones provide a means with which to break the link by antagonizing dopamine. A single injection of haloperidol has been found to reduce excessive grooming in cats for a variable period of weeks to months.¹⁹ More research is needed in this area.

Opioid Antagonists

Opioid antagonists block central endorphin receptors and include the drugs naloxone, nalmefene, naltrexone, and diprenorphine; the latter three are considered to be long-acting.^{4,17} This group of drugs has been used in the treatment of stereotypic behaviors because endogenous opioids (endorphins) are thought to be involved in the development of a stereotypy. Endorphins may also stimulate pleasure centers in the brain leading to reinforcement of the behavior.⁸ Gastrointestinal disturbances such as diarrhea are reported side effects of these drugs.¹⁴

It has been stated that naloxone and naltrexone are too short-acting to be of any practical use for repetitive behavioral



Callie, a 2-year-old spayed female DSH cat often exhibits hypervocalization.

problems.⁶ However, a study found that a single, SC injection of naloxone had a beneficial effect on excessive grooming in cats for a median of three months.¹⁹ These effects were only seen with stereotypies that had existed for less than one year.¹⁹ This

led to the hypothesis that naloxone was only effective in counteracting recently developed stereotypies and that perhaps the release of endorphins declines after a stereotypy becomes persistent.¹⁹

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) have three effects: 1) sedation, 2) peripheral and central anticholinergic action, and 3) potentiation of biogenic amines in the CNS by blockage of presynaptic uptake.⁴ TCAs prevent neuronal uptake of serotonin (5-HT), allowing for a prolonged action of the neurotransmitter.²⁰ TCAs include amitriptyline HCl, imipramine HCl, clomipramine HCl, and doxepin HCl.⁴

The most frequently used TCAs are amitriptyline and clomipramine, which are used to treat stereotypies,^{14,17} urine spraying/marking,^{6,21} and hypervocalization.²² They are thought to be effective in treating affective aggression.⁶

TCAs are bound to plasma proteins, and competing drugs such as phenylbutazone and aspirin can potentiate their effects.²⁰ This group of drugs is oxidized by hepatic microsomal enzymes⁴ and most TCAs will moderately raise serum alkaline phosphatase in the absence of clinical signs.²³ The behavioral effects of these anti-depressants may not be evident until three to four weeks after initiating treatment.⁶

Side effects include dry mouth, constipation, urine retention, tachycardia, arrhythmias, syncope, ataxia, disorientation, generalized depression, and inappetance.⁴ High doses can produce a sick euthyroid syndrome, convulsions, and hepatotoxicity.⁴ Hematologic and biochemical profiles along with a thorough cardiac work-up should be

performed prior to initiating therapy. Continued monitoring during therapy is also necessary.

Carbamazepine is a TCA derivative.⁴ It is a tricyclic compound with anticonvulsant and mild anticholinergic properties.²⁴ It has been used to treat aggression in cats. Side effects are similar to TCAs and include dyspnea, ataxia, convulsions, vomiting, defecation, and adverse skin reactions.²⁴

Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs) are a type of antidepressant that blocks the oxidative deamination of monoamine neurotransmitters in the brain.²⁰ This results in a rapid and extended increase in the levels of dopamine, norepinephrine, and serotonin.²⁰ The rise in the levels of these neurotransmitters appears to result in a mood elevation.^{4,10} MAOIs include phenelzine sulfate, moclobemide, and deprenyl.²⁰ Side effects include anticholinergic effects (dry mouth, constipation, urine retention, tachycardia), weight gain, restlessness, and rarely, liver damage.²⁰ MAOIs have seldom been found useful in companion animal therapy.⁴

Specific Serotonin Re-Uptake Inhibitors

Specific serotonin re-uptake inhibitors (SSRIs) are another group of antidepressants that act to specifically increase serotonin (5-HT) levels by preventing neuronal uptake.^{4,20} SSRIs include fluoxetine and sertraline. They lack the anticholinergic and cardiovascular side effects seen with TCAs and MAOIs, but can cause nausea, insomnia, and anorexia.²⁰ This group of drugs has recently been introduced to veterinary medicine and has been used to treat stereotypic behaviors.¹⁴

Miscellany

The following drug groups are not routinely used in veterinary medicine and are mentioned for the sake of completeness. In most cases, behavioral disorders would be better treated by pharmacologic agents previously mentioned.

Beta-Blockers Beta-adrenergic blockers such as propranolol (beta₁ and beta₂ blocker) and pindolol (mixed beta agonist/antagonist) have been used to treat anxiety, fear, and aggression-related disorders and have met with mixed success.^{4,14} It is thought that beta-blockers exert their effects indirectly by acting on adrenergic receptors on muscle spindles. This results in decreased muscle tension, decreased afferent bombardment of the CNS, and decreased arousal level.⁶ Beta-blockers act to prevent the sympathetic physiologic response that is a component of behavioral disorders.⁴

The side effects of beta-blockers are minimal and include bradycardia and exercise intolerance.¹⁴ Pindolol has also been reported to cause urinary incontinence.⁶

Antihistamines Antihistamines competitively inhibit histamine₁ receptor sites and may have anticholinergic effects.⁴ Chlorpheniramine maleate can be used in the cat to provide mild sedation in cases of hyperactivity or apprehension such as a car ride, late-night activity, pacing, and vocalization.⁴

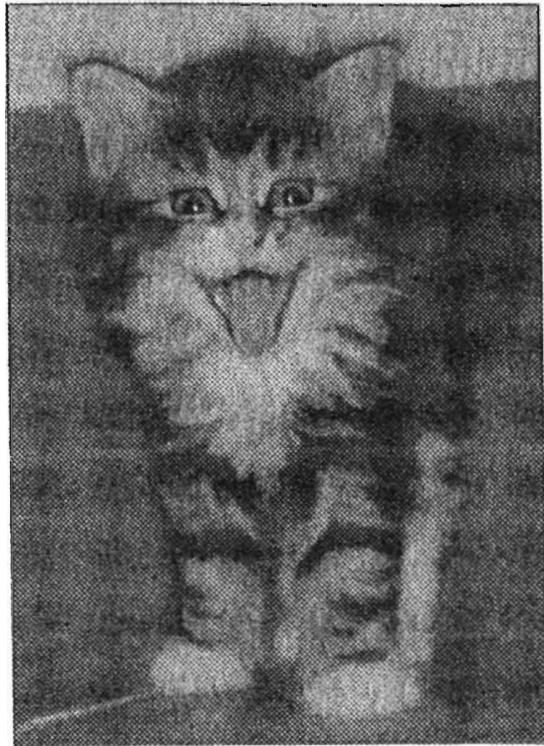
Barbiturates Small doses of phenobarbital have been successful in controlling excessive feline vocalization while traveling.⁴

Conclusion

The treatment of feline behavioral disorders is a rapidly developing field in veterinary medicine. It is necessary to understand the specific indications for a certain drug or drug group, the means by which its effects are exerted, and any reported side effects in order to provide rational therapy. The continuing expansion of knowledge in the area of behavioral disorders provides hope for future advancement of pharmacologic therapy. ♦

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Jeanne Budgin

Bellamy, an 8-week-old neutered male DLH cat, was a feral kitten before being adopted. He now displays some aggressive tendencies.

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What's Your Radiographic Diagnosis?

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A 10-day-old Maine Anjou heifer calf was presented to the Veterinary Teaching Hospital at Iowa State University for evaluation of a non-weight bearing lameness of the right hind leg. The lameness had been present since birth. This calf was born by traction-assisted delivery. The owner had treated the calf for 5 days with antibiotics which had not improved the lameness. No treatment had been given for the past 5 days.

The physical examination confirmed the non-weight bearing lameness of the right hind leg. Palpation of the leg revealed

crepitus with motion of the femur and hip joint. The calf was otherwise healthy. Radiographic evaluation of the pelvis and femur was done (see Figure 1).

Radiographic findings

Separation along the right capital femoral physis is evident. The femoral head remains within the acetabulum. The neck of the femur is displaced lateral-cranial by approximately 50% of the contact surface. Dorsal to ventral displacement cannot be determined from this view. All other physal regions are radiographically normal.

Turn to page 49 for the diagnosis.

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