Pharmacological modification of behavior in dogs and cats

Karen Overall,
MA, DVM, PhD
Center for Neurobiology and Behavior, Psychiatry Department, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Dr. Karen Overall is a Diplomate of the American College of Veterinary Behavior and is a Certified Applied Animal Behaviorist. She works at the faculty of the Center for Neurobiology and Behavior in the Psychiatry Department at Penn Med as a Research Associate where her research focuses on neurobehavioral genetics of canine cognitive, anxiety and noise reactivity. Her new book, Manual of Small Animal Clinical Behavioral Medicine, will be published by Elsevier this year, accompanied by an instructional video. Dr. Overall is the editor-in-chief for Journal of Veterinary Behavior: Clinical Applications and Research. In 2005, Dr. Overall was voted the Small Animal Speaker of the Year at the North American Veterinary Conference.

KEY POINTS

- Acceptance of veterinary behavioral medicine has been aided by developments in neuropsychopharmacology
- Psychotherapeutic agents employed alongside behavioral and environmental modification has led to better and faster treatment outcomes
- Non-specific treatment of behavioral complaints and signs is not acceptable. Specific diagnostic criteria and treatment that addresses the mechanisms underlying the diagnosis are essential

Introduction

Medication should be used as part of an integrated treatment program when treating behavioral problems. There is no substitute for the hard work involved in behavior modification, but some medications make it easier to implement the modification. Those seeking 'quick fix' solutions will be disappointed: inappropriate drug use will at best only blunt or mask a behavior without alteration of processes or environments that produced the behavior. Furthermore, the newer, more specific, more efficacious drugs can have a relatively long lag time between initiation of treatment and apparent changes in the patient's behavior. Without understanding the mechanisms of action explained in this paper, both clients and veterinarians may pronounce treatment a failure when it could be a huge success.

Simply put, neither veterinary behavioral medicine, nor the treatment of behavioral conditions affecting pets is easy, but with an informed, logical approach veterinarians can play an essential role in both saving lives and improving the quality of life of their patients and their owners. It is worth noting that behavioral complaints and problems remain the single highest cause of euthanasia and/or relinquishment of pet dogs and cats.

The role for accurate diagnosis

Most behavioral conditions are best represented by non-linear models (*i.e.* those that represent multifactorial, heterogeneous disorders). For example, there is no one ideal drug to treat feline spraying: spraying can be a behavioral description,

a species-typical normal behavior, a nonspecific sign, or a phenotypic diagnosis. Spraying behavior is caused by a variety of social circumstances and may be the result of various, interacting neurochemical systems. Essentially, not all patients exhibiting the same diagnosis are affected for the same reasons, and understanding that such variation exists is vital for rational use of behavioral medications. For example, all selective serotonin reuptake inhibitors (SSRIs) vary in structure, and all of these vary to some extent in structure and effect when compared with the tricyclic antidepressants (TCAs) and other groups of useful medications. If an animal does not respond to the first medication of choice, it may respond to another simply because this patient's neurochemical profile is not the same as another patient's, although they have been diagnosed with the same behavioral condition.

Will medication work?

While medication alone may render an animal globally less anxious, if the animal is still being provoked by social or physical environmental stimuli any benefit from medication will be minimized, and this facile and inappropriate use of medication has led many veterinarians to falsely believe that medication does not work. Nothing could be further from the truth: many newer drugs and enhanced dietary regimes have a huge potential to improve life for troubled pets and their distressed owners, and rational drug use should now be considered a basic part of humane treatment for our patients.

Adverse effects

Clients worry about side effects, so the veterinary team must have an accurate understanding of relevant risk. 'Common' side effects are actually not very common and generally manifest themselves as *transient* changes; typically signs may include gastrointestinal disturbance, appetite change, sedation, or alterations – usually increases – in heart rate. For the overwhelming majority of patients any side effects will truly be transient, occurring within the first week; however, if any side effect is ***not*** transient, clients need to understand that their pet may have a serious problem. For this reason, it is important to encourage clients to monitor their animal's response to the medication and any side effects that may develop.

While many benzodiazepines (BZ) can be sedatory, the BZ's now used most commonly (*e.g.*, alprazolam, oxazepam, clonazepam) are less sedative than diazepam and chlorazepate. However clients should be encouraged to give any BZ when they can monitor the patient, and so initial doses should be given when the owner is home and can watch the animal.

Because the most severe side effects of TCAs and SSRIs can involve cardiac affects, clients should learn to take the pet's pulse rate. Slight increases in pulse rate are not worrisome, whilst huge, sustained increases in heart rate *are* problematic and may be the first sign of developing serotonin syndrome, and owners should be mentored to recognize what is and is not significant. For this reason, baseline ECGs are recommended for any patient with a history of any arrhythmia, heart disease, prior drug reactions, is on more than one medication, or who may be undergoing anesthesia or sedation (1) ***(Figure 1)***.

Most behavioral drugs are metabolized through renal and hepatic pathways so it is essential to have baseline, pre-medication values. Liver dyscrasias and cardiac arrhythmias may not preclude the use of a drug, but knowing that they exist can serve as a guide to dosage and anticipated side effects.

Clients should receive a complete written list of all potential adverse responses and should be encouraged to communicate with the veterinarian at the first sign of any problem; educated clients will monitor their pets better and will be more willing to use medications and behavior modification appropriately. Recognition of the animal with atypical or serious sedative responses is essential, allowing more appropriate medications to be employed as necessary ***(Figure 2)***.

Ancillary concerns

All psychotropic medications can interact with other medications. For example, use of TCAs, SSRIs and related drug classes will cause thyroidal values - whether or not supplementation is involved – to read falsely low. There has been a cyclic vogue for non-specifically treating dogs with behavioral concerns and borderline thyroid values with thyroxin. There is now good evidence showing that most behavioral concerns are not directly associated with any thyroid dysfunction, although such dysfunction may certainly affect behavior.

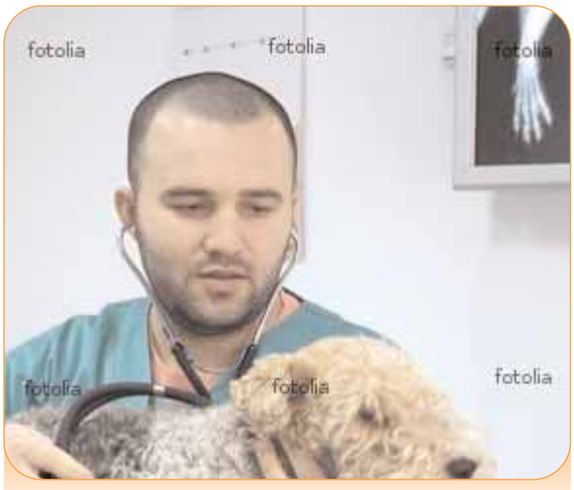

Figure 1.

Cardiac assessment is a prerequisite for any animal before prescribing behavioural drugs.

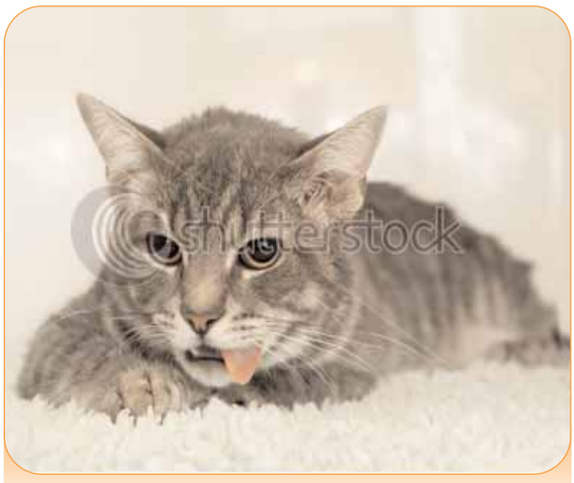

Figure 2.

The owner should be encouraged to report to the veterinarian if their pet demonstrates odd behavior after administration of drugs.

Many serotonergic agents are thought to lower seizure thresholds and are recommended with caution in epileptic patients. There is now evidence that anxiety may lower seizure thresholds and so treating the anxiety may actually raise the seizure threshold, allowing a decrease in the amount of seizure medication needed.

Finally, the client household must be considered when deciding whether to use behavioral drugs. Substance abuse is commonplace and some medications used to treat animal behavioral conditions have a high human abuse potential.

Efficacy and mechanism of action

A review of the neurochemical functions and characteristics will lead to a logical understanding of what medications are available to treat which conditions.

Serotonin

There are 14 identified classes of serotonin receptors, but the 5-HT_1 receptors are the primary receptors thought to affect mood and behavior. Urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA) is a measure of 5-HT turnover and has been used to assess neurochemical abnormalities in human psychiatric patients, and is beginning to show potential for veterinary behavioral medicine. The medications that most affect serotonin receptors are the TCAs and SSRIs, which act to inhibit reuptake of serontin, and partial agonists like buspirone. Note that nutraceuticals designed to augment or supplement 5-HT may not engender the same response as the pharmacologic agents because 5-HT does not easily pass the blood brain barrier.

Noradrenaline / norepinephrine (NA/NE)

NE has been postulated to affect mood, functional reward systems, and arousal. NE has been shown to be decreased in depression, and increased in manic states. TCAs and serotonin-norepinephrine reuptake inhibitors (SNRIs; *e.g.* venlafaxine) exert their affects, in part, through NE. SSRIs have quite small, but variable effects on NE.

Dopamine

The distribution of dopamine in the brain is non-uniform, but a large proportion is found in the corpus striatum, the part of the extrapyramidal system concerned with coordinated movement. Dopamine is metabolized in part into homovanillic acid (HVA), which has been used to assess dopamine turnover in humans; as yet this has been little explored in veterinary medicine. There are several types of dopamine receptor in the brain, most of which are affected in mood disorders and stereotypies; excess dopamine is associated with the development of stereotypies.

Gamma amino butyric acid (GABA)

GABA is an inhibitory neurotransmitter and there are two main groupings of GABA receptors

(A and B); of primary interest here is the first group which can be potentiated by barbiturates and benzodiazepines.

Excitatory Amino Acids (EAAs)

EAAs (glutamate, aspartate, and, possibly, homocysteate) are the primary fast excitatory neurotransmitters and are produced in abnormal levels in aggressive, impulse, and schizophrenic disorders. Calcium channel blockers may affect conditions associated with increased glutamate.

Both barbiturates and progesterone suppress excitatory responses to glutamate, as does the human drug memantine which has been approved for treatment of Alzheimer's disease.

Other chemical mediators

Nitric oxide (NO) and arachidonic acid metabolites (*e.g.* prostaglandins) can mediate neurotransmitter release. These are synthesized on demand and are activated by an increase in calcium, so may be affected by calcium channel blockers.

Most useful medication classes for veterinary behavioral medicine

Note that anti-histamines, anti-convulsants, progestins/estrogens, sympathomimetics/stimulants, tranquilizers and narcotic agonists/antagonists have limited use in modern behavioral medicine.

Tranquilizers

Tranquilizers deserve some special attention, as they decrease spontaneous activity, resulting in decreased response to external or social stimuli, interfering profoundly with any behavioral modification.

- Neuroleptic butyrophenones like haloperidol decrease both appropriate and inappropriate activity, and because of side effects associated with the most effective mode of delivery (i/v) have limited use.

- Use of phenothiazines (*e.g.* chlorpromazine, promazine, acetylpromazine) is outdated. All phenothiazines have side effects from long-standing use (*e.g.* cardiovascular disturbance, extrapyramidal signs). Acepromazine makes animals more reactive to noises and startle but less able to do anything about it, and so can render the animal *more* anxious with time; it is wholly inappropriate for use in noise phobic patients. Acepromazine should never be used as a behavioral medication unless the intent is to completely sedate the dog.

Benzodiazepines (BZ)

Compared with barbiturates, cortical function is relatively unimpaired by BZ. Barbiturates and BZs both affect $GABA_A$ receptors but because of detrimental effects on cognition barbiturates have been superseded by BZs and TCAs in the treatment of anxiety and aggression. At low dosages, BZs act as calming agents or mild sedatives, facilitating calmer activity by tempering excitement. At moderate dosages they act as antianxiety agents, facilitating social interaction in a more proactive manner. At high dosages they act as hypnotics, facilitating sleep. Ataxia and profound sedation usually only occur at dosages beyond those needed for anxiolytic effects. BZs decrease muscle tone independent of the sedative effect, but this may function as a non-specific anxiolytic effect since many distressed animals tense their muscles. Some newer BZs like clonazepam have muscle relaxation effects at smaller dosages than those needed for behavioral effects.

BZs are essential for treatment of sporadic events involving profound anxiety or fear such as storms (2), fireworks, and panic associated with departures of humans signaled by an outside indicator like an alarm clock. For these drugs to be efficacious they should be given to the patient at least 1 h before the anticipated stimulus, and preferably before the patient exhibits signs of distress. BZs can also be used as interventional drugs. Advance planning allows repeat dosing and permits concomitant use with daily TCA or SSRI treatment. The preferred paradigm for the use of alprazolam is found in ***Table 1***.

Monoamine oxidase inhibitors (MAOIs)

MAOIs act by increasing dopamine, norepinephrine, epinephrine, and 5HT substances and thus elevating mood. The MAOI selegiline is used for the treatment of cognitive dysfunction in cats and dogs; it is fairly specific for dopamine and slows destruction of neurons which may aid decreasing cognitive abilities. Because of the life-stage of the

Table 1.

Generalized paradigm for using alprazolam for panic and severe distress

Alprazolam: The preferred dosage range for dogs is 0.02-0.04 mg/kg. For example, for a medium-sized dog this can mean 0.25 - 0.5 mg every 12 h or q. 4-6 h as needed.
Alprazolam is the 'panicolytic' medication of choice for dogs and can be invaluable. It can be used in 3 ways: as a preventative, as an interventional medication, and in a truly panicolytic context. Many patients will benefit from all three modalities.
Preventative: To use as a true preventative the client must be able to anticipate when there will be a provocative stimulus: a guest, the last walk of the day when there is traffic, an approaching storm. Give a 0.25 mg tablet 2 hours before the anticipated event and repeat a full or half dose 30 minutes before event. Repeat every 4-6 h as needed using either the low or high dose. Start with the low dose, as dosing is cumulative.
Interventional: If the dog is reacting to some stimulus (a surprise storm, panic at discovering it is alone) - and cannot return to baseline within 5 minutes of the client trying to passively calm the dog, give a half or a whole 0.25 mg tablet. If the dog becomes distressed outside on a walk (*e.g.* triggered by a noise) the client can continue or discontinue the walk depending on the dog's response, but it is vital that the dog does not make a memory of the fear and the response to it, and again it may be desirable to give the dog a half or a whole 0.25 mg tablet. Clients learn to judge between when medication is unnecessary and when to intervene early enough to avoid distress that will generate a memory.
Obviously, on distressing days a combination of the above strategies is the best choice. For example, clients can give a dose on awakening, repeat the dose in 2 hours and then again at 30 minutes before the anticipated upsetting event, and continue to give 1/2 - 1 tablet as needed depending on upset. If a client is able to medicate the pet before distress develops the dog will always need less medication.
Panicolytic: If the dog has a full-blown panic attack give the full dose immediately. If the dog is still distressed after 30 minutes, repeat with a half or a whole dose. Remember, the pill can be dissolved in a tiny amount of liquid or will dissolve in the dog's cheeks.
Similar patterns for alprazolam use – albeit at much lower dosages – will also benefit distressed cats. The most important uses of alprazolam for cats may be prior to/after visiting the veterinarian and for any travel.

pet when selegiline is likely to be recommended, treatment should be considered life-long, barring serious side effects. Animals

without cognitive impairment will not benefit from selegiline and may become agitated due to its amphetamine-like metabolites.

Tricyclic anti-depressants (TCAs)

TCAs are structurally related to the phenothiazine antipsychotics and are used in humans to treat various mental conditions although they often have side effects (*e.g.* dry mouth, sedation, hypotension); side effects are rarer in dogs but may include gastrointestinal distress, changes in appetite and discomfort associated with unremitting tachycardia; these resolve if the drug is withdrawn. TCAs histamine-blocking side effects may be useful in treating pruritic conditions in veterinary medicine, and this is the primary use of the TCA doxepin. Note that animals experiencing sedation or other side effects with a parent compound may do well when treated with the intermediate metabolite alone. For example, cats that become sedated or nauseous when treated with amitriptyline may respond well when treated with nortriptyline at the same dose.

Use of TCAs is contraindicated in animals with a history of urinary retention, glaucoma and uncontrolled cardiac arrhythmias (1). In high doses, TCAs have been implicated in sick euthyroid syndrome. In older or compromised animals complete laboratory evaluation is urged since high doses of TCAs can alter liver enzyme levels. Extremely high doses are associated with convulsions, cardiac abnormalities, and hepatotoxicity. Note that cats are likely to be more sensitive to all TCAs than dogs. However these

Table 2.

Suggested TCA/SSRI choice for clincial conditions

Diagnosis / Type of condition	First drug of choice
Narcolepsy	Imipramine
Milder, relatively non-specific anxieties	Amitriptyline
Milder, relatively non-specific anxieties with avoidance of sedation	Nortriptyline
Social phobias / anxieties concerning social interaction	Paroxetine
Panic / generalized anxiety	Sertraline
Outburst aggression / related anxieties	Fluoxetine
Ritualistic behavior associated with anxiety, including OCD	Clomipramine

medications are extremely successful in treating many canine and feline conditions including separation anxiety, generalized anxiety that may be a precursor to some elimination and aggressive behaviors, pruritic conditions that may be involved in or precursors to conditions involving self-mutilation, acral lick dermatitis, compulsive grooming, and some narcoleptic disorders.

Amitriptyline is very successful in treating both separation and generalized anxiety. Imipramine has been useful in treating human mild attention deficit disorders, and may be useful in dogs since it has been used to treat mild narcolepsy. A TCA derivative, carbamazepine, has been successfully used to control aberrant activity in canine psychomotor seizures. Clomipramine, which has an intermediate metabolite that acts as a SSRI, has been successful in the treatment of human and canine obsessive compulsive disorders (OCDs) (3).

Partial serotonin agonists

Partial serotonin agonists (*e.g.* buspirone) have few side effects, do not negatively affect cognition, aid rehabilitation by influencing attention, arousal, cognition, and mood regulation, and may aid in treating aggression associated with impaired social interaction. Buspirone has been used with variable success in the treatment of canine aggression, canine and feline ritualistic or stereotypic behaviors, self-mutilation and possible OCDs, thunderstorm phobias, and feline spraying, but may be useful in treating a victim in true inter-cat aggression. However buspirone acts by making the cat less anxious and more interactive/assertive, which may lead to confrontations.

Selective serotonin reuptake inhibitors (SSRIs)

The SSRIs (fluoxetine, paroxetine, sertraline and fluvoxamine, and clomipramine that is converted into an SSRI) are derivatives of TCAs. Fluoxetine is efficacious in the treatment of profound aggressions, separation anxiety (4), panic, and OCDs. Paroxetine is efficacious in the treatment of depression, social anxiety and agitation associated with depression. Sertraline is useful particularly for generalized anxiety and panic disorder. Treatment must continue for a minimum of six to eight weeks before efficacy can be determined. ***Table 2*** shows a suggested preference for TCA and SSRI use.

Serotonin 2A antagonist/reuptake inhibitors (SARIs)

Recent attention has been given to the SARI trazadone, which may be useful for panic and phobias as an adjuvant to BZ, TCA and/or SSRI treatment. There is no established dosage, with a range of 1.7 - 9.5 mg/kg/day being reported (6).

Other adjunctive agents

Beta-blockers are used in humans to treat a variety of problems including self-injurious behavior, conduct disorders, dementia, autism and schizophrenia. Older beta-blockers, like propranolol, have not been hugely successful in treating animal aggression, but have shown mixed success in combination with TCAs or SSRIs to treat some anxieties and noise phobias. Pindolol has been used successfully to potentiate the action of the TCAs and SSRIs and accelerate treatment onset (7).

A list of the medications discussed and relevant dosages can be found in ***Table 3a and 3b***.

Table 3a.

Selected psychopharmacological agents that may be useful in the treatment of feline behavioral diagnoses

Drug and presentation	Dosage and notes on usage
Alprazolam (tablets: 0.25, 0.5, 1, 2 mg (1 and 2 mg tablets scored)	0.0125-0.025 mg/kg po q. 12 h, to start (due to differences in mass-dependent metabolism; smaller cats may take the relatively high end of the dose and larger cats may take the relatively smaller end of the dose; and since all BZs are lipophilic fat cats may store drug which suggests starting at a lower dose. Dosages should be gradually increased to see if a desired effect can be achieved. NOTE: All BZs can cause rare paradoxical reactions in dogs, cats, and primates, but a reaction to one BZ does not mean that you will have a reaction to another.
Amitriptyline (tablets: 10, 25, 50, 75, 100, 150 mg)	0.5-2.0 mg/kg po q. 12-24 h; start at 0.5 mg/kg po q. 12 h
Clomipramine (capsules: 25, 50, 75 mg in human formulation; 20, 40, 80 mg scored tablets in veterinary formulation)	0.5 mg/kg po q. 24 h
Clonazepam (tablets: 0.125, 0.25, 0.5, 1.0, 2.0 mg)	0.1-0.2 mg/kg po q. 12-24 h
Clorazepate (tablets: 3.75, 7.5, 11.25, 15, 22.5; capsules: 3.75, 7.5, 15 mg)	0.5-2.2 mg/kg po prn for profound distress; 0.2-0.4 mg/kg q. 12-24 h
Diazepam (tablets: 1, 2, 5, 10 mg; solution: 5 mg/mL)	0.2-0.4 mg/kg po q. 12-24 h (start at 0.2 mg/kg po q. 12 h)
Doxepin (capsules: 10, 25, 50, 75, 100, 150 mg; solution: 10 mg/mL)	0.5-1.0 mg/kg po q. 12-24 h (start low)
Fluoxetine (capsules: 10, 20 mg; solution: 5 mg/mL)	0.5-1.0 mg/kg po q. 24 h
Fluvoxamine (capsules: 10, 20 mg)	0.25-0.5 mg/kg po q. 24 h
Imipramine (tablettes: 10, 25, 50 mg; capsules 75, 100, 125, 150 mg)	0.5-1.0 mg/kg po q. 12-24 h (start at 0.5 mg/kg po q. 12 h)
Nortriptyline (capsules: 10, 25, 50, 75 mg)	0.5-2.0 mg/kg po q. 12 -24 h
Oxazepam (tablets: 15 mg; capsules: 10, 15, 30 mg)	0.2-0.5 mg/kg po q. 12-24 h; high dose:1.0-2.5 mg/kg po q. 12-24 h; 3 mg/kg po as a bolus for appetite stimulation
Paroxetine (tablettes: 10, 20, 30, 40 mg; suspension: 10 mg/5 ml)	0.5 mg/kg po q. 24 h x 6-8 weeks to start
Protriptyline (tablets: 5, 10 mg)	0.5-1.0 mg/kg po q. 12-24 h (start at 0.5 mg/kg po q. 12 h)
Selegiline (tablets: 5, 10, 15, 30 mg)	0.25-0.5 mg/kg po q. 12-24 h; start low
Sertraline (tablets: 25, 50, 100 mg)	0.5 mg/kg po q. 24 h x 6-8 weeks to start
Triazolam (tablets: 0.125, 0.25 mg)	2.5-5 mg/cat po q. 8 h

Polypharmacy, client management and patient monitoring

It is preferable to withdraw most patients from one class of drug before starting another; however polypharmacy can be safe, rational, and cheap, and can save animals' lives, but really requires an understanding of how these medications act. Some examples of potentially efficacious combinations of these medications are found in ***(Table 4)***. SSRIs should not be used with MAOIs because of risks of serotonin syndrome (5) and buspirone and SSRIs should be used together with care. If changing between SSRIs and MAOIs the recommended drug-free time in dogs is two weeks.

Concomitant use of TCAs or BZ increases the plasma levels of both of these and may prolong the excretion of fluoxetine. SSRIs can be added to TCAs and may then exhibit a faster onset of action than when they are given alone; combination treatment allows low dosage for both compounds, minimizing side effects while maximizing efficacy. Furthermore, BZs can be used to blunt or prevent acute anxiety-

Table 3b.

Selected psychopharmacological agents that may be useful in the treatment of canine behavioral diagnoses

Drug and presentation	Dosage and notes on usage
Alprazolam (tablets: 0.25, 0.5, 1, 2 mg; (1 and 2 mg tablets scored)	0.01-0.1 mg/kg po prn for phobic or panic attacks; profound lethargy and incoordination may result at high dosages (0.75-4.0 mg/dog / day; may increase slowly over 4.0 mg/dog/day if obtaining some effect at a lower dose) (Start with 1 mg, max, for a 25 kg dog; alternatively can start at 0.25 mg and repeat every 2-4 h to effect – that then becomes new starting dose. If there is no effect at 4 mg dose this is unlikely to be a useful drug for that dog.)
Amitriptyline (tablets: 10, 25, 50, 75, 100, 150 mg)	1-2 mg/kg po q. 12 h to start
Buspirone (tablets: 5, 10 mg)	1 mg/kg po q. 8-24 h (mild anxiety) 2.5-10 mg/dog q. 8-24 h (mild anxiety) 10-15 mg/dog po q. 8-12 h (more severe anxiety; use high dose for thunderstorm phobia)
Carbamazepine (tablets: 200 mg [scored]; chewable tablets: 100 mg [scored])	4-8 mg/kg po q. 12 h; 0.5-1.25 mg/kg po q. 8 h; 4-10 mg/kg/day divided q. 8 h
Chlordiazepoxide (tablets: 5, 10, 25 mg; also available as a powder for injection)	2.2-6.6 mg/kg po prn (start low)
Clomipramine* (capsules: 25, 50, 75 mg in human formulation ; 20, 40, 80 mg scored tablets in veterinary formulation)	1 mg/kg po q. 12 h X 2 weeks, then 2 mg/kg po q. 12 h X 2 weeks, then 3 mg/kg po q. 12 h X 4 weeks and then as maintenance dose - or - 2 mg/kg po q. 12 h x 8 weeks to start. May need higher maintenance dose. Constant dosage associated with slight increase in GI side effects. NB: q. 24 h dosing insufficient for vast majority of animals, particularly those with multiple signs, early age onset, or long-standing complaint.
Clonazepam (tablets: 0.125, 0.25, 0.5, 1.0, 2.0 mg)	0.125-1.0 mg/kg po q. 12 h; range: 0.01-0.1 mg/kg po prn for phobic or panic attacks, profound lethargy and incoordination may result at dosages over 4.0 mg/day, but higher dosages may be used incrementally if there has been some effect at a lower dose (start with 1-2 mg for a 25 kg dog)
Clorazepate (tablets: 3.75, 7.5, 11.25, 15, 22.5; capsules: 3.75, 7.5, 15 mg)	0.5-2.2 mg/kg po at least 1 hour before provocative stimulus (departure) or anticipated noise (storm, fireworks); repeat q. 4-6 h prn; 11.25-22.5 mg/dog po q. 24 h (~ 22.5 mg/large dogs; ~ 11,25 mg/medium dogs; ~ 5.6 mg/small dogs)
Diazepam (tablets: 1, 2, 5, 10 mg; solution 5 mg/ml)	0.5-2.2 mg/kg po at least 1 hour before provocative stimulus (departure) or anticipated noise (storm, fireworks); repeat q. 4-6 h prn
Doxepin capsules: 10, 25, 50, 75, 100, 150 mg; solution: 10 mg/ml)	3-5 mg/kg po q. 8-12 h
Fluoxetine (capsules: 10, 20 mg; solution: 5 mg/ml)	1 mg/kg po q. 12-24 h x 6-8 weeks to start
Fluvoxamine (tablets: 25, 550, 100 mg)	1 mg/kg po q. 12-24 h x 6-8 weeks to start
Imipramine (tablettes: 10, 25, 50 mg; capsules 75, 100, 125, 150 mg)	2.2-4.4 mg/kg po q. 12-24 h; 1-2 or 2-4 mg/kg po q. 12-24 h (start low)
Nortriptyline (capsules: 10, 25, 50, 75 mg; solution 10 mg/5 ml)	1-2 mg/kg po q. 12 h
Oxazepam (tablets: 15 mg; capsules: 10, 15, 30 mg)	0.2-1.0 mg/kg po q. 12-24 h
Paroxetine (tablettes: 10, 20, 30, 40 mg; suspension: 10 mg/5 ml)	1 mg/kg po q. 24 h x 6-8 weeks to start
Protriptyline (tablets: 5, 10 mg)	5-10 mg/dog po q. 12-24 h (narcolepsy)
Selegiline* (tablets: 5, 10, 15, 30 mg	0.5-1.0 mg/kg po q. 24 h x 6-8 weeks to start
Sertraline (tablets: 25, 50, 100 mg)	1.0 mg/kg po q. 24 h to start
Triazolam (tablets: 0.125, 0.5 mg)	0.125-1.0 mg/kg po q. 12 h; range: 0.01-0.1 mg/kg po prn

prn = pro re nata (as needed) * veterinary license for some canine and feline conditions; license depends on country and species

related outbursts on an as-needed basis in patients for whom daily treatment with a TCA or an SSRI is ongoing. Together, BZ and TCAs/SSRIs combinations may hasten improvement and prevent acute anxiety-provoking stimuli from interfering with treatment of more regularly occurring anxieties.

Clients must understand that newer, more specific, more efficacious drugs have a relatively long lag time between initiation of treatment and apparent changes in the patient's behavior. Furthermore patient monitoring is essential. Annual physical and laboratory evaluation should be done for all patients; for older patients the frequency should be increased. Age-related changes cause a decrease in clearance of some TCAs. Adjustment in drug dosages may be necessary with age. Obviously, if any patient becomes ill for any reason or shows signs of side effects, re-assessment is essential.

When stopping a behavioral medication, weaning is preferred to stopping abruptly. A model for weaning is found in ***Table 5***. Weaning minimizes potential central withdrawal signs, including those associated with serotonin dyscontinuation syndrome (8,9) and allows determination of the lowest effective dosage. Patients with dyscontinuation or cessation syndrome become moody and lethargic, but these effects usually pass within a week; however if signs persist, re-assessment of the wisdom of stopping medication is warranted. Medications that have the longest $t_{1/2}$ of intermediate metabolites (*e.g.* fluoxetine) are less likely to cause problems if withdrawn quickly than those with short half-lives or no functional intermediate metabolites (*e.g.* paroxetine); SSRIs that have the greatest *in vivo* reuptake capabilities (*e.g.* paroxetine) may be more likely to cause serotonin syndrome.

Long-term treatment may be the rule with many of these medications and conditions, but maintenance may be at a considerably lower level of drug than the initial dose. The only way the veterinarian will discover if this is so is to withdraw the medication slowly. Prior to any anesthesia animals should not have medication withdrawn but instead the pre-medication sedation should be adjusted so that fewer interactions - particularly of the adrenergic variety - can be expected.

Finally, many animals appear to stop responding to medication. Staying the course may be the best decision in some of these cases because multiple medication changes may just make the animal more - not less - refractory.

Table 4.

Sample combinations of medications that may allow the dosage of each to be lowered with enhanced efficacy

Amitriptyline (TCA) + Fluoxetine (SSRI)
Amitriptyline (TCA + Fluoxetine (SSRI) + alprazolam (BZ)
Amitriptyline (TCA) + Alprazolam (BZ)
Fluoxetine (SSRI) + Alprazolam (BZ)
Clomipramine (TCA) + Alprazolam (BZ)
Clomipramine (TCA) + Diazepam (BZ)*
Amitriptyline (TCA) + Diazepam (BZ) *
Selegiline (MAO-I) + Diazepam (BZ
Selegiline (MAO-I) + Alprazolam (BZ)
Paroxetine (SSRI) + Alprazolam (BZ)

*could be fairly sedating

Table 5.

Algorithm for treatment length and weaning schedule

1. Treat for as long as it takes to begin to assess effects : • 7-10 days for relatively non-specific TCAs • 3-5 weeks minimum for SSRIs and more specific TCAs
2. Treat until "well" and either have no signs associated with diagnosis or some low, consistent level: this should be a minimum of 1-2 months
3. Treat for the amount of time it took to attain the level discussed in **2.** so that reliability of assessment is reasonably assured: this should be a minimum of another 1-2 months
4. Wean over the time it took to get to **1.** or more slowly. Remember, it may take 1 + months for signs to reappear. While there are no acute side effects associated with sudden cessation of medication, a relapse in unwanted behavior is a profound "side effect". Full-blown relapse may not be responsive to re-initiated treatment with the same drug and, or the same dose.
TOTAL: Treat for a minimum of 4-6 months

Figure 3.

Behavioral aids such as training headcollars can be invaluable.

Conclusion

In the industrial world, behavioral problems in pets are responsible for more relinquishment and death than infectious disease, neoplasia and cardiac disease combined. Rational use of behavioral medication represents a real and ongoing chance for veterinarians to treat their patients more humanely. Investing time and knowledge to help these troubled patients and their distressed owners can be hugely rewarding and can change the future of veterinary medicine for the better. However drugs alone cannot accomplish these goals; no discussion of behavioral medication should occur without a consideration of "true" behavioral modification that effects cognitive change to assist troubled pets to alter their behaviors. Behavioral improvement can be hastened with the use of medication, and the veterinarian should also consider the use of canine head collars and harnesses ***(Figure 3)***, the cognitive needs of 'captive' cats and dogs, the role of appropriate and repeated exercise and the need for rational use of pain medications, dietary supplements and other treatments as necessary. Integration of all of these treatment modalities into modern veterinary medicine is a truly "holistic" approach that will benefit the veterinarian as much as it benefits patients and clients.

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* Space allowed for only the most informative of the references to be included here. Anyone wishing a complete list should contact the author.