PHARMACEUTICALS

Psychotropic drugs can be excellent tools for treating many behavior problems. The main reason for using these medications to treat behavior problems is twofold; to prevent suffering, as in many cases of separation anxiety or severe phobias, and to aid with behavior modification. Used alone, medications rarely solve behavior problems. They may initially help enough to give the owners the impression that the problem is solved, but they do not usually lead to dramatic, lasting behavior changes. An active program of behavior modification is almost always necessary to do that.

When medications do appear to be working without behavior modification, clients should be aware that if they only give medication, the pet may require it for the rest of its life and with some, tolerance may develop and their efficacy decrease over time. When used in conjunction with behavior modification, the goal is often to eventually stop using medication, or at least decrease the dosage to the lowest possible amount that will still help with the control of the problem behavior. However, there will always be some individuals that will require medication for the remainder of their life.

At the time of this writing, only three psychotropic medications have been FDA approved for use in animals with behavior problems. They are Clomicalm® (clomipramine), Reconcile® (fluoxetine) and Anipryl® (selegiline). All other psychotropics, while used frequently in veterinary behavioral medicine are being used in an off label manner and the practice should have an informed consent statement signed by the owner in order to limit liability and to be sure that pet owners are aware that while the drugs have been used often, they are nevertheless not approved for this use in pets.

Generally speaking, I like to separate the psychotropic drugs into two groups; “event” medications and long-term medications. Event medications are those that act rapidly and are typically short lived. The most common example of these are the benzodiazepines but recently, trazodone, gabapentin and clonidine are also receiving use as event medications. These medications can readily be used on an as needed basis and only when the animal is expected to need medication to help it deal with a particular stimulus or situation. These medications can also be given regularly, but they do not have to be in order to be effective or useful.

The “long term” medications are the medications that typically take several weeks to take effect. Because of that, they will be ineffective if people try to give them only “as needed.” Pet owners must be well educated about their use so that they understand that the drugs must be given regularly as instructed in order for them to be effective, and that they must be patient and give them time to take effect. It is very common for most behaviorists to use both an event medication and a long-term medication together in order to best manage a pet’s behavior problem.

Another way in which psychotropic drugs are often categorized is based on the neurotransmitters that they target. Which neurotransmitter is affected also helps to explain what the common side effects and contraindications are for each particular drug.
**Benzodiazepines**

Benzodiazepines work by facilitating the transmission of gamma aminobutyric acid (GABA) in the central nervous system. GABA is the major inhibitory neurotransmitter in the brain. GABAergic neurons are widely distributed throughout the brain where they serve important regulatory functions such as vigilance, anxiety, muscle tension, memory and epileptogenic activity. The primary functions for which we use benzodiazepines in veterinary medicine are: reducing muscle movement and anxiety and controlling seizure activity.

Generally speaking, benzodiazepines have a rapid onset of action with effects that can last for a few to several hours. At low doses benzodiazepines have calming, anti-anxiety effects and at higher doses they may be sedating. Paradoxical excitation seems to be a relatively common problem noted with the benzodiazepines so pet owners should always be instructed to give a “test dose” when they can be home to observe the pet but before the pet is likely to experience exposure to what it fears. For example, when dealing with a thunderstorm phobic patient, the “test dose” should be given on a day when NO thunderstorms are expected. Always keep in mind that when we give any anxiolytic drug to an animal with a history of aggression, we must be prepared for the possibility that with anxiolysis we will disinhibit aggression and help the animal feel more confident about using aggression. Benzodiazepines are of particular concern in this regard and should be avoided in animals that have shown a tendency to aggression. Clients should always be warned that they should not be any more relaxed or careless with their aggressive dog when it is on medication than they would be without medication. Conversely, benzodiazepines can also lead to increased affiliative behavior.

Benzodiazepines have the potential to produce addiction so clients must be cautioned that after regular use of more than about a week, the drug should not be stopped abruptly. Tolerance to the drug is also common so be prepared to increase the dose when the animal must be on it for an extended period of time.

Benzodiazepines are metabolized in the liver and excreted by the kidneys so their use should be avoided if liver or kidney disease exists. Idiopathic hepatic necrosis has been documented in cats receiving diazepam so when prescribing diazepam to cats, blood work should be rechecked after 3-5 days of treatment. Other side effects include, ataxia, muscle relaxation, increased appetite, anxiety, hallucinations, muscle spasticity and insomnia. Contraindications for the use of most benzodiazepines also include glaucoma, pregnancy and lactation.

Some of the more common and practical uses for benzodiazepines include treatment of fear and anxiety, in particular, noise phobias, separation anxiety (usually in conjunction with a TCA or SSRI), feline urine marking, and as an appetite stimulant. Benzodiazepines are an excellent first choice of medication when dealing with a suspected fear or anxiety related problem. They simply do not have long term effects and different benzodiazepines last for different periods of time so practitioners should become familiar with several different ones that may be useful in behavior therapy; alprazolam, clonazepam, oxazepam and lorazepam, to mention a few.

Overdosage with a benzodiazepine may lead to ataxia, prostration, agitation, vomiting, hyperesthesia, muscle tremors, coma, hypersalivation, aggressiveness and paresis. Treatment of overdosage is primarily supportive but administration of flumenazil (Mazicon), a benzodiazepine receptor antagonist, may partially or fully reverse the effects. Activated charcoal can also be administered and if presented within 3 hours of ingestion, induction of vomiting and/or gastric lavage may also be helpful. All benzodiazepines have the potential for human abuse so care should be taken when prescribing and refilling prescriptions for benzodiazepines.
Tricyclic Antidepressants
The tricyclic antidepressants (TCAs) affect numerous different neurotransmitters and each TCA has varying degrees of effect on each of these neurotransmitters. To different degrees they may block norepinephrine and serotonin reuptake, have anticholinergic and antihistaminic effects and act as alpha adrenergic antagonists.

The TCAs have anxiolytic, anti-compulsive, antidepressant and anti-aggressive effects. However, I do not recommend that clinicians use TCAs alone to treat aggression. The limited research that has been done using TCAs to treat aggression used it in combination with behavior modification, and one study found this no more effective than placebo combined with behavior modification. The side effects of TCAs are numerous due to the widespread effects that they have on several different neurotransmitters. These include: appetite changes, urinary retention, sedation, constipation, diarrhea, ataxia, decreased tear production, xerostoma, mydriasis, cardiac arrhythmias, tachycardia, and changes in blood pressure.

The TCAs have an extremely bitter taste, making them difficult to use in animals unless well compounded or placed within gelatin capsules. They take several days to weeks to take effect so they should not be given on an as needed basis. Clients should be informed before beginning treatment of their pet with a TCA that it should be given for 6-8 weeks before deciding if it has an effect, assuming that no negative side-effects occur. If serious side effects occur, the medication should be stopped immediately. TCAs are not addictive and withdrawal symptoms are unlikely if the drug is withdrawn suddenly. However, if a patient has been on the drug for several months, it should be withdrawn slowly so as to observe for return of the behavioral symptoms. TCAs should not be given with MAOIs (discussed below) such as selegiline and amitraz (i.e. Certifect). They should be avoided in cases with existing cardiac disease, a history of seizures and pregnant or lactating females.

In veterinary practice, some of the more commonly used TCAs are clomipramine, amitriptyline and doxepin to name a few. They may be useful in the treatment of anxiety disorders and compulsive disorders in both dogs and cats, and urine marking, hyper-vocalization and psychogenic alopecia in cats. Although amitriptyline does not appear to be as cardiotoxic in dogs and cats as it is in humans, clomipramine has less cardiogenic effects entirely. Clomipramine is more specific for serotonin reuptake than the other TCAs so it has less of the unpleasant side effects seen with amitriptyline. For that reason, and the fact that it is actually approved for use in dogs, it is the TCA that I would use first in most cases. However, amitriptyline has more antihistaminic effects and is somewhat analgesic making it a better choice for some conditions. Clomipramine may decrease thyroxine levels so while not necessarily contraindicated in cases of thyroid disease, it can complicate treatment, requiring more frequent monitoring of thyroid levels. It is simply easier to use an SSRI in those situations. Doxepin is the TCA with the most antihistaminic effects of all medications in the class. It has less of the anticholinergic side effects and less effects on serotonin and norepinephrine. For this reason, it is not a bad choice when faced with a case where pruritus is leading to hair loss but anxiety or stress may be contributing as well.

In case of overdose with a TCA, the patient should be treated with supportive therapy. There is no antidote. Vomiting is contraindicated.

Selective Serotonin Reuptake Inhibitors
Selective serotonin reuptake inhibitors (SSRIs), as the name implies, lead to increased levels of serotonin in the synaptic cleft while having minimal effects on other neurotransmitters. The SSRIs are classified as antidepressants; however, they have anxiolytic, anti-compulsive and some anti-aggressive effects as well. They contribute to mood elevation and calming, with minimal sedation and no
impairment of learning. When pet owners report side effects of the SSRIs, anorexia and sedation are the most common. In most cases, the side effects decrease with time and they almost always disappear completely if the medication is discontinued. Other side effects that have been noted in a variety of species are: constipation, diarrhea, urinary retention, anxiety, irritability, agitation, tremors, insomnia, and decreased libido. Serotonin syndrome is a condition that has been reported in humans taking excessive quantities of medications that increase serotonin levels or other medications that are incompatible with the SSRIs at the same time as SSRIs. Signs may include: tachycardia, tremors, ataxia, restlessness, seizures, vomiting, nausea, hypotension or hypertension and sudden death. Due to the risk of serotonin syndrome, a thorough history needs to include a list of ALL medications being given to the animal. For example, some supplements such as St. John’s wort work by increasing levels of serotonin and if the client fails to mention that this supplement is being given, the addition of an SSRI could potentially lead to serotonin syndrome.

The SSRI fluoxetine has been shown to treat feline urine marking very effectively. The SSRIs may also be very useful when treating fear and anxiety disorders such as canine separation. Their anti-aggressive and anti-impulsivity effects make them useful for treating some forms of aggression, again with caution and an understanding of the possibility for disinhibition of aggression.

Like the TCAs, the SSRIs should not be used on an as needed basis. They can take several weeks to take effect, although some people note improvement within a matter of days. Telling the client that they should give the medication at least 4-6 weeks before deciding if it has an effect is a good rule of thumb. The SSRIs should not be given to animals receiving selegiline, amitraz dips (or Certifect), tryptophan or thioridazine. The use of SSRIs should also be avoided in geriatric patients or those with kidney or liver disease, diabetes, glaucoma and in pregnant or lactating females. Caution should be used in prescribing them to breeding animals because of the potential for decreased libido.

The SSRIs are not addictive but similar to the TCAs; gradual withdrawal is recommended. In case of overdose with an SSRI, treat as you would an overdose of the TCAs.

**Alpha 2-adrenergic Agonists**

Clonidine is a presynaptic alpha-2 adrenergic agonist. Its original use in humans was as a hypertensive agent but because of its widespread actions on the noradrenergic system, it has gained popularity as a psychopharmacologic agent. In veterinary medicine it has been used primarily in the dog to treat fear or anxiety-based problems such as noise phobias, separation anxiety and fear of car travel. It may be especially useful when paradoxical excitation prevents the use of benzodiazepines. Clonidine can be given regularly (2 times daily) but is most commonly used for situational anxieties and/or as an adjunct to other longer lasting medications such as SSRIs or TCAs. If used for situational anxiety, clonidine should be given about 2 hours prior to the fear inducing event. Side effects are uncommon but may include sedation, dry mouth, nausea or constipation. Clonidine can enhance the CNS effects of other CNS antidepressants such as trazodone, barbiturates and other sedative-hypnotics. If needed, the effects of clonidine can be reversed using yohimbine or atipamazole.

Sileo® is dexmedetomidine in an oromucosal gel for transdermal use. Another alpha-2 agonist, it has been shown in this form to alleviate acute fear and anxiety associated with noise in some dogs while used at sub sedative doses. Side effects are similar to those of other alpha-2 adrenergic drugs.

**Serotonin 2A Antagonist/reuptake Inhibitor**

Trazodone is structurally unrelated to the other SSRIs but is a weak inhibitor of serotonin reuptake and...
a potent antagonist of some serotonin receptors. In humans it has been used primarily to treat depression, anxiety and insomnia. Similar to clonidine, trazadone has been used in veterinary medicine as an adjunctive agent to treat anxiety related problems when benzodiazepines have been ineffective or not tolerated by the patient. Clonidine and trazadone should not be used at the same time as this can lead to a hypotensive event. Trazodone potentiates the effects of other CNS depressants and can increase levels of phenytoin and digoxin. The most common side effects associated with trazodone use are sedation, hypotension and nausea. Compared to other antidepressants, it is the one with the lowest risk of seizures.

**Gabapentin**
Gabapentin is a new anticonvulsant used as adjunctive therapy in the treatment of partial seizures in humans. In humans it has also been shown to be helpful in the relief of chronic neuropathic pain and has been shown to be an effective anti-depressant and mood stabilizer. It is structurally similar to GABA so it acts as an inhibitory neurotransmitter, and, therefore, has the potential to produce the following therapeutic effects: anxiolytic, analgesic, sedative and/or anticonvulsant activities, tranquilization, or skeletal muscle relaxation dependent on the dosage used.

**Non-Pharmaceuticals**
There are a huge variety of different products on the market claiming to decrease stress or anxiety in pets but unfortunately little if any sound data-based evidence exists to support the efficacy of some of these products. As a highly trained professional, you have a certain responsibility to help educate clients about what we do and do not know about these products. Not only is it helpful to be able to keep your client from wasting their money unnecessarily, but it is wise to keep in mind that when clients repeatedly spend money and waste time trying products that fail to meet up to their expectations, then quality, appropriate care for their pet’s problem is being postponed. This decreases the chance of successful treatment when the client finally seeks proper care. In addition, we know that the longer the pet owner lives with the problem and believes, no matter how erroneously, that they are trying and failing to treat it, then the damage to the human animal bond continues to worsen to the point that it may be irreparably damaged.

The products that are listed below are those for which some data exists to support their efficacy. Nevertheless, a good understanding of their proper use is important so that clients do not have unrealistic expectations that set the products up for perceived failure. The products must be used in the right cases and often are best used as adjunct therapy in combination with other treatments, including behavior modification and environmental management.

Aromatherapy-Lavender has been found to affect the cardiovascular system of Beagles causing a vagal response. Whether this equates with relaxation is not known. Some initial work with lavender and chamomile in a shelter environment indicates that dogs are less likely to vocalize, are less active and more likely to rest when provided with those scents. Lavender was found to increase resting and sitting and decrease moving and vocalizing in dogs during car travel.

Feliway Classic ® (CEVA)-When a cat rubs its cheek on humans or other objects, it is marking that area with a F3 facial pheromone which allows it to identify safe items in its environment and the boundaries of its territory. This appears to be reassuring to the cat. Feliway® reduces signs associated with stress by providing that chemical reassurance. Feliway® is available as a diffuser, wipe or spray. The diffuser has the advantage of releasing the pheromone into the environment reaching multiple cats. It lasts for approximately 30 days. F3 pheromone has a long and well-studied desired effect on a number of behaviors including decreased urine marking, decreased scratching-marking, increased grooming, increased grooming, increased grooming,
increased interest in food and decreased number of symptomatic days in cats with idiopathic cystitis. Feliway® has also been shown to be useful at decreasing anxiety in cats in the veterinary clinic and many clinicians and hospitals now use it in exam rooms, kennels and on their own clothing to further aid in the calming of their patients.

Adaptil® (CEVA) is a synthetic copy of dog appeasing pheromone (DAP), the pheromone released from the mammary glands of the mother dog, which promotes calm behavior. This appeasing effect helps dogs deal with new environments and stressful situations, such as noise phobias, traveling, puppy adoptions, separation from the owner or other causes of stress and anxiety. Adaptil® is available in a spray, a diffusor and a collar form. The spray can be applied to the blanket, neckerchief, carrier, cage or car at least 10-15 minutes prior to use to help decrease anxiety or stress associated with certain events or stimuli. DAP diffusers have been used with some success to decrease signs of stress both in the shelter and the veterinary clinic. DAP collars have been successfully used to decrease stressful interactions for newly acquired puppies and puppies undergoing training and socialization with positive long-term effects on behavior.

Feliway Multicat® (CEVA) is one of the newest pheromones for cats on the market. It is a synthetic analogue of the feline appeasing pheromone. Similar to the dog, queens begin producing the pheromone when they give birth and the pheromone seems to stop being produced at about the time the kittens are weaned. In studies of multi cat homes where conflict is present between the cats, the pheromone has been shown to significantly decrease the conflict. It is only available in a diffusor form at this time.

Anxitane® (Virbac) contains L-theanine, a green tea extract that increases brain dopamine, serotonin and GABA levels. Several clinical trials have shown a reduction in global anxiety scores in both dogs and cats when treated with Anxitane®. A single double-blind placebo-controlled study showed reduced fear of human beings in a laboratory model of anxiety-related behavior in beagles. Anxitane® is licensed for use in both dogs and cats.

Alpha-S1 tryptic casein is the active ingredient in Zylkene® (Vetoquinol). It binds to GABA-A receptors in the brain, mimicking the action of GABA, an inhibitory neurotransmitter. It has been found to have anti-anxiolytic effects in humans, dogs, cats, rats and horses. Zylkene® is licensed for use in both cats and dogs.

Calm Diet® (Royal Canin) contains alpha-casozepine (tryptic bovine alpha s1-casein hydrolysate) and L-tryptophan as well as an increased ratio of tryptophan to large neutral amino acids compared to commonly available commercial diets. It also contains nicotinamide, which increases the affinity of GABA for its receptors, creating a calming effect. A single study that assessed efficacy of this product found that it may help some individual dogs cope with stressful events. Because of the concentration of active ingredients in this product it is only effective in animals under 15 kg (33 lbs). A second study looking at the efficacy of caseinate hydrolysate alone on signs of stress in dogs had similar findings. Efficacy of this product has not been independently tested in cats, but the product is licensed for use in both cats and dogs.

Solliquin™ (Nutramax) contains a unique combination of ingredients, L-theanine, Magnolia/Philodendron extracts and a whey protein concentration. Magnolia and Philodendron extracts appear to be synergistic, with the combination controlling stress and anxiety more effectively than either compound used alone. The whey protein concentrate contains NMXSLQ05®, a trademarked high-quality protein source which supplements ten essential amino acids including the precursors of glutathione and serotonin. Limited research has been performed on this product but more is known about the actual
ingredients than can be said for many other nutraceuticals so it is worth trying.

A single study examined the efficacy of the Anxiety Wrap® in the treatment of thunderstorm phobias in dogs with 89% of owners reported at least some positive response. However, this study was not blinded nor placebo controlled and relied on self-reporting by the owner. There may have been a marked placebo effect or the wrap may have restricted movement, leading to decreased activity and the false impression that anxiety had been reduced.

A placebo study looked at the efficacy of the Strom Defender Cape® in treating thunderstorm phobias in dogs. This study also relied on owner reported response. There was no difference in effect between the tested product and the sham cape, however, owners did report a positive response to both. It is not known if this was due to a placebo effect or if wrapping ("swaddling effect") impedes movement or somehow decreases anxiety.

**Multimodal Therapy**

Multimodal therapy is the norm when treating behaver problems in pets. Since we do not know nearly enough about appropriate dosages for every medication in every circumstance, we must always be prepared to adjust dosages according to the animal's response. If we are not getting the response we expect, we can increase dosages in many circumstances. However, if one begins to get to the higher dosages in the recommended range, the chance of side effects goes up as well. Alternatively, if multiple agents are used, it may be easier to get the response you need using moderate dosages of several drugs rather than very high dosages of one drug, since many of these drugs work on different neurotransmitters. Understanding the actions of each can also help to see how multiple different agents working on different neurotransmitters can be very helpful in certain situations. It is not uncommon for multiple agents that work on the same neurotransmitters to be used together as well, but caution must be used so as to avoid side effects. Utilizing agents such as pheromones combined with a nutraceutical of some type, in addition to psychotropic drugs can also be extremely helpful.

**Summary**

Many pharmaceutical and non-pharmaceutical agents are available today for dealing with pet behavior problems. In order to use them most effectively you need to have a basic understanding of how they work both separately and in combination with other products. Pet owners also need to be encouraged to document frequency and severity of their pets' clinical signs and symptoms so as to help them evaluate their pets’ responses. The placebo effect is very powerful in some cases so objective data is really needed in order to be certain that you are improving the pet’s symptoms. Otherwise, many pets may continue to be treated with interventions that may not be truly helping. This can only increase the length of time that it takes to achieve significant lasting improvement for the pet, thus increasing the chance that the owner will become frustrated and begin to give up on the pet. Once this happens, the bond between the owner and the pet can be irreversibly damaged or broken completely and euthanasia or relinquishment become more likely. Appropriate use of pharmaceutical and non-pharmaceutical agents can help prevent suffering and keep pets in their home, something all veterinarians should be very interested in doing.
## Doses for some commonly used benzodiazepines (Unless otherwise noted all doses are for PO administration)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dog dose</th>
<th>Cat dose</th>
<th>Useful information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam (Xanax)</td>
<td>0.02-0.1 mg/kg q 4h or PRN</td>
<td>0.125-0.25 mg/kg q 8h</td>
<td>Minimal active metabolites; rapid onset of action</td>
</tr>
<tr>
<td>Clonazepam (Klonopin)</td>
<td>0.1-1 mg/kg q 8-12h</td>
<td>0.05-0.2 mg/kg q 12-24 h</td>
<td>Extensive liver metabolism but less toxic to cats</td>
</tr>
<tr>
<td>Diazepam (Valium)</td>
<td>0.5-2.0 mg/kg q 4-6 h</td>
<td>0.2-0.5 mg/kg q 12-24 h</td>
<td>Multiple active metabolites Short half-life; may potentiate organophosphates</td>
</tr>
<tr>
<td>Oxazepam (Serax)</td>
<td>0.2-1 mg/kg q 12-24 h</td>
<td>0.2-0.5 mg/kg q 12-24h</td>
<td>No active metabolites Slower onset but longer duration of action – safer when liver disease is present</td>
</tr>
</tbody>
</table>
### Doses for some commonly used SSRIs (Unless otherwise noted all doses are for PO administration)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dog dose</th>
<th>Cat dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine (Prozac)</td>
<td>1.0-2.0 mg/kg once daily</td>
<td>0.5-1.5 mg/kg once daily</td>
</tr>
<tr>
<td>Paroxetine (Paxil)</td>
<td>1.0-1.5 mg/kg once daily</td>
<td>0.5-1.5 mg/kg once daily</td>
</tr>
</tbody>
</table>

### Doses for some commonly used TCAs (Unless otherwise noted all doses are for PO administration)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dog dose</th>
<th>Cat dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>1.0-6.0 mg/kg q 12h</td>
<td>0.5-2.0 mg/kg q 12-24h</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>1.0-3.0 mg/kg q 12h</td>
<td>0.25-1.3 mg/kg q 24h</td>
</tr>
<tr>
<td>Doxepin</td>
<td>3.0-5.0 mg/kg q 8-12h</td>
<td>0.5-1.0mg/kg q 12h</td>
</tr>
</tbody>
</table>

### Doses for other commonly used psychotropic drugs (Unless otherwise noted all doses are for PO administration)

<table>
<thead>
<tr>
<th>Miscellaneous Drugs</th>
<th>Dog Dose</th>
<th>Cat Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trazodone</td>
<td>3-7 mg/kg q 12h</td>
<td>1-2 mg/kg PO q 12h</td>
</tr>
<tr>
<td>Clonidine</td>
<td>0.01-0.05 mg/kg PRN (q 12h)</td>
<td>N/A</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>10 mg/kg q 8-12 h</td>
<td>3-10 mg/kg q 12 h</td>
</tr>
</tbody>
</table>