**Behavior Products and Medications**
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**Pheromones, Nutraceutical and diet information:**

**Adaptil (Ceva)**- Adaptil is a copy of the pheromone released from the mother dog after having a litter of puppies—it provides a sense of reassurance and calm. This appeasing effect helps dogs deal with new environments and stressful situations, such as noise phobias, traveling, adoption or other causes of stress. The collar should be left on continuously and lasts for 30 days. It functions by releasing a vapor cloud when in contact with warm skin, consequently the collar must be left on all the time and applied snugly. The diffuser has the advantage of releasing the pheromone into the environment reaching multiple dogs. It lasts for approximately 30 days, then the liquid pack (not the diffuser unit) will need to be replaced. The spray has an alcohol carrier that must dissipate prior to exposing the pet.

**Feliway (Ceva)**- Feliway is the synthetic version of a fraction of the facial pheromone that cats deposit in their environment when they bunt (rub their faces on objects/people). It helps to relieve stress by helping the cat feel comfortable in unfamiliar or stressful environments, much like if they came upon previously self-marked locations in their home.

**Feliway Multi-Cat (Ceva)**- this is the synthetic version of the maternal appeasing pheromone that queens produce when nursing their kittens. It works in a similar fashion to Adaptil in terms of being able to comfort and relax cats in stressful situations (to include single-cat households or environments such as the veterinary office).

**Anxitane (Virbac)**- **Still backordered** Anxitane is made of L-Theanine, an amino acid found in green tea which increases GABA concentrations, an inhibitory neurotransmitter, which dampens anxiety responses by stopping neural transmission and the excessive firing associated with anxiety. It can also increase serotonin and dopamine levels as well making it well suited to help in a variety of different situational and global anxiety disorders.

**Solliquin (Nutramax Labs)**- Solliquin is composed of L-theanine and two plant derived extracts, Phellodendron amurense and Magnolia officinalis. L-theanine is an amino acid found in green tea which increases GABA concentrations, an inhibitory neurotransmitter, which dampens anxiety responses by stopping neural transmission and the excessive firing associated with anxiety. It can also increase serotonin and dopamine levels as well making it well suited to help in a variety of different situational and global anxiety disorders. The plant extracts from the Amur Cork and Magnolia trees and have been shown to help calm dogs during thunderstorm activity, and therefore should be useful for other anxiety disorders as well.

**Zylkene (Vetoquinol)**- Zylkene contains alpha-casozepine which is a protein derived from milk. Alpha-casozepine binds to the benzodiazepine receptors in the brain, causing calm and
relaxation without the sedation that can sometimes be seen with the benzodiazepine class of medication.

**Calm diet (Royal Canin)** - The Calm diet contains alpha-casozepine and tryptophan, in addition to their GI formulation, and the S/O Index. Tryptophan is a precursor for our bodies to make serotonin, a neurotransmitter that is often deficient in anxious animals. Alpha-casozepine binds to the benzodiazepine receptors in the brain, causing calm and relaxation without the sedation that can sometimes be seen with the benzodiazepine class of medication.

**i/d + Stress (Hills Science Diet)** - This diet contains alpha-casozepine and tryptophan, in addition to the normal i/d formulation. Tryptophan is a precursor for our bodies to make serotonin, a neurotransmitter that is often deficient in anxious animals. Alpha-casozepine binds to the benzodiazepine receptors in the brain, causing calm and relaxation without the sedation that can sometimes be seen with the benzodiazepine class of medication.

**c/d Urinary Multicare Stress (Hills Science Diet)** - this diet contains alpha-casozepine and tryptophan in addition to the normal c/d formulation. Tryptophan is a precursor for our bodies to make serotonin, a neurotransmitter that is often deficient in anxious animals. Alpha-casozepine binds to the benzodiazepine receptors in the brain, causing calm and relaxation without the sedation that can sometimes be seen with the benzodiazepine class of medication.

**Pharmaceuticals:**

**Alpha-2 agonists** - Clonidine has traditionally been used in human medicine for its anti-hypertensive effects, but has been used off-label by psychiatrists for its action on hyperarousal, hypervigilance, PTSD, ADHD and impulsivity. It blocks norepinephrine release by activating the alpha-2 receptors in the locus ceruleus. It has been shown to be effective as a situational medication prior to stressful events, including veterinary visits, but caution must be exercised when using it in conjunction with general anesthetics due to its hypotensive effects. A recent addition to the pharmaceutical market, Sileo by Zoetis, is an oral transmucosal preparation of dexmedetomidine that is FDA approved for use in noise phobias (storms, fireworks). It has a rapid onset of action after OTM absorption but only a 25% bioavailability which results in its anxiolytic effects without the profound sedation seen in hospital usage of IM or IV Domitor.

**Alpha-2-delta ligands** - This class of medication binds to the alpha-2-delta subunit of presynaptic voltage sensitive calcium channels and blocks the release of glutamate when there is excessive neurotransmission. Gabapentin is the most common drug in this class used in veterinary behavioral medicine. Since the mechanism of action of gabapentin is vastly different than the SSRIs, TCAs, SARIs, or benzodiazepines, this medication may be of benefit for those patients that have been intolerant of the other classes, or as an adjunct for incomplete resolution of clinical signs when using other agents. Gabapentin has been shown
to decrease anxiety, aggression, avoidance behavior and inappetance associated with pain. There are currently no studies on its use for cats prior to veterinary visits, but it is anecdotally used by many behaviorists, anesthesiologists, and feline practitioners at 50 or 100 mg/cat or 20 mg/kg 60-90 minutes prior to examination. It appears to be palatable when a capsule is broken open and mixed with a small amount of canned food, and it appears to be well-tolerated clinically. No studies are currently available at the time of writing to support dosages or usage in specific behavioral situations.

**Azapirones**- Buspirone is an azapirone antianxiety medication that acts as a partial serotonin agonist. It may take 2 to 4 weeks to see a behavioral effect and is best administered two to three times daily for best efficacy. Side effects include irritability, gastrointestinal effects, increased affection and sociability, and occasional paradoxical increase in anxiety and/or excitement. It is considered anxioselective and therefore should not be sedating. Buspirone has been used in urine spraying and in intercat aggression when it is most commonly given to the victim because it appears to reduce fear and increase assertive behaviors.

**Benzodiazepines**- This class of medication facilitates behavioral calm by its action on GABA, an inhibitory neurotransmitter. It is used situationally for acute panic disorders since its onset of action is 60-90 minutes and depending on the particular medication, may only last for 4 hours. There may be paradoxical excitation associated with any situational medication and thus it must be tried at home prior to the pet experiencing the stressor/trigger. Although bite disinhibition can occur with any psychotropic medications, as a class, the benzodiazepines appear to cause this more frequently and caution should be exercised when using benzodiazepines in dogs with aggression. Care should be taken with how many pills are dispensed at one time and how often the drug is refilled due to the highly addictive nature and potential for abuse by owners.

**Selective serotonin reuptake inhibitors (SSRI)**- This class of medication acts to increase the amount of serotonin in the neural synapse by blocking its reuptake back into the presynaptic neuron. Although side effects and some clinical effects may be seen as early as the first several weeks, true clinical effect may not be seen until 6-8 weeks after starting the medication or after any dose change. This is a serotonergic drug and should be used cautiously with other serotonergic medications such as TCAs, SSRIs, MAOis, Amitraz-containing parasiticides and Tramadol. The most common drugs in this class are fluoxetine (Prozac), sertraline (Zoloft), and paroxetine (Paxil).

**Trazodone**- Trazodone is a serotonin agonist reuptake inhibitor (SARI) a class of drugs that in humans is used as an antidepressant, hypnotic and anxiolytic. It acts by blocking select serotonin receptors and inhibiting the reuptake of dopamine, serotonin and/or norepinephrine. It has a mildly sedating effect which can be very advantageous in pets that panic and/or are destructive. Research has shown efficacy for post-surgical confinement purposes where behavioral calming is needed. Although traditionally used as a situational
medication, there are some patients that need to have this administered twice daily. This is a serotonergic drug and should be used cautiously with other serotonergic medications such as TCAs, SSRIs, MAOis, Amitraz-containing parasiticides and Tramadol.

**Tricyclic antidepressants**—This drug alters neurochemistry in the brain by increasing serotonin. It helps to reduce anxiety and decrease repetitive behaviors. It may take 4 weeks to see its maximum effect after starting or after any dose change. This is a serotonergic drug and should be used cautiously with other serotonergic medications such as TCAs, SSRIs, MAOis, Amitraz-containing parasiticides and Tramadol. The most common drugs in this class are clomipramine (Clomicalm by Novartis) and amitriptyline (Elavil).

**PRECAUTIONS:**

**Extra label usage**-
Other than Clomicalm and Anipryl there are no FDA labeled psychotropic medications for dogs and cats. Clomicalm is only labeled for separation anxiety in dogs in conjunction with behavior modification. Anipryl is only labeled for cognitive dysfunction in dogs. All other use is extra label and the owner should be informed and sign a consent form that they understand this fact.

- The off-label status of most drugs means that the substantial safety and efficacy trials required by the FDA for on-label use have not been conducted. In many cases, for economic reasons such trials will never be conducted, despite substantial scientific evidence that a given drug has a real usefulness, with minimal side effects for a particular problem.” Excerpt from Veterinary Psychopharmacology, by Sharon Crowell-Davis, DVM, DACVB

**Bite disinhibition**-
Bite disinhibition is a phenomenon that can occur when using psychotropic medication. The concept is that if the anxiety itself is holding the dog back from becoming aggressive, you relieve the anxiety with products or medication, and the dog may be more likely to become aggressive, to include biting. This seems to happen more frequently with the benzodiazepine class of medication. In dogs that are already using aggression (especially biting) as a behavioral strategy are already showing a lack of inhibition and are therefore unlikely to experience this phenomenon, but owners must still be warned since there may be an increase in frequency and intensity of the aggression already present.

**Withdrawal of medication**-
When the behavior appears changed and stable, attempts to withdraw medication can begin. The general recommendation is to decrease the weekly total dosage no more than 25% a week while watching for an increase in the targeted behavior. If unwanted behavior begins to surface, remaining at the lower dose for several weeks may allow stabilization. If the behavior does not
stabilize, the higher dose should be instituted if that can be done safely and maintained for another 1 to 3 months before attempting weaning again. Severe withdrawal side effects can occur if medication administration is stopped abruptly.

**Long-Term Therapy**
Some cases may require long-term treatment, and the lowest possible dosage should be administered. In some cases, especially with long-acting agents, dosing every other day may be useful to maintain progress. Animals on long-term therapy should have routine blood chemistry screenings yearly or semi-yearly depending on the age and health of the animal.

**Switching Medication**
Some SSRIs have a long half-life; therefore, weaning and a washout period of 3 to 5 weeks is recommended when switching from an SSRI to another drug. When switching from a TCA to an SSRI, a 1-to-3-week washout is suggested.

**Transdermal Administration**
At the present time no long-term studies of transdermal administration of psychotropic medication has shown that this method is efficacious. Ciribassi and colleagues showed that although fluoxetine was absorbed through the skin in cats, the relative bioavailability was only 10% of that for the oral route of administration, but higher doses of the medication resulted in severe dermatologic reactions. Mealey and colleagues looked at the systemic absorption of amitriptyline and buspirone after oral and transdermal administration to healthy cats and found that systemic absorption of both drugs was poor when compared to the oral route of administration. Based on these studies and the lack of others, an appropriate dosage for transdermal administration of psychotropic medications has not yet been established and this route of administration is currently not recommended.

**Reformulated Preparations**
No formal studies are available to assess the potency and absorption of psychotropic medications once they have been reformulated into a liquid or some other distribution vehicle. For medication to be effective when given orally it must be soluble and stable in the stomach and intestines so it can absorb appropriately into the blood stream. When a medication is altered by reformulation it is unclear if the absorption has been altered as well and, if so, to what extent. Medication failures may be due to lack of availability of the medication rather than unsuitability as a treatment for the unwanted behavior.

**Cytochrome P450**
Cytochrome P450 is an enzyme system critical in hormone synthesis, biotransformation, and metabolism of many different types of medication. SSRIs are competitive inhibitors of many P450 enzymes, and when a patient is on another drug that is also metabolized by P450 enzymes, altered plasma levels and potential toxic side effects are possible.
Serotonin syndrome-
This syndrome may occur when excessive quantities of medication that increase serotonin are ingested or administered, when two drugs that alter serotonin levels are administered together, or when two drugs taken together are not compatible in regard to serotonin metabolism. No diagnostic test is available. Diagnosis is made based on clinical signs and the complete history of all medications given to the pet, including herbal medicines. Signs and symptoms include mental changes, neuromuscular changes, and autonomic changes. Clinicians should advise all owners of the risks of serotonin syndrome. Anecdotally, this syndrome has been seen by the author at clinically appropriate dosages of a single agent.

References:


