

BEHAVIORAL PSYCHOPHARMACOLOGY: WHAT MEDICATION TO USE & WHY

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MEDICATION BASICS

There are four major classes of molecules that are of particular interest: neurotransmitters, receptors, signal transducing proteins, and cellular second messengers. Drugs that act at any of these sites may modify behavior. Upon release by a presynaptic neuron, neurotransmitters cross the synapse to stimulate or inhibit the postsynaptic neuron. The important neurotransmitters in behavior therapy are: acetylcholine, dopamine, norepinephrine (NE), serotonin (5-HT), glutamate, and GABA. Receptors recognize specific molecules, which result in signal transduction. Many of the clinically useful psychoactive drugs have their activity because of their interaction with the receptor

Psychoactive medications produce changes in behavior and/or motivation. Most psychoactive medications in veterinary medicine are used extra-label meaning that the medication is NOT FDA-approved for use in a specific species for a specific purpose at a specific dose range. There are four behavioral medications that are FDA-approved for use in veterinary behavior: Reconcile® (an SSRI), Clomicalm™ (a TCA), Anipryl™ (an SSRI) and Sileo®. For most psychoactive medications, there are few controlled studies in the pet population and their use is extrapolated from human psychiatry. Drugs labeled for human psychiatric problems may have different side-effect profiles and toxicities in companion animals. The exact mechanisms for behavioral effects are unknown. They are usually most effective when used as an adjunct to behavior modification and environmental modification. It is rare for a pill to provide a “cure”. Client compliance is very important in determining which drug is chosen.

Dosing schedule: Once a day? Twice a day? More?

Form of the drug: Can owner pill pet? Especially a concern with cats

Abuse potential?? Know your client and your patient

Antidepressants

Used extensively in the treatment of behavior problems in small animals with a heterogeneous range of behavioral effects. There is a wide range of effects on central neurotransmitters and a wide range of side-effects. The action is on 5-HT and NE reuptake inhibition. Their general use in animals include anxiety, fears and phobias, compulsive disorders, anxiety/fear-motivated aggression, and urine marking.

Tri-Cyclic Antidepressants (TCAs)

Uses in Dogs: anxiolytic effect, fears, phobias, aggression secondary to anxiety/fear, lick granuloma, compulsive disorder, urine marking.

Uses in Cats: anxiolytic effect, fears, phobias, aggression secondary to anxiety/fear, compulsive disorder, urine spraying, hypervocalization.

TCAs are well absorbed from the GI tract, metabolized in the liver, and eliminated through urine & feces. They are highly lipophilic and can cross the placenta and into maternal milk – therefore, do not give to pregnant animals. They have a very bitter taste.

Common TCAs used: Amitriptyline (Elavil®), Clomipramine (Clomicalm™, Anafranil®), Doxepin (Sinequan®), and Imipramine (Tofranil®).

The therapeutic effects involve increasing norepinephrine levels which affect general arousal, attention, mood reactivity, and stress response modulation. Increasing serotonin regulates mood states, decreases fear & stress responses, affects feeding behavior, and decreases impulsive behavior. The side-effects include α -adrenergic orthostatic hypotension, dizziness, syncope, sedation, vasoconstriction, smooth muscle contraction. The cholinergic side-effects include dry mouth, dental pathology, stomatitis, mydriasis, decreased tear production, impaired visual accommodation - blurred vision, urinary retention, bronchodilation. The histaminic side-effects include anti-pruritis, sedation,

anti-ulcer activity, weight gain. The cardiovascular effects include arrhythmias, sinus tachycardia (NE), ↓ conduction time, heart block, myocardial infarction, stroke. GI effects include nausea, vomiting, constipation, paralytic ileus, anorexia, abdominal cramping, diarrhea. Behavioral side effects include anxiety, restlessness, agitation, sleep disorders, sedation, fatigue, headache, ataxia. Other effects include lowered seizure threshold, altered blood glucose levels, and bone marrow suppression.

The TCAs have 2 – 4 week latency. Stabilize for 1 – 2 months to see true effect. When ready to stop, gradual withdrawal is recommended. Certain conditions require long-term treatment. When withdrawing a TCA, decrease the original dose by ½ for 2-4 weeks. If all is okay, decrease dose by ½ for another 2-4 weeks. If all is okay, decrease dose again either by ½ daily or give every other day. If at any time “undesirable” behavior resumes, go back to last controllable dose. The process should take several months.

The goal is to have the pet off the medication or to be on the lowest possible dose that controls the behavior.

Drug Interactions include anticholinergics, sympathomimetics, cardiac toxicity, MAOIs & SSRIs, thyroid supplements, anti-thyroid agents, agranulocytosis, cytochrome P450 competition, antidepressants, antipsychotics, psychostimulants. See <http://medicine.iupui.edu/flockhart/table.htm> for more information.

Drug Precautions include glaucoma, urinary retention, cardiac disease, thyroid disease, seizure disorder, adrenal tumors, liver disease, and kidney disease.

TCA Toxicity

The TCAs have a narrow therapeutic index. A 10-day supply for pet could be fatal to adult human!! There is **NO ANDIDOTE** so make sure that drug is kept safely away from pet in child-proof cap.

Clomipramine dose:

Dogs 1-3 mg/kg PO q12h
Cats 0.25 – 1.3 mg/kg PO q24h

Amitriptyline dose:

Dogs 1-6 mg/kg q12h
Cats 0.5 – 2 mg/kg q 12-24h

Start low and work up to avoid side-effects

Selective Serotonin Reuptake Inhibitors - SSRIs

Inhibition of serotonin reuptake resulting in increased serotonergic neurotransmission by allowing serotonin molecules to act for extended periods of time. In dogs and cats common uses include anxiety and fear issues. Serotonin is involved in modulation of aggression, therefore, medications which increase central serotonergic activity should produce a decrease in affective aggression and decrease the tendency to engage in sudden outbursts. Side-effects of SSRIs include GI signs – decreased appetite, vomiting, diarrhea/constipation, anxiety, irritability, insomnia, anorexia, and aggression. Contraindications include diabetes mellitus and hepatic disease. *Do NOT use with an MAOI or TCA* as it may result in serotonin syndrome. SSRIs have a slow onset of action and result in neurotransmitter/receptor changes. They are metabolized in liver and excreted through kidneys. They have 1-4 week latency to effect and a long t½. Start at the lower dose and work up to avoid side-effects.

Fluoxetine dose:

Dogs 1.0-2 mg/kg PO q24h
Cats 0.5-1.5 mg/kg PO q24h – **Typically 2.5-5mg/cat/day**

Paroxetine dose:

Dogs 1.0 – 1.5 mg/kg PO q24h
Cats 0.5 – 1.0 mg/kg PO q24h - **Typically 2.5-5mg/cat/day**

Sertraline dose:

Dogs 0.5 – 4.0 mg/kg PO q24h
Cats 0.5 – 1.0 mg/kg PO q24h

Monoamine Oxidase Inhibitors – MAOIs

Monoamine Oxidase is the enzyme that destroys NE, DA, and 5HT. There are 2 subtypes: A and B. MAO-A destroys NE, DA - those most closely linked to depression. MAO-B converts amine substances into toxins. Inhibition of MAO-A is linked to *antidepressant action* and to the side effect of *hypertension*. Inhibition of MAO-B is linked to the *prevention of neurodegenerative processes*, such as those seen in Parkinson's disease and Alzheimer's disease. Selegiline Hydrochloride (L-deprenyl) is a *selective & irreversible inhibitor of MAO-B*. It also has antioxidant activity. ANIPRYL® is FDA-Approved for Canine Cognitive Dysfunction Syndrome at the dose of 0.5 – 1.0 mg/kg/day. The onset of action is variable, 4 to 12 weeks. Increased improvement may be seen with extended use. 69-75% of dogs improved in at least one clinical sign after 1 month of treatment. Side effects include vomiting, diarrhea, restlessness, hyperactivity, anorexia, neurologic, lethargy, and salivation. In humans, selegiline is contraindicated for use with meperidine (Demerol®) and other opioids. In humans: MAOIs + alpha-2 agonists = BP fluctuations and Selegiline + TCAs or SSRIs = CNS toxicity. **No concurrent use of ephedrine, phenylpropanolamine, or potential MAOIs such as Amitraz.** At least 14 days between discontinuation of selegiline and initiation of treatment with TCA or SSRI, and a 5-week wash-out period for fluoxetine before starting selegiline.

Anipryl® dose:

FDA-approved for canine CDS 0.5 – 1.0 mg/kg/day – to be given in the morning
Same dose can be given to cats – for those with signs of CDS

Initially, dogs dosed to the nearest whole tablet and make adjustments based on response and tolerance.

Keep in Mind...Separation Anxiety is not uncommonly a first sign of Canine Cognitive Dysfunction Syndrome. SA can manifest in older dogs as discrete disease. Rule out CDS prior to treatment with Clomicalm™. If SA case proceeds to clearer case of CDS, wean dog off Clomicalm™: ½ dose for 2 weeks, ¼ dose for 2 weeks, then quit. Wait 2 weeks to start treatment with Anipryl®

WARNING: Do not every give the 3 oral medications that are FDA-approved together: Anipryl® (selegiline, an MAOI), Reconcile® (fluoxetine, an SSRI), and Clomicalm™ (a TCA).

Anxiolytics are widely used in phobias and anxiety-related problems such as noise phobias, submissive urination, fear of people or animals – without aggression, fear of objects, fear of anything new, separation anxiety, fear of going outside.

Benzodiazepines facilitate GABA in the CNS by binding to GABA_A receptors and are used for anxiety and fear issues alone or in combination with TCA or SSRI. Side-effects include sedation, muscle relaxation, increased appetite, [possible] idiopathic hepatic necrosis in cats (Valium®), and paradoxical excitement. Test the lowest dose to make sure animal is not unusually sensitive (ataxic, sedated) and does not show paradoxical excitement and then test in actual situation – e.g. owner leaves, thunderstorm. If sufficient, maintain that dose. If insufficient, incrementally increase the dose. May need to increase dose over time to maintain effect due to tolerance. The advantage is rapid onset of effect in the treatment of anxiety (30-60min), but there is the *potential for human abuse*. They are very effective when used in combination with maintenance medications (SSRIs, TCAs, MAOIs) to address the “panic” portion of the behavior. **Use with caution in fear aggression** as leaned inhibition may be lost. Withdraw gradually as sudden termination can cause rebound and resumption of more intense symptoms.

There is an **antidote**: Flumazenil (Mazicon®) – BZD antagonist.

Alprazolam dose:

Dogs	0.02 – 0.1 mg/kg PO 30-60 min prior to anxiety-provoking event Repeat every 4-6 hours as needed
Cats	0.125 – 0.25mg/cat q12 - 24 h prn

Clonazepam dose:

Dogs	0.05 – 0.2mg/kg PO q 8-12h
Cats	0.015 – 0.1mg/kg PO q 8-12h

Diazepam dose:

Dogs	0.5 – 2.0 mg/kg 1 hour prior to provoking stimulus - departure, storm Repeat every 6 hours as needed
Cats	0.1 – 0.5 mg/kg q.12-24h

Azapirones – Buspirone – a 5-HT₁ partial agonist – can be used alone or as an “augmenting” agent for SSRIs/TCAs. It is not dependent on serotonin levels. It has direct actions on the receptors so it may be able to “kick start” process. Initially, buspirone slows neuronal impulses which may help the neuron to replace its serotonin. It is used to treat anxiety, urine spraying, subordinate cats. It gives the victim “backbone” so that cats that have previously been timid in the face of repeated attacks may turn on their attacker – and many times that’s all it takes to turn the situation around. Side-effects are uncommon: agitation and GI effects. It is not sedating and there is no potential for human abuse. It has a relatively fast onset (1-3 weeks). There is no need to ramp up the dose or wean off, and there is no physical dependence. It does not lower the seizure threshold. Many owners report that their cat becomes more “affectionate”, rubbing them, sitting in their lap and otherwise seeking contact with them for greater frequencies and durations. Therefore, it can be good for the treatment of “Petting Intolerance”. It can be used in combination with SSRIs and TCAs – if so, decrease the dose of the other drugs accordingly. **Buspirone should NOT be given with any of the MAOIs.**

Buspirone dose:

Dogs	0.5 – 2.0mg/kg PO q 8-24h
Cats	2.5 – 7.5 mg/cat PO q 12-24h

Trazodone is a triazolopyridine derivative and member of the phenylperazine class of drugs. **It is classified as a SARI** (Serotonin Antagonist and Reuptake Inhibitor) on the basis of its primary pharmacological mechanism of action to antagonize serotonin 2A receptors and its secondary mechanism to inhibit serotonin reuptake. **In dogs**, trazodone can be an effective treatment for a variety of anxiety-based behaviors – alone or in conjunction with an SSRI or TCA. A general review of this medication and its uses can be found in the article: Use of trazodone as an adjunctive agent in the treatment of canine anxiety disorders: 56 cases (1995-2007) JAVMA, Vol 233, No. 12, December 15, 2008. A more recent article: Use of trazodone to facilitate postsurgical confinement in dogs JAVMA, Vol 245, No. 3, August 1, 2014, most (32/36 [89%]) of owners reported that their dogs, when given trazodone during the 8 to 12 weeks following orthopedic surgery, improved moderately or extremely with regard to confinement tolerance and calmness. **In cats**, a 50mg – 100mg [PO] dose of trazodone has been found to have a significant improvement in signs of anxiety during transport and ease of handling during veterinary examination. See: Efficacy of a single dose of trazodone hydrochloride given to cats prior to veterinary visits to reduce signs of transport- and examination-related anxiety JAVMA Vol 249, No. 2, July 15, 2016.

Gabapentin

The precise mechanisms by which gabapentin produces its analgesic and antiepileptic actions are unknown. Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA) but has no effect on GABA binding, uptake, or degradation. *In vitro* studies have shown that gabapentin binds with high-affinity to the $\alpha 2\delta$ subunit of voltage-activated calcium channels; however, the relationship of this binding to the therapeutic effects of gabapentin is unknown. **In cats**, a 100mg [PO] dose of gabapentin administered 90 minutes prior to placing cat in the carrier and transporting to the veterinary clinic resulted in significantly lower owner-assessed stress scores when compared with placebo.

Commonly, gabapentin is used in cats and dogs for conditions that appear to be caused by neuropathic pain: e.g. **feline hyperesthesia and acral lick granulomas**.

Gabapentin can be used alone or in combination with a TCA, SSRI, Trazodone, Buspirone or benzodiazepine. Titrate dose of each medication to effect.

Gabapentin dose:

Dogs 10-20mg/kg q. 8-12 hours

Cats 5-10mg/kg q. 8-12 hours
50-100mg **per cat** every 12 to 24 hours

The frequency of administration may be adjusted, PRN

Sileo

Dexmedetomidine oromucosal gel – FDA-approved in DOGS for noise aversion: thunder and fireworks. Dosing is based on weight. Sileo typically takes about 20 minutes to take effect and generally lasts 3-4 hours.

Based on personal experience, I have recommended that the gel be applied using a gloved finger instead of putting the plunger into the dog's mouth. This ensures that the gel actually gets applied to the dog's oromucosal surfaces and isn't swallowed.

Clonidine

Clonidine is an alpha-2-agonist typically used in human medicine as an anti-hypertensive agent. It also used off-label in psychiatry for hyperarousal, hypervigilance, PTSD, ADHD, and impulsivity. Therefore, it can be very useful when used alone or in combination synergistically with a maintenance anxiolytic medication [SSRI, TCA, buspirone] – to address reactivity. Can be used as a maintenance medication or for situational anxiety/reactivity – 1.5-2 hours prior to the provoking event.

Clonidine dose:

Dogs 0.01-0.15mg/kg q. 12-24 hours; some cases need q. 6-8 hours

Research: The use of clonidine in the treatment of fear-based behavior problems in dogs: An open trial Niwako Ogata, Nicholas H. Dodman, *Journal of Veterinary Behavior* (2011) 6, 130-137

Melatonin

Melatonin is secreted by the pineal gland and regulates the sleep-wake cycle. Darkness causes the body to produce more melatonin, which signals the body to prepare for sleep. 1-6 mg several hours before bedtime [Dogs and Cats]. Useful in cases where sleep is disrupted – such as with CDS.

In general, when using any of these medications, it is important to stabilize for 1 – 2 months to see the true effects – positive and negative. Ideally, the goal is to have at least 3 months of “good behavior” – the desired outcome. When ready to stop, gradual withdrawal is recommended. When withdrawing medication, decrease the original dose by $\frac{1}{2}$ for 2-4 weeks. If all is okay, decrease that new dose by $\frac{1}{2}$ for another 2-4 weeks. If all is okay, decrease that new dose again either by $\frac{1}{2}$ daily or give that dose every other day. If at any time “undesirable” behavior resumes, go back to last controllable dose. The wean-off process should take several months. Certain conditions require long-term treatment, but you may find that a lower dose is effective. This is one of the biggest reasons to wean off slowly – to find the lowest effective dose.