PSYCHOPHARMACOLOGY – WHICH DRUG AND WHY?

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Most of drug use in veterinary behavioral medicine is considered extra-label. Controlled studies in the pet population are limited, yet comparisons can be made between pets and people. Often, these medications were tested in animals prior to being approved for use in humans. It is important to realize that metabolism, side effects, and toxicity profiles often differ from humans. For most behavioral medications used in people or animals, the exact mechanism of action(s) are largely unknown. What we do know is that behavioral drugs are most effective when used as an adjunct to behavioral and environmental modification.

The minimum data base when prescribing behavioral drugs should include a complete behavioral history, physical exam and/or medical record evaluation, and clinical tests including a complete blood chemistry, serum biochemistry, and urinalysis. Pending the clinical profile and medications considered, a thyroid profile may be warranted. Medical diagnosis and a list of differentials should always be considered when presented with a behavioral problem. Ideally, a drug is chosen not only because it can benefit the pet's behavior, but because it may also be beneficial with existing medical problems. A client drug consent form which lists common potential side effects should be presented and discussed with the client at the time of prescribing. The client should also be made aware of when drugs are used in an extra label fashion.

Drug Selection

Drug selection is based on the behavioral diagnosis and all concurrent medical disorders. Choices should be made based on supporting behavioral drug studies when available. Potential side effects and contraindications must always be considered. The cost of the drug and current availability of the drug may be limiting factors. Certain drugs, notably benzodiazepines, have human abuse potential and should be prescribed in moderation. Behavioral drugs should not be used in competition animals for ethical reasons. Behavioral drugs should be avoided or used with caution in breeding animals.

There are no medications approved for use in aggressive patients and they are unlikely to be approved anytime in the future because of liability. Certain drugs have an increased potential to increase irritability and aggression. Benzodiazepines have been shown to disinhibit aggression. The veterinary label formulations Clomicalm™ (clomipramine) and Reconcile® (fluoxetine) are contraindicated in aggressive patients per the drug label. When treating aggressive patients and prescribing medication, an aggression release form can be helpful to protect oneself from liability. Realize any medication that may be helpful in reducing aggression, has the potential to increase aggression and the same can be said with regard to anti-anxiety medications.

Neurotransmitters

Neruotransmitters of importance include glutamate, gama-amino-butyric acid (GABA), acetylcholine (Ach), dopamine (DA), norepinephrine (NE), and serotonin (5-HT).

Glutamate is an excitatory amino acid that is widely distributed in the central nervous system. Barbiturates and progesterone suppress the excitatory responses of glutamate. In humans, glutamate is present in high levels in some aggressive, impulsive, and schizophrenic disorders.

Gama-amino-butyric acid is an inhibitory amino acid which is widely distributed in the central nervous system. It is synthesized from glutamate. GABA agonists include benzodiazepines and barbiturates. GABA dysregulation is associated with conditions related to fears and phobias.

Acetylcholine is an excitatory amino acid and is the most widely distributed neurotransmitter in the body. It is produced from acetyl COA and choline and inactivated by acetylcholinesterase. Subclasses of cholinergic synapses include muscarinic and nicotinic. The muscarinic synapses are found in smooth muscle, cardiac muscle, peripheral autonomic ganglia, CNS,

and parasympathetic post ganglionic neurons. Blockade of muscarinic cholinergic receptors is responsible for anticholinergic side effects of antipsychotics and tricyclic antidepressants. Side effects may include dry mouth, dry eye, increased intraocular pressure, mydriasis, urine retention, constipation, and cardiogenic (tachycardia) effects.

Monoamine neurotransmitters are concentrated in midbrain, hypothalamus, and limbic system. They are inactivated by reuptake from the synaptic cleft by the enzyme monoamine oxidase. Monoamine neurotransmitters consist of catecholamines and indoleamines. The catecholamines include norepinephrine, epinephrine, and dopamine. They are synthesized from dietary tyrosine and phenylalanine. Dopamine is a precursor for norepinephrine. The indoleamines include serotonin and melatonin. Indoleamines are synthesized from dietary tryptophan. Drugs that block or inhibit reuptake, or inhibit monoamine oxidase increase the availability and activity of neurotransmitters in the synaptic cleft. This is one proposed mechanism of action.

Dopamine is produced from L-dopa in the presynaptic vesicles of the brain. In humans, dopamine depletion is associated with behavioral quieting, depression, and possible extrapyramidal signs. Dopamine antagonists include phenothiazines and antipsychotics. Dopamine excess can induce stereotypic behavior. Dopamine agonists include amphetamines, apomorphine, and methylphenidate.

Norepinephrine is formed from the hydroxylation of dopamine and associated with activation of the sympathetic nervous system. In humans, norepinephrine depletion is associated with depression, while norepinephrine excess is associated with mania. Some tricyclic antidepressants inhibit norepinephrine reuptake. Side effects may include tachycardia, tachypnea, and hypertension.

Serotonin is inhibitory pre and post synaptically. It is responsible for modulation of the sleep-wake cycle, mood, emotion, and the suppression of impulsive behavior. In humans, serotonin depletion has been shown to increase irritability, hostility, and impulsiveness, while serotonin excess results in confidence, calmness, flexibility, and resilience.

Classes of Behavior Drugs

Classes of behavior drugs to be discussed include benzodiazepines, serotonin modulators, alpha-2 agonists, anticonvulsants, phenothiazines, sympathomimetics, narcotic antagonists/agonists, tricyclic antidepressants, selective serotonin reuptake inhibitors, and monoamine oxidase inhibitors.

Benzodiazepines

Benzodiazepines are indicated for treating acute fears, phobias, and anxiety related disorders. They may be used for their anticonvulsant properties or as an adjunct to mainstay therapy of tricyclic antidepressants or selective serotonin reuptake inhibitors. The onset of action is rapid. They are often administered one to two hours prior to situational anxiety. Common side effects may include polyphagia, muscle relaxation, and ataxia. Benzodiazepines are more likely to disinhibit aggression than other behavioral medications. Other side effects include inhibiting learning, amnesia, and paradoxical reactions. Chronic use may cause anemia, neutropenia, and jaundice.

Although rare, acute hepatic necrosis has been reported in cats with oral diazepam.[1] Marked increases in ALT are seen with jaundice and encephalopathy. Signs may be seen within 96 hours of the first exposure or delayed 8-9 days from exposure to the onset of clinical signs. In cats, diazepam has been reported to be effective in reducing spraying in 75% of cases, with 43% stopping entirely.[2] It is more effective in males and in multicat households. The recidivism rate of 91% has been reported when medication is withdrawn.[2] The half-life of diazepam has been reported to be 2.5 hours in the dog, and 5.5 to 20 hours in the cat.[3] In one retrospective study, diazepam was owner described as very (24% [9/37]) or somewhat (43% [16/37]) effective for anxiety disorders in dogs.[4] Only (49%) owners reported that they were still administering diazepam. The most common reasons for discontinuation included adverse effects (58%) and lack of efficacy (53%). Other benzodiazepines rather than diazepam may be better options in the dog.

Table 1: Benzodiazepines

Alprazolam (Xanax)	D	0.01-0.1mg/kg	PO	q6-12h
Lorazepam	D	0.1-0.2mg/kg	PO	prn
(Ativan)	C	0.05mg/kg	PO	q12-24h
Oxazepam	D	0.2-0.5mg/kg	PO	q12-24h
(Serax)	C	1-2.5mg/cat	PO	q12-24h
Clorazepate	D	0.55-2.2mg/kg	PO	q12-24h
(Tranxene)	C	1.875-3.75mg/cat	PO	q12-24h
Clonazepam	D	0.1-1.0 mg/kg	PO	q8-12
(Klonopin)	C	0.1-0.2 mg/kg	PO	q12-24

Serotonin Modulators

Azapirones are partial serotonin agonist, dopamine agonist, and dopamine 2 receptor antagonists. They have been used for treating mild fear and anxiety related disorders including feline urine marking and the victim of intercat aggression. In addition, they may be used as an adjunct to a tricyclic antidepressant and selective serotonin reuptake inhibitors. The onset of action is delayed and effects are usually seen by one to three weeks of treatment. Side effects are few, and may include gastrointestinal upset. One documented side effect in cats is social withdrawal.[5] Serotonin agonists have the potential to increase aggression in some species.

In one feline study evaluating urine spraying, 58% of multi-cat households responded favorably, with thirty four percent ceasing urine spraying.[6] Fifty percent of the cases relapsed with discontinued therapy.

Table 2: Serotonin Modulator - Buspirone

Busprione	D	1.0-2.0mg/kg	PO	q8-12h
(Buspar)	C	2.5-7.5mg/cat	PO	q8-12h

Trazodone increases the availability of serotonin, blocks histamine (h1) receptors, and alpha 1 adrenergic receptors. Trazodone has anti-anxiety (anxiolytic) and sleep-inducing (hypnotic) effects. Trazodone is most commonly used as an adjunct to mainstay medications such as SSRIs and TCAs, and one study gives evidence to benefits in treating a wide array of behavior problems.[7] Side effects may include sedation and hypotension. Trazodone is contraindicated in conjunction with MAOIs.

Table 3: Serotonin Modulator - Trazodone

Trazodone	D	Initially 1.0-2.0mg/kg	PO	q8-24h
(Desyrel)	D	Target 2-8mg/kg	PO	q8-24h

Alpha 2 agonist

Alpha 2 agonists such as clonidine may be helpful in cases of acute fear, phobias, and impulse control/aggression. The onset of action is rapid, often dosed 1-2 hours prior to situational anxiety. Side effects may include dry mouth, sedation, and hypotension. Clonidine is most commonly used as an adjunct to mainstay medications such as SSRIs and TCAs. In one study it was beneficial in treating fear based problems in dogs.[8] The only reported side effect in that study was increased noise sensitivity in one dog.

Table 4: Alpha 2 Agonist

Clonidine (Catapres)	D	0.01-0.05mg/kg	PO	Prn, up to q12h

Anticonvulsants

The anticonvulsant gabapentin is an excellent anti-anxiety medications and pain reliever. Gabapentin is often used by the author as a safe alternative to SSRIs and TCAs in patients that are epileptic. Cases with separation anxiety, generalized anxiety, and phobia appear to do well. Side

effects are rare and may include increased appetite and increased social facilitation. Gabapentin is thought to work by increasing synaptic concentration of GABA. Cognition may be impaired by its use.

Table 5: Anticonvulsant - Gabapentin

Gabapentin	D	1.0-2.0mg/kg	PO	q8-12h
(Neurontin)	C	2.5-7.5mg/cat	PO	q8-12h

Phenothiazines

Phenothiazines act as dopamine antagonists. The phenothiazines are best used for chemical restraint and sedation, not anti-anxiety. They also have an antiemetic effect. The onset of action is rapid and response is quite variable. Side effects include hypotension, bradycardia, hypothermia, idiosyncratic aggression, and extrapyramidal motor signs. They are contraindicated in cases of cardiac disease. Some still suggest they should not be used in patients with seizures.

Table 6: Phenothiazines

Acepromazine	D	0.05-2.2mg/kg	PO	prn
	C	0.1-2.2mg/kg	PO	prn
Chlorpromazine	D	0.5-3.3mg/kg	PO	prn
	C	Same as dog		

Sympathomimetics

Sympathomimetics are used for treating the rare conditions of hyperkinesis and narcolepsy. They have a rapid onset of action and a stimulant effect in most individuals. Patients who are truly hyperkinetic experience a paradoxical calming effect. Side effects may include increased heart rate and respiratory rate, anorexia, hyperthermia, and tremors. Contraindications include preexisting glaucoma, diabetes mellitus, hypertension, hyperthyroidism, and cardiac diseases.

Methylphenidate is best prescribed at the lowest dosage initially. Dosage may be gradually increased within the dosage range every 3 days. In the truly hyperkinetic patient, a calming effect will be seen prior to any excitation.

Table 7: Sympathomimetics

Methylphenidate (Ritalin)	D	1-4mg/kg	PO	q8-12h
Dextroamphetamine	D	0.2-1.3mg/kg	PO	prn

Narcotic Antagonists/Agonists

Opiates are released during stress, induce analgesia, and activate the dopaminergic system resulting in stereotypic behaviors. This is the rationale for using narcotic antagonists and agonists in cases of stereotypy and compulsion. Narcotic antagonists have been used for treating acral lick dermatitis and compulsive disorders in many species.[5] The onset of action of these drugs is rapid. Side effects most commonly seen include diarrhea and/or constipation.

The half-life of naltrexone has been reported to be 45-85 minutes in the dog.[9] The short half-life and expense make it impractical for most behavioral cases. Hydrocodone has been used for cases of acral lick dermatitis. Behavioral depression and the numbing effect may contribute to a decrease in the frequency of licking behavior. Hydrocodone is not thought to be anti-compulsive.

Table 8: Narcotic Antagonists/Agonists

Naltrexone	D	1-2.2mg/kg	PO	q12-24h
	C	0.2mg/kg	PO	q12-24h

Hydrocodone	D	0.25mg/kg	PO	q8-12h
	C	1.25-5mg/cat	PO	q12h

Tricyclic Antidepressants

Tricyclic antidepressants increase the availability of serotonin, norepinephrine, and dopamine. Amitriptyline and doxepin are the best drug option when a good antihistamine is needed. Doxepin is the most sedating of the tricyclics and the best antihistamine. Imipramine has been used for treating submissive urination in dogs because its anticholinergic effect increases urinary sphincter tone. In children, it is used for treating nocturnal enuresis. In veterinary patients, tricyclic medications are indicated for chronic fears, phobias, and anxiety conditions.

Clomicalm (Clomipramine) is FDA approved for treating separation anxiety in dogs in the United States. The half-life may be as short as 4 hours, necessitating using a dosing frequency of every 12 hours for best success. It is on label for treating compulsive disorders in Canada and for feline urine marking in Australia. Because clomipramine is selective for serotonin reuptake inhibition, it is the only tricyclic effective in treating compulsive disorders. One study give evidence of a beneficial effect in reducing the frequency of compulsive behavior in dogs.[10] In addition, although it is extra label, it is the most appropriate tricyclic for treating cases of aggression. Clomipramine (Clomicalm), while contraindicated for aggression per label, may be beneficial in specific cases of aggression due to its serotonin selectivity. In a study evaluating clomipramine for treating dominance related aggression in dogs, aggressiveness was not reduced when compared to placebo.[11] The dosage used in the study was considered low (1.5 mg/kg PO q12 hours). The onset of action of tricyclics is typically seen in 3-4 weeks, pending the condition. The onset of action may take longer in cases of compulsive disorders. Side effects include sedation, gastrointestinal upset, taste aversion, urinary retention (cats), and anticholinergic side effects. They are contraindicated in conditions of dry eye, glaucoma, diabetes mellitus, seizures, cardiac disease, prostate disease, and with concurrent thyroid medications.

The optimum dosage for clomipramine use in cats has been determined.[12] Clomipramine's success rate for urine marking in cats is reported to be up to 75% in reducing spraying.[13,14] In one study looking at mixed canine aggression, amitriptyline showed no effect.[15] The trial compared the use of amitriptyline plus behavior modification to behavior modification alone for mixed canine aggression. The result is not surprising as amitriptyline is not very serotonin selective.

Table 9: Tricyclic Antidepressants

Amitriptyline	D	2-4mg/kg	PO	q12h
(Elavil)	C	1-2mg/kg	PO	q12-24h
Clomipramine	D	2-4mg/kg	PO	q12h
(Clomicalm)	C	0.25-0.5mg/kg	PO	q24h
Doxepin	D	3-5mg/kg	PO	q12h
(Sinequan)	C	0.5-1mg/kg	PO	q12-24h
Imipramine	D	1-4.4mg/kg	PO	q12h
(Tofranil)				

Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors increase the availability of serotonin by blocking reuptake within the pre and post synaptic cleft. They are indicated for treating chronic fear, phobia, and anxiety related conditions. They are effective in treating compulsive disorders in many species. Reconcile (Fluoxetine) was FDA approved (USA) for treatment of separation anxiety in dogs. Drugs that modulate the serotonin system are the drugs of choice for treating aggression disorders. Fluoxetine is probably the drug of choice for treating aggression and it is least likely to disinhibit aggression when compared to other drugs. The onset of action is typically seen in 3-4 weeks. Side effects most commonly seen are sedation and reduced appetite. One study suggests fluoxetine is beneficial in treating compulsive disorders in dogs.[16] Paroxetine is more likely to cause mild anticholinergic side effects. Selective serotonin reuptake

inhibitors are contraindicated in conditions of seizures, diabetes mellitus, or with concurrent MAOIs. Use of other drugs/nutraceuticals that boost serotonin such as L-tryptophan supplementation, may increase the risk of serotonin syndrome. SSRIs should be avoided in breeding animals as it will decrease libido.

Serotonin syndrome is a potentially fatal condition of serotonin excess that may occur in some animals with therapeutic dosages. The clinical progression of the disorder is diarrhea; restlessness; extreme agitation, hyperreflexia, and autonomic instability with possible rapid fluctuations in vital signs; myoclonus, seizures, hyperthermia, uncontrollable shivering, and rigidity; and delerium, coma, status epilepticus, cardiovascular collapse, and death. It is fatal in 5-10% of human cases. Treatment is often supportive with discontinuance of medication. Anti-seritonergic drugs such as cyproheptadine may be helpful is cases of serotonin syndrome.

Fluoxetine has been reported to be effective in treating urine spraying cats. In one study, 90% responded by week 2 and 66% eliminated spraying entirely.[17] Fluoxetine has also been suggested for treating canine dominance aggression in one study.[18]

Table 10: Selective Serotonin Reuptake Inhibitors

Fluoxetine	D	1-2 mg/kg	PO	q24h
(Reconcile)	C	0.5-1mg/kg	PO	q24h
Paroxetine	D	1-2 mg/kg	PO	q24h
(Paxil)	C	0.5-1mg/kg	PO	q24h
Sertraline	D	1-3mg/kg	PO	q24h
(Zoloft)	C	0.5mg/kg	PO	q24h

Monoamine oxidase inhibitors

Monoamine oxidase inhibitors act by increasing the availability of serotonin, norepinephrine, and dopamine. Anipryl (Selegiline) is FDA approved (USA) for treating canine cognitive dysfunction syndrome.[19] Effective in treating chronic fears, phobias, and anxiety conditions, they have been used widely in Europe for treating aggression and anxiety related disorders. The onset of action typically takes 3-4 weeks, although with cognitive dysfunction, a 1-3 month period may be necessary. Side effects include vomiting and diarrhea, as well as, anticholinergic side effects. They are contraindicated when used with alpha 2 agonists, tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin modulators and MAOIs such as amitraz. MAOIs in combination with other serotonin modulators such as TCAs, SSRIs, tramadol, buspirone, trazodone, presents a high risk for the development of serotonin syndrome. Concurrent use with clonidine may cause blood pressure fluctuations.

Table 11: Monoamine Oxidase Inhibitors

Selegiline	D	0.5-1mg/kg	PO	q24h
(Anipryl)	C	0.5-1mg/kg	PO	q24h

General Guidelines for Drug Use

When prescribing psychoactive drugs, the clinician should follow some general guidelines. The drug must be used for appropriate length of treatment and at an effective dosage. Generally an effect should be seen in 3-4 weeks with most tricyclic antidepressants and selective serotonin reuptake inhibitors. If after 3-4 weeks, there is no change in the behavior; one should reevaluate the diagnosis and differentials. If no improvement or only moderate improvement is seen, typically the dosage is increased and the effect is reassessed in 3 or 4 weeks. If the drug is thought to be ineffective at the high end of the dose, then a change of medication is warranted. If a moderate effect is noted, polypharmacy may be considered to potentiate effects. The clinician must know that treatment of behavioral problems with psychoactive drugs is largely ineffective without current behavioral and environmental modification. Without behavioral modification, one is unable to eventually wean the patient off the drug and the drug may become less effective with time.

The duration of treatment must be sufficient to facilitate unlearning of the problem behavior. The minimum treatment duration is 3 months. Usually, most patients are on medication for a period of 6-12 months. One should treat the patient with medication for at least one month past the resolution of clinical signs. Then weaning may be considered. Weaning is recommended at some point in all patients, although lifelong therapy may be necessary in some patients when there is a chemical imbalance. Acute withdrawal of behavior medication often results in rebound anxiety. It is suggested to reduce the total dosage of medication by 25 percent. If the treatment duration is greater than 3 months, the dosage should be reduced every 2 weeks. If the treatment duration is greater than 6 months, the dosage should be reduced every 3 or 4 weeks. It appears that gradual weaning prevents recidivism. When weaning, it is important to maintain the same dosing frequency. If the behavior relapses, one should increase to the previous effective dosage and treat for a longer duration.

When switching between mainstay medications such as SSRIs and TCAs, there is no need to have a washout period when using conventional dosages. Simply switch mediations without discontinuation. With unconventional dosing, the half-life and patient should be considered and carefully monitored. Risk of serotonin syndrome is greater when switching between MAOIs and SSRIs. A washout period of at least 2 weeks and up to 5 weeks, errors on the side of caution. When a washout is impractical, dosages should be reduced prior to discontinuance and with the starting of the new medication.

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