PSYCHOPHARMACOLOGY

General Considerations:

Pharmacological treatment of behavior problems has been going on for at least 40 years. In the early days, vets used only phenobarbital, progestins, and acepromazine, and all these drugs either caused sedation or had other undesirable side effects. Diazepam (Valium®), also not without its problems, came along later (in the 1970s). The problem with early behavioral pharmacology was that it was not logically applied or specifically targeted. The first useful group of compounds to come along (in the 1980s) was the antidepressants, notably amitriptyline. For reasons that people did not understand, amitriptyline proved useful for treating certain behavior problems, like urine marking and separation anxiety.

The real explosion in behavioral pharmacology occurred in the late 1980s with the advent of more specific drugs like fluoxetine (Prozac®) and buspirone (Buspar®). These so-called "smart drugs" produced useful behavior modifying effects, while at the same time causing minimal "collateral" damage (side effects). The first report of the use of fluoxetine in veterinary medicine was in 1989. The 1990s was known as "the decade of the brain": An explosion of new CNS pharmaceuticals occurred at this time. Furthermore, numerous publications documenting the effectiveness of the new therapies lead to new theories of mood stabilization and behavioral control. Veterinary medicine lagged behind human medicine, but similar advances were being made in the wake of human and lab animal studies.

Two basic questions that arise are **why** and **when** should behavior modifying drugs be used. Antagonists of the behavioral pharmacology say that proponents might use drugs, for example, to stop a dog from jumping up (a problem that can easily be addressed by training); this is simply not true. Behavioral pharmacology is (or should be) employed when:

a.) Other options have been exhausted
b.) Owners are desperate for a rapid response
c.) When owner compliance is likely to be poor
d.) The pharmacological approach is the only one likely to work

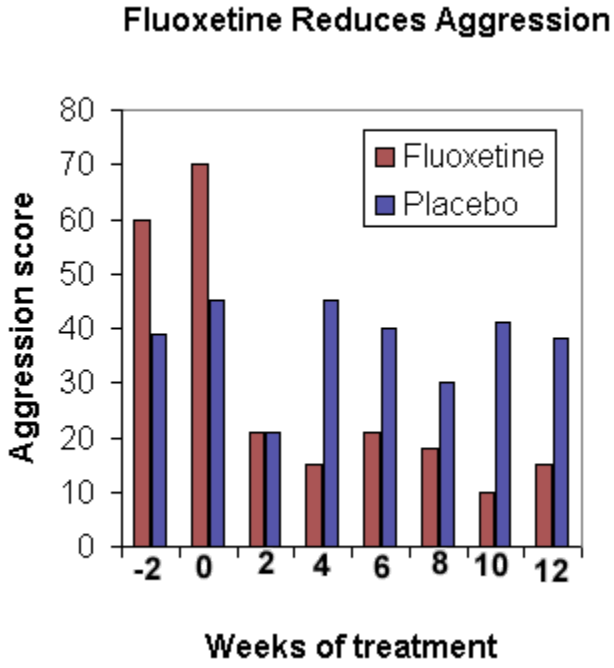
Selective Serotonin Reuptake Inhibitors:

<u>Fluoxetine</u>

Fluoxetine, a.k.a. Prozac or veterinary trade name Reconcile, is a member of a structurally disparate group of drugs known as serotonin reuptake inhibitors (SSRIs). Other members of this group include sertraline (Zoloft®), paroxetine (Paxil®), citalopram (Celexa®), and fluvoxamine (Luvox®). These drugs block the presynaptic serotonin (5HT) reuptake mechanism, thus

increasing the concentration of 5HT at central synapses. Most of these drugs have a long half-life and take time to achieve peak concentration in blood and tissues. Long-term neuronal changes, specifically the development of new neurons from progenitor cell in the hippocampus, also occur and account for SSRIs' long-term clinical efficacy. Typically, fluoxetine takes up to 4 weeks to become appreciably effective and up to 2 months or more to reach its peak effect.

Fluoxetine in aggression: Increasing brain serotonin—which occurs earlier than the aforementioned neuronal changes—decreases aggression across the species. Paradoxical increases in aggression are not a feature of fluoxetine's use.



NOTE: Dominance aggression in dogs is thought to be linked to fluctuations in concentrations of central serotonin (this may be why dominant dogs are often described by their owners as "Jekyll and Hyde" personalities or at least "moody"). Extrapolating and drawing from data in other species, the "dominant aggressive" dog would likely be in its most aggressive frame of mind when serotonin levels are low. Typically, this would be toward the end of the day as serotonin is metabolized to melatonin over the course of the day. Giving fluoxetine would be expected to stabilize serotonin and reduce aggression. This is what is observed.

ALSO NOTE: Testosterone depresses central serotonin. Castration allows serotonin to rise, and aggression is reduced. Castration reduces intermale aggression by ~50%, and owner-directed dominance aggression by about 30%.

Fluoxetine in fear/anxious conditions: Serotonin interacts with a range of neurotransmitters, perhaps accounting in part for the promising effects of the SSRIs in treating fearful/anxiety-based conditions. In humans, SSRIs are becoming one of the first-line treatments for "social anxiety". Animals may express social anxiety, too, and fluoxetine can help them progress. Fluoxetine has also been found effective for the treatment of separation anxiety and compulsive behaviors.

Side effects of fluoxetine: Not all animals show side effects. Side effects are usually occur after the first week of treatment and can last for 2 to 3 weeks. They are easily managed by dose titration. Appetite suppression and associated weight loss are the most common side effects. Some sensitive animals become lethargic. Other side effects include agitation, muscle twitching, social withdrawal, reduced playfulness, seizures and, potentially, "serotonin syndrome". The serotonin syndrome is characterized by alterations in cognition (disorientation,

confusion), behavior (agitation, restlessness), autonomic nervous system function (fever, shivering, diaphoresis, diarrhea), and neuromuscular (ataxia, hyperreflexia, myoclonus) activity.

Fluoxetine and other SSRIs are incredibly safe. No deaths have been reported as a result of therapy. SSRIs can be given for as long as necessary to control a problem. Some dogs and cats require lifelong therapy. It is wise to periodically check the physical status of a patient on long-term therapy with an SSRI. Annual blood work is indicated. At Tufts, we advise a "liver profile" each year at the time of the annual physical exam. We have yet to see a case in which liver enzymes are elevated.

Tricyclic Antidepressants:

Clomipramine

Clomipramine, veterinary trade name Clomicalm, is probably the best TCA, though several others, like amitriptyline (Elavil®) and imipramine (Tofranil®), have been used and may sometimes offer advantages. The tricyclic family of drugs blocks the reuptake of serotonin and norepinephrine. In addition, all have anticholinergic effects. Side effects are more common with this class of drugs than with SSRIs. Specifically, sedation, hypotension, urinary retention, dry mouth, and increased thirst may occur. Of the group, clomipramine has the most potent serotonin reuptake blocking properties and is probably the best choice for treating aggression. Increased aggression might rarely be seen as a result of treatment with clomipramine, and there is a warning about this in the Clomicalm package insert.

That said, the most likely effect of clomipramine is to cause a decrease in aggression, and we have used it to treat aggression in numerous cases. Some veterinarians have used amitriptyline to decrease aggression, but our experience is that amitriptyline is more likely to cause a paradoxical increase in aggression than clomipramine, possibly due to its weaker 5HT reuptake blocking properties.

Buspirone (Buspar®)

In a class of its own, buspirone is an anti-anxiety drug (officially an "anxioselective"). It is a serotonin agonist that works on $5HT_{1A}$ receptors. Buspirone, like fluoxetine, is a smart drug. It produces a narrow spectrum of biological activity and is thus associated with minimal side effects. It has little organ toxicity, is non-addictive, and there is no withdrawal reaction following abrupt termination. Buspirone has been used most commonly in cats to treat anxiety/fear-based conditions like social phobia, fear aggression, urine marking, and psychogenic alopecia. In dogs it has been used successfully to attenuate thunderstorm phobia and separation anxiety. Horses with inanimate and situational fears have responded well to buspirone.

The only side effects of buspirone in cats are increased affection/playfulness, post-pilling

excitement (~15% of cats), and occasional aggression. No side effects have been reported in dogs or horses. Disadvantages of buspirone include its relatively weak effect and bitterness to taste. In addition, buspirone must be given twice daily.

Beta Blockers

Propranolol is the best known beta-blocking agent. Beta blockers, such as propranolol, are most often used to treat heart disease, but they have behavioral effects, too. Beta blockers work by antagonizing the beta effects of norepinephrine centrally, and they also block central autoreceptors for 5HT, increasing its release. In addition, beta blockers reduce tone in muscle spindles, decreasing proprioceptive afferent bombardment of the reticular activating system (a system that otherwise maintains alertness and vigilance). Beta blockers are used in human medicine to treat over anxiousness that occurs in stage fright, performance anxiety in musicians, and fear of public speaking. Fearful responses are attenuated by direct and indirect (bio-feedback) actions.

Propranolol and other beta blockers provide a safe, relatively side-effect-free, though somewhat weak anti-anxiety effect. In veterinary medicine, they have been used to treat fear-based conditions such as storm phobia, noise phobia, and separation anxiety and have also been used to treat fear aggression.

The half-life of propranolol is short in dogs, so the long-acting preparation, Inderal LA, is best to use, though it is very expensive. It is prudent to monitor the heart rate during the administration of a beta blocker. If the heart rate drops below 50 bpm, the dose should be reduced. Beta blockers should not be given to patients with asthma (cats) and should be used with caution in diabetes as they increase blood sugar. Pindolol is another beta blocker that is more potent and possibly more effective than propranolol.

Dopamine Antagonists

Acepromazine, best known as a sedative, is one of the best known drugs in veterinary medicine. Its primary action is to block central dopamine receptors, causing reduced alertness and activity. Drugs of this type are classed as *neuroleptics*. Three types of neuroleptics exist: Low potency, high potency, and atypical. Acepromazine belongs to the low potency group. These drugs require higher milligram/kilogram doses and are more sedating. Drugs like haloperidol and fluphenazine below to the high potency group. Very small milligram doses produce clinical effects with less sedation. Unfortunately, unacceptable side effects (especially dyskinesia) are more common with high potency neuroleptics. Atypical (or "novel") neuroleptics are epitomized by clozapine (Clozaril®). These drugs target specific dopamine receptors and/or may block or inhibit re-uptake of serotonin. It is believed that they are associated with a lower risk of dyskinesia.

In veterinary medicine, high potency neuroleptics and atypical neuroleptics haven't really worked out in terms of their clinical usefulness, and we tend to rely on our old standby,

acepromazine. While acepromazine is useful for short-term chemical restraint of fractious dogs, it is not really a viable option for long-term treatment. Reasons for this are that it causes sedation and that long-term (tardive) side effects may occur. Some vets use acepromazine situationally to control behavior problems like thunderstorm phobia and separation anxiety, but there are usually better options.

Benzodiazepines

"Benzos" like diazepam and alprazolam are agonists at gamma aminobutyric acid (GABA) receptors. Their clinical effect of anxiety reduction (anxiolysis) is achieved through hyperpolarization of cell membranes. Because of this action, benzodiazepines have anticonvulsant activity. The "taming effect" of benzodiazepines on wild animals is legend. However, if anxiety is inhibiting aggression, aggression may be enhanced (so-called paradoxical effect). The possibility of increasing aggression is the main reason that benzodiazepines are not more widely used. That said, benzodiazepines can sometimes be successfully employed to treat agonistic behavior between cats. Other uses for benzodiazepines include adjunctive treatment of thunderstorm phobia (dogs), separation anxiety (dogs), and urine marking (cats).

Side effects of diazepam-like drugs include increased appetite, weight gain, and ataxia. Benzodiazepines are addictive, and withdrawal reactions occur if benzodiazepines are withdrawn too quickly following prolonged use. Diazepam has been linked to fulminating hepatic failure in cats. For this reason, it is advisable to avoid it and use alprazolam instead in felines.

Anticonvulsants

Sometimes anticonvulsants are helpful in the treatment of behavior problems, especially when partial seizures are involved in the etiology is the behavior. Tail chasing in bull terriers and German shepherds may sometimes involve a seizure component, even though these conditions are usually described as "compulsive disorders". Other problem behaviors that may respond to treatment with anticonvulsants include rage, some extreme fear-based behaviors, and some appetitive disorders (pica). The old standby is phenobarbital with sodium or potassium bromide, a useful add-on treatment. Side effects of phenobarbital include drowsiness, increased thirst and urination, and sometimes hyperactivity. Levetiracetam (Keppra) is another useful anticonvulsant, though it is expensive. Other drugs commonly used to treat partial seizures in humans are too short-acting to be of much use.