Drug Therapy in Veterinary Behavior – Show me the Evidence
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Psychotropic drugs and natural products can be useful for reducing the signs associated with phobic, panic or chronic anxiety and to improve trainability in situations where the pet is anxious, fearful, or aroused. Drugs may also have a dramatic effect when there is brain pathology, as with compulsive disorders, impulse dyscontrol or cognitive dysfunction syndrome. Drugs may also be useful for feline urine marking and some forms of aggression. However, drugs do not change the relationship with the stimulus so that concurrent behaviour modification will also be needed to desensitize, countercondition and train desirable responses.

Show me the evidence
Evidence based decision making allows treatment options to be selected by using the available evidence together with the clinician’s expertise as to the patient, client and problem. Using the Oxford Centre for Evidence Based Medicine Scoring System, the weakest level of evidence is in vitro research, case based studies or expert opinion without critical appraisal.1 The highest level would be a systematic review with homogeneity of randomized control trials (RCT). However, with few published trials for most veterinary behavior drugs there is no real access to this process. In fact, to date only one meta-analysis examining the effects of therapeutic agents on urine marking in cats has been published.2 The importance of using RCT’s to validate efficacy is of particular importance in veterinary behavior where the placebo effect can reach 50% or higher. In one study of separation anxiety over 65% of dogs on fluoxetine improved compared to over 51% of the placebo group.3

In veterinary behavior much of our drug information is extrapolated from human literature; however, drug metabolism and receptor effects vary between species and between individuals. For example the clearance half life diazepam and its intermediate metabolite nordiazepam in dogs is 2.5 and 3 hours in cats 5.5 and 21 hours, and 20-50 and up to 200 hours in humans. This can lead to inaccurate assumptions with respect to dose, duration of effect, contraindications and side effects. Therefore, drugs licensed for pets should first be considered since there is data with respect to safety, efficacy, side effects, contraindications, toxicity and pharmacokinetics. In addition, technical support from the manufacturer provides additional expertise, especially in the event of adverse events. There are also legal requirements in some jurisdictions to prescribe veterinary drugs first (prescribers cascade). When dose, compliance or availability is an issue compounding might be considered; however, stability, storage and bio-availability are a concern. In addition, for transdermal medications, one study found the bioavailability of fluoxetine to be 10% of oral dosing, while systemic absorption of amitriptyline and buspirone was negligible.4,5 A physical examination and blood and urine tests should be part of a minimum database prior to dispensing drugs.

Finding the evidence
While a meta-analysis of randomized placebo controlled clinical trials is the gold standard for assessing the efficacy of a therapeutic agent, few if any drugs or natural products in veterinary behavior have been subjected to such rigorous standards. Recently laboratory models have been developed for dogs and cats to evaluate learning and memory, fear of noises and fear of humans, allowing for the assessment of drugs, supplements and behavior products in a controlled environment with minimal subject variability, validated measures, and removal of owner bias. These models have proven invaluable in validating the efficacy of a number of diets, supplements and drugs for use in dogs and cats.6-10

Antidepressants
Antidepressants may reduce anxiety, panic and impulsivity. They may take 4 weeks or longer to achieve full therapeutic effect since initial reuptake inhibition will induce down-regulation of postsynaptic receptors. They cause little or no sedation and are unlikely to inhibit learning or memory.

Clomipramine and fluoxetine are licensed for dogs for separation anxiety.11,12 There is also evidence of efficacy for clomipramine (a tricyclic antidepressant) and selective serotonin reuptake inhibitor (SSRI) for the treatment of compulsive disorders and urine marking in cats.13-18 SSRI’s might also be useful for generalized anxiety, fears and phobias and some forms of aggression in pets.19-21
SSRI's or clomipramine on an ongoing basis might be combined with a benzodiazepine or trazodone on an as needed basis prior to fear or anxiety evoking events (e.g. fear, anxiety, aggression).22-25

The primary mechanism of action of TCA's is blockade of serotonin and noradrenaline reuptake with varying degrees of anticholinergic, antihistaminic and alpha adrenergic effects. Clomipramine is the most selective inhibitor of serotonin reuptake of the TCA's. Doxepin has marked antihistaminic effects and moderate effects on noradrenaline but minimal effects on serotonin. The alpha-adrenergic effects of imipramine may aid in improving sphincter control in pets with enuresis, or conflict, excitement or submissive urination while also ameliorating anxiety. Amitriptyline has moderate effects on both serotonin and noradrenaline, and strong antihistaminic and anticholinergic effects. However, there are no studies that have demonstrated a significant effect of these other tricyclic antidepressants in pets.26,27

Serotonin syndrome is a serious and potentially fatal concern which may arise when antidepressants that inhibit serotonin reuptake are used at high doses or in combination with other drugs that may increase serotonin. They should not be used concurrently with other antidepressants or MAO inhibitors such as selegiline and amitraz. Caution should also be used when combining with St. Johns Wort, amphetamines, and possibly tramadol, tryptophan, metoclopramide, or dextromethorphan as well as serotonin receptor agonists such as buspirone and bromocriptine. Signs of serotonin syndrome include confusion, shivering, shaking, hyperthermia, tachycardia, diarrhea, twitching, tremors, seizures, coma and death. Since, SSRI's inhibit cytochrome P-450 enzymes they can lead to increased toxicity if combined with drugs metabolized by these enzymes.28

Anxiolytics

Buspirone is a serotonin receptor agonist and dopamine agonist. It has been used for mild fear and anxiety and feline urine marking.29 It is non-sedating, does not stimulate appetite, does not appear to inhibit memory and may take a week or more to reach effect. Adding buspirone to an SSRI or TCA might increase the pool of available serotonin. Since anxiolytics such as buspirone or benzodiazepines may disinhibit, they could potentially contribute to an increase in aggression.

Benzodiazepines potentiate the effects of GABA, an inhibitory neurotransmitter. They cause a decrease in anxiety, hyperphagia, and muscle relaxation but may cause paradoxical excitability and may have a rebound effect on withdrawal. They reach peak effect shortly after each dose and can be used alone or in combination with other drugs on an as needed basis (e.g. prior to departure or storms).24,30 In one study diazepam was very effective or somewhat effective in 67% of anxiety-related behavior cases, primarily as adjunctive therapy in dogs with thunderstorm fears and separation anxiety.30 When doses of 0.8 mg/kg or greater were used, there were greater reports of increased activity.30 Diazepam may be effective in the reduction of feline urine marking but comparatively less than fluoxetine or clomipramine.29,31 Benzodiazepines may also be useful for counterconditioning especially in victim cats both to reduce anxiety and increase appetite. Rare cases of hepatotoxicity have been reported with diazepam in cats.32 Since clonazepam, oxazepam and lorazepam have no active intermediate metabolites they may be 'safer' with respect to hepatic metabolism.

Beta blockers, such as propranolol reduce physiologic signs of anxiety by blocking noradrenaline effects (heart rate, respiratory rate, trembling). They may therefore be useful in combination with drugs that diminish behavioral signs.30

More recently, clonidine a selective alpha-2 agonist that blocks noradrenaline and therefore autonomic responses of anxiety, has been used together with SSRI's for situational use about 1.5 hours prior to the event (and up to twice daily) for fear or territorial aggression, separation anxiety, nocturnal barking, or storm and noise phobias.33 At higher doses it can cause sedation.

Trazodone is a serotonin 2A antagonist-reuptake inhibitor (SARI). It may be useful as an adjunctive treatment to other behavioral medications such as SSRI's or TCA's for generalized anxiety, separation anxiety, noise phobias, some forms of aggression.23 Since it can be calming after a single dose, it might be used on an as needed basis for situational anxiety (e.g. veterinary visits, car rides, separation anxiety).

Anticonvulsants

Anticonvulsants may be indicated when clinical signs (e.g. spinning, tail chasing, hyperesthesia) might be caused by a seizure, a focal (partial) seizure or for persistent post-ictal signs such as aggression. In one case series 5 of 7 spinning bull terriers responded to phenobarbital.34 Since focal seizures may be indistinguishable from compulsive disorders, a therapeutic response trial may warranted. Temporal lobe (limbic) epilepsy, may present with mood alterations, hallucinatory behavior, self-trauma or
aggression associated with ictal, postictal or interictal stages. Phenobarbital has been used alone or in combination with other behavioral drugs (e.g. benzodiazepines, propranolol, selegiline) for behavioral calming prior to a stressful or phobic event (e.g. veterinary visit, thunderstorm) or on an ongoing basis. Clonazepam and potassium bromide have been used in the treatment of sleep behavior disorders (RBMI). 35,36 Levetiracetam might be particularly useful for focal seizures (partial epilepsy) as well as for anxiety, stress, panic, and mood disorders and Tourettes. 37 Gabapentin can be used in combination with SSRI’s for impulse control, noise phobias and neuropathic pain. Pregabalin can also be used as an anticonvulsant in dogs, with possible applications for anxiety and neuropathic pain. 38 Carbamazepine may act as a mood stabilizer and for some forms of explosive types of aggression in dogs. 39

Neuroleptics

Neuroleptics such as acepromazine are dopamine agonists that decrease motor function at the basal ganglia, elevate prolactin and may reduce aggression. Phenothiazines have sedating effects but do not reduce anxiety.

Progestins

Medroxyprogesterone and megestrol acetate have been used for androgen influenced behaviors including aggression to urine marking. 31,40 However they have the potential for causing gynecomastia, mammary tumors, adrenal and bone marrow suppression, acromegaly and diabetes.

Selegiline

Selegiline is an MAOB inhibitor which enhances catecholamine transmission. While it is used in North America for canine cognitive dysfunction syndrome, in Europe it is used for the treatment of “emotional disorders”. In one study dogs with chronic stress and high anxiety associated with stereotypic and displacement behaviors and autonomic signs had high prolactin levels, while dogs with acute fears had lower prolactin levels. Therefore selegiline might be more effective for chronic stress while fluoxetine might be more effective for acute anxiety. 41 Selegiline combined with propranolol, alprazolam and behavior modification was effective for social and sound phobias. 30

NMDA Antagonists

Altered glutaminergic neurotransmission may be a factor in the pathogenesis of compulsive disorders, in which case blocking glutamate sensitive NMDA with drugs such as memantine, amantadine or dextromethorphan may be effective therapeutic agents alone or together with SSRI’s. 42-44 However dextromethorphan may be less reliable, due to its short half-life, rapid clearance and variable absorption in dogs. 45 NMDA antagonists may also be useful as adjunctive therapy for pain management.

<table>
<thead>
<tr>
<th></th>
<th>Dog</th>
<th>Cat</th>
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<tbody>
<tr>
<td>Alprazolam</td>
<td>0.02-0.1 mg/kg bid to qid</td>
<td>.125-.25 mg/cat sid – tid</td>
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<tr>
<td>Diazepam</td>
<td>0.5-2 mg/kg prn (e.g. q 6h)</td>
<td>.2-.5 mg /kg bid to tid</td>
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<td>Oxazepam</td>
<td>0.2-1 mg/kg sid-bid</td>
<td>.2 -.5 mg/kg sid to bid</td>
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<td>Clonazepam</td>
<td>0.1-1.0 mg/kg bid-tid</td>
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<td>Lorazepam</td>
<td>.025-.2 mg/kg sid to prn</td>
<td>.025-.05 mg/kg sid-bid</td>
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<td>Amitriptyline</td>
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<td>.5 -1 mg/kg sid</td>
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<td>Clomipramine</td>
<td>1-2 mg/kg bid</td>
<td>.3 - .5 mg/kg sid</td>
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<td>Doxepin</td>
<td>3-5 mg/kg bid – tid</td>
<td>.5-1 mg/kg sid – bid</td>
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<td>Imipramine</td>
<td>.5-4 mg/kg bid</td>
<td>.5-1 mg/kg sid – bid</td>
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<td>Medication</td>
<td>Dosing Information</td>
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<tr>
<td>Fluoxetine</td>
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<td>Buspirone</td>
<td>0.5-2.0 mg/kg tid 5.5 to 1 mg/kg bid</td>
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<tr>
<td>Trazodone</td>
<td>2 to 5 mg/kg prn to 8-10 mg/kg bid-tid</td>
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<td>Carbamazepine</td>
<td>4-8 mg/kg bid to tid 2-6 mg/kg sid-bid</td>
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<td>Phenobarbital</td>
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<td>Gabapentin</td>
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<td>Potassium bromide</td>
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<td>Levetiracetam</td>
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<td>Pregabalin</td>
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<td>Dextromethorphan</td>
<td>2 mg/kg bid –qid .5-2 mg/kg up to tid</td>
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30. Notari L. Combined use of selegiline and behaviour modifications in the treatment of cases in which fear and phobias are involved: a review of 4 cases. In: Mills et al. Current Research in Veterinary Behavioral Medicine, Purdue Press, 2006;267-269
36. Bergman L. To sleep, perchance to dream: REM sleep disorder and interdog aggression. Proc. ACVB/AVSAB Symposium, Atlanta, 2010, 5