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Behavior Medications: Which Medication, Which Patient?

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The best treatment approaches in veterinary behavioral medicine are often multimodal. At the core of state-of-the art multimodal treatment is smart, rational, and effective use of behavioral medication. Which medication do you choose for which condition, how do you know if it is working, what are the risks, and what advantages might you gain for your patient by combining medications?

The keys to effective treatment of behavioral problems are no different than for somatic medical problems:

- Identify the constellation of relevant signs/changes.
- Nest these within a diagnosis or diagnoses.
- Understand the factors that contribute to the development and maintenance of the diagnosis.
- Use your treatment to modulate these factors in a manner that can be measured and tracked by alterations in the clinical signs and profile.

Unfortunately, practitioners often feel helpless in the face of behavioral complaints because the signs seem so nonspecific. As is true in internal medicine, relevant clinical signs in behavioral medicine are not specific, but too few veterinarians are taught to recognize and quantify behavioral signs and to do so as part of routine evaluation. As for all other conditions in veterinary medicine, the best and most successful treatment is early treatment. The earlier appropriate behavioral medication is prescribed, the less the patient will suffer from fear, anxiety, or aggression and the cognitive and social changes that result from these pathologic conditions.

A helpful approach to understanding the thought process involved in choosing medications is to consider practical diagnostic examples, review the signs exhibited in these examples and the regions of the brain involved, and review effects of medications on those regions and on neurochemicals affecting these regions. An advantage of this approach is that the clinical signs provide a baseline against which targeted signs can be assessed for response to medication and other treatment.

RECOGNIZING CLINICAL SIGNS AND COMORBID CONDITIONS

Consider patients with 2 common behavioral diagnoses: separation anxiety and noise reactivity

phobia. These are commonly comorbid conditions,[1] as is the rule among anxiety disorders.[2,3] Because the development of both conditions ranges from subtle to explosive, veterinarians should screen for them at each appointment using a standardized clinical assessment tool[4] to identify and treat them early. Results of these routine clinical assessments should be recorded and evaluated to determine whether they meet diagnostic criteria (**Box 1**). Signs of distress should be evaluated in currency and terminology that are meaningful for the individual patient because the most commonly reported behaviors (elimination, destruction, excessive vocalization) are only the most readily apparent and easily recognizable signs of anxiety for the clients and veterinary team. Drooling, panting, freezing, withdrawal, and cognitive signs of anxiety are less commonly diagnosed because they are less apparent to people, but dogs displaying them may be even more profoundly affected than dogs that show more obvious signs (**Box 2** lists signs of anxiety).

Dogs that are distressed when exposed to noises or storms but do not meet the criteria for a noise phobia may best be classified as "reactive" and assessed for treatment. The risk for worsening in these dogs is nontrivial. Even the mildest signs should be treated if a dog has any history of reacting to noises.[6] Clients may insist that they can simply hold the dog while it pants and shakes or that the dog calms itself by hiding in the closet. In fact, these patients are suffering and need behavioral medication.

Video is a powerful tool for accurate diagnosis and an even better way to assess response to medication and other treatment.

CHOOSING MEDICATIONS ACCORDING TO PATIENT PRESENTATION

When choosing medication for patients with separation anxiety, noise reactivity, or both, practitioners should be guided by expected changes in relevant signs, regions of the brain that may be affecting those signs, and distributions of neurochemical receptors in the regions that may be affected by the medication chosen. Some dogs show suites of correlated behaviors; for example, salivation appears to be more common in dogs that freeze and become immobile. If we alter the salivation, do we alter any part of the feedback system that maintains the anxiety? In fact, by

BOX 1. Diagnostic Criteria for Common Behavioral Disorders[5]

Separation anxiety
Behavioral condition resulting in the following signs of distress exhibited by the patient only in the absence of, or lack of access to (a virtual absence), the client:

- Physical (injury, uneven nail wear, scored teeth)
- Physiologic (salivation, increased heart rate)
- Behavioral, cognitive, or emotional (social withdrawal, agitation, lack of focus)

Noise phobia

- Behavioral abnormality resulting in profound, nongraded, extreme response to noise, manifested as intense avoidance, escape, or anxiety, associated with sympathetic nervous system signs.
- Dogs can shut down and freeze or run without caution.
- Decreased sensitivity to pain or social stimuli is often concomitant.
- Once established, repeated exposure results in an invariant pattern of response, but not all dogs show a full-blown invariant response.

Panic disorder/panic

- Behavioral abnormality resulting in a sudden, all-or-nothing, profound, abnormal response that results in extremely fearful behaviors (catatonia, mania, escape) where the provocative stimulus may be unknown/unclear, situational, internal, and/or generalized.
- Differs from conditions involving phobias, where the provocative stimulus is more discrete and identifiable, and where the level of distress characteristic of panic may not be achieved.
- The term *panic disorder* should be restricted to a described pattern of like events.
- A *panic event* is a singular or infrequent event where the patient exhibits these behaviors, but the data are insufficient to determine whether the consistent pattern exists as required for panic disorder.
- The risk that a patient will experience another panic event after having had one is great.

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affecting salivation we may affect related regions of the amygdala associated with distress.[7]

Medications commonly used to treat fears, anxieties, and aggression in dogs are listed in **Table 1**. Many other medications used to treat some aspect of behavioral abnormalities are beyond the scope of this article and so are not discussed here (but see Overall 2013[5]).

Table 1 compares many of these medications, by class, with respect to their effects on noradrenaline/norepinephrine (NA/NE) and serotonin (5-HT) receptors and sedation and anticholinergic effects. **Table 2** indicates the relative effects of these medications on receptor classes.

CONSIDERING RISK FACTORS

Because so many behavioral conditions are comorbid or have wildly different behavioral presentations within a diagnosis (eg, dogs with noise phobia can freeze and hide or may run and destroy in panic), the best approach is probably one that allows combination of medications to address the neurochemical profile of the behavioral abnormality but minimizes somatic risk. **Box 3** provides a general model for such an approach.

BOX 2. Common Nonspecific Signs of Anxiety[5]

- Urination
- Defecation
- Anal sac expression
- Panting
- Increased respiration and heart rates
- Trembling/shaking
- Muscle rigidity (usually with tremors)
- Lip licking
- Nose licking
- Grimace (retraction of lips)
- Head shaking
- Smacking or popping lips/jaws together
- Salivation/hypersalivation
- Vocalization (excessive and/or out of context); often frequent repetitive sounds (including high-pitched whines, like those associated with isolation)
- Yawning
- Immobility/freezing or profoundly decreased activity
- Pacing and profoundly increased activity
- Hiding or hiding attempts
- Escaping or escape attempts
- Body language of social disengagement (turning head or body away from signaler)
- Lowering of head and neck
- Inability to meet a direct gaze
- Staring at some middle distance
- Body posture lower (in fear, the body is extremely lowered and tail tucked)
- Ears lowered and possibly droopy because of changes in facial muscle tone
- Mydriasis
- Scanning
- Hypervigilance/hyperalertness (may be noticed only when dog or cat is touched or interrupted; animal may hyperreact to stimuli that otherwise would not elicit this reaction)
- Shifting legs
- Lifting paw in an intention movement
- Increased closeness to preferred associates
- Decreased closeness to preferred associates
- Profound alterations in eating and drinking (acute stress is usually associated with decreases in appetite and thirst; chronic stress is often associated with increases)
- Increased grooming, possibly with self-mutilation
- Decreased grooming
- Possible appearance of ritualized or repetitive activities
- Changes in other behaviors, including increased reactivity and increased aggressiveness (may be nonspecific)

Most of these medications are metabolized through the cytochrome P-450 system. **Table 3** lists inducers and inhibitors that affect how these behavioral compounds are metabolized. Understanding such P-450 enzyme system interactions allows medication adjustment to minimize adverse events. Although most available information is for humans, some studies have measured CYP effects for dogs,[11–14] with particularly strong conservation for CYP 1A enzymes. Isoforms are sufficiently similar between humans and dogs that inference from human information may serve as a good precaution.

TAILORING THERAPY: CLINICAL EXAMPLES

Applying an approach that seeks to tailor treatment in behavioral medicine to specific presentations and targeted signs is not difficult but does require thought.

Separation Anxiety

A dog with separation anxiety that involves salivation will benefit from any anticholinergic agent because the undesirable effect may be part of a reinforcing feedback cycle. Medications classified as anticholinergics are not used in

TABLE 1 Relative Effects of Medications on Noradrenaline/Norepinephrine and Serotonin Receptors and for Sedation or Anticholinergic Effects[8–10]

PARENT COMPOUND	NA/NE	5-HT	POTENTIAL FOR SEDATION	POTENTIAL FOR ANTICHOLINERGIC EFFECTS
TCAs				
Imipramine	+++	++	Moderate	Moderate
Amitriptyline	++	++	High	High
Nortriptyline	+	+	Moderate	Moderate
Clomipramine	++	+++	High	High
SSRIs				
Fluoxetine	+	+++	Moderate	Low
Paroxetine		++	High	High
Sertraline	+	+++	Moderate	Moderate
Fluvoxamine		+++	Moderate	
Citalopram		+++	Moderate	Moderate
SARIs				
Trazodone		++	High	Low
Benzodiazepines				
Alprazolam			Low to moderate	
Lorazepam			Low to moderate	
Diazepam			High	
Clonazepam			Moderate	
α-Agonists				
Clonidine			Moderate	
OTM dexmedetomidine			Low	

+, some effect; ++, moderate effect; +++, large effect; 5HT, 5-hydroxytryptamine (serotonin); NA/NE, noradrenaline/norepinephrine; OTM, oral transmucosal; SARI, serotonin antagonist/reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

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veterinary medicine; however, many medications have anticholinergic effects as part of their pharmacologic profile. Anticholinergic effects are common for many tricyclic antidepressants (TCAs), and although they have the potential for undesirable events, in this example, a medication with some anticholinergic effect may be beneficial.

Additionally, a region in the central nucleus of the amygdala contributes to salivation, suggesting that medications that affect serotonin and norepinephrine regulation will be useful.

Accordingly, amitriptyline or clomipramine may be rational choices, but clomipramine comes in a canine form (Clomicalm) with scored tablets, is a relatively more specific compound because of its intermediate metabolites, and affects a wide range of receptor types. It may be a good choice here. If the dog is vocalizing or blocks or destroys doors through which clients leave, the behaviors are associated with affiliation and social needs and loss. A medication that has a profound effect on 5HT receptors, especially the 5-HT_{1A} receptors that are involved in social anxieties, may benefit the patient.

Unfortunately, medication costs and formulations change frequently. What do we do if clients cannot afford or obtain any formulation of clomipramine, a particular problem in the United States in the past few years? By reverting to the idea that distress about absences lies at the core of separation anxiety, pick a selective serotonin reuptake inhibitor (SSRI) affecting the 5-HT_{1A} receptor because this receptor

TABLE 2 Relative Medication Effects on Most Common Receptors (Antagonist Role Unless Otherwise Specified)[8–10]

PARENT COMPOUND	5-HT 1A	5-HT 1B	5HT1D	5HT2A	5-HT 2B	5-HT 2C	5-HT 3	α1A	α 2A	α 1B	α 2B	D1	D2	H1[a]	ACh
TCAs															
Imipramine				++		++		++						+++	+++
Amitriptyline	+			+++		+++		+++						+++	+++
Nortriptyline	+			+++		+++		+++						+++	+++
Clomipramine				+++		+++	+++	+++				+	++	+++	+++
SSRIs															
Fluoxetine	+++	+	+	+	+	++	+	+				+			
Paroxetine	++													+	+++
Sertraline	+++							+++							
Fluvoxamine[b]															
Citalopram	+++														
SARIs															
Trazodone	++			+++		+		+						+	
α-Agonists															
Clonidine								+	+	++	+++				
OTM dexmedetomidine									+++						
β-blockers/antagonists															
Propranolol										++	++				
Pindolol										++	++				

+, some effect; ++, moderate effect; +++, large effect; ACh, acetylcholine; SARI, serotonin antagonist/reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
[a]Potency at the H1 receptor correlates with weight gain in humans.[9]
[b]Primarily affects transporters.

has been widely experimentally associated with social anxieties. If broader coverage is needed, combine it with a less specific TCA (amitriptyline, nortriptyline) and lower the dosage of both.

Separation Anxiety Plus Noise Reactivity

What are the concerns if the patient also reacts badly to noises? Here, we need to distinguish between panicking and being distressed (**Box 1**). If the dog is distressed, any of the benzodiazepines may lower its reactivity level by providing central inhibition of responses. Benzodiazepines can be calming agents, antianxiety agents, or sedative and analgesic agents, depending on dose, route, and choice of medication. Alprazolam is considered the only truly "panicolytic" benzodiazepine. These compounds should not be used to treat patients in households where humans have addiction or substance abuse difficulties.

Dogs that are distressed about noise or departures may respond to lorazepam and become calmer, while others may need longer-lasting benzodiazepines (diazepam, clonazepam), which may also make them sleep more. Additional and deeper sleep may not always be an adverse or sedative effect of a behavioral medication, but with long-term use benzodiazepines can disrupt natural sleep rhythms. This is not a major concern for short-term treatment.

Anxious dogs likely have interrupted sleep cycles; clients often say they notice that once the dog begins to respond to medication, the dog sleeps longer or more deeply. Good, restorative sleep should be a treatment goal. In contrast, excessive sedation, including persistent cognitive impairment, lack of motor coordination, or paradoxical excitement, is an undesired effect. The key with benzodiazepines is finding the right dose for the patient; these medications have highly variable effects. Having clients test benzodiazepines for adverse events, such as excessive sedation or paradoxical excitation, when no stimulation is expected is an important step. If no adverse effects are observed, clients should then help test and record the effects of increasing dosages to see if they can find one that provides relief.

Clonidine, an $\alpha 2$ agonist, may also aid distressed dogs by decreasing both central and peripheral signs of sympathetic arousal. At higher dosages, clonidine can be both sedative (impairing cognition) and hypotensive (rendering patients

BOX 3. Sample Combinations of Medications That May Allow Dosage of Each to Be Lowered With Enhanced Efficacy[5]

- Amitriptyline (TCA) [anxiety-related diagnosis] + fluoxetine (SSRI) [anxiety-related diagnosis]
- Amitriptyline (TCA) [anxiety-related diagnosis] + fluoxetine (SSRI) [anxiety-related diagnosis] + alprazolam (BZD) [panic/phobia/severe distress with known trigger]
- Amitriptyline (TCA) [anxiety-related diagnosis] + alprazolam (BZD) [panic/phobia]
- Fluoxetine (SSRI) [anxiety-related diagnosis] + alprazolam (BZD) [panic/phobia]
- Clomipramine (TCA, relatively specific) [anxiety-related diagnosis] + alprazolam (BZD) [panic/phobia]
- Clomipramine (TCA, relatively specific) [anxiety-related diagnosis] + diazepam (BZD) [panic/phobia]—could be fairly sedating
- Amitriptyline (TCA) [anxiety-related diagnosis] + diazepam (BZD) [panic/phobia]—could be fairly sedating
- Paroxetine (SSRI) (social anxiety) + alprazolam (BZD) [panic/appetite stimulation in cats]

BZD, benzodiazepine; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

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TABLE 3 Behavioral Medications That Act as Substrates to Inhibit or Induce the CYP Enzyme in Humans

P-450 ENZYME	SUBSTRATE	INHIBITOR	INDUCER
CYP 1A2	TCAs Fluvoxamine Mirtazapine Duloxetine	Fluvoxamine Fluoxetine Paroxetine Sertraline Some TCAs Fluoroquinolones[a]	Phenobarbital[a] Carbamazepine[a] Phenytoin[a]
CYP 2A6			Barbiturates[a]
CYP 2B6			Phenobarbital[a]
2 CYP C9/ CYP 2C9/10	Sertraline Fluoxetine Amitriptyline	Fluvoxamine Fluoxetine Sertraline Fluconazole[a] Sulfaphenazole[a]	Carbamazepine[a] Phenobarbital[a] Phenytoin[a]
2C19/CYP 2C19	Citaprolam Sertraline Clomipramine Imipramine	Fluvoxamine Fluoxetine Sertraline Omeprazole[a]	Carbamazepine[a]
CYP 2D6	Fluoxetine Fluvoxamine Citalopram Duloxetine Paroxetine Venlafaxine Trazodone Nefazodone TCAs	Duloxetine Fluoxetine Paroxetine Norfluoxetine Citalopram Sertraline Some TCAs	
CYP 2E1			
CYP 3A4	Nefazodone Sertraline Venlafaxine Trazodone TCAs	Fluvoxamine Norfluoxetine TCAs, barbiturates Dexamethasone/long-term glucocorticoids Phenytoin St. John's wort[b] Flucloxacillin Nefazodone[a] Fluconazole[a] Ketoconazole[a] Cimetidine[a] Macrolides: clarithromycin, erythromycin[a] Propofol	Carbamazepine[a] Barbiturates[a] Dexamethasone/long-term glucocorticoids[a] Phenytoin[a] St. John's wort[a,b] Flucloxacillin[a]

Inducers slow the rate at which the substrate medication is available and lower the amount available. Inhibitors increase the rate at which the substrate medication is available and increase the amount available. There are few detailed studies for dogs, but the patterns identified to date do not deviate from these, so consideration should be given to monitoring patients carefully when medications from these classes are combined. TCA, tricyclic antidepressant.
Adapted from Overall.[5]
[a]*Medications used for nonbehavioral conditions.*
[b]*Hyperforin is the compound that is the inducer.*

unstable on stairs or as they move through complex environments). If these effects appear, lowering the dose may ameliorate them.

Trazodone, a serotonin antagonist/reuptake inhibitor (SARI), may help the dog to calm its activity level because the main effect of this drug is a slightly sedative one—trazodone increases sleep time,[15–17] and its receptor profile (5-HTA/B antagonist, partial 5-HT_{1A} agonist) is consistent with this.

Panic

If the dog is panicking, there are 2 additional suitable choices. The first, alprazolam, can be given before or during the distressing event. In fact, if it is given regularly (usually q12h but up to q6h) before anticipated events, it can raise the threshold for reaction but provide central inhibitory effects, as well as peripheral effects on muscle tension that may accompany and provide a positive feedback response associated with panic.

The second choice is dexmedetomidine, which has anxiolytic, sedative, analgesic, and sympatholytic properties.[18] As an oral transmucosal (OTM) gel (Sileo; zoetisus.com), it has no first-pass effects; instead, it directly exerts agonist effects on presynaptic α2 receptors in the locus ceruleus. The locus ceruleus is the region of the brainstem that gives rise to all NA/NE brain tracts and is where sympathetic arousal may originate and is modulated. In essence, this region is the source of anticipatory anxiety and arousal. Accordingly, without involving the CYP 450 enzyme system, OTM dexmedetomidine may have profound panicolytic effects and may prevent and/or modulate the arousal that makes it so difficult for humans to use any behavioral or environmental management strategies or for dogs to use any operant or cognitive-behavior management skills they may have learned.

Nausea

With both separation anxiety and noise phobia/reactivity, dogs may feel nauseous. Distressed dogs cannot eat because of antagonism of parasympathetic effects due to sympathetic arousal. However, the distress itself may contribute to nausea. For dogs that retch, salivate, chew on nonfood substances, have diarrhea before or after the event, stop eating before the event, and take a long time to eat after the event, we should consider whether maropitant (Cerenia; cereniadvm.com), the neurokinin 1 receptor antagonist/substance P blocker, could be beneficial. This compound may have a role in directly treating aspects of depression, fear, and anxiety[19] but may be helpful for the more immediate gastrointestinal effects that may be associated with distress.

In dogs with combined abnormalities that cause them to react to noise and absences, medications from 2 to 4 classes may need to be combined to achieve maximal resolution of signs. As to be expected from the patterns of receptor response, when medications that share a direct mechanism of action and/or a potential adverse effect are combined (eg, sedation, shared CYP 450 enzymes), dosages should be lowered. Occasionally, frequencies may be altered, rather than dosages lowered, depending on the dog's response. If 2 medications that are combined both affect serotonin, reduce the dose of both to minimize the risk for serotonin syndrome. This condition is rare and usually idiopathic, and data in dogs are lacking; however, it can be tragic. Although not discussed here, monoamine oxidase inhibitors (eg, selegiline) should not be combined with TCAs, SSRIs, or SARIs.

SUMMARY

Behavioral medicine and neuroscience are about pattern recognition. This brief introduction to thinking in a neurobehavioral mechanistic manner is intended to introduce clinicians to how to recognize and use relevant patterns for the benefit of the patients. We are learning more about genetic and functional patterns daily, and new applications for medications may result. By using the tables in this article to inform medication choice and to become comfortable with a few different treatment combinations, clinicians can make great improvements in their patients' mental health and in everyone's quality of life. **TVP**

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