B - Behaviour

QUICK SUMMARY OF HOW AND WHY THREE KEY DRUGS WORK

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Rationale: The addition of psychotherapeutic agents to routine behavioral treatments, such as behavioral and environmental modification, has lead to better and faster treatment outcomes. In addition to facilitating better treatment of domestic animals and humans, psychopharmacological developments have permitted hypotheses about underlying mechanistic pathology to be tested. Mere treatment of non-specific behavioral complaints and signs is outdated (eg., treat barking by cutting the vocal cords) and has been replaced with an approach that includes ensuring that you meet the criteria for diagnosis, prior to treatment, followed by treatment that addresses the specific mechanism underlying the neurochemical contribution to the pathology (1).

The use of medication should occur and is most effective as part of an integrated treatment program. There is no substitute for the hard work involved in behavior modification; however, some medications may be able to make it easier to implement the modification (2-4). Those seeking 'quick fix' solutions will doubtless be disappointed: inappropriate drug use will not alter the processes or environments that produced the behavior. While medication, alone, may render an animal globally less anxious, if the animal is still being provoked my social or physical environmental stimuli the benefit of treatment with medication will be minimized. It is partly this facile and inappropriate use of medication that has led many practitioners to falsely believe that medication does not work. Nothing could be further from the truth: the newer serotonin-affecting medications, protective neutraceutical, and enhanced dietary regimes have a huge potential improve life for troubled pets and their distressed people. In fact, rational drug use should now minimally be considered part of basic humane treatment of our patients. The 3 most commonly used - and most useful drugs - in veterinary behavioral medicine come from 3 classes: benzodiazepines (alprazolam); tricyclic antidepressants (TCAs: amitriptyline, clomipramine); and selective serotonin re-uptakes inhibitors (SSRIs: fluoxetine).

Adverse effects: The neurotransmitters affected by behavioral medications are acetylcholine, serotonin, norepinephrine (noradrenaline), dopamine, gamma amino butyric acid (GABA), and excitatory amino acids. Common adverse effects of psychotherapeutic drugs are usually caused by a blockage of the muscarinic acetylcholine receptors, which have diffuse connections throughout the brain. These 'common' side effects are actually quite rare and generally manifest themselves as transient changes in GI function or heart rate. If these side effect ARE NOT transient, clients need to understand that their pet may be experiencing a serious problem. For this reason, it is important to encourage clients to help monitor both their anima;'s response to the medication, and any side effects that they may have. Clients can easily learn to take pulse rates. Slight increases in pulse rate when treated with any medications affecting norepinephrine - as most the anti-anxiety agents do - are not worrisome. Huge, sustained increases are problematic. If clients know that their dog's resting heart rate is 65 bpm and with medication this changes to 150 bpm, they can immediately bring this change to their vet's attention. Likewise, if the increase is minor (65 to 75 bpm) they can relax and not worry. Educated clients will monitor their pets better, will be more willing to use medications and behavior mod appropriately, and will also be less likely to take the veterinarian's time needlessly. While many benzodiazepines (BZ) can be sedative, newer BZ have decreased sedative effects. Still, because dogs and cats, like humans, can experience a huge range of effects when given a BZ, clients should be encouraged to give any BZ when they can monitor the patient. This practice is extremely helpful in ensuring that we recognize

animals with atypical or serious sedative responses so that we can find more appropriate medications with which to treat them.

Most behavioral drugs are metabolized through renal and hepatic pathways so knowledge of baseline values is essential. That said, these medications can be used in compromised animals if adjustments are made and the animal is monitored behaviorally and biochemically.

All psychotropic medications can interact with other medications. For example, use of most anti-anxiety agents will cause thyroidal values - whether or not supplementation is involved - for read falsely low. Many of serotnergic agents are thought to lower seizure thresholds and so are recommended with caution in patients treated with seizures. That said, there is now evidence in both the human and canine literature that anxiety may lower seizure thresholds and so treatment of the anxiety may allow the patient to successfully decrease the amount of seizure medication needed.

Efficacy and mechanism of action: It's important for clients to understand that newer, more specific, more efficacious drugs have a relatively long lag time between initiation of treatment and apparent changes in the patient's behavior. This delay is due to the mechanism of action of the tricyclic antidepressants (TCAs) and the selective serotonin re-uptake inhibitors (SSRIs) which employ second messenger systems to alter transcription of receptor proteins.

Serotonin (5-HT) receptors are all G-protein-coupled receptors. There are 14 identified classes of serotonin receptors. The 5-HT_1 receptors are linked to the inhibition of adenylate cyclase and affect mood and behavior. Presynaptic 5-HT_{1A}-receptors predominate in dorsal and median raphé nuclei; post-synaptic 5-HT^{1A}-receptors predominant in limbic regions (hippocampus and septum) and some cortical layers. Activation of pre-synaptic receptors by agonists results in decreased firing of serotonergic neurons leading to transient suppression of 5-HT synthesis and decreased 5-HT release; activation of post-synaptic receptors decreases firing of post-synaptic cells. These are 'thermostatic' effects, not integrated outcomes of receptor activation. The overall effect depends on regulation of second messengers (cAMP, Ca^{2+}, cGMP, IP_3) and their effects on protein kinases which then alter neuronal metabolism and receptor protein transcription (5). The subclasses of 5-HT receptors vary in their affects. 5-HT_{1A} receptors affect mood and behavior. 5-HT_{1D} receptors affect cerebral blood vessels and appear to be involved in the development of migraine. These last two classes of receptor subtypes are the primary focus of many behavioral drugs. Urinary excretion of 5-HIAA (5-hydroxy indoleacetic acid) is a measure of 5-HT turnover and has been used to assess neurochemical abnormalities in human psychiatric patients, and has potential in this regard for veterinary behavioral medicine.

Neutraceuticals designed to augment 5-HT or 5-HT supplements may not engender the same response as to pharmacologic agents because 5-HT does not pass easily through the blood brain barrier (BBB), and instead requires the help of a transport protein. This transport protein is also used to move other amino acids across the BBB, and so - even if 5HT containing substances are absorbed unchanged from the GI tract, they may be excreted depending on the pharmacodynamics of the other amino acids present (6).

Noradrenaline / norepinephrine (NE): The most prominent collection of noradrenergic neurons is found in the *locus coeruleus* of the grey matter of the pons and in the lateral tegmental nuclei. There is also a cluster in the medulla. NE has been postulated to affect (1) mood [NE decreases in depression and increases in mania], (2) functional reward systems, and (3) arousal.

Dopamine: The distribution of dopamine in the brain is non-uniform, but is more restrictive than that of NE. Dopaminergic nuclei are found primarily in: (1) the *substantia nigra pars compacta* which projects to the striatum and is largely concerned with coordinated movement; (2) the ventral tegmental area which projects to the frontal and cingulate cortex, *nucleus acumbens*, and other limbic structures; and (3) the arcuate nucleus of the hypothalamus which projects to the pituitary. A large proportion of the brain's dopamine is found in the *corpus striatum*, the part of the extrapyramidal system concerned with coordinated movement.

Dopamine is metabolized by monamine oxidase (MAO) and catechol-O-methyl transferase (COMT) into dihydroxyphenyl acetic acid (DOPAC) and homovanillic acid (HVA). HVA is used as a peripheral index of central dopamine turnover in humans, but this use has been little explored in veterinary medicine. All dopaminergic receptors are G-protein-coupled transmembrane receptors. The D_1 receptors exhibit their post-synaptic inhibition in the limbic system and are affected in mood disorders and stereotypies. The D_2, D_3, and D_4 receptors are all affected in mood disorders and stereotypies. Excess dopamine, as produced by dopamine releasing agents (amphetamines and dopamine agonists, like apomorphine) is associated with the development of stereotypies. Because of this - and because acepromazine is a neuroleptic agent that scrambles memory but does not prevent or treat anxiety - ACEPROMAZINE SHOULD NEVER BE USED AS A BEHAVIORAL MEDICATION OR AS A TREATMENT FOR STORM PHOBIAS.

Gamma amino butyric acid (GABA): GABA,

the inhibitory neurotransmitter found in short interneurons, is produced in large amounts only in the brain and serves as a neurotransmitter in ~30% of the synapses in the human CNS. The only long GABA-ergic tracts run to the cerebellum and striatum. GABA is formed from the excitatory amino acid (EEA) glutamate via glutamic acid decarboxylase (GAD), catalyzed by GABA-transaminase (GABA-T) and destroyed by transamination. There are two main groupings of GABA receptors - $GABA_A$ and $GABA_B$. $GABA_A$ receptors, ligand-gated ion channels, mediate post-synaptic inhibition by increasing Cl- influx. Barbiturates and benzodiazepines are a potentiators of GABAA; however they do so by increasing the amount of time channels remain open - a relatively non-specific change. It is for this reason why these are NOT suitable behavioral medications, and why one is more likley to get a sedated, rather than a less anxious dog, when the dog is treated with phenobarbital for behavioral reasons. $GABA_B$ receptors are involved in the fine-tuning of inhibitory synaptic transmission: presynaptic $GABA_B$ receptors inhibit neurotransmitter release via high voltage activated Ca^{++} channels; postsynaptic $GABA_B$ receptors decrease neuronal excitability by activating inwardly rectifying K^+ conductance underlying the late inhibitory post synaptic potential.

GABA also has a variety of tropic effects on developing brain cells. During ontogeny GABAergic axons move through areas where other neurotransmitter phenotypes are being produced, and so may be related to later monoaminergic imbalances. The extent such ontogenic effects are relevant for behavioral conditions is currently unknown but bears investigating.

EAAs (glutamate, aspartate, and, possibly, homocysteate): EEAs have a role as central neurotransmitters and are produced in abnormal levels in aggressive, impulse, and schizophrenic disorders. The main fast excitatory transmitters in the CNS are EEAs. Glutamate, widely and uniformly distributed in the CNS, is involved in carbohydrate and nitrogen metabolism. It is stored in synaptic vesicles and released by Ca^{2+} dependent exocytosis, so calcium channel blockers may affect conditions associated with increased glutamate. Both barbiturates and progesterone suppress excitatory responses to glutamate. Pre-synaptic barbiturates inhibit calcium uptake and decrease synaptosomal release of neurotransmitters, including GABA and glutamate.

Roles for neuronal stimulation, synaptic plasticity, and receptor protein transcription and translation: What makes TCAs and SSRIs special and why are they so useful for anxiety disorders? The key to the success of these drugs is that they utilize the same second messenger systems and transcription pathways that are used to develop cellular memory or to "learn" something. This pathway involves cAMP, cytosolic response element binding protein (CREB), brain derived neurotrophic factor (BDNF), NMDA receptors, protein tyrosine kinases (PTK) - particularly Src - which regulate activity of NMDA receptors and other ion channels and mediates the induction of LTP (long-term potentiation = synaptic plasticity) in the CA1 region of the hippocampus.

There are two phases of TCA and SSRI treatment: short-term effects and long-term effects. Short-term effects result in a synaptic increase of the relevant monoamine associated with re-uptake inhibition. The somatodendric autoreceptor of the pre-synaptic neuron decreases the firing rate of that cell as a thermostatic response. Regardless, there is increased saturation of the post-synaptic receptors resulting in stimulation of the -adrenergic coupled cAMP system. cAMP leads to an increase in PTK as the first step in the long-term effects. PTK translocates into the nucleus of the post-synaptic cell where it increases CREB, which has been postulated to be the post-receptor target for these drugs. Increases in CREB lead to increases in BDNF and tyrosine kinases (e.g., trkB) which then stimulate mRNA transcription of new receptor proteins. The altered conformation of the post-synaptic receptors renders serotonin stimulation and signal transduction more efficient.

Knowledge of the molecular basis for the action of these drugs can aid in choosing treatment protocols. For example, the pre-synaptic somatodendritic autoreceptor is blocked by pindolol (a -adrenoreceptor antagonist) so augmentation of TCA and SSRI treatment with pindolol can accelerate treatment onset. Long-term treatment, particularly with the more specific TCAs (e.g., clomipramine) and SSRIs, employs the same pathway used in LTP to alter reception function and structure through transcriptional and translational alterations in receptor protein. This can be thought of as a form of *in vivo* "gene therapy" that works to augment neurotransmitter levels and production thereby making the neuron and the interactions between neurons more coordinated and efficient. In some patients short-term treatment appears to be sufficient to produce continued "normal" functioning of the neurotransmitter system. That there are some patients who require life-long treatment suggests that the effect of the drugs is reversible in some patients, further illustrating the underlying

heterogeneity of the patient population considered to have the same diagnosis.

Monitoring: Monitoring of side-effects is critical for any practitioner dispensing behavioral medication. The first tier of this involves the same tests mandated in the pre-medication physical and laboratory evaluation. Age-related changes in hepatic mass, function, blood flow, plasma drug binding, et cetera cause a decrease in clearance of some TCAs, so it is prudent to monitor hepatic and renal enzymes annually in younger animals, biannually in older, and always as warranted by clinical signs. Adjustment in drug dosages may be necessary with age.

It is generally preferable - but not necessarily required - to withdraw most patients from one class of drug before starting another. For most medications this is done so that one can be sure which medication is associated with any noted change in behavior. When changing between SSRIs and MAOIs a washout period is mandatory because of the potential for serotonin syndrom.....the recommended drug-free time in humans and dogs is two weeks (2 + half-lives: the general rule of thumb for withdrawal of any drug).

Polypharmacy: Oddly, because of the cytochrome systems that metabolize medication, it may be safer for the animal and more efficacious in terms improvement of the condition to combine medications. When medications are combined a knowledge of side effects and specific mechanisms of action is essential. That said, medications within related classes can usually be combined and such combination can allow a lower dose of each of the medications to be given. Medications of different classes can often be combined, if the potential side effects are compatible, and if the practitioner has a clear understanding of what conditions will or should respond to each medication.

For example, tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) can be combined with each other, and, if needed, with other medication within the class. For this to be done rationally, however, understanding potentiation of effect and side effects is essential. TCAs generally exert their largest effects on serotonin (5-HT) receptors, norepinephrine (NE) receptors, and some histaminic receptors (H). Additionally, they can have effects on some of the adrenergic receptors. The latter is important primarily when premedication for anesthesia is involved. SSRIs primarily affect 5-HT receptors, and most have an affinity for the 5-HT1a subtype receptor. Additionally, there are some weak effects on NE receptors. TCAs that are less specific (eg, amitiptyline) and SSRIs that are more specific (eg, fluoxetine) will be the easiest to combine since the overlap effects on the receptor will be less, while the generalized sensitization of the receptors in the class will be augmented.

Combination treatment allows the clinician to use the lower end of the dosage for both compounds which minimizes side effects while maximizing efficacy. Furthermore, benzodiazepines can be used to blunt or prevent acute anxiety-related outbursts on an as needed basis in patients for whom daily treatment with a TCA or an SSRI is ongoing. Together, the combination of benzodiazepines and TCAs / SSRIs may hasten improvement and prevent acute anxiety-provoking stimuli from interfering with treatment of more regularly occurring anxieties.

When stopping a drug, weaning is preferred to stopping abruptly (7). A model for how to do this is found below (7). Weaning minimizes potential central withdrawal signs, including those associated with serotonin dyscontinuation syndrome (8,9) and allows determination of the lowest dosage that is still effective. If patients are withdrawn fully, rather than weaned from medication, they may not have the same response to the medication that they had originally. Patients with dyscontinuation or cessation syndrome become moody and lethargic, but these effects usually pass within a week. If they do not, re-assessment of the wisdom of stopping medication is warranted. Medications that have the longest $t_{1/2}$ of intermediate metabolites (eg, fluoxetine) are less likely to cause problems when withdrawn quickly than are those with short half-lives or no functional intermediate metabolites (eg, paroxetine). However, SSRIs that have the greatest *in vivo* reuptake capabilities (eg, paroxetine) may be more at risk for involvement in serotonin syndrome. Long-term treatment may be the rule with many of these medications and conditions, but maintenance may be at a considerably lower level of drug than was prescribed at the outset. The only way the practitioner will discover if this is so is to withdraw the medication slowly.

Because of these patterns, it is best NOT to withdraw animals from medication prior to anesthesia, but instead to adjust the pre-medication sedation so that fewer interactions - particularly of the adrenegic variety - can be expected.

Finally, many animals appear to stop responding to medication. Staying the course may be the best decision in some of these cases because the CPY system is an inducible one, and multiple medication changes may just make the animal more - not less - refractory (10). Additionally, there is a huge range of genetic polymorphisms that determine how this system acts (11). These are all poorly understood in dogs because they

have been so little investigated. However, given their importance in human psychiatry we'd be remiss if we didn't start to believe that such patterns may no be independent of disease state. Polypharmacy can be safe, rational, and cheap, and can save animals' lives. But this is an area that really requires an understanding of how these medications act. Fortunately, the functioning of these medications is easy to understand.

Sample combinations (12) :

amitriptyline	(TCA) + fluoxetine (SSRI)
amitriptyline	(TCA) + fluoxetine (SSRI) + alprazolam (BZ)
amitriptyline	(TCA) [anxiety] + alprazolam (BZ) [panic]
fluoxetine	(SSRI) [anxiety] + alprazolam (BZ) [panic]
clomipramine	(TCA - relatively specific) [anxiety] + alprazolam (BZ) [panic]
clomipramine	(TCA - relatively specific) [anxiety] + diazepam (BZ) [panic / phobias] - could be pretty sedating
amitriptyline	(TCA) [anxiety] + diazepam (BZ) [panic / phobias] - could be pretty sedating
selegiline	(MAO-I) (cognitive dysfunction) + diazepam (BZ) [panic / phobias]
selegiline	(MAO-I) (cognitive dysfunction) + alprazolam (BZ) [panic]
paroxetine	(SSRI) (social anxiety) + alprazolam (BZ) [panic / appetite stimulation in cats]

"Gestalt" of TCA and SSRI use based on t1/2 of parent compounds and active intermediate metabolites, relative effects on NE and 5-HT, and extrapolations from multi-center human studies (7)

Diagnosis / Type of condition	First drug of choice
Narcolepsy	imipramine
Milder, relatively non-specific anxieties	amitriptyline
Milder, relatively non-specific anxieties with avoidance of sedation	nortriptyline
Social phobias / anxieties concerning social interaction	paroxetine
Panic / generalized anxiety	sertraline
Outburst aggression / related anxieties	fluoxetine
Ritualistic behavior associated with anxiety, including OCD	clomipramine

Algorithm for treatment length and weaning schedule (7)

(1) Treat for as long as it takes to begin to assess effects:
7-10 days for relatively non-specific TCAs
3-5 weeks minimum for SSRIs and more specific TCAs
PLUS
(2) Treat until "well" and either have no signs associated with diagnosis or some low, consistent level:
minimum of another 1-2 months
PLUS
(3) Treat for the amount of time it took you to attain the level discussed in (2) so that reliability of assessment is reasonably assured:
minimum of another 1-2 months
PLUS
(4) Wean over the amount of time it took to get to (1) or more slowly. Remember, if receptor conformation reverts it may take 1+ months to notice the signs of this. While there are no acute side effects associated with sudden cessation of medication, a recidivistic event is a profound "side effect". Full-blown recidivistic events may not be responsive to re-initiated treatment with the same drug and, or the same dose:
7-10 days for relatively non-specific TCAs
3-5 weeks minimum for SSRIs and more specific TCAs
TOTAL: Treat for a minimum of 4-6 months

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