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Paradigms for pharmacologic use as a treatment component in feline behavioral medicine

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Summary Veterinary behavioral medicine remains an under-supported, under-appreciated, and under-taught specialty within veterinary medicine. Neuropsychopharmacology is the aspect that has provided the field with the most scientific legitimacy, but is also one of the most hotly debated. Paradigms for use of pharmacologic intervention include firstly ruling out any underlying medical cause. If a behavioral diagnosis can be made, treatment with psychotropic medication may be considered, although their use is most effective as part of an integrated treatment program that includes behavior modification. Used without an understanding of the mechanism of action, pharmacologic intervention may only blunt or mask behavior without altering processes or environments that produced the behavior. This paper reviews specific drugs, mechanism of action of those drugs, and relevant uses are reviewed for cats.

Future advances in treatment in veterinary behavioral medicine will be pharmacological and neurophysiological. As the field of veterinary behavioral medicine expands, its paradigm will enlarge to include routine combination therapy and the implementation of neuropharmacological intervention as a diagnostic tool.

Introduction

A quarter of a century after its introduction into select veterinary curricula, veterinary behavioral medicine remains an under-supported, under-appreciated, and under-taught specialty within veterinary medicine. Oddly, the aspect that has provided the field with the most scientific legitimacy is also one of the most hotly debated: neuropsychopharmacology. It is important to acknowledge the extent to which a country's treatment 'culture' affects whether medication is prescribed. This association is clear from scientific meetings, industry-sponsored round-tables, sales data on the two pharmacologic agents licensed for use in dogs and/or cats (Clomicalm® [Novartis Animal Health]; Anipryl® [Pfizer]), discussions on list-serves, and from reading the primary literature and recent multi-authored texts (e.g., Horwitz et al., 2002). Culture and finances interact to affect attitudes toward maintaining and having pets (American Veterinary Medical Association, 2002), and the extent to which behaviors are viewed as undesirable or 'abnormal'. This is also true for humans (American Psychiatric Association, 1994).

The paradigms involving rational treatment of behavioral problems are affected by such cultural influences because interpretations of behaviors are also influenced by culture. For example, if one views 'spraying' in cats as a variant of 'normal' behavior, one is going to react differently in modify ing the cat's behavior or environment than if one views spraying as 'abnormal' or, alternatively,

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'undesirable'. Such linguistic, cultural, and epistemological arguments are doubtless the result of incomplete knowledge and a relative absence of scholarship.

Our knowledge is more complete regarding neuropharmacologic and neuropsychopharmacologic agents. In fact, the one area in veterinary behavioral medicine where repeatable data involving hypothesis testing have been collected is in neuropharmacology. While most mechanistic paradigms have involved rodent and human models, extrapolation and independent testing is possible for both cats and dog. Unfortunately, the data lag behind the possibilities. Published data show that the addition of psychotherapeutic agents to more general treatments, such as behavioral and environmental modification, have lead to better treatment outcomes (Dodman et al., 1996; Hewson et al., 1998a; Moon-Fanelli and Dodman, 1998; Overall, 1994a; Overall and Dunham, 2002a) and faster improvement (King et al., 2000a, 2003; Overall and Dunham, 2002a). Mere treatment of non-specific behavioral complaints and signs—especially for cats—is to be avoided. This outdated approach—where we treat spraying, rather than its underlying basis—has been replaced with one that includes criteria for diagnosis (see Overall, 1997a for one approach using necessary and sufficient criteria) and pursuit of treatment that addresses specific underlying the neurochemical mechanisms (Hewson et al., 1998b; Overall, 2001; Waagepetersen et al., 1999).

Paradigms for use of pharmacologic intervention

First, any underlying medical cause (FLUTD, cystitis, UTI, obstruction, anatomical abnormalities, infectious disease, neoplasia, etc) must be ruled out as part of an investigation into any behavioral complaint (Overall, 2003). Should there be no apparent underlying 'medical' or 'organic' reason for the complaint, and a behavioral diagnosis can be made, treatment with psychotropic medication may be a consideration. 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. That said, medications that affect molecular changes associated with long-term potentiation (LTP) such as the tricyclic antidepressants (TCAs) and the selective serotonin re-uptake inhibitors (SSRIs) facilitate implementation of behavioral and environmental modification (King et al., 2000a). This means that there are neither 'magic' pills nor 'quick fix' solutions. Used cavalierly and without an understanding of the mechanism of action, pharmacologic intervention may only blunt or mask behavior without altering processes or environments that produced the behavior. Furthermore, the newer, more specific, more efficacious drugs have a relatively long lag time between initiation of treatment and apparent changes in the patient's behavior associated with the medication. This delay is due to the fact that TCAs and SSRIs employ second messenger systems to alter transcription of receptor proteins (Daniel et al., 1998; Duman, 1998). Without this understanding, veterinary surgeons will not choose the right drug, will use the drug for an insufficient time, and will leapfrog through a variety of drugs—some of which may have been useful given appropriate treatment regimes—with neither personal enlightenment nor improvement in the patient's behavior. Accordingly, this paper reviews specific drugs, mechanism of action of those drugs, and relevant uses for cats.

About labels and diagnoses

Criteria for making a behavioral diagnosis and drug recommendations for specific behavioral diagnoses have been discussed elsewhere (Overall, 1997a, 1998a,b,c, 1999a,b,c, 2001). The ability to make a diagnosis is a function of our state of knowledge. As is also true for human psychiatry, our knowledge is incomplete. The fundamental problem is actually simple to understand: diagnoses are phenotypic labels for complex processes that are reflections of the integration of all organ system responses to the genetic/genomic, molecular, neurochemical, neuroanatomical, and social environments (Overall, 1997a). The labels neither accurately reflect these processes nor can they be expected to do so. Our terminology has not kept pace with what we have learned from recent advances in neurobiology, suggesting that the entire field needs a paradigm shift. That said, even in our relative ignorance of complex interactions, we can come to understand how we now think medications work, and we can develop treatment paradigms that not only take advantage of that knowledge, but which also prepare us for alterations in thought processes about conditions.

Transcending the diagnostic label

Most behavioral conditions are best represented by non-linear models (i.e., those that represent multifactorial, heterogeneous disorders). Hence, there is no one drug to treat feline 'spraying':

spraying can be a behavioral description, a non-specific sign, or a phenotypic diagnosis (Overall, 1997a, 1998a,b). Spraying can be caused by a variety of social circumstances and may be the result of the interactions of a variety of involved neural substrates. Likewise, not all feline aggression is neurochemically identical, either in impetus, or outcome (Adamec, 1975, 1990). Still, if diagnoses are made using rigorous, repeatable criteria, and if the patient population is sufficiently large, failure of some significant portion of the population to respond to one medication when another significant portion responds well suggests that there is neurochemical and/or molecular variability within the diagnosis. In human psychiatry, large, multi-centre treatment trials are common and serve to identify sub-populations of patients who share a phenotypic diagnosis but perhaps not a specific neurochemical mechanism for that diagnosis. For example, all SSRIs vary in structure so if one subpopulation responds better to one SSRI than to another in a repeatable way, a re-examination of the effect of the medication at the molecular level may suggest causal differences for the underlying condition and its heterogeneity. In this way clinical and bench neuromolecular pharmacology can work in tandem to advance understanding of the complex integration of all organ system and environmental responses that we call 'behavior'. There are currently no large-scale studies in veterinary behavioral medicine that would permit the use of the type of empiricism that is possible in human psychiatry.

By examining the neurotransmitters that the most commonly used drugs affect, the distribution of neurotransmitter tracts, the roles of synaptic plasticity and receptor protein transcription and translation, and the mechanism of action at the molecular level, we can transcend the difficulty inherent in labels and focus on the biology that is most relevant for our patients. In more simple terms this means that not all patients exhibiting the same phenotypic/phenomenological/functional diagnosis are affected for the same reasons. This is an important, albeit very simple corollary of logical thought that every veterinary surgeon can employ. Rather than viewing some cases as 'treatment failures', veterinary surgeons should appreciate that when cats do not respond to a medication commonly thought to be effective, this is a clue about an alternative mechanism. These feline patients are telling the veterinary surgeons that they are 'different'. If the patient population is sufficiently large, the practitioner will be able to begin to ask how those cats are different. The 'same' vs. 'different' comparison is the fundamental comparison that is at the foundation of all scientific investigation. It is only by returning to the patient and learning how the cat of 'failed' treatment outcome is different from the successfully treated cat that the veterinary surgeon can grow in his or her knowledge of veterinary behavioral medicine. Hence, knowledge of how modern pharmaceuticals act can be priceless.

Pre-medication considerations

Prior to incorporating behavioral pharmacology into any treatment program the following conditions must be met:

1. A reasonable diagnosis or a list of diagnoses should be formulated. This is different from a list of non-specific signs.
2. The veterinary surgeon should have some insight into the neurochemistry relevant to the condition.
3. The veterinary surgeons should have an appreciation for the putative mechanism of action of the chosen medication.
4. The veterinary surgeons should have a clear understanding of any potential side effects.
5. The veterinary surgeons and client should have some clear concept of how the prescribed drug will alter the behavior in question. Clients should receive a complete list of all potential adverse responses and should be encouraged to communicate with the veterinary surgeons at the first sign of any problem. Clients are often very distressed after a behavioral consultation and need a written reminder of situations for which they should be alert. An honest discussion of a written summary of the mechanism of action of the drugs and potential concerns is critical because it will help clients to watch for side-effects and improvements and can help the veterinary surgeons confirm or reject the diagnosis. These types of guidelines are often ignored when the medication used is an antimicrobial; however, behavioral pharmacology is always long-term compared to most antimicrobial use, and so requires greater client compliance. Knowledge enhances compliance.

Without these five guidelines, behavioral drugs may not be given long enough or at a sufficient dosage to attain the desired effect, the clients will be unable to participate in the evaluation process, there will be no objective behavioral criteria that will allow the veterinarian to assess improvement, and drug selection is liable to be similar to alchemy.

Prior to prescribing any drug a complete behavioral and medical history should be taken. Should the animal be older, suffer from any endocrine or cardiac abnormalities, be on treatments for any concurrent medical treatment, caution is urged. All animals should have complete laboratory and physical examinations. A complete laboratory evaluation in a cat includes a complete blood count, a serum biochemistry panel, a urinalysis-preferably with a culture and sensitivity (Overall et al., 2003)—a thyroid panel for older cats, and, minimally, a lead II ECG to rule out cardiomyopathy in any cat for whom cardiac disease may be a concern. The latter also allows the practitioner to monitor potential cardiac side effects of some of the commonly used medications for cats at risk. Baseline ECGs are recommended for in any human patient who has had a history of any arrhythmia, heart disease, prior drug reactions, who is on more than one medication, and who may be undergoing anesthesia or sedation. Similar protocols are recommended for cats and dogs (Nattal and Mittleman, 1984; Pouchelon et al., 2000; Reich et al., 2000; Yokota et al., 1987). Because cardiac disease in cats can be occult, routine cardiac evaluation of targeted populations is reasonable.

Most behavioral drugs are metabolized through renal and hepatic pathways therefore knowledge of baseline values is essential. Because so many of the drugs used to treat behavioral conditions are metabolized via glucuronidation, any factors that affect the urea cycle, portal circulation, or plasma proteins are important. Indirect evaluation of these functions assayed in routine laboratory evaluation include creatinine, BUN, albumin, total bilirubin, hematocrit, and red and white cell counts. Cats more sensitive to all factors affecting glucuronidation, a process that is relatively inefficient in cats. In a small study (Overall and Dunham, 2002b) 3 of 8 cats treated with TCAs and SSRIs experienced increases in ALT without clinical signs, and none of the elevations of any liver-associated enzymes reached levels seen in treatment with glucocorticoids or anti-convulsants (Center, 1995). For these cats the mean age at first treatment was 80.5 months (range: 12–135 months) and the mean duration of treatment was 21.8 months (range: 1–72 months). No cats experienced increased in AST, the enzyme considered a more sensitive predictor of liver disease (Center, 1995).

Liver dyscrasias and cardiac arrhythmias may not rule out the use of a drug, but knowing that they exist can serve as a guide to dosage and anticipated side effects. Once alerted to potential adverse reactions clients are generally extremely willing to comply with all monitoring and with the extensive communication needs of behavioral cases. Concurrent use of medication that is metabolized using the same pathways may have an additive effect on affected cytochrome P450 systems, potentiating one or both medications (Harvey and Preskorn, 1996). SSRIs are often considered 'safer' than many TCAs, but because of the small sizes of clinical trials necessary to bring drugs to market for humans the exact incidence of potential side effects is often unknown in the absence of post-marketing surveillance (Capella et al., 1999). One must accept that this problem is magnified in veterinary behavioral medicine, where good, placebo controlled, double-blinded studies, or sophisticated studies involving risk calculation are neither encouraged nor routinely funded.

Finally, the client household must be considered when the decision to use behavioral drugs is made. Substance abuse is rampant in humans and many psychotropic medications used for behavioral pharmacology, particularly the benzodiazepines, have high abuse potential.

Neurotransmitters

The neurotransmitters affected by behavioral medications are acetylcholine, serotonin, norepinephrine (noradrenaline), dopamine, gamma amino butyric acid (GABA), and excitatory amino acids (EAA). Most of the applicable drugs for feline behavioral disorders affect serotonin (5-HT), norepinephrine (NE), or gamma amino butyric acid (GABA), with dopamine (DA) playing a lesser role.

Classes of drugs used and misused in behavioral medicine include anti-histamines, anti-convulsants, progestins/estrogens, sympathomimetics/stimulants, narcotic agonists/antagonists, and mood stabilizers/antipsychotics. These have been broadly discussed elsewhere (Overall, 1997a; Simpson and Papich, 2003). With the exception of the last class they are now considered to have limited use in modern behavioral medicine. Focus here is on the medications affecting NE, GABA, 5-HT, and monoamine oxidase (MAO).

Tranquilizers

Because of their misuse, a few words on tranquilizers are warranted. Tranquilizers decrease spontaneous activity, resulting in decreased-response to external or social stimuli. They profoundly interfere with any behavioral modification. Neuroleptic butyrophenones like haloperidol decrease both appropriate and inappropriate activity, and because of side effects associated

Table 1 Half-lives of parent compounds and intermediate metabolites of target benzodiazepines in humans (Kaplan and Sadock, 1993) (Tables 1–5 have been previously published in Overall, 2001)

Parent compound	$t_{1/2}$ parent compound (h)	$t_{1/2}$ intermediate metabolite (h)	Overall duration of action (h)
Triazolam	2–4	2	Ultra short: 6
Oxazepam	8–12		Short: 12–18
Alprazolam	6–12	6	Medium: 24
Diazepam	24–40	60	Long: 24–48
Clonazepam	50		Long: 24–48

with the most effective mode of delivery (i.e., IV), have limited use. Use of phenothiazines (e.g., chlorpromazine, promazine, acetylpromazine/acepromazine, and thioridazine), which target the dopamine receptor, is outdated in veterinary behavioral medicine because the level and duration of tranquilization varies, and because both normal and abnormal behaviors are blunted. No one should be using any behavioral medication for the purposes of 'drugging', sedating, or 'slowing down' an animal. All phenothiazines have side effects from long standing use (e.g., cardiovascular disturbance, extrapyramidal signs). Acetylpromazine makes animals more reactive to noises and startle, and so is wholly inappropriate for use in noise phobic and panicky patients. In fact, the dissociative effect of acetylpromazine renders anxious animals more uncertain and less able to deal with their anxiety—and hence 'worse'. Accordingly, phenothiazine use should be avoided in these patients.

Benzodiazepines are usually classified as tranquilizers. The exact mechanism of action of the benzodiazepines (e.g., diazepam, alprazolam, and oxazepam) is incompletely understood. Calming effects may be due to limbic system and reticular formation effects. All benzodiazepines potentiate the effects of GABA by increasing binding affinity of the GABA receptor for GABA. Although barbiturates also affect GABA via decreases in its synaptosomal release, cortical function is relatively unimpaired by benzodiazepines when compared with barbiturates.

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. 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. EAAs (glutamate, aspartate, and, possibly, homocysteate), the main fast excitatory transmitters in the CNS, have a role as central neurotransmitters and are produced in abnormal levels in aggressive, impulse, and schizophrenic disorders in humans, and possibly in explosive/impulsive states in dogs (Overall, 1997b).

Table 2 Duration of action of parent compound, diazepam, and its intermediate metabolite, nordiazepam (*N*-desmethyl diazepam) in selected domestic animals

Species	Diazepam (h)	N-desmethyl diazepam (h)
Horse	24–48	51–120
Cat	5.5	21
Dog	3.2	3–6

GABA also has a variety of trophic effects on developing brain cells (Waagepetersen et al., 1999). During ontogeny GABAergic axons move through areas where other neurotransmitter are being produced; this may be related to later monoaminergic imbalances (Lauder et al., 1998). The extent such ontogenic effects are relevant for behavioral conditions is currently unknown but bears investigating.

At low dosages, benzodiazepines act as mild sedatives, facilitating daytime activity by tempering excitement. At moderate dosages they act as anti-anxiety agents, facilitating social interaction in a more proactive manner. At high dosages they act as hypnotics, facilitating sleep. Ataxia and profound sedation usually only occur at dosages beyond those needed for anxiolytic effects. Benzodiazepines decrease muscle tone by a central action that is independent of the sedative effect, but may function as a non-specific anxiolytic effect. Some newer benzodiazepines like clonazepam have muscle relaxation effects at smaller dosages than those needed for behavioral effects. Many of the long-term effects and side effects of benzodiazepines are the result of intermediate metabolite function. Parent compound and intermediate metabolite $t_{1/2}$ are found in Table 1 for humans and Table 2 for domestic species (Greenblatt et al., 1981, 1983; Schwartz et al., 1965).

Benzodiazepines are essential for treatment of sporadic events involving profound anxiety or panic (e.g., thunderstorms, fireworks, panic associated with departures of humans signaled by an outside indicator like an alarm clock) (Crowell-Davis et al., 2003; Overall, 2002). For these drugs to be efficacious they must be given to the patient at least an hour before the anticipated stimulus, and minimally before the patients exhibit signs of distress. This timing allows repeat dosing that makes use of the $t_{1/2}$ of parent compounds and intermediate metabolites and permits concomitant use with daily TCA or SSRI treatment.

Non-tranquilizers—TCAs

TCAs are structurally related to the phenothiazine antipsychotics. In humans, they are commonly used to treat endogenous depression, panic attacks, phobic and obsessive states, neuropathic pain states, and pediatric enuresis. The antidepressant effect is due to inhibition of prejunctional re-uptake of norepinephrine and serotonin. There are three major effects of TCAs that vary in degree depending on the individual drug: (1) sedation, (2) peripheral and central anticholinergic action, and (3) potentiation of CNS biogenic amines by blocking their re-uptake presynaptically. The ability of TCAs to inhibit prejunctional re-uptake of NE and 5-HT are largely responsible for their antidepressant effect. Many TCAs also have potent muscarinic, α1-adrenergic, and H_1 and H_2 blocking activity, which can account for their common side effects (dry mouth, sedation, hypotension). The H_1 and H_2 effects, however, may be useful in treating pruritic conditions (e.g., doxepin).

NE has been postulated to affect (1) mood (NE decreases in depression and increases in mania) (2) functional reward systems, and (3) arousal.

Serotonin tracts are diffusely distributed throughout the hippocampus and frontal cortex—regions of the brain involved in learned and complex social behaviors. Of the 14 identified classes of 5-HT receptors, the 5-HT_1 receptor is most germane for anxiety disorders. 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 of stimulation of serotonin receptors 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.

The tertiary amines including amitriptyline, imipramine, doxepin, and clomipramine are metabolized to secondary amines that may also be available as parent compounds (e.g., nortriptyline). These classes of anti-depressants are among the most widely and safely used drugs in companion animal behavioral medicine when compared with benzodiazepines, phenothiazines, barbiturates, and sympathomimetic agents.

TCAs are incompletely absorbed from the gastrointestinal tract and have significant first-pass effects. They are over 50% protein bound and highly lipid soluble. In humans, TCAs reach peak plasma levels 8–12 h after the last dose and reach steady state levels after 5–7 days of consistent dosing. There is variation in response in humans: a 30–50 fold difference in plasma levels of individuals given the same dose has been reported. There is also considerable variation in plasma levels in dogs if the results from studies on clomipramine generalize (Hewson et al., 1998b; King et al., 2000b).

In general, TCA metabolites are more potent inhibitors of NE uptake, while parent compounds are more potent inhibitors of 5-HT uptake. Metabolites usually have similar or longer half-lives compared with the parent compound. Imipramine's intermediate metabolite, norimipramine, is a more potent inhibitor of NE uptake than is imipramine (it is also an active intermediate metabolite of other anti-anxiety agents) and has its own active intermediate metabolite (Table 3). Doxepin's intermediate metabolite, nordoxepin, fully retains the pharmacological properties of the parent compound, and its $t_{1/2}$ is 33–88 h in humans compared with a $t_{1/2}$ of 8–25 h for doxepin. Norclomipramine (*N*-desmethylclomipramine), one of the active intermediate metabolites of clomipramine, is also a more potent inhibitor of NE than is clomipramine and has an elimination $t_{1/2}$ 1.5 times longer than that of clomipramine (Mårtensson et al., 1984). Not only do these findings have profound implications for calculating how long one expects effects to last, but it is interesting to note that the ability to metabolize drugs into intermediate metabolites is subject to genetic polymorphism in the human population. One can only imagine the complexity for the canine and feline populations. Most dogs treated with clomipramine (Clomicalm, Novartis Animal Health) reach steady state levels in 3–5 days, attain peak plasma concentrations in approximately 1–3 h, and experience $t_{1/2}$ of 1–16 h of the parent compound and 1–2 h of the active

Table 3 Relative effects of TCA parent compounds and intermediate metabolites on NE and 5-HT re-uptake (adapted from Kaplan and Sadock, 1993)

Parent compound	Intermediate metabolite	NE	5-HT
Desipramine		++	+
Imipramine	Desipramine	+++	++
Amitriptyline	Nortriptyline	++	++
Nortriptyline		+	+
Clomipramine	*N*-desmethyl clomipramine+clomipramine*	++	+++

*Does not include the specific effect of the intermediate metabolite as a selective serotonin reuptake inhibitor (SSRI)

intermediate metabolites (Hewson et al., 1998a; King et al., 2000b), suggesting that dogs may require higher dosages or more frequent dosing than do humans treated with such medications.

Knowledge of intermediate metabolites can be important: animals experiencing sedation or other side effects with the parent compound may do quite well when treated with the intermediate metabolite, alone. For example, cats that become sedated or nauseous when treated with amitriptyline may respond well when treated with nortriptyline at the same dose. Table 3 lists parent compounds, intermediate metabolites, and their relative effects on NE and 5-HT.

Various side effects in humans that may also be applicable to cats include a dry mouth, constipation, urinary retention, tachycardias and other arrhythmias, syncope associated with orthostatic hypotension and α-adrenergic blockade, ataxia, disorientation, and generalized depression and inappetence (Wiersma et al., 2000). Symptoms usually abate upon decrease or cessation of drug administration. Use of TCAs is contraindicated in animals with a history of urinary retention and severe, uncontrolled cardiac arrhythmias and a cardiac consult, including a rhythm strip, should be a part of standard, pre-dispensation work-up. The common side-effects of TCAs as manifest on ECG include: flattened T waves, prolonged Q-T intervals, and depressed S-T segments (Pouchelon et al., 2000; Reich et al., 2000). In high doses TCAs have been implicated in sick euthyroid syndrome. In older or compromised animals complete laboratory evaluations are urged since high doses of TCAs are known to alter liver enzyme levels. Extremely high doses are associated with convulsions, cardiac abnormalities, and hepatotoxicity. TCAs can interfere with thyroid medication necessitating conscientious monitoring if administrations of both medications is concurrent (Gullikers and Panciera, 2002; Simpson and Papich, 2003). Cats are likely to be more sensitive to all TCAs than are dogs because TCAs are metabolized through glucuronidation.

TCAs are extremely successful in treating many canine and feline conditions including separation anxiety, generalized anxiety that may be a precursor to some elimination and aggressive behaviors, pruritic conditions that may be involved in acral lick dermatitis (ALD), compulsive grooming, and some narcoleptic disorders. Amitriptyline is very successful in treating both dogs and cats for mild separation anxiety and generalized anxiety, and for anxiety associated with some canine aggressions (Virga et al., 2001). Imipramine has been useful in treating mild attention deficit disorders in people, and may be useful in dogs since it has been used to treat mild narcolepsy. Clomipramine has been inordinately successful in the treatment of human and canine obsessive compulsive disorders (Ananth, 1986; Flament et al., 1985; Hewson et al., 1998b; McTavish and Benfield, 1990; Moon-Fanelli and Dodman, 1998; Overall, 1994a; Overall and Dunham, 2002a; Perse, 1988; Seksel and Lindeman, 1998; Thoren et al., 1980). Clomipramine has one active, intermediate metabolite, clomipramine, that acts as a serotonin re-uptake inhibitor (Ananth, 1986; Duman, 1998).

Non-tranquilizers—the SSRIs

The SSRIs (fluoxetine, paroxetine, sertraline, and fluvoxamine) are derivatives of TCAs. These drugs have a long half-life, and after 2–3 weeks plasma levels peak within 4–8 h. Treatment must continue for a minimum of 6–8 weeks before a determination about efficacy can be made since these drugs act to induce receptor conformation changes—an action that can take 3–5 weeks. Most of the SSRI effects are due to highly selective blockade of the re-uptake of 5-HT_{1A} into pre-synaptic neurons without effects on NE, dopamine, acetylcholine, histaminic, and α1-adrenergic receptors. The SSRIs should not be used with MAOIs because of risks of serotonin syndrome (Brown et al., 1996).

Fluoxetine is efficacious in the treatment of profound aggressions (Dodman et al., 1996;

Overall, 1995), animal models of obsessive-compulsive disorders (wheel running, anorexia, weight loss) (Altemus et al., 1993), companion animal separation anxiety (King et al., 2000a), panic, avoidance disorders, including post-traumatic stress disorder (Meltzer-Brody et al., 2000), and obsessive-compulsive disorders. Paroxetine is efficacious in the treatment of depression, social anxiety, and agitation associated with depression (Allgulander et al., 1997). Sertraline is useful particularly for generalized anxiety and panic disorder (Hyman Rapaport et al., 1998).

Most of the effect of fluoxetine seems to be via a highly selective blockade of the re-uptake of 5-HT into pre-synaptic neurons. Concomitant use of TCAs or benzodiazepines increases the plasma levels of SSRIs and may prolong the excretion of fluoxetine. Co-administration of buspirone may decrease the efficacy of buspirone and potentiate extrapyramidal symptoms, however there have also been reports of synergistic effects

Non-tranquilizers—MAO-Is

MAO-Is act by blocking oxidative deamination of brain amines (dopamine, nor-epinephrine, epinephrine, 5-OH-tryptamine), increasing these substances, and elevating mood. The MAO-B inhibitor, selegiline is used to treat 'cognitive dysfunction' in aged cats and dogs, but in dogs deamination of catecholamines is controlled by MAO-A. Selegiline is fairly specific for dopamine and slows the destruction of synaptic knobs of presynaptic neurons.

The distribution of dopamine in the brain is non-uniform, but is more restrictive than that of NE. Dopamine is metabolized by monoamine 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. The D_1 receptors exhibit their post-synaptic inhibition in the limbic system and are affected in mood disorders and stereotypies. Low dopamine levels have been implicated in cognitive disorders, primarily those involved in aging (Houpt, 2001). Excess dopamine, as produced by dopamine releasing agents (amphetamines and dopamine agonists, like apomorphine) is associated with the development of stereotypies.

Serotonin agonists

Buspirone is a non-specific anxiolytic that is a presynaptic 5-HT_{1A} agonist. Buspirone can be used to treat intercat aggression (with or without marking) but it should only be used for the victim. This drug has the reputation for making animals more aggressive, a conclusion that is wrong, given the data (Overall, 1994b), Buspirone decreases social and performance anxiety and makes animals more outgoing and assertive. Accordingly, animals may place themselves into situations where agonist interactions may be an expected outcome. Clients should be warned about this mode of action. Buspirone acts as a partial 5-HT agonist and so should not be used in combinations with TCAs or SSRIs to avoid the risk of serotonin syndrome. Its side-effects are negligible, but when they occur they are not substantially different from those for many anti-anxiety drugs. Clients should be warned that potential side effects include inappetence, lethargy, and possible interference with thyroid medication. If the any of the side effects are not transient, the drug should be withdrawn. Partial 5-$HT_{1A/B}$ agonists have few side effects, do not negatively affect cognition, allow rehabilitation by influencing cognition, attention, arousal, and mood regulation, and may aid in treating aggression associated with impaired social interaction. Buspirone has been used with varying, but unimpressive success, in the treatment of canine aggression of dominance or idiopathic origins, canine and feline ritualistic or stereotypic behaviors, self-mutilation and possible obsessive compulsive disorders, thunderstorm phobias (Marder, 1991), and feline spraying (Hart et al., 1993).

Roles for neuronal stimulation, synaptic plasticity, and receptor protein transcription and translation

Why are 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. The pathway involved uses cAMP, cytosolic response element binding protein (CREB), brain derived neurotrophic factor (BDNF), NMDA receptors, protein tyrosine kinases (PTK) which regulate activity of NMDA receptors and other ion channels and mediate the induction of LTP (long-term potentiation=synaptic plasticity) in the CA1 region of the hippocampus (Daniel et al., 1998; Salter, 1998; Trotti et al., 1998).

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 actually decreases the firing rate of that cell as a thermostatic response. Regardless, despite initially lowered serotonin levels, there is increased saturation of the post-synaptic receptors resulting in stimulation of the α-adrenergic coupled cAMP system in the post-synaptic neuron. 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 (Duman, 1998; Duman et al., 1997).

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 (an α-adrenoreceptor antagonist). Through augmentation of TCA and SSRI treatment with pindolol, treatment onset can be accelerated (Stein et al., 2001). 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 engender continued 'normal' functioning of the neurotransmitter system. There are some patients who require life-long treatment (see Overall and Dunham, 2002a for examples), suggesting that the effect of SSRIs and TCAs can be reversible in some patients, but relatively permanent in others. This further illustrates 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. To re-emphasize, the first tier of monitoring 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 and SSRIs, 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 preferable to withdraw most patients from one class of drug before starting another. For changing between SSRIs and MAOIs 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). SSRIs can be added to TCAs and may then exhibit a faster onset of action than when they are given alone. This is due to the shared molecular effects on second messenger systems of both TCAs and SSRIs. Combination treatment allows the veterinary surgeons 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. A model for how to do this is found in Table 4. Weaning minimizes potential central withdrawal signs, and allows determination of the lowest dosage that is still effective (Overall, 1997a, 1999a, 2001). 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.

A note on transdermal routes for mediation

Because cats are notoriously difficult to medicate, transdermal routes may be desirable as has been true for analgesia medications (Franks et al., 2002; Gellasch et al., 2002), but they are largely unexplored for behavioral drugs. Please do not expect psychopharmacological agents, particularly those that rely on 1st pass metabolism for conversion, or those that have alpha-adrenergic effects (e.g., TCAs) to behave the same when delivered orally—their standard route—v. transdermally. They may, in fact, behave differently. The Clinical Pharmacology Laboratory at Texas A & M CVM is examining the pharmacokinetics for many

Table 4 Algorithm for treatment length and weaning schedule

X (1) Treat for as long as it takes to begin to assess effects
X 7–10 days for relatively non-specific TCAs
X 3–5 weeks minimum for SSRIs and more specific TCAs

PLUS
X (2) Treat until "well" and either have no signs associated with diagnosis or some low, consistent level
X minimum of another 1–2 months

PLUS
X (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
X minimum of another 1–2 months

PLUS
X (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.
X 7–10 days for relatively non-specific TCAs
X 3–5 weeks minimum for SSRIs and more specific TCAs

TOTAL: Treat for a minimum of 4–6 months

medications. Their program can be tracked via the following web site: http://www.cvm.tamu.edu/VCPI/Transdermal/transderm_mail.html. Many of the drugs discussed here can be compounded into gels that are topically non-irritants. The questions then become, "Should we do so?" "Does this route work?" and if so, "Do the pharmacokinetics and pharmacodynamics mirror those for the oral route?" We currently know nothing about the pharmacodynamics or the pharmacokinetics of using oral preparations in transdermal form, with the exception of some recently presented work on a transdermal form of fluoxetine (Ciribassi et al., 2003). In this small but elegantly executed study of transdermally applied fluoxetine relative bioavailablity of two transdermal doses of fluoxetine (5 or 10 mg/kg) was only 10% that provided by oral drug delivery. Also, peak absorption of fluoxetine (C_{max}) was $1/4$ (5 mg/kg) to $1/3$ (10 mg/kg) that of the orally administered compound. This study shows how far a veterinary surgeon could be misled by simply delivering an oral dose in a transdermal vehicle.

For now it may be best to remember that most psychotropic medications can be repackaged or recompounded in oral solutions or capsules that cats may find more palatable. Palatability is a non-trivial concern because most of these medications are bitter. If clients begin to teach their cats—as kittens—how to take capsules as part of routine handling, difficulties can be minimized. Recommendations for how to do this can be found in a variety of sources (Overall et al., 2003; Seksel, 2001).

Pheromones

Treatment involving a synthetic analogue of feline cheek gland secretions (ie, pheromones) (Feliway™; Abbott Laboratories) may show some promise for spraying that has recently started and is related to the introduction of a new individual (human or animal), or to disruptions in the colony scent, however, no rigorous double-blind studies have been conducted. The need for such studies is more critical in this situation than in those involving some oral medications because of the manner in which the pheromone is applied and the need for clients to be cautious in their interpretations. One study that has examined the use of Feliway™ for the treatment of spraying found that in many cases there was a statistically significant reduction in spraying in cats also treated with medication, but few to no cats stopped spraying all together (Frank et al., 1999). That is to be expected if the problem is about anxiety and not about the actual olfactory/pheromonal environment. In some cases the concomitant use of pheromonal agents and anti-anxiety medications may produce a quicker resolution than would be produced by either alone. The neurochemical mechanism by which such pheromonal sprays may work is unknown (Pageat

Table 5 Selected psychopharmacological agents that may be useful in the treatment of feline behavioral diagnoses

Alprazolam (tablets: 0.25, 0.5, 1, 2 mg [1 and 2 mg tablets scored])	0.0125–0.025 mg/kg po q. 12 h (or at high end dose 1/4 0.25 mg tablet for a 3 kg cat)
Amitriptyline (tablets: 10, 25, 50, 75, 100, 150 mg)	0.5–2.0 mg/kg po q. 12–24 h; start at 0.5 mg/kg po q. 12 h
*Clomipramine (capsules: 25, 50, 75 mg in human formulation [Anafranil]; 20, 40, 80 mg scored tablets in veterinary formulation [Clomicalm/Novartis][5 mg scored tablets available in Australia and Europe])	0.5 mg/kg po q. 24 h
Clonazepam (tablets: 0.125, 0.25, 0.5, 1.0, 2.0 mg)	0.1–0.2 mg/kg po q. 12–24 h
Clorazepate (tablets: 3.75, 7.5, 11.25, 15, 22.5; capsules: 3.75, 7.5, 15 mg)	0.5–2.2 mg/kg po prn for profound distress; 0.2–0.4 mg/kg q. 12–24 h
Diazepam (tablets: 1, 2, 5, 10 mg; solution: 5 mg/ml)	0.2–0.4 mg/kg po q. 12–24 h (start at 0.2 mg/kg po q. 12 h)
Doxepin (capsules: 10, 25, 50, 75, 100, 150 mg; solution: 10 mg/ml)	0.5–1.0 mg/kg po q. 12–24 h (start low)
Fluoxetine (capsules: 10, 20 mg; solution: 5 mg/ml)	0.5–1.0 mg/kg po q. 24 h
Fluvoxamine (capsules: 10, 20 mg)	0.25–0.5 mg/kg po q. 24 h
Imipramine (tablets: 10, 25, 50 mg; capsules 75, 100, 125, 150 mg)	0.5–1.0 mg/kg po q. 12–24 h (start at 0.5 mg/kg po q. 12 h)
Nortriptyline (capsules: 10, 25, 50, 75 mg)	0.5–2.0 mg/kg po q. 12 –24 h
Oxazepam (tablets: 15 mg; capsules: 10, 15, 30 mg)	0.2–0.5 mg/kg po q. 12–24 h; high dose:1.0–2.5 mg/kg po q. 12–24 h; 3 mg/kg po as a bolus for appetite stimulation
Paroxetine (tablets: 10, 20, 30, 40 mg; suspension: 10 mg/5 ml)	0.5 mg/kg po q. 24 h×6–8 weeks to start
Protriptyline (tablets: 5, 10 mg)	0.5–1.0 mg/kg po q. 12–24 h (start at 0.5 mg/kg po q. 12 h)
*Selegiline (tablets: 5, 10, 15, 30 mg [Anipryl/ Pfizer; Selgan/Sanofi/CEVA])	0.25–0.5 mg/kg po q. 12–24 h; start low
Sertraline (tablets: 25, 50, 100 mg)	0.5 mg/kg po q. 24 h×6–8 weeks to start
Triazolam (tablets: 0.125, 0.25 mg)	2.5–5 mg/cat po q. 8 h

*Veterinary label for some canine and feline conditions; label depends on country and species.

Table 6 Medication choices for cats involved in intercat aggression

Medication class	Indication
Benzodiazepines: diazepam or oxazepam	For victim if very fearful and withdrawn; will render less anxious and more outgoing; good with food treats; disinhibits
Tricyclic antidepressants: amitriptyline, nortriptyline, clomipramine	For victim or aggressor if aggression about uncertainty or anxiety associated with social interactions
Selective serotonin reuptake inhibitors: paroxetine, sertraline, fluvoxamine, fluoxetine	For victim if needs to be more confident in interactions (paroxetine or sertraline); for aggressor if aggression is outburst and assertive (fluoxetine)
Partial serotonin agonists (buspirone)	Victim, only! Will make more outgoing and may result in cat asserting herself more—relies on resultant social interactions to affect change

and Gaultier, 2003), but it might be worthwhile, given the data, to explore the extent to which pheromones can act as aerosolizable anxiolytics.

Choosing specific drugs for the treatment of specific behavioral conditions

A summary of the drugs discussed can be found in Table 5. Implicit in the recommendations for treatment are that the diagnostic criteria are met (e.g., as in Overall, 1997a) (i.e., the practitioner is addressing a specific diagnosis, not a non-specific correlate or sign) and the relevant pharmacodynamics discussed above are understood and used in the diagnosis.

Specific treatment for urine marking, particularly urine spraying, has been discussed elsewhere (Neilson, 2003). Because pharmacological treatment for intercat aggression (defined here as consistent, volitional, proactive aggression on the part of the aggressor that is not contextual given the social signals, interactions, threat circumstances, or response received from the victim (Overall, 1997a)) is such an important issue, suggested treatments are discussed here (Table 6). Remember, before treating any cat with medication for a behavioral problem, rule out any medical problems (Overall, 2003), and conduct a full, pre-medication physical and laboratory evaluation.

Future advances in treatment in veterinary behavioral medicine will be pharmacological and neurophysiological. As the field of veterinary behavioral medicine expands, its paradigm will enlarge to include routine combination therapy and the implementation of neuropharmacological intervention as a diagnostic tool.

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