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Review

Pharmacological Treatment in Behavioural Medicine: The Importance of Neurochemistry, Molecular Biology and Mechanistic Hypotheses

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SUMMARY

Psychopharmacology has become a popular, and sometimes mandatory addition to treatment regimes for canine and feline patients with behavioural problems; however, clients and practitioners should be dissuaded that behavioural drugs are 'quick fixes'. Veterinarians should only prescribe psychotropic medication when they have a specific idea of how the mechanism of action of the drug will affect the target behaviours associated with a specific diagnosis. The diagnosis must be treated rather than non-specific signs. Newer psychotropic medications demonstrate the extent to which truly abnormal behaviours are dysfunctions of neurochemistry; synaptic or cellular metabolism; or genetic encoding and 'learning', or LTP, hence there is a clear role for the interaction of neuropharmacology and behavioural and environmental modification.

Future advances in treatment in behavioural medicine will be pharmacological and neurophysiological. As the field of behavioural medicine expands, its paradigm will enlarge to include combination therapy and the implementation of neuropharmacological intervention as a diagnostic tool. At present, the veterinary practitioner can effectively aid many common behavioural problems using extant drugs to treat animals with true behavioural pathology.

Rational pharmacological therapy requires complete medical and behavioural histories, requisite laboratory work, complete client understanding and compliance, and an honest and ongoing dialogue between the client and veterinarian that includes frequent follow-ups and re-examinations.

KEYWORDS: Psychopharmacology; tricyclic antidepressant (TCA); selective serotonin re-uptake inhibitor (SSRI); serotonin; 5-HT; gamma amino butyric acid (GABA); norepinephrine (NE); cytosolic response element binding protein (CREB); brain derived neurotrophic factor (BDNF); synaptic plasticity.

INTRODUCTION

Acceptance of veterinary behavioural medicine has been aided by developments in neuropsychopharmacology and behavioural/neuropsychiatric genetics. The addition of pyschotherapeutic agents to more general treatments, such as behavioural and environmental modification, has led to better (Overall, 1994; Dodman *et al.*, 1996; Hewson *et al.*, 1998b; Moon-Fanelli & Dodman, 1998) and faster (King *et al.*, 2000a) 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.

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Mere treatment of non-specific behavioural complaints and signs is outdated and has been replaced with an approach that includes necessary and sufficient criteria for diagnosis and pursuit of treatment that addresses the specific mechanism underlying the neurochemical contribution to the pathology (Overall, 1997).

The use of medication should occur and is most effective as part of an integrated treatment programme. There is no substitute for the hard work involved in behaviour modification; however, some medications may be able to make it easier to implement the modification (King *et al.*, 2000a). Those seeking 'quick fix' solutions will doubtless be disappointed: inappropriate drug use will only blunt or mask a behaviour without alteration of processes or environments that produced the behaviour. 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 behaviour. This delay is due to the mechanism of action of the tricyclic antidepressants (TCAs) and the selective serotonin reuptake inhibitors (SSRIs) which employ second messenger systems to alter transcription of receptor proteins.

Criteria for making a behavioural diagnosis and specific drug recommendations for specific behavioural diagnoses have been discussed elsewhere (Overall, 1997; 1998a–c; 1999b,c). Rather than repeating such discussions here, this paper provides a rational context for the use of behavioural drugs by examining the neurotransmitters that these 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. The primary focus is on the main groups of drugs now recommended for use: those drugs affecting serotonin (5-HT) and gamma amino butyric acid (GABA).

USING TREATMENT TO HELP TEST DIAGNOSTIC HYPOTHESES

Most behavioural 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 behavioural description, a non-specific sign, or a phenotypic diagnosis (Overall, 1997; 1998a,b). It is caused by a variety of social circumstances and may be the result of the interactions of a variety of neural substrates. Likewise, not all aggression is neurochemically identical either in impetus or outcome. Diagnosis by pharmacological treatment is usually doomed to failure. *If* the clinician is using a drug that has very specific properties *and* they are able to monitor very specific behavioural changes, pharmacological treatment can help the clinician reject an hypothesis about an underlying neurophysiological mechanism; however, response to drug treatment, alone, seldom confirms a causal link.

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 more simple terms, this means that not all patients exhibiting the same phenotypic, phenomenological, or functional diagnosis are affected for the same reasons.

In human psychiatry, large, multi-centre treatment trials are common and serve to identify subpopulations 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 work in tandem to advance understanding of the complex integration of all organ system and environmental responses that we call 'behaviour'. There are no large-scale studies in veterinary behavioural medicine that would permit the use of this type of empiricism that is possible in human psychiatry. However, dogs are often the models for toxicological and tolerance studies of human psychotropic medications and the areas of the brain primarily affected by TCAs and SSRIs involve ancient areas so humans can serve as treatment models for many canine conditions.

PRE-MEDICATION CONSIDERATIONS

Prior to incorporating behavioural pharmacology into any treatment programme, 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 clinician should have some insight into the neurochemistry relevant to the condition.
3. The clinician should have an appreciation for the putative mechanism of action of the chosen medication.
4. The clinician should have a clear understanding of any potential side effects.
5. The clinician and client should have some clear concept of how the prescribed drug will alter the behaviour in question. The latter is critical because it will help clients to watch for side effects and improvements and can help the clinician confirm or reject the diagnosis.

Without these five guidelines, behavioural 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 behavioural 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 behavioural and medical history should be taken. Should the animal be older, suffer from any metabolic or cardiac abnormalities, or be on any concurrent medical therapy, caution is urged. All animals should have complete laboratory and physical examinations. Most behavioural drugs are metabolized through renal and hepatic pathways so knowledge of baseline values is essential. For example, SSRIs are often considered 'safer' than many TCAs, but because of the small sizes of clinical trials necessary to bring drugs to market, the exact incidence of potential side effects is often unknown in the absence of post-marketing surveillance. One recent study reports that, in contrast to the commonly held view that SSRIs are 'safe', 229 cases of acute hepatitis reported by the World Health Organization (WHO) International Programme for Drug Monitoring have been attributed to the SSRI fluoxetine, 54 to the SSRI fluvoxamine, 80 to the SSRI paroxetine, and 65 to the SSRI sertraline (Capella *et al.*, 1999). These data present a different picture from those portrayed by the clinical trials that indicate only a 0.5% increase in liver enzymes among 3000 patients (Cooper, 1988), but still may represent a very small number of serious problems for the number of patients actually exposed to the drugs.

Many of the more commonly used (and, oddly, 'safer') behavioural medications can have cardiac side effects. Baseline ECGs are recommended for any patient who has had a history of any arrhythmia, heart disease, prior drug reactions, is on more than one medication, and who may be undergoing anaesthesia or sedation (Nattel & Mittleman, 1984; Pouchelon *et al.*, 2000; Reich *et al.*, 2000). 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 extremely willing to comply with all monitoring and with the extensive communication needs of behavioural cases. Clients should receive a complete list of all potential adverse responses and should be encouraged to communicate with the clinician at the first sign of any problem. Clients are often very distressed after a behavioural consultation and need a written reminder of situations for which they should be alert.

In the USA, extra-label use of human drugs, including psychopharmacological agents, for the treatment of pets hinges on a valid client/veterinarian/patient relationship. This means that a behavioural history was taken, a tentative diagnosis was formulated, and a treatment plan was developed. If any veterinarian is uncomfortable with complying with these guidelines, they should refer their behavioural cases to a specialist in behavioural medicine. Consultations directly with a client by fax, phone, mail, or e-mail, in the absence of actual visual inspection of the patient, most often do not meet the criteria of a valid client/veterinarian/patient relationship. Caution is urged. The preferred mode of consultation, if the clinician cannot have a visual inspection of the patient, is for the consultation to take place directly with the specialist and the referring clinician, who is then responsible for treatment and follow-up.

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

NEUROTRANSMITTERS AND NEUROCHEMICAL TRACTS

The neurotransmitters affected by behavioural 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.

Serotonin (5-hydroxy-tryptamine [5-HT])

Serotonin 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 behaviour. Presynaptic 5-HT_{1A}-receptors predominate in dorsal and median raphé nuclei; postsynaptic 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. The subclasses of 5-HT receptors vary in their affects. 5-HT_{1A} receptors affect mood and behaviour. 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 behavioural drugs. Urinary excretion of 5-HIAA (5-hydroxyindoleacetic 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 behavioural medicine.

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.

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), catalysed 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 potentiators of $GABA_A$. $GABA_B$ receptors are involved in the fine-tuning of inhibitory synaptic transmission: presynaptic $GABA_B$ receptors inhibit neurotransmitter release via high-voltage activated Ca^{++} channels; and postsynaptic $GABA_B$ receptors decrease neuronal excitability by activating inwardly rectifying K^+ conductance underlying the late inhibitory post-synaptic potential (Lauder *et al.*, 1998).

GABA also has a variety of tropic effects on developing brain cells (Waagepetersen *et al.*, 1999). During ontogeny GABAergic axons move through areas where other neurotransmitter phenotypes

are being produced, and so may be related to later monoaminergic imbalances (Lauder *et al.*, 1998). The extent to which such ontogenic effects are relevant for behavioural 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 (Sohn & Ferrendelli, 1976; Taubøll & Gjerstad, 1993). Pre-synaptic barbiturates inhibit calcium uptake and decrease synaptosomal release of neurotransmitters, including GABA and glutamate (deBoer *et al.*, 1982).

Other chemical mediators

Nitric oxide (NO) and arachidonic acid metabolites (e.g. prostaglandins) can mediate neurotransmitter release. These are synthesized on demand and released by diffusion, requiring no specialized vesicles or receptors. Like encapsulated neurotransmitters (i.e. ACh) that are extruded through exocytosis after binding with the synaptic membrane, these chemical mediators are activated by an increase in calcium, so may be affected by calcium channel blockers.

CLASSES OF DRUGS USED AND MISUSED IN BEHAVIOURAL MEDICINE

Anti-histamines, anti-convulsants, progestins/oestrogens, sympathomimetics/stimulants, narcotic agonists/antagonists, and mood stabilizers/antipsychotics have been discussed elsewhere (Overall, 1997). With the exception of the last class, they have limited use in modern behavioural medicine. Focus here is on the medications affecting GABA and 5-HT: the benzodiazepine tranquilizers, MAO-Is, TCAs, SSRIs, and 5-HT agonists.

Tranquilizers decrease spontaneous activity, resulting in decreased response to external or social stimuli. They interfere profoundly with any behavioural modification. Neuroleptic butyrophenones like haloperidol decrease both appropriate and inappropriate activity, and because of side effects associated with the most effective mode of delivery (i.e. IV), have limited use. Use of phenothiazines (e.g. chlorpromazine, promazine, acetylpromazine, and thioridazine), which target the dopamine receptor, is outdated – the level and duration of tranquilization varies and both normal and abnormal behaviours are blunted. 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 patients.

The exact mechanism of action of the benzodiazepines (e.g. diazepam, chlordiazepoxide, clorazepate, lorazepam, alprazolam and clonazepam) is poorly understood. Calming effects may be due to limbic system and reticular formation effects. Compared with barbiturates, cortical function is relatively unimpaired by benzodiazepines. All benzodiazepines potentiate the effects of GABA by increasing binding affinity of the GABA receptor for GABA and increasing the flow of chloride ions into the neuron, affecting primarily $GABA_A$ receptors. Barbiturates also affect the GABA receptor-benzodiazepine receptor-chloride ion channel complex, but because of detrimental effects on cognition barbiturates have been superseded by benzodiazepines and tricyclic anti-depressants in the treatment of aggression. Binding of diazepam is highest in the cerebral cortex compared with the limbic system and midbrain, which are, in turn, higher than the brainstem and the spinal cord, paralleling that of $GABA_A$ receptors.

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 behavioural 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 I for humans and Table II for domestic species (Schwartz *et al.*, 1965; Greenblatt *et al.*, 1981,1983).

Table I
Half-lives of parent compounds and intermediate metabolites of target benzodiazepines in humans (Kaplan & Sadock, 1993)

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

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

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

Benzodiazepines are essential for treatment of sporadic events involving profound anxiety or panic (e.g. thunderstorms, fireworks, panic associated with departures of humans signalled by an outside indicator, e.g. an alarm clock). For these drugs to be efficacious they must be given to the patient at least 1 h 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.

Monoamine oxidase (MAO) inhibitors (I) 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 destruction of synaptic knobs of presynaptic neurons.

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 paediatric 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 norepinephrine and serotonin are largely responsible for their antidepressant effect. Many TCAs also have potent muscarinic, αl-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).

The tertiary amines (amitriptyline, imipramine, doxepin, trimipramine and clomipramine) are metabolized to secondary amines (desipramine, nortriptyline and protriptyline). These classes of anti-depressants are among the most widely and safely (compared with benzodiazepines, phenothiazines, barbiturates and sympathomimetic agents) used drugs in companion animal behavioural medicine.

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 five to seven 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.*, 1998a; King *et al.*, 2000a). Nortriptyline is a little different from other TCAs in that it has a therapeutic window: plasma levels of over 150 μg/mL may reduce efficacy in humans. TCAs act primarily through a reuptake blockage of norepinephrine and serotonin. In the long term they may cause a decrease in number of β-adrenergic and 5-HT_2 receptors.

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. 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 with 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 does this have profound implications for calculating how long one expects effects to last, but it is also interesting to note that the ability to formulate 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 three to five 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 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 III lists parent compounds, intermediate metabolites, and their relative effects on NE and 5-HT. Side effects in humans can 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. Based on over 1000 dogs treated with TCAs and SSRIs at VHUP, side effects appear rare in canine patients; the most common side effect has been GI distress. More rare side effects include profound increases in appetite and discomfort associated with unremitting tachycardia that resolves when drugs are withdrawn. One dog treated with clomipramine experienced collapse, hyperthermia, and seizure activity, from which he recovered with supportive care (King *et al.*, 2000a). Other researchers report less successful use (Hewson *et al.*, 1998b), which leads one to ask about expectations and comfort level of clients and diagnostic and treatment protocols. Use of TCAs is contraindicated in animals with a history of urinary retention and severe, uncontrolled cardiac arrhythmias (Pouchelon *et al.*, 2000; Reich *et al.*, 2000) 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. 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.

Table III
Relative effects of TCA parent compounds and intermediate metabolites on NE and 5-HT reuptake (adapted from Kaplan & 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)

TCAs can interfere with thyroid medication necessitating conscientious monitoring if administrations of both medications is concurrent. Cats are likely to be more sensitive to all TCAs than are dogs because TCAs are metabolized through glucuronidation.

These drugs 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 behaviours, pruritic conditions that may be involved in acral lick dermatitis (ALD), compulsive grooming, and some narcoleptic disorders. Amitriptyline is very successful in treating separation anxiety and generalized anxiety. 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. A TCA derivative, carbamazepine, has been successfully used to control aberrant activity in psychomotor seizures (Holland, 1988). Clomipramine has been inordinantly successful in the treatment of human and canine obsessive compulsive disorders (Thoren *et al.*, 1980; Flament *et al.*, 1985; Ananth, 1986; Perse, 1988; McTavish & Benfield, 1990; Overall, 1994; Hewson *et al.*, 1998b; Moon-Fanelli & Dodman, 1998; Seksel & Lindeman, 1998). Clomipramine has one active, intermediate metabolite, clomipramine, that acts as a serotonin re-uptake inhibitor (Ananth, 1986; Duman, 1998).

The only pure 5-HT_{1A} agonist is the serenic eltoprazine [DU 28853]. Serenics leave defensive behaviours intact without sedation or muscle relaxation and decrease aggression while concomitantly increasing social interest. Partial 5-$HT_{1A/B}$ agonists (e.g. buspirone) 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 behaviours, self-mutilation and possible obsessive compulsive disorders, thunderstorm phobias (Marder, 1991), and feline spraying (Hart *et al.*, 1993).

The SSRIs (fluoxetine, paroxetine, sertraline and fluvoxamine) are derivatives of TCAs. These drugs have a long half-life, and after two to three weeks plasma levels peak within 4–8 h. Treatment must continue for a minimum of six to eight weeks before a determination about efficacy can be made since these drugs act to induce receptor conformation changes – an action that can take three to five 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, animal models of obsessive-compulsive disorders (wheel running, anorexia and weight loss) (Altemus *et al.*, 1993), companion animal separation anxiety (King *et al.*, 2000), 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. Fluoxetine appears to have no effects on NE or dopamine, no anticholinergic, no antihistaminic, and no anti-α1-adrenergic activities, so most of the side effects associated with anti-depressants are absent or minimized. Concomitant use of TCAs or benzodiazepines increases the plasma levels of these and may prolong the excretion of fluoxetine. Co-administration of buspirone may decrease the efficacy of buspirone and potentiate extrapyramidal symptoms, but there have also been reports of synergistic effects. Fluoxetine should not be used with MAOIs. Table IV contains an algorithm for the 'gestalt' of TCA and SSRI use. This algorithm is extrapolated from the human literature based on the similarity of dogs and humans with respect to pharmacokinetics and pharmacodynamics when treated with TCAs or SSRIs (Yokota *et al.*, 1987; Hewson et al., 1998a; King et al., 2000b).

Beta-adrenergic receptor antagonists (β-blockers) are used in humans to treat self-injurious behaviour, intermittent explosive disorder, conduct disorders, dementia, brain disease/injury, autism and schizophrenia. Older β-blockers, like propranolol [a β-1 and β-2 blocker], have not been as successful as hoped in treating canine or feline aggression, but have been used with mixed success in combination with TCAs or SSRIs to treat some anxieties and noise phobias.

Table IV
'Gestalt' of TCA and SSRI use based on $t_{1/2}$ of parent compounds and active intermediate metabolites, relative effects on NE and 5-HT, and extrapolations from multicentre human studies

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 behaviour associated with anxiety, including OCD	Clomipramine

Other agents (e.g. pindolol) have been used successfully to potentiate the action of the TCAs and SSRIs by blocking the pre-synaptic autoreceptor. Blockade of the pre-synaptic autoreceptor – the 'thermostat' – aborts the initial 'down-regulation' phase of monoamine release: the relevant monoamine continues to be produced despite accumulation in the synaptic cleft due to pre-synaptic re-uptake inhibition (Duman *et al.*, 1997; Duman, 1998).

Cholecystokinin (CCK) has been postulated to act as a mediator in panic attacks, and has been implicated in situations involving self-medication with food. CCK-B receptors (central brain receptors) appear involved in the opening and closing of cat jaws, and may function in obsessive-compulsive disorders such as over-grooming and wool-chewing or sucking (Singh *et al.*, 1991; Kennedy *et al.*, 1999). Agents affecting CCK are being developed and tested.

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 and protein tyrosine kinases (PTK) – particularly Src – 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 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 β-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 (Duman *et al.*, 1997; Duman, 1998).

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 β-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 behavioural 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 etc. 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 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 (two + 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 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.

Table V
Algorithm for treatment length and weaning schedule

1. Treat for as long as it takes to begin to assess effects
   - seven to 10 days for relatively non-specific TCAs
   - three to five 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 one to two 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 one to two 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.
   - seven to 10 days for relatively non-specific TCAs
   - three to five weeks minimum for SSRIs and more specific TCAs

TOTAL: Treat for a minimum of four to six months

Table VIA
Selected psychopharmacological agents that may be useful in the treatment of feline behavioural diagnoses

ALPRAZOLAM (tablets: 0.25, 0.5, 1, 2 mg [1 and 2 mg tablets scored])	0.01–0.02 mg/kg po q. 12 h
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)	0.05–0.2 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 × 6–8 weeks to start
FLUVOXAMINE (capsules: 10, 20 mg)	0.25–0.5 mg/kg po q. 24 h × 6–8 weeks to start
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 × six to eight weeks to start
TRIAZOLAM (tablets: 0.125, 0.25 mg)	0.1–0.2 mg/kg po q. 8–12

When stopping a drug, weaning is preferred to stopping abruptly. A model for how to do this is found in Table V. Weaning minimizes potential central withdrawal signs, and allows determination of the lowest dosage that is still effective (Overall, 1997; 1999a; 2000). 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.

CHOOSING SPECIFIC DRUGS FOR THE TREATMENT OF SPECIFIC BEHAVIOURAL CONDITIONS

A summary of the drugs discussed can be found in Table VI. Implicit in the recommendations for treatment are that the necessary and sufficient conditions for diagnosis (Overall, 1997) are met (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.

Table VIB
Selected psychopharmacological agents that may be useful in the treatment of canine behavioural diagnoses

ALPRAZOLAM (tablets: 0.25, 0.5, 1, 2 mg mg tablets scored [1 and 2])	0.125–1 mg/kg po q. 12 h; range: 0.01–0.1 mg/kg po prn for phobic or panic attacks, not to exceed 4 mg/dog/day – profound lethargy and incoordination may result (0.75–4 mg/dog/day; may increase slowly over 4 mg/dog/day if obtaining some effect at a lower dose) (Start with 1–2 mg for a 25 kg dog)
AMITRIPTYLINE (tablets: 10, 25, 50, 75, 100, 150 mg)	1–2 mg/kg po q. 12 h to start
BUSPIRONE (tablets: 5, 10 mg)	1 mg/kg po q. 8–24 h (mild anxiety) 2.5–10 mg/dog q. 8–24 h (mild anxiety) 10–15 mg/dog po q. 8–12 h (more severe anxiety; use high dose for thunderstorm phobia)
CARBAMAZEPINE (tablets: 200 mg [scored]; chewable tablets: 100 mg [scored])	4–8 mg/kg po q. 12 h; 0.5–1.25 mg/kg po q. 8 h; 4–10 mg/kg/day divided q. 8 h
CHLORDIAZEPOXIDE (tablets: 5, 10, 25 mg; also available as a powder for injection)	2.2–6.6 mg/kg po prn (start low)
*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])	1 mg/kg po q. 12 h × two weeks, then 2 mg/kg po q. 12 h × two weeks, then 3 mg/kg po q. 12 h × 4 weeks and then as maintenance dose or 2 mg/kg po q. 12 h × eight weeks to start. May need higher maintenance dose. Constant dosage associated with slight increase in GI side effects. NB: q. 24 h dosing insufficient for vast majority of animals, particularly those with multiple signs, early age onset, or long-standing complaint.
CLONAZEPAM (tablets: 0.125, 0.25, 0.5, 1.0, 2.0 mg)	0.125–1.0 mg/kg po q. 12 h; range: 0.01–0.1 mg/kg po prn for phobic or panic attacks, profound lethargy and incoordination may result at dosages over 4 mg/day, but higher dosages may be used incrementally if there has been some effect at a lower dose (Start with 1–2 mg for a 25 kg dog)
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 at least 1 h before provocative stimulus (departure) or anticipated noise (storm, fireworks); repeat q. 4–6 h prn; 11.25–22.5 mg/dog po q. 24 h (~22.5 mg/large dogs; ~11.25 mg/medium dogs; ~5.6 mg/small dogs)
DIAZEPAM (tablets: 1, 2, 5, 10 mg; solution 5 mg/mL)	0.5–2.2 mg/kg po at least 1 hour before provocative stimulus (departure) or anticipated noise (storm, fireworks); repeat q. 4–6 h prn
DOXEPIN (capsules: 10, 25, 50, 75, 100, 150 mg; solution: 10 mg/mL)	3–5 mg/kg po q. 8–12 h
FLUOXETINE (capsules: 10, 20 mg; solution: 5 mg/mL)	1 mg/kg po q. 12–24 h × six to eight weeks to start; can increase mg/kg
FLUVOXAMINE (tablets: 25, 550, 100 mg)	1 mg/kg po q. 12–24 h × six to eight weeks to start; can increase mg/kg
IMIPRAMINE (tablets: 10, 25, 50 mg; capsules 75, 100, 125, 150 mg)	2.2–4.4 mg/kg po q. 12–24 h; 1–2 or 2–4 mg/kg po q. 12–24 h (start low)

NORTRIPTYLINE (capsules: 10, 25, 50, 75 mg; solution 10 mg/5 mL)	1–2 mg/kg po q. 12 h
OXAZEPAM (tablets: 15 mg; capsules: 10, 15, 30 mg)	0.2–1 mg/kg po q. 12–24 h
PAROXETINE (tablets: 10, 20, 30, 40 mg; suspension: 10 mg/5 mL)	1 mg/kg po q. 24 h × six to eight weeks to start; can increase mg/kg
PROTRIPTYLINE (tablets: 5, 10 mg)	5–10 mg/dog po q. 12–24 h (narcolepsy)
*SELEGILINE (tablets: 5, 10, 15, 30 mg [Anipryl, Pfizer; Selgan, Sanofi])	0.5–1 mg/kg po q. 24 h × six to eight weeks to start
SERTRALINE (tablets: 25, 50, 100 mg)	1 mg/kg po q. 24 h to start × 6–8 weeks to start; can increase mg/kg
TRIAZOLAM (tablets: 0.125, 0.5 mg)	0.125–1 mg/kg po q. 12 h; range: 0.01–0.1 mg/kg po prn

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

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Book Review

Feeding Systems and Feed Evaluation Models
Eds Theodorou, M. K. and France J. Wallingford, Oxon, CABI Publishing, 2000. 496 pp. £75 (hard)
ISBN 085199346X

Do not be misled by the first part of the title. If you wish to know the practicalities of feeding animals this book is not for you. You will not find here anything on grazing management systems, on systems of concentrate distribution such as feeding to yield, flat rate feeding, on use of complete diets and feed lot systems for ruminants, on choice feeding or free range systems for pigs and poultry. This is a book about methods of calculating the value of feedingstuffs and of calculating the nutrient requirements of animals. Furthermore, the book is mainly concerned with energy and protein. Lipids, minerals and vitamins receive only brief mention.

This is a multiple-author work with chapters written by 32 experts in their field drawn from all over the world. The first five chapters deal critically with methods of feed evaluation, of predicting digestibility and measuring energy metabolism. The next six chapters review current feeding standards for dairy cows, beef cattle, sheep, pigs, poultry and horses. These are useful in that several make comparisons between the different systems adopted in various countries. This highlights the areas of uncertainty and the unsatisfactory nature of many of today's standards. In the case of ruminants, despite recent advances with the adoption of metabolizable protein, 'appropriate schemes for predicting animal response. ... to nutrients are not presently available within the UK'. This naturally leads on to seven chapters on development of dynamic deterministic models to replace current static empirical models. Four chapters deal with the development of dynamic models of the response of ruminants to variation in nutrient supply. A further three chapters deal with modelling of responses to nutrients and environmental factors in pigs, poultry and fish. These models will undoubtedly be the basis of the next generation of nutrient requirement publications. They aim not only to indicate the approximate need for any given level of production but also the marginal response to a change in nutrient supply from the current status.

The strength of the book is the bringing together of current work on modelling in many different species. The final chapter on nutrition of companion animals, including cats, dogs, birds, ornamental fish, rabbits and rats, attempts to complete the domesticated species, but there is a lack of research-based data and consequently the treatment is at a more elementary level than the rest of the book.

Throughout, the text is supported by extensive references to the original literature. Each chapter stands alone so the reader may dip in where ever the interest lies. In this respect this is not a standard text book for undergraduates in animal nutrition but is aimed at those researching and teaching animal agriculture including postgraduate students and extension workers. However, it is also suitable for advanced study by undergraduate students. The book should be in the libraries of every institute of advanced teaching and research in animal nutrition and on the shelves of those working towards better systems of feed evaluation and animal requirements.

E. L. MILLER