Review Article

AN OVERVIEW OF BEHAVIORAL DISORDERS AND ITS THERAPEUTIC MANAGEMENT IN DOGS AND CATS

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ABSTRACT

Many of the dogs and cats lives affected with behavioral disorders have been ended either in euthanasia, relinquishment, chronic suffering or would have handed over to shelters. Various types of behavioral disorders in dogs and cats include nonspecific/ idiopathic aggression, fear, phobia, anxiety disorder and stereotyping behavior. The goal of therapy should be the modification of the abnormal behavior by environmental management, training with pharmacological intervention being adjunct to the behavioral modification training. Major classes of behavioral modifying drugs used in pets are selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (TCA), monoamine oxidase inhibitors (MAOI), antipsychotic agents, anticonvulsants and benzodiazepines. The mechanism of action has been attributed to modification of the availability or function of various neurotransmitters implicated in the behavioral disorders. Presently, the approved drugs for veterinary use has been limited to: selegiline, a SSRI, for canine cognitive dysfunction and clomipramine, a TCA, for separation anxiety in dogs, with majority drugs being used on extra label fashion with the extrapolation of human data. The article reviews about the pathophysiology of behavioral disorders, diagnostic approaches and drugs available for the treatment of abnormal behavior caused by variation in neurotransmitter.

Keywords: Behavioral disorder, Canine cognitive dysfunction, Separation anxiety, SSRI, TCA

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Behavior means the way in which one acts or conducts oneself, towards others or the way in which an animal/person behaves in response to a particular situation or stimulus (de Passillé *et al*., 1996).Abnormal behavior is defined as an untypical reaction to a particular combination of motivational factors and stimuli. All animals were not behaved identically when exposed with the same conditions. These

individual differences in the expression of their behavior could be due to many factors. Neurological problems, medical conditions, pain (musculoskeletal, gastrointestinal and dermatological conditions), the most common sign of pain in animals is a change in behavior. Pathophysiological disorders, hereditary abnormalities, undiagnosed disease and species-typical behavior (strongly pronounced hunting instinct, cats scratching furniture, dog aggression towards each other etc.). Thyroid hormones play an important role, regarding behavioral control. Both hypothyroidism and hyperthyroidism have been related to behavioral changes. New neuro-imaging studies provide objective evidence that brain structure and function are altered in hypothyroid patients, both in laboratory animals and in humans. The most common problems are tumors that affect central nervous system silent zones, mild traumatic brain injury, ischemic attacks, and epilepsy. Environmental condition or stressful situations; exposure to strong aversive external irritants; endocrine diseases and vomeronasal organ alterations (Ksenofontova *et al*., 2020 and Camps *et al*., 2019). Behavioral drugs can help manage these problems but not all drugs are equally useful, and their use is not always indicated. Psychopharmacology is a sub discipline of pharmacology focused on the study of the use of drugs (medications) in treating mental disorders (Crowell-Davis *et al*., 2019). Extra labelisan "Actual use or intended use of a drug in an animal in a manner that is, not in accordance with the approved labeling (Sinn, 2018).

Pathophysiology of behavioral disorders in dogs and cats

Neurotransmitters are endogenous chemical messengers that initiate neuronal signal transduction and communicate between two neurons occurs at the level of the connection space between the two, i.e. at the synapse or synaptic cleft.

Based on their molecular structure, three major categories of neurotransmitters exist:

1. Monoamines (serotonin, dopamine, norepinephrine, adrenaline, acetylcholine, histamine)

2. Amino acids (primarily glutamate, gamma-aminobutyric acid (GABA), aspartate and glycine) and

3. Peptides (vasopressin, somatostatin, neurotensin).

But also, hormones, purines and even gases such as nitric oxide (NO) and carbon monoxide (CO) can function as brain neurotransmitters. Serotonin, dopamine, norepinephrine, GABA, the hypothalamic-pituitary-adrenal axis producing glucocorticoids, and glutamate will be examined successively within the framework of anxiety (Vermeire *et al.*, 2011).

Common behavioral disorders/ abnormalities in animals

Various types of behavioral disorders in dogs and cats include nonspecific/idiopathic aggression, fear, phobia, anxiety disorder and stereotyping behavior (Ksenofontova *et al*., 2020).

Dogs: Compulsive repetitive behavior (flank sucking, fly snapping, shadow and light chasing), nuisance behavior (coprophagia, digging, jumping on people, mounting, mouthing/play biting), excitement urination, marking behavior, submissive urination, disobedience, excessive barking, destructiveness, inappropriate urination and/or defecation, cannibalism and over-excitability

Cats: Indoor Spraying, soiling in the home (house soiling), intermittent litter tray usage, inappropriate hunting, fabric eating and wool sucking, destructive scratching, periodic absence and insecurity, psychogenic alopecia and over grooming.

Dog and Cat: Mourning behavior, aggression, scratching, anxiety, fears/phobias (separation anxiety**,** acryl lick dermatitis, thunderstorm), urine spraying behavior, compulsive repetitive behavior (licking, pica, tail chasing and recurring 'habits' (OCD)), and nuisance behavior (vocalization, soliciting behavior, nocturnal, predatory behavior, chewing, hyperactivity) (Horwitz, 2018).

Canine Cognitive Dysfunction Syndrome: It is similar to Alzheimer's disease that affects humans, affects the brain of elderly dogs, causing confusion, forgetfulness about many lifelong habits. The chemical and physiological changes that occur in an older dog's brain, accelerating degeneration of the brain.

Diagnostic aspects

To differentiate normal behavior from abnormal behavior and to exclude any medical problems. Therefore, a complete diagnostic plan should contain the following elements: Detailed history (medical and behavioral), observation, minimum database, knowledge of medical differentials for common problem behaviors, understanding of specific diagnostic criteria for common problem behaviors and ability to assess prognosis.

Among these a detailed history is the primary diagnostic tool of the behavior case, it include sex, breed, and age of animal (breed predispositions); age at onset of condition or complaint, duration of condition or complaint, description of undesirable behavior, frequency (hourly, daily, weekly, monthly), duration of bouts, any changes in pattern, frequency, intensity, and duration of bouts; corrective measures tried and the response, if any and 24-hr schedule of animal and owner, as well as any day-to-day variability (Stelow, 2018).

Therapeutic management of behavioral disorder

The primary goal of treatment in any behavioral disorder is modification of that behavior. Some behavior problems can be managed by behavior modification alone, it includes treatment of any concurrent disease and surgery such as castration/ neutering (for aggression, urine spraying etc.). Environmental management and appropriate behavior modification should always be used in conjunction with medication. Training techniques were grouped according to learning theory (punishment and rewards) and the intention the owner pursues when applying each type of training technique (reward-based responses to unwanted behavior). Arhant *et al*. (2010) reported the first group of training

methods, was called reward-based responses to unwanted behavior. The most common of these was comforting the dog by petting or speaking to it. The second group of training methods, was called punishment-based responses (scolding the dog verbally, jerking the leash, shaking the scruff, slapping the dog) to unwanted behavior.

Pharmacological agents

Behavior modifying drugs should always be associate in adjunct to psychotherapy, not a replacement. Most behavior issues are not 'cured' however is managed or controlled. When choosing a drug for anxiety, aggression, or compulsive disorder, it is important to remember that each patient is unique. All are trial-and-error testing. An initial treatment should be selected based on the patient's behavior problem and medical conditions, the side effects and safety role of the drug, other medications that the patient is already receiving, and the client's budget.

Premedication Considerations

The only two medications have been approved by FDA for behavior problems in animals: selegiline for canine cognitive dysfunction, and clomipramine for the treatment of separation anxiety in dogs (if used in combination with behavior modification). Other use of either of these drugs or other psychoactive drugs is extra label. Client signed consent form should always be obtained before proceeding with off or extra label drug use. It lists the risks, limitations, length of treatment required and potential adverse effects of the drug being prescribed (Crowell-Davis, 2006).

Classification of behavioral agents

Depression, anxiety, fear and phobia may be associated with genuine long-term neurotransmitter and synaptic changes in the CNS, but these changes are reversible through new learning in combination with medication. Many medications have anxiolytic properties, which are very useful because fear and anxiety are most common at the root of behavior problems in pets. Drugs with anxiolytic properties include benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, and azaperones (Table).

Monitoring

Monitoring of side effects is critical for any practitioner dispensing behavioral medication. The first tier of this involves the same tests mandated in the premedication work-up. Age-related changes in hepatic mass, function, blood flow, or plasma drug binding cause a decrease in clearance of some TCAs. Accordingly, monitoring hepatic and renal enzymes annually in younger animals, biannually in older animals, and as warranted by clinical Signs is prudent. Adjustment in drug dosages may be necessary with age.

Overall (1997) concluded that because of potential interactions, withdrawing one class of drug before starting another is preferable for most patients. Drugs should be discontinued by weaning rather than abruptly. Not only does this minimize any central withdrawal signs, but it allows the practitioner to determine the lowest dosage that is still effective. Unless the patient exhibits adverse effects, that treatment should be tried for at least 1 week for benzodiazepines or 1 month for the other drugs discussed. If

Table. Dosage, route and frequency of administration of drugs used in treatment of behavioral abnormalities of dogs and cats (Seksel, 2008)

S. No	Behavior modifying drugs	Dosages (mg/kg)		Route of administration	Frequency	Description
		Dog	Cat			
1.	**Antihistamines**					Not preferred as first-choice in the treatment of anxiety problems, not preferrable within two weeks of administration of MAOIs
	Cyproheptadine	0.3–2	0.4–0.5	PO	q.12 h	
	Diphenhydramine	2–4	2–4	PO	q.8-12 h	
	Hydroxyzine	0.5–2.2	2.2	PO	q.8-12 h	
2.	**Antipsychotics (neuroleptics)**					i) Aggression, anxiety-related problems and aberrant motor activity. Not used in epileptic patients.
	i) Phenothiazines					
	Acetylpromazine	0.1–2.2	0.5–2.2	PO	q.6–24 h	ii) Used experimentally in dogs, rats and monkeys.
	Chlorpromazine	0.5–3.3	0.5–3.3	PO	q.6–24 h	
	Thioridazine	1.1–2.2		PO	q.12–24 h	
	ii) Butyrophenones					
	Haloperidol	0.05–4	0.1–1.0	PO	q.12 h	
3.	**Anticonvulsants**					
	Phenobarbital (phenobarbitone),	1–4	1–4	PO	D - q.12 h or as needed up to 16 mg/kg/day C - q. 12–24 h or as needed	Its use is less in veterinary behavioral medicine. Its used to manage excessive vocalization and hyperesthesia syndrome in cats, 'rage syndrome' and spinning or tail chasing.Long-term use of phenobarbital may cause hepatotoxicity
	Carbamazepine	4–10	25	PO	D - q.8 h or 5–10 mg/kg q.12 h C - q. 12–24 h or 4–8 mg/kg q. 12 h	
4.	**β-blockers**					This blocker can have a calming effect on anxious animals. Care must be taken while using in diabetic patients.
	Propranolol	0.5–3.0	0.2–1.0	PO	q.8 h	
	Pindolol	0.125–0.25	-	PO	q.12 h	

5.	**Opioid agonists/ antagonists**				Self-mutilation, acral lick dermatitis and tail chasing. Naloxone is preferred as diagnostic tool for compulsive disorders. Naltrexone (opioid antagonist) has been used commonly in therapeutic conditions because it's a longer acting and cost effective.
	Naloxone	11–22 µg/ kg	-	SC, IM, IV PO	or 0.5 mg q.12 h
	Naltrexone	2.2	2–4		D - q.12–24 h C - q.24 h (up to 25–50 mg/cat)
				PO	
	Hydrocodone	0.25	0.25–1.0		D - q.8–12 h C – q.12-24 h
6.	**CNS stimulants – amfetamines**				These drugs have an inexplicable calming effect on really hyperactive dogs whereas in docile dogs they increase excitement and activity.
	Methylphenidate	0.05–0.25	-	PO	q.12–24 h
	Dexamfetamine	1.25 mg/ dog	1.25	PO	needed
7.	**Benzodiazepines**				Alprazolam has a rapid onset of action and good anti-panic effect and has been beneficial in treating storm phobia. Clonazepam to be less toxic to cats. Diazepam is probably the most common benzodiazepine in veterinary medicine but is occasionally hepatotoxic in cats.
	Alprazolam	0.25–2.0 mg/dog	0.0125–0.25 mg/cat	PO	q.8–12 h
			0.2–0.5		
	Diazepam	0.5–2.0		PO	D - q.4–12 h
			0.5–2.0		C – q. 12-24 h
	Clorazepate dipotassium	0.5–2.0		PO	q.8–24 h
	Clonazepam		0.016		
		0.1–0.5		PO	D - q.8–12 h
	Oxazepam		0.2–1.0		C - q.6–24 h
	Lorazepam	0.2–0.5	-	PO	q.8–24 h
	Flurazepam	0.02–0.5	0.2–0.4	PO	q.12–24 h
		0.2–0.4		PO	4–7 days

8.	**Antidepressants**					
	i)Tricyclic antidepressants					i) It has been most commonly suggested as a part of treatment protocol for anxiety-related disorders.
	Amitriptyline	1–4	0.5–1.0	PO	D - q.12–24 h C – q.24 h	
	Clomipramine	1–2	0.25–0.5	PO	D- every 12 h for 2 weeks, then 3 mg/kg orally every 24 h; sometimes it may need up to 4 mg/kg to control some disorders C – every 24 h; sometimes it may require up to 1 mg/kg to control some disorders	ii) Fluoxetine and paroxetine commonly used to treat marking behavior and anxiety-related disorders in cats.Fluoxetine and sertraline is used in the treatment of acral lick granulomas in dogs.
	Doxepin	3–5	0.5–1.0	PO	D - every.8–12 h once C - every.12–24 h once	iii) It is the first drug to be used as antide pressants. Moclobemide (MAO-A inhibitor) and selegiline (MAO-B inhibitor) are new antidepressant drugs. Only selegiline has been used in veterinary medicine for canine cognitive dysfunction syndrome in old dogs, and it may take around three months period to show the maximum behavioral benefits. It should require 2-week wash-out period and 5-week wash-out after TCA and fluoxetine therapy respectively.
	Imipramine	2.0–4.0	0.5–1	PO	every.12–24h once every 12–24h once	
	Nortriptyline	1–2	0.5–2.0	PO		
	ii) Selective serotonin reuptake inhibitors				q.24 h q.24 h	
	Fluoxetine				q.24 h; sometimes	
	Sertraline	1–2	0.5–1	PO	it not responds	
	iii) Monoamine oxidase inhibitors	1–3	0.5–1	PO	even after 4 weeks also, 1.0 mg/kg PO q.24 h.	
	Selegiline	0.5	0.5–1.0	PO		

9.	**Azaspirodecanediones**					Buspirone showing beneficial effects than benzodiazepines because of lack of sedation and a high safety margin.
	Buspirone	1.0–2.0	0.5–1	PO	q.8–24 h	
10.	**Hormones**					They are effective within the treatment of issues starting from roaming, sexual activity, raucous behavior, neurotic barking, digging behavior, automotive chasing, excessive timidity and poultry killing to marking behavior and aggression. It should not be recommended in intact females, breeding animals, diabetes mellitus patients (because it increases insulin resistance) and animals in corticosteroid treatment.
	Megestrol acetate	1.1–2.2	2.5–10	PO	D – every 24 h for two weeks, then 11/2 dose for next 2 weeks then one-quarter dose for last three weeks C – every 24 h for one week, then reduced to very minimal dose. maximum 3 times per year	
	Medroxyprogesterone acetate (MPA-50)	5–11	50 mg (females) 100 mg (males)	SC or IM		
11.	**α-adrenergic agonists**					The sympathetic drugs are primarily utilized in the treatment of urinary incontinence. It should not be used with MAOI therapy, prostatic hypertrophy etc.,
	Ephedrine	15–50	2-4 mg/cat	PO	q.12 h	
	Phenylpropanolamine	1.1–4.4	12.5	PO	q.8 h	
12.	**α - a d r e n e r g i c antagonists** Nicergoline	0.25–0.5	0.25–0.5	PO	It should give q.24 h in the morning for a period of at least 30 days. Repeat monthly once or as when its required	It is suggested for treating dogs with canine cognitive dysfunction syndrome and cerebral insufficiency of vascular origin.

13.	**Pheromones**	-	-	-	-	Feliway is preferred to treat urine marking or anxiety in domestic cats and cheetahs. Dog appeasement pheromone has been utilized in the treatment of noise phobias and separation anxiety etc.,
13.	**Ergot alkaloids**					
	Bromocriptine	0.01–0.10	2–4 mg/cat	Once PO in dog S/C in cat	or divided twice per 24 h repeat after 2–4 weeks	It is used for urine spraying in cats and pseudocyesis in dogs.
14.	Lithium carbonate	3–12	-	PO	q.12–24 h	In dogs it is used to treat unpredictable and severe aggression cases.
15.	**Xanthine derivative glial cell modulators**				It is divided into two equal doses and administered orally 1 h before feeding for at least a period of 30 days, then continue indefinitely	It is usually suggested to help dullness, lethargy and overall demeanor in senile dogs.
	Propentofylline	6–11	-	PO		

D – dog, C – cat, q – every, PO – oral, SC – subcutaneous, IM – intramuscular, IV – intravenous

after 1 month there are no adverse effects but the patient has improved insufficiently, the dose can be increased. If the maximum dose is reached or if adverse effects occur at levels lower than the maximum dose and the problem is still not adequately resolved, another drug should be tried. The fact that a patient does not respond as desired to one drug does not mean there will not be a beneficial effect from another drug, even one in the same family.

Once the required result is achieved, it should be made to gradually wean off therapy and maintained for duration of 2–3 months. Weaning can be done rapidly (i.e., decrease the dose by approximately 25% every week) in pets with minor problems that have responded rapidly to treatment. In some patients condition that will require long term therapy and this should be explained clear to the owner at the commencement of therapy. The use of medication by itself is not a permanent cure of behavior problems. Even in patients that respond very well to medication, the ultimate goal is to wean the patient from medication.

Failure of therapy

The most common reasons for apparent treatment failures when behavior modifying medications are prescribed include:

Inappropriate selection of medicine for the abnormal behavior. An insufficient time is allowed for the treatment protocol to get desired effect. Use of medications as 'stand-alone' medical aid when they should have been combined with a psychotherapy program (Seibert and Landsberg 2008).

Conclusion

When choosing a drug for anxiety, aggression, or compulsive disorder, it is important to remember that each patient is unique. The only option for a given patient is trial-and-error testing. An initial treatment should be selected based on the patient's behavior problem and medical conditions, the side effects and safety profile of the drug, other medications that the patient is already receiving, and the client's budget. If the maximum dose is reached or if adverse effects occur at levels lower than the maximum dose and the problem is still not adequately resolved, another drug should be tried. The fact that a patient does not respond as desired to one drug does not mean there will not be a beneficial effect from another drug, even one in the same family. Environmental management and appropriate behavior modification should always be used in conjunction with medication. Weaning can be done rapidly (i.e., decrease the dose by approximately 25% every week) in pets with minor problems that have responded rapidly to treatment.

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