Diagnosis and Treatment of Behavior Problems in Cats and Dogs

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Diagnosis and Treatment of Behavior Problems in Animals: History, Ethics and Legal Issues

Veterinary Behavior

- That branch of veterinary medicine which deals with the prevention, diagnosis and treatment of behavior problems in non-human animals.

- Clients often have questions about animal behavior and behavior problems.
- They expect their veterinarian to provide them with accurate, useful information.
- There are a lot of pop-culture myths about animal behavior and self-professed experts in behavior who give out a lot of misinformation.
- Several million dogs and cats are euthanized or abandoned each year due to unacceptable behavior.
- Often, these behavior problems could have been treated or prevented.
- Each year, in the United States alone
  - Several million people are bitten
  - 20+ people are killed by dogs

Societal norms?

- Any good behaviorist can figure out what “provoked”, i.e. caused, the dog to bite.
- As a society, we must decide what is and is not an acceptable provocation for dogs living among us.

General Practice

- First contact by pet owners confronted by behavior problems
- Presented with a chief complaint
- Diagnose
- Decide on an appropriate treatment plan

- Behavior Problems vs. Training
- Veterinary Behaviorists may use certain training techniques in the treatment of certain problems, especially with dogs. However, training is only one part of a comprehensive treatment plan.
- School teachers and Psychiatrists do not do the same thing!!!!

Practice of veterinary medicine:

- To diagnose, treat, correct, change, relieve or prevent animal disease, deformity, defect, injury, or other physical or mental conditions; including the prescription or administration of any drug, medicine, biologic,…or to render advice or recommendation with regard to any of the above.

- Model Practice Act, AVMA
- Psychoactive Medications
- Medications that produce changes in behavior and/or motivation
- Most use of psychoactive medications in veterinary medicine is extra-label.
- ONLY exceptions are
  - Anipryl® for Canine Cognitive Dysfunction
  - Clomicalm™ for Canine Separation Anxiety
• Reconcile™ for Canine Separation Anxiety

Animal Medicinal Drug Use Clarification Act (AMDUCA 1994)
• Requirements for extra-label use
• Valid client/veterinarian/patient relationship
• Animal Medicinal Drug Use Clarification Act (AMDUCA 1994)
• Behavioral history MUST be taken
• For any chief complaint which is behavioral in nature you must do an appropriate and adequate medical and behavioral evaluation to justify coming to a diagnosis.
• Animal Medicinal Drug Use Clarification Act (AMDUCA 1994)
• Just because the owner or the dog trainer says the dog has dominance aggression (or any other diagnosis) it does not mean that the dog does have dominance aggression. It may have fear aggression, hip dysplasia, be inadequately exercised, not have been appropriately trained to not jump up on people, or a variety of other problems instead.

Veterinarian has established a diagnosis
• Not the dog trainer
• Not the veterinary technician who has an interest in behavior
• Not the “behaviorist” who is not a veterinarian, even if they have some kind of certification
• Not the owner who saw on 20/20 last night that Prozac cures thunderphobia
• Must be a specific rationale, and its use is accepted under current medical conditions.
• Keep up with the literature
• This is a rapidly advancing field

Extra-label usage
• Inform client of the extra-label status of the drug.
• If necessary, explain to the client what extra-label means.
• Inform the client of known side-effects.
• Signed informed consent statement.

While the veterinarian can obtain valuable information and assistance from
• Veterinary Technicians who are educated and experienced in techniques of treating animal behavior
• PhD’s who focus on domestic and applied animal behavior
• Ethical trainers who use humane training techniques
• The veterinarian is legally and ethically responsible for all decisions regarding treatment of a given case.

AVSAB
• American Veterinary Society of Animal Behavior
• www.avsabonline.org for membership and other information

American College of Veterinary Behaviorists
• www.dacvb.org for list of and contact information on behavior college diplomates

SVBT
• Society of Veterinary Behavior Technicians
• www.svbt.org for membership and other information

• When should a general practitioner call a specialist?
• Anytime you have a question about how to handle the case…
• scrowell@uga.edu
• 706-542-8343

• When to refer to a specialist?
• Anytime the case is so complex or presents such dangers that you feel uncomfortable attempting to pursue diagnosis and treatment yourself, with or without correspondence with a specialist, or if the patient is not responding to treatment as expected.
• Particularly consider referral in cases of serious aggression.

• American College of Veterinary Behaviorists
• Recognized by the AVMA in 1993
• All listed in the AVMA directory and on www.dacvb.org
• One year general internship or equivalent
• 2-3 year conforming residency
• additional pre-requisites for two year residency
• non-conforming residency option exists
• learning and effort must be equivalent to a conforming residency

Learning

Learning
An enduring change in behavior which results from experience with environmental events.

Habituation
A decrease in response as a consequence of repeated exposure to a stimulus.

Startle reactions to noise
The initial response is innate, not learned. It is the decrease in the response that is learned. Habituation is not the same thing as Extinction, in which a learned response is lost.

Classical Conditioning
Also called Pavlovian Conditioning
The process by which a Neutral Stimulus comes to elicit a Response that it would not naturally elicit.

Unconditioned Stimulus (US)---->Unconditioned Response (UR)
Neutral Stimulus (NS) + US---->Unconditioned Response (UR)
NS becomes a Conditioned Stimulus (CS)----> Conditioned Response (CR)

Classical Conditioning involves

Emotional responses
Food anticipation
Playfulness
“Anger”
Arousal
Relaxation
Amusement

**Physiological responses**
Insulin release
Hormone release
Respiration rate
Pulse rate
Sweating (in species that sweat)

Stimulus that determines if the response will occur happens before the behavior and is the cause of the behavior.

Classical Conditioning-Example
Fear in the dog
US=Being yelled at, hit
UR=Fear
NS=Sight of owner or sound of owner’s voice.
Various stimuli associated with the owner become CS’s which elicit a CR of Fear

Classical Conditioning-Auditory Stimuli
Specific words
Tone of voice
Depth of voice (low to high)
Specific voices
Specific non-voice sounds
Rain on roof
Popping noises
Cracking noises

Classical conditioning-Visual stimuli
Colors
Shapes
Patterns
Brightness
Movement

Classical conditioning-Tactile stimuli
Touch in certain locations
Certain types of touching

Classical conditioning-Olfactory stimuli
Hard for humans to identify
Specific perfumes
Specific natural animal odors
Artificial odors generated by human environment
Classical Conditioning-Stimulus Discrimination
Only specific, discrete stimuli elicit the response

Classical Conditioning-Stimulus Generalization
The response is elicited by a diverse, but related, group of stimuli.

Classical Conditioning-Extinction
If the animal is repeatedly exposed to the CS without further pairing with the US, the animal’s response to the CS will eventually cease. When this happens, extinction is said to have occurred.

Flooding
Term used for the deliberate exposure of the animal to a stimulus until the response extinguishes or the animal habituates.

Flooding-Problems
Once a flooding session is initiated, exposure to the stimulus must continue until the response ceases. Otherwise the behavior may be reinforced. Animals with strong fears may injure themselves, other animals or people in the vicinity, or damage their surroundings.

Operant Conditioning
Also called Instrumental Conditioning
Behavior is affected by its consequences.

Eliciting Stimulus(ES)--->Response(R)--->Controlling Stimulus(CS*)

Operant Conditioning-Reinforcement
The probability that the behavior will recur is *Increased*

Operant Conditioning-Punishment
The probability that the behavior will recur is *Decreased*

Operant Conditioning-Positive
The Controlling Stimulus is present or occurs as a consequence of the response occurring.

Operant Conditioning-Negative
The Controlling Stimulus is absent or is removed as a consequence of the response occurring.

Positive Reinforcement
Negative Reinforcement
Positive Punishment (Punishment)
Negative Punishment (Time Out)

Operant Conditioning-Positive Reinforcement
The probability that the behavior will recur *increases* as a consequence of a specific stimulus occurring immediately subsequent to the behavior.
If you do X and good things happen, keep doing X.
Say ‘Sit’ (eliciting stimulus) while holding a treat over a dog’s head.
If the dog sits, give it the treat.
If it does not sit, do not give it the treat.

Operant Conditioning-Prompting and Fading
Strongly prompt behavior, e.g. by pushing animal into position, while giving an eliciting signal, such as the word “SIT”.
Give reinforcer (reward)
With repetition, gradually fade the intensity of the prompt.

Operant Conditioning-Shaping
Elicit a behavior that would be the “first step” towards the final behavior.
Gradually require the animal to engage in a behavior that is more and more like the final behavior before it is rewarded.

Operant Conditioning-Negative Reinforcement
The probability that the behavior will recur increases as a consequence of the controlling stimulus being absent or removed if the behavior occurs.
If you do X and bad things go away or stay away, keep doing X.

Operant Conditioning-Negative Reinforcement-Escape
A dog is in a cage with access to a platform and a floor which can shock the dog.
Turn on the shock and the dog will jump around.
Eventually it will jump onto the platform.
Jumping onto the platform is negatively reinforced.
The shock is both the eliciting and the controlling stimulus.

Operant Conditioning-Negative Reinforcement-Avoidance
In the same cage as before, have a light which turns on immediately prior to the electrical current being turned on.
The dog will learn to jump onto the platform when the light goes on.
The light is the eliciting stimulus.
The shock is the controlling stimulus.

Aggression to children
If a child is causing a dog pain, the dog growls, and the child goes away, growling is negatively reinforced.

Operant Conditioning-Positive Punishment
Usually referred to as “Punishment”
The probability that the behavior will recur decreases as a consequence of a specific stimulus occurring immediately subsequence to the behavior.
If you do X and bad things happen, stop doing X.

For punishment to be effective, three conditions must be met.
The punishment must occur immediately.
The punishment must be consistent, i.e. occur every time
The punishment must be appropriate for the individual animal

Operant Conditioning-Punishment-Immediacy
As the animal is exhibiting the behavior or within 1 second of stopping.

Operant Conditioning-Punishment-Consistency
If punishment occurs under only some circumstances, animals often discriminate the circumstances in which the aversive stimulus does not occur.

Operant Conditioning-Punishment-Appropriateness
The punisher should be strong enough to stop the behavior, but not strong enough to cause fear.

If these three conditions are not met, use of “punishment” is unlikely to be successful, i.e. the behavior will not decrease or stop.

Use of the aversive stimuli typical of punishment introduces the risk of causing fear related problems.

Operant Conditioning-Punishment-Effective Use
Human-directed aggressive play in cats
Easy to do
  o every time
  o immediately
  o just need to identify appropriate punisher

Operant Conditioning-Negative Punishment
Usually referred to as “Time out”
The probability that the behavior will recur decreases as a consequence of the controlling stimulus being absent or removed if the behavior occurs.
If you do X and a good thing doesn’t happen or stops happening, don’t do X.

If you poke your sister again, you won’t get any dessert.
  Not commonly used in veterinary behavior.
  Teaching puppies inhibited bite
  Social isolation (time out) is effective in certain cases.

Operant Conditioning-Common Errors
Punishment and Negative Reinforcement are not the same thing.
  Confusion of term “negative” with “aversive”
  Political correctness

Operant Conditioning-Schedules of Reinforcement
Continuous
Fixed Ratio
Variable Ratio
Fixed Interval
Variable Interval
Continuous Reinforcement
Reinforcement is provided every time the response occurs.
Most effective method when an animal is initially learning a new response.

Variable Ratio
Reinforcement is provided after varying numbers of repetitions of the response.
Example: every 1st, 2nd or 3rd time the response occurs after the last response.
If an animal is on a steadily increasing variable ratio schedule, the behavior tends to become very persistent.

Problems
Gambling in Humans
Barking
Jumping up

Training and Treatment
Any behavior we wish to become persistent.

Operant Conditioning-Extinction
If the reinforcer (CS*) totally stops occurring, the response will eventually cease occurring subsequent to the ES.
When that occurs, the operantly conditioned response has extinguished.

Reinforcers and Motivation
The animal’s motivation also affects how fast and well learning occurs.
A hungry animal responds better to food rewards than a satiated animal.
Animals learn better for highly palatable food treats than for low palatability food treats.

Secondary Reinforcers and Punishers
Due to Classical Conditioning a NS can come to have a similar rewarding or punishing value as an unconditioned stimulus.
Clicker can be associated with food treats
Click→Treat
Buzz can become associated with shock
Buzz→Shock

Two Process Theory
In most learning situations, both operant and classical conditioning are happening simultaneously.
This can profoundly effect long-term
Emotional status
Physiological status

Reinforcers, Punishers and Emotional State: Two Processes occurring simultaneously

Because of classical conditioning the consistent use of pleasant or aversive training techniques will profoundly affect the animals’ emotional status in the training context.
Use of aversive training techniques can cause behavior problems, including fear aggression, excessive timidity, submissive urination.

Use of aversive training techniques can generate animal welfare concerns.

Positive Reinforcement
Reliability?
Done correctly, very reliable

Desensitization
The animal is exposed to a stimulus that elicits a given response, but at such a low level that the response is not elicited. Over time and successive repetitions, then intensity of the stimulus is gradually increased, ideally without eliciting the response.

Must be able to control the intensity of the stimulus

Counter-conditioning
A response is elicited which is behaviorally and physiologically incompatible with another response.
Food treats
Play
Massage

Social Organization and Communication in the Cat

Solitary
• A species in which individuals form no enduring social relationships, living most of their lives in a solitary condition, and forming no enduring pair bonds.

Asocial
• Literally, Not Social
  – A species in which individuals do not engage in social interactions with each other

Aggregation
• A group of animals which gather around a common resource, such as food or water. It is the resource, and not any internal organization of the group which causes the proximity of the individuals, and cooperative behavior does not occur within the group.

Social
• A species is classified as social if members form long-term pair bonds, live in family groups, or live in larger groups with a relatively stable long-term membership.
• In addition, members of the social group exhibit individual recognition, cooperative behavior and reciprocal communication.

Dominance
• “An individual to which another consistently gives way is said to be dominant in the relationship, the
other being subordinate…”
– Immelman and Beer 1989
– A Dictionary of Ethology

Dominance hierarchy
• The order of ranks within a group of animals
• Construct by humans, using mathematics
• Animals may or may not recognize the relationships between other individuals
  – A may know that she is dominant to B and to C, but may not know that B is dominant to C.

Linearity?
– May or may not be linear
– Linear: A-> B ->C->D
– Non-linear: A->B->C  D is subordinate to C, but dominant to B

– Within a given species, a variety of variables, including group size and environmental conditions, will affect whether or not the hierarchy within a given group is linear.

Social organization in cats-Matriarchal
“Adult females associate in lineages which are the building blocks of cat society.”
  MacDonald, Yamaguchi & Kerby 2000

• Queens cooperatively rear young
  – Communal nesting
  – Nursing
  – Grooming
  – Guarding
  – Midwifing
• Often, but not necessarily, related

Preferred associates
  [Determined by relative frequency within 1 meter (Wolfe 2001)]
• Can be
  – female-female pairs
  – male-male pairs
  – male-female pairs
• Multiple sets of preferred associates may effectively form trios or tetrads of cats that form a ‘clique’ within the larger group.

• Intact males may
  – be preferred associates
  – allorub
  – allogroom
  – rest together
• At this point, there is no direct evidence that they form alliances, as male lions do.
Preferred associates
• Allogroom more
• Allorub more
• Are in physical contact more
  – than non preferred associate
    • (Wolfe 2001)
• Preferred associates do not associate exclusively at specific sites of preferred resources, e.g. food, resting sites. Instead, they are often found together in a large number of sites. (Chi-square: Association was random with regard to location.)
• This rules out the hypothesis that they simply tend to go to the same resources at the same time of day, or are forming aggregations.
• They are together for another reason, i.e. a social bond.

Allogrooming
• As with horses, is often done in an area that is difficult for the cat being groomed to reach.
• One advantage to colony living--you get your head cleaned

Allorubbing
• By ad libitum reports, occurs more when cats return to the colony after being gone for awhile, presumably hunting
• May serve to exchange scent
  – Colony odor?
• Significance of tactile contact and communication?

Friendly greeting: Tail Up
• Allorubbing is usually preceded by a tail-up approach by at least one cat and is most likely to occur if both cats approach tail-up.
  – (Brown 1993; Bernstein and Strack 1996; Cameron-Beaumont 1997)

Physical contact
• Occurs even in hot, humid weather
• Serves another function than thermoregulation

Play
• Adult cats, including free-living and feral cats which must hunt to survive, play.

Time together
• For pairs of cats, the longer they have been together, the less overt aggression occurs. This is consistent with the formation of stable dominance relationships which rely on dominance signaling, rather than overt aggression.
  – Barry and Crowell-Davis, 1999
Association
• Relatives and cats that a given cat is more familiar with are more likely to be nearest neighbors than non-relatives and cats a given cat is not familiar with. Being related is more important than familiarity
  – Curtis, Knowles and Crowell-Davis 2004
  – AJVR

Socialization of kittens and juveniles
• What roles do adults play in the social education of juveniles?

Raising kittens?
• Extensive social learning occurs from 2-16 weeks and beyond.
• Raising cats from 5-6 weeks onward with no contact with their own species can result in serious incompetence in social skills.

Non-group members?
• Recognized as “strangers” and are either driven from the group or, if they are successful in persistent attempts to join the group, cause a period of conflict and disorganization within the group.
  – e.g. MacDonald et al.1987, Wolfe 2001

Polygamous species
Males mate with multiple females AND females mate with multiple males.

Males
• Two major strategies
  – Spend most of their time with a particular group
    • Develop strong affiliative relationships with the queens in that group. Defend kittens.
  – Migrate from group to group, seeking estrous queens
    • Maximize opportunities to mate with multiple queens

Solitary activity
• Primary diet is small rodents
• One cat requires several small rodents a day
• Hunting technique involves quiet, slow stalk of rodent with sudden killing pounce.
• Most effectively done alone

Solitary life
Hunting-dispersion
• Spray marks may assist cats which are members of the same colony in dispersing, so that they do not interfere with each others hunting

How did they become social?
• Ancestor Felis libyca is presumed to be solitary and asocial
• Reclusive, cryptic cat about which little is known
Is Felis libyca really solitary?

- During field studies in North Africa, MacDonald (1996) observed *Felis libyca* joining a group of feral *Felis catus*.

- Smithers (1983) observed tame *F. libyca* females bringing food to each other when one or the other had kittens.

Selection pressure on ancestral *Felis libyca*

- Early human farming settlements in North Africa provided concentrated food resources which attracted large numbers of cats.
- Long period of maternal care as mother teaches growing kittens to hunt.
- With population density around concentrated food resources, cat families that extended cooperation and social behavior into adulthood would have been more successful than asocial or solitary individuals.

Dominance in Cats

- Dominance relationships do form between cats.
- For some dyads, the asymmetrical nature of the relationship is reinforced regularly, while for other dyads, cooperation is more obvious in the relationship than is agonistic interaction.
- Within the group, dominance hierarchies are formed (e.g. Natoli et al. 2001)

Dominance

- Ears up and rotated so aperture is more lateral
- Hind limbs extended and stiff
- Base of tail elevated/Remainder of tail drooped
- Head wag
- Approach
- Eye stare

Submission

- Ears down/back
- Tail down
- Head down
- Crouched
- Avoidance
- Rolling over
  - Feldman 1994

Fear aggression

- Arched back
- Ears back
- Tail arched or straight up
• Shows teeth
• Piloerection
• Hisses
• Growls

Psychopharmacology:
Serotonin and Norepinephrine Reuptake Inhibitors

Abbreviations
- SRI-Serotonin Reuptake Inhibitor
- SSRI-Selective Serotonin Reuptake Inhibitor
- SNRI-Serotonin and Norepinephrine Reuptake Inhibitor
- TCA-Tricyclic Antidepressant (a family of SNRI’s)

Cost: Old vs. New
- New SSRI’s and SNRI’s are typically very expensive
- We usually use the older ones in veterinary medicine because of cost issues

Action-SSRI’s
- Inhibition of serotonin reuptake. This increases serotonergic neurotransmission by allowing serotonin molecules to act for extended periods of time.

Action-SNRI’s
- 5-HT reuptake inhibition
- NE reuptake inhibition

- Chronic administration causes decreased numbers of β-adrenoceptors and serotonin receptors, as well as altered function of various serotonin receptors.

TCA’s also
- α-1 adrenergic antagonism
- Anticholinergic
- Antihistaminic

Uses in dogs and cats
- Anxiety and disorders motivated by anxiety, e.g. urine marking
- Aggression
- Compulsive Disorder, e.g. tail-chasing, lick granuloma

SSRI’s
- Side Effects
  - Sedation
  - Anorexia
  - Gastrointestinal signs
  - Anxiety
Irritability
Insomnia
Aggression
Decreased libido

Slow onset of action
Metabolized in liver
Excreted through kidneys
May have 1-4 week latency to effect
Long t1/2

Citalopram Hydrobromide
  Dogs: 0.5-1.0 mg/kg q24h
  Has been used to treat canine acral lick dermatitis

Fluoxetine Hydrochloride (Prozac®, Reconcile™)
  DOGS: 1.0-2.0 mg/kg q24h
  CATS 0.5-1.5 mg/kg q24h

  Available as:
    Chewable tablets (Reconcile™): 8, 16, 32, 64 mg
    Tablets: 10, 20 mg
    Capsules: 10, 20, 40 mg
    Slow release tablet: 90 mg (designed for human GI system)
    Solution: 20 mg/5 ml mint flavored
      Cats appear to find the mint flavoring offensive

  Absorption is poor when administered transdermally

Contraindications
  Reduce dose with patients with hepatic or kidney impairment
  Use cautiously with patients with diabetes mellitus (may decrease blood glucose)
  History of seizures
  Use cautiously with TCA
  DO NOT use with MAOI
Pharmacokinetics
Well absorbed after oral administration
Metabolized by cytochrome P450 enzyme system to norfluoxetine, which is active
In dogs, the elimination half-life of fluoxetine is 6-7 hours
Half-life of norfluoxetine is about 2 days

In an open trial of 65 dogs with psychogenic pruritis, acral lick granulomas, tail mutilation, separation anxiety and miscellaneous behavioral problems, onset of efficacy was 5 to 16 days

Reconcile™
8 week trial
End of week 1
42% of dogs on Reconcile showed improvement
18% of dogs on placebo showed improvement
End of 8 weeks
73% of dogs on Reconcile showed improvement
51% of dogs on placebo showed improvement

Fluoxetine in Cats (Pryor et al. 2001)
Cats treated with fluoxetine showed a significant decrease in spraying by the second week, and continued to exhibit a decreased frequency through the end of an 8 week study.

Paroxetine HCl Paxil®
CATS: 0.5-1.0 mg/kg
DOGS: 0.5-1.0 mg/kg

Oral Suspension
Orange flavored 2 mg/ml

FDA approved uses in humans
Depression
Obsessive Compulsive Disorder
Panic Disorder
Social Anxiety Disorder
Generalized Anxiety Disorder

Pharmacokinetics
Multiple metabolites, about 1/50 as potent as the parent compound.
Humans
10 days
64% excreted in the urine, 2% as parent compound and remainder as metabolites
36% excreted in feces, <1% as parent compound

Uses in animals
Published efficacy for
Urine spraying and aggression in cats
Generalized anxiety disorder in dogs
Weaving in horses
Sertraline (Zoloft®)
CATS: 0.5-1.0 mg/kg
DOGS: 0.5-4.0 mg/kg

Uses in animals
Published efficacy for
Acral lick dermatitis (ALD) in dogs
Aggressiveness in lizards (Anolis carolinensis)

TCA’s
Tricyclic Antidepressants
Named after chemical structure
Use in animals as for SSRI’s

Tertiary Amines
Have two methyl groups at the end of their side chain.
More potent inhibition of 5-HT uptake
More potent α-adrenergic, cholinergic, and histaminergic receptor blockade
Significant sedative effects
Amitriptyline
Clomipramine
Doxepin
Imipramine

Secondary Amines
One methyl group at the end of the side chain
More potent inhibition of NE reuptake
Desipramine
Nortriptyline

Biochemical Activity

Effects - Therapeutic
Norepinephrine
↓ General arousal
↑ Attention
↓ Mood reactivity
↑ Stress response modulation

Serotonin
Regulate mood states
↓ Fear responses
↓↑ Feeding behavior
↓ Stress response
↓ Impulsive behavior

Effects - α-Adrenergic
Orthostatic hypotension
  Dizziness
  Syncope
Sedation
Vasoconstriction
Smooth muscle contraction

Effects - Anticholinergic

**Urinary retention**
Dry mouth
  Dental pathology
  Stomatitis
Mydriasis
d† Tear production
Impaired visual accommodation
  Blurred vision
Bronchodilation

Effects – Anti-Histaminic

Anti-pruritic effect
Sedation
Anti-ulcer activity
Weight gain

Cardiovascular Effects: Much more profound in humans than in dogs and cats

**Tachycardia**
Arrhythmias
  Sinus tachycardia (NE)
d† Conduction time
Heart block
Myocardial infarction
Stroke

ECG Assessment in Dogs
Research on cardiac function in dogs given amitriptyline and clomipramine
No ECG changes between pre and post-treatment
No differences between untreated and treated dogs

Gastrointestinal Effects

Vomiting
Diarrhea
Anorexia
Constipation

Humans report
Nausea
Abdominal cramping
Behavioral Side Effects

**Sedation**
- Anxiety
- Restlessness, agitation
- Sleep disorders
- Fatigue
- Headache
- Ataxia

Other Effects
- Lowered seizure threshold
- Altered blood glucose levels
- Bone marrow suppression
- Bitter taste
  - Difficulty in medicating animals
  - Helps prevent overdosing

Dose Management
- 2 – 4 week latency to effect, sometimes longer
- Give daily or b.i.d., not “as needed”
- Stabilize for 1 – 2 months
- Gradual withdrawal
- Certain conditions require long-term treatment
- Metabolized in liver
- Cleared primarily through urine

Pharmacokinetics
- Individual variation in metabolic rate
- Poor metabolizers”
  - Hepatic P450 enzymes
- Decreased renal clearance in human geriatric patients

Drug Interactions
- MAOIs
- Anticholinergics
- Sympathomimetics
  - Cardiac toxicity
- Thyroid supplements
- Anti-thyroid agents
  - Agranulocytosis

Drug Interactions
- Cytochrome P450 competition
  - Antidepressants
  - Antipsychotics
  - Psychostimulants

Precautions
Glaucoma
Urinary retention
Cardiac disease
Thyroid disease
Seizure disorder
Adrenal tumors
Liver disease
Kidney disease
Pregnant female
Lactating female

TCA Toxicity
Narrow therapeutic index in humans
1 week supply for a dog could be fatal to a human
Toxicity at 2-6 x concentration
5% human fatality rate for overdoses

Ataxia
Convulsions
Lethargy
Stupor, coma
Respiratory depression
Hypotension
Hyperthermia
Pulmonary edema
Hepatotoxicity
Dilated pupils
Agitation
Hyperreflexia
Muscle rigidity
Vomiting
Vocalizing
ECG changes
Cardiac arrhythmias

Toxicity in Companion Animals

- Illinois Animal Poison Information Center
  456 calls (1985-1989)
  Accidental ingestion of TCAs
  > 7% fatality rate
  ≥ 15 mg/kg PO potentially fatal

TCA Toxicity: Treatment
No specific antidote
Emetics not indicated except in first 30 minutes
Supportive care
Airway support
Gastric lavage
Activated charcoal
Diazepam for seizures
Na bicarbonate for acidosis
Physostigmine IV helps with CNS and cardiac toxic effects in humans

Amitriptyline (Elavil)
Forms available
Tablets: 10, 25, 50, 75, 100, 150 mg
Injectable: 10 mg/ml

- Dog 1-6 mg/kg q12-24 h
- Cat 0.5-2.0 mg/kg q12-24 h
- Parrot 1-5 mg/kg q12-24 h

Transdermal?
Absorption is poor when administered transdermally as opposed to orally.
Transdermal administration not recommended at this time.

Amitriptyline – Uses in Dogs?
- Urine marking
- Anxieties, fears, and phobias
  - Separation anxiety
  - Situational fears
- Aggression?
- Tail chasing
- Acral lick dermatitis

TCA with most potent H₁ blockade
Dogs
Significantly less effective than clomipramine for compulsive disorder (Overall and Dunham 2002)
May be useful for separation anxiety Takeuchi et al, 2000

Used effectively in cats for
- Idiopathic cystitis
- Excessive vocalization in a cat
- Psychogenic alopecia

Clomipramine (Anafranil)
Dog 1-3 mg/kg q12 hr
Cat 0.25-2.0 mg/kg q24h
Parrots 2.0-4.0 mg/kg q12h

Pharmacokinetics
- Most serotonin selective of the TCA’s
- Metabolites
Desmethylclomipramine
Higher concentration than parent compound in humans, but not in dogs
Potent NE uptake inhibitor
\[ t_{\text{(human)}} = 15-60 \text{ hr} \]
\[ t_{\text{(dog)}} = \leq 4 \text{ hr (King et al, 2000)} \]
2 – 9 hr (fasting)
3 – 21 hr (non-fasting)
Peak plasma level in dog-3 hr
Peak plasma levels of desmethylclomipramine 4-6 hr
\[ t_{\text{(dog)}} \text{ desmethylclomipramine about 4 hours} \]

In dog, 80% eliminated through bile within 4 days.

When dogs dosed daily, steady-state plasma concentrations achieved in 4 days.
Faster and more absorption in fed dogs than fasted dogs
Half-life of both clomipramine and desmethylclomipramine increases with increased dosage.
Main route of elimination of both may be saturable
Increasing numbers of molecules may directly inhibit the elimination process.

Comparative Pharmacokinetics
Clomipramine: Desmethylclomipramine concentration
Dog 3:1
Human 1:2.5

May be reason adverse events more common in humans
Desmethylclomipramine has stronger anticholinergic activity than clomipramine

Most common side effects
Mild sedation, usually transient
Vomiting
Appetite changes
Also mydriasis and urinary retention

Clomipramine - Toxicity
Dogs treated daily for 8 days
12.5, 50, and 100 mg/kg PO
Mortality only at 100 mg/kg dose
Spermatogenesis affected at 50 mg/kg

Dogs given continuous IV infusion until cardiotoxicity occurred, exhibited cardiotoxic effects at an average of 64 mg/kg (range 53-72)

Dogs given 3 mg/kg clomipramine q12h for 112 days have significant decreases in total thyroxin (T4), free thyroxin(fT4) and triiodothyronin. However, clinical hypothyroidism did not occur and there was no change TSH or thyrotropin release hormone levels (Gulikers and Panciera 2003).
Effectively used in cats for
- Urine marking
- Hypervocalization
- Offensive Affective aggression
- Hyperesthesia syndrome
- Compulsive disorder
  - Displacement grooming/Over grooming (Psychogenic alopecia)
- Wool sucking

Clomipramine-Urine spraying
King et al. 2004
Double-blind placebo-controlled multicenter clinical trial of 67 neutered cats.
All doses more effective than placebo
Decrease in frequency was dose related with 0.5-1.0 mg/kg daily being the most effective

Has been used effectively in dogs for
- Affective aggression
- Compulsive disorder
- Separation anxiety
- Other fears and phobias, including storm phobia

Treating Separation Anxiety with CLOMICALM
Administration
- Single or divided dose
- 2-4 mg/kg (total daily label dose)
- With or without food (administration with food may reduce incidence of emesis)
- In practice, I often go up to 6 mg/kg tdd

Course of Treatment
- Determined case-by-case according to each dog’s response to therapy; raise or lower dose
- Improvement may be seen a month or less after treatment begins
- Behavioral modification should continue after treatment with medication

Clomicalm-Efficacy
- In clinical trials, 75% of dogs were considered improved by their owners after one month of dosing

Clomicalm-Safety
- Well tolerated at the recommended label dose
- In a 6-month safety study:
  - Beagle dogs were dosed at 5x-10x the recommended daily dose (20 mg/kg/day)
  - Emesis and decreased activity was seen, but there were no treatment-related changes observed (body weight, EKG, blood chemistries)
- Higher doses more effective than lower doses (Simpson 1997; King et al. 2000)
- I only use low dose (1 mg/kg b.i.d.) in geriatric patients or patients with mild compromise of liver or kidney function

Stereotypies/Compulsive Disorder
- Effective in open and more effective than placebo in placebo controlled trials or amitriptyline or
desipramine in drug comparison trials (Overall and Dunham 2002; Hewson et al. 1998b; Moon-Fanelli and Dodman 1998; Thornton 1995; Overall 1994; Goldberger and Rapoport 1991)

Desipramine (Norpramin)
Forms available
Tablets: 10, 25, 50, 75, 100, 150 mg
Dog 1.5-3.5 mg/kg q24h

Pharmacokinetics
Most biochemically selective TCA
Blocks NE reuptake at low concentrations unlikely to affect 5-HT
t\(_d\) (human) = 10-30 hr
Primary metabolite is 2-hydroxydesipramine

Effective in CD, but not as effective as clomipramine
Effective for cataplexy in dogs, but not as effective as nortriptyline

Doxepin (Sinequan)
Available as
Capsule: 10, 25, 50, 75, 100, 150 mg
* Oral concentrate: 10 mg/ml
* Cream: 50 mg/g (3g - $31.00)

Cat 0.5-1.0 mg/kg q12h
Dog 3.0-5.0 mg/kg q8-12h
Parrot 0.5-5.0 mg/kg q12h

Pharmacokinetics
\(t_d\) (human) = 16 hr
Active metabolites
Desmethyldoxepin
\(t_d\) = 28 – 52 hr
Nordoxepin
\(t_d\) = 33 – 88 hr

Uses in humans
Anxiety
Depression
The cream is used as an antipruritic

Uses in dogs
Self-injurious behaviors
Associated with
Injury or irritation
Seasonal allergens
Imipramine (Tofranil®)
Forms available
Capsules: 75, 100, 125, 150 mg
Tablets: 10, 25, 50 mg
Injectable: 12.5 mg/ml in 2 ml amps

Cat 0.5-1.0 mg/kg q12-24h
Dog 0.5-2.0 mg/kg q8-12h
Horse 0.75-2.0 mg/kg q12h

Pharmacokinetics
t₁ (human) = 12 – 28 hr
Active metabolites
Desipramine
  2° amine
Norimipramine
  Own active intermediate metabolite
Cattle
t₁ 145 ± 15 minutes

Anti-enuretic effect
In humans is used for depression and childhood enuresis
  Canine submissive urination
  Canine excitement-induced urination
  Urinary incontinence (dogs and cats)
Mild OCD

Nortriptyline (Pamelor®)
Forms available
Capsules: 10, 25, 50, 75 mg
  * Solution: 2 mg/ml
Cat 0.5-2.0 mg/kg q12-24h
Dogs 1.0-2.0 mg/kg q12h

Pharmacokinetics
t₁ (human) = 20-55 hr
Less sedating than amitriptyline

Used for
  Anxiety-related problems
  Feline hyperesthesia syndrome
  Acral lick dermatitis
Psychopharmacology: Benzodiazepines

Benzodiazepines
- DEA Class IV
- Rapid onset of action
- Potential for human abuse
  - Psychological dependency
  - Physical dependency
- Can be safely used with many other psychoactive medications

Action:
- Facilitates GABA in the CNS by binding to GABA$_A$ receptors.
- Behavioral effects due to action on the hypotalamus and limbic system

Benzodiazepines: Uses
- Anxiety and phobias in all species
- Submissive urination (dogs)
- Urine marking in dogs and cats
- Feather-picking in birds
- Foal rejection due to fear

Wide usage in phobias and anxiety-related problems
- Noise phobias (e.g. thunderphobia)
- Submissive urination
- Fear of people or animals, without aggression
- Fear of objects
- Separation anxiety
- Fear of going outside

Aggression
- Evidence in literature is contradictory. Aggression may increase or decrease depending on
  - Species
  - Sex
  - Type of aggression
  - Specific benzodiazepine
  - Specific dose
  - Single-dose vs. repeated dosing

- Lack a specific anti-aggressive mechanism
- May help with fear-induced aggression
- Use with caution in fear aggression. Learned inhibition of aggression may be lost.

Affiliative Behavior
- May increase, depending on
  - Species
  - Sex
  - Type of aggression
  - Specific benzodiazepine
Specific dose
Single-dose vs. repeated dosing

Benzodiazepines: Side-effects
Sedation
Muscle relaxation
Increased appetite
Paradoxical excitation
Increased friendliness
  Anxiety
  Hallucinations
  Muscle spasticity
  Insomnia
  Idiopathic hepatic necrosis in cats (Diazepam)

Excreted in milk
Passes through the placenta
Changes in absorption, distribution, metabolism and excretion occur in various disease states, e.g. impaired hepatic or renal function

Decrease dose in patients that are
  Old
  Obese
  Impaired renal function
  Impaired liver function
  Taking other medications that are metabolized by the cytochrome P450 enzyme system

Do not give to patients with narrow angle glaucoma

May or may not interfere with learning
Can have an amnestic effect

Wide variation in optimum dose for individual animal
Tolerance can develop in patients that are on a benzodiazepine for a long period of time, resulting in the need to repeatedly raise the dose to maintain efficacy.

Withdraw gradually
If patient has been on higher dose daily for several weeks, eventually becomes physically addicted. Gradual withdrawal can avoid side-effects that abrupt withdrawal can cause.
Gradual reduction allows identification of specific dose that may still be required to control the problem.
Sudden termination in a patient that has been on continuously for a long period of time can result in rebound, i.e. a resumption of symptoms which may be more intense than prior to treatment. Most likely if has been on a short-acting benzodiazepine.

In case of overdose:
  Supportive
  Cats, give 0.05 mg/kg apomorphine SC or 1 mg/kg xylazine SC to induce vomiting.
Give activated charcoal
3 hours after ingestion, do not induce vomiting or conduct gastric lavage
Flumazenil (Mazicon) benzodiazepine receptor antagonist

Overdose: Dogs (on order of prevalence)
Ataxia
Prostration
Agitation
Vomiting
Hyperesthesia
Muscle tremors
Coma
Hypersalivation
Aggressiveness
Paresis

Overdose: Cats (in order of prevalence)
Prostration
Ataxia
Muscle tremors
Agitation
Coma
Mydriasis
Polypnea
Decubitus
Bradyprnea
Vomiting

To begin
Begin when situation for which drug is being used does not exist, e.g. owner home and no storms.
Test lowest dose to make sure animal is not unusually sensitive (ataxic, sedated) and does not show paradoxical excitement.

Test in actual situation, e.g. thunderstorm, owner leaves (videotape)
If sufficient, maintain that dose
If insufficient, incrementally increase the dose until
Find effective dose or
Experience unacceptable side-effects

If cannot find effective dose without side-effects, change medication.
   Diazepam _ Alprazolam
   Alprazolam _ Diazepam

The fact that one medication does not work well does not mean that another will not.

When discontinuing, common rule of thumb is to decrease dose no faster than 25% each week
Do more slowly if
Patient has been on medication a long time (months)
Particular concerns about relapse

Alprazola (Xanax and generic)
Available as 0.25, 0.5, 1.0 and 2.0 mg tablets
Also available as a 1 mg/ml colorless, odorless oral solution and as 0.5, 1.0, 2.0 and 3.0 mg extended release tablets
Generic is inexpensive

Dogs 0.02-0.1 mg/kg q4h
Cats 0.0125-0.025 mg/kg q8h

Uses in humans:
  Generalized Anxiety Disorder
  Anxiety with Depression
  Panic Disorder with or without Agoraphobia
  Effective treatment requires several months on medication

Metabolites
  $\alpha$-hydroxy-alprazolam (active)
  A benzophenone (inactive)

Clinical Pharmacology
  Readily absorbed following oral administration
  Peak concentrations in plasma occur in 1-2 hours (humans)
  Plasma levels proportionate to dose given
  Mean plasma elimination half-life (healthy humans) 11.2 hours
  Half-life in African green monkeys is 5.7 hours

Oral LD$_{50}$
  Rat 331-2171 mg/kg

For veterinary patients
  Sporadic use, as in thunderphobia
  Regular use, as in SA

  Alone or as a supplement to another medication with anxiolytic properties such as a TCA or SSRI.
  Short term use in severe cases until a delayed onset of action medication has time to take effect.

Use in thunderstorms
  Most effective if given 30-60 minutes BEFORE occurrence of the earliest stimuli that elicit fear responses. Owners must monitor weather conditions closely. If in doubt, medicate.
  If dog is already showing fear, give anyway as may help some, but not as effective

Dogs given overdoses up to 5.55 mg/kg
  Ataxia
  Disorientation
  Depression
Hyperactivity
Vomiting
Weakness
Tremors
Vocalization
Tachycardia
Tachypnea
Hypothermia
Diarrhea
Hypersalivation

Dogs given escalating dose over 18 to 26 until achieve a dose of 12 mg/kg q.i.d., then maintained on that dose for three weeks become physically addicted.

Liver failure?
Not yet reported in veterinary patients, but has occurred as a rare event in humans.

Chlordiazepoxide (Librium and generic)
Available as 5, 10 and 25 mg capsules
Dogs 2.0-6.5 mg/kg q8h
Cats 0.2-1.0 mg/kg q12h

Uses in humans
Anxiety disorders
Short-term relief of anxiety

Dog
Plasma levels peak around 2-5 hours after a single dose of 0.5-0.8 mg/kg
Plasma levels peak around 7-8 hours after a single dose of 4 or 20 mg/kg.
Doses of 2.5-20 mg/kg stimulate appetite
Doses of 10-40 mg/kg cause ataxia
Given doses up to 50 mg/kg PO for 6 months have not shown adverse effects.

Metabolites
Desmethyldiazepam (nordiazepam; active)
Demoxepam (active)
Half-life of 10-20 hours in the dog
Desmethylchlordiazepoxide (active)
Oxazepam (active)

Oral LD₅₀
Rabbits 590 mg/kg
Rats 1315 mg/kg
Mice 620 mg/kg

Cats: Dose of 200 mg/kg PO fatal in 5 days
Dogs given 80 mg/kg showed non-specific toxic changes
2/6 dogs given 127 mg/kg died from circulatory collapse
6/6 dogs given 200 mg/kg died

Nervous/timid dogs become less timid at 3.5 mg/kg daily in the morning
Used to tame zoo animals for handling

Clonazepam (Klonopin and generic)
Available as 0.5, 1.0 and 2.0 mg tablets

Dogs 0.1-0.5 mg/kg q8-12h
Cats 0.15-0.2 mg/kg q8h

Extensive metabolism in the liver to various inactive metabolites. Not the best choice for patients with liver disease

Dogs given 0.5 mg/kg q12h
   Week 1; half-life 2 hours
   Week 3; half-life 8 hours

Dogs given clonazepam q12h for three or more weeks, then acutely withdrawn, exhibit anorexia, hyperthermia and weight loss

Cats given 1000 mg/kg survived

Clorazepate dipotassium (Tranxene® & generic)
Available as 3.75, 7.5, 11.25, 15.0, 22.5 and 5.0 mg tablets and 3.75, 7.5 and 15 mg capsules

DOGS 0.5-2.0 mg/kg q4h
CATS 0.5-2.0 mg/kg q12h

In the acidity of the GI tract, it is decarboxylated to form nordiazepam (active)

Plasma nordiazepam is metabolized by hydroxylation to conjugated oxazepam (3-hydroxynordiazepam) and ρ-hydroxynordiazepam.

Dogs given a single dose of 2 mg/kg PO have peak plasma concentrations of nordiazepam at 1-3 hours.

Mean elimination half-life of nordiazepam is 284 minutes (almost 5 hours) after a single dose and 355 minutes (almost 6 hours) after multiple doses given q12h.
Half-life much longer in humans.

Diazepam (Valium® & generic)

Available as 2, 5, and 10 mg tablets; 1 mg/ml and 5 mg/ml oral suspension; 5 mg/ml injectable solution; 2.5, 5, 10, 15 and 20 mg rectal gel

Dogs 0.5-2.0 mg/kg q4h
Cats 0.1-1.0 mg/kg q4h
Horse 10-30 mg q8h
Rabbit 0.1-0.6 mg/kg
Parrots 2 drops of 5 mg/ml solution/oz of drinking water

Uses in humans
- Relief of symptoms of anxiety and management of anxiety disorders
- Treatment of compulsive disorders
- Relief of skeletal muscle spasms

Blood concentrations are proportional to dose given.

Half-life
- Dog 2.5-3.2 hours
- Cat 5.5 hours
- Horse 7-22 hours

Multiple metabolites: nordiazepam, oxazepam, temazepam

Half-life of nordiazepam
- Dog 3-5.7 hours
- Cat 21.3 hours
- Horse 12 hours

Half-life of oxazepam
- Dog 3-5.7 hours
- Horse 18-28 hours

Oral LD$_{50}$
- Mice 720 mg/kg
- Rats 1240 mg/kg

Cats: 500 mg/kg PO is fatal within 1 day

Acute withdrawal of diazepam dependent dogs by administration of flumazenil.
- Tremors, twitches, jerks, seizures
- Martin et al. 1990

Reports of death due to acute hepatic necrosis reported in cats beginning in 1994.
- Clinical signs as soon as 5 days after beginning daily administration.
- Death within 24 hours in spite of aggressive supportive treatment.
- Some do survive

Various brands

Possible cause?
- Substance incorporated during tablet production?
- Multiple brands have caused the problem
- Speculation that there is accumulation of a toxic intermediate metabolite unique to some cats?
Diazepam (Hughes et al. 1996)
In a study of “Acute hepatic necrosis and liver failure associated with benzodiazepine therapy in six cats”, all the subjects had cardiac, pancreatic or renal disease.
Incidental finding?
Prior disease potentiating hepatotoxic insult?
Speculation that a virus was occurring in cats at the time of these deaths?
No conclusive evidence as to why diazepam caused fatal hepatic necrosis.

Take baseline blood chemistry before start.
Check at 3-5 days.
If elevated Alanine Transaminase (ALT) or Aspartate Transaminase (AST), discontinue.
While there is a real risk of fatal liver disease when using diazepam, it is RARE.
Consider if
Owner willing to take risk and cost is an important consideration.
Multiple other, safer treatments have been used without effect.

Spraying
Diazepam is 55-75% effective in significantly improving or resolving spraying
Most cats relapse when taken off Diazepam
Lethargy and ataxia are common side-effects
Feral cats:
Injection of 1 mg/kg show decreased defensive aggression, no change in flight behavior

Stallions that have been classically conditioned (fear/aversion) to have inhibited sexual behavior, regain normal sexual behavior when given 0.05 mg/kg diazepam by slow IV injection.

Rhesus monkeys
2.5-5 mg/kg PO daily produces dose-dependent increases in
Social grooming
Approach
Contact
Self grooming
Feeding
Resting with the eyes open
And dose-dependent decreases in
Vigilance
aggression

Flurazepam (Dalmane and generic)
Available as 15 and 30 mg capsules
Dogs 0.1-0.5 mg/kg q12h
Cats 0.1-0.2 mg/kg q12h

Uses in humans
Insomnia

Half-life in humans is 2.3 hours.
Major metabolite is N₁-desalkyl-flurazepam, which has a half-life of 47-100 hours
More effective on second and third nights of consecutive use than on first night, probably due to metabolite.

Cats die within 1 hour if given 400 mg/kg PO
May be preferred benzodiazepine for pets that wake at night, but no research or clinical reports on this or other uses of flurazepam.

Lorazepam (Ativan and generic)
Available as 0.5, 1.0 and 2.0 mg tablets and 2 mg/ml oral solution
Dogs 0.02-0.5 mg/kg q18-12h
Cats 0.03-0.08 mg/kg q12h

Uses in humans
Short-term relief of symptoms of anxiety and management of anxiety disorders

Major metabolite is lorazepam glucuronide, which has no significant CNS activity.

Formation of lorazepam glucuronide is much faster in dogs than in humans. Peak plasma levels of unchanged lorazepam are almost identical in humans and dogs if dogs are given a dose 30X higher than humans on a per kg basis.

Cats do glucuronidate lorazepam!

Peak plasma concentration
Dog 0.5 hours at 1 mg/kg PO
Cat 12 hours at 20 mg/kg PO
Pig 3 hours at 0.04 mg/kg PO

Good separation between anxiety-reducing doses and sedative-hypnotic doses

Rhesus monkeys
0.5-1.0 mg/kg PO daily produces dose-dependent increases in
Social grooming
Approach
Contact
Self grooming
Feeding
Resting with the eyes open
And dose-dependent decreases in
Vigilance
aggression

Reduces conflict behavior in rats
In mice, suppresses foot shock induced fighting

Oxazepam (Serax and generic)
Available as 10, 15 and 30 mg capsules and as 15 and 30 mg tablets.
Dog  0.04-1.0 mg/kg q6h
Cat  0.2-1.0 mg/kg q12h

Uses in humans
管理系统 of anxiety disorders
短期缓解焦虑症状
考虑到特别有用在老年患者因为没有活性代谢物

No active intermediate metabolites
Main metabolite is an inactive glucuronide conjugation of oxazepam.
May be best benzodiazepine for geriatric patients and patients with liver disease or obesity.

Dogs given 5-10 mg/kg oxazepam PO exhibit peak plasma levels in 4-6 hours.
Wide separation of clinically effective doses and doses that produce side-effects
Has a larger spread between clinically effective dose and dose that produces side-effects than chlordiazepoxide or diazepam.

Mice LD$_{50}$  5000+ mg/kg
Dogs given 480 mg/kg daily for 4 weeks or 120 mg/kg daily for 52 weeks showed no specific toxic changes.
At doses of 960 mg/kg 25% of dogs die with circulatory collapse.

Cats: Good appetite stimulant with longer duration of action than diazepam. No reported incidents of liver failure. If liver failure is due to problems of metabolism in some individuals, oxazepam is probably unlikely to cause this problem.

**But I Thought Your Ankle Was a Mouse!**

**Human-Directed Aggression in the Cat**

Human-directed aggression
- Play
- Fear
- Petting Intolerance
- Status related
- Redirected
- Sexual

Play Aggression
- More likely in young cats
- Very common problem
- Usually, but not necessarily directed to moving stimuli
- May be directed to only to some members of the household
- Cat approaches victim
– Crouches waiting
– Stalk
– Chase
– Tail twitching
– Focused stare

History and Management?
• Using hands or feet to play with the cat
• Inadequate opportunity for acceptable play

Play Aggression: Ears forward, not back
• Does not assume stiff-legged walking toward victim
• Often referred to as “vicious”
  – Serious injury may happen to the victim, even though this is play
  – Deep bite wounds
  – Serious scratches
  – Can be very frightening to victim

Play Aggression-Treatment
• Avoid situations that elicit the behavior
  – Enter via a different door
  – Don’t wear particular clothes that appear to elicit play aggression
  – Shut cat in own room during particular times and situations when problem is likely to be worse.
• Redirect play
  – Have balls, paper wads, etc. readily available to distract cat when it appears to be in a playful mood
• Provide DAILY opportunities for acceptable play
  – Drag string
  – Roll balls
  – Toss paper wads
  – Set out paper grocery bags
• Feathers
• “Fishing Rod”
• Trees
• Other cats to play with
• Punishment
  – Consistent
  – Immediate
  – Appropriate
• Punish inappropriate play
  – Water pistol
  – Water sprayer
  – Air horn
Combine
• +++Appropriate Play
• ---Unacceptable Play

Medication??
• Generally not indicated
• This is a management problem
• If aggression severe and accompanied by high arousal, a TCA or SSRI may be useful.

Fear Aggression
• Ears back
• Body lowered
• Tail lowered
• Avoids person or persons
• Aggression occurs when approached, reached for or groomed

• History of poor socialization or feral living may predispose
• Can occur in any cat
  – Any age
  – Any breed
  – Either sex
  – Neutered or Intact

Classical Conditioning
• Unconditioned Stimulus (US) Fruit bowl crashing on floor beside cat, pieces of fruit and broken bowl probably strike cat---->Unconditioned Response (UR) FEAR
• Neutral Stimulus (NS) Owner + US----->Unconditioned Response (UR) FEAR
• NS becomes a Conditioned Stimulus (CS) Owner----> Conditioned Response (CR) FEAR

• Cat now runs away from owner
• Becomes aggressive, with fear signaling, if owner attempts to touch or pick up
• Stimulus Discrimination: Cat is only afraid of the owner who was present during the incident

• Stimulus Generalization: Cat is afraid of all people

• May develop suddenly or slowly for unknown reasons
  – Genetic predisposition to respond intensely to even mildly fear-inducing events
  – Early experience may have same consequence
  – Event may occur which owner is unaware of; e.g. something frightens the cat and maintains fright until the owner gets home. Cat remains frightened of other (identifiable or unidentifiable stimuli) and owner

Fear Aggression-Treatment
• Desensitization
• Counter-conditioning

DS & CC: Individualize for the cat
• Drag string
  – Good with cats that like to chase the string or whatever is on it.
  – Begin at whatever distance is necessary for the cat to pursue.
  – Gradually shorten string over many days.

• Roll ball
  – Again, good with cats that like to chase rolling balls
  – Roll ball to whatever distance is necessary for the cat to chase it

  – Treats: Thrown or laid out
    • For cats that are less motivated by play and more motivated by food
    • Have very tasty treat that can be gently tossed.
    • Sit or stand and toss to suitable distance
      – Some cats will like the play aspect of tossing paired with food motivation
    • Lay out trail to near person

  – Sit near food bowls
    • Often the only method to use in early taming of feral cats
    • When cat is hungry, place bowl of highly palatable food out
    • Sit quietly as far away as is necessary for the cat to approach and eat
    • Gradually sit closer and closer

      If the cat is only afraid of certain people
      Have person who can handle the cat play with it and/or give it treats while a person
      the cat is afraid of sits quietly nearby.
      Over time, the person the cat is afraid of gradually comes closer.

Fear Aggression- Treatment
Clomipramine HCl (Anafranil®, Clomicalmä)
  0.25-0.5mg/kg q24h
Fluoxetine HCl (Prozac®)
  0.5-1.0 mg/kg q24h
Paroxetine HCl Paxil®
  0.5-1.0 mg/kg q24h
Sertaline (Zoloft ®)
  0.5-1.0 mg/kg q24h
Petting Intolerance
- If owner initiates petting, cat is aggressive
- After a certain amount of petting, cat becomes aggressive
- Occurs in both males and females
- Etiology is controversial
- May be status related
Cats primarily groom each other on the head and neck

Petting Intolerance-Treatment
- Pet only or predominantly on the head and neck.
- Species specific behavior

Preaggression cues:
  Watch for preagression cues
  Owner may not realize they’re happening until you point them out
  Tail twitching
  Low growling
  Skin twitching
  Mydriasis

- Owner vs. cat initiating petting
- May need to restrict petting to cat initiated petting.

- Evaluate complete Owner X Cat interaction
Owner X Cat interactions
- Time limit:
  - Is there a time period that the cat will typically tolerate petting?
  - Stop BEFORE that threshold
  - Example:
    - Cat starts showing preagression cues as early as 30 seconds
    - Never pet for more than 20-25 seconds
- RESTRICT PETTING
- If owner really wants tactile contact with a lap cat they need
  - A different cat
  - A stuffed cat

Petting Intolerance-Treatment
- Clomipramine HCl (Anafranil®, Clomicalm®)
  - 0.25-0.5mg/kg q24h
- Fluoxetine HCl (Prozac®)
  - 0.5-1.0 mg/kg q24h
- Paroxetine HCl Paxil®
  - 0.5-1.0 mg/kg q24h
Sertraline (Zoloft ®)
· 0.5-1.0 mg/kg q24h

Status (Dominance) Related
• Appears to be uncommon in cats, but does occur
• Show dominance displays to one or more persons

Dominance Display
Status-related
• Medication
  – SSRI
  – TCA
  – Progestins
• Owner control resources
• Punishment of ritual dominance display

Redirected Aggression
• Occurs during interference in situations which have caused the cat to become aroused.
  – Cat fight
  – Dog aggressive to cat

Redirected Aggression-Treatment
• Avoid interfering in situations that cause arousal
• Treat primary problem

Sexual Aggression
• Cat mounts owner’s limb, grabs skin, initiates pelvic thrusting, growls

Sexual Aggression-Treatment
• Punishment
  – Before cat mounts limb!
  – Squirt or use other punisher when cat first focuses on limb
• SRI
• Progestin Therapy
The Peaceful House: Diagnosing and treating intercat aggression

Examine households where cats are getting along well

- Most households that have cats have two or more cats
- There are many households that have 5, 10 or more cats in which no significant aggression occurs
- We need to improve our understanding of how to facilitate affiliative behaviors
  - Allogrooming
  - Allorubbing
  - Playing together
  - Maintaining proximity

Prevent and treat aggression

What produces stable social groups with little to no overt aggression and high levels of affiliative behavior?

- Group size (regardless of space)?
- Related? Specific relationship?
- Familiarity with each other?
- Space per cat?
- Management issues?
  - Access to toys, dispersion of food, type of food, trees to climb on, access to natural prey, etc.
- Breed?
- Individual differences?-genetic, specific learned experiences

Time together

- For pairs of cats, the longer they have been together, the less overt aggression occurs. This is consistent with the formation of stable dominance relationships which rely on dominance signaling, rather than overt aggression.
  - Barry and Crowell-Davis, 1999

Association

- Relatives and cats that a given cat is more familiar with are more likely to be nearest neighbors and to groom each other than non-relatives and cats a given cat is not familiar with. Being related is more important than familiarity.
  - Curtis, Knowles and Crowell-Davis, 2003

Socialization of kittens and juveniles

- Socially competent adult cats play an important role in the socialization of kittens and juveniles

Raising kittens?

- Extensive social learning occurs from 2-16 weeks and beyond.
• Raising cats from 5-6 weeks onward with no contact with their own species can result in serious incompetence in social skills.

Intraspecies Aggression:

a selected list

• Introduction of a new cat
• Dominance-related Aggression
• Fear Aggression
• Play Aggression
• Arousal-related Aggression

Introduction of a new cat

• Cat societies are insular.
• Strangers are not readily accepted.

• When a new cat is brought into the house, do not simply put it in the same room with the other cats and hope things will work out.
• Kittens and juveniles are generally easier to introduce than are adults.
• Gradual exposure with rewards for appropriate behavior.
• Keep the new cat in a separate room from cats established in the household.
• Rotate the cats location in the house so that they can be exposed to each others scent.

• If possible, separate by glass (allows sight and sound) or screen (allows sight, sound and scent) door.
• Do not force interactions. Allow the cats to approach or leave the door freely.
• Alternatives:
  — Door tied and blocked so opens about 1 inch
  — Stacked baby gates

• Get several small cloths, such as washcloths.
• Rub the perioral area of a cat
  — Make it a pleasant experience
• Rotate the cloths
• Exchange bedding

• If significant aggression occurs, use systematic desensitization and counter-conditioning

DS & CC: cat to cat

• Caging
• This method will only work if the cats are comfortable being shut in a cage.
• Put treat (food and/or toy) in cage.
• If both cats aggressive, put both cats in cages
  – Gradually move the cages closer over many days
• If only one cat is aggressive, put the aggressor in the cage.
  – Allow the other cat to move around freely and choose when to approach.
  – Approach can be encouraged but not forced with play and treats, e.g. move food bowl a little closer to the cage each day.

Introduction of a new cat
• Human handlers
  – One person responsible for each cat
  – Ideally, have the cats in harnesses
  – Take cats to distance necessary for relaxation and focus on treats and play
  – Over several to many days, gradually move the cats closer to each other

Dominance-related Aggression
• Cats have previously established a relationship, i.e. not a “new cat” issue.
• Aggressor chases, growls, and attacks other cat or cats. Shows dominance postures, e.g. ears up and rotated to the side, but does not stop at simple posturing and control of space. May totally control resources.

Attacked cats may respond with
  – similar behavior, resulting in significant fights
  – fear aggression, usually resulting in chasing and control of resources by the dominant cat, but there may be fighting
  – or fear and hiding, resulting in the subordinate cat not having access to essential resource

Problems of dominance aggression may present as an elimination behavior problem
• A subordinate cat may be blocked from access to resources, including
  – Litterbox
  – Food
  – Preferred sleeping area
• May be but is not always initiated by an identifiable disruptive event, e.g.
  – Illness of one cat
  – Fight that occurs as a consequence of displaced aggression when strange cat approaches home
  – New cat added to household disrupts existing relationships

• May present as different problem, e.g. elimination behavior problem
• High ranking cat or cats control resources (e.g. litterbox)
• Low ranking cat or cats will be attacked if they approach the resource, as well as in other contexts.
• Therefore, they avoid the litterbox and eliminate elsewhere.
Dominance Aggression-Treatment

- In multi-cat households, identify which cats still get along and keep them together as much as possible
- Keep cats that are in conflict separate when not being supervised
- Punish the aggressor
  - Select cases—make sure requirements for successful use of punishment can be met. Every time
    - Watch cats when they have access to each other
  - Immediately
    - Punish during initial threats that reliably are followed by an attack
    - Do not wait for actual attack
  - Appropriate punisher
    - E.g. Water sprayer

- Desensitize and Counter-condition as described in Introduction of a New Cat.
- If individual cats have a preferred core area, conduct desensitization in a neutral area
- Rub towels on all cats in the house daily (scent exchange)

- Aggressive/Dominant cats-
  - Serotonin Reuptake Inhibitors
    - Fluoxetine (Prozac®)
    - Paroxetine (Paxil®)
    - Sertraline (Zoloft®)
    - Clomipramine (Clomicalm™, Anafranil®)
  - Avoid medications with some, but little SRI effect, e.g. Amitriptyline

Buspirone
- Cats that have previously been timid in the face of repeated attacks may turn on their attacker. This can be beneficial or harmful, depending on the situation.

Azapirones
- Many owners report that their cat becomes more “affectionate”, rubbing them, sitting in their lap and otherwise seeking contact with them for greater frequencies and durations

Fear Aggression
- Cat hisses and growls at other cats when they come near or are seen.
- Shows signs of fear, e.g. ears back, crouching, urinating.
- Usually hides rather than chasing and attacking, but may chase.
• When occurs between cats that have historically gotten along well, usually initiated by classical conditioning.

Classical Conditioning
US (Something SCARY) -> UR (Fear with aggression)

US + NS (Buddy) -> UR (Fear with aggression)

NS (Buddy) becomes CS -> CR (Fear with aggression)

Fear Aggression-Treatment
• “Safe place”
  – Keep cats separate when not being supervised.
• Antianxiety medication
  – SSRI
  – TCA
• Desensitization
• Counter-conditioning
• Supervise carefully when cats have access to each other
• Make sure any subordinate cat has regular access to critical resources, e.g. food, litter.

Intraspecies Play Aggression
• Bouts of wrestling play escalate

Wrestling Play is Normal

• Normal behavior?
  – Is either cat being injured?
  – Does one cat end or attempt to end the play bout when the intensity of play escalates?
  – Does the other cat allow termination of play that is escalating in intensity, or does it continue the escalation from play to fighting?
  – If the answers are No-Yes-Yes, this is normal

Intraspecies Play Aggression-Treatment
• What if play does escalate into fighting?
  – Keep separate when not being supervised
  – Allow play when supervised, but disrupt play when escalation begins
  – Do not wait for escalation to reach the point of actual fighting
  – May be more of a problem with cats that were raised in social isolation from their own species and have not learned appropriate social behavior

Arousal related aggression
• Identify the cause of arousal and treat that
- May need to separate cats at certain times of the day
- Medication
  - SRI

Territoriality
- “When winning or losing is determined by the location of the contest arena, and when that produces learning specific to location, then we may invoke the concept of “territoritality”. In such cases we acknowledge that the directionality of the agonistic relationship is predictable based on geography.”
  - Bernstein, 1981. Dominance: The baby and the bathwater

Territorial Aggression
- Defense of a specific area by one or more cats against others?
- True territorial defense in this species has not been verified by empirical scientific studies.
- There is no such thing as a “floating territory”. Cats that aggress and win against other cats that enter their personal space are higher ranking in the dominance hierarchy.