Introduction to Veterinary Psychopharmacology
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Synapse Physiology
**Neurotransmitter** – remain within the synapse to transmit action potential to post synaptic membrane
**Neuromodulator** – released into synapse in large amounts and diffuse out of synapse to affect the activity of numerous neurons
**Hormone** – released by specialized cells into the circulation and affects a wide variety of cells, including neurons.

**Synapse**
Junction of pre-synaptic axon terminal button and the membrane of the post-synaptic neuron

**Termination of Post Synaptic Potential**
**Enzymatic Deactivation** – For example, the activation of acetyl cholinesterase to neutralize the activity of acetylcholine.
**Reuptake** – Reabsorption of neurotransmitter into the pre-synaptic cytoplasm via membrane channels.

**Principle Neurotransmitters**
**GABA (gamma amino butyric acid)** – inhibitory neurotransmitter. Potentiated by benzodiazepines.
**Glutamate** – excitatory amino acid.
**Acetylcholine** – Wide distribution in the body. Many drugs have anticholinergic side effects (dry mouth, urine/fecal retention, cardiac arrhythmias)
**Monoamines (dopamine, norepinephrine, serotonin)** found in midbrain, hypothalamus and limbic system. Tyrosine is precursor for Dopamine and Norepinephrine. Tryptophan is the precursor for Serotonin.

**Considerations When Using Psychoactive Pharmaceuticals**
- Drugs are rarely the sole treatment method
- Rule out medical issues (pre and post treatment exams and lab work)
- Allow ample time for drug to take effect. Maximum effect for the TCA’s, SSRI’s, Selegiline and Buspirone can take as long as 6-8 weeks.
- Safety factors, side effects, lack of FDA approval. Consider signed informed consent
- Clear client communication before and after dispensing medication
- Caution with combination drug therapy particularly with drugs effecting serotonin (SSRI’s, TCA’s and MAO’s)
- Serotonin Syndrome – excessive levels of serotonin causing increased blood pressure, tremors, decreased mental state, hyperreflexia, hyperthermia and restlessness.
- Dosage form (tablet, liquid, transdermal), frequency, ease of administration
- Clear knowledge of a few drugs
- Drug trial
  - Lack of desirable effect then choose drug from alternate drug class
  - If beneficial but side effects then alternate drug from same class

**Pharmaceutical Classes**

**Neuroleptics (chlorpromazine, acepromazine)**
*Act as dopamine antagonists at the basal nuclei and limbic system. Causes atarexia which is decreased emotional reactivity and indifference to stressful situations.*
Side Effects:
Sedation, alpha adrenergic blockade (hypotension), lowered seizure threshold and inconsistency of
response.
Applications:
Tranquillization and reduced responsiveness (as an adjunct in treating storm phobias and night waking, for example)

Tricyclic Antidepressants
Tricyclic Antidepressants (TCA’s) block the reuptake of serotonin and norepinephrine from synapse causing higher levels of these neurotransmitters to remain in the synaptic cleft and to exert greater effect on the postsynaptic receptors. Clomipramine is the most serotonin specific of the TCA’s.

Side Effects
• Sedation, anticholinergic effects, cardiovascular effects (tachycardia, decreased blood pressure, arrhythmias), antihistaminic effects.
• Can also see increased anxiety or aggression. Potential hepatic effects (enzyme induction, hepatic necrosis)
• Less side effects seen with the SSRI’s in terms of reduced anticholinergic or antihistaminic effects.
• Imipramine – Also has anti-enceuretic effect making it useful in conditions where urine retention may be useful.
• Amitriptyline – Has significant antihistaminic effects and can be helpful when pruritic.
• Clomipramine – Most significant amount of serotonin re-uptake blocking activity.

Selective Serotonin Reuptake Inhibitors
Selectively blocks the reuptake of serotonin into the pre-synaptic neuron causing an elevation of the hormone and increased binding to the post-synaptic receptors. This results in changes in protein production and receptor structure and alteration in learning potential.
• Less side effects than seen with TCA’s. Primarily sedation and anorexia. May also see paradoxic increase in anxiety.
• Hepatic abnormalities and leukopenia
• Longer half life than TCA’s. Allow 6-8 weeks for maximum effect.
• Fluoxetine (Prozac)
• Sertraline (Zoloft)
• Paroxetine (Paxil)

Benzodiazepines (diazepam, lorazepam, oxazepam, alprazolam, clorazepate)
Binds to GABA receptors and promotes inhibitory activity of GABA (cerebral cortex and limbic system). Has a short duration of behavioral effects.
• Sedation, cortical depression, muscle relaxation, idiosyncratic hepatic necrosis, and may interfere with learning.
• Lorazepam and Oxazepam metabolized via conjugation and not oxidation so are better choices in hepatic disease. Only BZD’s without active metabolites.
• Discontinuation Syndrome – occurs after rapid withdrawal after chronic use. Rebound anxiety.
• Disinhibition – Caution if used in fear aggression. May cause increased aggression if animal is released from fear based inhibitions.

Miscellaneous Agents
Monoamine Oxidase Inhibitors (Selegiline, Deprenyl, Amitraz)
Blocks the metabolism of monoamines (particularly dopamine) resulting in elevated levels of the amine. Do not use with TCA’s and SSRI’s to avoid excessive levels of monoamines.

Buspirone
Blocks pre and postsynaptic serotonin receptors. Effect depends on existing serotonin levels.
Low serotonin – blocks presynaptic reuptake
High serotonin – blocks postsynaptic serotonin effects. Very Few Side Effects Noted.

**Antihistamines (Diphenhydramine, Chlorpheneramine)**
Primarily used for its sedative effects. Can be helpful for situations where mild relaxation is needed such as with night waking.

**Note:** **Cyproheptadine** can be used for spraying or other male dominated behaviors in cats. (anti-testosterone effects)

**Anticonvulsants (Phenobarbital, Primadone, Phenytoin, Neurontin)**
Can be used for overactive behaviors related to psychomotor epilepsy. Also used with feline vocalization, feline hyperesthesia syndrome. Sedation and need for therapeutic blood level monitoring.

**Progestins/Estrogens (Medroxyprogesterone, megesterol, diethylstibesterol)**
Suppresses male stereotypic behavior (male aggression, urine marking)
Diabetogenic, gynecomastia, mammary hyperplasia/adenocarcinoma, adrenal suppression, endometrial hyperplasia and pyometra.

**Stimulants (Dexamphetamine, methylphenidate)**
Diagnosis and treatment of true hyperactivity or hyperkinesis (paradoxical calming effect) Stimulates CNS, increases HR, RR, anorexia, tremors, glaucoma, CV disease

**Trazadone**
- Classified as an SARI (Serotonin Antagonist and Reuptake Inhibitor)
- Often used as an adjunct to a TCA or SSRI
- Used mainly in anxiety related disorders

**Clonidine**
- Classified as an alpha 2 agonist in that it tends to suppress monoamines in the brain (norepinephrine particularly)
- Often used on a prn basis and is given 2 hours before anticipated exposure to stimulus (thunderstorms, strange dog or person exposure, etc)

**Application to Behavior Problems**

**Canine Behavioral Disorders**
- Aggression
- Fears and Phobias
- Elimination Disorders

**Conflict Aggression**
*Is a learned set of behaviors in which the dog has learned to use aggression as a means of achieving desired goals. This can be cessation of certain activities (petting, movement, brushing, etc.) performed by owners or to obtain resources (food, resting areas, etc.). Punishment tends to create conflict in that the dog becomes more anxious in being not certain how various encounters will turn out with owners. At times the dog may receive attention and at others, punishment. Inconsistency makes this situation worse.*
- SSRI’s (Fluoxetine, Paroxetine)
- Benzodiazepines (alprazolam, lorazepam, diazepam) for episodic behaviors with predictable triggers.
- Clonidine also an option in these situations

**Fear Based Aggression**
Aggression that occurs as a response to perceived threatening stimuli. Aggression is rewarded by a successful outcome and increases the likelihood of aggression being used in future similar situations. Fear can be an inherited trait with aggression as a response developing over time. Inadequate socialization or use of punishment in an anxious dog can worsen the condition.

- SSRI’s such as Fluoxetine, Sertraline (Zoloft) or Paroxetine (Paxil)
- Clonidine used prn for triggering situations

Avoid BZD’s due to potential for disinhibition

Clomipramine – Label exclusion for aggression

**Territorial Aggression**

*Instinctual behavior in which a resource (territory) is guarded. Territory can be extended to attachment to owner during leash walks. Behavior is intensified as animal has more opportunities to practice without redirection. Intensified when behavior co-exists with fear based aggression.*

- Use of SSRI’s when fear or anxiety is a component of the territorial behavior
- Add Clonidine if insufficient improvement in anxiety using SSRI alone

**Anxiety Disorders**

- **Anxiety** – Apprehensive anticipation of future danger. May be internally or externally derived.
- **Fear** – Feeling of apprehension associated with the presence or proximity of an individual, object or situation.
- **Phobia** – Profound and quickly developed fear reaction that does not diminish with gradual exposure over time. Profound, exaggerated responses (panic).

**Separation Anxiety**

*Symptoms of anxiety, distress or panic exhibited when animals are left alone. Characterized by pacing, drooling, vocalization, destruction, and elimination which are not related to other behavioral disorders.*

- Tricyclic Antidepressants (Clomipramine, Amitriptyline) or SSRI
- Benzodiazepines (Alprazolam, Clorazepate) of panic at departure is a component of the behavior
- Add Trazodone of insufficient response to initial approach

**Thunderstorm/Noise Phobia**

*Overwhelming display of panic and anxiety in response to stimuli related to onset of weather disturbances (wind, rain, thunder, lightening, hail, etc.) or random noises. Behaviors often become anticipatory of triggering stimuli.*

Thunderstorm/Noise Phobia

- Chronic Dosing: TCA’s (Clomipramine/Amitriptyline), SSRI (Fluoxetine)
- Weaning Protocol: Decrease 25-50% if OK after 2-3 storms. Discontinue during off season if no sign of noise phobia
- Acute Dosing (When storm is expected): BZD (Alprazolam, Clorazepate), or Clonidine

**Compulsive Disorder**

*Repetition of a normal, species-specific behavior but occurring out of context and interfering with normal daily activities. Often is difficult for owners to easily interrupt and does not require the owners to be present for the behavior to be preformed (not attention seeking).*

- Clomipramine - Work dose up to the higher end of the dose range for best chance of reducing CD.
- Fluoxetine

**Elimination Disorders**
Urine Marking
Depositing of urine on vertical surfaces (though can see horizontal marking) for the purpose of depositing pheromones for territorial or anxiety driven displays. Associated with mostly normal patterns for the elimination of urine and stool
- Clomipramine
- Fluoxetine (Particularly if aggression is a component of the behavior)

Feline Behavior Disorders
Fear Based Aggression
Elimination Disorders

Fear Based Aggression
Aggressive behavior (hissing, growling, lunging, scratching) as a result of fear when placed in certain situations (presence of strangers, for example)
- Benzodiazepines (Lorazepam, Oxazepam)
- Buspirone

Territorial Aggression
Occurs mostly as a means of defending territory when space is limiting factor. Commonly occurs when an adult cat is introduced to a household or when a resident cat returns from boarding or veterinary visits.

For the Aggressor:
- Benzodiazepines (Lorazepam, Oxazepam)
- SSRI (Paxil, Fluoxetine)

For the Victim (when fear response is increasing the aggression):
- Buspirone
- Benzodiazepines

Redirected Aggression
Aggression which is directed at a stimulus other than the original target. Occurs commonly when an owner intervenes while the cat is aroused by stimuli such as stray cats on the property or during cat fights within the household.
- Benzodiazepines (Lorazepam, Oxazepam)
- Buspirone

Status Related/Petting Induced Aggression
Aggression occurring when owners attempt assertive interactions with the cat (lifting, petting, remove from elevated surface). Can occur with cat soliciting attention.

Drugs are usually not utilized with this type of aggression.

Predatory Aggression
Aggression characterized by premeditated stalking and attack of quickly moving stimuli. Is typically stealth (non vocal) in character. Similar to play aggression but without the animated components. Can be very severe and dangerous.
Very dangerous, though uncommon. Best to consider not keeping cat or devise strategy to avoid access to target. Drugs typically not indicated.

Intercat Aggression
Aggression between cats of the same household or unfamiliar cats. Has its basis as fear, territoriality or redirected behavior.
For the Aggressor:
- Benzodiazepines (Lorazepam, Oxazepam)
- SSRI (Paxil, Fluoxetine)

For the Victim (when fear response is increasing the aggression):
- Buspirone
- Benzodiazepines

Housesoiling
Inappropriate litter box use as a result of problems involving “toileting issues”. Can include location aversion or preference issues and/or substrate aversion or preference problems. Isolation with preferred litter. Drugs not indicated.

Marking Behavior
Characterized by the deposition of waste material (primarily urine) for the purpose of placement of pheromones due to territoriality or due to anxiety related circumstances in the household. Can be seen as vertical or horizontal marking.

- Clomipramine
- Fluoxetine
- Benzodiazepines (Lorazepam, Oxazepam)

Doses Taken From:
Landsberg G, Hunthausen W, Ackerman L. “handbook of behaviour problems of the dog and cat” Butterworth and Heinmann, Oxford 1997 pg 195-198

Clomipramine 1-3 mg/kg bid (dog) 0.5 mg/kg sid (cat)
Amitriptyline 1.6 mg/kg sid-bid (dog) 0.5-1.0 mg/kg (cat)
Imipramine 2.2-4.4 mg/kg sid-bid (dog) 1-2 mg/kg bid-tid (cat)
Fluoxetine 1.0 mg/kg sid (dog) 0.5-1.0 mg/kg (cat)
Sertraline 1.3 mg/kg prn (dog)
Paroxetine 1.0 mg/kg sid (cat)
Alprazolam 0.02-0.10 mg/kg or 0.25-2.0 mg/dog bid-tid (dog)
0.125-0.25 mg/cat bid or prn (cat)
0.1 mg/kg tid or prn (cat)
Clorazepate 0.55-2.2 mg/kg sid-bid or prn (dog)
0.55-2.20 mg/kg sid-bid or prn (cat)
Diazepam 0.5-2.2 mg/kg tid or prn (dog)
0.2-0.4 mg/kg sid-bid (cat)
Oxazepam 0.2 mg/kg sid-bid or 1.2 mg/cat bid
Lorazepam (personal experience) 1.0 mg (sm. dog) 2.0 mg (med. dog) 4.0 mg (Lg. Dog) bid or prn
0.125-0.25 mg/cat bid or prn

Methylphenidat 0.05-0.25 mg/kg bid (dogs - narcolepsy)
Dextroamphetamine 2-4 mg/kg bid-tid (dogs – hyperkinesis)
Acepromazine 0.1-2.2 mg/kg sid-qid (dogs)
0.1-2.2 mg/kg prn (cats)
Chlorpromazine 0.5-3.3 mg/kg sid-qid (dogs)
0.5-3.3 mg/kg sid-qid (cats)
Promazine  1.0-4.4 mg/kg prn (dogs)
          2.0-4.0 mg/kg prn (cats)
Haloperidol  1- 4 mg bid
Diphenhydramine  2-4 mg/kg bid-tid or 0.5-5.0 mg/dog tid (dog)
          2-4 mg/kg bid-tid (cat)
Chlorpheneramine  2.2 mg/kg bid-tid or 0.2-0.8 mg/kg tid (dog)  (max. 1 mg/kg/24 hrs)
          2.2 mg/kg bid-tid or 0.4-0.7 mg/kg (cat)
Cyproheptadine  0.3-2.0 mg/kg bid (dog)  2-4 mg/cat bid-tid (cat)
Buspirone  1-2 mg/kg sid-tid (dog)
          0.5-1 mg/kg sid-tid (cat)
Deprenyl  0.5 mg/kg sid (Cognitive Dysfunction)
          1-2 mg/kg sid (Cushing’s Disease)
Trazodone  1.0-3.0 mg/kg prn or up to bid
Clonidine  0.01-0.05 mg/kg prn given 2 hrs before exposure