Justification

- Neurotransmitters affect neuro-activity in the CNS, including that involved with emotion and learning
- Fear and anxiety are major components of most animal behavior problems
- Reducing fear and anxiety using psychotropic drugs facilitates learning and behavior modification

Indications for psychotropic medication

- Adjunct to behavior therapy (e.g., separation anxiety)
- When behavior problem is due to underlying pathology (e.g., cognitive dysfunction)
- To improve animal’s well-being (e.g., anxiety)

*Never use drugs in the absence of safety or behavior modification*

Before You Prescribe

AMDUCA – Animal Medical Drug Use Clarification Act

- Valid veterinary-client-patient relationship
- Inform clients of extra-label use (signed consent)
- Rechecks required for refills (3 months to 1 year)

Understand efficacy and side effects of drugs

Understand liability issues

- Basic health status of animal
  - Physical
  - CBC/chemistry panel/urinalysis – baseline values
  - Thyroid
    - Mature and geriatric cats – Yes!
    - Dogs –?
    - Competition animal?

- Know your client’s goals and expectations
- Medication will not “cure” a problem, but may be a useful part of treatment plan
- Are the owners being safe?
- Have you given appropriate behavior modification advice or referred to an appropriate professional?
Neurotransmitters

- Basis of chemical transmission in CNS
- Target of psychotropic drugs
  - **Agonists** – mimic NT activity
  - **Antagonists** – block normal NT activity

Neurotransmitter Classes

**Biogenic amines**
- Indoleamine
  - Serotonin (5HT)
- Catecholamines
  - Dopamine
  - Norepinephrine
  - Epinephrine

**Amino acids**
- Glutamate
- GABA
  - *Most psychotropic meds affect multiple NTs directly or indirectly at high doses*

Receptors

**Ionotropic:**
- NT binds to receptor → immediate conformational changes to channel → flow of ions
- *Fast*

**Metabotropic (G-protein linked):**
- NT (1st message) binds to receptor → 2nd messenger cascade
- Usually changes gene expression
- *Slow and sustained*

**GABA (γ-aminobutyric acid)**
- Major inhibitory NT in brain
- Glutamate is precursor
- **GABA_A** – primary post-synaptic receptor (chloride channel)
• Inactivation
  – Reuptake transporter (GAT)
  – Metabolized by GABA-transaminase (GABA-T)

Benzodiazepines
• Increases frequency of GABA-A receptor opening (= enhanced inhibitory effects)
• Anxiolytic; muscle relaxant; anti-seizure
• Good for predictable stimuli
• *Quick onset and short-acting*
• Give *BEFORE* fear or panic onset

Benzodiazepine Side Effects
• Sedation
• Ataxia
• Increased appetite
• Paradoxical excitement
  – Give test dose prior to exposure to stimuli
• Disinhibition of aggression
• Hallucinations
• Decreased learning
• Feline idiopathic hepatic necrosis (oral diazepam)
  – Insufficient glucuronic metabolism

Class IV controlled substance

Chronic use may lead to:
• **Tolerance**
  – Need higher dose to obtain same effect

• **Chemical dependency**
  – Decrease 25%/week to avoid withdrawal signs of rebound anxiety or seizures

Be aware of human abuse potential!
Benzodiazepines

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dogs</th>
<th>Cats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>0.02-0.1 mg/kg q4h</td>
<td>0.0125-0.25 mg/kg q8h</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.1-0.5 mg/kg q8-12h</td>
<td>0.015-0.2 mg/kg q8h</td>
</tr>
<tr>
<td>Clorazepate dipotassium</td>
<td>0.5-2.0 mg/kg q4h</td>
<td>0.5-2.0 mg/kg q12h</td>
</tr>
<tr>
<td>Diazepam</td>
<td>0.5-2.0 mg/kg q4h</td>
<td>0.1-1.0 mg/kg q4h</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.02-0.5 mg/kg q8-12h</td>
<td>0.03-0.08 mg/kg q12h</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>0.04-0.5 mg/kg q6h</td>
<td>0.2-1.0 mg/kg q12-24h</td>
</tr>
</tbody>
</table>

Note: All doses are orally and are given as needed until the desired effect is reached. The hourly schedules are the maximum frequency at which the medication should be given. As a general rule, start at the lowest dose and increase to effect. (Adapted from Landsberg, et al. 2013)

How to Choose?
- Health of patient
  - Oxazepam and lorazepam have no intermediate metabolites and considered safest
- Duration
- HUGE individual variation – trial and error

Serotonin (5HT)
- Indoleamine biogenic amine
  - Modulates mood, sleep/wake cycle, impulsive aggression (?)
  - Involved in anxiety, panic, compulsive disorders, depression
  - Metabotropic receptors
  - Inactivation by SERT (transporter) and MAO (enzyme)

Norepinephrine
- Catecholamine biogenic amine NT
  - Also is NT of sympathetic postganglionic neurons
  - Metabotropic receptors: α- and β-adrenergic
  - Inactivated by NET (transporter) and MAO
  - CNS stimulating, affects mood and arousal, vigilant concentration
Dopamine (DA)

- **Catecholamine biogenic amine**
- Metabotropic receptors
- **DA depletion** – Quieting, depression, extrapyramidal signs (Parkinson’s)
- **DA excess** – Stereotypical behaviors, psychotic symptoms
- Inactivated by DAT (transporter) and MAO (enzyme)

Dopaminergic Pathways

- **Mesolimbic Pathway**
  - Associated with pleasure, reward, and goal-directed behavior

- **Mesocortical Pathway**
  - Associated with motivational and emotional responses

- **Nigrostriatal Pathway**
  - Involved in coordination of movement (part of basal ganglia motor loop)

- **Tuberoinfundibular Pathway**
  - Regulates secretion of prolactin by pituitary gland and involved in maternal behavior

Selective Serotonin Reuptake Inhibitors (SSRIs)

- Increasing serotonin (5HT) is the primary mechanism for reducing anxiety (& depression)
- SSRIs increase serotonin in synaptic cleft
- Desensitization of receptors
  - $5\text{HT}_{1A}$ desensitization = increased firing → more 5HT
  - Other postsynaptic receptor desensitization = decreased side effects
  - Stimulates production of brain derived neurotrophic factor (BDNF)
- Anxiolytic, anti-aggression, anti-compulsive
- Maintenance medication, not PRN
- Fairly long half-life (approx. 5 days)
- **Start at half-dose for first 2 weeks**
- Choice depends on symptoms of anxiety and other problems
  - E.g., keeping owners up at night – choose one that is more sedating (paroxetine)
SSRI Side effects
- Vomiting, diarrhea
- Constipation, urinary retention (M₁ receptor)
- Initial, temporary anorexia (5HT₃,₄ receptors)
- Increased agitation (5HT₂A,₂C receptors)
- Seizure or other neurologic signs
- Abnormal bleeding

SSRIs

<table>
<thead>
<tr>
<th>SSRI</th>
<th>Properties</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>Serotonin reuptake inhibitor (SRI); Mild anti-histaminic (H₁)</td>
<td>Dogs may metabolize to more toxic metabolite – not first choice in dogs; use for OCD, anxiety; aggression</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>SRI (5HT₂C); Norepinephrine reuptake inhibitor (NRI) at high dose</td>
<td>Good basic first line for anxiety, aggression, OCD</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>SRI</td>
<td>Human OCD, not commonly used in vet med but could be alternative</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>SRI, mild NRI, Anti-muscarinic (M₁)</td>
<td>Sedating SSRI; anxiety, aggression, OCD</td>
</tr>
<tr>
<td>Sertraline</td>
<td>SRI, Dopamine reuptake inhibitor (DRI)</td>
<td>Least side effects – aggression, anxiety; OCD</td>
</tr>
</tbody>
</table>

Reconcile®
- Fluoxetine hydrochloride
- FDA approved for treatment of canine separation anxiety
- Elanco Animal Health

Buspirone (Buspar®)
- Azapirone; 5HT₁A/B partial agonist
- Monotherapy for generalized anxiety
- Not a good first choice (monotherapy) for aggressive animals
- Augment of SSRI response
  - SSRIs may deplete 5HT stores
  - Buspirone may slow impulse and allow vesicles to replenish
• Very few side effects

**Tricyclic Antidepressants (TCAs)**
- Block reuptake of serotonin, and to lesser extent, norepinephrine
- Anxiolytic, anti-compulsive, anti-aggressive
- **Clomipramine** very selective for 5HT, used almost interchangeably with SSRIs
- Amitriptyline – save for dermatologic cases, *not* first line for behavior cases

**TCA Side Effects**
- Potential for serotonin syndrome
- Weight gain, sedation (H1 receptor)
- Constipation, urinary retention (M1 receptor)
- Sedation, dizziness, hypotension (α1 receptor)
- Cardiac arrhythmia and blocks – Na channel blocker
- Also binds T3, T4, TSH (monitor thyroid function)
- *Start at half-dose first 1-2 weeks to reduce side effects*

**Tricyclic Antidepressants (TCAs)**

**Table 11.1** Acute *in vitro* biochemical activity of selected tricyclic antidepressants

<table>
<thead>
<tr>
<th>TCA</th>
<th>NE</th>
<th>5-HT</th>
<th>α1</th>
<th>α2</th>
<th>H1</th>
<th>Musc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>±</td>
<td>++</td>
<td>+++</td>
<td>±</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>0</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Despiramine</td>
<td>+++</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Doxepin</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>0</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Imipramine</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>0</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>++</td>
<td>±</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

Source: Potter 1984; Potter et al. 1991; Richelson and Nelson 1984a; Richelson and Pfenning 1984b; Potter et al. 1995.
Clomicalm®
  • FDA approved for canine separation anxiety
  • Clomipramine hydrochloride
  • Novartis (Elanco)

Monoamine Oxidase Inhibitor
  • MAO = enzyme that metabolizes NE, DA, 5HT
  • Subtypes:
    – MAO-A, preferential substrates are 5HT, NE
    – MAO-B, preferential substrate is DA (and other amines)
    – DA metabolized by either MAO-A or MAO-B

Selegiline (Anipryl®)
  • FDA approved for Canine Cognitive Dysfunction
  • Selective irreversible MAO-B inhibitor
  • Increases dopamine (DA)
    – Decreases destruction of DA
    – Inhibits DAT (transporter)
    – Increases DA release by inhibiting DA autoreceptor
  • Enhances endogenous free radical scavengers; reduces free radical output from MAO
  • l-methamphetamine and other metabolites
  • Do NOT use with SSRIs or TCAs → Serotonin Syndrome

Serotonin Syndrome
  • Excessive serotonin activity in CNS and at peripheral 5HT receptors
  • Neurologic signs: Mentation change, ataxia, hyperesthesia, tremors, seizures
  • Cardiovascular signs: Tachycardia, respiratory distress; Fever
  • GI signs: Diarrhea, abdominal pain, hypersalivation, anorexia
  • Potentially life-threatening
  • Usually results from use of combination of serotonergic meds (especially MAO-I); amitraz; tramadol
  • Usually is acute onset
  • Treatment – supportive
    – 5HT antagonist (Cyproheptadine)?
    – Benzodiazepines for agitation?
Trazodone
- **Serotonin antagonist and reuptake inhibitor (SARI)**
  - Antagonist primarily of $5HT_{2A}$
- Use for anxiety, aggression
- Usually given in combo with antidepressants and/or benzodiazepines
- PRN or maintenance drug
- Not controlled, no dependency
- Low side effect risk – GI, agitation
- If you consider using ace, use trazodone instead

Clonidine
- $\alpha_2$ adrenergic agonist (autoreceptor in locus ceruleus)
- Decreases NE release
- Use PRN – predictable stimuli
- Can use in combo with antidepressants or trazodone
- Side effects – seem to be low risk; hypotension, agitation; need more research

Sileo®
- SILEO® (dexmedetomidine oromucosal gel)
- FDA approved for the treatment of canine noise aversion
- Anxiolytic effect mediated through locus coeruleus
- Potent and selective $\alpha_2$ adrenergic agonist → prevents release of NE

Pexion (imepitoin)
- Imepitoin
  - Anticonvulsant
  - Anxiolytic
  - $GABA_A$ partial agonist
- FDA approved for canine noise aversion
- Boehringer Ingelheim

GABA Analogs
- $\alpha_2\delta$ subunit ($Ca^{2+}$ channel) ligands
  - Gabapentin (Neurontin)
Pregabalin (Lyrica)

- Block neuronal firing by binding to $\alpha_2\beta$ subunit of Ca$^{2+}$ channel
- Anxiolytic
- **Neuropathic pain***

**Antipsychotics**
- **Dopamine receptor antagonist**
  - Conventional – block DA in all 4 pathways
    - Haloperidol
    - Phenothiazines (acepromazine, fluphenazine)
  - Atypical antipsychotics – also antagonize 5HT-2A; acts as antagonist on some DA receptors
    - End result is lower side effect profile
  - Blunts reactions, but *not* anxiolytic

**Fluphenazine**
- High potency phenothiazine
- Low cardiac and ANS effects
- High extrapyramidal signs (EPS)
- Popular horse tranquilizer
  - Banned for performance
  - Consider testing for it when buying a horse
  - Unpredictable individual effects

**Acepromazine**
- Low potency phenothiazine
- Used as pre-anesthetic, tranquilizer, antiemetic
- CNS depressant
- Some $M_1$, $H_1$, $\alpha$-adrenergic antagonistic effects
- **Side effects**: hypotension, bradycardia, ataxia, aggression, paradoxical excitement, *increased noise sensitivity*, priapism
- Not anxiolytic
- Reserve for cases where bodily harm is a big concern
- Consider trazodone instead of ace
Comorbidities

- Hepatic disease
  - **SSRIs**: Reduce dose by 50%
  - **Benzos**: Lorazepam

- Renal disease
  - **SSRIs**: Fluoxetine & sertraline generally well tolerated
  - **Gabapentin**: 60-70% excreted by kidneys in dogs

- Cardiac disease
  - Avoid clonidine
  - **Trazodone & TCAs**: May be arrhythmogenic

- Seizure disorder
  - Consider gabapentin or benzodiazepine
  - In humans, new incidences of seizures is low with SSRIs

- Chronic pain
  - Consider gabapentin or TCA

- TCAs
  - Use with caution with kidney disease, hepatic disease, heart disease, & seizure disorders

Test Dose

- **PRN medications**
  - **Benzodiazepines**: monitor for paradoxical excitation
  - **Trazodone & gabapentin**: assess time to response
  - **Clonidine**: monitor for signs of hypotension

Maintenance (Daily) versus PRN

**Maintenance:**
- Severe clinical signs
- Frequent occurrence
- Uncontrollable triggers

**PRN:**
- Mild to moderate clinical signs
- Infrequent occurrence
- Controllable (or predictable) triggers
Maintenance
- SSRI
- TCA
- MAOI
- Buspirone

PRN
- Benzodiazepine
- Trazodone
- Clonidine
- Gabapentin

Polypharmacy
- Augmentation of SSRIs, TCAs, or MAOIs
  - Benzodiazepines: PRN for situational anxiety
  - Gabapentin: Good for neuropathic pain
- Common combos with SSRIs or TCAs
  - Trazodone: Monitor for signs of serotonin toxicity
  - Buspirone: Monitor for signs of serotonin toxicity
  - Clonidine: Monitor for cardiac side effects

Discontinue
- Severe adverse events
  - Inappetence or anorexia
  - Excessive sedation
  - Paradoxical excitation
  - Increased sound sensitivity
  - “Not him/herself”

Discontinue or Adjust
- Inadequate response
  - Increase dose?
  - Polypharmacy?
  - Adjust behavior plan?
- Once behavior is stabilized
  - Wean slowly (reduce by 10-25% every month) to achieve lowest effective dose or to discontinue medication
Hormones

- Progestins
  - Inhibit gonadotropins and testosterone
  - Bind GABA_A
  - May increase endogenous opioids
- Can have calming effect
- Likely side effects, but not common in horses
  - May interfere with reproductive cycling or cause uterine hyperplasia
  - Small Animals – Diabetes, endometrial hyperplasia, neoplasia, pyometra
- Last resort in small animals

Probiotics

- Purina® Pro Plan® Veterinary Calming Care
- Bifidobacterium longum (BL999)
- For dogs displaying anxious behaviors

Nutraceuticals

- Many act via GABA or serotonin
- Anti-anxiety
  - Zylkene® – Alpha casozepine, milk casein
  - Harmonease® – Magnolia and Phellodendron extract
  - Solliquin® – L-theanine, Magnolia and Phellodendron extract, whey protein concentrate
  - Rescue Remedy – Valerian, Bach
  - St Johns Wort – serotoninergic
- Cognitive enhancing drugs – basically antioxidants and neuroprotectors
  - Senilife® (Ginko biloba, phosphatidylserine, Vitamin B6, Vitamin E)
  - Neutricks® (Apoaequorin)

Diet

- Hill’s® b/d®
- Purina® Pro Plan® Veterinary Diets NC NeuroCare™