Psychopharmacology – VT VMA – Feb 2023

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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 (1^{st} message) binds to receptor → 2^{nd} 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

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

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
  - $5HT_{1A}$ 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 (M_1 receptor)
- Initial, temporary anorexia ($5HT_{3,4}$ receptors)
- Increased agitation ($5HT_{2A,2C}$ receptors)
- Seizure or other neurologic signs
- Abnormal bleeding

SSRIs

SSRI	Properties	Effects
Citalopram	Serotonin reuptake inhibitor (SRI); Mild anti-histaminic (H_1)	Dogs may metabolize to more toxic metabolite – not first choice in dogs; use for OCD, anxiety; aggression
Fluoxetine	SRI ($5HT_{2C}$); Norepinephrine reuptake inhibitor (NRI) at high dose	**Good basic first line for anxiety, aggression, OCD**
Fluvoxamine	SRI	Human OCD, not commonly used in vet med but could be alternative
Paroxetine	SRI, mild NRI, Anti-muscarinic (M_1)	**Sedating** SSRI; anxiety, aggression, OCD
Sertraline	SRI, Dopamine reuptake inhibitor (DRI)	**Least side effects** – aggression, anxiety; OCD

Reconcile®

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

Buspirone (Buspar®)

- Azapirone; **$5HT_{1A/B}$ 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 (H_1 receptor)
- Constipation, urinary retention (M_1 receptor)
- Sedation, dizziness, hypotension (α_1 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

TCA	NE	5-HT	α_1	α_2	H_1	Musc.
Amitriptyline	±	++	+++	±	++++	++++
Clomipramine	+	+++	++	0	+	++
Despiramine	+++	0	+	0	0	+
Doxepin	++	+	++	0	+++	++
Imipramine	+	+	++	0	+	++
Nortriptyline	++	±	+	0	+	++

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

- **α_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 α_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 $\alpha_2\delta$ subunit of Ca^{2+} channel
- Anxiolytic
- **Neuropathic pain***

Antipsychotics

- **Dopamine receptor antagonist**
- Conventional – block DA in all 4 pathways
  - Halperidol
  - 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, α-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™