Two major categories of medications

“Daily” (standing) drugs
- Given daily, regardless of situation
- Weeks to take effect

“Event” medication
- Given for stress events
- Quick onset, last for set # of hours
- Sometimes used daily as part of poly-therapy

Indications for a daily drug
- Generalized anxiety
- Fearful behavior or aggression
- Inter-pet aggression
- Separation anxiety
- Cognitive Dysfunction Syndrome
- Urine marking
- Stress related toileting
- Compulsive disorders
  - Spinning, licking, tail-chasing

Common classes

Selective serotonin reuptake inhibitors (SSRIs)
- Fluoxetine (Prozac®/Reconcile®)
- Paroxetine (Paxil®)
- Sertraline (Zoloft®)
- Citalopram (Celexa®)

Tricyclic antidepressants (TCAs)
- Clomicalm® (clomipramine)
- Amitriptyline (Elavil®)

Azapirones
- Buspirone (Buspar®)

Selective serotonin/norepinephrine reuptake inhibitors (SNRIs)
- Venlafaxine (Effexor®)

Monoamine oxidase inhibitor (MAOI)
- Selegiline (Anipryl®)
SSRIs

- Block the reuptake transporter for serotonin (5HT) in the presynaptic neuron, prolonging 5HT’s availability in the synaptic cleft.

Initially 5HT floods all of its receptors

- Reason for initial side effects
- Most receptors down-regulate over 4-6 weeks and side effects wane
- Postsynaptic autoreceptor does not down-regulate – becomes more active with time.

Why do SSRIs take 4-6 weeks to work?

- Presynaptic 5-HT1A autoreceptor
  - Activation inhibits serotonin synthesis and release from axons
  - Wait for desensitization of 5-HT1A autoreceptor

Prozac® - fluoxetine HCL

Effects of a selective serotonin reuptake inhibitor on urine spraying behavior in cats
Patricia A. Pryor, DVM; Benjamin L. Hart, DVM, DACVB, Kelly D. Cliff, DVM; Melissa J. Bain, DVM

- Proven efficacy for separation anxiety (FDA label for Reconcile) and compulsive disorders in dogs
- 100% urine marking cats saw >90% improvement
- Studies on psychogenic alopecia in cats, aggression in dogs

Prozac® - side effects

Common:
- Decreased appetite
  - CAUTION with finicky or obese cats
- Lethargy/decreased grooming

Uncommon:
- Gastrointestinal upset (typically v and d)
- Urine retention
  - Rare but can cause functional blocking
  - ER!!
- Make sure owners monitor appetite and elimination during initial treatment phase!

Prozac® - fluoxetine other concerns

- Potential to cause hypoglycemia in DM patients
- May see hyperglycemia upon D/C of drug
**Paxil® – paroxetine HCL**

- Case series and case reports on urine marking, aggression in dogs and cats, and generalized anxiety in dogs
- No placebo controlled clinical trials in dogs or cats
- Suspect similar efficacy to Prozac with different S/E profile

**Paxil® – side effects**

- Tends to be appetite enhancing
- Lethargy/decreased grooming
- Mild anticholinergic effects
  - Dry eyes, dry mouth, urine retention, constipation
  - May be a beneficial effect in pets with chronic loose stools
  - Avoid in pets with history of constipation, blocking
- Rare, but severe urine retention in cats
- Short half-life
- Discontinuation syndrome

**Zoloft® – sertraline HCL**

- Case series and case reports on psychogenic alopecia and aggression in dogs
- No placebo controlled clinical trials in dogs or cats
- Suspect similar efficacy to Prozac with different S/E profile

**Zoloft® – side effects**

- Occasional decrease in appetite
- Lethargy
- Decreased grooming
- Gastrointestinal upset (v or d)
- Severe urine retention in cats
- Rare but can cause functional blocking – ER!!

**Zoloft® - other considerations**

- Primarily eliminated via fecal excretion
- No dose adjustment needed for CKD
- Used in some human patients with hepatic disease
- Likely the safest daily med for epileptic patients

**Tricyclic antidepressants - TCAs**

- Block the reuptake transporter for serotonin (5HT) & norepinephrine (NE), prolonging availability
- Also antihistaminic and anticholinergic effects
- Efficacy in ~4 weeks
Behavioral Medicine

Most benefits are from serotonin
- NE also regulates anxiety and behavior
- Antihistamine effects lead to greater calming effects
- Anticholinergic effects lead to a higher side effect profile

Clomicalm® - clomipramine HCL
- FDA label for canine separation anxiety
- Canadian label for urine marking in cats
- Placebo-controlled trial in canine compulsive disorders
- Multiple publications on various anxiety-related disorders
- TS phobia, generalized anxiety, aggression

Clomicalm® - side effects
- Sedation (antihistamine fx)
- Moderate anticholinergic effects
  - Dry eye, dry mouth, urine retention, constipation
  - AVOID in pets with history of constipation, KCS, glaucoma
- Arrhythmogenic (longer p-wave duration)
  - AVOID in CV compromised patients
- Lowering of seizure threshold
  - AVOID in epileptic patients
- Severe urine retention
  - Uncommon but can cause functional blocking – ER!!
  - Testicular hypoplasia – AVOID in breeding males

Elavil® – amitriptyline
- Studied in cats with feline interstitial cystitis (FIC)
  - Some efficacy in chronic, recurrent cases
  - Moderate to severe sedation reported
  - Neuropathic pain, acral lick in dogs
  - Not typically a first choice for 1st anxiety disorders
  - An acceptable 3rd or 4th line of treatment
  - “Poor man’s Clomicalm”?  
    - Poorer efficacy, greater side effect profile, but definitely cheaper!

Elavil® – side effects
- Sedation (antihistamine fx)
- Substantial anticholinergic effects
  - Dry eye, dry mouth, urine retention, constipation
  - AVOID in pets with history of constipation, KCS, glaucoma
- Arrhythmogenic (decreased Q-T interval)
  - AVOID in CV compromised patients
- Lowering of seizure threshold
  - AVOID in epileptic patients
- Severe urine retention
  - Uncommon but can cause functional blocking – ER!!

Azapirones
- Serotonin agonist
  - Binding at presynaptic 5HT autoreceptor ↑ 5HT production
  - Binding at postsynaptic 5HT autoreceptor mimics effects of 5HT
    - ↓ anxiety
    - ↑ boldness

Clomicalm® - Clomipramine HCL
Effects of Clomipramine on Cats Presented for Urine Marking
Gary M. Landsberg, BSc, DVM, Diplomate ACVIM
Andrea L. Wilson, BSc, DVM

Elavil® – amitriptyline
Amitriptyline treatment for severe recurrent idiopathic cystitis in cats.
Chew DJ, Buffington CA, Kendall MS, DiBartola SP, Woodworth BE
JAVMA 1998
### Buspirone (Buspar®)

- The “bravery” drug
- Used to treat FEARFUL, NON-AGGRESSIVE pets
- Great for victim cats, globally fearful dogs
- Some efficacy in urine marking (~55%)
- Faster acting - therapeutic effects in 1-2 weeks

**Effectiveness of buspirone on urine spraying and inappropriate urination in cats.**

Hart BL, Eckstein RA, Powell KL, Dodman NH JAVMA 1993

### Buspirone – side effects

- Common
  - Increased friendliness
  - More assertive social interactions
  - Exacerbation of existing aggression
- Uncommon
  - Sedation
  - Agitation

### Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)

- Block the reuptake transporter for serotonin (5HT) & norepinephrine (NE), prolonging availability
- No antihistaminic nor anticholinergic effects
- Efficacy in 4-5 weeks

### Venlafaxine (Effexor®)

- No placebo-controlled clinical trials in dogs or cats
- Published reports for treatment of narcolepsy in dogs
- Case examples and anecdotal treatment for anxiety, aggression, phobias
- Chronic neuropathic pain in human patients
- One of the most commonly reported drug toxicities in cats (from ingesting owner’s meds)

### Effexor® - side effects

- Lethargy
- GI upset (v +/- d)
- Agitation (uncommon)
- Lowered seizure threshold
- Short half-life
- Discontinuation syndrome

### Monoamine oxidase inhibitors (MAOIs)

- Inhibits monoamine oxidase B
  - Monoamines: Norepinephrine, dopamine, serotonin
- FDA approved for Canine CDS
- Used off label for cats

### Selegiline HCl (Anipryl®)

- FDA approved for Canine CDS
- Used off label for cats

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*Image credits: [Buspirone](https://www.360vet.com/breath-of-life-buspirone-buspar®), [Venlafaxine](https://www.effexor.com), [Monoamine oxidase inhibitors](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5893463/).*
Selegiline – side effects

- Uncommon
  - Sedation, decreased appetite, GI upset, irritability

- Caution with drug interactions**
  - Tramadol, opioids
  - Amitraz
  - SSRIs, TCAs
  - Cisapride

Serotonin syndrome

- Too much serotonin in the synaptic cleft
- Typically a result of an overdose or combination of serotonergic meds (tramadol + Clomicalm)

- Symptoms:
  - Agitation
  - Tremors
  - Seizures
  - Hyperthermia
  - Tachycardia
  - Diarrhea

How to choose?

Need additional antihistamine calming? – choose a TCA
Can’t afford Clomicalm? – Consider SSRI + traz, or try amitriptyline
Health concerns? – Avoid TCAs for seizure, cardiac, constipation, KCS/glaucoma patients

Want to avoid sedative effects? – choose an SSRI or SNRI,
  - Prozac has the most research behind it
  - Is appetite a concern? – Avoid Prozac, consider Paxil
  - Is twice daily dosing going to be problematic? – consider Zoloft
  - Are seizures a concern? – Zoloft may be safest choice
  - Any renal insufficiency? – Zoloft may be safest choice
  - History of chronic/intermittent loose stools? – Paxil may firm up stools
  - Is there a comorbid painful condition? – Effexor may have benefits

Event Drugs

Indications for event drugs

- Veterinary visits
- Car travel
- Separation anxiety
- Visitors
- Noise phobias
- New baby
- Bridge med
- Adjunct to daily med

Common classes

- Serotonin antagonist and reuptake inhibitors (SARIs)
  - Trazodone
- Alpha-2 agonists
  - Clonidine
- GABA analogues
  - Gabapentin
- Phenothiazine neuroleptics
  - Acepromazine
- Benzodiazepines
  - Lorazepam (Ativan)
  - Diazepam (Valium)
  - Alprazolam (Xanax)
  - Clonazepam (Klonipin)
  - Clorazepate (Tranxene)
Trazodone for daily use

- Used as a bridge medication
- Gives immediate relief while you await SSRIs/TCAs to reach therapeutic effects
- Used as an adjunct medication
- Synergy between trazodone and SSRIs/TCAs
- Can add to daily SSRI/TCA therapy to boost effect
- Can be used q8h every day
- May skip bedtime dose if sleep time isn’t an issue, but keep am and afternoon doses no greater than 8 hours apart if possible to avoid the “witching hours”

Clonidine

- Alpha-2A and imidazoline receptor agonist
- Slows NE release in the reticular activating system, decreasing anxiety and alertness

Trazodone aka “vitamin T”

PROS
- Adverse events rare
- Safe even at high doses
- Not controlled
- Lots of published data

CONS
- Takes 2 hours to reach full fx
- May wear off in 4-6 hours
- Large, bitter pills
- Lowers seizure threshold

Trazodone

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>Extensive hepatic metabolism into active metabolites, main = meta-Chlorophenylpiperazine (mCPP); renal and fecal excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>CATS: 50-100mg/cat DOGS: 2-18mg/kg up to q8h</td>
</tr>
<tr>
<td>Class</td>
<td>Serotonin 2A Antagonist (Potent)/Reuptake inhibitor (weak) (SARI); phenylpiperazine</td>
</tr>
<tr>
<td>MOA</td>
<td>Some selective inhibition of SHT reuptake, antagonizes SHT2A releasing SHT1A; antagonizes SHT2C at high doses; α2-antagonist, antihistamine</td>
</tr>
<tr>
<td>Onset of action</td>
<td>60-120 minutes</td>
</tr>
<tr>
<td>Duration of action</td>
<td>About 8 hours (can be less in many patients)</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Use caution in patients with severe systemic disease; caution with epileptics</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Do not combine with MAOIs, slight caution with other SRIs</td>
</tr>
</tbody>
</table>

Clonidine

| Dose       | DOGS: 0.01-0.05mg/kg PO; CATS: 5-10µg/kg PO |
| Class      | Alpha-2 agonist, imidazoline agonist |
| MOA        | Activates inhibitory alpha2 autorec - slows release of NE in CNS, decreasing anxiety, HR, BP, pupil dilation |
| Onset of action | 30-90 minutes |
| Duration of action | 4-8 hours |
| Contraindications | Cardiovascular disease, severe renal disease, hypotensive patients |
| Drug interactions | Beta-blockers may enhance bradycardia, other antihypertensive drugs (Ace?8) |
| Side effects | Likely: Sedation, mild hypotension; Possible: Agitation, GI upset, collapse, bradycardia; Sudden d/c can result in rebound hypertension |
Clonidine

**PROS**
- Fast-acting (~30 minutes)
- Greater calming effect in hyperkinetic dogs

**CONS**
- May be more sedating
- Hypotension possible
- May only last 4 hours in some dogs

Sileo® OM gel

**PROS**
- FDA label - noise phobias in dogs
- Significant reduction in signs of fear and anxiety when given 1hr prior to fireworks or at start of them

**CONS**
- Adjust dose stop before dispensing
- Owners should wear gloves

Gabapentin - Neurontin®

- GABA analogue, but minimal anticonvulsant effects
- Traditionally a treatment for chronic and neuropathic pain (spinal cord injuries, limb amputation)
- Lowers MAC of isoflurane and time to extubation when given 2 hours prior to anesthesia (2019)
- 100mg reduced stress and handling compliance in cats when given 90 minutes prior to being put into a carrier (2017)

Gabapentin

**PROS**
- Very safe if kidneys are healthy
- Low side effect profile
- Also treats pain
- No bitter taste

**CONS**
- Variable levels of sedation
- Smallest size is 100mg capsule
- Seizures possible with abrupt discontinuation

Benzodiazepines

- GABA receptor agonists
- Sedative/hypnotic (+amnesic)
- Anxiolytic (anti-panic)
- Muscle relaxant
- Appetite stimulant
- Anticonvulsant

**Gabapentin**

<table>
<thead>
<tr>
<th>Dose</th>
<th>CATS: 50-100mg/cat PO; difficult to overdose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class</td>
<td>GABA analogue; anticonvulsant</td>
</tr>
<tr>
<td>MOA</td>
<td>blocks release of excitatory NTs (substance p, glutamate, NE)</td>
</tr>
<tr>
<td>Onset of action</td>
<td>60-90 minutes</td>
</tr>
<tr>
<td>Duration of action</td>
<td>6-8 hours</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Caution in patients with severe renal insufficiency</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Antacids block absorption</td>
</tr>
<tr>
<td>Side effects</td>
<td>Likely: sedation; Uncommon: GI upset, agitation, increased appetite, seizures possible with abrupt discontinuation of daily use</td>
</tr>
</tbody>
</table>

Caution: Human Neurontin® oral solution contains xylitol
Oral benzodiazepines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose in dogs</th>
<th>Duration of</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam (Xanax)</td>
<td>0.05-0.25mg/kg</td>
<td>2-3 hours</td>
</tr>
<tr>
<td>Diazepam (Valium)</td>
<td>0.5-2.2mg/kg</td>
<td>4-6 hours</td>
</tr>
<tr>
<td>Clorazepate (Tranxene)</td>
<td>0.5-2.2mg/kg</td>
<td>8-10 hours</td>
</tr>
<tr>
<td>Lorazepam (Ativan)*</td>
<td>0.1-0.5mg/kg</td>
<td>6-8 hours</td>
</tr>
<tr>
<td>Clonazepam (Klonopin)</td>
<td>0.05-0.5mg/kg</td>
<td>10-12 hours</td>
</tr>
<tr>
<td>Oxazepam* (Serax)</td>
<td>0.2-1mg/kg</td>
<td>10-12 hours</td>
</tr>
<tr>
<td>Chlordiazepoxide (Librium)</td>
<td>2-6.5mg/gk</td>
<td>10-12 hours</td>
</tr>
</tbody>
</table>

*Expensive and hard to get
*No active liver metabolites

Benzo reversal = flumazenil

Pros
- Shortest acting benzo
- Minimal sedation with repeated dosing
- Great for events of brief duration

Cons
- Paradoxical excitation common
- Disinhibition of aggression in dogs possible
- Ataxia common and not well tolerated by owners
- Dependence and tolerance with extended daily use

Benzo reversal = flumazenil

Alprazolam (Xanax)

- Shortest acting benzo
- Minimal sedation with repeated dosing
- Great for events of brief duration

Use of clomipramine, alprazolam, and behavior modification for treatment of storm phobia in dogs

- Clomipramine
- Alprazolam
- Behavior modification

Combined pharmacological therapy of alprazolam-fluoxetine for the treatment of anxiety-related problems in dogs. 2017

Diazepam (Valium)

- Short duration of action
- Slightly more sedating than alprazolam
- Better timing for TS phobias
- Not for cats!

Retrospective evaluation of the effects of diazepam in dogs with anxiety-related behavior problems

- Diazepam has been associated with acute hepatic necrosis after PO administration in cats.
### Lorazepam (Ativan®)

<table>
<thead>
<tr>
<th>Dose</th>
<th>CATS: 0.05-0.25mg/kg PO  DOGS: 0.1-0.5mg/kg PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class</td>
<td>Benzodiazepine</td>
</tr>
<tr>
<td>MOA</td>
<td>Potentiates GABA activity;</td>
</tr>
<tr>
<td>Metabolites</td>
<td>Hepatic into inactive lorazepam glucuronidate; renal excretion - dogs, renal and fecal - cats</td>
</tr>
<tr>
<td>CYP 450</td>
<td>9</td>
</tr>
<tr>
<td>Onset of action</td>
<td>30-60 minutes</td>
</tr>
<tr>
<td>Duration of action</td>
<td>6-8 hours</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Severe respiratory insufficiency, caution in aggressive patients</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Caution with other CNS depressants</td>
</tr>
<tr>
<td>Side effects</td>
<td>Likely: increased appetite, sedation; Possible: ataxia, aggression, paradoxical excitation</td>
</tr>
</tbody>
</table>

No reports of hepatic issues in cats with lorazepam. No active liver metabolites – risk should be lower.

### Clonazepam (Klonopin®)

<table>
<thead>
<tr>
<th>Dose</th>
<th>CATS: 0.015-0.2mg/kg PO  DOGS: 0.1-0.5mg/kg PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class</td>
<td>Benzodiazepine</td>
</tr>
<tr>
<td>MOA</td>
<td>Potentiates GABA activity;</td>
</tr>
<tr>
<td>Metabolites</td>
<td>Extensive hepatic into metabolites. Not great for hepatic dz</td>
</tr>
<tr>
<td>CYP 450</td>
<td>CYP 3A4 substrate</td>
</tr>
<tr>
<td>Onset of action</td>
<td>60-90 minutes</td>
</tr>
<tr>
<td>Duration of action</td>
<td>10-12 hours with prolonged use</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Glaucoma, severe liver or kidney dz; caution in aggressive patients</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Caution with other CNS depressants</td>
</tr>
<tr>
<td>Side effects</td>
<td>Likely: increased appetite, sedation; Possible: ataxia, aggression, paradoxical excitation</td>
</tr>
</tbody>
</table>

1000mg/kg did not kill cats (Randall and Kappell 1973)

### Acepromazine

<table>
<thead>
<tr>
<th>Dose</th>
<th>CATS: 1.1-2.2mg/kg PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class</td>
<td>Phenothiazine tranquilizer; antipsychotic</td>
</tr>
<tr>
<td>MOA</td>
<td>Block post-synaptic dopamine receptors in CNS, depressing RAS (↓ alertness)</td>
</tr>
<tr>
<td>Onset of action</td>
<td>30-90 minutes</td>
</tr>
<tr>
<td>Duration of action</td>
<td>8-12 hours</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Seizures, severe cardiovascular disease, hypotensive patients, aggressive patients</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Antacids block absorption, caution with other CNS depressants</td>
</tr>
<tr>
<td>Side effects</td>
<td>Likely: sedation, hypotension; Possible: Collapse, seizures, bradycardia, agitation, noise sensitivity</td>
</tr>
</tbody>
</table>
Imepitoin (Pexion®)

- Anticonvulsant
- Partial agonist of GABA_A
- Reduced fear and anxiety during storms @30mg/kg BID
- Adjunct for epileptics with fears/anxiety?

Effectiveness of imepitoin for the control of anxiety and fear associated with noise phobia in dogs

Polytherapy?

- Is the patient’s behavior concerning enough that immediate relief is needed? Either for safety, welfare, or client patience level reasons they can’t wait 4-6 weeks?
  - Start event med q8-12h first, then add daily med once effective dose established; may be able to wean off of event med once daily drug reaches therapeutic levels
- Do you suspect a pain component to patient’s behavior?
  - Gabapentin should be first choice as you bridge med
- Are there anticipated stressful events that trigger panic that is likely to override the effects of SSRI/TCA therapy alone?
  - Start daily med and have client give test doses of an event med in a few days.

Administering medications

Tablets and capsules

- Gel caps to mask bitterness
- Pill Pockets®, Easy Cheese, canned food, braunschweiger
- 3 meatball trick
- Add crunchy texture
- Try to avoid “pilling”
  - Coat with butter

Liquid compounding

- Tuna, chicken, other meat flavors
  - Mix with canned tuna or chicken, baby food, canned food
- Typically doesn’t work well to directly administer

Treat compounding

- Pounce® treats/Minis (Stoke’s Pharmacy)
- Flavor tabs (Wedgewood Pharmacy)
Transdermal

- Bioavailability often greatly reduced
  ~10% fluoxetine absorbed
- May need to increase dose to achieve bioavailability

Health monitoring

- PE, CBC, chem profile, total T4 and urinalysis
  **PRIOR to starting and repeated yearly

The end

Candra

- Diagnosis: Noise phobia
- Behavior modification
  - Desensitization and counter conditioning to storm sounds
  - Safe haven in area of hiding: White noise, classical music, Feliway

Case Example: Cora

- Cora 7 YO FS DLH
- Presenting complaint: hypersalivation, trembling, urinating, defecating and hiding during storms, power washing, fireworks
- PE/CBC/Chem/UA/T4: WNL

Medications

- Test lorazepam 0.125mg PO 30-60 minutes prior to storm
- Start buspirone after lorazepam effects established at 2.5mg PO q12hrs

Side effects

- Munchies
- Increased friendliness
Candra

- Discontinued lorazepam after 3 months
- Weaned buspirone 9 months after presentation
- Ongoing issues: pill demands, managed with treat administration, ongoing cuddles