Two major categories of medications

“Daily” (standing) drugs
- Given daily, regardless of situation
- Takes 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)
- Paroxetine (Paxil)
- Sertraline (Zoloft)
- Citalopram (Celexa)

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

Azapirones
- Buspirone

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

Monoamine oxidase inhibitor (MAOIs)
- Selegiline
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 auto-receptor

Prozac® - fluoxetine HCL

*Effects of a selective serotonin reuptake inhibitor on urine spraying behavior in cats*

- 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 eye, 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 (SHT) & norepinephrine (NE), prolonging availability
- Also antihistaminic and anticholinergic effects
- Efficacy in ~4 weeks

**Most benefits are from serotonin**
- NE also regulates anxiety and behavior
- Antihistaminic effects lead to greater calming effects
- Anticholinergic effects lead to a higher side effect profile
Clomicalm® - clo mipramine 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, anal lick in dogs
• Not typically a first choice for 1º anxiety disorders
• An acceptable 3º or 4º 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

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 clinical trials in dogs or cats
- Case 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

**Selegiline HCl (Anipryl ®)**
- Inhibits monoamine oxidase B
  - Monoamines: Norepinephrine, dopamine, serotonin
- FDA approved for Canine CDS
- Used off label for cats

**Selegiline – side effects**
- Uncommon
  - Sedation, decreased appetite, GI upset, irritability
- Caution with drug interactions**
  - Tramadol, opioids
  - Amitraz
  - SSRI, TCAs
  - Cisapride
Serotonin syndrome

- Too much serotonin in the synaptic cleft
- Typically a result of an overdose or combination of serotonergic meds
- Symptoms:
  - Agitation
  - Tremors
  - Seizures
  - Hyperthermia
  - Tachycardia
  - Diarrhea

Indications for event drugs

- Veterinary visits
- Car travel
- Separation anxiety
- Visitors
- Noise phobias
- New baby

Event Drugs

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 (Klonopin)
  - Clorazepate (Tranxene)

Trazodone for daily use

- 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”
- Offers an immediate bridge while you await SSRIs/TCAs to reach therapeutic effects
- Synergy between trazodone and SSRIs/TCAs
- Can ADD to daily SSRI/TCA therapy to boost effect
**Trazodone**

**Metabolism**
- Extensive hepatic metabolism into active metabolites, main = meta-Chlorophenylpiperazine (mCPP); renal and fecal excretion

**Dose**
- CATS: 30-100mg/cat
- DOGS: 2-18mg/kg up to q8h

**Class**
- Serotonin 2A Antagonist (Potent)/Reuptake inhibitor (weak) (SARI); phenylpiperazine

**MOA**
- Some selective inhibition of SHT reuptake, antagonizes SHT2A releasing SHT; antagonizes SHT2C at high doses; α1-antagonist, antihistamine

**Onset of action**
- 60-120 minutes

**Duration of action**
- About 8 hours (can be less in many patients)

**Contraindications**
- Use caution in patients with severe systemic disease; caution with epileptics

**Drug interactions**
- Do not combine with MAOIs, slight caution with other SSRIs

**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

---

**Clonidine**

**MOA**
- Activates inhibitory α2 autoreceptors; slows release of NE in CNS, decreasing anxiety, HR, BF, 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 (ACEi)

**Side effects**
- Likely: Sedation, mild hypotension; Possible: Agitation, GI upset, collapse, bradycardia

**Sudden d/c can result in rebound hypertension**

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**Gabapentin - Neurontin®**

**MOA**
- GABA analogue, but minimal anticonvulsant effects
- Traditionally a treatment for chronic and neuropathic pain (spinal cord injuries, limb amputation)

**Effects of oral administration of gabapentin on the minimum alveolar concentration of isoflurane in dogs and cats.**

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

**CONS**
- GABA analogue, but minimal anticonvulsant effects
- Traditionally a treatment for chronic and neuropathic pain (spinal cord injuries, limb amputation)

**Lower MAC of isoflurane and time to exubation 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

**Dose**
- CATS: 50-100mg/cat PO; difficult to overdose

**Class**
- GABA analogue; anticonvulsant

**MOA**
- Blocks release of excitatory NTs (substance p, glutamate, NMDA)

**Onset of action**
- 60-90 minutes

**Duration of action**
- 6-8 hours

**Contraindications**
- Caution in patients with severe renal insufficiency

**Drug interactions**
- Antacids block absorption

**Side effects**
- Likely: sedation
- Uncommon: GI upset, agitation, increased appetite, seizures possible with abrupt discontinuation of daily use

Caution: Human Neurontin® oral solution contains xylitol

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**Benzodiazepines**

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

---

**Oral benzodiazepines**

- **Drug**
  - Alprazolam (Xanax) 0.05-0.25mg/kg 2-3 hours
  - Diazepam (Valium) 0.5-2.2mg/kg 4-6 hours
  - Clorazepate (Tranxene) 0.5-2.2mg/kg 6-8 hours
  - Lorazepam (Ativan) 0.1-0.5mg/kg 2-4 hours
  - Clonazepam (Klonopin) 0.05-0.5mg/kg 10-12 hours
  - Oxazepam (Serax) 0.2-1mg/kg 10-12 hours
  - Chlordiazepoxide (Librium) 2-6.5mg/gk 10-12 hours

*Expensive and hard to get

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**Alprazolam**

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

**Use of clomipramine, alprazolam, and behavior modification for treatment of anxiety-related problems in dogs. 2017**

**Combined pharmacological therapy of alprazolam-fluoxetine for the treatment of anxiety-related problems in dogs. 2017**
**Alprazolam (Xanax)**

<table>
<thead>
<tr>
<th>Dose</th>
<th>CATS: 0.0125-0.25mg/kg PO</th>
<th>DOGS: 0.01-0.1mg/kg PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class</td>
<td>Benzoiazepine</td>
<td></td>
</tr>
<tr>
<td>MOA</td>
<td>Potentiates GABA activity;</td>
<td></td>
</tr>
<tr>
<td>Metabolites</td>
<td>a-hydroxyalprazolam (1/2 active as alprazolam), a benzophenone (inactive)</td>
<td></td>
</tr>
<tr>
<td>CYP 450</td>
<td>CYP substrate – caution with drugs that inhibit 3A4 (fluvoxamine, fluoxetine, citalopram)</td>
<td></td>
</tr>
<tr>
<td>Onset of action</td>
<td>30-60 minutes FAST</td>
<td></td>
</tr>
<tr>
<td>Duration of action</td>
<td>2-4 hours SHORT</td>
<td></td>
</tr>
<tr>
<td>Contraindications</td>
<td>Glaucoma, severe renal/hepatic dz, caution in aggressive patients</td>
<td></td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Caution with other CNS depressants</td>
<td></td>
</tr>
<tr>
<td>Side effects</td>
<td>Likely: increased appetite, sedation; Possible: otitis, aggression, paradoxical excitation</td>
<td></td>
</tr>
</tbody>
</table>

**Diazepam (Valium)**

<table>
<thead>
<tr>
<th>Dose</th>
<th>CATS: AVOID</th>
<th>DOGS: 0.5-2.2mg/kg PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class</td>
<td>Benzodiazepine</td>
<td></td>
</tr>
<tr>
<td>MOA</td>
<td>Potentiates GABA activity;</td>
<td></td>
</tr>
<tr>
<td>Metabolites</td>
<td>Extensive 1st pass hepatic metabolism; nordiazepam, temazepam, oxazepam - all active; renal and fecal (34%) excretion in dogs</td>
<td></td>
</tr>
<tr>
<td>CYP 450</td>
<td>CYP 3A12 and 1A1/2 substrate – caution with grapefruit juice</td>
<td></td>
</tr>
<tr>
<td>Onset of action</td>
<td>30-60 minutes FAST</td>
<td></td>
</tr>
<tr>
<td>Duration of action</td>
<td>4-6 hours SHORT</td>
<td></td>
</tr>
<tr>
<td>Contraindications</td>
<td>Glaucoma, severe renal/hepatic dz, caution in aggressive patients</td>
<td></td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Caution with other CNS depressants</td>
<td></td>
</tr>
<tr>
<td>Side effects</td>
<td>Likely: increased appetite, sedation; Possible: otitis, aggression, paradoxical excitation</td>
<td></td>
</tr>
</tbody>
</table>

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

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

**Clonazepam**

- Short duration of action
- Slightly more sedating than alprazolam
- Better timing for T5 phobias
- Not for cats!

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

![Dogs with diazepam]
**Clonazepam (Klonopin®)**

<table>
<thead>
<tr>
<th>Dose</th>
<th>CATS: 0.015 - 0.2mg/kg PO</th>
<th>DOGS: 0.1 - 0.5mg/kg PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class</td>
<td>Benzodiazepine</td>
<td></td>
</tr>
<tr>
<td>MOA</td>
<td>Potentiates GABA activity</td>
<td></td>
</tr>
<tr>
<td>Metabolites</td>
<td>Extensive hepatic into metabolites. Not great for hepatic dz</td>
<td></td>
</tr>
<tr>
<td>CYP 450</td>
<td>CYP 3A4 substrate</td>
<td></td>
</tr>
<tr>
<td>Onset of action</td>
<td>60 - 90 minutes</td>
<td></td>
</tr>
<tr>
<td>Duration of action</td>
<td>10 - 12 hours, 1/2 increases with prolonged use</td>
<td></td>
</tr>
<tr>
<td>Contraindications</td>
<td>Glaucoma, severe liver or kidney dz; caution in aggressive patients</td>
<td></td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Caution with other CNS depressants</td>
<td></td>
</tr>
<tr>
<td>Side effects</td>
<td>Likely increased appetite, sedation; Possible: ataxia, aggression, paradoxical excitation</td>
<td></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>

**Administering medications**

- 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
- Tablets and capsules

**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