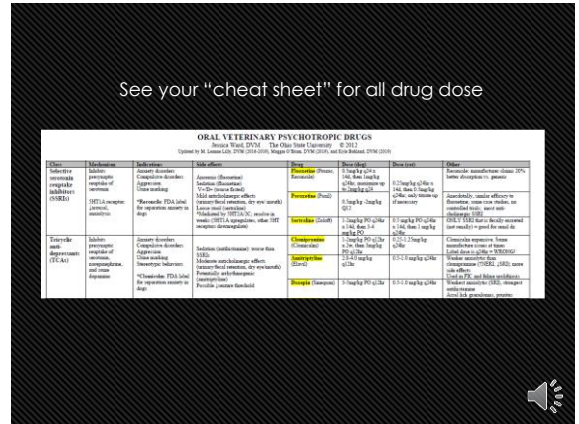




1



2

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



3

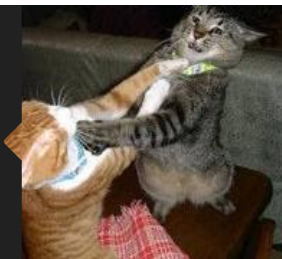


Daily drugs

4

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



5

Common classes

- Selective serotonin reuptake inhibitors (SSRIs)**
 - Fluoxetine (Prozac® / Reconcile®)
 - Paroxetine (Paxil®)
 - Sertraline (Zoloft®)
 - Citalopram (Celexa®)
- Tricyclic antidepressants (TCAs)**
 - Clomicalm® (clomipramine)
 - Amitriptyline (Elavil®)
- Azapirones**
 - Bupropion (Wellbutrin®)
- Selective serotonin/norepinephrine reuptake inhibitors (SNRIs)**
 - Venlafaxine (Effexor®)
- Monooamine oxidase inhibitor (MAOI)**
 - Selegiline (Anipryl®)

6

SSRIs

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

7

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.

8

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

9

Prozac® - fluoxetine HCL

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

Patricia A. Pryor, DVM; Benjamin L. Hart, DVM, PhD, DACVB; Kelly D. Cliff, DVM; Melissa J. Bain, DVM

Irimajiri, M. (2005). "Effect of fluoxetine hydrochloride in treating canine compulsive disorder.". *Current issues and research in veterinary behavioral medicine.*

Effectiveness of fluoxetine chewable tablets in the treatment of canine separation anxiety

Gary M. Landsberg, BSc, DVM, DACVB, Dipl. ECVIM-CA*, Patrick Melese, MA, DVM, DACVB*, Barbara L. Sherman, MS, PhD, DVM, DACVB*, Jacqueline C. Neilson, BS, DVM, DACVB*, Alan Zimmerman, PhD*, Terrence P. Clarke, DVM, PhD, DACVP*

- 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

10

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 (cats) – ER!!
- Make sure owners monitor appetite and elimination during initial treatment phase!

11

Prozac® - fluoxetine other concerns

- Potential to cause hypoglycemia in DM patient
- May see hyperglycemia upon D/C of drug

12

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



13

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 obstipation, blocking
- Rare, but severe urine retention in cats
- Short half-life
 - Discontinuation syndrome



14

Zoloff® – 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



15

Zoloff® – 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!!



16

Zoloff® - other considerations

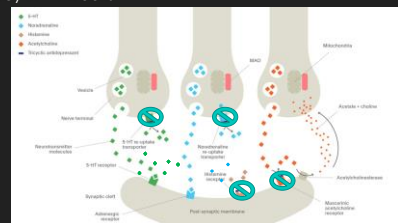
- Primarily eliminated via fecal excretion
 - No dose adjustment needed for CKD
- Used in some human patients with hepatic disease
- Likely the safest daily med for epileptic patients



17

Tricyclic antidepressants - TCAs

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



18



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



19

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

Treatment of separation anxiety in dogs with clomipramine: results from a prospective, randomized, double-blind, placebo-controlled, parallel-group, multicenter clinical trial

J.N. King, B.S. Sappington, K.L. O'neill, D. Applegate, P. Prigioni, C. Ross, J.P. Chantrel, S. Haskel, C. Basso, A.B. Swain, G. Molloy, T. Paris, B.G. Butts, J. Parker, S. Petti, J. Wren, The CLOCSA (Clomipramine as Canine Separation Anxiety) Study Group

(https://doi.org/10.1016/j.jafr.2018.08.001)

Effects of Clomipramine on Cats Presented for Urine Marking

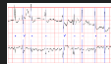
Gary M. Landsberg, BSc, DVM
Diplomate ACVB

Andrea L. Wilson, BSc, DVM



20

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



21

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 1^o anxiety disorders
 - An acceptable 3rd or 4th line of treatment
 - “Poor man’s Clomicalm”?
 - Poorer efficacy, greater side effect profile, but definitely cheaper!

Amitriptyline treatment for severe recurrent idiopathic cystitis in cats.
Chew DJ, Buffington CA, Kendall MS, DiBarola SP, Woodworth BE
JAVMA 1998



22

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!!

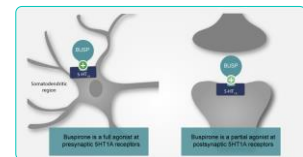


23

Azapirones

Serotonin agonist

- Binding at presynaptic 5HT autoreceptor ↑ 5HT production
- Binding at postsynaptic 5HT autoreceptor mimics effects of 5HT
 - -anxiety
 - + boldness



24

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



25

Buspirone – side effects

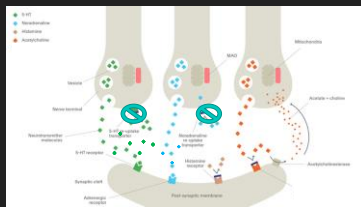
- Common
 - Increased friendliness
 - More assertive social interactions
 - Exacerbation of existing aggression
- Uncommon
 - Sedation
 - Agitation



26

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



27

Venlafaxine (Effexor®)

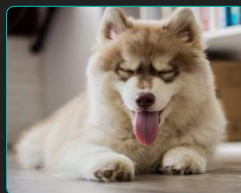
- No placebo-controlled clinical trials in dogs or cats
- Published reports for treatment of narcolepsy in dogs
- Case examples and anecdotal treatment for anxiety, aggression, phobias
- Chronic neuropathic pain in human patients
- One of the most commonly reported drug toxicities in cats (from ingesting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



28

Effexor® - side effects

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



29

Monoamine oxidase inhibitors (MAOIs)

Selegiline HCl (Anipryl®)

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

Summary Therapeutics • Vol. 2, No. 1, Winter 2001

A Noncomparative Open-Label Study Evaluating the Effect of Selegiline Hydrochloride in a Clinical Setting*

Sharon Campbell, DVM, MS, DACVIM
 Amy Trachten, DVM
 Brenda Kozan, BS



30

Selegiline – side effects

- Uncommon
 - Sedation, decreased appetite, GI upset, irritability
- Caution with drug interactions**
 - Tramadol, opioids
 - Amitraz
 - SSRIs, TCAs
 - Cisapride



31

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

32


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 Zoloff
 Are seizures a concern? – Zoloff may be safest choice
 Any renal insufficiency? – Zoloff 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

33



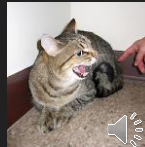
Event Drugs



34

Indications for event drugs

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

35

Common classes

- Serotonin antagonist and reuptake inhibitors (SARIs)**
 - Trazodone
- Alpha-2 agonists**
 - Clonidine
 - Sileo (Dexmedetomidine gel)
- GABA analogues**
 - Gabapentin
- Phenothiazine neuroleptics**
 - Acepromazine
- Benzodiazepines**
 - Lorazepam (Ativan)
 - Diazepam (Valium)
 - Alprazolam (Xanax)
 - Clonazepam (Klonopin)
 - Clorazepate (Tranxene)

36

Effects of trazodone on behavioral signs of stress in hospitalized dogs

Shana E. Gilbert-Gregory ^{1,MD}
 Jason W. Stull ^{1,MD, PhD}
 Mary Rose Rice ^{1,BS}
 Meghan E. Herron ^{1,MS}

OBJECTIVE
 To determine the effects of trazodone treatment on behavioral signs of stress in hospitalized dogs.

DESIGN
 Prospective observational study

Use of trazodone to facilitate postsurgical confinement in dogs

Margaret E. Gruen, ^{1,MS, MPH}; Simon C. Roe, ^{MS, PhD}; Emily Griffith, ^{MS}; Alexandra Hamilton, ^{MS}; Barbara L. Sherman, ^{MS, PhD}

Canine Research
 Trazodone as a mediator of transitional stress in a shelter: Effects on illness, length of stay, and outcome
 Jennifer Abrams ^{1,MS}; Robin Brennen ¹; Sarah-Elizabeth Thysiere ²
1 Hospital and University of NY, New York, New York, USA
 2 Training Dog Lines, Department of Pathology, Cornell College, City University of New York, New York, New York, USA

Trazodone
 Hospital stress
 Post-op confinement
 Shelter stress

37

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"

38

Trazodone aka "vitamin T"

PROS	CONS
<ul style="list-style-type: none"> ○ Adverse events rare ○ Safe even at high doses ○ Not controlled ○ Lots of published data 	<ul style="list-style-type: none"> ○ Takes 2 hours to reach full fx ○ May wear off in 4-6 hours ○ Large, bitter pills ○ Lowers seizure threshold

39

Clonidine

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

Primary α_2 in prefrontal cortex, also in LC

Responsible for sedation and hypotension

40

Clonidine

PROS	CONS
<ul style="list-style-type: none"> ○ Fast-acting (~30 minutes) ○ Greater calming effect in hyperkinetic dogs 	<ul style="list-style-type: none"> ○ May be more sedating ○ Hypotension possible ○ May only last 4 hours in some dogs

41

Sileo® OM gel

○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

○Adjust dose stop before dispensing

○Owners should wear gloves

Desmethylclonidine amorphous gel for noise-associated acute anxiety and fear in dogs—a randomised, double-blind, placebo-controlled clinical study
 © 2019, VCA, Inc. All rights reserved. VCA Animal Health

42

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)

Effects of a single preappointment dose of gabapentin on signs of stress in cats during transportation and veterinary examination

OBJECTIVE
To determine the effects of oral gabapentin administration prior to and post transportation on signs of stress in cats.

DESIGN
Randomized, double-blind, crossover clinical trial.

Effect of oral administration of gabapentin on the minimum alveolar concentration of isoflurane in dogs

OBJECTIVE
To determine the effect of oral administration of gabapentin (20 mg/kg) on minimum alveolar concentration (MAC) of isoflurane in dogs.

ANIMALS
A 10-month-old dog (27 kg) and 2 females and 1 male with a weight of 22 kg and 22 kg.

43

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

44

Benzodiazepines

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

• Schematic illustration of a GABA_A receptor with its binding sites.

45

Oral benzodiazepines

○ Drug	Dose in dogs	Duration of
○ 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	8-10 hours
○ Lorazepam (Ativan)*	0.1-0.5mg/kg	6-8 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
 ○ *No active liver metabolites

Benzo reversal = flumazenil

46

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 storm phobia in dogs

Sharon L. Crowell-Davis, DVM, PhD, DACVP, Lynda M. Seibert, DVM, PhD, DACVP, Weidani Song, MS, Vaili Parthasarathy, MS, Terry M. Carrin, DVM

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

47

Diazepam

- 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

Meghan E. Herron, DVM, Frances S. Shofer, PhD, Ilana R. Reischer, DVM, PhD, DACVP

48

Lorazepam

- Best benzo choice for cats
 - Daily for inter-cat aggression
 - PRN for car travel, vet visits
- No active liver metabolites
- Less sedating than other benzos



49

Clonazepam

- Safe
- Long-acting
- Readily available and affordable
- Best for daily treatment of global fear in dogs



50

Benzodiazepines

PROS	CONS
<ul style="list-style-type: none"> ○ BEST treatment for panic and profound fear ○ Increased appetite helpful for behavior modification ○ Fast onset of action ○ Options for duration ○ Safe in epileptic patients 	<ul style="list-style-type: none"> ○ Paradoxical excitation common ○ Disinhibition of aggression in dogs possible ○ Ataxia common and not well tolerated by owners ○ Dependence and tolerance with extended daily use

51

Acepromazine

- Tranquilizer
- Not an anxiolytic
- Best used IN ADDITION to anxiolytic meds when greater sedation is needed
 - Trazodone
 - Benzos
 - Gabapentin

52

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

Dollia Engel¹ | Hans-Walter Müller² | Rebecca Klee³ | Bradley Francke³ | Daniel Simon MEd³



53

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.

54

Administering medications



55

Tablets and capsules

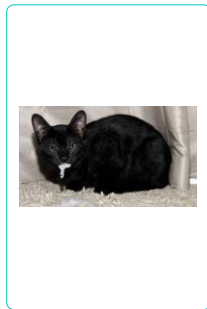
- Gel caps to mask bitterness
- Pill Pockets®, Easy Cheese, canned food, braunschweiger
- 3 meatball trick
- Add crunchy texture
- Try to avoid "pilling"
 - Coat with butter



56

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



57

Treat compounding

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



58

Transdermal

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



59

Health monitoring

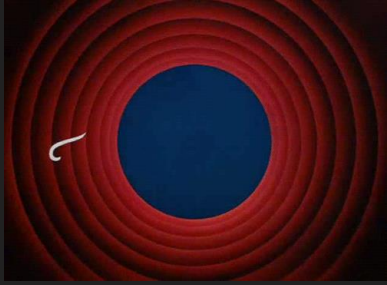


- PE, CBC, chem profile, total T4 and urinalysis
- **PRIOR to starting and repeated yearly



60

The end



61