

# Drugs Used to Manage Urinary Incontinence in Dogs & Cats

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Urinary incontinence is a common presenting complaint primarily affecting dogs and occasionally cats. The most common cause of urinary incontinence is urethral sphincter mechanism incompetence (USMI), which typically affects spayed female dogs and occasionally male dogs. Other causes include disorders such as urine retention and bladder outflow obstruction, which are more common in male dogs.

Therapeutic objectives include treating signs of incontinence-related disorders such as storage disorders (eg, USMI, ectopic ureter, overactive bladder) and emptying disorders (eg, detrusor-urethral dyssynergia, functional obstruction, urethrospasm, detrusor atony, neurogenic upper motor neuron bladder). Goals for treating storage disorders include increasing urethral sphincter smooth and striated muscle tone, increasing bladder compliance, and decreasing intravesicular pressures during filling and storage. Goals for treating emptying disorders include decreasing urethral sphincter smooth and striated muscle tone, increasing detrusor contraction, and reducing postvoid residual volume.

Following are therapeutic targets for the various causes of incontinence.

## DRUGS TO MANAGE STORAGE DISORDERS

### $\alpha$ -Adrenergic Drug

#### **Phenylpropanolamine**

Phenylpropanolamine is a nonselective  $\alpha$ -agonist that also has some  $\beta$ -agonist effects. It indirectly increases urethral smooth muscle tone and may also induce relaxation of the detrusor muscle via  $\beta$ -adrenergic effects. Its nonselectivity may lead to stimulation of vasoconstriction and overall sympathetic activation.

*Formulation* → Oral

*Dose (dogs, cats)* → 1-2 mg/kg PO q8-12h<sup>1</sup>

#### **Key Points**

- ▶ Dose escalation or increased frequency over time may be necessary.

USMI = urethral sphincter mechanism incompetence

- ▶ Adverse effects include hypertension, restlessness, decreased appetite, and aggression.<sup>2</sup>
- ▶ Should be used with caution in patients that are predisposed to hypertension because of comorbid conditions (eg, kidney disease, hyperadrenocorticism, hyperthyroidism)<sup>3</sup>
- ▶ May increase agitation in patients with anxiety disorders

## Estrogens

### Estriol

Estriol is a naturally occurring estrogen with affinity for both types of estrogen receptors. It can improve continence by increasing the number and sensitivity of  $\alpha$ -receptors in the urethral smooth muscle, and it has a trophic effect on periurethral tissues and vasculature.<sup>4</sup>

*Formulation* → Oral

*Dose (dogs only)* → 2 mg/dog PO q24h for 14 days, then reduce in 0.5-mg increments q7d to lowest effective dose<sup>1</sup>

### Key Points

- ▶ Efficacy in female dogs reported as 82% to 92% improved or complete continence<sup>5</sup>
- ▶ Although estrogens can lead to bone marrow suppression, this effect has not been reported when this drug is used at the recommended doses.
- ▶ Adverse effects include vulvar or mammary swelling, attractiveness to males, lethargy, vomiting, and diarrhea.
  - Most patients respond to dose reduction.
- ▶ Should not be used in intact females
- ▶ Use in males may lead to prostatic metaplasia.
- ▶ Overdose can lead to bone marrow suppression.
- ▶ Should not be used in cats

### Diethylstilbestrol

Diethylstilbestrol is a potent, synthetic, nonsteroidal estrogen that improves continence by increasing the number and sensitivity of  $\alpha$ -receptors in the urethral smooth muscle. It has a trophic effect on periurethral tissues and vasculature.

*Formulation* → Not commercially available; must be compounded

*Dose (dogs only)* → 0.5-1.0 mg/dog PO q24h for 3 to 5 days, then q7d<sup>1</sup>

Administration interval should be titrated to effect.<sup>1</sup>

### Key Points

- ▶ Reported efficacy of approximately 65% complete and 23% improved continence in female dogs<sup>6</sup>
- ▶ Although estrogens can lead to bone marrow suppression, this has not been reported at recommended doses.<sup>7</sup>
- ▶ Adverse effects include vulvar or mammary swelling, attractiveness to males, lethargy, vomiting, and diarrhea.
  - Most patients respond to dose reduction.
- ▶ Should not be used in intact females
- ▶ Use in males may lead to prostatic metaplasia.
- ▶ Overdose can lead to bone marrow suppression.
- ▶ Should not be used in cats

## Tricyclic Antidepressant

### Imipramine

Imipramine is a norepinephrine reuptake inhibitor and potential anticholinergic that indirectly increases  $\alpha$ -receptor stimulation in the urethral smooth muscle. This drug may increase bladder relaxation.

*Formulation* → Oral

*Dose (dogs)* → 5-15 mg/dog PO q12h<sup>1</sup>

*Dose (cats)* → 2.5-5 mg/cat PO q12h<sup>1</sup>

### Key Points

- ▶ Imipramine has complex mechanisms of action and appears to act through both stimulation of the sympathetic nervous system and inhibition of the parasympathetic nervous system.
- ▶ Evidence of efficacy in the treatment of urinary storage disorders in dogs and cats is lacking.
  - Rationale for use is extrapolated from in vitro studies and clinical evidence of the drug's effect in humans and healthy dogs.

## Diethylstilbestrol use in males may lead to prostatic metaplasia.

USMI = urethral sphincter mechanism incompetence

- ▶ Adverse effects include vomiting, diarrhea, hyperexcitability, seizure, and sedation.
- ▶ May lower seizure threshold in epileptic patients
- ▶ Should not be coadministered with monoamine oxidase inhibitors

## Testosterone Analog

### **Testosterone Cypionate**

Testosterone is thought to improve urethral smooth muscle tone; however, evidence of the mechanism and its efficacy in the treatment of urinary tract disorders in dogs and cats is lacking.

*Formulation* → Parenteral for IM injection

*Dose (dogs only)* → 2.2 mg/kg IM q30-60d<sup>1</sup>

#### **Key Points**

- ▶ Anecdotally considered to be less effective than phenylpropanolamine in male dogs with USMI
- ▶ Adverse effects include perianal adenoma and prostate enlargement in male patients and clitoral hypertrophy, masculinization, and aggression in female patients.
- ▶ Should not be used in patients with prostatic carcinoma and should be used with caution in patients with renal, cardiac, or hepatic disease
- ▶ May decrease insulin needs in diabetic patients<sup>1</sup>

## Gonadotropin-Releasing Hormone (GnRH) Analog

### **Leuprolide Acetate**

Leuprolide acetate is a GnRH analog that suppresses both follicle-stimulating hormone and luteinizing hormone increases after ovariectomy in dogs. Some evidence shows that the alteration of these hormones may play a larger role in USMI development as compared with a change in estrogen levels.<sup>8</sup> This drug does not appear to affect urethral pressures but can improve bladder relaxation and compliance.<sup>9,10</sup>

*Formulation* → Depot injection

Immediate-release form should be avoided.

*Dose (dogs)* → 20-30 mg IM q3mo<sup>10</sup>

Doses are extrapolated from the literature.<sup>10</sup> No standard dose regimen has been established.

#### **Key Points**

- ▶ Effects may last longer than 3 months.

- Treatment should be repeated as needed when clinical signs return.
- ▶ Most commonly used to treat endocrine diseases in ferrets and suppress egg formation in birds
- ▶ Little is known about adverse effects in dogs and cats.

## Antimuscarinic & Spasmolytic Drugs

### **Oxybutynin**

Oxybutynin has direct antimuscarinic effects on the smooth muscle of the bladder without affecting the smooth muscle of the vasculature.

*Formulation* → Oral

*Dose (dogs)* → 0.2 mg/kg PO q8-12h or 1.25-3.75 mg/dog PO q8-12h<sup>1</sup>

*Dose (cats; extra-label)* → 0.5-1.25 mg/cat PO q8-12h<sup>1</sup>

#### **Key Points**

- ▶ Primarily used in cases of suspected overactive bladder or detrusor instability
- ▶ Also acts as an antispasmodic and reduces maximum filling and emptying bladder pressures<sup>11</sup>
- ▶ Adverse effects include diarrhea, constipation, hypersalivation, urine retention, and sedation.
- ▶ Use with other sedatives may increase effect.
- ▶ Should be used with caution in patients with hypotension

### **Proprantheline**

Proprantheline is an antimuscarinic agent that has effects on the smooth muscle of the bladder and may reduce spasm related to detrusor hyperreflexia and associated urinary incontinence.

*Formulation* → Oral; injectable form available in Australia

*Dose (dogs)* → 7.5-30 mg/dog PO q8-24h<sup>1</sup>

*Dose (cats)* → 5-7.5 mg/cat PO q8-72h; lowest effective dose should be used<sup>1</sup>

#### **Key Points**

- ▶ Variable absorption of the oral formulation in small animals; dose must be adjusted for each patient.
- ▶ Should not be used if urinary obstruction or urine retention is suspected
- ▶ Adverse effects include dry mouth, tachycardia, ileus, and constipation; vomiting and hypersalivation may be seen in cats.<sup>1</sup>

## DRUGS TO MANAGE EMPTYING DISORDERS

### $\alpha$ -Adrenergic Blocking Drugs & Smooth Muscle Relaxants

#### **Prazosin**

Prazosin is a nonselective  $\alpha_1$ -inhibitor used to block  $\alpha$ -receptors in the urethral smooth muscle and treat functional urethral obstruction.<sup>12</sup>

*Formulation* → Oral

*Dose (dogs)* → 1 mg/dog PO q8-12h for dogs weighing <15 kg;  
2 mg/dog PO q8-12h for dogs weighing >15 kg<sup>1</sup>

*Dose (cats)* → 0.25-1 mg/cat PO q8-12h<sup>1</sup>

#### **Key Points**

- ▶ The nonselective nature of prazosin also leads to vasodilation and decreased vascular resistance.
- ▶ Hypotension is the primary adverse effect.
  - Patients should be monitored with each dose increase.
  - Caution should be used when administering with  $\beta$ -blocking agents and calcium channel blockers, as prazosin may induce significant hypotension.
- ▶ Has been found to be more effective than phenoxybenzamine at decreasing urethral pressures<sup>13</sup>
- ▶ Rates of urethral reobstruction in cats treated with prazosin were lower than in those treated with phenoxybenzamine.<sup>14</sup>
- ▶ Prazosin may also be effective in treating ureterospasm in cases of ureteral obstruction or ureteritis.<sup>15</sup>

#### **Tamsulosin**

Tamsulosin is a selective  $\alpha_{1a}$ -adrenergic blocker that is more selective to the urinary tract (ie, prostatic urethra, bladder neck) and thus has more limited cardiovascular side effects.

*Formulation* → Oral

*Dose (dogs)* → 0.1-0.2 mg/10 kg (up to 0.4-mg total dose) PO q12-24h<sup>1</sup>

*Dose (cats)* → 0.004-0.006 mg/kg PO q12-24h<sup>1</sup>

#### **Key Points**

- ▶ Effectively inhibits hypogastric nerve-induced urethral pressure rise in dogs without clinically significant vasodilation and hypotension<sup>16</sup>
- ▶ May be useful in treating ureterospasm associated with ureteritis or ureteroliths<sup>15</sup>

- ▶ Oral bioavailability in dogs is about one-third of that in humans.<sup>17</sup>
  - Bioavailability may be increased when administered on an empty stomach.
- ▶ May take several days for effect
- ▶ High doses may lead to hypotension.
- ▶ Sustained-release formulations should not be crushed.

#### **Phenoxybenzamine**

Phenoxybenzamine is a pure  $\alpha$ -adrenergic blocker used to reduce urethral pressures and treat hypertension.

*Formulation* → Oral

*Dose (dogs)* → 0.25 mg/kg PO q12h or 5-20 mg/dog PO q12h<sup>1</sup>

*Dose (cats)* → 2.5-7.5 mg/cat PO q12-24h<sup>1</sup>

#### **Key Points**

- ▶ Cost is significantly higher as compared with other  $\alpha$ -adrenergic blockers.
- ▶ Often used to reduce pheochromocytoma-induced hypertension
- ▶ Blood pressure should be monitored.
- ▶ Adverse effects include hypotension, weakness, nausea, miosis, and sodium retention.
- ▶ Should be used with caution in patients with cardiac disease or other conditions predisposed to hypotension

## Skeletal Muscle Relaxants

### **Benzodiazepines**

#### **Diazepam**

Diazepam is a benzodiazepine used for relaxation of primarily skeletal muscle in the urethra in dogs with functional urethral obstruction.

*Formulation* → Oral, injectable

*Dose (dogs)* → 2-10 mg/dog PO 30 minutes before voiding (≤3 times a day)<sup>1</sup>

#### **Key Points**

- ▶ Serum half-life in dogs and cats is significantly shorter than in humans.<sup>1</sup>
- ▶ Adverse effects include CNS depression, appetite stimulation, and sedation.
- ▶ May cause disinhibition in aggressive patients

- ▶ Oral form should not be used in cats, as there is significant potential for hepatotoxicity.
- ▶ Should be used carefully in debilitated patients or those with liver dysfunction

#### Alprazolam

Alprazolam is a benzodiazepine that produces sedation, anxiolysis, and skeletal muscle relaxation. It may be used to relax the skeletal muscle of the urethra in patients with urethrospasm; however, no data on its use in this manner in either dogs or cats has been published.

*Formulation* → Oral

*Dose (dogs)* → 0.02-0.05 mg/kg PO q6-12h<sup>1</sup>

*Dose (cats)* → 0.125-0.25 mg/cat PO q8-24h<sup>1</sup>

Doses extrapolated from anxiolytic use

#### **Acepromazine**

Acepromazine is a phenothiazine that has antispasmodic and  $\alpha$ -adrenergic blocking effects. It is used in dogs and cats with functional urethral obstruction.

*Formulation* → Oral, injectable

*Dose (dogs, cats)* → 0.55-2.2 mg/kg PO q6-12h or to effect<sup>1</sup>

#### **Key Points**

- ▶ Has been shown to significantly decrease preprostatic and prostatic urethral pressures in intact male cats<sup>18</sup>
- ▶ Dose should be reduced in patients with possible breed-related *MDR1* mutations (eg, collies, Shetland sheepdogs, Australian shepherds).<sup>1,19</sup>
- ▶ Adverse effects include hypotension and prolapse of the nictitans.
- ▶ Should not be used in patients with hypotension, volume depletion, or shock
- ▶ Should be used carefully in patients with cardiac disease or hepatic dysfunction
- ▶ Caution: Dose should be reduced in patients with possible breed-related *MDR1* mutations (eg, collies, Shetland sheepdogs, Australian shepherds).<sup>1,19</sup>

#### **Baclofen**

Baclofen is a skeletal muscle relaxant that appears to act at the

level of the spinal cord. It has been shown to reduce urethral striated (skeletal) muscle sphincter tone in dogs.<sup>20</sup>

*Formulation* → Oral

*Dose (dogs only)* → 1-2 mg/kg PO q8h

#### **Key Points**

- ▶ Should be gradually discontinued to reduce risk for psychomotor effects (eg, seizures, hallucinations)
- ▶ Adverse effects include sedation, weakness, or GI cramping.
- ▶ Narrow margin of safety in dogs and should not be used in cats
  - Should be used with caution in patients with seizure disorders

#### **Dantrolene**

Dantrolene is a direct-acting muscle relaxant that has been used to treat patients that have functional urethral obstruction. Because of the availability of more effective and safer muscle relaxants, dantrolene is not recommended as a first-line treatment for detrusor-urethral dyssynergia.

*Formulation* → Oral; injectable is available but not practical for veterinary use

*Dose (dogs)* → 1-5 mg/kg PO q8-12h<sup>1</sup>

*Dose (cats)* → 0.5-2 mg/kg PO q12h<sup>1</sup>

#### **Key Points**

- ▶ May be less effective than baclofen
  - Several studies have indicated its effect on striated muscle is poor.<sup>21</sup>
- ▶ Adverse effects include hepatotoxicity, weakness, and sedation.
- ▶ Should not be used in patients with hepatic dysfunction
- ▶ Should be used with caution in patients with cardiac disease

#### **Cholinergic Agent**

##### **Bethanechol**

Bethanechol is a cholinergic that directly stimulates muscarinic receptors in the detrusor smooth muscle of the bladder.

*Formulation* → Oral

Only the oral formulation is commercially available in the United States; injectable formulations may be available outside the United States or through compounding pharmacies.

Dose (dogs) → 2.5-25 mg/dog PO q8h<sup>1</sup>

Dose (cats) → 1.25-7.5 mg/cat PO q8h<sup>1</sup>

### Key Points

- ▶ May not be effective in patients with chronic bladder overdistension resulting from loss of smooth muscle tight junctions
- ▶ Vomiting, diarrhea, decreased appetite, hypersalivation, and other SLUD (salivation, lacrimation, urination, defecation)-like effects may be seen at recommended doses.
- ▶ Overdose can lead to bradycardia, hypotension, and/or increased respiratory secretions.
- ▶ Should not be used in patients with untreated urethral obstruction or questionable bladder wall integrity

### Prokinetic Agent

#### Cisapride

Cisapride is a 5-HT<sub>4</sub>-receptor agonist that indirectly leads to acetylcholine release and smooth muscle (eg, GI, detrusor) contraction.

Formulation → Must be compounded; no commercial products are available in the United States, Europe, or India.

Dose (dogs) → 0.1-0.5 mg/kg PO q8-12h<sup>1</sup>

Dose (cats) → 2.5-7.5 mg/cat PO q8-12h<sup>1</sup>

### Key Points

- ▶ May help increase bladder contraction and reduce residual urine volume<sup>22</sup>
- ▶ Commonly used to treat cats with megacolon
- ▶ Removed from commercial manufacture in 2002 because of arrhythmias seen in humans<sup>23</sup>
  - These effects are not well demonstrated in dogs and cats.
- ▶ Adverse effects include diarrhea, vomiting, and ataxia.
  - Administration should start at low end of dose range and titrate up to avoid these effects.
- ▶ Cisapride is metabolized by the cytochrome P450 CYP3A and should be used with caution in patients receiving CYP3A-inhibitors (eg, azole antifungals, cimetidine, diltiazem, chloramphenicol).
- ▶ Dose reduction may be necessary in patients that have hepatic dysfunction.
- ▶ Use should be avoided in patients with GI obstruction. ■

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