URINARY TRACT NERVOUS SYSTEM DISORDERS: DRUG THERAPY REVIEW

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Ian Battersby discusses urine storage and voiding, and explains some of the drug therapies that can be utilised in the event of nervous system problems

When managing neurological disorders of the urinary tract in dogs and cats, a variety of treatment and management techniques are utilised, including bladder expression, urinary catheterisation (intermittent or indwelling), tube cystotomies and drug therapy.

To fully utilise the drug therapies available in these cases, a clinician must first have a good understanding of the normal physiological processes involved in urination.

This article aims to review the neuroanatomical components and processes involved in the storage and voiding of urine, in addition to the drug therapies that can be prescribed.

Neuroanatomical components

• Pelvic nerve (S1-S3; parasympathetic)

The motor portion of this parasympathetic nerve is dominant when voiding urine. It stimulates the muscarinic cholinergic receptors in the bladder, which leads to detrusor muscle contraction and bladder emptying.

• Pudendal nerve (S1-S3) As well as having sensory and motor function to the anus, vulva and

prepuce, the pudendal nerve allows conscious control of the external urethral sphincter (striated muscle).

• **Hypogastric nerve (L1-L4 dog, L2-L5 in cats; sympathetic)**

This stimulates ? fibres in the detrusor muscles. This leads to detrusor relaxation. It also stimulates á fibres in the urethra and trigone, which constrict the internal urethra sphincter (smooth muscle).

• **Stretch and pain receptors**

Stretch receptors and pain receptors in the bladder relay information back to the central nervous system (CNS) via the pelvic and hypogastric nerves. The pudendal nerve transmits information from the stretch receptors in the urethra.

In the case of lower motor neurone bladders, such as those that can occur with sacral injures, bladder over-distension can still be perceived as painful if the hypogastric nerve remains intact.

• **Central nervous system**

The micturition centre in the pons is responsible for coordinating the different phases of micturition. Voluntary control of urination is influenced by the cerebral cortex.

Urination (micturition)

In puppies and kittens, reflex arcs control urination. However, in adulthood, higher centres control these reflexes.

House training, and behaviours such as scent marking, are possible due to the ability of the cerebral cortex to inhibit and initiate the detrusor reflex.

• **Storage phase**

In the urine storage phase, the sympathetic nervous system predominates to encourage a state of bladder filling.

– The hypogastric nerve stimulates relaxation of the detrusor muscle of the bladder by stimulation of ?-adrenergic receptors.

– At the same time, the hypogastric nerve induces constriction of the smooth muscle of the urethra via ?-adrenergic receptors.

– The striated muscle of the external urethral sphincter is constricted under the influence of the

pudendal nerve (nicotinic ACh receptors).

– Stretch and pain receptors relay information to the CNS as the bladder fills.

– The sympathetic system also inhibits the cholinergic signals to the detrusor muscle to allow low-pressure bladder filling.

• **Urination**

During urination, sympathetic input to the lower urinary tract is inhibited, and parasympathetic input stimulates the detrusor reflex. As the bladder fills, stretch receptors relay information back to the pontine micturition centre and the cerebral cor tex. When the bladder is full, efferent signals are transmitted down the spinal cord to promote bladder emptying. For urination to occur, coordinated detrusor muscle contraction and relaxation of the urethral muscles must occur. This is achieved as follows:

– parasympathetic stimulation of the detrusor muscle via the pelvic nerve stimulates contractions of the bladder;

– as the detrusor muscle contracts, afferent impulses inhibit the cell bodies of the hypogastric and pudendal nerve. This means constriction of the urethra is inhibited when detrusor contraction occurs; and

– inhibition of the pudendal nerves'influences on the external urethra muscles.

Drugs

The main pharmacological agents used to manipulate the bladder and urethral tone have remained unchanged for some time. There have been supply problems, making some drugs hard to source.

For all the drugs listed, readers are advised to consult the BSAVA formulary for possible drug interactions.

• **Drugs used to increase urethral tone in incontinence**

– **Phenylpropanolamine** (1mg/kg tid PO or 1.5mg/kg PO bid – ?-agonist). This increases urethral sphincter tone and outflow resistance. The onset of action may take several days. Side effects may include restlessness, aggressiveness, irritability and hypertension.

– **Estriol.** This is a synthetic, short-acting oestrogen analogue with a high affinity for oestrogen receptors in the lower urogenital tract. It increases muscle tone in the urethra and is indicated in the management of urethral sphincter mechanism incompetence, which develops in spayed bitches.

Due to side effects, do not use this in intact bitches, or if polyuria/ polydipsia are present. Oestrogenic effects are seen in five to nine per cent of bitches receiving the maximum dose.

– **Testosterone** (male dogs: 2.2mg/kg IM once a month). Testosterone has an unknown mechanism of action. Side effects include behavioural changes and aggression.

• Drugs used to increase bladder tone

– **Bethanechol** (off licence). This is a muscarinic agent that increases urinary bladder detrusor muscle tone and contraction. Bethanechol may increase urethral resistance, so it should not be used in cases were urethral resistance is increased, unless in combination with agents that lower urethral tone. Side effects include vomiting, diarrhoea and abdominal cramping.

An overdose should be treated with atropine. Avoid providing this to animals that have an empty stomach, as this may increase the likelihood of the gastrointestinal side effects.

– **Cisapride** (off licence; 0.5mg/kg PO tid).

This increases acetylcholine release, and is only available via importation under special licence (contact the VMD for details).

• Drugs to reduce detrusor hyperreflexia

– **Propantheline bromide** (off licence, dogs 0.4mg/kg tid, cats 7.5mg per cat every three days). This is an anticholinergic, and side effects can include mydriasis, ileus, tachycardia, dry mucous membranes and increased intraocular pressure.

• Drugs used to reduce internal urethral sphincter tone

– **Prazosin** (off licence). This is a post-synaptic ?-one- blocking agent. As a consequence, it causes vasodilatation and reduces internal urethra tone. Side effects include hypotension, drowsiness and weakness. The use of blood pressure monitoring is imperative.

– **Phenoxybenzamine** (off licence). This is an ?-adrenergic blocker (presynaptic and postsynaptic) and, similar to prazosin, it is used to reduce internal urethral tone and hypertension.

Side effects include weakness, hypotension, miosis, tachycardia and nasal congestion. When using ?-blocking agents, dosages should only be increased if no response is seen within three to four days. Rapid dose changes should be avoided. In humans, uroselective ?-one antagonists, such as terazosin, doxazosin and tamsulosin, are used in men with prostatic hypertrophy to modulate prostatic and urethral smooth muscles. The author is not aware of these drugs being trialled in dogs or cats.

• Drugs used to reduce external urethral sphincter tone

– **Dantrolene** (off licence). This inhibits calcium release from the sarcoplasmic reticulum of the muscle, which results in muscle relaxation. Therefore, it is used in external urethral muscle spasms. Side effects include hepatitis with chronic use – therefore, it should be avoided in patients with preexisting hepatic disease.

Dosages should be increased slowly. Monitor liver function while on therapy, and use with caution if cardiac or respiratory function is impaired.

– **Diazepam** (off licence). In addition to its anticonvulsant properties, diazepam is also a muscle relaxant. In cats, repeated dosing is associated with hepatic necrosis.

– **Baclofen** (off licence, dogs 1mg/kg to 2mg/kg PO).

This is a skeletal muscle relaxant. Side effects reported in dogs include sedation, weakness, pruritus and gastrointestinal disorders.

Neurological dysfunction: drug therapy examples

Urethral sphincter mechanism incompetence, detrusor hyperreflexia/ instability and dysautonomia will not be discussed in this article and the reader is directed to other texts.

• Bladder dysfunction associated with spinal injuries

Observing urination and palpation of the bladder before and after urination should always be performed in a paralysed patient, so that appropriate therapeutic measures can be introduced. It should never be assumed that spinal patients can urinate normally.

• Lower motor neurone bladder (LMN)

This occurs if the sacral spinal cord or sacral nerves within the pelvic canal are affected. The most characteristic sign is a large bladder that is easily expressed. An LMN injury causes both detrusor and urethral hyporeflexia. Some innervation to the internal sphincter (constriction) and bladder wall (relaxation and pain sensation) remains via the hypogastric nerve.

Once the bladder is full, there can also be overflow leakage of urine. Patients normally have other neurological deficits, such as poor anal tone, a flaccid tail and an absence of bulbospongiosus and perineal reflexes.

• Treatment options in LMN bladder

– Manual expression three to four times a day. The bladder is often difficult to appreciate as it is often flaccid. Efferent activity from the hypogastric nerve on the internal urethral sphincter can make this more difficult, and this – in addition to bladder flaccidity – can mean manual expression is ineffective.

– Manual bladder expression is often ineffective because of flaccidity and sustained contraction of the smooth muscle urethral sphincter, therefore, ?-antagonists that reduce internal urethral tone may improve manual evacuation of urine.

– Nursing measures can be used to prevent complications, such as urine scalding, decubital ulcers and recurrent urinary tract infections.

– Drugs (such as bethanechol) can be used to increase bladder tone, but, as outlined above, drugs to reduce internal urethral tone should also be used due to the hypogastric nerve activity.

• **Upper motor neurone bladder**

This occurs when a spinal lesion is present between the pons and L7. In this situation, the bladder is large and hard to express. It occurs due to the disinhibition of the spinal cord neuronal pools involved in urination – in effect, the pudendal nerve is not inhibited. In these cases, there is no voluntary control of micturition and the urethral sphincter is hyperexcitable. Paradoxical incontinence occurs when the intravesical pressure exceeds that of the urethra, and overflow incontinence ensues. Manual expression of the bladder is difficult due to normal or increased tone in the urethral sphincters.

• **Treatment options for upper motor bladder injury**

– Catheterisation (indwelling or intermittent).

– Drugs to reduce internal and external urethral tone.

• **Reflex dyssynergia**

This is seen primarily in medium to large-breed male dogs. The detrusor urethral dyssynergia is an inability to co-ordinate the contraction of the detrusor muscle and the relaxation of the internal or external urethra sphincter during urination. The aetiology is unknown.

When urination is observed, the initial stream can be normal. However, this is followed by a narrow urine stream or spurts of urine. In some cases, urination is obstructed and the patient will continue to strain to urinate. Palpation of the abdomen after urination will reveal a full bladder that is difficult to express, but easy to catheterise.

The main differentials for functional disorders like dyssynergia are anatomical, such as prostatic disease, calculi, neoplasia and urethral stricture. Therefore, investigations (including radiographic contrast studies) should be performed in any suspected case.

Unfortunately, patients with reflex dyssynergia often suffer from chronic bladder over-distension and subsequent bladder atony due to disruption of the hermetic unions between the fibres of the smooth musculature of the bladder.

• **Treatment for reflex dyssynergia**

– Pharmacological manipulation to reduce the internal and external urethral tone.

– Bladder rest. Bladder atony is a common complication. To allow the bladder a chance to recover (unfortunately, it doesn’t always do so), it should be kept as small as possible for the first five to seven days. This can be achieved either by regular catheterisation, an indwelling catheter or a cystotomy tube. Unfortunately, in cases that have developed bladder atony, the prognosis is guarded.

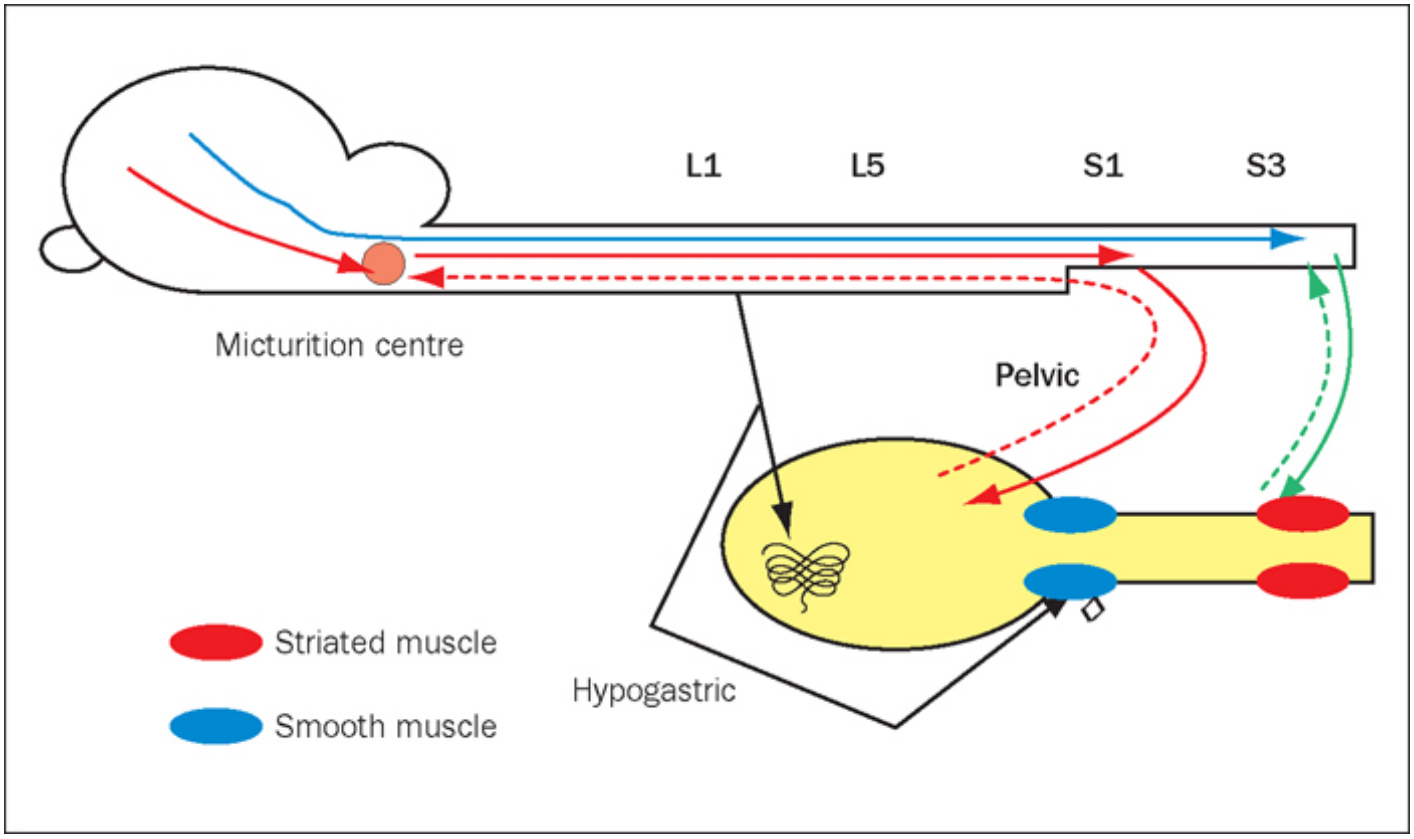
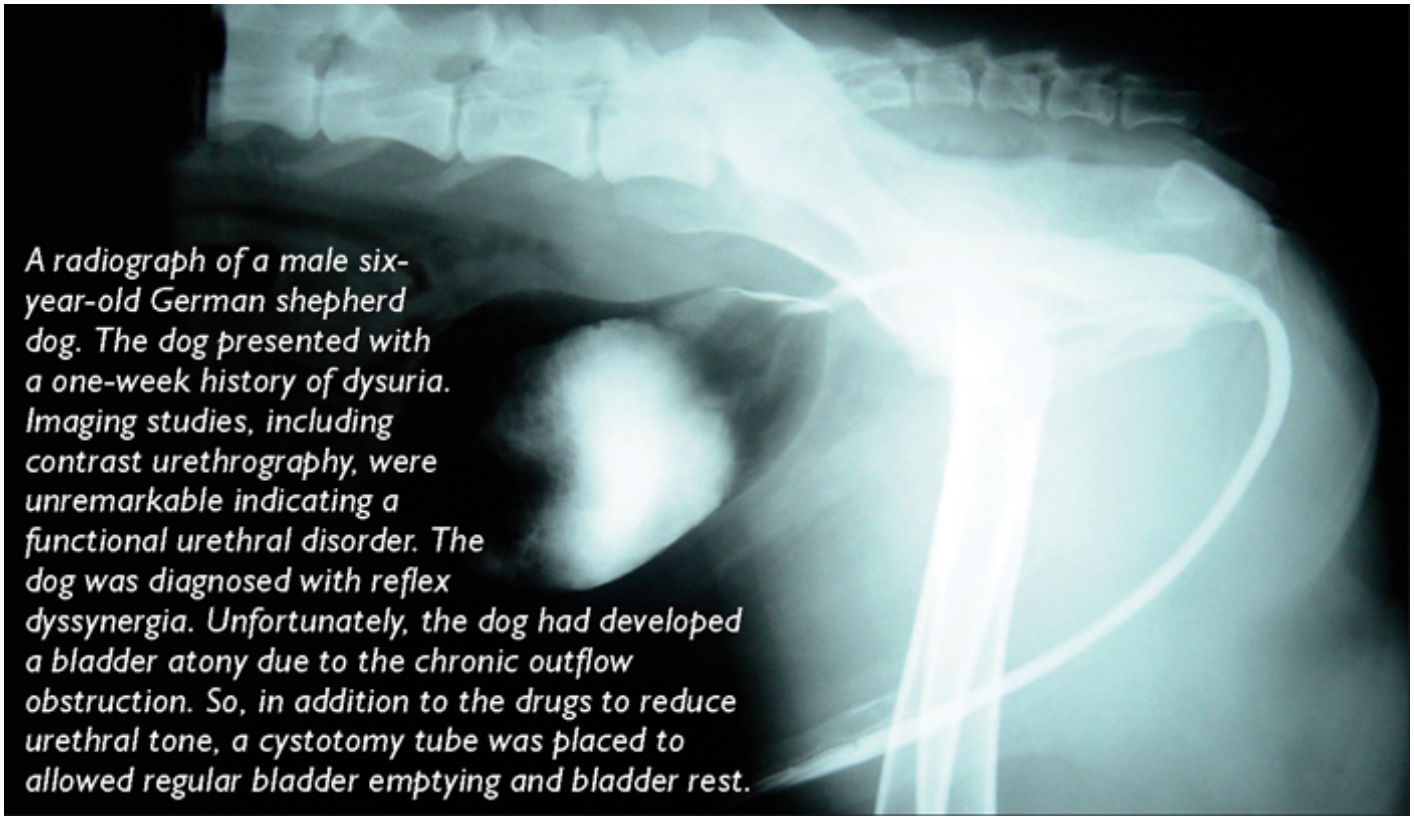


Figure 1. Lower urinary tract neuroanatomy showing the nerves and muscles involved in urination.



A radiograph of a male six-year-old German shepherd dog. The dog presented with a one-week history of dysuria. Imaging studies, including contrast urethrography, were unremarkable indicating a functional urethral disorder. The dog was diagnosed with reflex dyssynergia. Unfortunately, the dog had developed a bladder atony due to the chronic outflow obstruction. So, in addition to the drugs to reduce urethral tone, a cystotomy tube was placed to allowed regular bladder emptying and bladder rest.