The physiology and pharmacology of the lower urinary tract

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Abstract

The lower urinary tract comprises the urinary bladder, the urethra and prostate in men, and is concerned with the storage of urine and its voluntary expulsion from the body when socially convenient. These mutually exclusive states are mediated by complex neural networks that when dysfunctional generate bothersome and highly prevalent lower urinary tract symptoms (LUTS). Lower urinary tract symptoms are often idiopathic and not pathology specific and most result from bladder outflow obstruction, disorders of bladder contractility or conditions which increase bladder sensitivity and a combination of any of these states. Despite the precise mechanisms of symptom generation being unclear, the receptor mechanisms involved in controlling lower urinary tract function can be pharmacologically manipulated to achieve useful clinical outcomes.

Keywords Bladder dysfunction; lower urinary tract symptoms; overactive bladder

Functional anatomy and physiology of the lower urinary tract

The urinary bladder

The urinary bladder lies in an extraperitoneal position in the pelvis and becomes oval when full. It consists of predominantly of smooth muscle, and has an apex that connects the urachus to the anterior abdominal wall, a body that lies above the ureteric orifices and a base comprising the trigone and bladder neck (Figure 1). In males, the seminal vesicles, ampullae of the vas deferens and terminal ureter are closely related to the bladder base, whereas in the female, the bladder base rests on the anterior vaginal wall and cervix. In both sexes the bladder is supported by the pelvic floor musculature which, particularly in the female, plays an important role in maintaining continence.

The ureters enter the bladder base posteriorly, and travel obliquely in the wall for 1–2 cm before terminating at the ureteric orifices. This arrangement, together with a fibromuscular sheath that covers the distal ends of the ureters, ensures that they are compressed as the bladder fills providing a valve-like mechanism which prevents the retrograde flow of urine under pressure. The trigone is triangular in shape and stabilizes the attachment of the ureters to the bladder, and the otherwise mobile bladder to the pelvic fascia. It has three distinct layers, the superficial layer originates from the longitudinal smooth muscle of the ureters and terminates at the verumontanum, an intermediate detrusor layer that is continuous with the bladder wall, and a deep layer formed from the fibromuscular sheath that terminates at the bladder neck.

Transitional cell epithelium lines the lumen of the bladder and is usually 5–6 cells thick, except at the trigone where it is thinner, and also comprises three distinct layers. Basal cells resting on lamina propria, a multilayer of intermediate cells, and a layer of multinucleated umbrella cells joined together by tight junctions at the luminal surface. Each umbrella cell covers several underlying smaller intermediate cells with a stem that extends to the lamina propria, and can alter their surface area significantly to accommodate bladder distention. Covering the umbrella cells is a layer of glycosaminoglycans, which protects the urothelium from damage by urinary constituents and bacterial adherence. Despite this multilayer barrier, the urothelium remains permeable to solutes and water through processes of active transport, osmotic and passive diffusion. Sodium ions enter umbrella cells through the luminal membrane and leave by the basolateral route both by active transport mechanisms. The role of sodium movement is unknown but may be important in generating the sensation of bladder fullness.

Lying deep to the urothelium is a richly innervated and vascularized sub-urothelial layer containing interstitial cells. Bladder afferent nerves originate here, and it is believed that these are activated by ATP release from urothelial stretch during bladder filling. The permeability of the urothelium may increase when there is a defect in the glycosaminoglycan layer and up-regulation of the sensory mechanism associated with this may be responsible for generating bladder pain syndromes.

The bladder wall contains detrusor smooth muscle, the fibres of which are randomly arranged and separated by variable amounts of connective tissue. Quantitative changes in connective tissue contribute to the loss of bladder compliance and contractility disorders that characterize bladder outflow obstruction and are implicated in the generation of lower urinary tract symptoms. At the bladder neck and trigone, the fibres become finer and more organized into layers. In males, the inner layer becomes continuous with that of the urethra, while the middle layer forms a pre-prostatic ring around the bladder neck that can function as an internal urinary sphincter. The outer layer forms the backing of the ureters and a loop around the anterior bladder neck. In females, only the inner longitudinal layer definitively exists at the bladder neck while the presence of the middle and outer layers is doubtful. The detrusor muscle is innervated by both parasympathetic (pelvic nerves) and parasympathetic (hypogastric) nerves.

The bladder neck and prostate

The bladder neck is a circular continuation of detrusor muscle under adrenergic neuromuscular control and is involuntary. In men, it actively contracts as part of the ejaculatory reflex preventing retrograde ejaculation into the bladder, and during bladder filling the bladder neck remains closed although generally not sufficiently alone to provide continence. The prostate

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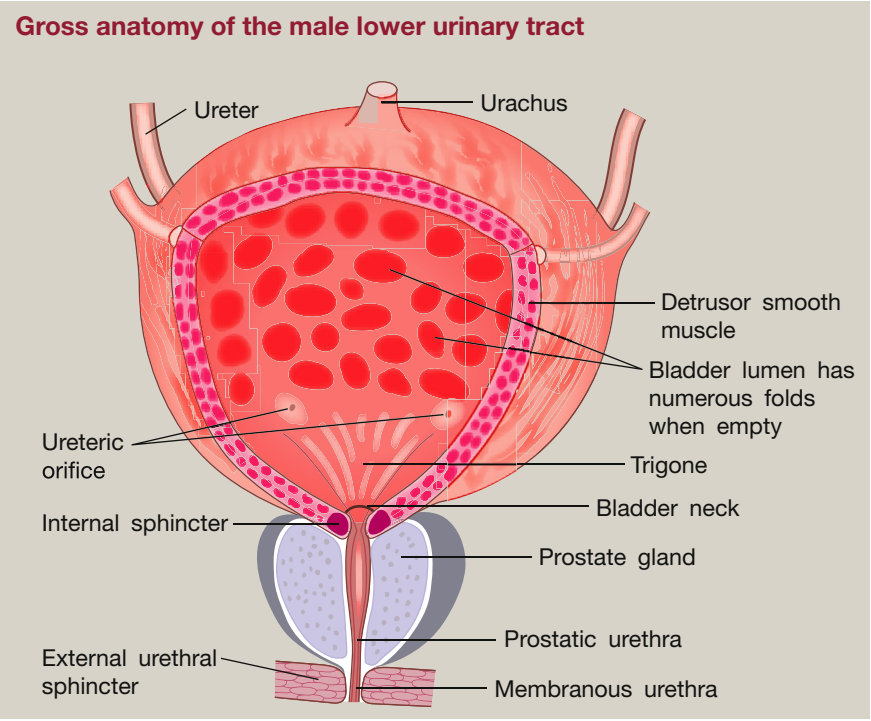


Figure 1

gland merges with the bladder neck and contributes resistance to urine flow during voiding in two ways. The prostate consists of secretory tubular-acinar glands lined by epithelium, and a supporting fibromuscular stroma consisting of fibroblasts, connective tissue and a considerable amount of adrenergically innervated smooth muscle. This, like the bladder neck, generates a contractile tone mediated by α1-adrenoreceptors sufficient to mediate a variable bladder outflow tract resistance. In addition to this dynamic obstruction, growth factor-mediated enlargement of the stromal and epithelial cells in the transitional zone and periurethral areas of the prostate gives rise to benign prostatic hyperplasia (BPH), and static structural obstruction to the outflow tract.

Urethra and sphincter mechanism

The external urinary sphincter consists of three elements. The membranous urethra itself has viscoelastic properties that endow sphincteric function and also contains a thin smooth muscle layer extending along its length that is under sympathetic neuromuscular control. Situated around this is the horseshoe-shaped rhabdosphincter that consists of slow-twitch skeletal muscle and is under voluntary control. The rhabdosphincter is situated just distal to the prostate apex encircling the membranous urethra in men and at the mid-urethra in women, and is deficient posteriorly. It provides the primary continence mechanism by maintaining a constant tone, and damage as a result of prostate surgery, neurolopathy or childbirth causes incontinence. The periurethral striated muscles of the pelvic floor lie external to the rhabdosphincter, and sphincteric activity can be increased by voluntary contraction of the pelvic floor muscles in both sexes. In females, a hammock-like sling of endopelvic fascia within the pelvic floor supports the mid urethra and plays a crucial additional role in maintaining continence when the mobile urethra is compressed against it during rises in intra-abdominal pressure.

The cellular mechanism of detrusor muscle contraction

Detrusor smooth muscle consists of spindle-shaped cells up to 200 μm in length and 5 μm in diameter, each containing thin actin and thick myosin myofilaments that repeat along its length in a lattice pattern. The cells are electrically and mechanically connected and contain intermediate filaments binding the contractile proteins to dense bodies which distribute contractile forces to neighbouring cells (Figure 2). Smooth muscle contraction occurs by a different mechanism than skeletal and cardiac muscle. The arrival of a nerve impulse at the parasympathetic nerve terminal leads to the release of acetylcholine (Ach) that activates muscarinic M3 detrusor receptors. This hydrolyses phospholipase-C to inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG) (Figure 3). IP3 triggers the release of intracellular calcium from the sarcoplasmic reticulum whereas DAG acts on the L-gated channels in the plasma membrane to allow an influx of extracellular calcium. The calcium then binds to the protein calmodulin and activates myosin light chain kinase. This enzyme acts as a catalyst in the transfer of phosphate from adenosine triphosphate (ATP) to myosin, causing ATPase enzyme activation on the myosin heads that allow contractile proteins to interact and generate force. The contraction of smooth muscle is characteristically slow and sustained because ATP is hydrolysed at a slower rate and allows tension to be generated and maintained without much energy expenditure, this confers resistance to fatigue. Although M3 receptors mediate contraction, M2 muscarinic receptors are more abundant and are

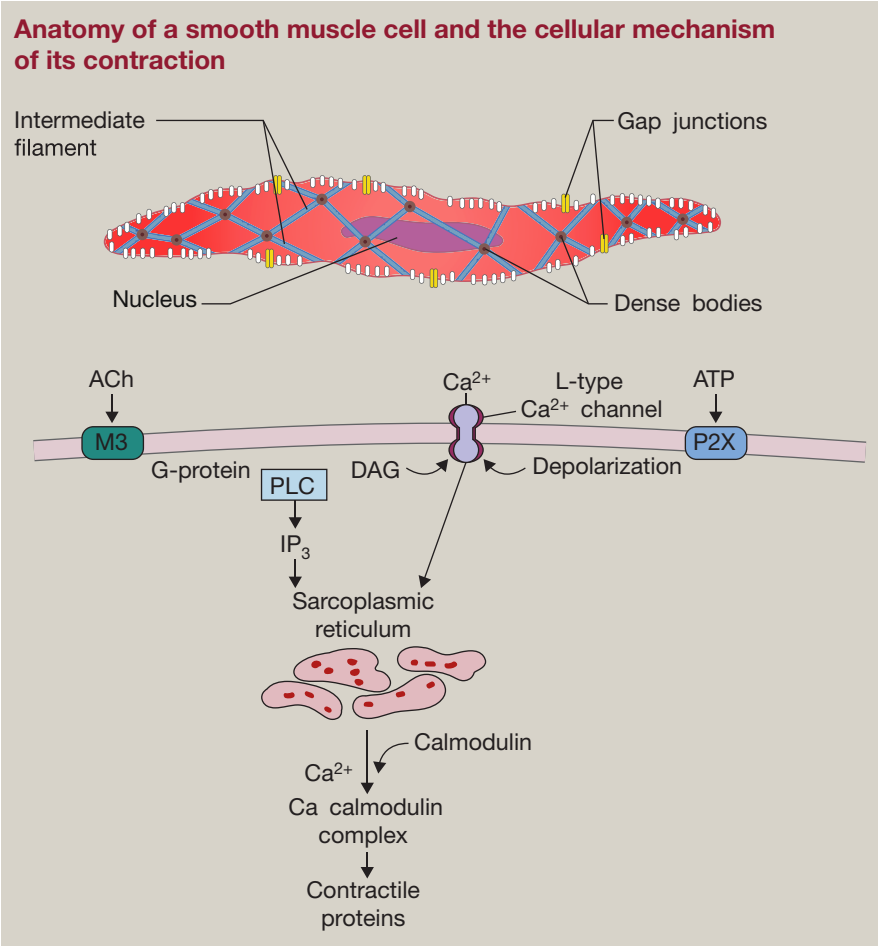


Figure 2

thought to enhance the action of M3 receptors by suppressing sympathetic activity through the inhibition of adenylate cyclase. In obstructed or denervated bladders, M2 receptors may become functionally more important.

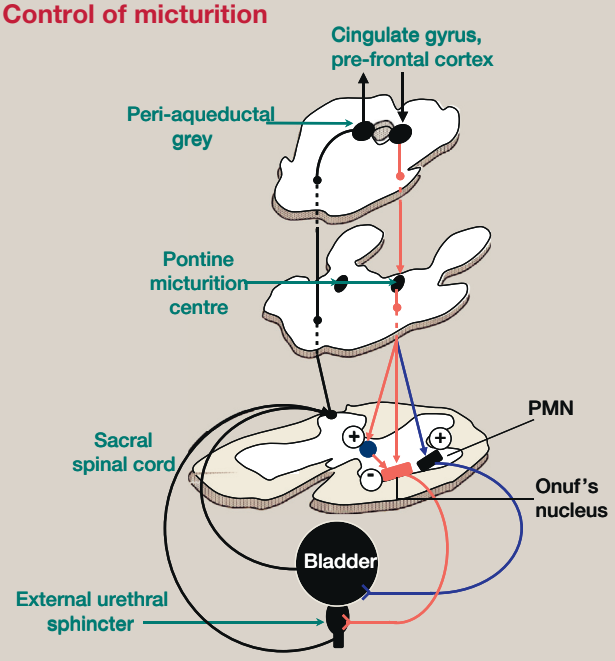
Postganglionic parasympathetic fibres synapsing on detrusor smooth muscle release ATP in addition to Ach. Cholinergic neurotransmission generates short forceful bladder contractions in animals thought to be important for scent marking activity and may represent a vestigial mechanism in humans. Organ bath experiments comparing detrusor from functionally normal human bladders with that from overactive bladders suggest that cholinergic-mediated contraction is not apparent in normal detrusor but becomes functionally expressed in overactive bladder. The mechanisms for this are unclear.

The micturition cycle and its neurological control

The urinary bladder stores the accumulating urine that is continuously produced by the kidneys and actively expels it under the control of higher cortical centres in the brain. These functions are mutually exclusive and controlled by complex neural networks, which are influenced by conscious neurological activity to switch between the two states. The bladder spends over 98% of the time in storage mode, initiation of voiding is influenced by the perceived sense of bladder fullness and the social practicality of voiding, a conscious decision.

Central control of micturition occurs in three distinct areas of the central nervous system. The sacral micturition centre, situated in the sacral spinal cord, is responsible for co-ordinated bladder and sphincter activity. It receives afferent information regarding bladder wall stretch and fullness and gives rise to both efferent parasympathetic fibres to the detrusor, and somatic efferents to the rhabdosphincter that originate in Onuf's nucleus in the medial part of the anterior horn of the spinal cord. The pontine micturition centre in the brain stem acts as a relay and switches the bladder between storage and voiding modes, and the cerebral cortex inhibits the sacral centre and provides conscious input to the pontine centre, activating the micturition reflex when required.

Urine storage phase: during bladder filling, the highly compliant bladder is able to hold increasing volumes of urine with little increase in wall tension or intravesical pressure. This receptive relaxation is due to the viscoelastic properties of the detrusor connective tissue and the ability of the smooth muscle cells to increase their length without generating tension. Bladder filling is also facilitated by low-level efferent sympathetic nervous activity to the detrusor. This is transmitted by preganglionic fibres in the intermediolateral column of spinal segments T10 to L2 synapsing with postganglionic fibres in the sympathetic chain ganglia. Postganglionic fibres travel in the hypogastric nerve to act on



Shown are three levels of the central nervous system: the upper pons, more caudal pons and the sacral spinal cord. Descending tracts from the pontine micturition centre are shown to go to the parasympathetic motor nucleus (PMN) and directly to Onuf's nucleus or indirectly via an inhibitory interneuron. The signs adjacent to the PMN and Onuf's nucleus show the prevailing excitatory (+) or inhibitory (minus) influences during micturition.

Figure 3

detrusor β3-adrenergic receptors mediating detrusor relaxation, and also terminate on parasympathetic ganglia where they reflexly inhibit bladder efferents. Postganglionic sympathetic fibres also pass to the bladder neck and urethra where they stimulate α-receptors to increase bladder outlet resistance during bladder filling. Additional reflex activity within the somatic pudendal nerve causes increasing tone of the external urethral sphincter during bladder filling to maintain continence — the guarding reflex.

During bladder filling, afferent impulses travel in pelvic, hypogastric and pudendal nerves to secondary interneurons in the spinal cord. These afferents include myelinated Aδ fibres which monitor wall tension, and unmyelinated C fibres which sense bladder volume and nociception to over-distension. The majority of the latter remain silent during normal conditions but become more prominent and form new functional afferent pathways in neuropathic and inflammatory conditions of the bladder causing urinary urgency and bladder pain. The afferent impulses are transmitted to the pontine micturition centre via the spinothalamic tract and then to higher cortical centres. If it is not convenient to pass urine, inhibitory signals are passed back to the sacral micturition centre to inhibit the parasympathetic pathways to the detrusor and stimulate the sympathetic and pudendal pathways to contract the sphincter and bladder neck, preventing involuntary bladder emptying.

Voiding phase: the voiding phase is usually under voluntary control with input from the orbitofrontal cortex, cingulate gyrus and peri-aqueductal grey matter deciding when it is convenient to void. Involuntary voiding is seen in infants because these cerebral pathways have not matured. It is also seen in those with neuropathic bladders that have escaped higher centre control. When the stimulatory signals from the bladder afferents reach threshold intensity, or a conscious decision to void has been made, the inhibitory signals from the cortex are withheld, and the pontine micturition centre switches from storage to voiding function. The pontine micturition centre transmits this to the sacral centre containing both the parasympathetic motor nucleus mediating detrusor contraction, and the somatic Onuf's nucleus which supplies the rhabdosphincter. These nuclei are connected by inhibitory GABA-releasing spinal interneurons. To initiate voiding, impulses in parasympathetic fibres exit the spinal cord and travel in the pelvic nerves synapsing in the pelvic plexus and in ganglia located within the detrusor muscle itself. Post-ganglionic fibres release acetylcholine which acts on M3 muscarinic receptors expressed throughout the detrusor to cause contraction. At the same time, somatic efferent activity from Onuf's nucleus, travelling in the perineal branch of the pudendal nerve to provide motor input to the rhabdosphincter, is inhibited by activity in the spinal interneurons, and the sphincter relaxes.

Pathophysiology of the lower urinary tract

Pathology of the lower urinary tract gives rise to a variety of highly prevalent and bothersome Lower urinary tract symptoms (LUTS). These are classified according to whether they occur during the urine storage or voiding phases. Storage symptoms include urinary frequency, urgency with or without incontinence and nocturia (getting up at night to pass urine), whereas voiding symptoms include poor flow, hesitancy and feelings of incomplete bladder emptying. However, while pure voiding symptoms are often caused by bladder outlet obstruction, and storage symptoms by overactive or underactive bladder dysfunction or increased bladder sensitivity, lower urinary tract symptoms are not disease, organ or even sex specific and storage and voiding types frequently coexist.

Storage lower urinary tract symptoms may result from bladder outlet obstruction by mechanisms that have yet to be fully elucidated. In animal models bladder obstruction leads to reduced detrusor muscle blood flow, an increase in hypoxia-induced growth factors and muscle cell hypertrophy that is thought to give rise to involuntary bladder activity and symptoms. It is also thought that nitric oxide (NO) released by bladder urothelium in response to stretch plays a critical role in bladder dysfunction as it modulates the bladder response to obstruction and LUTS associated with BPH. Furthermore, urinary levels of ATP are significantly higher in animal models with partial BOO suggesting that patients with obstructed bladders release higher amounts of ATP from the urothelium and this may stimulates sensory pathways.

Storage symptoms may also be caused by conditions that lead to an increase in bladder sensory stimulation due to urothelial inflammation and these include tumours and carcinoma in-situ, bladder stones and stagnating residual urine. They may in part (urinary frequency, urgency and nocturia) also result from excessive urine production and may therefore a sign of polyuric metabolic disorders.

Given its complexity it is not surprising that the effects of disruption to the neurogenic control of the lower urinary tract by trauma or neurological disease can be also complex and the type and symptoms of spinal cord injury depends on the level and completeness of the lesion. Spinal cord lesions at vertebral level L1 and above may have neurogenic detrusor overactivity, resulting from disconnection of the bladder from stabilizing cortical control, and detrusor sphincter dyssynergia (discoordination of bladder contraction and sphincter relaxation). Lesions below L1 may have detrusor areflexia preventing bladder contraction. This can be combined with either loss of external sphincter control resulting in incontinence, or intact sphincter innervation, as it originates at a higher spinal level, making bladder emptying difficult.

Storage symptoms alone often occur in the absence of any clear pathological cause when it is termed the overactive bladder syndrome (OAB). Detrusor smooth muscle samples contract spontaneously *in vitro*, and this may be increased in pathological bladders. The spontaneous activity may be driven by ATP release from the urothelium as it is significantly reduced in experimentally urothelial denuded samples. The clinical usefulness of investigating bladder activity in OAB is limited, however, as involuntary bladder contractions can readily be detected during pressure flow urodynamics in both symptomatic and normal subjects and are often absent in those with symptoms. So despite the nomenclature, whether overactive bladder symptoms are generated by spontaneous detrusor overactivity or not, is unclear and the role of spontaneous detrusor activity in the generation of symptoms is poorly understood.

Pharmacology of the lower urinary tract

Several classes of pharmacological agents are available for the treatment of LUTS, these include α-blockers, 5α-reductase inhibitors, antimuscarinics, phosphodiesterase type 5 inhibitors (PDE5Is) and intradetrusor botulinum toxin A injections. Despite the potential targets revealed by in-vitro work, particularly those concerning the role of purinergically mediated afferent and efferent neurotransmission in overactive bladder, there have been few pharmacological advances over the last decade.

Decreasing bladder outlet resistance in males with bladder outlet obstruction

There have been no major advances in the medical treatment of LUTS attributed to BPH over the last few years. Initial trials of drug combination therapies yielded promising initial results but have failed to show outcomes superior to the traditional alpha-blockers. While the two drug classes actively used in this field remain widely used and effective for moderately bothersome symptoms, surgical options provide a more lasting and certainly overall cheaper alternative for bladder outlet obstruction due to BPH.

Adrenoceptor receptor antagonists (α-blockers)

The use of α-blockers not only improves voiding symptoms in men with LUTS secondary to BPH but also can help with storage symptoms. There are several subtypes of alpha-adrenoreceptors. α1A-adrenoreceptors are present throughout the bladder base, neck, proximal urethra and within the prostate stroma whereas α1B-adrenoceptors are predominantly located in the brain and spinal cord. Contraction of smooth muscle in the LUT is principally mediated by the α1A subtype whereas the α1B-subtype are more significant in the inhibition of the afferent pathways of the micturition reflex. Alpha-blockers induce relaxation of prostatic stromal and bladder neck smooth muscle leading to a decrease in urethral resistance and improvement in LUTS. They have become the mainstay of management of BPH for mild to moderate LUTS, and are well tolerated and beneficial in almost one-third of patients. However, half of men who take the drug will stop using it within 3 years due to a perceived lack of efficacy.

Tamsulosin is an α1A subtype selective antagonist and is the most commonly used in this class of drugs. It has selectivity for the bladder neck and prostate stroma rather than in the vascular system and is effective and tolerable. Although its effects are dose dependent, the 0.8 mg dose is associated with more side effects than the standard 0.4 mg and not used. Tamsulosin is associated with a greater risk of anejaculation, due to paralysis of the bladder neck, and floppy iris syndrome. This may complicate cataract surgery, and is due to the α1A receptors located on the iris and is characterized by failure of pupil dilation, iris billowing and prolapse, and progressive intraoperative meiosis. This can be prevented by appropriately stopping the drug preoperatively.

5α-Reductase inhibitors

Two main drugs exist in this class for the management of BPH related LUTS: finasteride and dutasteride. These inhibit the enzyme involved in the conversion of testosterone to the more potent dihydrotestosterone. This causes apoptosis of the prostatic epithelium and reduction in prostatic volume, reducing the static component of prostatic obstruction by up to 30%. Two isoforms of the enzyme exist; type 1 is found in the liver and skin whereas type 2 is found in the prostate. Finasteride only inhibits the type 2 enzyme and dihydrotestosterone levels do not fall, unlike with dutasteride which inhibits both isoforms. The clinical impact of this is unknown as the two drugs have not been compared in a clinical setting. The main side effects include sexual dysfunction including reduced libido, erectile dysfunction and reduced volume ejaculate. Long-term use of finasteride has shown a relative risk reduction of acute urinary retention by 43%. Additionally, these drugs are often used to help with haematuria secondary to prostatic tissue regrowth after resection and in combination with α blockers to reduce the risk of urinary retention or the need for surgery by almost half. As they act by reducing anatomical bladder outlet obstruction, these agents are more effective in patients with larger prostates.

Intraprostatic injections

NX-1207 is a fexapotide trilfutate that reduces prostate volume at a cellular level through selective apoptosis when injected directly into the prostate. Phase two trials have demonstrated symptomatic improvement in males with LUTS secondary to BPH; however, the effects are unlikely to be as apparent as the recently approved procedure of injecting steam into the prostate which is currently attracting attention.

Increasing bladder outflow resistance

The only agent licensed for use in the category is the selective serotonin and norepinephrine reuptake inhibitor antidepressant

duloxetine. Duloxetine acts by inhibiting neurotransmitter uptake in adrenergic synapses and both increases tone in the external urinary sphincter and produces a degree of detrusor relaxation, thereby suggesting use in stress incontinence. However its side effect profile is significant, and is not recommended for widespread use, its only niche is in women with stress incontinence who prefer the drug to more effective surgical intervention.

Drugs acting on bladder contractility

Despite a huge clinical demand, there are currently no drugs available to increase bladder contractility. The following agents decrease bladder contractility and are used for overactive bladder and the treatment of storage lower urinary tract symptoms in general.

Antimuscarinic drugs

Antimuscarinic drugs are the mainstay of treatment of OAB. By blocking the effect of the acetylcholine released from parasympathetic fibres acting on the detrusor muscle, they reduce detrusor contractility and increase bladder capacity, also increasing post void residual urine volumes in patients with bladder outlet obstruction. Antimuscarinic drugs are not effective in all patients and are often discontinued due to adverse side effects or decreasing efficacy. Furthermore, caution is advised in the elderly population because of increased risk of cognitive impairment. Antimuscarinic agents appear more effective during bladder filling, suggesting that they may target bladder afferent activity. In experimental models they reduce stretch-activated urothelial ATP release.

There are two broad groups of antimuscarinic drugs, the tertiary and quaternary amines (Table 1). The former generally have a higher lipophilicity and molecular charge, and include atropine, darifenacin, fesoterodine, oxybutynin, propiverine, solifenacin, and tolterodine. The quaternary amines include propantheline and trospium, are not well absorbed, and pass into the central nervous system (CNS) to a limited extent to cause unwanted effects since they act not only on muscarinic receptors in the bladder. These drugs should be used with caution in patients with cardiac disorders, as they can cause an increase in heart rate and prolong the QT interval, and they are contraindicated in those with myasthenia gravis and inflammatory bowel disease.

Oxybutynin is an older antimuscarinic drug and is still the most widely prescribed agent for storage LUTS and is available in a number of different formulations. It is subject to first-pass hepatic metabolism, and one of the active metabolites formed is N-desethyloxybutynin (DEO) which is responsible for the majority of side effects, the most troublesome of which is dry mouth due to action on cholinergically mediated saliva production, and constipation. Newer formulations of oxybutinin reduce these, with prolonged release preparations slowly releasing the drug into the large intestine over 24 h, with less production of DEO.

Uroselective antimuscarinic drugs have been developed to reduce unwanted anticholinergic side effects. Tolterodine acts preferentially on the bladder compared to the salivary glands and Solifenacin is more selective for the M3 than the M2 receptor, although M3 receptors are still found in the salivary gland and dry mouth remains an issue.

β3-Adrenoceptor agonists

Activation of detrusor adrenoceptors (AR) causes muscle relaxation through activation of adenylyl cyclase and the formation of cyclic AMP. The predominant receptor subtype in detrusor is β3. The principal behind of AR agonists are to cause relief from storage symptoms while avoiding the unwanted effects of antimuscarinic drugs. Despite the promise of β3-adrenoceptor agonists for over a decade, mirabegron (Betmiga) is still the only selective β3-adrenoceptor agonist licensed for use in OAB syndrome. Recent studies have shown efficacy and safety in combination therapy such as mirabegron plus solifenacin and mirabegron plus α-blockers in male patients. Although phase three studies have not demonstrated a risk for increasing hypertension, regular blood pressure monitoring is required, while it should be avoided in severe uncontrolled hypertension. The main side effects of mirabegron include nasopharyngitis, urinary tract infections and headache. Unlike antimuscarinics, the drug does not decrease bladder contractility and may therefore be more useful in patients with bladder outlet obstruction.

Characteristic features of common antimuscarinic agents and their different formulations

Drug	Formulation	Dose	Receptor selectivity	Notes
Oxybutynin	Immediate release	5 mg three times daily	M1, M3	Has greater impact on cognitive function and should be used cautiously in the elderly. Newer formulations produce less DEO and unwanted side effects
	Extended release	5 mg once daily		
	Transdermal	3.9 mg/day, applied twice weekly		
	Gel	3 pumps (84 mg/day) applied once daily		
Solifenacin	Tablets	5 or 10 mg daily	M3	Newer uroselective drugs with less untoward antimuscarinic side effects
Darifenacin	Tablets	7.5 mg or 15 mg daily	M3	
Tolterodine	Immediate release	1 or 2 mg twice daily	Non selective	Low incidence of CNS side effects
	Extended release	2 or 4 mg daily		
Fesoterodine	Tablets	4 or 8 mg daily	Non selective	
Trospium	Immediate release	20 mg twice a day	Non selective	Less cognitive effects by not crossing the blood brain barrier. Not metabolized by p450
	Extended release	60 mg daily		

Table 1

Intravesical instillations of onabotulinum toxin A

Onabotulinum toxin A (Botox®) is a licensed preparation in the UK for the treatment of both neurogenic and non-neurogenic detrusor overactivity. The agent is produced by *Clostridium botulinum* and consists of a heavy and light chain connected by a disulphide bond. In the neuromuscular synaptic cleft, it binds to a synaptic protein and is taken up into the nerve terminal preventing neurotransmitter containing vesicles from binding to the plasma membrane. Acetylcholine is therefore not released at the neuromuscular junction.

Botox is used as second-line therapy in patients who have failed to benefit from antimuscarinic drugs or mirabegron, and is injected into the detrusor directly under either a local or general anaesthetic via a cystoscope. There is also an effect on afferent nerves through a reduction in release of transmitters such as substance P that improves sensory symptoms such as urinary urgency. The effects of Botox are temporary and on average last up to 6 months, requiring repeated intravesical injections. However, there does not appear to be a loss of efficacy with repeated injections over time. The main side effects include pain at the site of injection, transient haematuria and urinary tract infections. There is a significant risk of urinary retention due to detrusor paralysis and all patients must be capable of performing self-catheterization before injections. While onabotulinum toxin A (Botox) has been approved for both NDO and IDO, another toxin, abobotulinum toxin A (Dysport) has been shown to result in significant improvements in NDO patients. Botox has also been tried cautiously for detrusor activity in children with detrusor-sphincter dyssynergia and for patients with bladder pain syndrome with mixed results.

Phosphodiesterase inhibitors

With advancing age, erectile dysfunction and LUTS increasingly co-exist and this has led to the use of phosphodiesterase inhibitors to treat both disorders. The underlying pathophysiology linking the two is not well understood but may involve autonomic hyperactivity, pelvic atherosclerosis and reduced NO-cGMP signalling. PDE5 agents block the breakdown of cyclic nucleotides thereby inducing smooth muscle relaxation. Several randomized controlled trials have demonstrated that PDE5 agents significantly improve male LUTS and both tadalafil and Vardenafil has been shown to improve storage symptoms in both male and female patients.

Gabapentin and other antiepileptic drugs

These drugs have shown promise in preclinical models. A small study compared gabapentin and solifenacin to placebo and were both found to be effective for OAB symptoms reduction. Gabapentin had the added benefit of reducing nocturia episodes. Antiepileptics may act on the corticotrophin releasing factor pathway or may have central sensitization effects. ◆

FURTHER READING

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