The pharmacology of paediatric incontinence

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Introduction

The clinical uropharmacology of the lower urinary tract is based on an appreciation of the innervation and receptor content of the bladder and its related anatomical structures. The anatomy, neuroanatomy and neurophysiology of the bladder is reviewed. Classes of drugs are discussed in relation to the possible functional targets of pharmacological intervention and finally some specific applications in paediatric voiding dysfunction are discussed.

Pharmacological interactions

A short review of anatomy, neuroanatomy and neurophysiology is essential to understand pharmacological interactions. These interactions with effects on bladder function can occur on different levels, i.e. on bladder mucosa, bladder smooth muscle or bladder outlet striated muscle, on receptor subtypes, on nerve terminals, on peripheral nerves and ganglia, on the spinal cord and on some supraspinal areas. The lower urinary tract consists of the bladder, which mainly contains smooth muscle cells, and a sphincter, which mainly contains striated muscle. Although this is an over-simplification of the real anatomy of the lower urinary tract, it is useful pharmacologically. Between the bladder and the urethral sphincter there is a zone of transition where smooth muscle cells play the role of a functional sphincter [1]. In adult urology this zone has a major role in the pharmacological treatment of infravesical obstruction, especially in men with BPH. Its role in paediatric pathological conditions remains unclear. The lower urinary tract differs from other visceral structures by its dependence on the CNS. This makes the bladder a unique organ where viscero-somatic integration takes places. Indeed, most autonomic nerve systems must provide tonic activity to visceral organs. However, bladder function demands a phasic autonomic activity with voluntary control. Bladder function consists of the storage of urine and timely evacuation at socially acceptable and convenient places and times. Bladder storage requires:

- the accommodation of increasing volumes of urine at a low intravesical pressure and with appropriate sensation
- a bladder outlet that is closed and remains so during increases in intra-abdominal pressures
- and absence of involuntary bladder contractions [2].

In children the development of continence and voluntary voiding involves maturation of the nervous system and behavioural learning. Toilet training mainly depends on the cognitive perception of the maturing urinary tract. This implies a high sensibility for the development of dysfunctions [3]. The storage and evacuation of urine are controlled by two functional units in the lower urinary tract, i.e. the reservoir (the bladder) and an outlet (consisting of the bladder neck, urethra and striated muscles of the pelvic floor). In the bladder, two regions (Fig. 1a) are distinguishable from their innervation and response to pharmacological agents: the body, which lies cranial to the level of the ureteric orifices, and the base, which is caudal to this level [4]. In the outlet two functional units are distinguished, an anatomical striated sphincter and a physiological internal sphincter. The internal sphincter is more a functional than an anatomical structure, and keeps the bladder neck and the proximal urethra closed during bladder filling. The autonomic and somatic innervation of the bladder and the outlet are well known. Other neuronal systems, i.e. purinergic, peptidergic, γ-aminobutyric acid (GABA) and serotonin, are known to be apparent in the bladder but their effect on bladder function remains obscure. This review mainly focuses on the autonomic and somatic nervous systems. All nerves are able to transport information from the organ to the CNS (afferent impulses), mainly a sensory function, and to transport information from the CNS to the organ (efferent impulses), mainly a motor function.

The peripheral nerve system

Afferent

Nerve cells in the dorsal spinal root ganglia project their axons to the bladder wall. Different kinds of receptors
Fig. 1. a, Two bladder regions are distinguished based on their innervation and response to pharmacological agents: the body, which lies cranial to the level of the ureteric orifices; and the base, which is caudal to this level. b, shows the distribution of muscarinic receptors (blue), and α- and β-adrenergic binding sites (red and green, respectively) in human bladder and urethral tissues. c, shows the effect of anticholinergic or antimuscarinic agents, i.e. a decrease in parasympathetic input to the bladder increases bladder capacity by decreasing bladder contractility. d, shows the noradrenergic effects on the bladder: whereas α-adrenergic agonists (red) increase outlet resistance, β-adrenergic agonists (green) can cause a significant increase in bladder capacity.
(pressure, pain, temperature, tension) are able to intercept signals from the bladder and convey them to the CNS, where they can be perceived at the spinal cord level and generate reflexes, or where they can become conscious stimuli which can be modified by behaviour. The receptors in the bladder form the most distal level where pharmacological agents can interact.

**Efferent**

Parasympathetic or cholinergic innervation is provided by the sacral parasympathetic pelvic nerves (S2–S4). The sacral parasympathetic efferents to the lower urinary tract are carried within the pelvic splanchnic nerves, and are the principal excitatory input to the bladder.

Radioligand studies have confirmed that the bladder body and base (Fig. 1b) contain muscarinic receptors [5], stimulated by acetylcholine. In the bladder this stimulation provokes a bladder contraction and a rise in intravesical pressure. These effects can be abolished by atropine, but not completely (atropine resistance) because there are co-transmitters (e.g. ATP). Physostigmine, which inhibits acetylcholine degradation, also enhances bladder contraction. However, cholinergic agonists do not cause voiding, as they often cause simultaneous contractions of the bladder and the bladder neck. There seems to be a parasympathetic activity to the urethra resulting in relaxation, although this is mediated by a noncholinergic transmitter and is not fully understood.

Orthosympathetic or adrenergic innervation is provided by the thoracolumbar sympathetic hypogastric nerve and sympathetic chain (T10-L2). The sympathetic nerves to the lower urinary tract emerge from the paravertebral ganglia of the lumbar sympathetic chain as the superior hypogastric plexus, which bifurcates into left and right hypogastric nerves. These hypogastric nerves intermingle with the pelvic parasympathetic nerves to form the pelvic plexus.

There are α- and β-adrenergic binding sites in human bladder and urethral tissues (Fig. 1b), with β-receptors predominantly at the bladder dome and α-receptors at the base and the outlet. It is thought that the adrenergic pathways facilitate bladder storage by relaxing the detrusor and contracting the outlet [6]. This theory is not accepted by all and remains in debate [7].

The β-adrenergic receptor agonists increase bladder capacity and reduce the amplitude of uninhibited detrusor contractions [8]. β-antagonists like propranolol increase bladder pressure [9]. α-blockade in vivo decreases the amplitude of uninhibited bladder contractions in the neurogenic bladder [10]. Although sympathetic pathways appear to play a minor role in lower urinary tract function, as judged by pharmacological and electrostimulation data, it may be that in denervation, decentralization and smooth muscle hypertrophy trigger changes in adrenergic mechanisms that regulate bladder/urethral function. In paediatric voiding dysfunction muscle hypertrophy is often apparent. There may be a higher content of adrenergic receptors in the paediatric dysfunctional bladder.

Somatic innervation to the pelvic floor and the perineal muscles originates in Onuf’s nucleus in the anterior horn of the S2–S4 segments of the spinal cord. They form the pudendal nerve that supplies the pelvic floor muscles and the striated urethral sphincter [11]. However, the innervation of the striated urethral sphincter is still under debate, as autonomic innervation has been suggested by some [12].

**The CNS**

Neural control of the lower urinary tract occurs at different levels of the CNS and is less well understood. The main influences are inhibition of the micturition reflex, inhibition of spontaneous detrusor reflex contractions, coordination of detrusor contraction and sphincter relaxation. The cerebral cortex, thalamus, hypothalamus, limbic system, basal ganglia, cerebellum, brain stem with the ‘pontine micturition centre’ and spinal cord with the ‘sacral micturition centre’, are involved [3]. From the sacral micturition centre afferent and efferent pathways connect to the lower brain stem. Two ascending tracts (the pelvic sensory in the dorsal funiculus and the sacrobulbar in the lateral funiculus) and three descending tracts (a lateral reticulospinal tract which promotes detrusor contraction, a ventral reticulospinal tract which inhibits detrusor contraction and a medial reticulospinal tract which promotes sphincter contraction) have been described. These tracts terminate in the pontine micturition centre in the anterior pons, which is inhibitory. This centre is connected to the cerebral cortex which is also inhibitory. Pharmacological influences on the CNS will not be discussed systematically.

**The pharmacology of reservoir function**

An overview of this aspect is given in Table 1. As storage dysfunction is often seen in paediatric voiding dysfunction, these drugs will be discussed in more detail.

**Pharmacological action on smooth muscle cells**

By influencing smooth muscle activity the bladder reservoir function can be altered. Inhibitors of smooth muscle activity will increase bladder capacity or decrease the occurrence of unstable or hyper-reflexive contractions. However, pharmacological stimulation of smooth muscle cells is currently not possible. The site of action of
these agents is distal to the cholinergic receptor mechanism. Oxybutynin hydrochloride, a tertiary amine, is a moderately potent anticholinergic agent with strong musculotropic relaxant and local anaesthetic activity (twice that of lidocaine). In animal studies it has weak anticholinergic activities (8% of the potency of propantheline bromide) but strong spasmolytic effects (twice the effect of propantheline bromide) [13]. The side-effects are those of all antimuscarinic agents and include inhibition of salivary secretion (dry mouth), blockade of the ciliary muscle of the lens (disturbed accommodation, blurred vision), facial flushing during exercise, tachycardia, drowsiness and inhibition of gut motility, leading to constipation.

Tolterodine, a new agent with a more pronounced antimuscarinic effect on the urinary bladder than on the salivary gland, has recently been used in children. In adults it effectively decreased the symptoms of detrusor overactivity and caused fewer side-effects than oxybutynin.

Flavoxate hydrochloride directly inhibits smooth muscle, in addition to having weak anticholinergic and local analgesic properties. Side-effects are rare and primarily anticholinergic.

Calcium antagonists; calcium is a messenger in linking extracellular stimuli to the intracellular environment. Interference with calcium inflow is a very potent mechanism for bladder smooth-muscle relaxation. Common side-effects are hypotension, facial flushing, headache, dizziness, constipation, nausea and palpitations. Because of these side-effects, calcium antagonists are unpopular in children. Nifedipine has a blocking effect on the noncholinergic portion of bladder contraction.

Table 1 The pharmacology of reservoir function and the bladder outlet

<table>
<thead>
<tr>
<th>Level</th>
<th>Increase</th>
<th>Decrease</th>
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<tbody>
<tr>
<td><strong>Reservoir</strong></td>
<td>Relaxation of smooth muscle</td>
<td>Tonification of smooth muscle</td>
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<tr>
<td>Smooth muscle</td>
<td>Oxybutynin</td>
<td>Not available</td>
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<td></td>
<td>Flavoxate</td>
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<td></td>
<td>Calcium antagonist</td>
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<td>Potassium channel openers</td>
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<td>Prostaglandin inhibitors</td>
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<tr>
<td><strong>Afferent peripheral nerves</strong></td>
<td>Decrease bladder sensibility</td>
<td>Increase bladder sensibility</td>
</tr>
<tr>
<td></td>
<td>Capsaicin (instillation)</td>
<td>Not available</td>
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<tr>
<td></td>
<td>DMSO (instillation)</td>
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<td></td>
<td>Oxybutynin</td>
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<td>Flavoxate</td>
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<td>Tricyclic antidepressants</td>
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<td><strong>Efferent peripheral parasympathetic nerves</strong></td>
<td>Decrease bladder contractility</td>
<td>Increase bladder contractility</td>
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<td>Anticholinergics</td>
<td>Parasym patheticomimetics</td>
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<td></td>
<td>Atropine</td>
<td>Acetylcholine</td>
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<td>Propantheline</td>
<td>Betanechol chloride</td>
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<td></td>
<td>Hyoscyamine</td>
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<td></td>
<td>Oxybutynin</td>
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<td><strong>Efferent peripheral orthosympathetic nerves</strong></td>
<td>Decrease bladder contractility</td>
<td>Increase bladder contractility</td>
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<td></td>
<td>β-adrenergic agonists</td>
<td>α-adrenergic antagonist</td>
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<td></td>
<td>Tricyclic antidepressants</td>
<td>(no clinical use to date)</td>
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<tr>
<td></td>
<td>Imipramine</td>
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<td><strong>Bladder outlet</strong></td>
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<td>Striated urethral sphincter</td>
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<td>Benzodiazepines</td>
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<td><strong>Efferent peripheral orthosympathetic nerves</strong></td>
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<td>Ephedrine</td>
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<td>Phenylpropanolamine</td>
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<td>Imipramine</td>
<td>Prazosin</td>
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<td>Alfuzosin</td>
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Potassium-channel openers relax smooth muscle cells by increasing potassium efflux, and thus might be attractive for treating detrusor instability without decreasing contractile ability in response to the voluntary initiation of micturition [14]. Although a theoretical effect on bladder function is expected, currently no clinically useful agents are available.

Prostaglandin inhibitors or NSAIDs can theoretically influence smooth muscle contractions but objective evidence that this occurs at the level of the bladder is scant. They can even influence neurotransmission to the bladder and influence urethral tone during the storage phase. Apart from their direct effect they can influence bladder function by their effect on renal function and diuresis. Side-effects are interference with platelet function and adverse renal effects.

**Pharmacological action on afferent peripheral nerves**

Increasing bladder capacity by decreasing afferent sensory input seems a reasonable treatment for hypersensitivity disorders of the bladder. Apart from systemically administered drugs like oxybutynin, flavoxate and imipramine, all of which have dedicated local analgesic effects on bladder mucosa, it is possible to influence the bladder receptor by instilling drugs into the bladder.

A 50% solution of DMSO has been reported to have good to excellent results in treating interstitial cystitis [15] but its efficacy in other hypersensitivity disorders of the bladder has not been reported.

Capsaicin is an irritant and algogenic compound obtained from the chilli pepper, and which has a highly selective effect on sensory neurones. The instillation of capsaicin into the bladder induces desensitization and inactivation of sensory neurones [2]. Because it has the undesirable effect of inducing pain it is not applicable in children.

As noted, oxybutynin has a potent local anaesthetic effect. Because systemic application produces significant side-effects, topical administration was introduced and has been shown to be effective in treating various bladder conditions, e.g. instability, hypersensitivity and hyperreflexia [16]. Whether the effect is through antispasmodic or local anaesthetic effects is unknown. This opens new possibilities, especially for patients using intermittent catheterization. Good results with long-term intravesical treatment have been described in children with myelodysplasia [17].

**Efferent peripheral nerves: parasympathetic**

Anticholinergic or antimuscarinic agents decrease parasympathetic input to the bladder and can influence bladder capacity by decreasing bladder contractility (Fig. 1c).

Atropine depresses involuntary bladder contractions of any aetiology but in humans the effect is only partial (atropine resistance). Other transmitters than acetylcholine may possibly be involved in bladder contraction.

Propantheline bromide is the most commonly used oral anticholinergic agent in pathology of the lower urinary tract. Side-effects are dry mouth, tachycardia, blurred vision, drowsiness and constipation. The usual adult dose is 15–30 mg every 6 h. In children we prefer to start with 7.5 mg every 8 h and depending on the effect, the dose is increased to 15 mg every 8 h.

Other antimuscarinic agents, e.g. glycopyrrolate, isopropamide, hyoscyamine, anisotropine and methyl bromide, have the same effect on bladder smooth muscle as propantheline.

Parasympathicomimetic agents can be useful in the treatment of weak contractile bladders but are only rarely indicated in children. The best known agent is betanechol chloride, which has a relatively selective action on the bladder. Side-effects like flushing, nausea, vomiting, diarrhoea, gastrointestinal cramps, salivation and sweating are important, and limit the use of this drug, especially in children.

**Efferent peripheral nerves: orthosympathetic**

β-adrenergic agonists can cause significant increases in the capacity of the bladder (Fig. 1d). Terbutaline has been tested in clinical trials but is not commonly used; the side-effects include palpitations, tachycardia and tremor.

Tricyclic antidepressants are useful agents for facilitating urine storage, by both decreasing detrusor contractility and increasing outlet resistance. They are especially popular for treating monosymptomatic nocturnal enuresis (MNE). The precise mechanism of action in enuresis remains unclear. A recent placebo-controlled study suggested that the efficacy is not through their antidepressant effect [18]. Although they are known to have anticholinergic effects, anticholinergic drugs are ineffective in MNE [19]; thus a direct noradrenergic effect on the bladder could explain the observed effect (Fig. 1d).

Imipramine is the most widely used tricyclic antidepressant for treating nocturnal enuresis in children. Imipramine has only weak anticholinergic effects on bladder muscle; as well as adrenergic effects, they may exert a local anaesthetic-like action on the bladder. Clinically, the drug is effective by decreasing bladder contractility and increasing outlet resistance. Stimulation of the β-receptor by peripheral blockade of noradrenaline re-uptake could account for the decrease in bladder body contractility, and stimulation of the α-receptors in the smooth muscle of the bladder base and proximal urethra.
could account for the increase in outlet resistance. Side-effects include fatigue, tremor, sedation, nausea, vomiting, headache, lethargy, irritability and possible cardiotoxicity. However, these effects are rare in patients receiving smaller doses for lower urinary tract dysfunction [20]. Imipramine should be discontinued gradually, as abrupt cessation can cause significant side-effects. It also carries a risk of accidental poisoning if swallowed by younger siblings. The provision of good parental information can prevent this.

**Pharmacology of the bladder outlet**

An overview of this topic is also given in Table 1. Although outlet problems are important in children with functional and neurogenic voiding disorders, they are rarely treated with drugs. The functional voiding disorders (‘dysfunctional voiding’) particularly are more logically treated with bladder training and pelvic-floor training. In neurogenic voiding dysfunctions drugs are more frequently used in paediatric practice, as in spastic training. In neurogenic voiding dysfunctions drugs are more frequently used in paediatric practice, as in spastic tetraplegia and cerebral palsy. With the increasing use of α-blocking agents in adults and the availability of more specific α-blockers, their application may in future be extended to children; the available products are discussed.

**Pharmacological action on striated urethral sphincter muscle**

There is no class of pharmacological agents that selectively relaxes the striated musculature of the pelvic floor. Three different types of drugs have been used to treat voiding dysfunction caused by striated sphincter activity during voiding. They are all very unspecific and have important side-effects. Their main application is in spastic disorders.

Benzodiazepines potentate the action of GABA, the major inhibitory transmitter in the spinal cord; they reduce the release of transmitters of afferent fibres and reduce reflex activity in patients with spasticity. Diazepam is the most common drug used for this purpose. It can be used successfully in children who present with urinary retention after urethral instrumentation. Whether the muscle-relaxing or the anti-anxiety effect is responsible for the result is unknown. Side-effects are over-sedation and impairment of cerebral function.

Baclofen is thought to be a GABA agonist; it decreases excitatory transmitter release by afferent fibres but is only applicable in patients with general spasticity caused by a neurological lesion. It may impair the ability to walk or stand and must therefore be used very carefully. Other side-effects include drowsiness, insomnia and dizziness.

Dantrolene is the only pharmacological agent with a direct action on skeletal muscle. The effect on the bladder outlet has not been confirmed.

**Pharmacological actions on efferent and orthosympathetic peripheral nerves**

α-adrenergic agonists can increase outlet resistance, as α-adrenergic receptors predominate in the bladder neck and proximal urethra. The side-effects of these drugs are hypertension, anxiety, insomnia, headache, tremor, palpitations and respiratory difficulties.

Ephedrine, pseudo-ephedrine, norephedrine chloride and ephedrine sulphate have been used to treat adults with sphincteric incontinence. Good results are obtained in those patients with minimal to moderate wetting. Currently we are using α-adrenergic agonists to treat urge syndrome in children. Children with urge syndrome often have an open bladder neck secondary to the unstable contractions. An open bladder neck can provoke further unstable contractions as the presence of urine in the proximal urethra can induce bladder contractions. Phenylpropanolamine hydrochloride is available for the treatment of nasal and sinus congestion; its effects on the bladder outlet are the same as those obtained with ephedrine.

The possible effects of imipramine on the bladder outlet have been described previously; the inhibition of noradrenaline re-uptake can provide α-adrenergic stimulation.

α-blockers are currently very popular for treating BPH. The concept of the physiological internal sphincter controlled by α-adrenergic receptors in the smooth musculature of the bladder neck and proximal urethra was popularized in the 1970s [6]. Although the theoretical expected effect would be best in those patients with bladder neck obstruction, good results are described in patients with detrusor sphincter dyssynergia, suggesting that there may also be an effect on striated sphincter tone. To date, α-blockers have no application in children. Theoretically they could have a place in treating obstructive outlet conditions, as in dysfunctional voiding. The side-effects are orthostatic hypotension, reflex tachycardia and a possible ‘first-dose phenomenon’ with faintness, dizziness, palpitations and syncope.

Phenoxybenzamine has been the most commonly used α-blocker in voiding dysfunction; because it is theoretically mutagenic its use is no longer advised.

Prazosin is an antihypertensive agent with effects on bladder smooth musculature; because it has important circulatory side-effects it is no longer used for voiding dysfunction. Terazosin, alfuzosin and other similar new drugs are selective α1-blockers and therefore more selective for the urinary tract. Their use in BPH is

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currently approved but clinical trials in children are needed.

Pharmacological treatment of paediatric voiding dysfunction

Monosymptomatic bedwetting

Although nonpharmacological treatments, e.g. conditioning therapy with an alarm system, are better for MNE, pharmacotherapy continues to be popular among physicians and families [21,22]. Antidepressants, anticholinergics and prostaglandin inhibitors are discussed.

Tricyclic antidepressants; although the mechanism of action of these agents is currently unknown (e.g. antidepressant effect, antispasmodic and/or anticholinergic effect, alterations in arousal and sleep, increase in ADH levels, adrenergic reuptake blockade) several studies have confirmed their benefits in MNE [18,23]. Drugs like imipramine are generally not given to children under the age of 6 years. Possible side-effects and risks of accidental poisoning must be considered when prescribing these drugs. On a body-weight basis the recommended starting dose is 0.9–1.5 mg/kg, given 1–2 h before bedtime.

Anticholinergic agents have no place in the treatment of MNE. In the only double-blind controlled study in children with MNE, oxybutynin was shown to be no better than placebo [24].

Prostaglandin inhibitors have been used successfully for treating MNE [25,26]. A direct effect on bladder smooth muscle or indirect effect on diuresis, by influencing the GFR and ADH, have been proposed as mechanisms of action in nocturnal enuresis. Although both the cited studies were placebo-controlled, the use of prostaglandin inhibitors in MNE is currently not recommended.

Urinary incontinence

In paediatric functional voiding dysfunction most incontinence problems are related to storage-phase dysfunctions, mainly detrusor instability (motor urgency) and detrusor hypersensitivity (sensory urgency). Dysfunctional voiding, which is sphincter activity during voiding, is a voiding-phase dysfunction that can maintain the storage-phase dysfunctions.

Detrusor instability Theoretically, detrusor instability can be treated by antispasmodics, anticholinergics and adrenergic agonists. Oxybutynin has antispasmodic and anticholinergic effects and has been used most for this indication; the drug is safe in children [27]. Reports of an effect in treating daytime wetting in children are sparse. Aubert et al. [28] reported an 87% success rate in a group of 77 children with daytime incontinence. Scholteijer and van Mastrigt [29] showed that oxybutynin could decrease detrusor contractility and the degree of reflux. The usual reported dose is 0.3–0.5 mg/kg/day given in three doses.

Tolterodine has recently been used to treat detrusor instability in children [30]; its safety and efficacy were confirmed. There was a dose-related decrease in the number of micturitions and number of incontinence episodes: 1 mg twice daily seems to be the optimal dose for children aged 5–10 years.

Proprophylactic bromide, a pure anticholinergic agent, is safe in older children; the initial dose in children >6 years old is 7.5 mg three times daily. If no side-effects are reported the dose can be increased to 15 mg three times daily.

Although the exact site of action of imipramine remains unclear it is has confirmed beneficial effects on bladder storage function. As imipramine may have an adrenergic agonist action there is a place for combining it with antispasmodic or anticholinergic drugs. To treat daytime incontinence imipramine is given three times daily, which increases the risk of side-effects and toxicity: thus careful clinical monitoring is warranted. A dose of 10–25 mg (in children over 12 years old) three times daily is usual.

Detrusor hypersensitivity with no instability is difficult to treat, but drugs having a local anaesthetic action on the bladder mucosa can be used. Oxybutynin and flavoxate also have the advantage of having antispasmodic and anticholinergic activities.

Dysfunctional voiding (overactivity of the pelvic floor muscles during micturition) responds best to bladder and pelvic-floor training. Drugs are currently not used for treating this condition, although theoretically there is a place for those drugs acting on outlet resistance. With more selective drugs available, prospective double-blind studies are awaited to confirm their efficacy in dysfunctional voiding. Phenoxybenzamine and diazepam have been used for this condition but are not recommended because they have important side-effects [31].

Neurogenic voiding dysfunctions (congenital malformations of the CNS)

In children with a neurogenic bladder the combination of a high-pressure hyper-reflexive bladder with a closed sphincter caused by detrusor sphincter dyssynergia carries a risk of subsequent urinary tract changes, e.g. reflux and hydronephrosis. The prophylactic use of clean intermittent catheterization with concomitant anticholinergic medication prevents urinary tract damage.
Further research in this field will open new perspectives in understanding and treating bladder dysfunctions, their application in children is limited, largely because of the side-effects arising from their low specificity. Future objectives include the development of more selective drugs to extend the possibilities for pharmacological therapy in paediatric voiding dysfunctions, and a greater understanding of the innervation of the bladder outlet may account for some of the effects obtained with α-blockers in neurogenic bladders. There is a theoretical place for drugs that decrease outlet resistance (at the level of the striated sphincter and the internal sphincter) in treating detrusor sphincter dyssynergia but their use has not been reported in children. As their effect will include more problems with incontinence, they will have limited use for treating neurogenic dysfunctions in children.

### Congenital structural abnormalities

Congenital structural abnormalities (exstrophy, caudal regression sequence, PUV and other urethral anomalies) cover a wide range of bladder dysfunctions. The description of the bladder dysfunction in these conditions depends mainly on urodynamic data and treatment is adapted to urodynamic findings. The details of the treatment of these complex dysfunctions is beyond the scope of this review and will not be addressed. However, the general information on the drugs described above is also applicable in these conditions.

### Conclusion

Although many drugs are available for treating bladder dysfunctions, their application in children is limited, largely because of the side-effects arising from their low specificity. Future objectives include the development of more selective drugs to extend the possibilities for pharmacological therapy in paediatric voiding dysfunctions, and a greater understanding of the innervation of the normal bladder and that in pathological conditions. Further research in this field will open new perspectives for pharmacological treatment.

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