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# Treatment modalities for paediatric functional daytime lower urinary tract disorders: an updated review

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***Abstract*:** Paediatric functional bladder disorders especially those causing daytime symptoms are a common cause of significant psychosocial and/or physical morbidity and impaired quality of life. Despite the availability of many therapeutic modalities, a significant number of children appear to be refractory to treatment and continue to have symptoms. In this review, we aim to evaluate the current evidence in the use of existing and novel therapeutic options for the management of daytime lower urinary tract disorders in children. We also aim to highlight the controversies around the terminology and diagnosis of paediatric lower urinary tract dysfunction (LUTD) and specific conditions. The article will then provide a reasonable critique of the existing and emerging treatment modalities in functional daytime LUTD in children including their mode of action, efficacy, indications, and recent advances. These include standard urotherapy, specific urotherapy comprised of biofeedback, alarm therapy and electrical neural stimulation and pharmacotherapy involving selective and non-selective anticholinergics, $ß_3$ adrenergic agonists, alpha blockers and botulinum toxin. A better understanding of this common clinical problem may help clinicians achieve better profiling of these children's diagnoses to further enable specific, targeted treatment.

## Plain language summary

### A review article about new treatment options for otherwise healthy children with long-term urinary symptoms occurring during the daytime

Management of paediatric functional daytime LUT disorders is complex and may benefit from a combination of treatment modalities. Urotherapy and anticholinergics appear to be effective in the majority however, non-responders warrant careful re-evaluation to characterize the specific type of LUTD to target appropriate treatment. Various novel therapies and adjuncts have been shown effective and range from smartphone apps, bladder alarms, neuromodulation systems and more effective drug delivery systems. Despite being effective, non-selective antimuscarinics are less favoured for long-term use in children due to the side-effect profile. Therefore, more selective anticholinergics, ß3 agonists and combination treatment options are being evaluated to improve compliance while maintaining/enhancing treatment efficacy. Use of alpha blockers and intravesical injection of botulinum toxin have shown promising results especially in refractory cases.

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## Introduction

The term paediatric functional lower urinary tract disorders denotes a spectrum of clinical conditions in children where lower urinary tract dysfunction (LUTD) is evident without an apparent underlying cause. This is a common condition with epidemiological studies demonstrating a prevalence of about 20%.[1] In addition to that, this is associated with a significant negative impact on the quality of life, school performance, and family and social relationships of affected children.[2] It is believed that some of the lower urinary tract symptoms in childhood may resolve on its own corresponding to the age-related maturity of the lower urinary tract. However, several epidemiological studies have demonstrated that in a significant proportion of patients, some of these childhood lower urinary tract symptoms such as urinary incontinence may persist into their adulthood causing ongoing morbidity and distress.[3] This narrative review of the recent literature presents an up-to-date understanding of the current and/or novel therapies in the management of this common but challenging clinical entity. Treatment of nocturnal enuresis and proven neurogenic bladder is beyond the scope of this manuscript.

## Nomenclature and background

Functional lower urinary tract disorders in children could occur in isolation or associated with bowel dysfunction. When it is associated with concomitant bowel dysfunction as evidenced by significant constipation or retentive faecal incontinence, it can be termed bladder bowel dysfunction (BBD), a term introduced by the International Children's Continence Society (ICCS).[4] Different mechanisms have been hypothesized to explain the co-occurrence of LUT and bowel dysfunction in BBD. There is evidence to suggest that pathological changes in one system could induce cross-organ sensitization resulting in dysfunction of the other which appears to be induced *via* neural pathways with contributions from endocrine, paracrine and immune systems.[5]

The ICCS has introduced many individually recognizable conditions that can be grouped under the broad term, functional lower urinary tract disorders. However, it is understood that there is considerable overlap between conditions and this classification system is not entirely evidence-based. These conditions include BBD, overactive bladder, voiding postponement, underactive bladder, dysfunctional voiding, bladder outlet obstruction, stress incontinence, vaginal reflux, giggle incontinence, extraordinary daytime-only urinary frequency and primary bladder neck dysfunction.[4]

Van Batavia *et al.*,[6] based on clinical and non-invasive urodynamic evaluation, classified children with functional LUT disorders into four distinct conditions. They are (1) dysfunctional voiding (DV) – condition characterized by clinically evident irritative LUT symptoms associated with active pelvic floor during voiding, (2) idiopathic detrusor overactivity disorder (IDOD) – urgency associated with a quiet pelvic floor during voiding with a reduced (<2 s) EMG lag time (IDOD-A) or normal (2–6 s) EMG lag time (IDOD-B), (3) detrusor underutilization disorder (DUD) – consistently high voided volumes in excess of EBC due to wilful deferred voiding and (4) primary bladder neck dysfunction (PBND) – presenting with hesitancy associated with a long EMG lag time with a quiet pelvic floor during voiding.[7,8]

These proposed definitions are selectively useful and lead to a robust academic discourse. However, in our experience, it appears that a significant percentage of children have overlapping features of more than one specific pattern of LUT dysfunction.

## Diagnosis

The diagnosis of functional lower urinary tract disorders in children and categorization of them into different conditions is based on clinical history, examination, bladder diary, bladder ultrasonography and non-invasive urodynamic studies such as uroflowmetry with pelvic EMG.[9] The initial diagnosis, assessment of severity and response to treatment of LUT disorders are heavily dependent on parental reporting of symptoms, and therefore reporting and recall bias are significant concerns when evaluating data published on LUT disorders in children.[10] These limitations must be remembered while dealing with refractory cases.

In select cases, additional investigations such as micturating cystourethrogram (MCUG), MRI spine and invasive urodynamic studies would be indicated. The details are beyond the scope of this manuscript.

During the process of developing reliable, non-invasive tests for the diagnosis of LUTD, the role of urine biomarkers has been increasingly highlighted in recent literature. Nerve growth factor (NGF) and brain-derived neurotrophic factor are

urine biomarkers that are expected to increase in urine in patients with overactive bladder (OAB).[11] A growing number of evidence has confirmed a positive correlation between elevated NGF levels in adults with OAB.[12] Therefore, its utility as an initial diagnostic tool and to monitor response to treatment has been explored. A meta-analysis of published literature in children recommended NGF normalized to urine creatinine ratio (NGF/Cr) as a potential biomarker for the diagnosis and evaluation of children with OAB.[13] However, more robust data from large-scale studies may be required before adopting urine biomarkers into the diagnostic armamentarium for children.

## Treatment

### *Principles of therapy*

- Careful history and objective tests to establish a rigorous most probable diagnosis (a large proportion of children may have features of more than one condition)
- Urotherapy-based initial treatment
- Reassessment after urotherapy and re-test if necessary to re-establish diagnosis
- Specific treatments including pharmacotherapy, neuromodulation or other invasive therapies as indicated after a risk/benefit analysis

### *Standard urotherapy*

First-line therapy in children with functional lower urinary tract disorders is aimed at improving their voiding habits using urotherapy. Urotherapy is defined as a conservative-based therapy of LUT dysfunction that aims to rehabilitate the LUT. It is broadly categorized into standard urotherapy and specific urotherapy. The ICCS recommends standard urotherapy (SU) as the first-line treatment for most functional lower urinary tract disorders in children.[14] It involves patient education and lifestyle modifications to regulate fluid intake, optimize voiding patterns, and avoid constipation and bladder irritants.[15] The efficacy of SU depends on several factors such as patient compliance and motivation and also varies between different types of LUT disorder. In children with daytime urinary incontinence, this has shown to be effective in 56% while a 40% cure rate has been achieved in children with voiding postponement.[9,16] To improve compliance, especially among adolescents, a smartphone app (URApp) has been recently tested with promising results.[17]

Specific urotherapy in the form of alarm therapy, biofeedback and neuromodulation involves a multidisciplinary team approach and is only recommended in specific types of functional lower urinary tract disorders that are refractory to SU.[14] These are discussed in later sections.

### *Biofeedback therapy*

*Mechanism of action.* Biofeedback therapy (BF) works by increasing the awareness of children in the lower urinary tract to prevent involuntary contractions of the pelvic floor during voiding. It is aimed at teaching appropriate micturition and defecation habits to retrain pelvic musculature and bladder–brain connection.

*Indications.* It is a well-established, non-invasive treatment method for children with DV which is defined as intermittent contractions of the periurethral striated or levator ani muscles during voiding in neurologically normal children.[4] It is also proven effective in children with combined BBD.

*Efficacy.* In children with DV, it helps achieve symptom resolution in 60–80%.[18]

*New developments.* Despite being used in the treatment of patients with LUTD since the 1990s, the treatment duration, frequency and indications for maintenance therapy remain largely unknown. Das *et al.*[19] reviewed 490 children undergoing biofeedback therapy for LUTD and concluded that the maximum beneficial effect is achieved by about 3 months in the majority and in some patients, it may take about 9 months of therapy. A study conducted by Donmez *et al.* demonstrated the value of maintenance BF sessions for children with DV who relapsed following successful treatment with BF. The authors recommend surveillance of children with higher symptom scores after initial successful BF sessions, to identify those who are at risk of recurrence.[18]

Recently, the positive effects of combining a game-based core exercise programme with standard BF have been shown to improve the outcomes of children with functional LUTD.[20]

### *Alarm therapy*

*Mechanism of action.* It works by giving feedback once a wetting episode has occurred or by notifying the child at set intervals prompting them to go to the toilet at regular intervals.

*Indications.* Alarm therapy is a widely used adjunct in urotherapy which is well established in the management of children with nocturnal enuresis.[21] However, its beneficial effects on children with daytime urinary incontinence (DUI) are currently being evaluated.

*Efficacy.* A meta-analysis by de Wall *et al.*[22] reported an overall continence rate of 48% following alarm therapy; however, varied treatment adherence rate between 10% and 90% was identified as a potential issue by the authors.

*New developments.* The existing types of alarms do not achieve the desired objective of teaching the child to interpret bladder sensations that precede the wetting incident. In view of overcoming these limitations, a new wearable bladder sensor, the SENS-U was introduced recently. This is a small, ultrasonic sensor, which continuously monitors bladder filling and notifies the child when it is time to void. This can be customized based on the child's bladder capacity and functional voiding capacity to send an alarm at a specific percentage of bladder filling. Over time, the SENS-U is predicted to increase the child's awareness of the sensation of a full bladder.[23–25] A randomized controlled trial is currently underway to evaluate the efficacy of SENS-U in children with DUI.[26]

### *Electrical neural stimulation (neuromodulation) of the lower urinary tract*

Electrical neural stimulation for LUTD can be performed with surface electrodes (transcutaneous electrical nerve stimulation), needle electrodes (percutaneous electrical nerve stimulation) or implantable devices (sacral neuromodulation). In transcutaneous electrical nerve stimulation (TENS), surface electrodes are placed over the third sacral foramen in the back (parasacral TENS) or posterior tibial nerve at the ankle. In the percutaneous method, instead of surface electrodes, needle electrodes are used at these sites.[14]

*Mechanism of action.* The exact mechanism of action of neural stimulation on the human LUT is unclear. In sacral neuromodulation, there is evidence to suggest stimulation of afferent sensory fibres modulating voiding and continence reflex pathways in the central nervous system (CNS). With regard to TENS, reduced neuronal metabolic activity of the spinal cord innervating the detrusor has been hypothesized and a supraspinal effect has also been proposed.[27]

Parasacral TENS has been recommended as a treatment option for children with OAB refractory to SU. An international, multicentre, prospective study demonstrated its efficacy in reducing OAB-related symptoms and improving the quality of life in up to 73% of patients.[28,29] Combined with urotherapy, this has proven effective in symptom reduction in 67% of children with OAB who failed initial treatment.[9]

Transcutaneous posterior tibial nerve stimulation (TPTNS) is another non-invasive treatment method that is proven effective in children with functional LUT disorders. Evaluated in a cohort of 44 children with LUT disorders, Jafarov *et al.*[30] found that it significantly improves frequency, episodes of incontinence, voiding scores and QOL scores.

Percutaneous posterior tibial nerve stimulation (PPTNS) is a minimally invasive technique that involves placing a needle at the medial malleolus of the ankle. De Wall *et al.*[31] reported a 42% improvement in therapy-resistant children with LUT disorders. A study to compare the tolerability and efficacy of PPTNS with TPTNS in children has been proposed as the second part of a double-blinded randomized controlled study.[32]

Peroneal electrical transcutaneous neuromodulation (peroneal eTNM) using the URIS® neuromodulation system is proposed as a novel therapy that works on the principle of selective stimulation of the peroneal nerve. It is a non-invasive, highly selective method of nerve stimulation that has proven efficacy in adults with refractory OAB symptoms. It has also been evaluated as a mode of home treatment in patients with OAB and has demonstrated about 80% symptom resolution.[33,34] It has not yet been tested in the paediatric population.

*Sacral neuromodulation.* Even though sacral neuromodulation using implantable devices has been used in children since the early 2000s, there is a paucity of studies in the literature. The invasiveness of the technique and device-related complications requiring reoperation may be some of the reasons for its low popularity among this patient population. Recently, Boswell *et al.* published results of one of the largest paediatric series involving 187 paediatric patients with refractory BBD who underwent sacral neuromodulation using the implantable sacral device. After a median follow-up of 3.9 years, 74% of the

children have reported symptom improvement with 24% opting for device removal either for significant improvement or complete resolution of symptoms. On the other hand, 68% of the patients required reoperation under another anaesthetic restricting its utility.[35]

## Pharmacological treatment

Pharmacotherapy of paediatric LUT dysfunction is guided by the understanding of the autonomic receptors in the urinary tract.

Most classes of drugs are aimed at treating children with OAB. According to the ICCS definition, OAB is defined by the presence of urgency. Even though it is presumed to be associated with detrusor overactivity, no urodynamic proof is required to make the above diagnosis.[4] On the other hand, the symptom of urgency could be associated with several LUT disorders. Van Batavia *et al.* identified urgency as a symptom of all four EMG-defined LUT conditions including detrusor underutilization and primary bladder neck dysfunction. In their study, only 62% of children with urgency fulfilled the criteria for a diagnosis of OAB, whereas 23% had alternative diagnoses.[6] Therefore, we recommend confirming the diagnosis of OAB prior to starting pharmacotherapy.

### *Antimuscarinics*

The exact pathophysiology of OAB is not yet fully understood; however, both myogenic and neurogenic aetiologies are postulated. The mainstay of pharmacotherapy of OAB in children is anticholinergic therapy using antimuscarinic agents. They act by inhibiting the binding of acetylcholine to the muscarinic receptors $M_2$ and $M_3$ on the detrusor smooth muscle cells, thereby preventing muscular contraction.[36]

On the other hand, recent evidence suggests that symptoms of OAB such as urgency are caused by a sensory issue. It is also demonstrated that antimuscarinics have a better affinity on the afferent (sensory) limb of the reflex arc compared to the efferent (motor) limb.[37,38] Therapeutic approaches that selectively target the afferent limb of the micturition cycle would be the mainstay of treatment, in the future.

At present, there are seven antimuscarinic agents marketed for use in adults with OAB: oxybutynin, tolterodine, solifenacin, trospium, darifenacin, propiverine and fesoterodine.

In 2019, a Cochrane database review evaluated various types of treatment methods used in functional DUI in children. According to the review, there was no conclusive evidence demonstrating the efficacy of anticholinergics over measures such as pelvic floor muscle training, biofeedback therapy or electrical nerve stimulation in the treatment of DUI.[39]

### *Oxybutynin*

Oxybutynin chloride is a nonselective tertiary amine with antimuscarinic properties which was approved for the use of children in the early 2000s.[40] It is the most prescribed antimuscarinic agent and is available for administration *via* the oral, transdermal and intravesical routes. Despite being used in children for many years, it has not been tested in a randomized controlled trial against a placebo.[9] The oral preparation is available in the form of immediate release (IR) and extended release (ER) types.

IR oxybutynin which is available as a 5-mg tablet and 1 mg/ml suspension is recommended at a dosage of 0.3–0.6 mg/kg/day with a maximum daily dose of 15 mg. Considering the recommended dosage frequency of 2–3/day and also the side-effect profile, other formulations such as the ER type of oxybutynin have been introduced.[40] ER oxybutynin only requires once-daily administration and appears to have fewer side effects in children, even though the data are conflicting. Additionally, the ER preparation is shown to be superior to the IR form in terms of reducing the number of episodes of urinary incontinence and increasing the voided volumes.[41,42] The unavailability of a suspension form of ER oxybutynin limits its use in children.

The oxybutynin transdermal delivery system (TDDS) has been developed as a more attractive alternative to overcome the shortcomings inherent to the oral route such as low bioavailability and bothersome side effects. The transdermal patch was the first TDDS to be introduced into the market. In adults, it has shown equal efficacy to the IR preparation with the advantage of less incidence of dry mouth.[43,44] In children, data regarding its safety and efficacy are limited to only one study conducted by Gleason *et al.* which demonstrated 96% improvement in OAB symptoms as well as a significant increase in bladder

capacity of the participants. However, adverse skin reactions ranging from local erythema, pruritus to severe skin irritation could be bothersome side effects of this formulation which was reported in 35% of children in this study.[45]

The efficacy and safety of oxybutynin transdermal/topical gel were evaluated by two randomized, double-blind, placebo-controlled multicentre studies involving a total of 1415 adult patients with OAB symptoms. They showed a significant reduction in symptoms with no reports of severe adverse events.[46,47] However, high drug content and large amounts of ethanol were applied to enhance skin permeation which leads to a relatively low bioavailability.[48] So far, there are no data available for its use in children.

Nanosuspension is an emerging technology which is proven effective in the enhancement of transdermal permeation. Recently, this technology was used to construct oxybutynin nanosuspension gel (OXY-NG) and Sheng *et al.*[48] demonstrated a fourfold skin permeation of oxybutynin both *in vitro* and *in vivo* using mice. This is yet to be tested in humans; however, OXY-NG appears a promising method of TDDS in patients with OAB.

Intravesical instillation of oxybutynin *via* a bladder catheter is effective and safe in the long term in both children and adults with neurogenic detrusor overactivity.[49,50] Its role in children with non-neurogenic OAB is unknown.

### *Tolterodine*

Tolterodine was released in the United States and Europe in 1998 with the expectation of increased efficacy combined with better tolerability.[51] In comparison to oxybutynin, tolterodine is better tolerated among children due to a lower incidence of adverse effects, especially dry mouth. With regard to its efficacy as an antimuscarinic agent, the evidence seems to be conflicting. In a study conducted by Reinberg *et al.* involving 132 children with urinary incontinence, the efficacy of ER oxybutynin was compared with both IR and long-acting forms of tolterodine. The authors concluded that ER oxybutynin is superior in efficacy to both types of tolterodine.[52] However, a review conducted by Medhi *et al.* in 2013 concluded that tolterodine has comparable efficacy to oxybutynin.[53]

### *Trospium*

Trospium is an anticholinergic with the added advantage of being less lipophilic, thereby having less CNS side effects due to its inability to cross the blood–brain barrier.[51] Two studies published in 1998 and 2003 regarding its use in children with OAB showed promising results; however, no recent data are available on the paediatric population. The need for it to be taken on an empty stomach, 1 h before a meal, is a likely deterrent to its popularity among children.[40]

### *Darifenacin*

Darifenacin is a novel antimuscarinic drug that is highly specific for the $M_3$ muscarinic receptor, thereby selectively acting on the bladder smooth muscle. There are large-scale data available on its safety and efficacy in adults with OAB; however, there are no published data on the paediatric population.[40]

### *Solifenacin*

Solifenacin is a selective $M_3$ receptor antagonist with great bioavailability and long half-life with limited data on children with non-neurogenic OAB. Based on available data on children, an overall symptom reduction of 85–94% was demonstrated in most studies.[54,55] A recent systematic review by Raman *et al.* on the safety and tolerability of solifenacin demonstrated a lower incidence of side effects compared to oxybutynin and recommended it as an alternative anticholinergic for children with OAB. However, considering the quality of data available, the authors recommend a cautious approach to its use in children and close monitoring for potential adverse effects.[56]

### *Fesoterodine*

Fesoterodine is a prodrug that is structurally and functionally related to tolterodine. There are two published trials involving a total of 93 children with OAB which demonstrated significant improvement of their symptoms following treatment with fesoterodine with no reports of serious side effects.[57,58] On the other hand, a randomized, crossover trial comparing the efficacy of fesoterodine and oxybutynin failed to demonstrate any significant difference in the efficacy between the two drugs.[58]

### *Propiverine*

In 2017, propiverine was approved in Canada for the treatment of OAB in children. In a multicentre, observational, cohort study published in 2010, the efficacy and safety of propiverine were compared to oxybutynin, and similar efficacy and better tolerability were reported among children using propiverine.[59] Furthermore, a shorter duration of treatment was required to achieve continence with propiverine. A retrospective study by Lapointe *et al.*[60] highlighting the North American experience demonstrated a significant increase in mean bladder capacity with a rate of increase of EBC of 0.5% per month.

### *DA-8010*

DA-8010 is a novel $M_3$ receptor antagonist which has shown a very high affinity to bladder smooth muscle cells, *in vivo* studies.[61] Data of the first-in-human phase I study have been published recently showing promising results on safety, tolerability and pharmacokinetics.[62]

## β3-agonists

### *Mirabegron*

In 2012, mirabegron was introduced as the first beta-3 agonist for the treatment of OAB. It stimulates the β3-adrenoceptors resulting in relaxation of the detrusor and improving bladder compliance and capacity without impacting voiding pressure or post-void residual volume.[40] The safety and efficacy of mirabegron in children were shown in a systematic review by Kim *et al.*[63] where it was declared a safe adjunct/alternative treatment in the management of paediatric OAB. They also demonstrated an excellent side-effect profile with headache, constipation and nasopharyngitis being the most commonly reported.

### *Vibegron*

Vibegron is the most recent β3-agonist developed for the treatment of OAB. To date, there are minimal data about its use in children. Hyuga *et al.*[64] published results of a study involving 57 children with daytime urinary incontinence (DUI) and concluded vibegron as an effective drug which showed its efficacy within a short period of time. In the future, it can be anticipated to play a significant role in the treatment of urinary incontinence in children.

### *Combination therapy*

In adults with refractory OAB, combination therapy of mirabegron and a low-dose antimuscarinic is shown to improve treatment efficacy without the addition of bothersome side effects that may typically follow high-dose monotherapy.[65] Similar results were demonstrated in the first off-label study in the paediatric population, using add-on mirabegron.[66]

### *Alpha blockers*

Alpha-adrenergic receptors are mostly concentrated in the bladder neck and along the human urethra (Figure 1).[67] While stimulation of these receptors causes smooth muscle contraction and bladder outflow obstruction, blockade reverses these effects. Alpha blockers have an established role in the management of children with primary bladder neck dysfunction (PBND) and dysfunctional voiding (DV).[68,69] Some authors have claimed to use alpha-adrenergic blockers in the management of children with OAB either alone or in combination with antimuscarinics.[70] These patients may have OAB symptoms in the background of PBND or DV. Additionally, the authors entertain the possibility of a central action for alpha blockers that extends beyond the action on the bladder neck in alleviating OAB symptoms.[71]

Since the first description of the use of alpha-adrenergic blockers in children with DV by Austin *et al.* in 1999, they have been recognized as an integral part of the armamentarium of drugs for children with functional lower urinary tract disorders.[72] The alpha blocker, doxazocin was compared with biofeedback therapy by Yucel *et al.*[73] and showed a greater parental satisfaction rate in the medication group. They also recommended combination therapy with alpha blockers and biofeedback therapy in resistant cases of DV. However, more robust data from large-scale, multicentred, randomized trials are required for the wider acceptance of this class of drugs in the paediatric population with LUTD.

### *Botulinum toxin*

*Mechanism of action.* Botulinum toxin A (BoNT-A) is a potent neurotoxin produced by the Gram-negative bacillus *Clostridium Botulinum* which predominantly acts by inhibiting the release of acetylcholine at the presynaptic neuromuscular junction of the peripheral nerve endings. Thus, it interferes with efferent nerve impulses resulting in

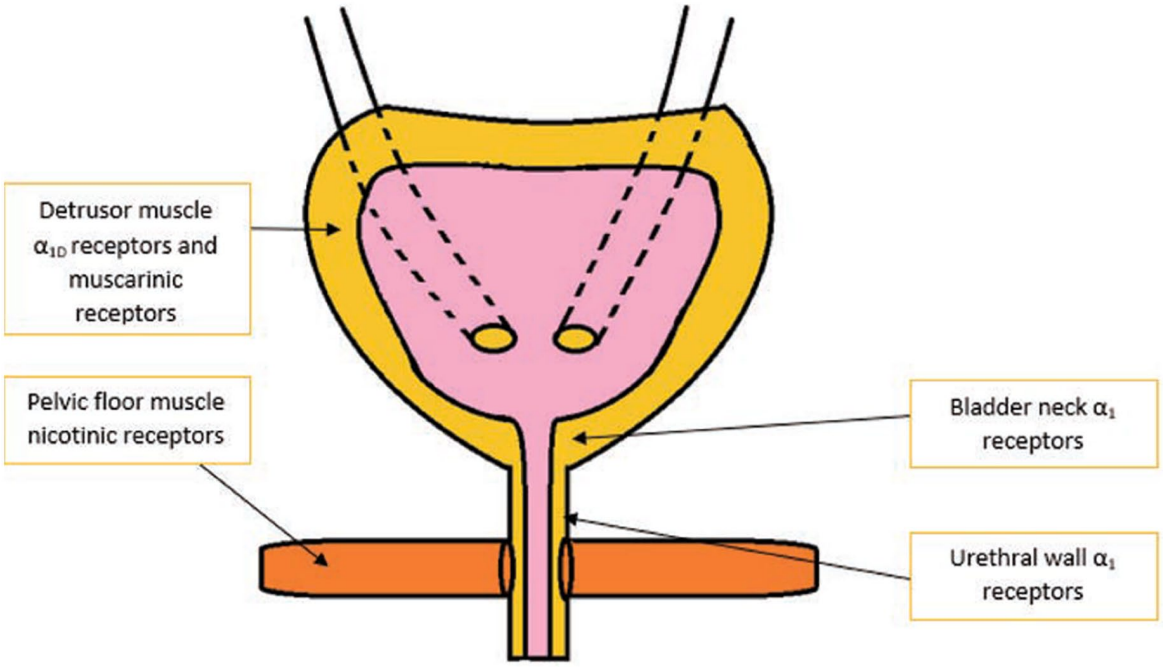


**Figure 1.** Distribution of alpha receptors within the lower urinary tract. Alpha blockers acting predominantly on the bladder neck cause improvement of symptoms in PBND. Non-selective alpha blockers acting on the $\alpha_{1D}$ receptors in detrusor smooth muscle can have a minor detrusor relaxing effect.
PBND, primary bladder neck dysfunction.

flaccid, but reversible, paralysis of the detrusor muscle. In addition to this, there is evidence to support that BoNT-A also acts on the bladder sensory (afferent) pathways by reducing the expression of sensory receptors in the suburothelial nerves.[74]

*Indications.* To date, the commercial preparations of botulinum toxin A are licensed for use in adults with OAB and neurogenic detrusor overactivity.[75] Its role in the management of children with functional LUT disorders is evolving.

*Efficacy.* The efficacy and safety of intradetrusor injection of botulinum toxin in children with neurogenic OAB and DO have been established.[76] Evidence supporting its utility in children with non-neurogenic LUTD is limited. Hoebeke *et al.* demonstrated excellent results after using botulinum toxin in a cohort of 21 children with therapy-resistant, non-neurogenic detrusor overactivity.[77] Greer *et al.* published results of 15 children with non-neurogenic OAB who had intravesical BoNT-A injection and reported >90% symptom resolution in all patients with a median response time of 6 months.[78] Lambregts *et al.* retrospectively evaluated the results of 50 children with refractory non-neurogenic OAB who underwent intravesical BoNT-A injection and demonstrated improved urinary incontinence up to 72% in the short term.[79]

Considering its mode of action, it is likely to be effective in relaxing the external urethral sphincter in patients with DV and this has been proven in adults.[80] The results in the paediatric population have been variable so far, with 't Hoen *et al.* demonstrating 90% efficacy of intrasphincteric BoNT-A injection in children with DV and Greer *et al.* reporting 45% complete symptoms resolution.[78,81]

Many aspects of the technique of injection are not standardized, so far. In children, BoNT-A is typically injected with cystoscopic guidance under general anaesthesia. Considering the invasiveness, a novel, less invasive method of administering the drug without anaesthesia would be a very attractive option in children. Electromotive administration of BoNT-A appears to be a promising technique; however, the results are limited to preliminary evidence.[82]

In children, the optimal dosage and frequency of administration are yet to be determined. Traditionally, in children with detrusor overactivity, a

single dose of 100–300 IU (max: 10–12 units/kg) has been used based on adult data.[83] In DV, a single dose of 100 IU is recommended for intrasphincteric injection.[84]

There is debate about whether to spare the trigone during injection or not. In OAB, the preferred site of injection of BoNT-A is supra trigonally, into the detrusor. However, it is known that the majority of autonomic innervation of the bladder is below the ureteric orifices within the trigone; therefore, consideration of changing the injection site might have lasting effects in refractory cases.[85]

## Special situations

### *Management of underactive bladder*

Underactive bladder and its current treatment options deserve special mentioning since it is a poorly understood condition that is extremely difficult to manage. There is a lack of understanding about its aetiology and pathophysiology in both adults and children. Children with underactive bladder seem to differ from children with voiding postponement who have normal urodynamic parameters and respond well to SU.[86] They usually present with low voiding frequency. However, it is not uncommon for them to present with increased frequency due to incomplete emptying of the bladder with prompt refilling. Unless carefully evaluated, mislabelling these children as having overactive bladder could lead to a worsening of the condition since most of the anticholinergics prescribed for OAB symptoms may cause detrusor underactivity as an adverse effect.

Treatment starts with the elimination of anatomical causes of bladder outlet obstruction. Patients with bladder neck dysfunction may respond well to alpha blockers. It works by relieving the resistance at the bladder neck thereby, allowing the weakened detrusor to empty better.

In cases where the obstruction is at the external urethral sphincter, treatment of constipation, biofeedback therapy and injection of botulinum toxin are all acceptable treatment methods.

Improving the detrusor contractility using medications has been challenging. The use of tegaserod, a serotonin agonist which was used to treat constipation, led to a marked reduction in post void residue volume and OAB symptoms in some patients. Prucalopride which is a selective serotonin (5-HT4) receptor agonist also appears to improve bladder emptying in select patients.

### *Management of DUI in toilet-trained children with vesicoureteric reflux*

The exact role of functional LUTD in non-resolving vesicoureteric reflux and/or daytime lower urinary tract symptoms has long been suspected and discussed.[87] Studies offering antimuscarinics and alpha blockers have been reported.[88] The efficacy of pharmacotherapy in these small studies ranges between 45% and 82%.[89,72] Such treatment strategies are often a supplement to urotherapy and surgical interventions. High-quality studies discussing pre-emptive management of LUT dysfunction in children with VUR are indicated. Analysis of data of children with daytime LUT symptoms and VUR at our institute demonstrated urodynamic abnormalities suggestive of LUT dysfunction in 63% (unpublished personal data).

### *Management of DUI in children with posterior urethral valves*

Bladder dysfunction is seen in a very high proportion of children born with posterior urethral valves. Detailed discussion is beyond the scope of this manuscript. Changing bladder behaviour at varying ages requires adaptive treatment plans.[90] Alpha blockers are being increasingly explored to improve bladder emptying especially in infants with bladder-neck hypertrophy and high PVRs.[91] The role of antimuscarinics is debatable.[92] Urodynamics-based therapy of bladder dysfunction should be incorporated in robustly developed algorithms to reduce bladder dysfunction, decrease chronic kidney disease risk, and improve quality of life.

### *Management of DUI in children with ADHD/ASD or other disorders*

This is a rapidly growing area of need in practice in paediatric urology. A large proportion of children with behavioural disorders develop DUI with/without other LUT symptoms. The detailed discussion has been captured in other manuscripts.[15,93,94] A multidisciplinary approach with participation by therapists, paediatricians and urologists may be required in some cases. The adequate management of the underlying behavioural disorder generally should take priority

alongside SU. The effect of psychoactive medications on the bladder needs to be studied further. Functional MRI-based understanding of the role of micturition centre physiology in these children is also an important future area of study.[95]

## Conclusion

Management of paediatric functional daytime LUT disorders is complex and may benefit from a combination of treatment modalities. Urotherapy and anticholinergics appear to be effective in the majority; however, non-responders warrant careful re-evaluation to characterize the specific type of LUTD to target appropriate treatment. Various novel therapies and adjuncts have been shown effective and range from smartphone apps, bladder alarms, neuromodulation systems and more effective drug delivery systems. Despite being effective, non-selective antimuscarinics are less favoured for long-term use in children due to the side-effect profile. Therefore, more selective anticholinergics, $ß_3$ agonists and combination treatment options are being evaluated to improve compliance while maintaining/enhancing treatment efficacy. The use of alpha blockers and intravesical injection of botulinum toxin has shown promising results, especially in refractory cases.

## Key learning points

1. Urotherapy is an effective first-line treatment for most children with functional LUT disorders (Table 1). Its efficacy is shown to be enhanced further by new adjuncts such as smartphone apps and wearable bladder sensor devices.
2. Neural stimulation of the LUT (neuromodulation) has a limited but perhaps a growing role in these children at present. Novel non-invasive, highly selective methods have been introduced recently which could have a significant impact on their outcome.
3. Pharmacotherapies involving anticholinergics, β agonists and alpha blockers continue to play a significant role in these children. Commencement of medication should only be done after careful consideration of the diagnosis, compliance, side-effect profile and response to other previous treatment modalities. Periodic re-evaluation is recommended to understand the optimum type/s, dose and combination of medication with the highest efficacy and tolerability for an individual child.
4. Intravesical and intrasphincteric injection of Botulinum toxin A has emerged as an important therapeutic modality in children.

**Table 1.** Summary of treatment modalities used in functional daytime LUT disorders in children.

| Treatment modality | Indication | limitations | New advances |
|---|---|---|---|
| Standard urotherapy | All types of LUTD | Poor compliance | Smartphone apps to improve compliance |
| Specific urotherapy | | | |
| Alarm therapy | Mainly for nocturnal enuresis. Currently being evaluated for daytime LUT disorders | Poor compliance | Wearable bladder sensor devices |
| Biofeedback | DV | Poor compliance | Combine with a game-based core exercise programme |
| Electrical neural stimulation | OAB | Invasiveness and complications | Peroneal eTNM (non-invasive, highly selective method) |
| Pharmacotherapy | | | |
| Antimuscarinics | OAB | Side effects | Oxybutynin nanosuspension gel |
| β3 agonists | OAB | Lack of long-term data | Vibegron |

*(Continued)*

**Table 1.** (Continued)

| Treatment modality | Indication | limitations | New advances |
|---|---|---|---|
| Alpha blockers | PBND<br>DV<br>OAB-type symptoms in other LUT disorders | Lack of long-term data | |
| Botulinum toxin | OAB<br>DV | Lack of long-term data<br>Invasiveness | Less invasive techniques of administration<br>Injection into external sphincter in DV |
| Serotonin agonists | Underactive bladder | Lack of long-term data | Prucalopride (selective 5-HT4 agonist) |

DV, dysfunctional voiding, eTNM, electrical transcutaneous neuromodulation, LUT, lower urinary tract, OAB, overactive bladder, PBND, primary bladder neck dysfunction.

## Declarations

### *Ethics approval and consent to participate*
Not applicable.

### *Consent for publication*
Not applicable.

### *Author contributions*
**Naveen Wijekoon:** Conceptualization; Writing – original draft.

**Aniruddh Deshpande:** Conceptualization; Supervision; Writing – review & editing.

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