Curr Bladder Dysfunct Rep
DOI 10.1007/s11884-016-0347-6

Current Treatment Options for Nonneurogenic Overactive Bladder in Children

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Abstract Nonneurogenic overactive bladder (OAB) is one of the most common types of voiding dysfunction in children. Treatment options vary, ranging from conservative behavioral management to medical therapy and even surgical intervention. Treatment, however, should progress in a step-wise manner with surgery reserved for those refractory to more conservative interventions. Urotherapy is an important first step with bowel management of value in patients with both urinary and bowel symptoms. In addition, biofeedback can be used to treat pelvic floor dysfunction. Anticholinergics are the mainstay of medical treatment. Neuromodulation is another means of controlling urinary symptoms and includes temporary patches or needles as well as surgically placed permanent leads. Botulinum toxin injections are another surgical option, albeit with concerns for only temporary response. Despite OAB being associated with significant morbidity for both patient and parent, various treatment options exist to address this all too commonly seen problem.

Keywords Pediatric · Nonneurogenic overactive bladder · Incontinence · Urgency · Anticholinergic · Neuromodulation

This article is part of the Topical Collection on *Overactive Bladder*

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Published online: 11 February 2016

Introduction

Nonneurogenic overactive bladder (OAB) is one of the most common types of voiding dysfunction in children [1]. It has a reported overall incidence of 16.6–17.8 % and prevalence of 0.2–9.0 % [2•, 3, 4]. It has been most recently defined by the International Children's Continence Society as daytime "urinary urgency, usually accompanied by frequency and nocturia, with or without urinary incontinence, in the absence of urinary tract infection or other obvious pathology" [5••]. On urodynamics (UDS), OAB is marked by involuntary detrusor contractions on filling cystometry, called detrusor overactivity (DO) [5••, 6]. Oftentimes, these contractions or sense of urgency are difficult to postpone, resulting in incontinence.

The impact of nonneurogenic OAB can be significant, causing both patient morbidity and family distress. Sensations of recurrent frequency and urgency can be noxious and disruptive to one's routine. Incontinence can negatively impact a child's self-esteem and their social and psychological development [7–9, 10••]. Certainly, from an anecdotal clinical experience, OAB can be distressing to both patient and family members witnessing the child's struggle with these symptoms. As a result, treatment options are essential to address this issue both in giving relief to the patient but also hope to the family.

Urotherapy

The first line of therapy for OAB is conservative management known as urotherapy [6]. Urotherapy refers to changing behaviors to try and control voiding symptoms, such as timed voiding, adjustments in fluid intake and diet, and the teaching of proper voiding body positions. It also includes managing

constipation and biofeedback therapy to retrain pelvic floor muscles [5••, 11, 12].

Timed Voiding, Diet Modification, Proper Voiding Body Positions

Techniques of timed voiding, diet modification, and proper body mechanisms can be quite effective. Timed voiding refers to voiding every 2–3 h on a schedule and is usually accompanied with double voiding or simply taking one's time voiding to ensure voiding to completion [12]. Outcomes of timed voiding are significantly improved by using a watch to maintain a schedule [13]. Proper body position means sitting relaxed on the toilet and spreading ones legs to prevent vaginal reflux in little girls and facilitate pelvic floor relaxation. Fluid intake can be adjusted to prevent concentrated urine acting as a bladder irritant and similarly diets can be adjusted to avoid known bladder irritants such as caffeine, highly acidic foods, and even some food dyes [11, 14, 15].

Historically, these maneuvers alone can result in continence in 45–74 % of patients with prior daytime urinary incontinence, although outcomes depend on patient compliance [16, 17]. One of the more recent studies on urotherapy evaluated the impact of a "voiding reeducation program" on urinary incontinence in 38 otherwise normal children. Nearly all (92 %) had DO on UDS. "Reeducation" consisted of timed voiding, voiding diary, instruction on drinking habits, biofeedback, and cognitive therapy. After 6 months of therapy, nearly all patients (92 %) had positive improvement in voiding symptoms, including 42 % who became completely dry and 24 % who had improvement from both day and night incontinence to incontinence only during the day or the night. DO on UDS improved in 37 % of children [18]. These same patients were reevaluated 2 years later in a follow-up study, showing continued improvement in OAB with improved DO on UDS in 82 % of children. There was a relapse of incontinence in eight of the 16 children initially dry at 6 months after treatment, suggesting the need for continued follow-up in this patient population [19•].

Bowel Treatment

It is well known that bowel and bladder function are often intertwined [20], with over 50 % of children with lower urinary tract symptoms having defecation disorders [21–23]. Given the proximity of the bowels and bladder in the pelvis, rectal distension by retained stool can cause mechanical compression of the bladder and thus bladder instability and may even compress and stimulate sacral reflexes initiating voiding. It is also possible that there is a common as of yet identified neuromuscular disorder linking bowel and bladder dysfunction [15, 24].

Treating bowel dysfunction has successfully treated OAB symptoms in several prior studies. Loening-Baucke et al. was one of the first to find that simply treating constipation improved urinary incontinence in up to 89 % of patients struggling with both symptoms [20]. Subsequent studies have similarly reported 70–77 % improvement in OAB symptoms simply by treating constipation [22].

Given these findings, one recent study investigated giving a laxative to all children with OAB regardless of constipation symptoms. In this study, patients with OAB symptoms were randomized to treatment with polyethylene glycol 3350 (PEG), a commonly used osmotic laxative, versus placebo. There was no significant difference in outcome between the groups but both placebo and PEG improved OAB symptoms in nearly 50 % of children after 1 month of treatment [25•].

Biofeedback

Biofeedback uses visual, auditory, or tactile clues to enable patients to identify their pelvic muscles and thus learn how to tighten or relax these muscles [14]. In doing so, patients can learn to abort an unwanted bladder spasm and/or relax their bladder outlet to prevent detrusor instability [1, 14, 26••]. Early studies of biofeedback report subjective cure of urinary symptoms in 51–84 % of patients with OAB or dysfunctional voiding (DV) [27–32], but without a good correlation between subjective improvement and objective measurements on UDS or uroflow [33]. More recent studies, however, have found significant improvement on uroflow such as in maximum flow rate (Qmax) ($p = 0.020$), average flow rate ($p = 0.026$), voiding time ($p = 0.001$), and post void residual (PVR) ($p = 0.005$). In OAB patients specifically, 41.2 % reported subjective cure while 47 % reported a nearly full or partial response [26••].

Another recent study evaluated an extreme biofeedback protocol composed of an inpatient training program. In this study, 70 patients with refractory urgency and urge incontinence were treated with 10 days of inpatient cognitive and biofeedback training. Patients were evaluated 6 months and 2 years after therapy. At 6 months, 42.9 % of children were symptom free with a reduction in symptoms in 31.4 %. At 2 years after treatment, 63.6 % of children still had good effect with 59.1 % objectively dry and 68.2 % with continued resolution of urge symptoms [2•]. While these results are encouraging, its feasibility and wide range applicability is questionable.

A recent meta-analysis evaluated all randomized controlled trials of biofeedback in treating lower urinary tract symptoms. It pooled the data of four studies totaling 382 participants and did not find biofeedback significantly impacted incontinence, Qmax, or rate of UTI. This study was limited, however, by heterogeneity between studies [34••]. The analysis highlights

the need for larger, better powered, randomized controlled trials to fully understand the utility of biofeedback in this patient population.

Pharmacologic Therapy

Anticholinergics

Anticholinergics have long been the gold standard medical treatment of OAB. Anticholinergics block muscarinic cholinergic receptors in the detrusor muscle, specifically M3, to prevent bladder contraction [8, 35, 36]. There are multiple types of anticholinergics currently available in the USA; however, only oxybutynin is FDA approved for use in children (children >5 years of age) [14].

The major drawback of anticholinergics is their propensity for side effects, limiting tolerability, and treatment adherence. Muscarinic cholinergic receptors occur in multiple locations in the body resulting in side effects such as constipation (18.5 % of patients), dry mouth (17.3 %), and flushing (13.6 %) [37].

Oxybutynin Chloride

Oxybutynin chloride is the oldest of the anticholinergics and the only anticholinergic FDA approved for use in children [14, 22, 36]. Oxybutynin has activity against M1, M2, and M3 receptors and has some activity as a calcium channel antagonist and bladder anesthetic [8, 38]. It has a relatively high side effect profile causing constipation, dry mouth, blurred vision, and heat intolerance [14, 39].

The therapeutic impact of oxybutynin in adult nonneurogenic OAB and pediatric neurogenic bladder overactivity is well known [40, 41]. Studies specifically evaluating the use of oxybutynin in pediatric nonneurogenic OAB, however, are limited. One of the only studies evaluating its use in this specific population reports curing incontinence in 38.3 % patients with another 54.4 % significantly or slightly improved. The only predictor of response was fewer initial wetting episodes [37]. These same authors found improved efficacy with the extended release (ER) form of oxybutynin as compared to regular oxybutynin, with improved continence in nearly half (48 %) of children treated with ER oxybutynin after failure of regular oxybutynin [42].

Recently, the European Bladder Dysfunction Study compared oxybutynin, placebo, and bladder training in 97 children with OAB symptoms. All children received standardized cognitive treatment to which interventions were randomly assigned. There was no difference in resolution of OAB symptoms between oxybutynin (43 %), placebo (39 %), and bladder training (44 %). Interestingly, only 33 % of patients with clinical OAB symptoms had correlating DO on UDS, suggesting a mismatch between objective data and clinical symptoms and perhaps explaining the equal efficacy of placebo and anticholinergic therapy in this study [43••].

Tolterodine Tartrate

Tolterodine tartrate is a nonselective anticholinergic that is often seen as a second line anticholinergic [36]. A complete response to nonneurogenic OAB symptoms has been reported in 60–80 % of patients refractory to or noncompliant with using oxybutynin, with a partial response noted in 37 % [44, 45]. Similar numbers have been reported when using tolterodine as a first-line treatment, resulting in a complete resolution of voiding symptoms in 63.6 % of patients and improvement in 31.8 % [46].

Historic studies have demonstrated a significant difference in efficacy between the formulations of tolterodine. In one study comparing the tolerability and efficacy of immediate release (IR) and long-acting (LA) tolterodine, they found that LA tolterodine was significantly more effective at resolving or improving daytime urinary incontinence in patients with OAB when compared to IR tolterodine ($p < 0.05$). Of note, this study also evaluated ER oxybutynin and found it to more effected than both IR and LA tolterodine for complete resolution or improvement of daytime incontinence ($p < 0.05$) and urinary frequency ($p < 0.01$). There was no significant difference in side effects between groups [47].

A more recent systemic review of the literature (including randomized and nonrandomized trials) comparing tolterodine to oxybutynin in pediatric OAB, however, came to a different conclusion. It found that tolterodine had comparable efficacy with oxybutynin but with better tolerability. It also found comparable efficacy between IR and LA tolterodine [10••].

Trospium Chloride, Solifenacin, Darifenacin

Trospium chloride, solifenacin, and darifenacin are newer anticholinergic agents, FDA approved for use in adults but still not approved for use in children. These medications are thought to be more bladder specific and thus with a more favorable side effect profile [36].

Trospium chloride is predominantly classified as an antispasmodic with some anticholinergic activity [48]. It is a nonselective quaternary amine and thus unable to cross the blood brain barrier, limiting potential central nervous system side effects [36]. There is only one study specifically evaluating trospium chloride use in pediatric patients. In this study, 58 children with OAB were randomly assigned to trospium chloride or placebo. 82 % of patients in the treatment group had a positive result (defined as excellent, good, or fair) compared to only 37.5 % treated with placebo ($p = 0.006$). There was a decrease in DO on UDS in 74 % of patients. Trospium chloride was well tolerated with side effects in only 10 % of patients [23].

Solifenacin is an M3- selective anticholinergic with early studies reporting cure of OAB-related incontinence in 45 % of children and improvement in 39 % [49, 50]. In an open-label study, 45 children who failed oxybutynin or tolterodine were treated with 1.25 to 10-mg solifenacin. With solifenacin treatment, there was a significant improvement in daily incontinent episodes from 3.0 to 0.3 ($p < 0.0001$). Side effects were reported in 27 % of patients [51]. This study was subsequently extended to include 191 patients with good subjective and objective response to solifenacin treatment. The overall success rate was 94 % with daily incontinent episodes improving from 2.8 to 0.5 and an improvement in Patient Perception of Bladder Condition scale score. Of note, 26 % of patients reported side effects with 16 % discontinuing treatment as a result [52•].

Darifenacin is an M3-selective anticholinergic with presumably an improved side effect profile due to its selectivity [53]. There are no studies evaluating its effect in the pediatric population.

Combination Treatment

Combination of anticholinergics with oxybutynin, tolterodine, or solifenacin has been evaluated to look for improved efficacy in the event of nonresponse to a single anticholinergic. This has been shown to provide continence to 40 % of patients initially refractory to a single agent and improve the mean number incontinent events a day from 3.5 to 0.5. Reported side effects, however, are high with 60–63 % of patients reporting constipation, headache, blurred vision, or dry mouth [54, 55].

Other Medications

Alpha-blockers are primarily indicated for primary bladder neck dysfunction or external sphincter dyssynergia. They may, however, have a role in OAB when used in combination with an anticholinergic [1].

Beta-3 adrenergic receptor agonist mirabegron is in phase 2 and 3 trials for treatment of OAB and has been shown to be efficacious and safe in adult patients thus far. It has not yet been evaluated in the pediatric population [56].

Surgical Therapy and Neuromodulation

Despite high rates of success with behavioral and medical management, up to 20 % of children with nonneurogenic OAB remain refractory to these more conservative measures [57••]. In addition, compliance with medical treatment can be poor, with adult studies demonstrating up to 25 % of patients discontinuing medication within 12 months [58]. Due to the success in the adult literature for emerging techniques such as use of botulinum toxin and neuromodulation, these treatments have emerged in treating the pediatric population with OAB. Surgical options are generally reserved for patients with OAB refractory to medical treatment [57••].

Botulinum Toxin

Botulinum toxin blocks muscle contractions by inhibiting the presynaptic neuromuscular release of acetylcholine [59•, 60•]. Blockage lasts approximately 3–6 months until new presynaptic nerves sprout. It is FDA approved for use in adults with OAB and thus has been similarly evaluated for use in children with OAB [1, 61, 62].

There have been multiple studies evaluating use of botulinum toxin in pediatric OAB demonstrating subjective improvement in OAB symptoms in 37–100 % of patients with complete resolution of urgency and incontinence in 37–75 % of patients [9, 59•, 60•, 62, 63]. Weekly incontinent episodes are cut by more than half (7.8 episodes to 3; $p = 0.004$) [59•]. Improvement on UDS has been reported with improved bladder compliance in up to 100 % of patients 1 year after injection [59•], but there have been mixed results on bladder capacity [62, 63]. Relatively good durability of 8–12 months has been reported in up to 70 % of patients after a single injection [62].

Botulinum toxin has some drawbacks, namely, its temporary effect and the need for repeated injections. Half of patients need a repeat procedure an average of 16 months after first injection [1, 63]. There are potential side effects, namely urinary retention with up to 45 % of patients requiring temporary intermittent self-catheterization. Other side effects include urinary tract infection, hematuria, vesicoureteral reflux, and allergic reaction [64–66]. There is also no clear pediatric data regarding dosage and injection placement [59•, 62].

Neuromodulation

Neuromodulation to control voiding was first described in the 1950s and 1960s [67]. The technique uses electrical stimulation to target sacral nerves involved in bladder control via one of several neuroanatomical pathways including directly at the S3 nerve root, via the pudendal nerve, and via the tibial nerve [68]. It can be given temporarily via patch or needle electrode or permanently via surgically placed lead [69, 70]. While its exact mechanism of action is unknown, neuromodulation likely works either centrally on the micturition centers in the brain or directly on the bladder by depolarizing afferent fibers and thus resetting inhibitory and excitatory impulses [57••, 71, 72].

Transcutaneous Electrical Nerve Stimulation (TENS)

TENS therapy was the first type of neuromodulation described in the pediatric population [69, 70]. It is a non-invasive, temporary form of neuromodulation. Electrical stimulation is achieved via patch electrode placed directly over the sacral

foramina at the level of the greater sciatic notch and about one finger breadth lateral to the midline spinous process to capture the S3 nerve root [70, 73]. Current treatment regimens include 20-minute sessions ranging from 1–2×/day to 3×/week.

Significant improvements in urge/frequency symptoms have been reported in 66.7–92.0 % of patients, with a complete response to treatment reported in up to 70.4 % of patients. There is improved continence in 73.3–81.3 % of patients with complete resolution of incontinence in 13–76 % of patients [73–75, 76•]. Its impact on uroflow parameters has been conflicted, historically, without any effect [1] but with more recent studies showing significant improvement on Qmax, bladder capacity, and PVR [76•]. Response to TENS appears durable with successful treatment documented in 73 % of patients up to 2 years after treatment with only 10 % having recurring symptoms after initially a full response [74].

There have been several randomized controlled trials of TENS. Lordelo et al. compared TENS treatment to sham controls (scapular stimulation) in 37 pediatric patients with OAB. They noted a significant resolution of symptoms in the TENS vs. sham group (61.9 % vs. 0 %, $p<0.001$) and a significant improvement in scores of success based on visual analog scale (VAS), a significant increase in the average and maximum voided volumes, and a decrease in urinary frequency [75]. In contrast, Sillen et al. did not find a significant difference in outcome between children with OAB randomized to standard urotherapy treatment and TENS + standard urotherapy. While both groups had improvement in continence, the groups were not significantly different ($p=0.303$). Patients felt nearly equally improved or symptom free (72 % vs. 80 %, respectively). TENS did appear to improve continence in patients who had never undergone prior treatment ($p=0.05$); however, overall, the authors felt TENS minimally added to standard therapy [77••].

Most recently, a randomized control trial compared oxybutynin to TENS for OAB, randomizing patients to TENS/placebo drug versus oxybutynin/sham scapular electrical therapy. There was no significant difference in complete resolution of symptoms between groups (46 % vs. 20 %, $p=0.204$). In the group treated with oxybutynin/sham stimulation, there was significant improvement in dysfunctional voiding symptom score (DVSS) and voiding diary records while constipation significantly improved only in the TENS/placebo group. There were significantly more side effects in the oxybutynin/sham group with no side effects reported in the TENS/placebo group. This study concluded that TENS was as effective as oxybutynin in treating OAB, but with fewer side effects and better activity against constipation [78••].

Posterior Tibial Nerve Stimulation (PTNS)

PTNS is another form of neuromodulation [57••, 68]. Stimulation can be via patch electrode or 34-gage stainless steel needle placed approximately 5 cm cephalad to the medial malleolus and posterior to the margin of the tibia. Sessions are generally 1–2×/week for 30 minute [1, 68, 79].

Older studies evaluating needle electrode PTNS in children with OAB report significant improvement in OAB symptoms in 61–80 % of patients (resolution in 25 %) and improvement in urinary incontinence in 56–69 % of patients. They also found significant improvement in bladder capacity. Chronic stimulation appears necessary; however, given only 41 % of those initially cured show a durable response 1 year later [80–82].

There have been two randomized controlled studies comparing PTNS via patch electrode to sham stimulation with conflicting outcomes. Boudaoud et al. randomized 20 children with OAB to PTNS or sham treatment. UDS parameters improved in the PTNS group, with an increase in bladder volume at first OAB contraction ($p=0.001$), an increase in voided volume at time of urgency ($p=0.002$), and an increase in maximum bladder capacity ($p=0.024$). Despite this, there was no significant difference in subjective symptoms based on a urinary score between groups ($p=0.65$). There was also a large placebo effect noted with 71 % of children in the sham group actually thinking they were being stimulated [83••]. In comparison, the only other randomized controlled trial found significant subjective improvement in OAB patients treated with PTNS as compared to sham patch electrodes. In the PTNS group, 66.7 % reported a full response to treatment as compared to no patients in the sham group ($p<0.0001$). Significantly, more patients were continent with PTNS (71.42 % vs. 12.5 %, $p<0.001$), with significant improvement in average voided volume, maximum voided volume, and number voids ($p<0.05$) [57••].

There has been one study to compare PTNS and TENS in the treatment of children with OAB. Using VAS and DVSS to determine outcome, they found a significant difference in the complete resolution of symptoms on VAS in TENS as compared to PTNS (70 % vs. 9 %; $p=0.02$), but with no difference in DVSS between groups [84••].

Sacral Nerve Stimulation (SNS)

SNS was FDA approved for use in adults with urge incontinence in 1997 and bladder overactivity in 1999. While it is not yet FDA approved for use in children younger than 16 years old, there are multiple reports documenting its safety and long-term efficacy [71, 85••]. In SNS, a permanent lead in the S3 foramen and an implantable pulse generator are placed surgically as part of a two-stage operation. With permanent placement, there is thought to be a more durable and consistent response than in other forms of neuromodulation [71].

SNS was first reportedly used in the pediatric population in 2006 by Humphreys et al. with an improvement in treating severe refractory dysfunctional elimination syndrome in 68 % of patients and resolution of incontinence in 16 % [86].

Similar success was observed by Groen et al. who reviewed their 15-year experience with SNS in children with OAB and Fowler syndrome and a mean follow-up of 28.8 months. Initially, 50 % of patients had a full response and 28 % had a partial response. There was a significant improvement in weekly incontinent episodes from 23.2 to 1.3 ($p < 0.05$). There was, however, a high reoperation rate with 50 % of patients needing surgical revision of their device, with subsequent complete response in 40 % of patients and partial response in 33 % [87]. Dwyer et al. similarly reviewed their 10-year experience with SNS finding that 94 % of patients at a mean follow-up of 2.72 years had subjective improvement in at least one of their symptoms of dysfunctional elimination syndrome. Of note, they similarly had a high reoperation rate of 56 % [88•].

Two studies have evaluated objective results of SNS on UDS, finding conflicting results. Haddad found that while more than 75 % of patients reported a positive subjective response to SNS, there was minimal improvement on UDS. Of note, the majority of patients included in this study had a neurologic lesion [89]. In contrast, a more recent study by Schober et al. did find a correlation between UDS findings and subjective improvement after SNS placement in children with OAB. They found significant improvement in voiding dysfunction scores based on validated questionnaire and that post treatment UDS showed a significant decrease in mean number uninhibited contractions ($p = 0.016$) and decrease in maximum detrusor pressure during filling ($p = 0.024$). There was a correlation between improvement on UDS and subjective improvement in 35 % of patients [85••].

In the only study to evaluate the impact of SNS on patient quality of life, Stephany et al. used validated pediatric questionnaires on quality of life (The PedsQL™ 4.0 Generic Core Scale) and bladder dysfunction. Of the 14 patients evaluated with a median follow-up of 6 months, there was significant improvement in mean psychosocial quality of life ($p = 0.02$), mean total quality of life ($p = 0.006$), and median voiding ($p < 0.001$) score after lead placement [90••].

Pudendal Nerve Stimulation (PNS)

The pudendal nerve is another potential route of neuromodulation, composed mainly of afferent sensory fibers originating from S1–S3 nerve roots. It can be accessed percutaneously via the ischiorectal space in a two-staged manner like SNS [91]. PNS has been previously described in the adult literature in patients who experience <50 % symptomatic improvement with SNS [68]. It can also be a potential treatment option in children lacking normal sacral anatomy precluding SNS placement.

The only published data on PNS in children evaluated outcomes in seven patients. Patients were treated for dysfunctional elimination syndrome and neurogenic bladder. In five of the children, PNS was performed after failed trial of SNS; in the other two, they underwent primary PNS. Three of the five patients who failed prior SNS had an initial full response with one going on to long-term failure. The other two patients undergoing PNS after failed SNS had a partial response with one ultimately failing. Of the two patients undergoing primary PNS, one had a full response while the other failed [87]. More studies in children are needed of this therapeutic option.

Conclusions

In conclusion, various treatment options for pediatric nonneurogenic OAB exist, ranging from conservative behavioral management to medical and electrical stimulation intervention to even surgical treatment. Treatment should progress in a step-wise manner with more invasive treatment reserved for those refractory to conservative measures.

Compliance with Ethical Standards

Conflict of Interest Dr. Ching declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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