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NEUROGENIC BLADDER (C POWELL, SECTION EDITOR)

Combination Therapy for Bladder Dysfunction in Patients with Neurogenic Detrusor Overactivity

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Abstract

Purpose of Review Neurogenic bladder is a common condition and top health priority present in 20–70% of patients with neurologic diseases including multiple sclerosis (MS), Parkinson's disease (PD), spinal cord injury (SCI), and cerebrovascular accidents (CVA). Current gold-standard medications for overactive bladder (OAB), such as anti-muscarinics, have undesirable side effects, or have limited data in neurogenic patients. Combining therapy for urinary urge incontinence (UUI) has shown the potential to increase efficacy while maintaining or improving tolerability of treatment. Our objective was to review and synthesize recent combination therapy studies for UUI in patients with neurogenic detrusor overactivity (NDO).

Recent Findings Non-pharmacologic and pharmacologic combination therapies have been investigated for UUI in patients with NDO. Adding intravaginal neuromuscular electrical stimulation (IVES) or transcutaneous tibial stimulation (TTNS) may not be superior to pelvic floor muscle training (PFMT) on its own. Recent studies on dual therapies have focused on combining drugs with different mechanisms. In adults, a combination of desmopressin with mirabegron showed superior efficacy compared to either drug alone or solifenacin. In children, combination studies have focused on adding gabapentin to drug regimens with promising safety and efficacy. Overall, there are few combination therapy trials for OAB in neurogenic patients compared to those in patients with idiopathic OAB.

Summary There is an unmet medical need for combination therapies in patients with UUI due to neurogenic bladder. It is important to gather practice patterns and encourage providers to share their experiences. In addition, more rigorous clinical studies are needed to explore new combinations.

Keywords Neurogenic bladder · Dual therapy · Combination therapy · Urge urinary incontinence · Mirabegron · Muscarinic antagonists

Introduction

Neurogenic bladder is a term that refers to an abnormal function of the lower urinary tract in patients with co-existing neurologic disease. Patients with a neurogenic bladder have symptoms related to neurogenic detrusor overactivity (NDO) including frequency, urgency, and urge urinary incontinence (UUI). NDO is a common condition present in 20–70% of patients with neurologic diseases including multiple sclerosis (MS), Parkinson's disease (PD), spinal cord injury (SCI), and cerebrovascular accidents (CVA) [1]. In patients with SCI, bladder function is often noted as a top health priority above motor function due to its detrimental impact on quality of life [2]. Additionally, neurogenic bladder dysfunction is associated with increased rates of urinary tract infections, hospitalization, and mortality risk in SCI patients [3].

Treatments available for neurogenic bladder include pharmacotherapies such as anti-muscarinics, alpha-blockers, and beta-3 adrenoreceptor agonists and assisted bladder drainage through catheterization, intravesical chemodenervation, neuromodulation, and surgical interventions as a last resort when less invasive therapies have failed. Anti-muscarinic

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medications are the mainstay of therapy and have been shown in randomized clinical trials to decrease maximum detrusor pressure, increase bladder capacity, and improve quality of life for these patients [4•]. These drugs, however, can cause undesirable side effects such as dry mouth, constipation, urinary retention, dizziness, and blurred vision that lead to problems with medication persistence and compliance [5]. Beta-3 agonists are a novel group of oral medications that have shown promise in patients with overactive bladder, but the majority of studies evaluating this medication is in patients with OAB of idiopathic origin and excludes those with neurogenic bladder [6, 7]. Failure of oral medications leads to third- and fourth-line therapies such as intravesical onabotulinumA toxin (Botox®), neuromodulation, and augmentation enterocystoplasty or urinary diversion.

Combining therapy for UUI has shown the potential to increase efficacy while maintaining or improving tolerability of treatment [8]. Multiple drug therapies have shown improved bladder compliance in patients with refractory, neurogenic bladder compared to single therapy [9•]. There exists a knowledge gap, however, on which combination of therapies is most efficacious in treating UUI in neurogenic bladder patients. Our objective was to review and synthesize recent combination therapy studies for UUI in patients with NDO. We hope this review will shed light on the current practices in combining treatments in this patient population and encourage new safety and efficacy studies on this topic.

Combination Therapies (Table 1)

Non-pharmacologic Treatments

Behavioral interventions are an important part of neurogenic bladder treatment and range from changes in diet and fluid intake to bladder training and pelvic floor muscle training (PFMT) [10]. Recent non-pharmacologic studies for improving symptoms associated with NDO have focused on combining pelvic floor muscle training (PFMT) with intravaginal electrical stimulation. One study evaluated the effect of intravaginal neuromuscular electrical stimulation (IVES) and transcutaneous tibial stimulation (TTNS) on lower urinary tract symptoms (LUTS) in women with MS undergoing pelvic floor muscle training (PFMT). Thirty women were randomly allocated to one of three treatment arms and followed for 12 weeks. Group 1 received PFMT with electromyographic (EMG) biofeedback and sham IVES, group 2 received PFMT with EMG biofeedback and IVES, and group 3 received PFMT with EMG biofeedback and TTNS. They reported baseline 24-h pad test, 3-day voiding diary, pelvic floor muscle function, urodynamic studies, and validated questionnaires for OAB using the Overactive Bladder Questionnaire (OAB-V8), International Consultation on Incontinence Questionnaire urinary incontinence short form (ICIQ-UI-SF), and the Qualiveen instrument. After 12 weeks, the study reported that all groups showed improvement in all outcomes, but subjects in group 2 with both IVES and TTNS with PFMT achieved significantly greater improvement in PFM assessment and OAB-V8 scores [11••].

Another study from Denmark reported an investigator-blinded, randomized clinical trial to compare the effect of 12 weeks of PFMT alone and combined with IVES on urinary incontinence in adult women with incomplete SCI. The ICIQ-UI-SF and daily episodes of incontinence were recorded at baseline, 12 weeks, and 24 weeks. This study showed no difference between the treatment arms for either questionnaire score or incontinence episode. Only the PFMT group had statistically significant changes in ICIQ-UI-SF score, by − 2.5 points, and number of daily incontinence episodes reduced by 0.6 [12••].

Taken together, these studies confirm that PFMT offers some benefit to patients with NDO, but whether there is added benefit with IVES or TTNS remains unsettled. Further studies investigating PFMT with drug therapies would therefore be of great relevance.

Pharmacologic Combination Therapy in Adults

In 2009, Amend and colleagues published results on one of the first studies to investigate dual anti-muscarinic therapies in adults with NDO [13•]. The study found that while maintaining a high dose of initial oxybutynin, tolterodine, or trospium, adding an additional anticholinergic medication improved continence and urodynamic (UDS) parameters, while maintaining tolerability. However, this study did not include a true placebo arm and used study subjects as their own controls in comparing two dual therapy regimens.

The most recent study to investigate anti-muscarinics assessed oxybutynin and trospium in the treatment of NDO in SCI patients. The study reported on 231 patients with suprasacral SCI on clean intermittent catheterization (CIC) with at least one urinary leakage episode a day on monotherapy with oxybutynin or trospium, or no treatment. Those who were already on monotherapy were started on the other anticholinergic medication ($n = 97$). They reported that 30 (31%) of the patients on two anti-muscarinic agents reported an increase of dry mouth and constipation compared to monotherapy [14•]. The study did not differentiate outcomes between the monotherapy and dual therapy patients.

Desmopressin (DDAVP), a synthetic analogue of arginine vasopressin commonly used for managing nocturia and nocturnal polyuria [15], is another agent that was investigated as a dual therapy with mirabegron in adults with MS. This multi-treatment arm divided 60 patients into four groups of $n = 15$ each. For a 12-week treatment period, group A received solifenacin 10 mg/daily, group B received mirabegron

Table 1 Summary of studies published in the last 5 years on combination therapies in patients with neurogenic overactive bladder

Author	Journal	Year published	Population	Treatment	Outcome measures	Results
Hadiji et al.	Spinal Cord	2014	Patients with SCI with CIC	Oxybutynin 5 mg tid + trospium mg 20 bid	BCmax IDC @ BL, 1 month	No association found between mono- or dual therapy and changes BCmax and IDC
Dash et al.	J Ped Surg.	2016	Children, age 3–19, with Spina bifida	- Oxybutynin 5 mg bid + CIC - Gabapentin 20 mg/kg + CIC - Oxybutynin 5 mg bid + gabapentin 20 mg/kg + CIC	3-day bladder diary DVSS UDS parameters @ BL, 6 months, 1 year	Maximal improvement in DVSS in combo group at 1 year All groups showed improvement in UDS at 6 months and 1 year
Lúcio et al.	J Wound Ostomy Continence Nurs.	2016	Women with MS and LUTS	- PFMT + TTNS - PFMT + IVES - PFMT + TTNS + IVES	24-h pad test 3-day bladder diary parameters PFM function UDS parameters OAB-V8 score ICIQ-UI-SF score Qualiveen instrument @ BL, 12 weeks	All groups showed improvement in all outcomes PFMT + TTNS + IVES: greater improvement on PFM and OAB-V8
Zachariou et al.	Can J Urol.	2017	Adults with multiple sclerosis and NDO	- Solifenacin 10 mg - Mirabegron 50 mg - Desmopressin 120mcg - Mirabegron 50 + desmopressin 120	Number of micturition/24 h Mean volume per micturition Urgency episodes Mean number of UI episodes Presence of UTI @ BL, 3 months	Combo group with improvement in micturition/24 h, urgency episodes, and mean number of UI
Elmelund et al.	Int Urogynecol J	2018	Women with incomplete SCI with urinary incontinence	- PFMT - PFMT + IVES	ICIQ-UI-SF score OUP 3-day bladder diary parameters 24-h pad test ICIQ-OAB SCI-QoL PGI-I @ BL, 12 and 24 weeks	PFMT + IVES is not superior to PFMT alone in reducing UI

BCmax maximum bladder capacity, Involuntary detrusor contractions, *DVSS* dysfunctional voiding symptom score, *BL* baseline, *PFMT* pelvic floor muscle training, *PFM* pelvic floor muscle function, *UDS* urodynamic studies, *OAB-V8* Overactive Bladder Questionnaire, *ICIQ-UI-SF* International Consultation on Incontinence Questionnaire urinary incontinence short form, *OUP* opening urethral pressure, *ICIQ-OAB* International Consultation on Incontinence Questionnaire overactive bladder, *SCI-QoL* International SCI Quality of Life Basic Data Set, *PGI-I* Patient Global Impression of Improvement scale

50 mg/daily, group C received DDAVP 120 mcg/daily, and group D received miragebron 50 mg/daily and desmopression 120 mcg/daily. Group D achieved statistically significant improvement in median daily frequency, bladder volume, urgency episodes, incontinences episodes, pads used, and urinary tract infections with good safety and tolerability with only two patients discontinuing treatment due to modest treatment side effects [16••]. The patients in this study were not randomized, and those who discontinued treatment were not included in the final analysis.

In summary, studies of combination drug therapy for urinary incontinence in adult patients with NDO show both efficacy and tolerability, but these studies have study design issues. A true randomized controlled trial where monotherapy and placebo are compared head-to-head with a dual muscarinic regimen is missing. Additional drug-drug combination trials are also needed.

Pharmacological Combination Therapy in Children

A study in 2009 found that dual anticholinergic therapy in a pediatric population with both neurogenic and idiopathic OAB improved UDS and continence in all subjects, with mild to moderate side effects experienced in 64% [17•]. More recent studies, however, have focused on gabapentin as an add-on agent to anticholinergics.

Gabapentin, an anti-epileptic and neuropathic pain medication, has been shown to act on pathways associated with neurogenic overactivity [18]. It was first proposed as an add-on therapy for neurogenic bladder in 2013 by Ansari and colleagues in a pediatric population [19]. This cohort study assessed improvement in OAB symptoms and changes in urodynamic indices of 31 children, the majority of whom had spina bifida or other spinal cord lesions and continued to have lower urinary tract symptoms (LUTS) on conventional anticholinergic medications. Voided volumes, bladder capacity, and maximal detrusor contraction all improved significantly, and 3-day voiding diary showed improved symptoms in those who responded. Continence improved in over half of the patients (53%); however, 14 (47%) of the patients failed to respond to gabapentin.

A randomized controlled trial was conducted on the role of gabapentin and anticholinergic medications in managing neurogenic bladder in children after repair of spina bifida. A total of 44 children, ages 3–19, were randomized to oxybutynin (5 mg twice a day) and CIC, gabapentin (20 mg/kg per day) and CIC, or a combination of both with CIC. Clinical and urodynamic outcomes were assessed at 6 months and at 1 year after starting therapy. The patients in the combination arm showed the best response of the treatment groups. Symptom scores reported by the dysfunctional voiding symptom score (DVSS) increased by a mean of 6.6 points after 1 year, and the mean improvement in bladder capacity by 37% for the combination therapy group, significantly greater than in the other treatment groups. Surprisingly, gabapentin alone showed similar improvement to oxybutynin in continence grade and DVSS, although oxybutynin showed improved UDS parameters. Rates of adverse effects in the gabapentin only, oxybutynin only, and combination groups were 30%, 57%, and 46% respectively [20••].

Overall, gabapentin seems to be the most studied drug to be added to first-line anti-muscarinics to augment treatment for OAB in children with NDO. While gabapentin appears to be well tolerated, its efficacy in combination regimens will require further studies.

Discussion/Conclusion

There are few studies in the recent literature that assess the utility of dual therapy for the treatment of NDO, and high-level evidence studies are lacking. While the evidence is limited, the EAU guideline on neuro-urology does recommend combination anti-muscarinic therapy with a grade B recommendation [21]. There are no clear guidelines or recommendations for other combination therapies for NDO.

Providers must be cautious when prescribing dual anti-muscarinic therapy. Anticholinergic medications were found to be associated with a 50% increased odds of dementia in middle-age and elderly patients [22, 23]. In these studies, cumulative anticholinergic exposure was measured by total standard daily dose (TSDD), grouped into five categories: no use, 1 to 90, 91–365, 366 to 1095, or greater than 1095. There was a dose-dependent relationship between rising TSDD and odds of dementia. Special attention is needed for Parkinson's patients, who may already be on anticholinergic anti-Parkinson drugs (benztropine, orphenadrine, procyclidine, trihexyphenidyl). Another concern is constipation, one of the known side effects of anticholinergic medications. In patients with neurogenic bladder who also have neurogenic bowels, dual anti-muscarinic therapy may worsen their constipation significantly. Therefore, it may be safer to move away from combination anti-muscarinic therapy and investigate combinations of drugs with different mechanisms.

Since the majority of evidence on combination therapies for OAB and LUTS has been conducted in patients with idiopathic UUI, as a starting point, safety and tolerability can be extrapolated from this data. A recent systematic review on combination therapies for LUTS in the non-neurogenic patient-reported anti-muscarinics, beta-3 agonists, alpha-1 blockers, phosphodiesterase type 5 inhibitors, gabapentanoids, desmopressin, estrogen, progesterone, phentapropanolamine, and phytotherapy are among the agents that have been investigated in combination regimens with acceptable tolerability [24]. Whether or not these therapies would be efficacious in neurogenic bladder patients

needs further evaluation. According to the same review, the combination of beta-3 agonists with anti-muscarinics, specifically solifenacin, appears as the most promising in terms of efficacy, without significant increase in adverse events [24].

The beta-3 agonist, mirabegron, has recently been approved by the FDA for single-agent use, as well as in combination with solifenacin succinate. The SYNERGY trial, a phase 3 randomized controlled study that supported mirabegron's combination approval, showed enhanced efficacy of the dual-agent therapy compared to either monotherapies for reducing number of incontinence episodes per day. However, this study excluded patients with neurogenic bladder dysfunction from participating in the study, and therefore, these results cannot be used to draw conclusions on the efficacy in this population. There is no doubt that beta-3 agonists as monotherapy are promising for neurogenic bladder. A recent study showed that the majority of patients with Parkinson's disease with NDO, unresponsive to anticholinergics, responded to monotherapy with mirabegron [25]. Also, preclinical data in rats with bladder dysfunction secondary to SCI demonstrated that muscarinic receptor inhibition and beta-3 adrenoceptor stimulation increased bladder compliance and remodeling more effectively compared to monotherapy [26]. Therefore, further evaluation of beta-3 agonists such as mirabegron, and the newer vibegron and solabegron, which are currently in clinical trials, as part of a dual regimen in patients with NDO is needed.

A recent study of combination mirebegron and solifenacin in a pediatric population showed improvements in bladder capacity and incontinence, with 7/35 (20%) patients reporting mild to moderate side effects [27]. While this study was conducted in patients with idiopathic OAB, it proved that this combination could be tolerated in children.

One more area of investigation that we found was missing from the recent literature is combination therapy with intravesical botox (BTX) in NDO. Although the goal of BTX injections after anticholinergic failure is to discontinue the oral therapy altogether, observational studies have shown that this is not always the case. In a European experience of NDO patients treated with BTX injections, 45 out of 163 patients originally on oral anticholinergics could discontinue treatment completely, while the remaining 118 were able to reduce their anticholinergic dose to a level that reduced systemic side effects [28]. Another observational study that looked at oxybutynin use after BTX injection described an initial reduction in oxybutynin use after BTX treatment, but dose increases were seen throughout follow-up [29]. Therefore, a combination of BTX injection with reduced-dose therapy may be an acceptable option while preventing progression to more invasive fourth-line options, but more studies are needed to elucidate the optimal oral therapy for this combination.

While we reviewed a handful of studies on combination therapies to treat symptoms of NDO, these studies are not without their limitations. The majority were conducted in a relatively small number of patients. Additional studies, with larger sample sizes, are necessary to confirm or deny the conclusions drawn in the studies above. How frequently combination anticholinergics, or other combination therapies, are being used in clinical practice is also unclear due to the sparsity of published literature on this topic. We must gather practice patterns when it comes to combination therapy in NDO and encourage providers to share their experiences.

The major challenge of studying neurogenic UUI is that the patient population is quite heterogeneous, comprising individuals with various central nervous system diseases. Despite these challenges, improving the management of bladder function and reducing the progression to third- and fourth-line therapies is imperative in this patient population. Combination therapies have the potential to offer minimally invasive yet efficacious options for patients suffering with UUI due to NDO.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have 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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