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Salvage Combination Therapies for Refractory Overactive Bladder

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Abstract

Purpose of Review With a high prevalence of overactive bladder (OAB) worldwide and rising health care costs for patients who fail first-, second-, and third-line treatments, there is a growing need to explore novel strategies to address the most refractory cases of OAB. The concept of utilizing combination treatment regimens to maximize efficacy while minimizing morbidity and side effects, in a cost-effective manner, is discussed in this review article.

Recent Findings A literature review over the last 10 years was performed, focusing on therapies used in combination for OAB including behavioral therapy, pharmacologic therapy, neuromodulation, and botulinum toxin. A separate literature review specifically for augmentation cystoplasty was also undertaken. Such "salvage" treatments suggested in the literature include pharmacologic therapy in combination or with behavioral modification, various forms of neuromodulation with medication, alternative forms of neuromodulation, with or without prior botulinum toxin injections, and lastly, augmentation cystoplasty.

Summary In this review article, we outline combination therapies such as adding mirabegron to solifenacin, anticholinergic medication in addition to either behavioral therapy or various types of neuromodulation and using neuromodulation after failed botulinum toxin injections are efficacious treatment approaches and have shown to be superior to monotherapy for the treatment non-neurogenic refractory OAB. In the most severe cases of refractory OAB, augmentation cystoplasty remains an option that provides acceptable results in the appropriately selected patient.

Keywords Overactive bladder · Anticholinergics · Mirabegron · Salvage therapy · Neuromodulation · Augmentation cystoplasty

Introduction

Overactive bladder (OAB) is defined by the International Continence Society as urinary urgency, with or without urgency incontinence, usually associated with increased daytime frequency and nocturia, and in the absence of infection or other pathology. OAB affects approximately 33 million Americans with a prevalence of approximately 16% [1]. Age and female gender are associated with higher rates of OAB [1]. The overall financial burden of OAB is substantial, with an estimated annual national cost in the USA of $66 billion in 2007, with a projected cost in 2020 of $82.6 billion [2, 3]. These costs include therapies for patients trialing multiple treatment regimens in an attempt to obtain relief of their symptoms.

Per American Urological Association (AUA) guidelines, first-line therapies include behavioral modifications and pelvic floor physical therapy while oral antimuscarinic (AM) and β_3-agonist medications are considered second-line therapies [4••]. Patients should continue therapy for 8 to 12 weeks before reassessment and change in management strategy. Third-line therapies include intradetrusor onabotulinumtoxin A (BTX), percutaneous tibial nerve stimulation (PTNS). and sacral neuromodulation (SNM) [4••, 5••, 6].

Despite these options, some patients will fail these therapies, either individually or in combination. There are currently no guidelines for OAB symptoms that do not adequately respond to standard therapies; in addition, there is no consensus on the definition of refractory OAB. In regard to combination therapies, the AUA guidelines are vague and state, "…combination therapeutic approaches should be assembled methodically, with the addition of new therapies occurring only when the relative

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efficacy of the preceding therapy is known." [6] Definitions in the literature range from subjective failures, intolerable side effects, and inadequate symptom response to behavioral and pharmacologic therapy after a variable amount of time. [1, 7] Many studies reference patients as "refractory" if urgency urinary incontinence has failed behavioral therapies and shown lack of response or intolerance to at least 2 AM medications [8•, 9]. This review article will focus on combination treatment approaches for patients with non-neurogenic, refractory OAB.

Combination Pharmacologic Therapy

Although no guidelines for medical management currently exist, a common algorithm used by many clinicians treating OAB with oral medication is to switch to another AM if a patient fails an initial medication. It is not uncommon for patients to try more than two medications in the same class before moving on to other therapies. In addition, insurance coverage for third-line therapies is currently predicated on patients having tried conservative measures (behavioral therapy) and at least two medications before approval. However, in a retrospective chart review by Chancellor et al. of 620 patients, most reported experiencing 3.6, 3.3, and 3.4 urgency incontinence episodes/day with 1, 2, and ≥ 3 anticholinergics trialed. This study reported 80% of patients requested additional treatment for their OAB symptoms, irrespective of how many anticholinergics were attempted. This suggests that cycling multiple AMs is unlikely to provide additional benefit of symptomatic relief [8•].

Given that switching AMs appears of limited benefit, there has been recent interest in studying the role of combining a β_3-agonist with an AM. The only FDA-approved β_3-agonist on the market currently is mirabegron. In the Symphony trial, a total of 1306 patients were randomized to 12 weeks of treatment in 1 of 12 groups: 6 combination groups (solifenacin 2.5, 5, or 10 mg plus mirabegron 25 or 50 mg), 5 monotherapy groups (solifenacin 2.5, 5, or 10 mg, or mirabegron 25 or 50 mg), or placebo. Combination groups demonstrated significantly improved mean voided volume, reduced micturition frequency and urgency episodes compared with solifenacin 5 mg monotherapy. Constipation was the only dose-related adverse side effect when comparing monotherapy to combination therapy [10]. In another open-label phase IV study in Japan, mirabegron 25 mg daily was "added on" to patients already on solifenacin 2.5 or 5 mg and then could be increased to 50 mg after 8 weeks of treatment. Combination therapy improved OAB symptoms scores, number of micturition events per 24 h, and number of urgency and urgency incontinence episodes per 24 h for up to 16 weeks. When mirabegron was increased to 50 mg, further improvement was noted. Regarding side effects, there were no significant changes in post-void residual volume, pulse rate or blood pressure, and no episodes of urinary retention [11]. In another double-blinded phase 3 trial, the BESIDE trial, 2174 patients were randomized to combination mirabegron and solifenacin, or monotherapy with solifenacin 5 mg or solifenacin 10 mg. This trial revealed that the combination group showed significant improvements in incontinence episodes per 24 h and mean daily micturition episodes. Significantly more patients became dry with combination therapy (46.0%) versus solifenacin 5 mg (37.9%) and 10 mg (40.2%); the odds ratios versus solifenacin 5 and 10 mg were 1.47 (95% CI, 1.17–1.84) and 1.28 (95% CI, 1.02–1.61), respectively [12••]. These studies suggest that adding a β_3-agonist to an AM will provide more symptomatic relief than switching to a different AM in patients who do not initially respond to AM therapy. Whether or not the same additive effect occurs with other commercially available anticholinergics in combination with mirabegron has yet to be studied.

One factor that must not be overlooked, however, are high patient noncompliance rates on AMs with a discontinuation rate of > 70% [5••]. A study by Yu et al. showed that about two-thirds of patients remained on their AM medication for less than 90 days and approximately three-fourths remained on it for less than 150 days [13]. Therefore, even if adding a β_3-agonist to an AM is a more efficacious treatment, patients must remain compliant with the medication(s) in order to see benefit. The BeDRI trial was a two-phase randomized controlled trial investigating whether patients could be taken off an AM if initial treatment was combined with behavioral therapy. Their hypothesis was that behavioral therapy would teach patient skills to prevent incontinence episodes, and that the benefits of training would persist after discontinuation of the medication. In this study, 237 patients were randomly assigned to 10 weeks of tolterodine 4 mg daily alone versus combined with behavioral training followed by discontinuation of medical therapy. At 8 months, there was no difference in successful discontinuation of drug therapy; however, a higher proportion of patients using combined therapy achieved ≥ 70% reduction of incontinence than in drug therapy alone at 10 weeks (69% vs. 58%) and yielded significantly better outcomes on the Urogenital Distress Inventory (UDI) and Overactive Bladder Questionnaire (OABq) on patient satisfaction and perceived improvement. This analysis concluded that the addition of behavioral training to drug therapy has a possible benefit for reducing incontinence frequency during active treatment, but does not maintain improvement if drug therapy is discontinued [14].

Combination Tibial Nerve Stimulation and Antimuscarinics

Posterior (percutaneous) tibial nerve stimulation (PTNS) is a minimally invasive third-line therapy for OAB commonly used in practice as an alternative to medication due to its low systemic side effect profile. The mechanism of tibial neuromodulation is not completely understood, but its effect

is possibly mediated through a combination of increasing cerebral endorphins, stimulation of somatic sacral and lumbar afferent fibers, and activation of efferent fibers to the striated urethral sphincter [15–17]. The concept of adding PTNS to pharmacotherapy was studied by Souto et al., who randomized 58 patients to three groups: 30-min TENS twice weekly, daily slow release 10 mg oxybutynin, and PTNS plus oxybutynin for 12 weeks [15]. Patients were then evaluated at the end of treatment (12 weeks) and at 12 weeks after treatment cessation with validated questionnaires, symptoms bother, and voiding diaries. Patients using combination treatment reported better quality of life with improvement regarding urgency and nocturia compared to those who received isolated treatments. Furthermore, patients in the oxybutynin monotherapy group had a significant increase in incontinence episodes after discontinuation of drugs, compared to the PTNS alone and combination therapy groups that maintained improvement after treatment. This was also observed with the International Consultation on Incontinence-Overactive Bladder (ICIQ-OAB) scores and symptoms bother, demonstrating that patients experience recurrence of OAB symptoms after stopping treatment with oxybutynin. These findings suggest that, while PTNS has a more lasting effect than drug therapy, AMs can work synergistically with PTNS for those refractory to monotherapy [15]. In theory, PTNS in combination with medical management could lower the therapeutic threshold for medication, thus decreasing side effects and possibly increasing patient compliance with medication.

Vecchioli-Scaldazza and Morosetti completed a randomized controlled trial of 105 women over 10 months to assess the effectiveness and durability of solifenacin 5 mg daily for 12 weeks versus weekly PTNS monotherapy for 12 weeks versus combination therapy with PTNS weekly for 8 weeks and solifenacin 5 mg on alternate days for 8 weeks. Combination therapy was more effective when compared to solifenacin or PTNS alone in terms of improvement in urgency and urge incontinence. Improvement in quality of life and increase in perception of improvement using the Patient Global Impression of Improvement questionnaire (PGI-I) was also statistically significant in favor of combination therapy compared to either monotherapy groups. This abridged version of the standard 12 weeks PTNS was developed to obtain improved patient adherence with reduction in side effects, time, and cost. Similar to the Souto study, PTNS as a monotherapy or in combination with solifenacin showed a longer duration of effectiveness than solifenacin alone [18•].

Combination of Sacral Neuromodulation with Other Treatment Modalities

The efficacy of sacral neuromodulation (SNM) has been demonstrated in multiple studies accompanied by an acceptable side effect profile. Like PTNS, SNM is considered a third-line therapy, yet there may be a role for combination with medications for a select group of patients. An alternative to permanent implantation of electrodes is intermittent percutaneous needle sacral nerve stimulation (IPN-SNS). Tang et al. evaluated the efficacy of IPN-SNS combined with tolterodine 2 mg daily compared to tolterodine alone in 240 patients. The duration of each IPN-SNS treatment was 30 min every 2 days for 3 months. The authors found significantly greater improvements in first desire to void, maximum cystometric capacity, daily average volumes, and daily single maximum voided volumes in the combination therapy group [16]. These findings again suggest that neuromodulation results may be enhanced when employed in combination with medical therapy. The study did not evaluate IPN-SNS alone, which may be superior to drug monotherapy.

Although not in combination with another OAB treatment, bilateral sacral stimulation has been suggested as an alternative approach to standard unilateral stimulation. In a retrospective chart review of 124 patients undergoing stage I SNM, patients were divided into two cohorts based on unilateral versus bilateral stage I lead placement [19]. Overall success was defined as progression from stage I to stage II placement. These authors found that successful stage I trials were reported in 32/55 (58%) and 53/69 (76%) of unilateral and bilateral cohorts, which was statistically significant. In another study by Marcelissen et al., patients in whom unilateral SNM with InterStim failed were evaluated with a temporary percutaneous nerve stimulation in the contralateral S3 foramen. Symptoms were self-recorded using a 3-day stimulation of only the new temporary lead (contralateral stimulation) followed by a 2-day washout and then a 3-day stimulation using both the temporary lead and original permanent lead (bilateral stimulation). Clinical success was defined as more than 50% improvement in at least 1 relevant voiding diary parameter. This study is limited by the sample size of 15 patients, of whom 3 were excluded due to lead migration. Only 4 of the remaining 12 patients demonstrated a successful response, of whom 3 were eventually implanted with a contralateral lead [20]. Schepeens et al. performed a prospective randomized crossover trial which showed no significant improvement of bilateral vs unilateral stimulation in 33 patients using a temporary test lead [21]. While bilateral SNM in theory could give patients more programming options, there remains a need to retain two leads and be able to easily switch from one to the other. No data presently suggests this approach increases the likelihood of long-term success. Currently available devices, however, cannot accommodate two leads and would require complete systems duplication which could potentially increase costs [22].

What about sacral and tibial neuromodulation in combination? An animal study by Li et al. evaluated the effects of combined sacral and tibial nerve stimulation. S3 neural

stimulators were implanted into 5 pigs and combined with contralateral tibial nerve stimulation with an external stimulator [17]. Acetic acid was then infused into the pigs' bladders which significantly reduced bladder capacity. Combined sacral and tibial nerve stimulation significantly increased bladder capacity and induced a superior inhibitory effect than either modality of stimulation alone. Unfortunately, to date, there are no human studies of combination sacral and tibial neuromodulation.

Comparison of SNM to Botulinum Toxin Injection Therapy

The Rosetta trial was a randomized controlled trial of 385 women with severe urgency incontinence (UUI) comparing SNM to 200 units intradetrusor botulinumtoxin A (BTX) injection therapy over a 2-year period. Refractory OAB was defined as women who experienced greater than 6 UUI episodes on a 3-day diary and failed behavioral interventions, physical therapy, and two medications. Both therapies had comparable success in reducing UUI symptoms and adverse events were low. Women in the BTX group reported higher satisfaction and endorsement of their treatment, but this was accompanied by a higher rate of urinary tract infection. The trial findings should be tempered by the fact that SNM implanters in this study required only limited experience, and that the use of 200 U is not the standard starting dose for non-neurogenic DO cases in clinical practice. Based on this study, it is reasonable to state both SNM and BTX offer similar efficacy in treatment of refractory OAB [23•].

BTX failure due to lack of efficacy or patient discontinuation due to urinary retention has been reported in up to 37% of patients [24]. SNM in the setting of BTX failure is a reasonable treatment option. Hoag et al. performed a retrospective chart review of 83 patients who underwent SNM for refractory OAB with 36/83 (43.4%) patients having had prior BTX treatment. In this study, 25/36 (69.4%) had discontinued BTX due to ineffectiveness, 9/36 (25.0%) due to retention, and 2/36 (5.6%) due to other adverse reactions. Success rates for patients with prior BTX (23/36, 64%) and in patients with prior ineffective BTX (16/25, 64%) did not differ significantly from the success rate in patients who were BTX naïve (33/47, 70%). Of the 23 patients who had successful first-stage S3 tined lead placement and underwent second-stage permanent implantable pulse generator (IPG) placement, 17 (73.9%) were satisfied and using the device at mean follow-up of 29.1 months [25••]. Smits et al. showed similar results with a 70% success rate for first-stage SNM in patients previously treated with BTX. Of the 14 patients who went on to subsequent insertion of IPG in their series, 11 (79%) were noted to be satisfied at 1-year follow-up [26]. These studies both demonstrate that SNM is still a viable option for salvage therapy after BTX failure.

To date, there are no studies looking at BTX after failed SNM therapy, although this is encountered not uncommonly and offered in our practice. The use of SNM and BTX in combination may be considered clinically in the most severe refractory OAB patients, given that both treatments work via different mechanisms: BTX works at the level of the detrusor muscle, while SNM works via central neural pathways. However, even though this has not been adequately studied at this point in the literature, this strategy may present an acceptable risk/benefit ratio for the patient prior to moving on to major reconstructive procedures, such as augmentation cystoplasty.

Augmentation Cystoplasty

Beyond first-, second-, and third-line therapies as outlined in the AUA guidelines, augmentation cystoplasty (AC) may be considered for severe, refractory, complicated patients with "end stage" OAB [25••]. The goal of AC is usually to accomplish one or more of the following: provide adequate urinary storage, protect the upper urinary tract, preserve renal function, provide continence, resist infection, and offer a convenient method of voluntary and complete emptying [27]. This procedure has become more of a historical treatment for refractory OAB due to the advent of the use of BTX and SNM as minimally invasive, highly efficacious, low side effect profile treatment options for non-neurogenic detrusor overactivity with decreased morbidity [28–31].

Nonetheless, there remains a portion of non-neurogenic patients who do not improve with the previously mentioned treatment and combination treatment modalities. Amongst these patients are those with OAB due to idiopathic detrusor overactivity (IDO), as well as those with infective and inflammatory bladder disorders (post-radiation cystitis, cystitis following chemotherapy, schistosomiasis, tuberculosis (TB), and interstitial cystitis) which lead to a low capacity and poorly compliant bladder [28, 32, 33]. For the latter, overall results for AC have been of variable success for schistosomiasis (80%) [33, 34], TB (90%) [32, 35, 36], post-radiation cystitis (70%) [36–38], and Hunner's lesion interstitial cystitis (63% complete relief and 25% improvement) [39–41]. For IDO patients, El-Azab et al. found in a prospective study where 31 patients were assigned (based on patient preference) to BTX ($n = 16$) or AC ($n = 15$). UDI and Incontinence Impact Questionnaire (IIQ-7) scores significantly improved after either procedure. However, overall OABq scores were significantly higher in the AC group [42]. Venn and Mundy published a 93% dry rate for IDO patients following AC [43]. More recently, Cheng et al. published a 10-year follow-up on patients after AC. Of the 40 patients, 70% (28/40) were

due to a neurogenic etiology, while 20% (8/40) were due to an inflammatory etiology (irradiation cystitis and TB cystitis) and 10% (4/40) were due to IDO. They did not report urodynamic, renal function, or metabolic outcomes separately for the etiologies, but overall, they reported increased bladder capacity, improved compliance, reduction in detrusor overactivity, preservation of renal function, and low metabolic complication rates [44•].

Despite these reports, there are potential short- and long-term complications associated with AC of which providers must be cognizant. Short-term/early complication rates include wound infection (5–7.1%) [45, 46], small bowel obstruction (3–5.7%) [46, 47], bleeding requiring re-operation (0–3.2%) [46, 48], and thromboembolic (7.1%) [47], respiratory, and cardiovascular events (2.7% for myocardial infarction) [36] that usually accompany a major abdominal procedure. Mortality from AC has been published between 0 and 2.7% [48]. Long-term complications rates include urinary tract infections (4–43%) [49–51], stone disease (3–40%) [27], spontaneous perforation (0.8–13%) [52–54], malignancy for enterocystoplasty (1.2%) [55], metabolic disturbance (16% for hyperchloremic acidosis requiring oral bicarbonate) [46], renal function deterioration (0–4%) [42, 47], incontinence including nocturnal enuresis (7–47%) [43, 46, 50, 56], incomplete emptying requiring clean intermittent catheterization (6–39%) [45, 46, 50, 57], and failure of the AC requiring revision surgery (5–42%) [27, 58].

Interestingly, some cases of AC failure have been treated with conservative measures starting with a trial of AM [30]. There have also been case reports for use of both BTX (into native bladder tissue) and SNM after AC with good success [59, 60]. It is important to note many of these studies report complications for a mixed population of both NDO and IDO patients. For those that did evaluate IDO rates separately, IDO rates of complications are in general much lower than NDO rates.

Similar contraindications for AC in IDO should be considered as for any situation in which bowel is used for augmentation or diversion. Patients with inflammatory bowel disease and short-bowel syndrome should not be considered for AC [27, 61]. A history of radiation to the pelvis is a relative contraindication; segments of bowel can be inspected intraoperatively with a secondary plan to use colon or stomach if appropriate [30]. Another relative contraindication is significant renal impairment. Some studies have revealed no change in renal function post AC [62] while others have shown patients with azotemia and a creatinine clearance less than 40 mL/min are at higher risk for metabolic acidosis [36]. Lastly, similar to BTX, patients must agree to be willing to perform clean intermittent catheterization (CIC) if in the event it is necessary post AC surgery. If they are unwilling/unable to perform CIC per urethra, the provider could offer a concomitant urinary stoma which may facilitate catheterization by the patient or caregiver [63].

Regarding cost effectiveness, Watanabe et al. performed a cost analysis comparing SNM, BTX, and AC for antimuscarinic refractory patients. They performed a sensitivity analysis and published a 3-year cumulative cost range of $25,384 to $27,357 for SNM, $4586 to $11,476 for BTX, and $12,315 to $16,830 for AC [64•]. They concluded at 3 years, SNM had the highest cost-end point of the three followed by AC and BTX, respectively. Reyblat et al. suggest that once 5- and 10-year data is available, it can be hypothesized that AC will become more cost-effective since both BTX and SNM will require repeat injection and battery replacement, respectively [63].

Although augmentation cystoplasty is still viewed as a salvage therapy for refractory OAB, the literature shows that it is still an invaluable option with excellent efficacy and quite possibly the most cost-effective treatment option long-term.

Conclusions

Combination therapy for difficult cases of OAB is still a relatively new concept but may be effective clinically in the setting of second- and third-line therapy failure. The use of solifenacin and mirabegron has shown the most promise. Third-line therapies such as SNM and BTX could be used in theory together due to their potential complementary mechanisms of action, but its role has yet to be elucidated. Augmentation cystoplasty is still an option in cases of third-line therapy failure.

Compliance with Ethical Standards

Conflict of Interest Sarah Martin declares that she has no conflict of interest.

Esther Han declares that she has no conflict of interest.

Jason Gilleran declares that he 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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- •• Of major importance

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