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REVIEW ARTICLE

# Combination therapy in overactive bladder-untapped research opportunities: A systematic review of the literature

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## Abstract

**Aims:** Overactive bladder (OAB) affects over 17% of the population and significantly effect the health-related quality of life. The treatments for OAB include first line (lifestyle modification, pelvic floor muscle training), second line (anticholinergic or beta-3 agonist medications), and third line therapies (intradetrusor botulinum toxin injection, sacral neurostimulation [SNM], or percutaneous tibial nerve stimulation [PTNS]). For those with urinary incontinence secondary to OAB, complete continence is the goal of therapy, though cure rates are only 5% to 40%. The use of combination therapies can be employed in refractory OAB, however, the efficacy of pooled modalities is relatively unknown. Our objective was to determine the volume of data supporting combination therapy in treating OAB.

**Methods:** We systematically reviewed PubMed, EMBASE, the Cochrane Library, and Google Scholar for articles published before October 2018. Each was independently reviewed by two reviewers and examined in detail if they met inclusion criteria.

**Results:** A total of 32 studies met inclusion criteria and were reviewed. Most large prospective studies evaluated combinations of medications with behavioral therapy or medications together. Combination therapy studies of third-line treatments were rare and centered on medication with PTNS. No studies examined intradetrusor botulinum toxin injections in combination with another therapy and only one retrospective study briefly examined SNM therapy in combination with medication.

**Conclusion:** Combination therapy, with certain first, second, and third-line OAB therapies, appears to be efficacious. There is a further need for carefully designed combination therapy studies, particularly those including third line modalities.

KEYWORDS

combination therapy, overactive bladder, urge urinary incontinence

  

## 1 | INTRODUCTION

Overactive bladder (OAB) is a symptom complex defined as urgency, with or without urge incontinence, usually with frequency and nocturia.[1] With a prevalence rate of up to 17% in men and women across the United States and Europe, OAB is common and can have a significant impact on health-related quality of life, especially in the setting where treatments fall short of their intended goal.[2,3]

Currently, a wide range of therapeutic options exist for the treatment of OAB. These include first-line therapies which focus on behavioral modifications, second-line therapies which are pharmacologic, and third-line therapies which either neuromodulate or chemodenervate the bladder (Table 1).[3,4] Despite numerous options, the efficacy of individual treatments vary, and complete remission is often not achieved. As has been adopted in the management of other medical conditions (such as refractory hypertension, benign prostatic hyperplasia, and cancer treatments) combining treatment modalities is thought to have a role in the setting of refractory OAB and is increasingly used in clinical practice.[5,6] The 2011 European Urologic Association guidelines on OAB state that there is little data to support the use of combination therapies and make no definitive statement on their use,[3] though more recent guidelines put forth in the American Urologic Association OAB guideline update endorse combination therapy with anticholinergic and beta-3 agonist medications for patients refractory to monotherapy.[7]

While these guidelines and several recent large studies supporting the use of beta-3 agonist medications in combination with anticholinergic medications to treat OAB, there remains little consensus, or data, on other therapy combinations for persons with refractory OAB.[8,9] Rather, most published algorithms simply follow a stepwise progression from first line to the second line to third line monotherapies without recognizing that by themselves, these modalities may only lead to improvement rather than complete symptom resolution. Our objective was to review the prevalence of OAB combination therapy research, provide a synopsis of the current results and identify areas that require further investigation.

## 2 | METHODS

We systematically reviewed the literature published before 1st October 2018 using searches on PubMed (includes MEDLINE), EMBASE, the Cochrane Library, and Google Scholar. Individual search strategies included but were not limited to the following terms: OAB, urinary urgency, multimodal therapy, behavioral therapy, pelvic floor muscle training, botulinum toxin, percutaneous tibial nerve stimulation, sacral nerve stimulation, anticholinergics, and beta-3 agonists. The searches excluded animal-only and non-English language studies. Complete search strategies for each database, including the database's native search syntax, are available upon request. The results of the database searches were uploaded to Covidence (http://covidence.org; Melbourne, Australia) for screening by two independent reviewers (AMK and CSE). The reviewers utilized the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to develop the review (Figure 1). Inclusion and exclusion criteria were used by each reviewer. Notable exclusions included unspecified urinary incontinence, off-label treatments, and neurogenic bladder (Table 2).

**TABLE 1** Standard treatment options for the management of overactive bladder

| Therapy | Examples |
|---|---|
| First line (behavioral) | Lifestyle modifications |
| | Pelvic floor muscle training |
| | Bladder training |
| | Timed voiding |
| Second line (pharmacologic) | Anticholinergic |
| | Beta-3 agonists |
| Third line (neuromodulation/ chemodenervation) | Percutaneous tibial nerve stimulation |
| | Sacral neuromodulation |
| | Intradetrusor botulinum toxin |

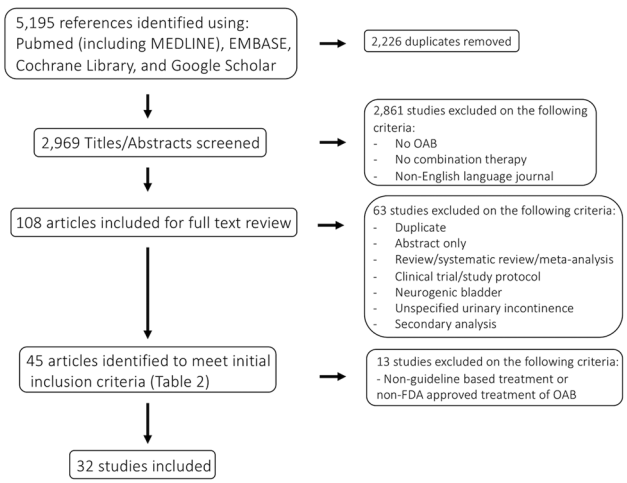


**FIGURE 1** PRISMA screening of articles. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

**TABLE 2** Inclusion and exclusion criteria for review

| Inclusion criteria | | Exclusion criteria |
|---|---|---|
| Patient selection | >18 y old | <18 y old |
| | Male or female | Mixed urinary incontinence |
| | Overactive bladder | Neurogenic OAB |
| | | Combination therapy with BPH medications |
| More than two OAB treatments | Pelvic floor physiotherapy | Combination therapy with vaginal estrogen |
| | Bladder training | Abstract |
| | Life style modification (eg, timed voiding) | On going clinical trial |
| | Anticholinergic | Review/systematic review |
| | Beta-3 agonist | Non-English language journal |
| | Percutaneous tibial nerve stimulation | Off-label treatments for OAB |
| | Sacral nerve modulator/stimulation | |
| | Intradetrusor botulinum toxin | |

Abbreviation: BPH, benign prostatic hypertrophy; OAB, overactive bladder.

## 3 | RESULTS

A total of 32 studies were found to meet inclusion criteria and are summarized below. All studies were prospective with the exception of one retrospective examination of combining of sacral neurostimulation (SNM) with an anticholinergic medication.

### 3.1 | Anticholinergic combination with anticholinergic

Four articles were identified that examined the use of anticholinergic medications in combination with each other (Table 3).[10-13] Three of the four studies were conducted by Kosilov et al at the Institute of Physical Health in Russia. The three studies, which had cohorts of 177 to 313 individuals, demonstrate that compared to placebo, combinations of trospium and solifenacin result in decreases in urinary urgency and urge incontinence, though only one of the studies achieves statistical significance. Likewise, Yi et al[13] found that in 49 patients, the combination therapy of propiverine or tolteridine with another anticholinergic medication improves urinary urgency and urge incontinence compared to baseline monotherapy in a statistically significant manner.

### 3.2 | Anticholinergic combination with beta-3 agonist

The most often studied OAB combination therapy is an anticholinergic medication with mirabegron (a beta-3 agonist; nine of 32 studies, 28.2%; Table 3).[8,9,14-20] These studies were all prospectively designed and demonstrate that the combination of a beta-3 agonist with an anticholinergic improves OAB symptoms. The three largest studies are the BESIDE, SYNERGY, and SYMPHONY studies which all demonstrate that combination therapy of an anticholinergic with a beta-3 agonist improves urinary frequency, urgency, and urge incontinence in those with OAB compared to monotherapy beta-3 agonist or anticholinergic alone in a statistically significant manner.[8,9,16]

### 3.3 | Bladder training combination with medications

We identified a total of 12 studies (all prospective in nature) examining bladder training in combination with medications (Table 3).[21-31,37] The bladder training regimens ranged from tailored or generic self-administered behavioral therapy to pelvic floor physiotherapy sessions with a trained professional, while the medications used in each study were anticholinergics. Only 50% of the reviewed studies show improvements in urinary frequency, urgency, urge incontinence, or OAB-q scores when an anticholinergic is combined with bladder training, and the majority do not show superiority over monotherapy (usually medication) alone.[22,25,26,37] The largest randomized study by Mattiasson et al[29] (n = 644) found that combination therapy (solfenacin with concurrent bladder training for 16 weeks) improved frequency and overall patient satisfaction though failed to improve episodes of urge incontinence.

### 3.4 | Posterior tibial nerve stimulation with medications

Four prospective studies have evaluated percutaneous tibial nerve stimulation (PTNS) in combination with anticholinergic medications (either tolterodine or solifenacin; Table 3).[32-35] All four studies include fewer than 40

**TABLE 3** Summarized findings of systematic review of OAB combination therapy

| Combination | Author | n | Summarized finding |
|---|---|---|---|
| Anticholinergic with anticholinergic | Kosilov et al[10] | 177 | Combination trospium and solifenacin significantly decreased episodes of urgency, UI compared to prior monotherapy of each and placebo |
| | Kosilov et al[11] | 341 | Combination either intermittent or continuous trospium and solifenacin decreased episodes of urgency, UI compared to placebo |
| | Kosilov et al[12] | 313 | Combination intermittent or continuous trospium and solifenacin decreased episodes of urgency and UI compared to placebo |
| | Yi et al[13] | 49 | Combination propiverine and an anticholinergic, or combination tolterodine and tropsium, reduced urgency, UI compared to monotherapy of each |
| Anticholinergic with beta-3 agonist | Shin et al[14] | 30 | Combination mirabegron+propiverine decreased PPBC scores, frequency, urgency, and UI episodes compared to monotherapy |
| | Kosilov et al[15] | 239 | Mirabegron and solifenacin combination decreased OAB-q scores, frequency and UI compared to placebo or monotherapy mirabegron |
| | Abrams et al[16] | 1306 | Combination solifenacin and mirabegron improved frequency and urgency compared to monotherapy of each |
| | Yamaguchi et al[17] | 223 | Combination solifenacin with mirabegron decreased frequency, urgency, and UI compared to montherapy solifenacin |
| | Gratzke et al[18] | 1794 | Combination solifenacin with mirabegron improved frequency and UI compared to monotherapy solifenacin |
| | Robinson et al[19] | 3527 | Combination solifenacin with mirabegron improved OAB-q symptom bother, HRQoL total score compared to montherapy of each and placebo |
| | Herschorn et al[8] | 3308 | Combination solifenacin with mirabegron therapy improved frequency and UI compared to montherapy of each and placebo |
| | MacDiarmid et al[20] | 2174 | Combination solifenacin with mirabegron improved HRQoL and PPBC scores compared to monotherapy solifenacin |
| | Drake et al[9] | 2174 | Combination solifenacin with mirabegron improved frequency, UI compared to monotherapy solifenacin |
| Bladder training with medication | Klutke et al[21] | 416 | Combination tolterodine with bladder therapy reduced frequency, UI compared to monotherapy behavioral intervention |
| | Lauti et al[22] | 57 | No improvement was seen compared to either monotherapy for combination oxytbutynin with bladder retraining for OAB-q, frequency, or UI |
| | Burgio et al[23] | 64 | No improvement was seen compared to monotherapy oxybutynin for combination oxybutynin and behavioral therapy for UI or patient satisfaction |
| | Burgio et al[24] | 307 | No improvement was seen compared to monotherapy tolterodine for combination tolterodine with behavioral training in urgency scores |
| | Burgio et al[25] | 307 | Combination therapy with tolterodine with behavioral modification improved UI compared to monotherapy tolterodine |
| | Burgio et al[26] | 197 | Combination therapy with oxybutynin with behavioral modification improved UI compared to monotherapy of each |
| | Kim et al[23] | 47 | No improvement was seen compared to monotherapy bladder training for combination propiverine and bladder training for frequency |
| | Kaya et al[27] | 46 | Combination therapy with trospium and physiotherapy improved frequency and UI compared to monotherapy of each |

(Continues)

**TABLE 3** (Continued)

| Combination | Author | n | Summarized finding |
|---|---|---|---|
| | Chancellor et al[28] | 200 | No improvement was seen compared to monotherapy darifenacin for combination darifenacin with behavioral modification for frequency, UI |
| | Mattiasson et al[29] | 644 | Combination solifenacin with bladder training improved frequency and satisfaction but not UI compared to monotherapy solifenacin |
| | Mattiasson et al[30] | 501 | Combination tolterodine with bladder training improved frequency but not UI compared to monotherapy tolterodine |
| | Song et al[31] | 139 | No improvement was seen compared to either monotherapy for combination tolterodine and bladder training for frequency or urgency |
| PTNS with medication | Vecchioli-Scaldazza et al[32] | 27 | Combination solifenacin with PTNS improved frequency, urgency, UI, and OAB-q compared to monotherapy of each |
| | Sancaktar et al[33] | 38 | Combination tolterodine with PTNS improved frequency, urgency, and UI compared to monotherapy tolterodine |
| | Eftekhar et al[34] | 30 | Combination tolterodine with PTNS improved UI compared to monotherapy tolterodine |
| | Kizilyel et al[35] | 30 | Combination tolterodine with PTNS improved frequency and UI compared to monotherapy of each |
| SNM with medication | George et al[36] | 88 | Review of all SNM placement over 8 y found 22.7% patients restart on anticholinergic after SNM, 84.2% found significant subjective improvement |

Abbreviations: HRQOL, health-related quality of life subscale; *OAB-q symptom bother, overactive bladder question symptom bother; PPBC, patient perception of bladder condition; PTNS, percutaneous tibial nerve stimulation; SNM, sacral neuromodulation.

patients, though universally report that combination therapy improves urinary frequency, urgency, and urge incontinence outcomes compared to either anticholinergic monotherapy or PTNS monotherapy. Three out of four of the studies achieve statistical significance, while Eftekhar et al[34] demonstrated variable significance depending on the specific symptom examined.

### 3.5 | Sacral neurostimulation with medications

The only study of combining SNM therapy with another OAB therapy is a retrospective review that examines the rate of restarting an anticholinergic medication after SNM device placement.[36] Overall, 22.7% of the study population were found to restart an anticholinergic after SNM placement. In persons combining the two modalities, 84.2% were noted to have significant improvement compared to SNM therapy alone, though this was based on subjective patient reports only and did not include more robust outcome measures.[36]

### 3.6 | Botulinum toxin A with another OAB therapy

No study examining the therapeutic benefit of combining botulinum toxin with another OAB therapy were found.

### 3.7 | Other

In addition to the 32 studies included in our systematic review, we encountered another 13 that investigate nonapproved OAB therapies in combination with an approved OAB therapy.[38-50] Overall, these studies were generally underpowered due to small sample sizes and demonstrate variable OAB improvements (Table 4).

## 4 | DISCUSSION

Despite a high prevalence of OAB within the general population and the addition of multiple options in the past 20 years (beta-3 agonists, botulinum toxin, SNM, and PTNS), the ability of the medical profession to provide adequate urinary symptom relief is far from optimal. Amongst first-line treatments (lifestyle modification, bladder training, and pelvic floor muscle therapy) successful treatment outcomes may result, however these therapies are often underutilized and poorly understood by treating physicians.[51] Amongst second-line pharmacologic agents, which are the most common form of OAB treatment, the adherence to anticholinergic or B-3 agonist medication is low.[52,53] In fact, of all medications used to treat chronic conditions, OAB medication therapy has the lowest patient adherence with a continuance rate

**TABLE 4** Alternative and off-label therapies for refractory OAB

| Combination | Author | n | Summarized finding |
|---|---|---|---|
| PFS with vaginal estrogen | Abdelbary et al[38] | 315 | Combination PFS and vaginal estrogen improved frequency, urgency, and UI versus montherapy of each |
| TENS with anticholinergic | Souto et al[39] | 75 | No improvement was seen for combination TENS of PTN and oxybutynin for frequency, urgency, or UI compared to monotherapy of each |
| WLT with anticholinergic | Xiao et al[43] | 146 | Combination tolterodine with WLT improved UI over WLT alone and placebo but not tolterodine alone |
| PTNS with PFMT | Scaldazza et al[44] | 60 | No improvement was seen compared to monotherapy PTNS for combination PTNS with PFMT and electrical stimulation for UI, frequency |
| Acupuncture with anticholinergic | Jin et al[45] | 71 | Combination electroacupuncture with tolterodine improved UI over monotherapy electroacupuncture |
| IPN-SNS with anticholinergic | Tang et al[46] | 240 | Combination tolterodine with IPN-SNS improved frequency over monotherapy tolterodine |
| TPTNS with anticholinergic | Abulseoud et al[47] | 30 | Combination trospium with TPTNS improved frequency and OABSS over monotherapy TPTNS |
| Sacral stimulation with PTN | Surbala et al[48] | 44 | Combination sacral foramina stimulation with PTN improved OABSS over monotherapy of each |
| Pregabalin with anticholinergic | Marencak et al[49] | 186 | No improvement was seen compared to monotherapy of each for combination tolterodine with pregabalin for OAB-q symptom bother |
| Desmopressin with anticholinergic | Han et al[50] | 68 | Combination solifenacin with desmopressin improved urgency over monotherapy of each |
| | Rovner et al[40] | 106 | No improvement was seen compared to monotherapy tolterodine for combination tolterodine with desmopressin for noctural voids |
| Physiotherapy with anticholinergic | Balci et al[41] | 270 | Combination trospium with biofeedback/physiotherapy improved UI over monotherapy of each |
| Vaginal estrogen with anticholinergic | Ellington et al[42] | 58 | No improvement was seen compared to monotherapy of each for combination tolterodine with vaginal estrogen for OAB-q symptom bother |

Abbreviations: IPN-SNS, intermittent percutaneous needle sacral nerve stimulation; OAB-q symptom bother, overactive bladder question symptom bother; *OABSS, overactive bladder symptom score; PFMT, pelvic floor muscle training; PFS, pelvic floor electrical stimulation; PTN, posterior tibial nerve; TENS, transcutaneous electrical neural stimulation; TPTNS, transcutaneous posterior tibial nerve electrostimulation; WLT, Weng-li-Tong.

of only 20% to 30% over the first 2 years.[54] Given the discontinuance rates, it appears that medication side effect profiles and OAB symptom improvements do not meet patient expectations.[55,56] In addition, amongst the large number of OAB patients who discontinue medical therapy (~70%), very few appear to progress to other treatment options with estimates of only 5% to 10% progressing to third line options such as botulinum toxin, SNM, or PTNS.[57]

In recognition of low OAB treatment adherence, significant efforts are being made to improve patient adherence and promote patient migration to third line therapies when first and second-line treatments have not met patient expectations. Amongst these efforts are the creation of the OAB Clinical Care Pathway (https://sufuorg.com/resources/overactive-bladder-ccp.aspx), which provides information on all OAB treatment options and what sequence of therapies a patient might expect to trial on their way to achieving symptom relief. Recent data has suggested that the OAB Clinical Care Pathway increases the rate of patient follow-up and progression to third-line therapies when first and second-line therapies have not provided appropriate clinical responses.[58] However, even when third-line options are used, the full dry rates when used as monotherapy for those with OAB associated incontinence are only 5% to 40% in randomized control trials.[59-62]

It is well established in other medical disciplines that monotherapies are often insufficient as a means to treat disease. From hypertension to benign prostatic hyperplasia to multimodal regimens for cancer care, there are countless examples where combination therapy is employed to bring about improved results.[5,38,63] In contrast, when compared to the scope of the condition, OAB research has failed to sufficiently explore therapy combinations as evidenced by our literature search. The limited data that does exist for combination therapy to treat OAB is predominantly focused on the use of bladder training programs

combined with anticholinergic medications, combinations of two anticholinergic medications together, or anticholinergics with a beta-3 agonist (mirabegron). Bladder training with anticholinergic medications have been examined in a dozen studies with about half demonstrating an improvement in symptoms when combined. While limited data suggest two anticholinergics in combination has a potential therapeutic benefit, there may be a ceiling effect on detrusor muscle response and anticholinergic side effects should increase.[40] Anticholinergic medications with a beta-3 agonist appear to have a better physiologic rationale, with separate mechanisms of action and an apparent lack of additive side effects, though polypharmacy is a concern in the OAB population and a provider should balance the potentially deleterious side effects that each medication might bring about. In addition, the trials of anticholinergics with the beta-3 agonist mirabegron are large, well designed and clearly demonstrate a therapeutic benefit over monotherapy with either an anticholinergic or beta-3 agonist alone.

Despite increasing numbers of patients undergoing third-line therapy for OAB, combination therapy with third-line options remains sparse. PTNS is the most studied, though is only represented by four small trials demonstrating a benefit when combined with anticholinergic medication. Combination therapy with SNM, is only examined in one study examining its potential combination with anticholinergic medication and is limited in that it is neither prospective nor randomized and examined subjective improvement only without a formal instrument of therapy effect. Similarly, no study to date has examined botulinum toxin in combination with another OAB therapy to assess for improved OAB symptom outcomes nor are studies available to examine combining two third-line therapies together (eg, SNM with botulinum toxin, SNM with PTNS, or botulinum toxin with PTNS)

We find it interesting that despite many combination therapy studies being less than robust in terms of design or number of patients studied, there is a significant body of research assessing the utility of off-label treatments in combination with approved OAB therapies. Several of these studies focus on nonapproved neuromodulation techniques that have yet to undergo proper clinical trials (even as monotherapies) while in other studies, the use of off-label medications such as desmopressin, pregabalin, vaginal estrogen, and Weng-li-Tong (an herbal medicine) were investigated.[42,43,49,50,64,65] Interestingly, several of these combinations were able to elicit a clinical benefit with improvements in OAB symptoms compared to monotherapy, however, as these treatments are not standard of care, it is not clear if they will garner widespread use. In addition, given a lack of data examining approved OAB therapies in combination, it is likely prudent that future efforts should be focused on combining guideline treatments first.

With few exceptions, combination therapy research in the treatment of OAB is a wide open opportunity for future research as the number of combinations and outcome measures that could be examined are innumerable. Future endeavors, however, will need to strive to generate proper study population sizes and use validated outcome study measures. Given that third-line therapies are potentially underutilized, it might be useful for planned studies to be done in a multi-institutional fashion for which the infrastructure provided by the Urinary Incontinence Treatment Network and the newly created SUFU Research Network provide excellent starting opportunities.[66,67]

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