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LOWER URINARY TRACT SYMPTOMS AND VOIDING DYSFUNCTION (J SANDHU, SECTION EDITOR)

Combination and Novel Pharmacologic Agents for OAB

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Abstract

Purpose of Review To evaluate recent literature on combination and novel pharmacologic therapies for overactive bladder (OAB).

Recent Findings Combination therapies demonstrating greater efficacy than monotherapy include combination anticholinergics, anticholinergic plus β-3 agonist, and anticholinergic with behavioral modification, percutaneous tibial nerve stimulation, or sacral neuromodulation. Promising novel therapies include new bladder selective anticholinergics, new β-3 agonists, and gabapentin.

Summary OAB is a symptom complex caused by dysfunction in the interconnected neural, muscular, and urothelial systems that control micturition. Although several therapeutic targets and treatment options exist, complete resolution is not always achieved, discontinuation rate for medical therapy is high, and few patients subsequently progress to third-line treatment options. Recent literature suggests combination therapy diversifying therapeutic targets is more effective than targeting a single pathway and novel treatments targeting additional pathways have promising results.

Keywords Overactive bladder · Combination therapy · Novel therapy

Introduction

Overactive bladder syndrome (OAB) is commonly defined as "urinary urgency, usually with urinary frequency and nocturia, with or without urgency incontinence" in the absence of urinary tract infection (UTI) [1••]. The most common symptom of OAB is urinary urgency, which is defined as "a sudden compelling desire to pass urine which is difficult to defer." Less commonly associated symptoms include urinary frequency, typically defined as more than seven or eight voids during the day, and nocturia, defined as more than one void that interrupts slumber [1••, 2, 3].

Prevalence estimates of OAB are generally determined via self-reported symptoms and thus are not consistent among studies. The National Overactive Bladder Evaluation (NOBLE) Program established in 2001 utilized a nationwide

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telephone survey that estimated the prevalence of OAB to be 16.9% among women and 16% among men above the age of 18. Furthermore, OAB in women was more frequently associated with urgency urinary incontinence (UI) (45%) than OAB in men (16%) [4]. The 2006 Epidemiology of Urinary Incontinence and Comorbidities (EPIC) study estimated prevalence of OAB via telephone surveys of adults in Sweden, Germany, Italy, Canada, and the UK. OAB was reported by 12.8% of women and 10.8% of men with increasing prevalence associated with advanced age [5]. Worldwide, an estimated 546 million individuals suffered from OAB in 2018 based on extrapolation of the EPIC trial to regional demographics of age and gender [6].

OAB is associated with significant burden and decline in quality of life due to associated comorbidities, such as UTIs, skin infections, sleep disturbances, depression, and possibly more frequent falls and hip fractures [7]. When compared to age and sex-matched OAB-negative controls, those with OAB reported significant lower quality of life when asked about physical function (carrying out daily activities), social functioning, mental health, and quality of sleep. These findings were more pronounced in individuals with OAB who experienced urgency incontinence [4]. The psychological impact of OAB has been well documented with eight studies from 2003 to 2011 reporting higher levels of depression among OAB participants when compared to OAB-negative controls [8]. OAB accounts for about $750 of healthcare spending per person per year or about 5% of total healthcare costs based on a systematic literature review [9]. The total cost of OAB in the USA is estimated to be $82.6 billion in 2020 [10].

Many mechanisms have been proposed for the etiology of OAB symptoms. Normally, urinary storage and emptying is achieved through a combination of signals from the central and peripheral nervous system (Fig. 1) and local biochemical networks at the urothelium (Fig. 2). During storage, sympathetic fibers from the T10-L2 spinal cord, forming the hypogastric nerve, release noradrenaline (NA) at the bladder and urethra. NA acts on β-3 adrenergic receptors in the bladder detrusor to relax smooth muscle and on α-1 adrenergic receptors at the internal urethral sphincter to contract smooth muscle. When voiding is initiated by the pontine micturition center, the pudendal nerve activates relaxation of the external urethral sphincter via release of acetylcholine (Ach) to excite nicotinic receptors on striated muscle [11••]. Parasympathetic fibers from the S2-S4 spinal cord release ACh at the bladder, which acts primarily on M3 muscarinic receptors to contract the detrusor muscle via intracellular Ca^{2+} release. Activation of M2 receptors inhibits adenylate cyclase, which enhances bladder contractions by suppressing sympathetic activation of adenylate cyclase, thus resulting in bladder emptying.

Disruption of this coordinated signaling can result in OAB. A 2019 systematic review proposed several pathophysiologic phenotypes for OAB, including aberrant detrusor function, urothelial dysfunction, autonomic nervous system dysfunction, metabolic syndrome, sex hormone deficiency, change in urinary microbiota, and more [12]. In the myogenic hypothesis, detrusor overactivity, defined by involuntary detrusor muscle contractions during the filling phase of urodynamics, may be attributed to abnormal electrical coupling of smooth muscle cells such that physiological micro-contractions trigger involuntary contractions. The urotheliogenic hypothesis attributes urgency to aberrant sensory function of the urothelium and is often associated with OAB without urodynamic evidence of detrusor overactivity. The neurogenic hypothesis suggests the role of dysfunctional integration of afferent sensory signals with supraspinal inhibitory control of the micturition reflex, which may present with or without detrusor overactivity.

Based on these proposed etiologies, several therapeutic targets have been proposed for the management of OAB. First-line treatment involves behavioral modification such as bladder training, pelvic floor muscle exercises, weight loss, and bladder irritant avoidance/caffeine limitation. Second-line treatment includes antimuscarinic pharmaceuticals that target M2 and/or M3-receptors responsible for detrusor contraction via parasympathetic excitation. β-agonists are used to target β-3 receptors responsible for detrusor relaxation. Third-line therapeutics involve sacral neuromodulation, percutaneous tibial nerve stimulation, or intradetrusor onabotulinumtoxin-A injections. In this article, we review combination and novel pharmacologic agents in the management of OAB.

Combination Agents for OAB

Despite many OAB treatment options, complete resolution is rarely achieved [13••] and discontinuation rates for medical management are approximately 70% [14–16]. Only 5–10% of patients subsequently progress to third-line treatment options [17]. Combination therapy may be of benefit for refractory OAB and has been utilized in clinical practice [18, 19]. While the combination of anticholinergic and β-3 agonist medications has been supported by the American Urologic Association (AUA) OAB guideline 2019 update [20, 21] few data exist on combination treatments beyond combination anticholinergics or anticholinergic and β-3 agonists [22••, 23••].

Data on potential adverse effects of combination therapy is conflicting. While many studies report no significant increase in adverse events with combination therapy [24–26] other studies do report increased anticholinergic effects and

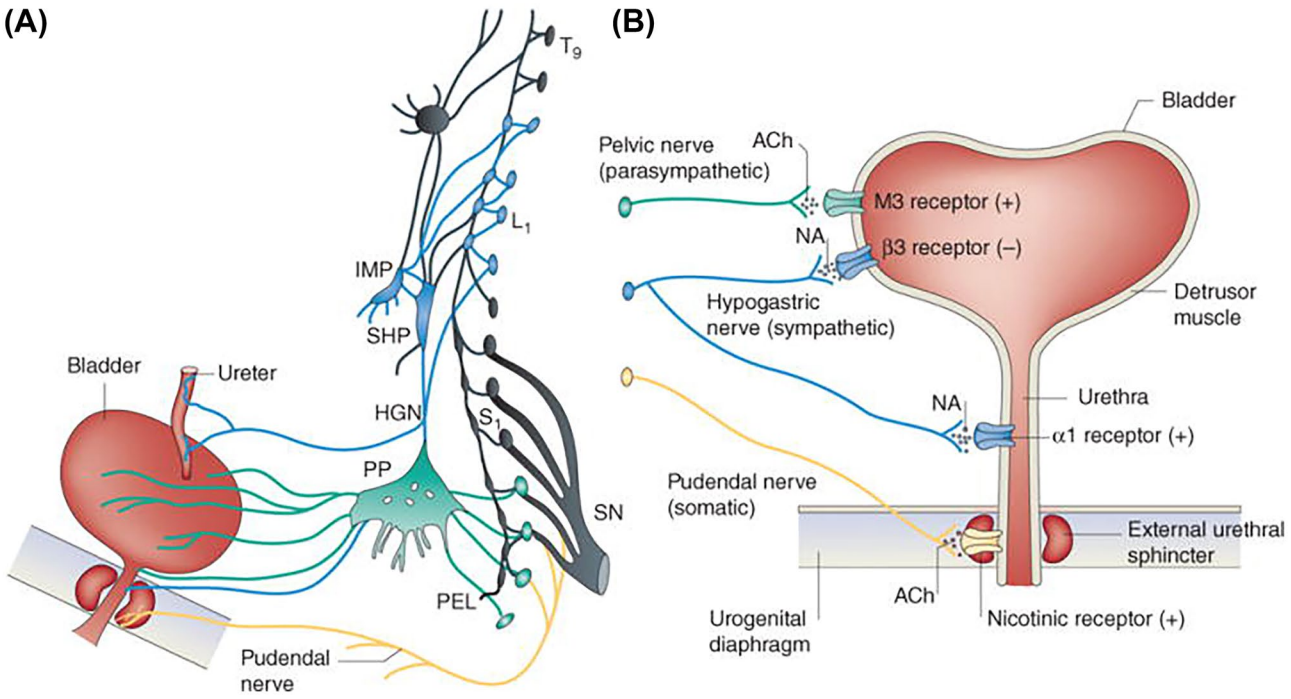

Fig. 1 Efferent pathways of the lower urinary tract. Efferent pathways of the lower urinary tract. (**A**) Innervation of the female lower urinary tract. Sympathetic fibers (shown in blue) originate in the T10-L2 segments in the spinal cord and run through the inferior mesenteric plexus (IMP) and the hypogastric nerve (HGN) or through the paravertebral chain to enter the pelvic nerves at the base of the bladder and the urethra. Parasympathetic preganglionic fibers (shown in green) arise from the S2-S4 spinal segments and travel in sacral roots and pelvic nerves (PEL) to ganglia in the pelvic plexus (PP) and in the bladder wall. This is where the postganglionic nerves that supply parasympathetic innervation to the bladder arise. Somatic motor nerves (shown in yellow) that supply the striated muscles of the external urethral sphincter arise from S2-S4 motor neurons and pass through the pudendal nerves. (**B**) Efferent pathways and neurotransmitter mechanisms that regulate the lower urinary tract. Parasympathetic postganglionic axons in the pelvic nerve release acetylcholine (ACh), which produces a bladder contraction by stimulating M3 muscarinic receptors in the bladder smooth muscle. Sympathetic postganglionic neurons release noradrenaline (NA), which activates β3 adrenergic receptors to relax bladder smooth muscle and activates α1 adrenergic receptors to contract urethral smooth muscle. Somatic axons in the pudendal nerve also release ACh, which produces a contraction of the external sphincter striated muscle by activating nicotinic cholinergic receptors. Parasympathetic postganglionic nerves also release ATP, which excites bladder smooth muscle, and nitric oxide, which relaxes urethral smooth muscle (not shown). L1, first lumbar root; S1, first sacral root; SHP, superior hypogastric plexus; SN, sciatic nerve; T9, ninth thoracic root (216). Figure adapted from de Groat, William C et al. "Neural control of the lower urinary tract." Comprehensive Physiology vol. 5,1 (2015): 327–96. https://doi.org/10.1002/cphy.c130056

risk of urinary retention compared to monotherapy [27–29]. As anticholinergics have been associated with worsening cognitive decline [30], and increased risk of adverse events associated with polypharmacy [31] additional studies are needed to evaluate the efficacy and side effects of combination third-line treatment options.

Studies evaluating combined treatment options for OAB with summarized findings can be found in Table 1.

Combination Anticholinergic Agents

Among the most well documented combination therapy options is the combination of two anticholinergic medications. The proposed mechanism of combining anticholinergic medications is to diversify the muscarinic receptor targets [32]. Multiple studies demonstrate statistically significant decreases in urinary urgency and UI with combination anticholinergic therapy, specifically trospium and solifenacin or tolterodine compared to monotherapy or placebo [13••].

Kosilov et al. [33] demonstrated that among patients over 65 years with moderate symptoms the combination of high dose trospium 60 mg/d and solifenacin 20 mg/d for short courses (10 weeks) significantly decreased incontinence episodes by 45–60% which was maintained for 6 months, and among those with severe symptoms, prolonged courses (20 weeks) decreased incontinence episodes by 55.3% as compared to placebo, notably without increasing post void residual volume (PVR). Kosilov et al. [33] also evaluated patient compliance with continuous and cyclic therapy and demonstrated that patient compliance was high (76–84%) with one year cyclic therapy of trospium and solifenacin, but compliance was low and withdrawals high (66%) with

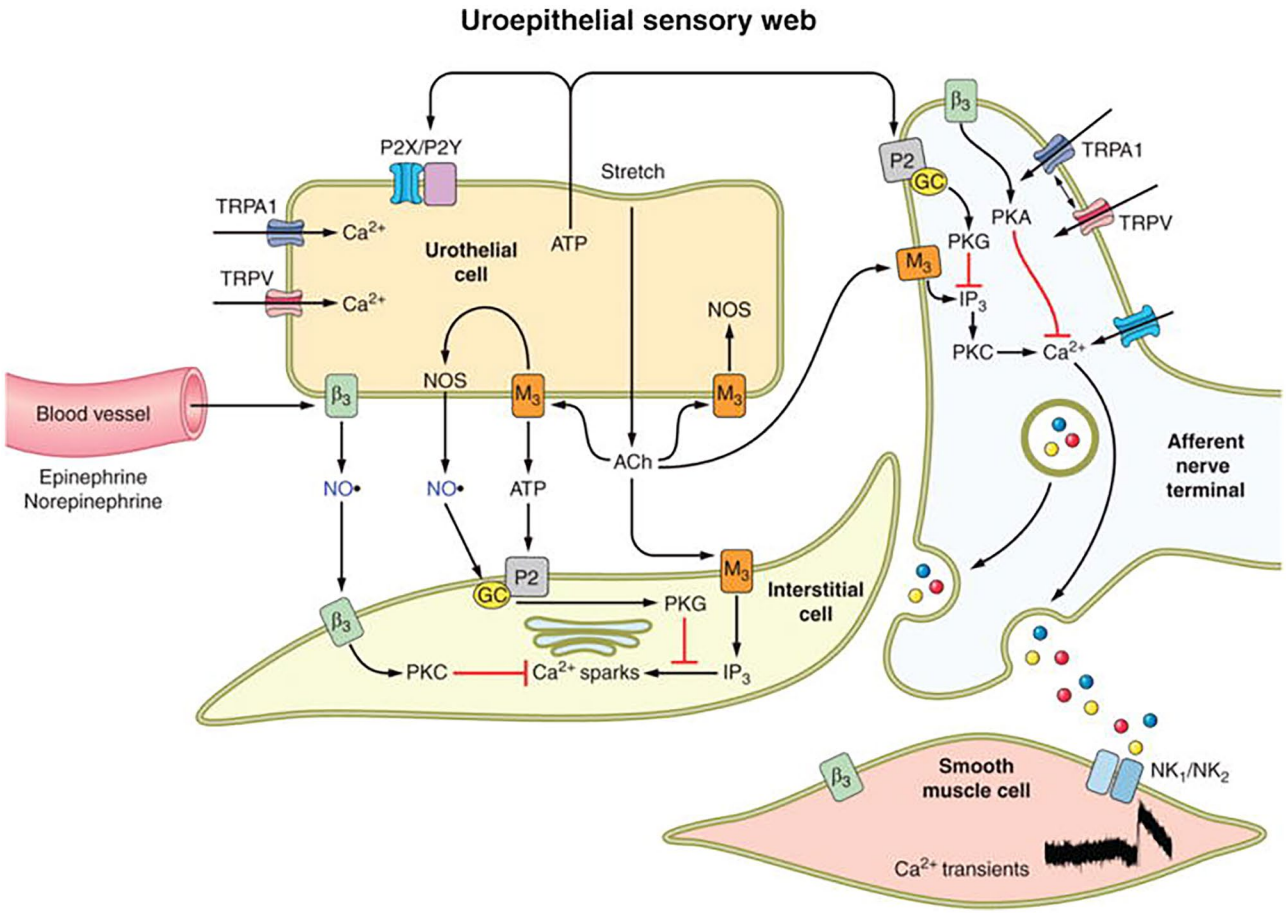

Fig. 2 Uroepithelial sensory web. Hypothetical model depicting possible interactions between bladder afferent nerves, urothelial cells, smooth muscle cells, interstitial cells, and blood vessels. Urothelial cells can also be targets for transmitters released from nerves or other cell types. Urothelial cells can be activated by either autocrine (i.e., autoregulation) or paracrine mechanisms (release from nearby nerves or other cells). Bladder stretch releases ATP which acts on P2 receptors on the afferent terminal or the interstitial cell and on P2 receptors on the urothelial cell. Stretch also releases ACh which acts on muscarinic receptors (M3) on the afferent terminal, the interstitial cell, or the urothelial cell. The latter action can release NO. Epinephrine or norepinephrine also release NO from the urothelial cell by activating β3 adrenergic receptors. Figure adapted from de Groat, William C et al. "Neural control of the lower urinary tract." Comprehensive Physiology vol. 5,1 (2015): 327–96. https://doi.org/10.1002/cphy.c130056

continuous dosing. Finally, they evaluated the cognitive effect of higher dose combination (solifenacin 20 mg/d and trospium 60 mg/d), lower dose combination (solifenacin 10 mg/d and trospium 30 mg/d) and placebo. They found that quality of life parameters were improved in the combination group regardless of dose while cognitive parameters did not differ among all three groups [34].

Anticholinergic Plus β-3 Agonist

The majority of studies that evaluate the combination of anticholinergic medications with β-3 agonists for refractory OAB focus on solifenacin with mirabegron. These studies demonstrate improvements in urinary frequency, urgency, UI, Patient's Perception of Bladder Condition (PPBC) scores, OAB-q scores, and health related quality of life (HRQoL) compared to monotherapy, placebo or both [13••] and similar safety profile among both participants older than 65 years and older than 75 years compared to the general population [26].

In the largest randomized double-blind study involving 435 sites, 42 countries and 3398 participants with OAB-wet (SYNERGY Trial), Herschorn et al. [22••] demonstrated that combination therapy (solifenacin 5 mg plus either 25 mg mirabegron or 50 mg mirabegron) was significantly better than monotherapy in decreasing episodes of urinary incontinence, micturitions, urgency episodes and nocturia in a 24-h period after 12 weeks of continuous therapy. In terms of UI episodes, those taking solifenacin 5 mg plus mirabegron 25 mg and solifenacin 5 mg plus mirabegron 50 mg had −0.70 and −0.65 UI episodes respectively compared to −0.37 UI episodes with mirabegron 25 mg monotherapy

Table 1 Summary of combination treatment review articles

Pub. year	Authors	Study design	Population	Intervention	Outcome
Anticholinergic plus anticholinergic					
2014	Kosilov et al. [54]	Randomized control trial, blind	*N* = 313 (62.6% female) Mean age: 68.6 (65 +) 50.4% had severe symptoms based on ICIQ-SF	Trospium + solifenacin	Decreased urgency and UUI with intermittent or continuous *trospium plus solifenacin* compared to placebo
2014	Kosilov et al. [33]	Randomized control trial, blind	*N* = 341 (54.5% female) Mean age: 69.9 (65 +) Severe symptoms (3 + incontinence per day)	Trospium + solifenacin	Decreased urgency and UUI with intermittent or continuous *trospium plus solifenacin* compared to placebo
2018	Kosilov et al. [34]	Randomized control trial, blind	*N* = 312 (100% female) Mean age: 69.4 (60–83) ICIQ-SF mean = 11.1	Trospium + solifenacin	No statistically significant decrease in cognitive parameters between high dose *trospium and solifenacin*, as compared to usual dose and placebo
Anticholinergic plus β-3 agonist					
2015	Kosilov et al. [55]	Randomized control trial	*N* = 239 (59.8% female) mean age: 71.2 (65 +)	Solifenacin + mirabegron	Improved OAB-q scores, frequency and UUI with *mirabegron plus solifenacin* compared to placebo or monotherapy mirabegron
2015	Abrams et al. [56]	Randomized, double blind phase II (Symphony)	*N* = 1306 (66.4% female) Mean age: 54.9 (18 +) Avg daily incontinence: 1.25	Solifenacin + mirabegron	Decreased frequency and urgency with *solifenacin plus mirabegron* compared to monotherapy solifenacin
2018	Gratzke et al. [57••]	Randomized, multicenter phase III (Synergy II)	*N* = 1794 (80% female) Median age: 60 (19–86) Mean BMI: 29 Avg daily incontinence: 3.1	Solifenacin + mirabegron	Decreased frequency and UUI with *solifenacin plus mirabegron* compared to monotherapy solifenacin
2018	Robinson et al. [3]	Secondary analysis of Synergy study	*N* = 3527 Participants aged > 18 years with symptoms of OAB for > 3 months who recorded > 8 micturitions/day, > 1 urgency episode/day, > 3 incontinence episodes/week	Solifenacin + mirabegron	Improved OAB-q symptom bother and HRQoL total score with *solifenacin plus mirabegron* compared to monotherapy solifenacin and placebo
2017	Herschorn et al. [22••]	Randomized, double blind, multicenter (Synergy I)	*N* = 3398 (77% female) Mostly white (80%) Mean age: 57.4 (18 +) Mean BMI: 28.5 Baseline mean UUI episodes/day: 2.9	Solifenacin + mirabegron	Significantly decreased frequency, UUI, nocturia with *solifenacin plus mirabegron* compared to monotherapy solifenacin and placebo
2016	Drake et al. [23••]	Randomized, double blind, multicenter phase IIIB (BEDSIDE)	*N* = 2174 (83% female) Mostly white (94%) Mean age: 57.4 (18 +) Mean BMI: 29 Baseline mean UUI episodes/day: 3.2	Solifenacin + mirabegron	Decreased frequency and UUI with solifenacin plus mirabegron compared to monotherapy solifenacin

Table 1 (continued)

Pub. year	Authors	Study design	Population	Intervention	Outcome
2016	MacDiarmid et al. [58]	Secondary analysis of BEDSIDE	*N* = 2174 (83% female) Mostly white (94%) Mean age: 57.4 (18 +) Mean BMI: 29 Baseline mean UUI episodes/day: 3.2	Solifenacin + mirabegron	Improved PPBC scores and HRQoL with solifenacin plus mirabegron compared to monotherapy solifenacin
2017	Gibson et al. [26]	Randomized, double blind (BESIDE)	*N* = 2174 (83% female) Mostly white (94%) Mean age: 57.4 (18 +) Mean BMI: 29 Baseline mean UUI episodes/day: 3.2	Solifenacin + mirabegron	Greatest improvement in OAB symptoms with solifenacin plus mirabegron compared to monotherapy and similar safety profile in older patients (older than 65 years old) and elderly patients (older than 75 years old) compared to general population
2019	Mitcheson et al. [35••]	Randomized, double blind, controlled, multicenter, phase IIb	*N* = 1395 (90% female) Mostly white (68.5%) and Asian (24.1%) Mean age: 58.6 (18 +) 37% with severe average daily micturitions (> 11.5)	Tolterodine + vibegron	No difference in improvement with vibegron monotherapy compared to vibegron plus tolterodine
Anticholinergic plus desmopressin					
2018	Rovner et al. [28]	Randomized, double-blind	*N* = 106 (100% female) Mean age: 53.4 (18 +) Mean BMI: 30.4 Mostly white (75%) Mean nocturnal voids: 3.24	Tolterodine + desmopressin	Decreased nocturia with *tolterodine plus desmopressin* compared to monotherapy tolterodine
Anticholinergic plus behavioral modification					
2011	Kaya et al. [59]	Randomized control trial	*N* = 46 (100% female) Mean age: 48.5 Mean BMI: 31.9 Mean UUI episodes/day: 2.1	Trospium + physiotherapy	Decreased frequency and UUI with *trospium plus physiotherapy* compared to monotherapy trospium
2010	Mattiasson et al. [36]	Multicenter, randomized control trial	*N* = 643, (85.7% female) Mean age: 58.4 (18–87) Mostly white (98.6%) 50.2% reported UUI	Solifenacin + bladder training	Decreased frequency and increased satisfaction but no change in UUI with *solifenacin plus bladder training* compared to monotherapy solifenacin

Table 1 (continued)

Pub. year	Authors	Study design	Population	Intervention	Outcome
2010	Burgio et al. [37]	Secondary analysis of RCT	*N* = 307 (100% female) Mean age: 56.9 (21–87) Mean BMI: 33.2 Mostly white (62%) with 18.5% African American and 10% Hispanic 69% reported > 14 UUI episodes/week	Tolterodine + bladder training	No improvement in UUI with *tolterodine plus bladder training* compared to monotherapy tolterodine
Anticholinergic plus PTNS					
2018	Vecchioli-Scaldazza and Morosetti [38]	Randomized control trial	*N* = 27 (100% female) Mean age: 62 (41–70)	Solifenacin + PTNS	Significantly decreased frequency, urgency, UUI, and OAB-q with *solifenacin plus PTNS* compared to monotherapy solifenacin
2015	Kizilyel et al. [60]		*N* = 30 (100% female) Mean age: 39 (20–59)	Tolterodine + PTNS	Significantly decreased frequency and UUI with *tolterodine plus PTNS* compared to monotherapy tolterodine
Anticholinergic plus SNM					
2011	George et al. [39]	Retrospective	*N* = 88 (100%) Mean age: 62 (16–89) Median parity: 2 (0–13) Mostly white (85%) with 6% Asian and 6% Hispanic 34% had 5–10 UUI episodes/day	Anti-cholinergic (varied) + SNM	Only 22.7% of patients were restarted on ACHs after SNM implantation. Of those, 84.2% reported significant subjective improvement in symptoms

ICIQ-SF, International Consultation on Incontinence Questionnaire-Short Form; *UUI*, urgency urinary incontinence; *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, *RCT*, randomized control trial, *ACHs*, anticholinergics

and −0.45 episodes for solifenacin 5 mg monotherapy. In terms of micturitions per day, those taking solifenacin 5 mg plus mirabegron 25 mg and solifenacin 5 mg plus mirabegron 50 mg experienced −0.85 and −0.95 micturitions respectively compared to either dose of mirabegron or solifenacin monotherapy. Adverse events were higher in the combined therapy groups, including urinary retention, but were classified as mild or moderate in severity and most often included dry mouth, dyspepsia, and constipation. Furthermore, Robinson et al. [3] evaluated patient reported outcomes of this population and demonstrated that quality of life and symptom bother were statistically significantly improved in the combination therapy group as compared to monotherapy.

Vibegron is a β-3 receptor agonist recently approved by the FDA in 2020. Mitcheson et al. [35••] evaluated combination vibegron plus tolterodine and demonstrated statistical improvement in micturitions ($p < 0.0010$, urgency incontinence episodes ($p = 0.027$), total incontinence episodes ($p = 0.038$), and urgency episodes ($p < 0.001$) of combination therapy compared to tolterodine 4 mg monotherapy but similar efficacy between combination therapy and vibegron monotherapy.

Anticholinergic Plus Desmopressin

Rovner et al. [28] evaluated safety and efficacy of desmopressin 25ug plus tolterodine 4 mg among 106 women with nocturia and demonstrated a non-significant decrease in nocturia episodes (−0.34; $p = 0.112$). However, a post hoc analysis of women with nocturnal polyuria ($N = 47$) did show a trend toward decreased nocturnal voids (−0.62, $p = 0.064$) and significant decrease in nocturnal void volume (−166.0 ml, $p = 0.034$) and increase in mean time to first nocturnal void (65.11 min, $p = 0.045$).

Anticholinergic Plus Behavioral Modification

The AUA endorses the addition of anticholinergic medications with behavioral modification for patients not satisfactorily improved on behavioral modification alone noting limited evidence does indicate that combination may improve lower urinary tract symptoms and quality of life [20, 21].

In a large systematic review only 50% of studies that were reviewed demonstrated improvement in urinary frequency, urgency, UI, or OAB-q scores with the combination of anticholinergic medication and bladder training and did not demonstrate improvement compared to medication monotherapy, although the bladder training programs were heterogenous [13••]. Mattiasson et al. [36] evaluated combination solifenacin plus 16-week bladder training program with solifenacin alone and demonstrated significant improvement in patient satisfaction measured by a visual analog scale (4.18 vs 3.72, respectively; $p = 0.025$) and decreased urinary frequency measured by micturitions in 24 h (−3.11 vs −2.42, $p < 0.001$) with combination therapy. In addition, they noted a 97% compliance with medication for both groups over 16 weeks which may not be generalizable. However, Burgio et al. [37] in a planned secondary analysis of a randomized control trial found no statistically significant improvement in urgency score between combination anticholinergic medication and behavioral modification as compared to monotherapy alone ($p = 0.30$) but did demonstrate improvement in voiding frequency ($p = 0.009$).

Anticholinergic Plus Percutaneous Tibial Nerve Stimulation (PTNS)

Studies demonstrate the combination of anticholinergics, specifically tolterodine and solifenacin, and PTNS significantly decrease symptoms of urinary frequency, urgency, and UI compared to either treatment alone [13••].

Vecchioli-Scaldazza and Morosetti [38] in a randomized control trial with 105 women compared combination anticholinergics with PTNS and monotherapy of each. The groups included: solifenacin 5 mg every other day plus PTNS weekly for 8 weeks compared to monotherapy solifenacin 5 mg daily for 12 weeks or PTNS weekly for 12 weeks. Patients were followed for 10 months. They demonstrated significant improvement with combination therapy compared to solifenacin or PTNS monotherapy in urgency ($p = 0.0005$, $p = 0.0225$, respectively) and urgency urinary incontinence ($p = 0.0003$, $p = 0.0015$, respectively) and significant improvement compared to solifenacin monotherapy in daytime and night-time frequency ($p = 0.0167$, $p = 0.0243$) but not PTNS monotherapy.

Anticholinergic Plus Sacral Neuromodulation (SNM)

Few studies examine combination therapy with SNM. In a retrospective review ($N = 88$), 22.7% of patients who underwent SNM restarted an anticholinergic medication and 10.2% were on anticholinergics at the time of implantation (of which six of the nine patients continued their oral therapy) resulting in 25% of patients on combination therapy [39]. Of those that restarted anticholinergics, 84.2% reported significant subjective improvement.

Others

To date no studies have evaluated the combination of β-3 agonists with third-line management options or oral medical management plus intradetrusor onabotulinumtoxin.

Novel Pharmacologic Agents for OAB

As mentioned, several treatment modalities, including behavioral modification, pharmacotherapies, chemo denervation, and neuromodulation have been utilized in OAB [40••]. Beyond traditional therapeutic agents for overactive bladder, several novel agents have been proposed in recent years, each with varying mechanisms of action and efficacy.

Imidafenacin

Oral antimuscarinics have been a mainstay in OAB treatment [41]. However, some of these drugs lack appropriate bladder selectivity, leaving patients with a flurry of adverse events, most commonly dry mouth and constipation [41, 42]. Imidafenacin, a novel antimuscarinic agent, has higher bladder selectivity, which decreases the incidence of dry mouth, constipation, and other anticholinergic side effects. A recent meta-analysis by Wu et al., evaluated 7 randomized-controlled trials (RCTs) comparing imidafenacin with other antimuscarinics, including solifenacin, propiverine, fesoterodine, and tolterodine. The primary endpoints included improvements in overactive bladder symptoms score (OABSS) and change in OAB symptoms. Secondary endpoints included occurrence of adverse events, including dry mouth, constipation, blurry vision, and headaches. The study reported outcomes at an average of 23.4 weeks and found imidafenacin to have similar efficacy in voids, urgency episodes, urgency incontinence episodes, incontinence episodes, and OABSS. Imidafenacin showed improved efficacy in nocturia episodes (mean difference = −0.24, 95% CI = −0.44 to −0.4, $p = 0.02$). Imidafenacin also showed statistically significantly lower adverse events, specifically regarding dry mouth (RR = 0.87, 95% CI = 0.75–1.00, $p = 0.04$), constipation (RR = 0.68, 95% CI = 0.50–0.93, $p = 0.01$), and withdrawal (patients stopping treatment due to adverse events) (RR = 0.51, 95% CI = 0.29–0.89, $p = 0.02$). Based on these results, imidafenacin may prove to be a superior agent when treating patients long-term for OAB.

Tarafenacin

Tarafenacin, a new quinuclidinol derivative with strong antimuscarinic activity but limited inhibitory effect on the submandibular gland, has also been proposed for treatment of OAB; however, its efficacy data is less encouraging [43]. A randomized, double-blind, placebo-controlled phase 2 study was completed by Song et al. in 2015 [44]. This study randomized 235 patients into one of three treatment groups: 0.2 mg tarafenacin daily, 0.4 mg tarafenacin daily, or placebo daily for 12 weeks. Patients were enrolled if they experienced 8 + micturitions and 3 + incontinence episodes per day or 6 + urgency episodes per 3 days. Results demonstrated a significant decrease in mean number of micturitions per 24 h from baseline in the 0.4 mg tarafenacin group (−2.43 + / −2.21, $p = 0.033$). However, there was no significant difference in urgency episodes per 24 h between the three groups, or any significant difference in adverse effects, specifically blurred vision and constipation [44].

Solabegron, Ritobegron, and Vibegron

Beta-3-adrenoreceptor agonists are also commonly utilized for treatment of OAB. Mirabegron has predominantly been the agent of choice, however, other β-3-adrenoreceptor agonists, such as solabegron, ritobegron, and vibegron have also been proposed as treatment alternatives. Solabegron has been tested in animal studies and demonstrated bladder strip relaxation up to 82% of maximum potential [43]. In a multicenter, double-blind, randomized, placebo-controlled trial, solabegron was tested in women with OAB, with patients qualifying if they experienced 1 + incontinence episodes and 8 + average micturitions in 24 h. Subjects were randomized into one of three groups: solabegron 50 mg, solabegron 125 mg, or placebo twice a day. Results indicated that solabegron 125 mg twice daily produced a statistically significant difference in percent change from baseline to week 8 in incontinence episodes over 24 h when compared with placebo (−20.9%, $p = 0.025$), as well as statistically significant reductions in micturitions over 24 h from baseline to week 4 (−2.5 + / −0.27, $p < 0.05$) and week 8 (−3.0 + / −0.28, $p < 0.05$). Solabegron 125 mg twice daily also demonstrated a significant increase in volume voided from baseline to week 8 (39.6 + / −5.28, $p < 0.05$) [45]. Although promising, solabegron remains in testing phase, having recently met primary endpoints in OAB treatment but still awaiting FDA approval. Ritobegron, another β-3-adrenoreceptor agonist, was designed for treatment of overactive bladder. In animal studies, ritobegron demonstrated decreased frequency and amplitude of non-voiding contractions, as well as lower rates of residual urine and dry mouth symptoms. However, in its first phase III study compared with placebo, ritobegron did not show significant improvements in mean number of micturitions over 24 h [43]. Ritobegron awaits further testing in its utility of OAB treatment. The most recently approved β-3-adrenoreceptor agonist, Vibegron, was recently highlighted in a systematic review completed by Shi et al. [46••]. In this systematic review, randomized-controlled trials including vibegron were targeted. Three RCTs comparing vibegron to placebo were included, including over 2000 patients. Data showed that vibegron was more effective in reducing mean micturitions per day (−0.77, 95% CI = −1.0 to −0.55, $p < 0.00001$); mean number of urgency episodes per day (−0.77; 95% CI = −1.03 to −0.52; $p < 0.00001$);

mean number of urgency incontinence episodes per day (−0.50; 95% CI = −0.64 to −0.35; $p < 0.00001$); and mean number of incontinence episodes per day (−0.45; 95% CI = −0.66 to −0.25; $p < 0.0001$). It was also noted to be more effective in increasing mean volume voided/micturition (22.22; 95% CI = 17.36 to 27.07, $p < 0.00001$).

Purine Receptor Targets

Newer proposed treatment modalities revolve around the role of various receptors in detecting bladder stretch and filling sensation. When the urothelium is stretched, ATP is released and stimulates purinergic receptors to sense filling and urgency, eventually initiating the voiding reflex. Sensory nerve fibers express P2X receptors that control purinergic ligand-gated ion channels, which mediate this response. Pathologic conditions, including bladder inflammation or neurogenic disorders, may change the regulation and sensitivity of these receptors. Thus, it has been proposed that these purinergic receptors may be of strong interest in the treatment of lower urinary tract symptoms and OAB [47]. A study performed by Hao et al. [48], demonstrated the roles of $P2X_1$, $P2Y_{12}$ and adenosine A2 receptors in the process of micturition. To do so, they created $P2Y_{12}$ and A2b-receptor knockout mice. Through their work, they demonstrated that bladder smooth muscle contraction initiation mainly relies on ATP activation of $P2X_1$ receptors, with both $P2Y_{12}$ and A2b receptors regulating smooth muscle purinergic contractility by modulating adenylyl-cyclase cyclic-AMP signaling. Deletion of $P2Y_{12}$ receptors in mice resulted in underactive bladder phenotypes, whereas deletion of A2b receptors in mice resulted in overactive bladder phenotypes. These results suggest $P2Y_{12}$ and A2b receptors are key targets for control of LUTS and OAB [48]. Current FDA-approved inhibitors of $P2Y_{12}$ and novel agents may translate into effective therapies for OAB.

TRP Antagonists

Other receptors involved in bladder stretch are the transient receptor potential (TRP) channels (TRPV1, TRPV4, TRPM8, TRPA1). These receptors have long been known to be expressed throughout the lower urinary tract, on the urothelium, interstitial cells, detrusor and urethral smooth muscle [47]. TRPV1 receptors are known to be involved in neurogenic lower urinary tract dysfunction (NLUTD), however, their role in normal bladder function is still debated. In NLUTD, TRPV1 is involved in the hyperreflexic spinal micturition reflex pathway. Current TRPV1 agonists, capsaicin and resiniferatoxin, have been used clinically for LUT disorders to desensitize TRP channels. TRP antagonists have been tested, but unfortunately were associated with adverse reactions, including hyperthermia and reduction of noxious heat sensation, leading to burn injuries. Newer TRPV1 blocking drugs have now been developed and do not induce these same adverse effects, however, their efficacy and testing in treatment of OAB is still under review [49]. TRPV4 has been involved in the treatment of cyclophosphamide-induced cystitis, but human testing is limited. TRPV4 blockers are thought to increase intercontraction intervals, bladder capacity, voided volume, and post void residuals but further testing is required to determine efficacy. TRPM8 has been correlated with bladder pain and increased voiding frequency, thus leading to its potential role as a target in treatment of LUTS. TRPM8 antagonists have shown to reduce frequency of volume-induced bladder contractions in rats, suggesting their potential use in human treatment of OAB. TRPM8 antagonists have been associated with hypothermia, leading to delay in their testing as OAB treatment agents [49]. TRPA1 channels function to detect noxious stimuli in the bladder. They have been associated with detrusor overactivity, thus leading to a possible role in the treatment of OAB. However, testing of their role in treatment of OAB has not progressed very far [49].

Others (Sildenafil, ENaC Antagonists, Nicorandil, Gabapentin)

Other novel targets for OAB treatment include drugs frequently used in treatment of other pathologies. Amiloride, an epithelial sodium channel (ENaC) inhibitor, has been used in treatment of heart failure. A study by Yamamoto et al. tested the association between ENaC and mineralocorticoid receptors (MR) in rats. They found that MR stimulation led to increased levels of ENaC, as well as significantly shorter intercontraction intervals. Utilization of amiloride normalized the intercontraction intervals, lending to amiloride's potential as a therapeutic agent in OAB [50]. Sildenafil, a phosphodiesterase-inhibitor, has largely been used in the treatment of erectile dysfunction. Its role in bladder muscle relaxation was tested by Oger et al. [51] to study the effect of NO-cGMP signaling on voiding and storage. The study involved 20 bladder samples obtained from patients undergoing cystectomy for bladder cancer. Results confirmed that sildenafil-mediated relaxation of detrusor muscle does occur and involves cGMP, cAMP, and potassium channel signaling pathways, with only minor involvement of nitrous oxide. While relaxation was demonstrated, further studies are needed to determine the role of sildenafil on the micturition reflex and improvement in OAB symptoms [51].

Gabapentin, a newer generation antiepileptic with use in neurogenic and psychiatric disorder treatment, was recently compared to solifenacin and placebo in treatment of OAB. A 12-week, randomized, double-blind, double dummy placebo-controlled study randomized 94 patients into 3 treatment groups: placebo, gabapentin (dose: 100 mg

once a day gradually reaching 100 mg 3 × per day at end of week 1, max dose 900 mg per day, titrated down to 100 mg per day for last 2 days), and solifenacin (5 mg once a day, max 10 mg once a day). Primary endpoints included micturitions and urgency episodes in 24 h. Improvements were also assessed by the OAB-questionnaire. Compared to placebo, both gabapentin and solifenacin demonstrated improvement in mean number of micturitions (AMD −1.179, 95% CI −1.98 to −0.38, $p < 0.001$; AMD −1.706, 95% CI −2.52 to −0.09, $p < 0.001$, respectively) and in mean number of urgency episodes per 24 h (AMD −0.903, 95%CI −1.44, −0.37; $p < 0.001$; −0.896, 95%CI −1.44, −0.35; $p < 0.001$). Gabapentin also showed superiority over solifenacin in mean nocturia episodes per 24 h (AMD −0.607, 95%CI −1.04, −0.18; $p < 0.001$) [52••]. These results indicated gabapentin's strong potential as a treatment in OAB.

Nicorandil, a vasodilatory drug used in treatment of angina, has been proposed as a potential treatment of OAB, largely due to the theory of ischemia induced OAB. A study completed by Saito et al. utilized nicorandil in spontaneously hypertensive rats. Rats were treated for 6 weeks with either 0, 3, or 10 mg/kg/day of nicorandil. Blood flow was then tested using hydrogen clearance. At the end of 6 weeks, both doses of nicorandil failed to decrease blood pressure, however, they did decrease micturition frequency and increase bladder blood flow. They concluded that nicorandil prevented hypertension-related bladder dysfunction, largely due to its role in increasing bladder blood flow [53].

Conclusion

OAB is a condition that can be caused by dysfunction of a multitude of neural, muscular, and urothelial systems that work in tandem to maintain continence between episodes of micturition. In the past 5 years, combination therapeutic agents targeting multiple pathways in voiding (combination anticholinergics, anticholinergic plus β-3 agonist, anticholinergic plus desmopressin, anticholinergic plus behavioral modification, anticholinergic plus neuromodulation) have been shown to be more effective than targeting a single pathway. Though current OAB treatments can significantly reduce symptoms, none are curative. Further investigation of therapeutics targeting novel neural and biochemical pathways in voiding may greatly enhance treatment of OAB, especially when combined with established agents.

Compliance with Ethical Standards

Conflict of Interest The authors do not have existing conflict of interests.

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.

References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1.•• Haylen BT, de Ridder D, Freeman RM, Swift SE, Berghmans B, Lee J, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Int Urogynecol J. 2010 Jan;21(1):5–26. **Widely accepted definitions of common voiding and urodynamic terms.**
2. Raju R, Linder BJ. Evaluation and treatment of overactive bladder in women. Mayo Clin Proc. 2020;95(2):370–7.
3. Robinson D, Kelleher C, Staskin D, Mueller ER, Falconer C, Wang J, et al. Patient-reported outcomes from SYNERGY, a randomized, double-blind, multicenter study evaluating combinations of mirabegron and solifenacin compared with monotherapy and placebo in OAB patients. Neurourol Urodyn. 2018;37(1):394–406.
4. Stewart WF, Van Rooyen JB, Cundiff GW, Abrams P, Herzog AR, Corey R, et al. Prevalence and burden of overactive bladder in the United States. World J Urol. 2003;20(6):327–36.
5. Irwin DE, Milsom I, Hunskaar S, Reilly K, Kopp Z, Herschorn S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. Eur Urol. 2006 Dec;50(6):1306–14; discussion 1314–1315.
6. Irwin DE, Kopp ZS, Agatep B, Milsom I, Abrams P. Worldwide prevalence estimates of lower urinary tract symptoms, overactive bladder, urinary incontinence and bladder outlet obstruction. BJU Int. 2011;108(7):1132–8.
7. Brown JS, McGhan WF, Chokroverty S. Comorbidities associated with overactive bladder. Am J Manag Care. 2000;6(11 Suppl):S574-579.
8. Kinsey D, Pretorius S, Glover L, Alexander T. The psychological impact of overactive bladder: a systematic review. J Health Psychol. 2016;21(1):69–81.
9. Powell LC, Szabo SM, Walker D, Gooch K. The economic burden of overactive bladder in the United States: a systematic literature review. Neurourol Urodyn. 2018;37(4):1241–9.
10. Coyne KS, Wein A, Nicholson S, Kvasz M, Chen C-I, Milsom I. Economic burden of urgency urinary incontinence in the United States: a systematic review. J Manag Care Pharm. 2014;20(2):130–40.
11.•• de Groat WC, Griffiths D, Yoshimura N. Neural control of the lower urinary tract. Compr Physiol. 2015 Jan;5(1):327–96. **Comprehensive review of neural control of the lower urinary tract.**
12. Peyronnet B, Mironska E, Chapple C, Cardozo L, Oelke M, Dmochowski R, et al. A comprehensive review of overactive bladder pathophysiology: on the way to tailored treatment. Eur Urol. 2019;75(6):988–1000.
13.•• Kasman A, Stave C, Elliott CS. Combination therapy in overactive bladder-untapped research opportunities: a systematic review of the literature. Neurourol Urodyn. 2019 Nov;38(8):2083–92. **Large systematic review of combination therapy for refractory OAB.**

14. Yeaw J, Benner JS, Walt JG, Sian S, Smith DB. Comparing adherence and persistence across 6 chronic medication classes. J Manag Care Pharm. 2009;15(9):728–40.
15. Chancellor MB, Migliaccio-Walle K, Bramley TJ, Chaudhari SL, Corbell C, Globe D. Long-term patterns of use and treatment failure with anticholinergic agents for overactive bladder. Clin Ther. 2013;35(11):1744–51.
16. Benner JS, Nichol MB, Rovner ES, Jumadilova Z, Alvir J, Hussein M, et al. Patient-reported reasons for discontinuing overactive bladder medication. BJU Int. 2010;105(9):1276–82.
17. Amundsen CL, Richter HE, Menefee SA, Komesu YM, Arya LA, Gregory WT, et al. OnabotulinumtoxinA vs sacral neuromodulation on refractory urgency urinary incontinence in women: a randomized clinical trial. JAMA. 2016;316(13):1366–74.
18. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. Hypertension. 2018;71(6):1269–324.
19. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2013;31(7):1281–357.
20. Lightner DJ, Gomelsky A, Souter L, Vasavada SP. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU Guideline Amendment 2019. J Urol. 2019;202(3):558–63.
21. Gormley EA, Lightner DJ, Burgio KL, Chai TC, Clemens JQ, Culkin DJ, et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline. J Urol. 2012;188(6 Suppl):2455–63.
22.•• Herschorn S, Chapple CR, Abrams P, Arlandis S, Mitcheson D, Lee K-S, et al. Efficacy and safety of combinations of mirabegron and solifenacin compared with monotherapy and placebo in patients with overactive bladder (SYNERGY study). BJU Int. 2017 Oct;120(4):562–75. **Large randomized control trial (N 3398) evaluating safety and efficacy of combination solifenacin plus mirabegron vs monotherapy over 18 weeks. Demonstrates strongest evidence for combination therapy.**
23.•• Drake MJ, Chapple C, Esen AA, Athanasiou S, Cambronero J, Mitcheson D, et al. Efficacy and safety of mirabegron add-on therapy to solifenacin in incontinent overactive bladder patients with an inadequate response to initial 4-week solifenacin monotherapy: a randomised double-blind multicentre phase 3B study (BESIDE). Eur Urol. 2016 Jul;70(1):136–45. **Large randomized control trial (N 2174) evaluating safety, efficacy, tolerability of combination solifenacin plus mirabegron. Demonstrates strongest evidence for combination therapy.**
24. Gratzke C, Chapple C, Mueller ER, Robinson D, Rolland C, Staskin D, et al. Efficacy and safety of combination pharmacotherapy for patients with overactive bladder: a rapid evidence assessment. Eur Urol. 2019;76(6):767–79.
25. Fogaing C, Mossa AH, Campeau L. Are beta 3 adrenergic agonists now the preferred pharmacologic management of overactive bladder?. Curr Urol Rep. 2020;21(12):49.
26. Gibson W, MacDiarmid S, Huang M, Siddiqui E, Stölzel M, Choudhury N, et al. Treating overactive bladder in older patients with a combination of mirabegron and solifenacin: a prespecified analysis from the BESIDE study. Eur Urol Focus. 2017;3(6):629–38.
27. Hsu FC, Weeks CE, Selph SS, Blazina I, Holmes RS, McDonagh MS. Updating the evidence on drugs to treat overactive bladder: a systematic review. Int Urogynecol J. 2019;30(10):1603–17.
28. Rovner ES, Raymond K, Andruczyk E, Juul KV. Low-dose desmopressin and tolterodine combination therapy for treating nocturia in women with overactive bladder: a double-blind, randomized, controlled study. Low Urin Tract Symptoms. 2018;10(3):221–30.
29. Kelleher C, Hakimi Z, Zur R, Siddiqui E, Maman K, Aballéa S, et al. Efficacy and tolerability of mirabegron compared with antimuscarinic monotherapy or combination therapies for overactive bladder: a systematic review and network meta-analysis. Eur Urol. 2018;74(3):324–33.
30. Campbell NL, Lane KA, Gao S, Boustani MA, Unverzagt F. Anticholinergics influence transition from normal cognition to mild cognitive impairment in older adults in primary care. Pharmacotherapy. 2018;38(5):511–9.
31. Wagg A, Arumi D, Herschorn S, Angulo Cuesta J, Haab F, Ntanios F, et al. A pooled analysis of the efficacy of fesoterodine for the treatment of overactive bladder, and the relationship between safety, co-morbidity and polypharmacy in patients aged 65 years or older. Age Ageing. 2017;46(4):620–6.
32. Amend B, Hennenlotter J, Schäfer T, Horstmann M, Stenzl A, Sievert K-D. Effective treatment of neurogenic detrusor dysfunction by combined high-dosed antimuscarinics without increased side-effects. Eur Urol. 2008;53(5):1021–8.
33. Kosilov K, Loparev S, Iwanowskaya M, Kosilova L. Effectiveness of combined high–dosed trospium and solifenacin depending on severity of OAB symptoms in elderly men and women under cyclic therapy. Cent European J Urol. 2014;67(1):43–8.
34. Kosilov K, Kuzina I, Loparev S, Gainullina Y, Kosilova L, Prokofyeva A. Influence of the short-term intake of high doses of solifenacin and trospium on cognitive function and health-related quality of life in older women with urinary incontinence. Int Neurourol J. 2018;22(1):41–50.
35.•• Mitcheson HD, Samanta S, Muldowney K, Pinto CA, Rocha B de A, Green S, et al. Vibegron (RVT-901/MK-4618/KRP-114V) Administered once daily as monotherapy or concomitantly with tolterodine in patients with an overactive bladder: a multicenter, phase IIb, randomized, double-blind, controlled trial. Eur Urol. 2019 Feb;75(2):274–82. **Only clinical study evaluating the beta-3 agonist vibegron plus tolterodine.**
36. Mattiasson A, Masala A, Morton R, Bolodeoku J, SOLAR Study Group. Efficacy of simplified bladder training in patients with overactive bladder receiving a solifenacin flexible-dose regimen: results from a randomized study. BJU Int. 2010 Apr;105(8):1126–35.
37. Burgio KL, Kraus SR, Borello-France D, Chai TC, Kenton K, Goode PS, et al. The effects of drug and behavior therapy on urgency and voiding frequency. Int Urogynecol J. 2010;21(6):711–9.
38. Vecchioli-Scaldazza C, Morosetti C. Effectiveness and durability of solifenacin versus percutaneous tibial nerve stimulation versus their combination for the treatment of women with overactive bladder syndrome: a randomized controlled study with a follow-up of ten months. Int braz j urol. 2018;44:102–8.
39. George E, Lane F, Noblett K. Use of combined anticholinergic medication and sacral neuromodulation in the treatment of refractory overactive bladder. Female Pelvic Med Reconstr Surg. 2011;17(2):97–9.
40.•• Olivera CK, Meriwether K, El-Nashar S, Grimes CL, Chen CCG, Orejuela F, et al. Nonantimuscarinic treatment for overactive bladder: a systematic review. American Journal of Obstetrics and Gynecology. 2016 Jul 1;215(1):34–57. **Systematic review overviewing various treatment options in OAB.**

41. Wu J-P, Peng L, Zeng X, Li H, Shen H, Luo D-Y. Is imidafenacin an alternative to current antimuscarinic drugs for patients with overactive bladder syndrome?. Int Urogynecol J. 2021;32(5):1117–27.
42. Wu Y (Maria), Welk B. Revisiting current treatment options for stress urinary incontinence and pelvic organ prolapse: a contemporary literature review. Res Rep Urol. 2019 Jun 19;11:179–88.
43. Thiagamoorthy G, Cardozo L, Robinson D. Current and future pharmacotherapy for treating overactive bladder. Expert Opin Pharmacother. 2016;17(10):1317–25.
44. Song M, Kim JH, Lee K-S, Lee JZ, Oh S-J, Seo JT, et al. The efficacy and tolerability of tarafenacin, a new muscarinic acetylcholine receptor M3 antagonist in patients with overactive bladder; randomised, double-blind, placebo-controlled phase 2 study. Int J Clin Pract. 2015;69(2):242–50.
45. Ohlstein EH, von Keitz A, Michel MC. A multicenter, double-blind, randomized, placebo-controlled trial of the β3-adrenoceptor agonist solabegron for overactive bladder. Eur Urol. 2012;62(5):834–40.
46.•• Shi H, Chen H, Zhang Y, Cui Y. The efficacy and safety of vibegron in treating overactive bladder: a systematic review and pooled analysis of randomized controlled trials. Neurourology and Urodynamics. 2020;39(5):1255–63. **Systematic review demonstrating efficacy of recently approved vibegron in treatment of OAB.**
47. Andersson K-E. Potential future pharmacological treatment of bladder dysfunction. Basic Clin Pharmacol Toxicol. 2016;119(S3):75–85.
48. Hao Y, Wang L, Chen H, Hill WG, Robson SC, Zeidel ML, et al. Targetable purinergic receptors P2Y12 and A2b antagonistically regulate bladder function. JCI Insight. 4(16):e122112.
49. Andersson K-E. Agents in early development for treatment of bladder dysfunction – promise of drugs acting at TRP channels?. Expert Opin Investig Drugs. 2019;28(9):749–55.
50. Yamamoto S, Hotta Y, Maeda K, Kataoka T, Maeda Y, Hamakawa T, et al. Mineralocorticoid receptor stimulation induces urinary storage dysfunction via upregulation of epithelial sodium channel expression in the rat urinary bladder epithelium. J Pharmacol Sci. 2016;130(4):219–25.
51. Oger S, Behr-Roussel D, Gorny D, Lebret T, Validire P, Cathelineau X, et al. Signalling pathways involved in sildenafil-induced relaxation of human bladder dome smooth muscle. Br J Pharmacol. 2010;160(5):1135–43.
52.•• Chua ME, See MC, Esmeña EB, Balingit JC, Morales ML. Efficacy and safety of gabapentin in comparison to solifenacin succinate in adult overactive bladder treatment. LUTS: Lower Urinary Tract Symptoms. 2018;10(2):135–42. **Randomized, double-blind trial demonstrating efficacy of known tolerable drug, gabapentin, in treating OAB.**
53. Saito M, Ohmasa F, Tsounapi P, Inoue S, Dimitriadis F, Kinoshita Y, et al. Nicorandil ameliorates hypertension-related bladder dysfunction in the rat. Neurourol Urodyn. 2012;31(5):695–701.
54. Kosilov KV, Loparev SA, Ivanovskaya MA, Kosilova LV. Randomized controlled trial of cyclic and continuous therapy with trospium and solifenacin combination for severe overactive bladder in elderly patients with regard to patient compliance. Ther Adv Urol. 2014;6(6):215–23.
55. Kosilov K, Loparev S, Ivanovskaya M, Kosilova L. A randomized, controlled trial of effectiveness and safety of management of OAB symptoms in elderly men and women with standard-dosed combination of solifenacin and mirabegron. Arch Gerontol Geriatr. 2015;61(2):212–6.
56. Abrams P, Kelleher C, Staskin D, Rechberger T, Kay R, Martina R, et al. Combination treatment with mirabegron and solifenacin in patients with overactive bladder: efficacy and safety results from a randomised, double-blind, dose-ranging, phase 2 study (Symphony). Eur Urol. 2015;67(3):577–88.
57.•• Gratzke C, van Maanen R, Chapple C, Abrams P, Herschorn S, Robinson D, et al. Long-term safety and efficacy of mirabegron and solifenacin in combination compared with monotherapy in patients with overactive bladder: a randomised, multicentre phase 3 study (SYNERGY II). Eur Urol. 2018 Oct;74(4):501–9. **Large randomized control trial (N 1829) evaluating safety and efficacy of combination solifenacin plus mirabegron over 12 months. Demonstrates strongest evidence for combination therapy.**
58. MacDiarmid S, Al-Shukri S, Barkin J, Fianu-Jonasson A, Grise P, Herschorn S, et al. Mirabegron as add-on treatment to solifenacin in patients with incontinent overactive bladder and an inadequate response to solifenacin monotherapy: responder analyses and patient-reported outcomes from the BESIDE study [corrected]. J Urol. 2016;196(3):809–18.
59. Kaya S, Akbayrak T, Beksaç S. Comparison of different treatment protocols in the treatment of idiopathic detrusor overactivity: a randomized controlled trial. Clin Rehabil. 2011;25(4):327–38.
60. Kızılyel S, Karakeçi A, Ozan T, Ünüş İ, Barut O, Onur R. Role of percutaneous posterior tibial nerve stimulation either alone or combined with an anticholinergic agent in treating patients with overactive bladder. Turk J Urol. 2015;41(4):208–14.