Current Bladder Dysfunction Reports (2019) 14:18–23
https://doi.org/10.1007/s11884-019-00501-2

OVERACTIVE BLADDER (U LEE AND S ADELSTEIN, SECTION EDITORS)

Recent Non-neurogenic Overactive Bladder Trials

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Published online: 19 January 2019

Abstract

Purpose of Review We sought to address the most important trials regarding overactive bladder (OAB) syndrome published in the past 5 years regarding pharmacological treatment and minimally invasive procedures (botulinum toxin A, percutaneous tibial nerve stimulation, and sacral neuromodulation).

Recent Findings Most of the randomized controlled trials related to OAB are studying anticholinergics and/or beta-adrenergics versus each other or to a placebo-comparator group. Studies have shown stability of using mirabegron and that combination therapy (anticholinergics plus beta-adrenoceptors) seems a good choice for patients with OAB. Percutaneous tibial nerve stimulation needs further studies with comparators to confirm its role. Regarding intra-vesical botulinic toxin or sacral neuromodulation for OAB, both options present good percentages of patient improvement, with no clinically significant difference between them to this moment.

Summary Despite a growing number of high-quality randomized trials on OAB, further studies are needed comparing different lines of treatment for this disease.

Keywords Overactive bladder · Randomized controlled trials · Treatment · Review

Introduction

Overactive bladder (OAB) is a disease characterized by urgency, with or without urgency incontinence, and may be followed by increased urinary frequency and nocturia, in the absence of urinary tract infection or other pathology [1]. It is estimated that 82.6 billion dollars will be spent in 2020 to treat this disease [2], causing an economic burden. Its prevalence increases with age, and it is estimated that around 29.8 million adults with more than 40 years have bothersome OAB symptoms [3].

Treatment for OAB is divided into several lines: first line is represented by behavioral therapy, second line by pharmacologic management, and third line treatment by sacral neuromodulation, percutaneous tibial nerve stimulation, or intra-vesical onabotulinumtoxinA therapy [4]. In the last 5 years, most of the randomized controlled studies were focused on the second and third line therapies [5]. In this narrative review, we sought to analyze the most important randomized controlled trials in the last 5 years about OAB treatment and its main results.

Antimuscarinics and Beta-adrenergics

Most of the guidelines recommend anticholinergics as a pharmacological option for non-neurogenic OAB, especially because they present a level-1 evidence of effect versus placebo [6]. However, the persistence rate with prescription of anticholinergics is low [7], and older people are more likely than younger patients to maintain the medication. It is still controversial whether one anticholinergic is superior to another [8]. Furthermore, there are some studies that are seeking a possible link between cumulative use of anticholinergics and incident dementia [9•]. Basically, antimuscarinics specific for M3 receptors impairs detrusor muscle contraction and causes few side effects with prescription.

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

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Another class of drugs that act as agonists, directly relaxing detrusor contraction, is beta-3-adrenoceptors. Mirabegron is a drug that presents similar efficacy when compared to anticholinergics and is superior to placebo [10]. Long-term studies have been showing a stable cardiovascular (CV) profile, concern that was noticed in the first publications regarding the drug. An analysis of almost 14,000 patients who received more than one dose of mirabegron as monotherapy was compared to placebo or antimuscarinics, and changes from baseline in blood pressure were similar among the groups and did not confer increased risk for CV events in the mirabegron group [11•]. Solabegron is another beta-adrenergic that was studied; however, no other RCT was found after 2012.

Data from literature search and from a recent systematic review with network meta-analysis [12•] have shown that comparable overall efficacy was seen for mirabegron 50 mg versus most active treatments, but solifenacin 10 mg monotherapy and solifenacin 5 mg plus mirabegron 25 or 50 mg in combination were more efficacious for some/all outcomes. Twenty-four RCTs were published since 2013 regarding antimuscarinics or anticholinergics for OAB; within this period, we have pooled data from all RCTs whose sample size were higher than 1000 patients (Table 1), comprising ten studies [13, 14, 15••, 16–22].

Studies with Combination Therapy (Antimuscarinics + Beta-adrenoceptors)

SYMPHONY Study [13]

This was a phase 2, factorial design, randomized, double-blind, placebo-controlled trial conducted at 141 sites and published at *European Urology*. A total of 1306 patients (66.4% female) were treated for 12 weeks into 1 of 12 groups: 6 combination groups (solifenacin 2.5, 5, or 10 mg plus mirabegron 25 or 50 mg), five monotherapy groups (solifenacin 2.5, 5, or 10 mg, or mirabegron 25 or 50 mg), or placebo. They have concluded that combination therapy with solifenacin/mirabegron significantly improved the mean volume voided per micturition (primary endpoint), micturition frequency, and urgency compared with solifenacin 5 mg monotherapy.

BESIDE Study [14]

This study aimed to evaluate if the combination of solifenacin 5 mg and mirabegron 50 mg ($n = 724$) would be superior to using solifenacin 5 ($n = 728$) or 10 mg ($n = 719$) in OAB patients with inadequate response after 4 weeks of solifenacin 5 mg, comprising 2174 patients. Primary endpoint was a change from baseline to end of treatment in the mean number of incontinence episodes per 24 h. They found that adding mirabegron 50 mg to solifenacin 5 mg further improved OAB symptoms versus solifenacin 5 or 10 mg. All treatments were well tolerated during a follow-up of 12 weeks.

SYNERGY Study [15••]

Another RCT was aiming to see whether the combination of solifenacin 5 mg with mirabegron 25 or 50 mg would be superior to monotherapy (solifenacin 5 mg, mirabegron 25 or 50 mg, placebo) for 12 weeks. It presents the largest sampling among all others and women accounted for 77% of the total. In this study, a 4-week placebo run-in period was present, as well as a 2-week single-blind, placebo run-out. They have also found that combined therapy with solifenacin 5 mg + mirabegron 25 or 50 mg improved the treatment efficacy compared with monotherapy, and most of the effects were observable after 4 weeks of treatment.

Studies with Monotherapy

Batista et al. [16] have compared mirabegron 50 mg ($n = 943$) versus solifenacin 5 mg ($n = 944$) in a non-inferiority study enrolling women with at least 3 months of OAB symptoms that were dissatisfied with their previous antimuscarinic treatments. The primary endpoint was the change from baseline to end of treatment in mean number of micturitions/24 h. Both treatments demonstrated clinically meaningful reductions in efficacy variables and were well tolerated, with a lower incidence of dry mouth with mirabegron.

The EIGHT trial [17] assessed the superiority of fesoterodine 8 mg ($n = 779$) vs 4 mg ($n = 790$) or placebo ($n = 386$) in reducing the number of urgency incontinence episodes, micturitions, and urgency. The authors, after a 12-week follow-up, have concluded that both doses of fesoterodine were more effective than placebo.

Herschorn et al. [18] have compared mirabegron 25 and 50 mg versus placebo in patients with OAB after a 2-week placebo run-in, comprising 1306 patients. They have analyzed changes to final visit in mean number of incontinence episodes and micturitions per 24 h. Both doses of mirabegron improved these endpoints versus placebo. No increase was seen in the incidence of adverse events in both arms of mirabegron.

Khullar et al. [19], in the same year, compared four groups: mirabegron 50 mg and 100 mg, placebo, and an antimuscarinic (tolterodine extended release [ER] 4 mg). A total of 1978 patients were randomized for a 12-week treatment period. Both doses of mirabegron (50 and 100 mg) improved the number of incontinence episodes and micturitions per 24 h comparatively to placebo. A similar study in Asia, 2 years later [20] utilized three

Table 1 Randomized controlled studies regarding OAB treatment with antimuscarinics and beta-adrenergics with sampling over 1000 patients, 2013–2018

Study (acronym)	Interventions	Patients and sample	Treatment duration
Abrams et al. (SYMPHONY) [13]	Mirabegron 50 mg Solifenacin and mirabegron	1306	12
	Solifenacin 5 mg		
	Solifenacin 10 mg		
	Placebo		
Drake et al. (BESIDE) [14]	Solifenacin 5 mg Mirabegron 25/50 mg	2174	12
	Solifenacin 5 mg		
	Solifenacin 10 mg		
Herschorn et al. (SYNERGY) [15••]	Mirabegron 25 mg Mirabegron 50 mg	3527	12
	Solifenacin 5 mg		
	Solifenacin 5 mg and mirabegron 25/50 mg		
	Placebo		
Batista et al. [16]	Mirabegron 50 mg Solifenacin 5 mg	1887	12
Chapple et al. (EIGHT) [17]	Fesoterodine 4 mg Fesoterodine 8 mg	2012	12
	Placebo		
Herschorn et al. [18]	Mirabegron 25 mg Mirabegron 50 mg	1306	12
	Placebo		
Khullar et al. [19]	Mirabegron 50 mg Mirabegron 100 mg	1987	12
	Tolterodine ER 4 mg		
	Placebo		
Kuo et al. [20]	Mirabegron 50 mg Tolterodine ER 4 mg	1126	12
	Placebo		
Nitti et al. [21]	Mirabegron 50 mg Mirabegron 100 mg	1329	12
	Placebo		
Yamaguchi et al. [22]	Mirabegron 50 mg Tolterodine ER 4 mg	1139	12
	Placebo		

groups (placebo, mirabegron, and tolterodine ER 4 mg) in 1126 patients using the same primary endpoint, and mirabegron was superior to placebo.

Nitti et al. [21] have compared mirabegron 50 mg, 100 mg versus placebo, and the groups have demonstrated statistically significantly greater mean decreases from baseline for incontinence episodes and micturitions per 24 h. Finally, Yamaguchi et al. [22] have studied three groups (placebo, $n = 381$; mirabegron 50 mg, $n = 380$; tolterodine 4 mg, $n = 378$) in a Japanese population with OAB symptoms present more than 6 months. Mirabegron was superior to placebo in almost all variables.

Percutaneous Tibial Nerve Stimulation

It is a peripheral neuromodulation technique that has been used as third line for OAB. We still have scarce evidence for this procedure. There are two systematic reviews dating from 2013 [23, 24] showing that there is a strong evidence comparing percutaneous tibial nerve stimulation (PTNS) versus a sham treatment. In the last 5 years, in our review, we have found three RCTs [25–27].

One RCT [25] compared solifenacin versus PTNS versus combination therapy in a group of 105 women. They have found that the combination therapy was more effective than

solifenacin and PTNS. Another [26] study compared PTNS versus electrical stimulation with pelvic floor muscle training (PFMT) in 60 women and both groups improved quality of life and reduction in the number of daily micturitions, episodes of nocturia, and urge incontinence. A third RCT [27] comparing PTNS versus tolterodine 2 mg ($n = 36$) did not find any differences between the groups, probably due to a type-II error (underpowered).

Looking back to previous studies, most of the sample sizes involving PTNS are not as large as from pharmacological studies. It is a modality that needs further investigation with other treatments.

Botulinum Toxin and Sacral Neuromodulation

These are minimally invasive procedures for OAB that is refractory to pharmacological treatment.

Intra-vesical or intradetrusor onabotulinumtoxinA is the most studied representative of the toxin, despite there is another preparation (abobotulinumtoxinA) [28]. In the last 5 years, we have found three RCTs [29•, 30, 31] regarding this treatment.

Chughtai et al. [29•] have performed a placebo-controlled RCT that compared onabotulinumtoxinA ($n = 15$) versus placebo ($n = 13$) for OAB secondary to bladder outlet obstruction (BOO) refractory to anticholinergic therapy. They have concluded that botulinum toxin improved quality of life score and reduced frequency episodes.

The EMBARK trial [30] gave a boost on evidence over onabotulinumtoxinA when they randomized 557 patients with OAB treatment failure with anticholinergics between this treatment with 100 U or placebo. Botulinum toxin significantly decreased the daily frequency of urinary incontinence episodes vs placebo, and 22.9% of patients became completely continent versus 6.5% in the placebo group. Similarly, in the same year, another RCT with the same arms conducted by Chapple et al. [31] with 548 patients followed by 12 weeks found the same findings, with superiority of botulinum toxin. In both studies, post-residual volume was higher in the botulinum toxin group.

It seems that trigone sparing during the intradetrusor application of botulinum toxin is no longer a problem. A recent systematic review [32] found that, after including eight studies, trigone-including onabotulinumtoxinA injection has superior efficacy to trigone-sparing without increasing complications.

Regarding sacral neuromodulation, this treatment modality has been FDA-approved for OAB for several years, and it consists by delivering electrical impulses to the sacral nerve roots via an implanted neurostimulator [33]. An RCT conducted by Siegel et al. [34], comparing sacral neuromodulation ($n = 70$) with InterStim therapy versus anticholinergic therapy ($n = 77$) for a 6-month period, has demonstrated a superior objective and subjective success of sacral neuromodulation.

The ROSETTA trial—a large, multicenter open-label RCT published in 2016 [35]—compared onabotulinumtoxinA versus sacral neuromodulation in 381 women in the US; 192 patients were injected 200 U by cystoscopy and 189 underwent sacral neuromodulation. The onabotulinumtoxinA group presented a statistically greater reduction of number of episodes of urgency incontinence per day in a 6-month follow-up period when compared to the sacral neuromodulation group, as well as treatment satisfaction and treatment endorsement. Conversely, they presented more urinary infections and need for self-catheterization. The authors have concluded that the results are of uncertain clinical importance. Results seem to persist after 2 years of follow-up on these patients [36].

Conclusion

It is also important to analyze the real-word evidence. Most of randomized controlled trials present an ideal evidence of medication use, with the presence of reminders or checking patients' adhesion to treatment. There are observational studies such as the PERSPECTIVE study that seek to identify factors associated with improved OAB treatment effectiveness looking from a patient perspective [37]. Another point is the conflict of interest; most of the studies are sponsored and funded by industry, which may introduce a bias. However, it is important to state that new possibilities are arising for women with OAB, and the ideal treatment has not arrived yet. Further studies with combination therapies, and possibly on the pathophysiology of this disease, are needed.

Compliance with Ethical Standards

Conflict of Interest The authors declare 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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