

Review Article

Overactive Bladder and Its Association with Irritable Bowel Syndrome: A Systematic Review

ABSTRACT

Background: In the absence of a confirmed infection or other evident diseases, overactive bladder (OAB) is defined by symptoms of urgency, with or without urgency incontinence, and typically with urine frequency and nocturia.

Methods: This is an updated systematic review of studies on the prevalence, and treatment of overactive bladder and its correlation to irritable bowel syndrome between 2013 and 2022. The PubMed and Google scholar databases were used to explore studies regarding our subject.

Results: Though 110 articles were obtained, only nine met the inclusion criteria. The studies included OAB patients. Three studies were cross-sectional, two studies were retrospective cohort studies, two clinical trials, one survey study while one was an observational study.

Conclusion: There was a high prevalence of overactive bladder symptoms among Middle Eastern women. The prevalence was higher in Hispanic women. However, no racial differences were reported as a risk factor for OAB. In mothers, the number of children was a significant risk factor for either urgency or nocturia. Trans-abdominal bladder ultrasonography (TABU) was recognized as a primary method for OAB diagnosing.

Keywords: Overactive, OAB, Bladder, Association, Irritable Bowel Syndrome, and IBS

INTRODUCTION

OAB, often known as an overactive bladder, is a prevalent disorder that can affect both sexes. There may be major effects on one's overall quality of life, sexual function, sleep, and mental health. The International Continence Society (ICS) defines OAB as urine urgency with or without urge incontinence, typically accompanied by frequency and nocturia. One urodynamic sign of OAB is detrusor overactivity (DO). There are sex-specific differences in the prevalence of different symptoms within the OAB complex, despite the fact that the overall prevalence of OAB is similar between the sexes. [1,2] Numerous studies have examined the incidence of OAB in industrialized nations and assessed how it affects people's quality of life.[3,4]

In a large-scale research study of people in the USA over the age of 18, 16.5% were found to have OAB. [5] Additionally, the incidence rate was 16.6% when adults over 40 were surveyed in 16 different European nations. [6] OAB is a common condition in Japanese adults over the age of 40, with a prevalence of 12.4% overall 14% in men, and 11% in women. IBS and OAB both affect the quality of life, and they are also relatively common. [6]

Irritable bowel syndrome (IBS) is a gastrointestinal disorder that, despite the absence of biological problems, manifests as stomach pain, discomfort, and a defecation disorder. In Europe and North America, IBS is a condition that affects a fair amount of people, with an incidence rate of between 10% to 20%. IBS's pathophysiology has not been precisely identified. Important IBS risk factors include psychiatry, the emotional component, and chronic stress. [7] IBS has recently been linked to intestinal infection, food resistance, immune system activation, and intestinal bacterial disorder, with intestinal motility problems and hypersensitive reactions serving as additional significant factors. [8]

Irritable Bowel Syndrome and OAB have the traits of being fairly common and degrading the quality of life. A previous study found that IBS patients often experience frequency, urgency, nocturia, and residual urine sensation. [9] Additionally, according to other studies, people who experience persistent constipation are more likely to have OAB. [10] Previous studies on OAB and functional intestinal disturbances have been conducted. [11] Several studies have also noted the importance of these correlations. Because the bladder and large intestine share a portion of an afferent nerve anatomically, there is a neurological intersection between them. [12, 13] However, the precise connection between OAB and IBS as well as their underlying mechanisms are yet unknown. The present systematic review aims to evaluate the prevalence and treatment of overactive bladder and its correlation to irritable bowel syndrome.

METHOD AND SEARCH STRATEGY

This systematic review complies with the PRISMA checklist guidelines for systematic reviews and meta-analyses [14]. Google Scholar and PubMed were the two databases that were searched. The two databases were utilized to survey for studies on our main topic, “the prevalence, treatment of overactive bladder and its correlation to irritable bowel syndrome”. The studies were published between 2013 and 2022. The searching process involved using different keywords, including “Overactive, OAB, Bladder, Prevalence, Treatment, Association, Irritable Bowel Syndrome, and IBS”. In addition, the involved keywords were employed to collect all relevant articles. This initial exploration resulted in the revision of all titles.

ELIGIBILITY CRITERIA

Only papers focusing on the prevalence, treatment of overactive bladder, and its correlation to irritable bowel syndrome were included after reviewing the titles of the prevalence, treatment of overactive bladder, and its correlation to irritable bowel syndrome before 2013 was excluded. The second phase involved selecting only original, English-language studies on the prevalence, and treatment of overactive bladder and its correlation to irritable bowel syndrome after evaluating the abstracts of the remaining articles. On the other hand, review articles, editor letters, and case reports were not included. The final stage included original English-language articles that discussed the prevalence and treatment of overactive bladder and its correlation to irritable bowel syndrome. These articles were further examined to exclude duplicates, non-full-text articles, and articles with unsatisfactory content, such as overlapped or incomplete data. Figure 1 displays a detailed explanation of the search approach.

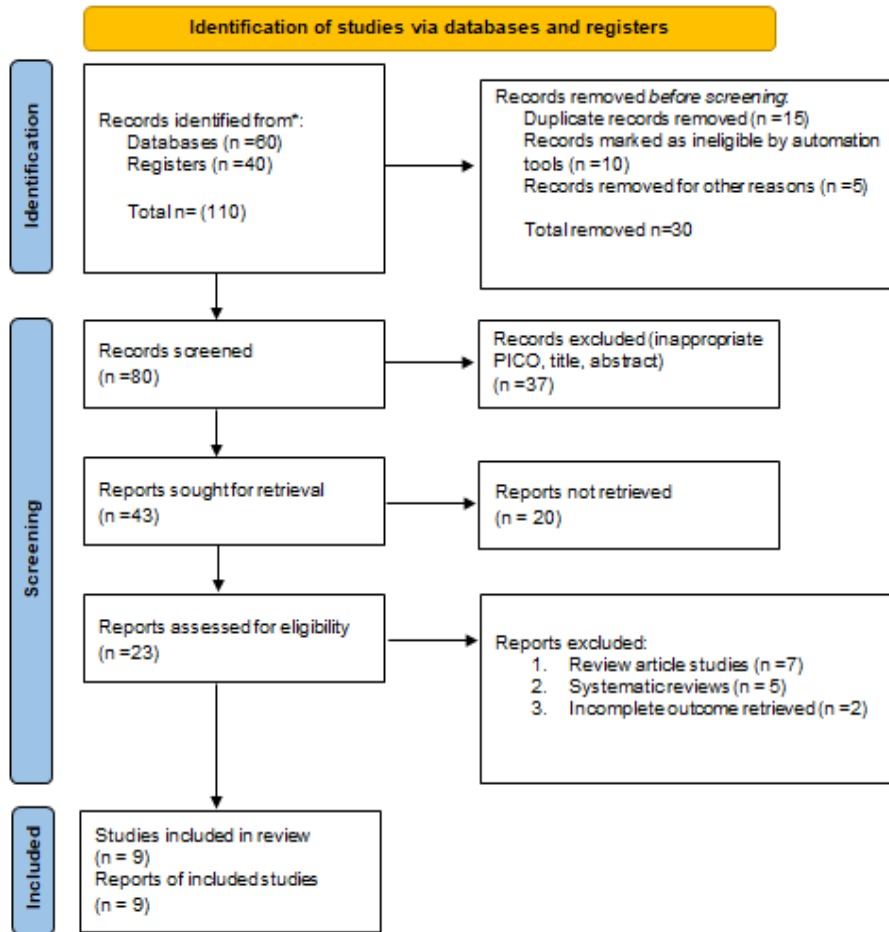


Fig1: Planning of Eligible criteria

DATA REVIEWING AND ANALYSIS

RESULTS

Eight studies met the eligibility criteria for this systematic review [15-23] (table 1). The included studies were either published in 2013 [22], 2015 [23], 2017 [19, 21], 2018 [16], 2019 [17], 2020 [18], and 2021 [15] or in 2022 [20]. Three studies were cross-sectional [15, 16, and 22], two studies were retrospective cohort studies [17, 23], two clinical trials [18, 19], one survey study [21], and one observational study [20]. The studies included OAB patients. The studies included both men and women. Three studies included women aged ≥ 18 years [16, 17, and 19], while one study included young female participants (aged under 45) [20] and another study involved women aged ≥ 40 years [15]. One study included both male and female OAB patients [21] and one study involved individuals with laboratory-confirmed giardiasis [23].

Four studies evaluated the prevalence and risk factors of overactive bladder syndrome (OAB) [15, 16, 17, and 23], while two studies discussed the treatment for OAB symptoms [18, 19]. One study assessed

transabdominal bladder ultrasonography (TABU), as a first-step diagnostic approach in OAB [20], whereas three studies investigated the relationship between irritable bowel syndrome (IBS) and overactive bladder (OAB) [21, 22, and 23].

The prevalence of OAB was found to be high in two studies [15, 16] among women from Algeria, Egypt, Jordan, Lebanon, and Saudi Arabia, while in one study [23], the prevalence was reported to be 18.7 % in the exposed group and 13.6 % in the control group [23]. In contrast, another study also reported a low prevalence (4.41%) of OAB symptoms which was highest in Hispanic women [17]. No racial differences were reported as a risk factor for OAB in one study [17]. Meanwhile, Study by [15, 16] showed the negative effects of OAB on women's quality of life. One study [15] reported that the majority had symptoms of urinary incontinence. Despite the high prevalence, most women had never received treatment [15]. A study by [16] found that the number of children was a significant risk factor for either urgency or nocturia. Both studies [15, 16] mentioned the need for comprehensive healthcare programs for the diagnosis and management of OAB syndrome.

The treatment of OAB was reported in two studies [18, 19]. Both studies assessed the efficacy of mirabegron, solifenacin, and tolterodine or combined therapy in the treatment of OAB. One study [18] affirmed the efficacy of using mirabegron, solifenacin, and tolterodine in adults of different age groups and sexes. Another study, [19] confirmed the efficacy of combined therapy with solifenacin 5 mg + mirabegron, 25 mg and solifenacin 5 mg + mirabegron 50 mg compared with the respective monotherapies, across most of the outcome parameters, with effect sizes generally consistent with additive effect.

One study assessed trans-abdominal bladder ultrasonography (TABU), as a primary method for diagnosing OAB [20]. TABU was able to assess detrusor hypertrophy associated with OAB, as well as bladder motility disturbances in IBS female patients. Multiple correlations were found between various symptoms and bladder measurements. Since not all patients displayed an increase in Bladder wall thickness (BWT) or Bladder ejection fraction (BEF) disturbances, TABU could select patients eligible for invasive urodynamics, from those with modified measurements.

Regarding the association between OAB and IBS, one study [21] showed that IBS in adults had no relationship with OAB. However, two other studies [22, 23] found participants reporting OAB symptoms also had concurrent IBS. One study [22] stated that the prevalence of concurrent IBS and OAB was unaffected by age, suggesting that age is not a contributing factor to this relationship. Whereas another study [23] documented that the association between OAB and IBS was strong in the control group but insignificant in the Giardia exposed. Sporadic IBS was associated with an increased risk of OAB, whereas post-infectious IBS was not.

DISCUSSION

In the absence of urinary tract infection or other visible diseases, overactive bladder (OAB) is a common disorder marked by urine urgency, which is typically accompanied by increased daytime frequency and/or nocturia, with or without urgent urinary incontinence. [24] OAB was expected to impact 546 million people globally in 2018 [25], with rates peaking in the 65–80 age group and total prevalence rising with advancing age. [26] OAB appears to affect around the same percentages of both men and women, while some of the research shows that women may have a little higher prevalence of the condition.[27] The pathological characteristics of overactive bladder and IBS, both of which have a negative impact on quality of life, are overactivity (irritability) of the bladder and bowel, respectively. Previous research has shown that these conditions frequently co-occur. [10] Compared to asymptomatic control subjects, IBS is more common in female patients with interstitial cystitis/painful bladder syndrome. [28] It is now possible that OAB and IBS have similar pathological characteristics. Consequently, the present systematic review aims to evaluate the prevalence and treatment of overactive bladder and its correlation to irritable bowel syndrome.

In the current systematic review study,[15,16] found a high prevalence of OAB among women from Egypt, Jordan, Lebanon, and Saudi Arabia, while [23] reported a prevalence of 18.7 % in the exposed group and 13.6 % in the control group. In contrast, study reported a low prevalence (4.41%) of OAB symptoms which was highest in Hispanic women[17]. No racial differences were reported as a risk factor for OAB. Meanwhile, a study showed the negative effects of OAB on women's quality of life[15,16]. Another study reported that the majority had symptoms of urinary incontinence. Despite the high prevalence, most women had never received treatment[15]. Another study found that the number of children was a significant risk factor for either urgency or nocturia. Both mentioned the need for comprehensive healthcare programs for the diagnosis and management of OAB syndrome[16]. Similarly, few studies have reported the incidence of OAB in the Middle East. The prevalence of OAB symptoms was found to be 40% in one community-based study by El-Azab et al. in Egypt [29], which is lower than the prevalence observed in this study for Egypt (57.5%). El-Azab et al. study [29] included younger women (20 years), and it is generally known that older people are more likely to experience OAB symptoms [30], which may account for the discrepancy.

The treatment of OAB was reported by two studies. Both studies assessed the efficacy of mirabegron, solifenacin, and tolterodine or combined therapy in the treatment of OAB. The study affirmed the efficacy of using mirabegron, solifenacin, and tolterodine in adults of different age groups and sexes. It was confirmed the efficacy of combined therapy with solifenacin 5 mg + mirabegron 25 mg and solifenacin 5 mg + mirabegron 50 mg compared with the respective monotherapies across most of the outcome parameters, with effect sizes generally consistent with additive effect. Importantly[18,19] strict reporting requirements for hypertension-related adverse events (AEs) were present in mirabegron studies, in contrast to earlier antimuscarinic studies that did not have such a requirement. This led to higher reporting rates for hypertension in mirabegron studies across all treatment groups. However, there was no evidence of an elevated cardiovascular risk for MIRA or AM over placebo in an examination of pooled mirabegron safety data from approximately 13000 individuals in 13 studies, including some studies in the current analysis. [31] Consistent with these findings, Post-void residual (PVR) was

marginally higher in the combined therapy groups compared to the solifenacin 5 mg and mirabegron monotherapy groups. Additionally, the combined therapy groups compared favorably to the monotherapy groups and placebo in terms of the incidence of complaints of dyspepsia, dry mouth, and constipation. However, the frequency of typical antimuscarinic side-effects was decreased in SYNERGY compared to earlier solifenacin 5 mg monotherapy investigations, where they were, respectively, 10%, 5%, and 1%. [32] This increase might not be the result of a mirabegron and solifenacin medication interaction because exposures in the groups receiving combined therapy were quite similar to those in the groups receiving monotherapies. It should be noted that a prior investigation did seem to imply the potential for a drug-drug interaction between mirabegron and solifenacin. [33]

In this review, assessed trans-abdominal bladder ultrasonography (TABU), as a first-step diagnostic approach in OAB. TABU was able to assess detrusor hypertrophy associated with OAB, as well as bladder motility disturbances in IBS female patients[20]. Multiple correlations were found between various symptoms and bladder measurements. Since not all patients displayed an increase in Bladder wall thickness (BWT) or Bladder ejection fraction (BEF) disturbances, TABU could select patients eligible for invasive urodynamics, from those with modified measurements. Since many years ago, researchers have been looking for an OAB diagnostic test that is non-invasive. Numerous variables were examined, such as free uroflowmetry, post-void residual volume, and prostate volume measurement. [34] The past ten years have seen a fast increase in interest in bladder wall thickness and, as a result, bladder wall weight. TABU has emerged as the simplest and least invasive method for determining bladder wall thickness. [35]

Regarding the association between OAB and IBS, a study showed that IBS in adults had no relationship with OAB[21]. However, two studies found that the participants reporting OAB symptoms also had concurrent IBS[22,23]. The study stated that the prevalence of concurrent IBS and OAB was unaffected by age, suggesting that age is not a contributing factor to this relationship. The study documented that the association between OAB and IBS was strong in the control group but insignificant in the Giardia exposed. Sporadic IBS was associated with an increased risk of OAB, whereas post-infectious IBS was not. The first study to show that people with IBS frequently have symptoms of an "irritable bladder" . [36] Since then, this association has been mentioned numerous times. [12] One could argue that IBS is more commonly linked to symptoms of the lower urinary tract in general than OAB specifically. [37] Rat experiments have also demonstrated the presence of bladder hyperesthesia and colon hyperalgesia, and the potential for neural communication between the bladder and large intestine. [38] Serotonin is one of the main neurotransmitters in the urinary and gastrointestinal tract, which suggests that serotonin receptors may play a role in the potential association between OAB and IBS. Through parasympathetic and sympathetic channels, the central nervous system communicates with the gastrointestinal and urinary tracts. Autonomic dysfunctions have been found in patients with IBS and OAB. [39]

CONCLUSION

The present systematic review demonstrated a high prevalence of overactive bladder (OAB) symptoms among Middle Eastern women. The prevalence was higher in Hispanic women; however, no racial differences were reported as a risk factor for OAB. In mothers, the number of children was a significant risk factor for either urgency or nocturia. This systematic review confirmed the efficacy of combined therapy with solifenacin 5 mg + mirabegron 25 mg or solifenacin 5 mg + mirabegron 50 mg compared with the respective monotherapies across most of the outcome parameters, with effect sizes generally consistent with additive effect. Trans-abdominal bladder ultrasonography (TABU) was recognized as a primary method for OAB diagnosing. TABU was able to assess detrusor hypertrophy associated with OAB, as well as bladder motility disturbances in IBS female patients. Regarding the association between OAB and IBS, we found that the participants reporting OAB symptoms also had concurrent IBS. The prevalence of concurrent IBS and OAB was unaffected by age, suggesting that age is not a contributing factor to this relationship. Sporadic IBS was associated with an increased risk of OAB, whereas post-infectious IBS was not.

REFERENCES

- Link CL, Steers WD, Kusek JW, McKinlay JB. The association of adiposity and overactive bladder appears to differ by gender: results from the Boston Area Community Health survey. *J Urol*. 2011;185(3):955–963 .1
- .
- Patra PB, Patra S. Sex differences in the physiology and pharmacology of the lower urinary tract. *Curr Urol*. 2013;6(4):179–18 .2
- .
- Herschorn S, Kaplan SA, Sun F, Ntanios F. Do patient characteristics predict responsiveness to treatment of overactive bladder with antimuscarinic agents? *Urology*. 2014;83(5):1023–1029 .3
- .
- Valentini FA, Marti BG, Robain G. Idiopathic and neurogenic detrusor overactivity: do the different patterns have urodynamic characteristics related to gender or neurological condition? *Int Braz J Urol*. 2013;39(5):663–670 .4
- .
- Stewart WF, Van Rooyen J, Cundiff G, Abrams P, Herzog A, Corey R, et al. Prevalence and burden of overactive bladder in the United States. *World journal of urology*. 2003 May;20:327-36 .5
- .
- Milsom I, Abrams P, Cardozo L, Roberts RG, Thüroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU international*. 2001 Jun;87(9):760-6 .6
- .
- De Giorgio R, Barbara G, Stanghellini V, Cremon C, Salvioli B, De Ponti F, et al. Diagnosis and therapy of irritable bowel syndrome. *Alimentary pharmacology & therapeutics*. 2004 Jul;20:10-22 .7
- .
- Barbara G, Stanghellini V, De Giorgio R, Corinaldesi R. Functional gastrointestinal disorders and mast cells: implications for therapy. *Neurogastroenterology & Motility*. 2006 Jan;18(1):6-17 .8

- .
Kuo YC, Kuo HC. Potential factors that can be used to differentiate between interstitial cystitis/painful bladder syndrome and bladder oversensitivity in women. *International journal of clinical practice*. 2012 Feb;66(2):146-51 .9
- .
Coyne KS, Cash B, Kopp Z, Gelhorn H, Milsom I, Berriman S, et al. The prevalence of chronic constipation and faecal incontinence among men and women with symptoms of overactive bladder. *BJU international*. 2011 Jan;107(2):254-61 .10
- .
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. *European urology*. 2019 Jun 1;75(6):988-1000 .11
- .
Matsuzaki J, Suzuki H, Fukushima Y, Hirata K, Fukuhara S, Okada S, et al. High frequency of overlap between functional dyspepsia and overactive bladder. *Neurogastroenterology & Motility*. 2012 Sep;24(9):821-7 .12
- .
Lai HH, Vetter J, Jain S, Andriole GL. Systemic nonurological symptoms in patients with overactive bladder. *The Journal of urology*. 2016 Aug;196(2):467-72 .13
- .
Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS medicine*. 2009;6(7):e1000100 .14
- .
Al Edwan G, Abdelazim MS, Salhab SE, Jamal YM, Soliman MA. The prevalence of overactive bladder symptoms in women in Algeria, Egypt, Jordan and Lebanon: A cross-sectional population-based survey. *Advances in therapy*. 2021 Feb;38(2):1155-67 .15
- .
Al Mousa R, Albagshi S, Alabbad A, Alshamsi H, Almuslim O. Overactive bladder amongst Saudi women: Its prevalence, risk factors, and effect on quality of life. *Arab Journal of Urology*. 2018 Dec 1;16(sup1):S4 .16

.

Mckellar K, Bellin E, Schoenbaum E, Abraham N. Prevalence, risk factors, and treatment for overactive bladder in a racially diverse population. *Urology*. 2019 Apr 1;126:70-5 .17

.

Chapple CR, Cruz F, Cardozo L, Staskin D, Herschorn S, Choudhury N, et al. Safety and efficacy of mirabegron: analysis of a large integrated clinical trial database of patients with overactive bladder receiving mirabegron, antimuscarinics, or placebo. *European urology*. 2020 Jan 1;77(1):119-28 .18

.

Herschorn S, Chapple CR, Abrams P, Arlandis S, Mitcheson D, Lee KS, et al. Efficacy and safety of combinations of mirabegron and solifenacin compared with monotherapy and placebo in patients with overactive bladder (SYNERGY study). *BJU international*. 2017 Oct;120(4):562-75 .19

.

Georgescu D, Petre I, Schiller A, Georgescu LA. BLADDER ULTRASONOGRAPHY AS FIRST STEP NONINVASIVE APPROACH IN FEMALE PATIENTS WITH IRRITABLE BOWEL SYNDROME AND OVERACTIVE BLADDER. *Ultrasound in Medicine & Biology*. 2022 Jan 1;48:S46 .20

.

Kim KS, Kim HJ, Lee SH, Cho ST, Moon HS. Association between irritable bowel syndrome and overactive bladder: a research survey. *Urology*. 2017 Nov 1;109:88-93 .21

.

Matsumoto S, Hashizume K, Wada N, Hori J, Tamaki G, Kita M, et al. Relationship between overactive bladder and irritable bowel syndrome: a large-scale internet survey in Japan using the overactive bladder symptom score and Rome III criteria. *BJU international*. 2013 Apr;111(4):647-52 .22

.

Persson R, Wensaas KA, Hanevik K, Eide GE, Langeland N, Rortveit G. The relationship between irritable bowel syndrome, functional dyspepsia, chronic fatigue and overactive bladder syndrome: a controlled study 6 years after acute gastrointestinal infection. *BMC gastroenterology*. 2015 Dec;15(1):1-7 .23

.

- D'Ancona C, Haylen B, Oelke M, Abranches-Monteiro L, Arnold E, Goldman H, et al. A. The International Continence Society (ICS) report on the terminology for adult male lower urinary tract and pelvic floor symptoms and dysfunction. *Neurourology and urodynamics*. 2019 Feb;38(2):433-77 .24
- .
- 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;108:1132–8 .25
- .
- Funada S, Kawaguchi T, Terada N, Negoro H, Tabara Y, Kosugi S, et al. Cross-sectional epidemiological analysis of the Nagahama study for correlates of overactive bladder: genetic and environmental considerations. *The Journal of Urology*. 2018 Mar 1;199(3):774-8 .26
- .
- Chuang YC, Liu SP, Lee KS, Liao L, Wang J, Yoo TK, et al. Prevalence of overactive bladder in China, Taiwan and South Korea: Results from a cross-sectional, population-based study. *LUTS: Lower Urinary Tract Symptoms*. 2019 Jan;11(1):48-55 .27
- .
- Nickel JC, Tripp DA, Pontari M, Moldwin R, Mayer R, Carr LK, et al. Interstitial cystitis/painful bladder syndrome and associated medical conditions with an emphasis on irritable bowel syndrome, fibromyalgia and chronic fatigue syndrome. *The Journal of urology*. 2010 Oct;184(4):1358-63 .28
- .
- El-Azab A. Clinical and epidemiological criteria of overactive bladder (OAB) among women: a population based study. 2007 .30
- .
- Milsom I, Abrams P, Cardozo L, Roberts RG, Thüroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU international*. 2001 Jun;87(9):760-6 .31
- .

White WB, Siddiqui E, Tat T, Franks B, Schermer CR. Cardiovascular safety of mirabegron: analysis of an integrated clinical trial database of patients with overactive bladder syndrome. *Journal of the American Society of Hypertension*. 2018 Nov 1;12(11):768-78 .32

.

Astellas Pharma US Inc. VESicare® Prescribing Information, 2016. Available at: <https://www.astellas.us/docs/vesicare.pdf>. Accessed May 2017 .33

.

Krauwinkel WJ, Kerbusch VM, Meijer J, Tretter R, Strabach G, Van Gelderen EM. Evaluation of the pharmacokinetic interaction between the β 3-adrenoceptor agonist mirabegron and the muscarinic receptor antagonist solifenacin in healthy subjects. *Clin Pharmacol Drug Dev* 2013; 2: 255– 63 .34

Oelke M, Hofner K, Jonas U, de la Rosette JJ, Ubbink DT, Wijkstra H. Diagnostic accuracy of noninvasive tests to evaluate bladder outlet obstruction in men: Detrusor wall thickness, uroflowmetry, postvoid residual urine, and prostate volume. *Eur Urol*. 2007;52:827–34 .35

.

Jequier S, Rousseau O. Sonographic measurements of the normal bladder wall in children. *AJR Am J Roentgenol*. 1987;149:563–6 .36

.

Whorwell PJ, McCallum M, Creed FH, Roberts CT. Non-colonic features of irritable bowel syndrome. *Gut*. 1986;27:37–40 .37

.

Bullones Rodriguez MA, Afari N, Buchwald DS. Evidence for overlap between urological and nonurological unexplained clinical conditions. *J Urol*. 2013;189:019 .38

.

Christianson JA, Liang R, Ustinova EE, Davis BM, Fraser MO, Pezzone MA. Convergence of bladder and colon sensory innervation occurs at the primary afferent level. *Pain*. 2007 Apr 1;128(3):235-43 .39

.

Atkinson W, Lockhart S, Whorwell PJ, Keevil B, Houghton LA. Altered 5-hydroxytryptamine signaling in patients with constipation-and diarrhea-predominant irritable bowel syndrome. *Gastroenterology*. 2006 Jan 1;130(1):34-43. .40

