


# Prevalence, Burden, and Treatment of Lower Urinary Tract Symptoms in Men Aged 50 and Older: A Systematic Review of the Literature

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## Abstract

We conducted a systematic review of literature from the years 2000 through 2017 on the prevalence and burden of lower urinary tract symptoms (LUTS) in men aged 50 and older, and medical treatments of and alternative nonmedical approaches to LUTS. EBSCOhost (Medline with Full Text) was searched for observational, experimental, and review studies in peer-reviewed journals in the English language. Our review found that LUTS were highly prevalent in the world and estimated to affect 2.3 billion people in 2018, with 44.7% being men. Men with LUTS suffer from not only burdensome symptoms such as nocturia and urgency but also adverse psychological consequences (e.g., anxiety and depression) and financial burden. Current medical treatments are clinically effective, but their efficacy is compromised by side effects and low compliance rates. Alternative nonmedical treatments for LUTS were also sought worldwide. There is evidence that lifestyle modifications such as pelvic muscle exercises and bladder training, physical activity, dietary modification, and nutritional supplements can alleviate LUTS and improve patient quality of life; however, evidence based on rigorous methodology remains minimal and cannot be generalized across populations. Evidence of effectiveness of weight loss programs to reduce LUTS is inconclusive. We conclude that although behavioral treatment is a promising approach to alleviating LUTS, especially when combined with medical treatments, well-designed randomized controlled and longitudinal clinical trials on behavioral treatments of LUTS are still needed. Minimally invasive procedures and neuromodulation therapy also show positive results of alleviating LUTS but require further research as well.

## Keywords

lower urinary tract symptoms, LUTS prevalence, LUTS burden, QOL, behavioral intervention

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## Introduction

Lower urinary tract symptoms (LUTS) are estimated to affect 2.3 billion individuals, or 45.8% of the world population in 2018, an increase of 18.4% since 2008 (Irwin, Kopp, Agatep, Milsom, & Abrams, 2011). According to the International Continence Society (2015), LUTS are defined as symptoms that result from conditions and diseases affecting the bladder and the urethra, including urinary incontinence (e.g., stress, urge, and mixed urinary incontinence); storage/overactive bladder symptoms (e.g., urgency, frequency, and nocturia, with or without incontinence); voiding (e.g., urinary retention, hesitancy, straining to void,

slow or interrupted stream); and postmicturition (e.g., postmicturition dribble). LUTS have multifactorial causes that present a challenge to the management of

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this chronic problem. Despite various options of medical treatments, LUTS remain a significant public health problem and economic burden on society.

LUTS prevail among men aged 50 and older and become increasingly common in American men as the population ages. During the past decade, best practice guidelines for LUTS treatments were published in the United States and Europe (see American Urological Association, 2010; Oelke et al., 2013 for LUTS due to benign prostatic hyperplasia [BPH]), and the guidelines recommended behavioral management in which health professionals play a significant role. Evidence of LUTS prevalence, treatments, and behavioral therapies has emerged. There is a review of evidence published before 2000 (Bruskewitz, 1999). Since then, there have been systematic review studies that focused on medical treatments or herbal treatments of LUTS across countries, but there is a lack of systematic reviews of the prevalence of LUTS or other alternative treatments (e.g., lifestyle, weight loss, dietary nutrition, and acupuncture) that have emerged worldwide over the past decades. Hence, we conducted a systematic review of literature since 2000 to present the prevalence of LUTS from a global perspective and a comprehensive review of LUTS treatments. This review fills in a gap in the literature by presenting the estimated global prevalence and impact of LUTS on quality of life (QOL) over past 18 years and examining newly emerged alternative treatments for LUTS. Our objective is to provide health-care providers, especially nurses, with evidence-based information on LUTS, its treatment, and management for improving clinical treatment strategies and reducing the impact of this significant problem.

## Methods

Extant research on LUTS prevalence, current medical treatments, and alternative treatments from January 2000 through 2017 were reviewed using database Medline with Full Text (EBSCOhost) that provides a reputable source of selective, qualifying biomedical and life science journal articles (National Institutes of Health, 2018). The systematic search generated 1,549 publications on LUTS. Using keywords of lower urinary tract symptoms (LUTS) AND prevalence, 442 references were found. Studies that were not available in English, did not use a population-based large database, or discussed the prevalence of LUTS in subpopulations with specific diseases (e.g., diabetes, Parkinson's disease, and cardiovascular disease) were excluded. Twenty-eight articles discussing the prevalence of LUTS in men in the general population were selected for review.

Examining the impact of LUTS, we used the keywords of lower urinary tract symptoms (LUTS) AND quality of life AND male. A total of 561 results were

generated. After excluding articles of drug efficacy, assessment and management of LUTS, physician perceptions of LUTS patients, and QOL in specific disease context (e.g., poststroke, muscular dystrophies, and diabetes), 18 articles regarding QOL in men with LUTS were selected for review.

For medical treatment of LUTS, using keywords of lower urinary tract symptoms (LUTS) AND current treatment OR intervention OR therapy, 180 references were found. After excluding studies that treated LUTS in patients with a specific disease (e.g., diabetes, heart diseases) or primarily focused on QOL as treatment outcomes, 18 studies that examined the effectiveness of current medical or surgical treatments of LUTS, medication adherence, and side effects, through systematic reviews or using a large database, were identified.

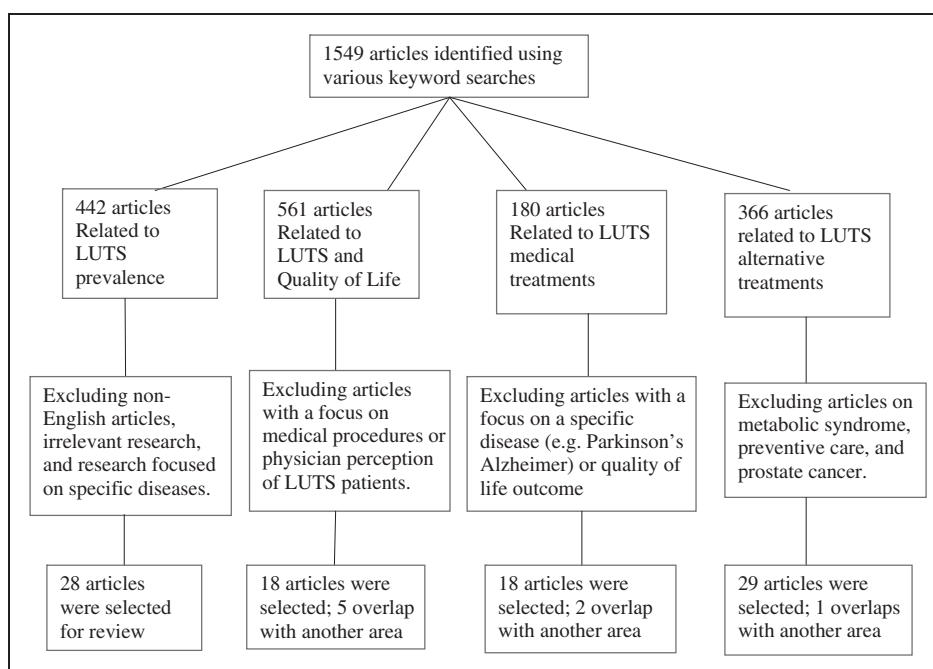
Finally, research on alternative nonmedical treatments of LUTS was reviewed extensively on both EBSCOhost and Medline (PubMed), because many studies in this area are newer or exploratory, and PubMed allows us to access them in open access journal articles and *in process* or ahead-of-print articles (National Institutes of Health, 2018). Using the keywords of lower urinary tract symptoms (LUTS), treatment, alternative, behavior, lifestyle, pelvic floor, pelvic floor exercises, bladder training, muscle strength, intervention, self-care, nonpharmacological interventions, exercise or physical activity, and diet, we identified 366 articles. Excluding articles on metabolic syndrome, preventive care, and prostate cancer, 29 articles were identified for the review, including 8 articles related to lifestyle modification, 4 articles focusing on physical activities and weight loss, 14 articles on nutrition and supplements, and 3 articles on acupuncture. Of these selected 93 articles, 8 articles were identified for review in two separate areas. Thus, the total number of publications selected for this review is 85. The following flowchart outlines this selection process (Figure 1).

## Results

The existing publications can be categorized in four main areas: the prevalence of LUTS, adverse health impact and burden of LUTS, existing medical treatments and effectiveness, and nonmedical, lifestyle interventions to LUTS and their effectiveness. Findings from the literature search concerning each of these areas are reported herein and summarized in Table 1.

### *The Prevalence of LUTS*

International studies provide a worldwide perspective of the prevalence of LUTS. In the European Prospective Investigation into Cancer and Nutrition (EPIC) study, a multinational population-based survey conducted in



**Figure 1.** Flowchart of the search process.  
LUTS = lower urinary tract symptoms.

Canada, Germany, Italy, Sweden, and the United Kingdom in 2005, 62.5% of men reported at least one LUTS, and more than 6% of men reported having moderate-to-severe LUTS (Irwin et al., 2009). In a population-representative Epidemiology of LUTS (EpiLUTS) study that surveyed 14,139 men from the United States, United Kingdom, and Sweden via the Internet, 72.3% reported at least one LUTS (Coyne et al., 2009b). A cross-sectional, population-representative, Internet-based study conducted in mainland China, Taiwan, and South Korea in 2015 reported that LUTS prevalence was 62.8% in men older than 40 years of age (Chapple et al., 2017). In Brazil's first nationwide epidemiological study of LUTS, the prevalence of LUTS in men was reported to be 69%, with 21% of them reporting moderate-to-severe symptoms that warranted treatment consideration (Soler, Gomes, Averbeck, & Koyama, 2017). Similarly, 19.2% to 25.1% reported moderate-to-severe LUTS in a population-based survey of 4,979 men living in four urban areas from Netherlands, France, United Kingdom, and South Korea (Boyle et al., 2003). In another population-based survey of 8,700 men in Denmark, the prevalence of moderate-to-severe LUTS was 28% (Nørby, Nordling, & Mortensen, 2005). Based on the EPIC study and the U.S. Census Bureau International Data Base, it was estimated that 1.9 billion individuals of the worldwide population (45.2%) were affected by LUTS in 2008, and 2.3 billion in 2018 (44.7% of men). The increasing cases of LUTS were

mostly seen in developing regions in African, South America, and Asia (Irwin et al., 2011).

Several studies of the prevalence of LUTS were carried out in the United States and reported that the prevalence was 18.7% to 98% in American men, depending on age and the level of severity (Litman et al., 2007; Taylor et al., 2006). The prevalence of LUTS increases by age. In the 2002–2005 Boston Area Community Health (BACH) Survey, 2,301 American men aged 30 to 79 years were surveyed, and 18.7% reported experiencing LUTS (Litman et al., 2007). Glasser, Carson, Kang, and Laumann (2007) studied 901 men aged 40 years and older and reported a 28% overall prevalence of LUTS. In a study of 448 men aged 51 and older, 42% of the men reported moderate-to-severe LUTS (international prostate symptom score [IPSS] > 7; Naslund et al., 2007). In the Third National Health and Nutrition Examination Survey (1988–1994), 59.9% of men aged 60 to 69 years and 75.1% men aged 70 and older reported having LUTS (Platz, Smit, Curhan, Nyberg, & Giovannucci, 2002). In the 2002 Osteoporotic Fractures in Men Study of 5,284 men aged 65 years and older without a cancer history, 98% of the men reported LUTS, with 39.6% moderate and 6.6% severe LUTS (Taylor et al., 2006).

The increase of LUTS prevalence by age has also been reported worldwide (Coyne et al., 2009a; Speakman, Kirby, Doyle, & Ioannou, 2015), and this is associated with enlarged prostate gland—BPH. More than 50% of

Table 1. A Summary of Reviewed Studies.

| No.                            | Author(s), Year      | Purpose  | Methodology   | Sample         | Main findings  | Limitations  |
|--------------------------------|----------------------|--|---|----------------|--|--|
| <i>U.S. prevalence of LUTS</i> |                      |  |   |                |  |  |
| 1                              | Irwin et al., 2009   | To describe the prevalence, severity, and symptom bother of LUTS in men with/without overactive bladder                          | Secondary data analysis of the EPIC study, a multinational population-based survey                      | N = 7,210      | More men with overactive bladder report moderate-to-severe LUTS than the general population (30% vs. 6%). Nocturia was the most common symptom.  | LUTS severity might be underestimated by the IPSS, which does not assess incontinence.   |
| 2                              | Coyne et al., 2009   | To assess the prevalence and associated bother of LUTS in the United States, the United Kingdom, and Sweden in the EpiLUTS study | Cross-sectional, population-based survey  | N = 14,139 men | 72.3% of men had at least one LUTS; bothersome LUTS are leaking urine during sexual activity (82.1%), urgency with fear of leaking (73.3%), leaking for no reason (72.1%), nocturnal enuresis (71.5%). |  |
| 3                              | Chapple et al., 2017 | To determine LUTS prevalence in China, Taiwan, and South Korea using International Continence Society 2002 criteria              | Internet-based self-administered survey study; descriptive statistics and post hoc significance testing | N = 8,284      | LUTS prevalence was slightly higher in men than women (62.8% vs. 59.6%; $p = .004$ ), increasing significantly with age ( $p = .001$ ).  | Conducting the study via Internet may result in bias by including only individuals with Internet access. The study selected China, South Korea, and Taiwan on the basis of the highest Internet penetration rates within Asia in 2015 (50%, 92%, and 84%, respectively). |
| 4                              | Soler et al., 2017   | To assess the prevalence and bother of LUTS in the population aged $\geq 40$ years in five major cities of Brazil                | Telephone survey with assessment of LUTS using a standardized protocol                                  | N = 5,184      | The prevalence of LUTS (symptoms occurring less than half the time or more) was 69% in men. Moderate-to-severe symptoms were present in 21% of men.  | Limitations included self-reporting of LUTS without medical evaluation, reliance upon telephone interviews during which individuals may not always provide accurate answers, and possible selection bias because of the requirement for telephone contact.               |
| 5                              | Boyle et al., 2003   | To evaluate the EpiLUTS among men and women in Netherlands, France, United Kingdom, and South Korea                              | Population-based, cross-sectional survey  | N = 4,979      | 19.2% to 25.1% reported moderate-to-severe LUTS in a population-based survey of 4,979 men  |  |

(continued)

Table 1. Continued.

| No. | Author(s), Year       | Purpose   | Methodology  | Sample            | Main findings  | Limitations   |
|-----|-----------------------|---|--|-------------------|--|---|
| 6   | Nørby et al., 2005    | To estimate the prevalence of LUTS in the elderly Danish population. Furthermore, to evaluate the QOL, the health-care seeking behavior and treatment with relation to LUTS | Mailed questionnaire   | N = 8,700         | The median IPSS was 4 in males. Overall 28% of males had significant LUTS (IPSS > 7).  |   |
| 7   | Irwin et al., 2011    | To estimate and predict worldwide and regional prevalence of LUTS in 2008, 2013, and 2018   | An estimation model using prevalence data from the EPIC study and population estimates from the U.S. Census Bureau International Data Base | N/A               | An estimated 45.2% of the 2008 worldwide population (4.3 billion) was affected by at least one LUTS. By 2018, an estimated 2.3 billion individuals will be affected by at least one LUTS (18.4% increase). | The prevalence results are approximations and not true values.  |
| 8   | Taylor et al., 2006   | To describe the prevalence, severity, and health correlates of LUTS in older community-dwelling U.S. men  | Secondary data analysis of the MrOS study  | N = 5,284         | LUTS were absent in 2.3%, mild in 51.6%, moderate in 39.6%, and severe in 6.6%.  | Results may not apply to younger, less healthy or institutionalized men, men with catheters.  |
| 9   | Litman et al., 2007   | To assess the influence of lifestyle factors and comorbidities on LUTS in Boston Community.   | Multistage stratified cluster random sample; epidemiologic survey  | N = 5,506         | LUTS prevalence was 18.7%, with similar rates by sex, race/ethnicity.  | Not discussed   |
| 10  | Glasser et al., 2007  | To assess the LUTS prevalence in U.S. men by age, race/ethnicity and comorbid ED  | Survey study   | N = 901           | The LUTS prevalence was 28%. The most frequent LUTS subtype was isolated storage symptoms (13%), followed by mixed (9%) and isolated voiding symptoms (6%).  | The prevalence of storage LUTS (13%) might be underestimated because patients with daytime frequency or nocturia without urgency were not considered. |
| 11  | Naslund et al., 2007  | To estimate the LUTS prevalence and assess patients' intent to discuss LUTS with their PCP  | Self-administered questionnaire; analyzable blood sample; digital rectal exam  | N = 448           | 42% men had IPSS > 7; 48% had an enlarged prostate based on digital rectal exam, and 43% had PSA more or equal to 1.5 ng/ml  | PCPs who see younger patients or less than 50 patients a week were excluded.  |
| 12  | Platz et al., 2002    | To estimate the prevalence of LUTS and assess whether it varies by race/ethnicity   | Survey study, using multistage stratified clustered probability sample   | N = 2,881         | Men without surgery, 59.9% of 60 to 69 years old and 75.1% ≥ 70 had at least one symptom. Older white and Black men were not different in having LUTS.   | Potential bias in self-reporting  |
| 13  | Speakman et al., 2015 | To assess the burden and unmet need from LUTS/BPH with focus on the United Kingdom.   | Systematic review  | N = 286 abstracts | The prevalence of LUTS increases by age, for example, 3.5% in men aged 45–49 up to > 30% in men aged > 85 years in United Kingdom.   | This study reviewed some global literature without inclusion of major European epidemiologic studies that did not focus on burden of LUTS.            |

(continued)

Table 1. Continued.

| No. | Author(s), Year          | Purpose   | Methodology   | Sample   | Main findings   | Limitations  |
|-----|--------------------------|---|---|--|---|--|
| 14  | Coyne et al., 2009b      | To explore the risk factors and comorbid conditions associated with subgroups of LUTS in the United States, the United Kingdom, and Sweden from the EpiLUTS study | Cross-sectional, population-representative survey   | N = 14,141 men                                       | Described comorbid conditions significantly associated with the voiding + storage + postmicturition subgroup of LUTS; risk factors for LUTS.  | The account of comorbid conditions is based on participant self-report of a clinical diagnosis rather than a diagnosis verified by a clinician.        |
| 15  | Berry et al., 1984       | Report the prevalence and growth rate of human BPH with age   | Review of 10 studies  | N > 1,000  | The prevalence of pathological BPH is 8% in 40th, but 50% between 51 to 60 years old.   | The data might be outdated.  |
| 16  | Wei et al., 2005         | Review health-care utilization and cost associated with BPH   | Review study  | N/A  | Summarizing the prevalence of BPH by age  | Data were available only through 2000.   |
| 17  | Liatsikos et al., 2011   | To review the medical and minimally invasive treatments for managing BPH  | Systematic review   | N/A  | Report nearly 30% of men > 60 years of age experience troublesome LUTS due to BPH.  | Findings might be limited by the keyword search and the use of search agent.   |
| 18  | McNicholas & Kirby, 2011 | To assess the effects of medical, herbal, and surgical treatments on BPH  | Systematic review   | 63 RCTs, systematic reviews or observational studies | LUTS/BPH related bladder outlet obstruction may affect up to 30% of men in their early 70s.   | Findings might be limited by the keyword search and the use of search agent.   |
| 19  | Markland et al., 2007    | To determine whether disparities exist in the reporting of LUTS across race/ethnicity   | Community-based cohort study, questionnaire   | N = 2,804  | Reported no significant difference in the prevalence of moderate or severe LUTS in non-Hispanic White (34%), Mexican-American (34%), African-American (33%) men.                                | Subjects may not have discussed urologic symptoms with physicians and may not recognize the severity of symptoms. Underreporting of symptom may exist. |
| 20  | Fowke et al., 2011       | To investigate the roles of education, income, marital status, and source of health insurance on LUTS reporting among Black and White U.S. men                    | Large-scale prospective cohort study; survey by telephone interview or mailed questionnaire | N = 6,676  | The prevalence of moderate/severe LUTS was not significantly associated with race. Higher IPSS scores were significantly associated with lower income, marital status, and source of insurance. | Possible self-report bias, possible measurement error related to race  |
| 21  | Maserejian et al., 2013  | To report the incidence of LUTS in a diverse population-based sample of men and women   | A prospective cohort study with random sampling method and in-person interview              | N = 3,301  | 5-year moderate-to-severe LUTS incidence was 8.5% for men. White men had lower LUTS incidence (7%) than all other sex and race subgroups (13%).   | Calculation of LUTS incidence might be different from other studies.   |

(continued)

Table 1. Continued.

| No.                   | Author(s), Year                 | Purpose  | Methodology   | Sample         | Main findings   | Limitations  |
|-----------------------|---------------------------------|--|---|----------------|---|--|
| 22                    | Kristal et al., 2007            | To examine risk factors for incident of BPH in the PCPT  | Secondary analysis of the PCPT data   | N = 5,667      | Risks for total BPH were 41% higher for Black ( $p < .03$ ) and Hispanic men ( $p < .06$ ) than White men, and for severe BPH were 68% ( $p < .01$ ) and 59% ( $p < .03$ ), respectively. | Self-report of symptoms is highly subjective and may differ across race, ethnic, and socioeconomic groups. |
| 23                    | Parsons, 2010                   | Review the prevalence of LUTS/BPH and risk factors   | Review  | N/A            | Discussed the prevalence and modifiable risk factors for LUTS/BPH   |  |
| 24                    | Vaughan et al., 2011            | To evaluate the association of vitamin D levels and LUTS among U.S. men  | Cross-sectional survey  | N = 2,387      | Vitamin D deficiency was a significant risk factor for LUTS   |  |
| 25                    | Coyne et al., 2009              | To evaluate the LUTS impact on urinary-specific HRQOL, generic health indices, depression, and anxiety             | Cross-sectional population-representative survey                              | N = 14,141 men | Subgroups of LUTS and their percentages were reported. The largest group had storage + voiding + postmicturition; the smallest group had storage + postmicturition.                       | Data are self-reported.  |
| 26                    | Rohrman, Katzke, & Kaaks, 2016  | To examine the prevalence of LUTS in men of the general population   | Survey study  | N = 8,627      | 54.8% reported worse LUTS, but 27.1% reported improvement in the 4th follow-up; nocturia was the most common symptom.   | Possible self-report bias  |
| 27                    | Coyne et al., 2008              | To determine particular symptoms cluster of LUTS   | Secondary analysis  | N = 13,519     | Nocturia of twice or more per night (12%); terminal dribble (11%); urgency (10%); multiple symptoms (9%); and postvoid incontinence (5%)  |  |
| 28                    | Wallner et al., 2015            | To characterize the progression and treatment of LUTS among men aged 45–69 in the California Men's Health Study    | A cohort study and survey   | N = 19,505     | Of the 9,640 men with no/mild baseline LUTS, 3,993 (41%) had moderate/severe LUTS at 4-year follow-up. Of them, 3,634 (91.0%) had no treatment recorded.                                  | 40% dropout at the follow-up. The participation bias cannot be excluded.                                   |
| <b>Burden of LUTS</b> |                                 |  |   |                |   |  |
| 29                    | Irwin et al., 2009 <sup>a</sup> | To describe LUTS prevalence, severity, and symptom bother in men with/without overactive bladder in the EPIC study | Secondary analysis of data from EPIC, a multinational population-based survey | N = 7,210      | Symptom bother significantly increased by the number of LUTS.   | LUTS severity might be underestimated by the IPSS, which does not assess incontinence.                     |

(continued)

Table 1. Continued.

| No. | Author(s), Year       | Purpose  | Methodology  | Sample         | Main findings  | Limitations  |
|-----|-----------------------|--|--|----------------|--|--|
| 30  | Agarwal et al., 2014  | To identify the population- and individual-level burden of LUTS  | Population-based cross-sectional study survey            | N = 1,709 men  | Reported LUTS burdens were urgency (7.9%), stress urinary incontinence (6.5%), nocturia (6.0%), postmicturition dribble (5.8%), and urgency urinary incontinence (5.0%).   | Did not collect information on seeking health care   |
| 31  | Coyne et al., 2009    | To assess the prevalence and associated bother of LUTS in the United States, the United Kingdom, and Sweden in the EpiLUTS study | Cross-sectional, population-based survey                 | N = 14,139 men | Men were bothered by urgency (73.3%), leakage especially during sexual activity (82.1%); and nocturia (71.5%).   |  |
| 32  | Fujimura et al., 2011 | To assess LUTS severity in men by IPSS and core lower urinary tract symptom score  | A convenience sample, using questionnaires               | N = 515        | All symptom scores were significantly increased in symptomatic men compared with controls.   | A cross-sectional study of Japanese men. Need longitudinal studies of those with cultural background to confirm study findings |
| 33  | Coyne et al., 2009    | To evaluate the LUTS impact on urinary-specific HRQOL, generic health indices, depression and anxiety                            | Cross-sectional population-representative survey         | N = 14,141 men | 35.9% of men meeting self-reported screening criteria for clinical anxiety and 29.8% of men for clinical depression.   | Data are self-reported. Clinically significant anxiety and depression might not correspond to clinical diagnoses.              |
| 34  | Rom et al., 2012      | To evaluate the relationship between LUTS and depression in men  | Cross-sectional observational study, using questionnaire | N = 673        | Odds ratio (adjusted for total testosterone and age) for LUTS impact on mild depression is 1.092, $p < .001$ ; moderate-to-severe depression is 1.093, $p = .003$ ; and severe depression is 1.176, $p = .006$ . | The measure of depression is a questionnaire, not a diagnostic tool.   |
| 35  | Fourcade et al., 2012 | To evaluate outcomes of medical treatments of LUTS and the impact of LUTS on general HRQOL                                       | Cross-sectional observational study                      | N = 1,098      | Approximately half of BPH patients medically treated report unsatisfactory outcomes. Moderate-to-severe LUTS impact general HRQOL significantly.   | The sample might not be representative.  |
| 36  | Haltbak et al., 2005  | To examine the impact of symptom severity on QOL in men with LUTS /BPH   | A convenience sample, questionnaire survey               | N = 480        | Severity of urinary incontinence was predictive of all QOL domains except general health, and sexual function was predictive of all QOL domains.   | Possible self-report bias  |

(continued)



Table 1. Continued.

| No. | Author(s), Year              | Purpose   | Methodology                                  | Sample            | Main findings  | Limitations  |
|-----|------------------------------|---|--|-------------------|--|--|
| 37  | Perchon et al., 2011         | To investigate QOL in elderly men and correlates of LUTS                                      | A case-control study                         | N = 200           | Moderate and severe LUTS significantly reduced QOL   | Subject selection bias<br>Possible inaccurate self-report of symptoms  |
| 38  | Wein et al., 2009            | To evaluate association between LUTS and ED, EjD, and premature ejaculation                   | Cross-sectional epidemiological study survey | N = 11,834        | Men with multiple LUTS had more severe ED and more frequent EjD and premature ejaculation. Age, hypertension, diabetes, depression, urgency, and leaking during sexual activity were significantly associated with ED. | Results are observational and descriptive.<br>Possible self-report bias  |
| 39  | Rosen et al., 2003           | To investigate the relationship between LUTS and sexual problems in aging men                 | Multinational survey                         | N = 12,815        | Sexual disorders and their bothersomeness were strongly related to both age and severity of LUTS.  | The potential effect of selection bias cannot be completely ruled out.   |
| 40  | Chitale et al., 2007         | To evaluate if LUTS and ED were treated in an integrated fashion in primary care              | A convenience sample, cross sectional        | N = 100           | 54% of the patients with LUTS also admitted to ED. Patients with more severe LUTS had more severe ED.  | Not discussed  |
| 41  | <b>Speakman et al., 2015</b> | To assess the burden and unmet need from LUTS/BPH with focus on the United Kingdom            | Systematic review                            | N = 286 abstracts | LUTS/BPH have a major impact on men, their families, health services, and society  | This review did not assess the impact of pharmacotherapies on the burden of LUTS.  |
| 42  | Kannan et al., 2009          | To determine the effect of LUTS on utility of health care and health outcome                  | Secondary data analysis                      | N = 13,957        | LUTS were associated with more emergency room visits (OR: -1.57), hospitalizations (OR: -1.56), medical provider visits (OR: -1.52), 8.03% greater overall work productivity loss ( $p < .001$ ).                      | Cannot verify accuracy of the reported data  |
| 43  | Marklund et al., 2014        | To examine QOL of partners of men with LUTS suggestive of benign prostatic obstruction        | A convenience sample, cross-sectional study  | N = 131           | Partners of men with LUTS/benign prostatic obstruction had poor QOL.   | The partner sample is relatively small ( $n = 131$ ).  |
| 44  | Gotoh et al., 2009           | To assess the impact of urinary incontinence on the psychological burden of family caregivers | Online survey                                | N = 757           | Caregivers ( $n = 452$ ) for those with urinary incontinence reported significantly more burden than other caregivers ( $n = 305$ ; mean, 40.7 vs. 34.7, $p < .001$ ).   | This Internet-based survey may be limited by selection bias because subjects with higher education, income, social status, and so forth may be more likely to participate in such studies. |

(continued)

Table 1. Continued.

| No.  | Author(s), Year                     | Purpose   | Methodology       | Sample  | Main findings   | Limitations  |
|--|-------------------------------------|---|-------------------|---|---|--|
| 45   | <b>Wei et al., 2005</b>             | Review health-care utilization and cost associated with BPH   | Review study      | N/A   | In 2000, 4.5 million office visits made for BPH, and the estimated direct cost of BPH is \$1.1 billion.   | Administrative data lack detailed patient-level information. Data were available only through 2000.  |
| 46   | Physicians Practice, 2008           | Cost burden of urological diseases  | Review article    | N/A   | The five most costly urological diseases, which account for \$9.1 billion, were urinary tract infection (\$3.5 billion), kidney stones (\$2 billion), prostate cancer (\$1.3 billion), bladder cancer (\$1.2 billion), and BPH (\$1.1 billion). |  |
| <i>Standard medical treatments and effectiveness</i> |                                     |   |                   |   |   |  |
| 47   | Soler et al., 2013                  | To review pathophysiological mechanisms for male LUTS   | Systematic review | N/A   | Reviewed several pathologic processes implicated in male LUTS.  | The discussion might be limited by the search agent and keyword.   |
| 48   | Gacci et al., 2016                  | Update of the latest evidence on the mechanisms of action, evaluate the current meta-analyses, and emphasize the results of pooled data analyses of PDE5-Is in LUTS/BPE | Systematic review | N = 8   | PDE5-Is improves LUTS (IPSS mean difference vs. placebo: 2.35–4.21) and erectile function (IIEF mean difference vs. placebo: 2.25–5.66).  | Data on the long-term effects prostate size, disease progression, or prostate cancer prevalence related to the use of PDE5-Is are not available.         |
| 49   | Silva et al., 2014                  | To review current medical treatment of LUTS   | Systematic review | N/A   | PDE5-I improves BPH/LUTS. Combination of PDE5-I with ABs provides better symptomatic control than ABs alone.  | The results might be limited by the keyword search and the use of search agent.  |
| 50   | MacDonald et al., 2018              | To evaluate the efficacy and adverse effects of newer drugs used to treat LUTS  | Systematic review | N = 9,000   | AB silodosin and PDE5-Is tadalafil were more effective than placebo in improving LUTS (moderate strength evidence), but these drugs had more adverse effects, including abnormal ejaculation (silodosin).                                       | Evidence was insufficient to assess long-term efficacy, prevention of symptom progression, need for surgical intervention, or long-term adverse effects. |
| 51   | <b>McNicholas &amp; Kirby, 2011</b> | To assess the effects of medical, herbal, and surgical treatments on LUTS   | Systematic review | N = 63 systematic reviews, RCTs, or observational studies | ABs improve symptoms compared with placebo. 5-ARIs improve symptoms and reduce the risk of complications of BPH.  | Findings might be limited by the keyword search and the use of search agent.   |

(continued)

Table 1. Continued.

| No. | Author(s), Year            | Purpose  | Methodology  | Sample  | Main findings  | Limitations  |
|-----|----------------------------|--|--|---|--|--|
| 52  | Dahm et al., 2017          | To assess the effectiveness and adverse effects of newer drugs on LUTS/BPH   | Systematic review  | 43 RCTs                                       | For all newer agents, the evidence was generally insufficient to assess long-term efficacy, prevention of symptom progression, or adverse effects.   | Focus on English language publications is a potential limitation.<br>Unable to evaluate adverse treatment effect such as disease progression leading to AUR and/or surgical intervention.  |
| 53  | Sebastianelli et al., 2017 | To evaluate the efficacy and safety of mirabegron treatment of storage symptom   | Systematic review and meta-analysis  | 8 trials evaluating 10,248 patients<br>N = 23 | Mirabegron 50 mg and 100 mg were associated with a significant reduction of nocturia episodes, compared with a placebo.<br>EjD was significantly more common with ABs (OR: 5.88) and 5-ARIs (OR: 2.73) when compared with placebo.                 | Despite the high quality of the included studies, most available data were from industry-led trials.<br>EjD may be underreported in RCTs, where validated tools to assess ejaculatory function were not routinely used. The definition of EjD was often not reported and inconsistent among studies. |
| 54  | Gacci et al., 2014         | To evaluate the impact of medical treatments for LUTS/BPH on ejaculatory function (EjD)  | Systematic review  | N = 23  | EjD was significantly more common with ABs (OR: 5.88) and 5-ARIs (OR: 2.73) when compared with placebo.  | EjD may be underreported in RCTs, where validated tools to assess ejaculatory function were not routinely used. The definition of EjD was often not reported and inconsistent among studies.   |
| 55  | Traish et al., 2014        | To review the adverse side effects of 5-ARIs therapy   | Review study   | N/A   | 5-ARIs have adverse effects such as reduced libido, ED, orgasmic dysfunction, increased high Gleason grade prostate cancer, heart failure, and cardiovascular events, depression   | Adverse events may have been underestimated in clinical trials.  |
| 56  | FDA, 2011                  | Informing that 5-ARI class of drugs has the increased risk of high-grade prostate cancer   | In review of randomized, double-blind, placebo-controlled, multicenter trial | N = 18,882<br>N = 8,231                       | The reduction in risk of prostate cancer was limited to Gleason score 6 or lower prostate cancers. However, there was an increased incidence of Gleason score 8–10 prostate cancers with finasteride versus placebo (1.8% vs. 1.1%, respectively). |  |
| 57  | Seftel et al., 2007        | To assess the provider perceptions of sexual dysfunction in men with LUTS/BPH and the effects of BPH treatments on sexual function | Large-scale epidemiology study; survey                                       | N = 1,275                                     | 19% patients reported medication side effect to urologists and 24% to their PCP.<br>The incidence of EjD due to medications was 32% estimated by urologists, 22% by PCP.   | The sample size of urologists and PCP was small, not representative.   |

(continued)

Table 1. Continued.

| No. | Author(s), Year               | Purpose   | Methodology  | Sample  | Main findings   | Limitations  |
|-----|-------------------------------|---|--|---|---|--|
| 58  | Cindolo et al., 2015          | To examine adherence to pharmacological therapy in men with LUTS  | A cohort study use an administrative prescription database and hospital discharge code | N = 1.5 million                                     | The 1-year adherence was 29% in patients exposed to at least 6-month therapy.   | The paucity of clinical measures and the absence of patient-reported outcomes.   |
| 59  | Koh et al., 2014              | To assess influence of patient characteristics and provider factors on the continuation of medication for 12 months in newly diagnosed BPH patients | A cohort study and telephone surveys   | N = 670   | 12-month compliance for medication was 36.6%. Independent predictors included larger prostate volume, higher PSA, income level, and a good patient-doctor relationship.   | Findings were mainly based on a retrospective review. Data were obtained through self-reporting or prescription records and not independently audited by pill counts or otherwise validated. |
| 60  | Masumori et al., 2007         | To evaluate treatment failure during a 4-year follow-up period  | A convenience sample, longitudinal observation   | N = 247   | Treatment failure occurred in 42 (17.0%) patients during the 4-year period.   | Subject dropout may affect the accuracy of the estimate of the treatment failure rate.   |
| 61  | <b>Liatsikos et al., 2011</b> | To review the medical and minimally invasive treatments for managing BPH  | Systematic review  | N/A   | Several minimally invasive techniques have showed promising results comparable with that of transurethral resection of the prostate.  | The results might be limited by the keyword search and the use of search agent.  |
| 62  | Yamanishi et al., 2015        | To review the mechanism of action, the type of neuromodulation, and the efficacy of neuromodulation in RCTs   | Systematic review  | N/A   | Neuromodulation therapies (pelvic floor electrical stimulation, interferential therapy, magnetic stimulation, percutaneous tibial nerve stimulation, and sacral nerve stimulation) were effective on treating overactive bladder or urgency urinary incontinence. | The respective cure or improvements are difficult to compare because neuromodulation was selected on occasion of lack of response to other conservative treatments.                          |
| 63  | Biester et al., 2012          | To assess the potential additional benefit of nonstandard vs. standard surgical treatments for BPH  | Systematic review  | 43 mainly low-quality RCTs involving 4,539 patients | Nonstandard procedure was not superior for symptom reduction. Holmium or thulium laser resections of the prostate may have additional benefits.   | Data quality is poor; studies lack scientific rigor. There is a paucity of data on long-term outcomes.   |
| 64  | Tennvall et al., 2006         | To evaluate the cost-utility of Microwave thermotherapy   | Health-economic simulation model   |   | ProstaLund Feedback Treatment appears to be cost-saving after 5 years.  | Lacking long-run data in this area, especially data from RCTs  |

(continued)

Table 1. Continued.

| No.                                   | Author(s), Year        | Purpose   | Methodology   | Sample  | Main findings  | Limitations   |
|---------------------------------------|------------------------|---|---|---------|--|---|
| <i>Alternative treatments of LUTS</i> |                        |   |   |         |  |   |
| 65                                    | Burgio et al., 2011    | To compare the effectiveness of behavioral treatment with that of antimuscarinic therapy in men with overactive bladder | Randomized, controlled, equivalence trial with 4-week AB run-in | N = 143 | The behavioral group showed greater reductions in nocturia (mean = -0.70 vs. -0.32 episodes/ night; $p = .05$ ). The drug group showed greater reductions in urgency scores (mean = -0.44 vs. -0.12; $p = .02$ ). Other between-group differences were nonsignificant. | The results may be generalized only to men without evidence of obstruction as determined by uroflowmetry, PVR, and a trial of an AB.<br>Not all possible drug combinations were tested. |
| 66                                    | Yap et al., 2009       | To assess the effect of an SMP on actual voiding behavior using frequency-volume chart data                             | RCT   | N = 140 | The total number of voids and episodes of nocturia were lower in the SMP group, with a mean decrease of 2.6 and 0.7 episodes, respectively than in standard care group.  | Potential differential impact of medication on study groups was not controlled.   |
| 67                                    | Brown & Emberton, 2009 | Self-management for men with LUTS   | Methodology article explaining a behavioral intervention        | N/A     | Self-management significantly reduced urinary symptoms (as effective as medication), suggesting that self-management be considered as first-line treatment for men with LUTS.  | Described the SMP and study outcome but provided a few details of the RCT   |
| 68                                    | Chen et al., 2012      | To evaluate the self-management interventions in improving LUTS/BPH and QOL in men                                      | RCT   | N = 222 | IPSS scores and QOL self-management interventional group scores were significantly lower than those of the standard care group at 3 and 6 months.  | Subject self-selection bias<br>Repeated measure analysis of variance was used to examine associations among study groups and measures; a lack of an objective measure.                  |
| 69                                    | Choi et al., 2015      | To evaluate the effect of community-based nurse-led interventions on Chinese patients with LUTS                         | Case-controlled intervention study                              | N = 720 | The intervention group reported increased self-efficacy, improved global health condition, doctor consultation, use of medication, and nondrug therapy.  | Absence of randomization and potential recall bias  |
| 70                                    | Soda et al., 2010      | To test the efficacy of lifestyle measures as a first step in treating nocturia   | A convenience sample, repeated measures                         | N = 56  | Mean nocturnal voids and nocturnal urine volume decreased significantly from 3.6 to 2.7 and from 923 to 768 ml, respectively. Twenty-six subjects (53.1%) showed an improvement of more than one episode.  | Absence of a control group<br>Did not collect data on how much patients had incorporated the behavioral recommendations.  |

(continued)

Table 1. Continued.

| No. | Author(s), Year       | Purpose   | Methodology   | Sample   | Main findings   | Limitations  |
|-----|-----------------------|---|---|--|---|--|
| 71  | Shafik & Shafik, 2003 | To assess the effect of pelvic floor muscle exercises on overactive bladder symptoms  | Nonrandomized, controlled trial                         | N = 28   | At pelvic floor muscle contraction, while the bladder was filled to the volume inducing involuntary voiding, the detrusor pressure decreased to a mean of $10.6 \pm 2.1$ cm H <sub>2</sub> O (range 6–12, $p < .01$ ) and the posterior urethral pressure increased to $86.6 \pm 7.9$ cm H <sub>2</sub> O (range 80–102, $p < .001$ ); involuntary voiding did not occur. | Not discussed  |
| 72  | de Jong et al., 2014  | To analyze the influence of body position on urodynamic parameters  | Systematic search was conducted on 14 medical databases | N = 11   | In men with LUTS, a significantly lower PVR ( $224.96$ ml; 95% CI 248.70 to 21.23) was shown in sitting position compared with standing.  | The results might be limited by the keyword search and the use of search agent.  |
| 73  | Fowke et al., 2013    | To determine the association between LUTS severity and physical activity (PA)   | Questionnaires  | N = 405  | The inverse association between PA energy expenditure LUTS severity was most evident among obese men (i.e., BMI > 30).  | The causal relationship between PA and LUTS could not be determined.   |
| 74  | Wolin et al., 2015    | To examine the association of PA with nocturia in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening trial                | Clinical trial  | Prevalent ( $n = 28,404$ )<br>Incident ( $n = 4,710$ ) | Men being active more than an hour per week were 13% less likely to report nocturia and 34% less likely to report severe nocturia than men reporting no PA.   | There may be an overreporting of PA due to the study question asked.   |
| 75  | Khoo et al., 2014     | To compare effects of a meal-replacement-based diet with isocaloric reduced-fat plan on LUTS and nutrient intake in obese Asian men | Randomized trial  | N = 46   | The meal-replacement group had significantly greater decreases in waist circumference, fat mass, fat intake, plasma C-reactive protein, and in storage LUTS score.  | The small sample size and lower statistic power.   |
| 76  | Yee et al., 2015      | To assess the effect of weight reduction on LUTS) and the relationship between obesity and LUTS                                     | RCT   | N = 130  | There was no statistical difference between the 2 groups on nocturia, LUTS severity, QOL, and uroflowmetry parameters.  | Most patients were overweight (BMI 25 to < 30 kg/m <sup>2</sup> ), not obese (BMI 30–35 kg/m <sup>2</sup> ), likely masking intervention effect. |
| 77  | Vidlar et al., 2010   | To evaluate efficacy and tolerability of cranberry (Vaccinium macrocarpon) powder   | Controlled trial  | N = 42   | The cranberry group had statistically significant improvement in IPSS, QOL, and urination parameters.   | A small sample size and inadequate consideration of the placebo effect.  |

(continued)

Table 1. Continued.

| No. | Author(s), Year          | Purpose   | Methodology                                    | Sample          | Main findings  | Limitations  |
|-----|--------------------------|---|--|-----------------|--|--|
| 78  | Ledda et al., 2016       | To evaluate the prophylactic effects of cranberry extract in men with LUTS/BPH  | Controlled trial                               | N = 44          | The cranberry oral supplementation was superior at reducing the mean number of urinary tract infections ( $p$ value = .0062).  | Small sample; bivariate statistics were used, did not control for covariates.                      |
| 79  | Spettel et al., 2013     | To assess the effect of a standardized grape product on urinary symptoms  | RCT  | N = 96          | There was no statistical difference between taking grape juice and placebo.  | Dose of grape juice may be inadequate. Subject self-selection bias.                                |
| 80  | Maserejian et al., 2013b | To examine association between beverage intake and LUTS in the Boston Area Community                                      | Prospective cohort study                       | N = 4,144       | Citrus juice intake was associated with 50% lower odds of LUTS progression in men ( $p$ = .02).  | Possible nonresponse bias  |
| 81  | Vaughan et al., 2011     | To evaluate the association of vitamin D levels and LUTS among U.S. men   | Cross-sectional survey                         | N = 2,387       | Vitamin D deficiency was associated with the presence of moderate-severe urinary incontinence (POR 1.8) and at least one LUTS (POR 1.4).   | Vitamin D level or LUTS data were missing for 42% of the sample that were largely young and White. |
| 82  | Espinosa et al., 2013    | To highlight the benefits of nutrition and dietary supplements in men with LUTS/BPH                                       | Review study                                   | N/A             | Discussed Vitamin D deficiency as a risk factor for BPH  |  |
| 83  | Espinosa et al., 2013    | To provide the most relevant data on the correlation between vitamin D and BPH  | A comprehensive review                         | N/A             | Vitamin D analogues of up to 6,000 IU/day have shown to decrease prostate volume in BPH patients.  | Not discussed  |
| 84  | Maserejian et al., 2011  | To test if carotenoid, vitamin A, and vitamin C intake were inversely associated with LUTS, voiding, and storage symptoms | Survey using a multistage random sample design | N = 1,466       | Men consuming greater dietary lycopene, b-carotene, total carotenoid, or vitamin A had 40% to 50% reduced odds of LUTS.  | Possible nonresponse bias  |
| 85  | Tacklind et al., 2009    | To assess the effects of <i>S. repens</i> in the treatment of LUTS/BPH  | Systematic review                              | Nine new trials | For nocturia, <i>S. repens</i> was significantly better than placebo but with significant heterogeneity (I <sup>2</sup> = 66%). A sensitivity analysis, utilizing higher quality, larger trials ( $\geq 40$ subjects), demonstrated no significant difference. | A small number of studies existed and were reviewed.   |

(continued)

Table 1. Continued.

| No. | Author(s), Year       | Purpose  | Methodology                         | Sample                             | Main findings  | Limitations   |
|-----|-----------------------|--|-------------------------------------|------------------------------------|--|---|
| 86  | Wilt et al., 2002     | To assess the effects of <i>S. repens</i> in the treatment of LUTS/BPH                         | Systematic review                   | Three new trials                   | Compared with finasteride, <i>S. repens</i> produced similar improvements in urinary symptom scores and peak urine flow.   | A small number of studies were reviewed.  |
| 87  | Bent et al., 2006     | To determine the efficacy of saw palmetto for the treatment of BPH                             | Randomized double-blind trial       | N = 225                            | There was no significant difference between the saw palmetto and placebo groups.   | A number of methodologic limitations including a failure to use validated symptom scores, and inadequate concealment of treatment assignment in 10 of the 21 studies              |
| 88  | Barry et al., 2011    | To determine the effect of saw palmetto extract at up to 3 times the standard dose on LUTS/BPH | Double-blind, multicenter RCT       | N = 369                            | Saw palmetto extract was no more effective than placebo for any secondary outcome.   | Only one extract was studied, and because the potential active ingredients and mechanisms are unknown, the findings may not be generalizable.                                     |
| 89  | Tacklind et al., 2012 | To examine the effect of <i>S. repens</i> on LUTS/BPH  | Systematic review                   | 32 RCTs involving 5,666 men        | Compared with placebo, <i>S. repens</i> , at double and triple the usual dose, provides no improvement for nocturia, peak urine flow, and symptom scores.  | Not discussed   |
| 90  | Damiano et al., 2016  | To analyze evidence on the role of <i>Cucurbita pepo</i> in the treatment of LUTS/BPH          | Systematic search                   | N = 16                             | In all studies an improvement in IPSS and uroflowmetry parameters has been reported. In four studies, an improvement in QOL has been reported.   | The few available studies were often outdated and enrolled a small number of patients, and only three RCTs were of good quality.  |
| 91  | Zhang et al., 2017    | To assess the therapeutic and adverse effects of acupuncture                                   | Systematic review and meta-analysis | 8 RCTs, involving 661 men with BPH | Data from three trials showed a short-term effect of acupuncture when compared with sham acupuncture. A meta-analysis indicated no significant effect on IPSS in two trials.   | Although two trials were published in English, the populations in the included trials were all Chinese. Most included trials (7/8) had follow-up periods no longer than 3 months. |
| 92  | Ricci et al., 2004    | To evaluate whether reflexotherapy can treat the irritative symptom of LUTS                    | Randomized controlled study         | N = 42                             | The daily voiding frequency decreased by 8% in those receiving a drug and by 20% in those ( <i>n</i> = 13) receiving reflexotherapy; the nocturnal micturitions decreased by 20% and 60% in drug vs. reflexotherapy group. | Small sample size   |

(continued)



Table 1. Continued.

| No. | Author(s), Year   | Purpose   | Methodology                 | Sample  | Main findings  | Limitations   |
|-----|-------------------|---|-----------------------------|---------|--|---|
| 93  | Wang et al., 2013 | To evaluate effects of electroacupuncture on LUTS severity (IPSS), PVR, and maximum urinary flow rate (Q <sub>max</sub> ) | Randomized controlled study | N = 100 | At the 6th week, treatment group had a 4.51 and 4.12 points greater decline in IPSS than the control group. At the 18th week, a 3.2 points ( $p = .001$ ) greater decline in IPSS. | Study treatment was 4 weeks and followed up till the 18th week. Long-term effects remain to be established. |

Note. LUTS = lower urinary tract symptoms; EPIC = European Prospective Investigation into Cancer and Nutrition; IPSS = international prostate symptom score; EpiLUTS = Epidemiology of LUTS; MirOS = Osteoporotic Fractures in Men Study; ED = erectile dysfunction; PCP = primary care providers; PSA = prostate-specific antigen; BPH = benign prostatic hyperplasia; RCT = randomized controlled trial; PCPT = Prostate Cancer Prevention Trial; QOL = quality of life; HRQoL = health-related quality of life; EJD = ejaculatory dysfunction; PDE5-Is = phosphodiesterase type 5 inhibitors; IIEF = International Index of Erectile Function; AUR = acute urinary retention; ABs = alpha blocker; 5-ARI = 5-alpha reductase inhibitor; PVR = postvoid residual urine; SMP = self-management program; POR = prevalence odds ratio; BMI = body mass index.

<sup>a</sup>Bold fonts indicate the article that was included in another area for review.

men aged of 51 to 60 years and 70% or more of the men older than 60 years have BPH (Berry, Coffey, Walsh, & Ewing, 1984; Wei, Calhoun, & Jacobsen, 2005). Of men older than the age of 60 years experiencing LUTS, 30% were due to BPH (Liatsikos, Kyriazis, Kallidonis, & Stolzenburg, 2011; McNicholas & Kirby, 2011). There are a few other sociodemographic risk factors, but many disease associations identified for LUTS. Several large survey studies in the United States did not detect racial difference in the prevalence of LUTS (Fowke et al., 2011; Litman et al., 2007; Markland, Thompson, Ankerst, Higgings, & Kraus, 2007; Platz et al., 2002). However, in the 2002–2005 BACH Survey, the 5-year incidence of moderate-to-severe LUTS (IPSS > 7) in 1,610 men was significantly lower in Whites (7%) than other racial groups (13%; Maserejian et al., 2013a), mirroring the Prostate Cancer Prevention Trial report that African American and Hispanic men had a significantly higher rate of BPH than White men (Kristal et al., 2007). Fowke et al.'s (2011) study showed that low income was significantly associated with the prevalence of LUTS, but having private insurance was associated with a lower risk of LUTS. Other risk factors for LUTS/BPH have also been identified, including genetics, childhood nocturnal enuresis, sex steroid hormones, modifiable lifestyle factors, and inflammation (Coyne et al., 2009a; Parsons, 2010). This suggests a broader genetic-environment interaction related to LUTS and other diseases. International studies have shown that LUTS are associated with a wide range of comorbid conditions, including arthritis, asthma, chronic anxiety, depression, diabetes, heart disease, irritable bowel syndrome, neurological conditions, recurrent urinary tract infection, sleep disorders, and vitamin D deficiency (Coyne et al., 2009a; Litman et al., 2007; Vaughan et al., 2011).

Symptom clusters of LUTS were reported in a few studies. In the EpiLUTS study, 47% of men had LUTS from more than one symptom category, with voiding + storage + postmicturition symptoms as the largest subgroup (24.3%) and storage + postmicturition symptoms as the smallest subgroup (2%; Coyne et al., 2009c). In a U.S. population-based study, "Male Attitudes Regarding Sexual Health," 2,173 American men reported the prevalence of storage (13%) and mixed (9%) symptoms higher than that of voiding symptoms (6%; Glasser et al., 2007). Nocturia has been reported as the most common symptom in several studies worldwide (Coyne et al., 2008; Irwin et al., 2009; Platz et al., 2002; Rohrmann, Katzke, & Kaaks, 2016).

LUTS progressively worsens over time. In the BACH Survey of men aged 30 to 79 years, 1 in 10 men in this age range newly developed LUTS over 5 years, with an 8.5% increase in men from no-to-mild LUTS at baseline, to moderate-to-severe LUTS in 5 years (Maserejian

et al., 2013a). In the 2002–2007 California Men's Health Study of 9,640 men aged 45 to 69 years, 3,993 men (41%) had changed from no-to-mild LUTS to moderate-to-severe LUTS at a 4-year follow-up, and only 9% of them received a medical treatment for LUTS (Wallner et al., 2015). This is the same trend observed in a large cohort of European men ( $N = 8,627$ ) of 48 to 79 years of age, of whom 24.7% had moderate-to-severe LUTS at baseline, but 54.8% reported worsening LUTS over a 3-year period (Rohrmann et al., 2016).

### Burden of LUTS

Data from the 2005 EPIC study surveying 19,165 adults in 5 countries showed that symptom bother significantly increased by the number of LUTS experienced (Irwin et al., 2009). Urgency and urge incontinence were commonly reported to be bothersome; nocturia also topped the list (Agarwal et al., 2014; Coyne et al., 2009b; Fujimura et al., 2011).

Symptom burden of LUTS is widespread and significant. Coyne et al. (2009c) surveyed 14,139 men in the United States, United Kingdom, and Sweden (the EpiLUTS study) and reported that 35.9% of men with LUTS have clinically diagnosable anxiety, and 29.8% have clinically diagnosable depression. Rom, Schatzl, Swietek, Rücklinger, and Kratzik (2012) detected a significant association between LUTS and various levels of depression in a sample of 673 healthy Austrian men. Other studies from France (Fourcade et al., 2012), Norway (Haltbakk, Hanestad, & Hunskaar, 2005), and Brazil (Perchon, Pintarelli, Bezerra, Thiel, & Dambros, 2011) reported a significantly diminished QOL in men with LUTS. The quality of sexual life significantly worsened. The EpiLUTS study data showed that leaking urine during sexual activities was the most frequently reported bothering symptom by 82% of participants (Coyne et al., 2009b) and that men with multiple LUTS had more severe erectile dysfunction and more frequent ejaculatory dysfunction and premature ejaculation (Wein et al., 2009). Other international and multinational survey studies confirmed associations between LUTS and poor quality of sexual life (Chitale, Collins, Hull, Smith, & Irving, 2007; Rosen et al., 2003).

LUTS places a tremendous economic burden on society (Speakman et al., 2015). The 2006 U.S. National Health and Wellness Survey data showed that LUTS is significantly associated with increasing emergency room visits, doctor visits, and hospitalizations (odds ratios: 1.57, 1.52, and 1.56, respectively), as well as greater loss of work productivity (8.03%) than normal controls (Kannan, Radican, Turpin, & Bolge, 2009). Evidence has shown that QOL in the caregivers and partners of men with LUTS was impaired (Gotoh et al., 2009; Marklund, Spångberg, & Edéll-Gustafsson, 2014). It was estimated

that BPH alone cost \$1.1 billion annually in 2000 in the United States (Wei et al., 2005). The cost can be much higher today, especially when all causes of LUTS are considered (Physicians Practice, 2008). Clearly, LUTS have become a public health concern and require effective management.

### Standard Medical Treatments and Effectiveness

LUTS have multiple pathological causes involving abnormal function in prostate, bladder, and urethra; neurological diseases; inflammation; and metabolic syndrome (Soler et al., 2013). Accordingly, a variety of medical treatments, including medication, surgery, minimally invasive procedures, and neuromodulation therapy are used to treat LUTS.

The combination therapy of alpha blockers (ABs) and 5-alpha reductase inhibitors (5-ARIs) is the first-line treatment of LUTS due to BPH. McNicholas and Kirby (2011) systematically reviewed 63 published studies and reported that ABs improved peak urinary flow significantly and 5-ARI relieved LUTS. The use of phosphodiesterase type 5 inhibitors alone or with ABs was shown to be safe and more effective than placebo in treating LUTS due to BPH (Gacci et al., 2016; MacDonald et al., 2018; Silva, Silva, & Cruz, 2014). Dahm et al. (2017) reviewed 43 clinical trials of newer drugs, including phosphodiesterase type 5 inhibitors, and concluded that traditional ABs treatment produces superior outcomes to the newer drug or drug combination because of a similar effectiveness but fewer side effects. Mirabegron is a new drug that treats urinary storage symptoms. A recent systematic review and meta-analysis evaluated eight clinical trials that compared mirabegron with placebo or tolterodine. Mirabegron was found to be an effective treatment for overactive bladder, with a slightly (nonsignificant) increased risk of side effects (Sebastianelli et al., 2017).

Despite their effectiveness, medications of LUTS were frequently reported for their side effects on cardiovascular events, higher Gleason score grade, depression, and particularly, erectile dysfunction (Gacci et al., 2014; Traish, Mulgaonkar, & Giordano, 2014). Based on two large clinical trials, the Prostate Cancer Prevention Trial and the Reduction by Dutasteride of Prostate Cancer Event, the U.S. Food and Drug Administration warned consumers in 2011 that 5-ARIs might increase the risk of high-grade prostate cancer, despite that they reduced the risk of low-grade (Gleason score  $\leq 6$ ) prostate cancer (Food and Drug Administration, 2011). Further, a 2003 survey of 1,275 U.S. physicians indicated that patients with BPH underreported treatment drug side effects, with 19% reporting to urologists and 24% to primary care providers (Seftel, Rosen, & Kuritzky, 2007). Moreover, patient compliance with medication

treatment is poor. A study of 1.5 million American men with BPH reported the 1-year adherence rate at 29% (Cindolo et al., 2015). Evidence from international communities also suggests that two thirds of newly diagnosed BPH patients with LUTS discontinue medication within 12 months (Koh, Cho, Kim, & Kim, 2014) and a 4-year adherence rate at 19% (Masumori, Hashimoto, Itoh, Tsukamoto, & The Sapporo Medical University Naftopidil Study Group, 2007).

When medication treatment fails, surgical procedures are considered. Transurethral resection of the prostate remains the gold standard approach for BPH, but various minimally invasive treatments have been used to treat LUTS, including transurethral and transrectal alternative and laser-based treatments. Based on a systematic review of the literature, Liatsikos et al. (2011) concluded that such minimally invasive treatments had comparable efficacy and minimal side effects and thus increasing popularity among patients. Further, Yamanishi, Kaga, Fuse, Shibata, and Uchiyama (2015) reviewed evidence of neuromodulation therapy of LUTS, including pelvic floor electrical stimulation, interferential therapy, magnetic stimulation, and percutaneous tibial nerve stimulation and sacral nerve stimulation across gender. They acknowledged an initial evidence for the superiority of these treatments over placebo and also urged further research of their effectiveness relative to other conservative treatments. Biester et al. (2012) reviewed 43 mainly low-quality clinical trials that compared standard surgery (e.g., transurethral resection of the prostate) with nonstandard treatments (e.g., laser ablation, interstitial laser coagulation, transurethral microwave therapy, and transurethral needle ablation). They concluded that these nonstandard treatments were not superior for symptom reduction, but holmium and thulium laser resections of the prostate might have an additional benefit to patients. Tennvall, Hjelmgren, and Malmberg (2006) reported that microwave thermotherapy (ProstaLund Feedback Treatment) was cost-effective after 5 years of the treatment in comparison with alpha-blockade drug therapy. In view of a moderate utility of minimally invasive treatments and low compliance for medication treatment, it would be prudent to consider alternative treatments of LUTS.

### *Alternative Treatments of LUTS Worldwide*

**Lifestyle.** One of the main alternative approaches to treating LUTS is to enhance patient self-management of LUTS through lifestyle modification. Two well-designed clinical trials were carried out. In the United States, Burgio et al. (2011) randomized 143 men who continued to have overactive bladder symptoms after a 4-week AB run-in to a behavioral treatment (pelvic floor muscle exercise [PFME], urge suppression, and delayed voiding;

$n=73$ ) or drug therapy ( $n=70$ ) over 8 weeks. Both groups continued AB therapy throughout the trial and showed a significant reduction of voiding episodes without detectable difference, while the behavioral treatment group showed more reduction in nocturia, and the drug therapy group showed more reduction in urgency. In the United Kingdom, a clinical trial was carried out to assess a behavioral intervention to lifestyle factors (e.g., fluid intake) and behavioral techniques (e.g., bladder training) among 140 men with LUTS. It was reported that the behavioral intervention plus standard care group ( $n=73$ ) had significantly higher voided volume by 57 ml, lower frequency of daily voids (by 2.6) and nocturnal episodes (by 0.7), less severe urinary symptoms, and better QOL than a standard care group ( $n=67$ ) over 12 months ( $p < .01$  for all; Brown & Emberton, 2009; Yap, Brown, Cromwell, Van Der Meulen, & Emberton, 2009).

More supporting evidence emerged from international studies that had relatively less methodological rigor. Reports from two studies (one was randomized and another was case-controlled) of 222 and 406 Chinese LUTS patients, respectively, showed evidence that a brief behavioral intervention consisting of PFMEs, fluid intake, and bladder training techniques resulted in a significant reduction of self-reported LUTS over a period of 3 to 12 months when compared with standard care (Chen et al., 2012; Choi et al., 2015). In a single-group study of 56 Japanese subjects (including 47 men and 9 women), a lifestyle modification requiring restricted fluid intake, moderate exercise, keeping warm in bed, and restrictive bed hours led to a significant reduction of nocturnal urine volume, from 923 to 768 ml, with an average reduction of one nocturia episode per night (Soda et al., 2010). Shafik and Shafik (2003) found a significant association between PFMEs and declined detrusor pressure in a small sample of 28 Egyptian men and women, lending support for the PFME effect on overactive bladder. Further, de Jong, Pinckaers, ten Brinck, à Nijeholt, and Dekkers (2014) conducted a systematic review of 11 published studies and reported that a sitting position is better than standing position in improving urodynamic parameters such as low postvoid residual volume in men with LUTS, although it made no difference in healthy men.

**Physical activity and weight loss.** Studies highlighted physical activity as an important lifestyle factor. Fowke et al. (2013) reported a significant association between physical activity and lower LUTS severity, with a strong association among the obese in a cross-sectional analysis of 405 cancer-free American men with LUTS. Wolin et al. (2015) used National Cancer Institute-sponsored Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial data to examine associations between

levels of physical activity and self-reported LUTS. They found that men who were physically active 1 hour or more weekly were 13% less likely to report nocturia—a significant bothersome symptom—and 34% less likely to report severe nocturia, when compared with men who were physically inactive.

Evidence on a weight loss intervention, however, was inconclusive. Khoo et al. (2014) tested an intervention of a 12-week reduced fat diet among 45 Singapore men and reported that a 10% weight loss was significantly associated with less self-reported LUTS. Yee et al. (2015) tested a weight loss program focusing on weight reduction and medical nutrition among 130 men in Hong Kong. They found no significant difference in weight difference or self-reported LUTS between the intervention and control groups over 48 weeks.

**Dietary nutrition.** Much research attention has been given to supplements and nutrition. In a randomized controlled trial that tested daily use of 1,500 mg of dried, powdered cranberries over 6 months in 42 Czech Republic men, investigators found that the intervention group ( $n=21$ ) reported significantly less LUTS and better QOL than the control group ( $n=21$ ), with 70% of the intervention participants showing a significant improvement in urinary flow rate, bladder voiding, and postvoid residual volumes based on uroflowmetry measurements (Vidlar et al., 2010). In a nonrandomized study of Italian men using 120 mg of a standardized cranberry extract (Anthocran) daily for 60 days, it was found that the intervention group ( $n=23$ ) significantly reduced the number of urinary tract infection episodes (from 3.2 to 0.8;  $p < .05$ ) during the intervention compared with the control group ( $n=21$ ; from 3.1 to 2.1; Ledda et al., 2016). In a randomized double-blind trial of 96 American men with LUTS, men taking 240 ml of 100% grape juice daily for 3 months ( $n=47$ ) showed no significant difference in LUTS compared with men in the control group ( $n=49$ ; Spettel et al., 2013). However, in the BACH study, citrus juice intake was found to be significantly associated with a 50% lower chance of LUTS progression in men, while greater coffee or baseline total caffeine intake significantly increased the chance of LUTS progression (Maserejian et al., 2013b).

In an analysis of 1,388 male participants of the 2005–2006 National Health and Nutrition Examination Survey, vitamin D deficiency was associated significantly with the presence of moderate-to-severe urinary incontinence and a symptom of LUTS (Vaughan et al., 2011). Espinosa and coworkers (Espinosa, 2013; Espinosa, Esposito, Kazzazi, & Djavan, 2013) concluded that a healthy level of vitamin D was associated with a decrease of prostate volume and a lower risk of BPH, based on a literature review. Moreover, in the BACH Survey, dietary intakes of carotenoids and vitamin C (not

supplements) were associated with a significantly lower chance of LUTS in men (Maserejian, Giovannucci, McVary, & McKinlay, 2011).

There was a debate over the effectiveness of saw palmetto (*Serenoa repens*) in the past decade. Following initial evidence of Cochrane meta-analysis in favor of saw palmetto on treating LUTS, especially nocturia (Tacklind, MacDonald, Rutks, & Wilt, 2009; Wilt, Ishani, & MacDonald, 2002), two randomized controlled clinical trials were published in the *New England Journal of Medicine* (Bent et al., 2006) and *JAMA* (Barry et al., 2011), followed by an updated Cochrane meta-analysis (Tacklind, MacDonald, Rutks, Stanke, & Wilt, 2012), all of which reported that saw palmetto was not superior to placebo in treating LUTS, including nocturia. In addition, the use of pumpkin seed (*Cucurbita pepo*) has been studied for treating LUTS. A systematic review evaluated 16 studies of pumpkin seed and reported an improvement of LUTS in all studies, and QOL in four studies (Damiano et al., 2016). The results are promising, but further clinical trials are recommended for confirming these findings.

**Acupuncture.** Evidence supports the use of acupuncture. Zhang, Ma, Bauer, Liu, and Lu (2017) reviewed eight randomized clinical trials that compared acupuncture with controls, placebo/sham acupuncture, or other treatments over 4 to 6 weeks. Acupuncture significantly reduced the severity of LUTS in the short term, but its clinical significance and long-term effect required further research (Zhang et al., 2017). Other studies reported that reflexology significantly reduced nocturnal frequency and micturition, with a 4-point deduction on IPSS in the treatment group when compared with the control group (Ricci, Minardi, Romoli, Galosi, & Muzzonigro, 2004; Wang et al., 2013).

## Conclusions and Suggestions for Future Direction

A decade of accumulated evidence has shown that LUTS is prevalent worldwide and affects men's QOL significantly. Medication treatment is effective but often compromised by poor compliance due to undesired side effects. Minimally invasive procedures and neuromodulation therapy have emerged but are not without side effects and have yet to be accepted widely.

Behavioral treatment is a promising approach to LUTS, especially when combined with medical treatments. Some clinical trials have shown the effectiveness of behavioral interventions to boost physical activity, as well as dietary nutrition such as vitamins C and D and certain fruit juices, resulting in a reduction of LUTS. Other studies have found some efficacy in nurse-led lifestyle modifications (e.g., adherence to medication, PFME, fluid restriction, and bladder training) for

LUTS reduction. Two well-designed clinical trials involving lifestyle modifications provided opposing results: One from the United States showed little evidence of the effectiveness of lifestyle modification relative to medication, but another trial from the United Kingdom showed a significant improvement in urinary measures in comparison with standard care. However, the majority of published studies involving lifestyle modification in the treatment of LUTS had methodological deficiencies, such as a small sample size, not randomized or controlled with a comparison group, or the intervention procedure was not reported as manualized or closely monitored. Many studies were conducted in different parts of the world, making it difficult to compare or interpret their results. Therefore, while some evidence of behavioral interventions is promising, the evidence of interventions to all-around lifestyle modification is at present slight and cannot be generalized across populations, times, and regions. Furthermore, specific mechanisms of such behavioral interventions to LUTS have not been studied.

The current state-of-the-art science of behavioral treatments for LUTS suggests that well-designed, randomized, and controlled longitudinal clinical trials with a large sample size are needed to systematically examine the effect and mechanisms of behavioral interventions to lifestyle factors in comparison with standard care. Such clinical trials need to carefully evaluate the added benefits of behavioral management and the magnitude of the effect, be rigorous in the behavioral intervention programs that incorporate evidence-based therapeutic components, be mindful of implementability of the behavioral intervention programs to be generalizable across clinical or community settings, and consider using technology to reach out to a diverse population of men with LUTS and empower them for better urinary health. With this effort, it is hopeful that we will identify an effective solution to the management of LUTS to improve men's QOL and reduce its societal burden in the United States and the world.

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