



The importance of multimodal diagnostic methods for therapeutic decision making for overactive bladder in women

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Abstract

Background and aim. Despite overactive bladder (OAB) being a symptomatic diagnosis, all patients require a basic assessment to confirm the diagnosis, as well as to exclude any other underlying cause for lower urinary tract dysfunction. While guidelines clearly define different methods of investigations for OAB, there are reasons to believe that these guidelines reflect more of a "one size fits all" model that may not be appropriate for use in all patients. The study aimed to elucidate the complex and advanced multidisciplinary methods of investigation of OAB patients.

Methods. PubMed, ScienceDirect, Cochrane Library, and Google Scholar databases were used to search for scientific publications from 2013 to 2023 using relevant keywords and phrases.

Results. Data from 708 publications were researched and synthesized, a systematic review was carried out and the detailed and coherent results presented the diagnostic aspects of overactive bladder in women. Relevant citations from selected articles were included, and a synthesis of key information was provided.

Conclusion. These discoveries may assist in detecting OAB earlier, allowing for prompt intervention and potentially preventing the condition from progressing to more severe stages and providing healthcare professionals with valuable tools to enhance the diagnosis and treatment of OAB, potentially improving the quality of life for patients affected by this condition.

Keywords: overactive bladder, women, urodynamics, autonomic nervous system

Introduction

The term "overactive bladder" was introduced in 1997 by Drs. Paul Abrams and Alan Wein. In 2002, the Standardisation Subcommittee of the ICS formally adopted this definition [1,2].

"The Standardisation of Terminology of Lower Urinary Tract Function: Report from the Standardisation Sub-committee of the International Continence Society" was published to present definitions of the symptoms, signs, urodynamic observations, and conditions associated with lower urinary tract dysfunction and urodynamic studies, and to restate or

update definitions presented in previous International Continence Society (ICS) Standardisation of Terminology reports [3].

The diagnosis of overactive bladder (OAB) requires an assessment of a woman's urinary signs and symptoms while ruling out other conditions. Despite OAB being a symptomatic diagnosis, all patients require a basic assessment to confirm the diagnosis as well as to exclude any other underlying cause for lower urinary tract dysfunction (LUTD). To make an accurate diagnosis, a thorough history and physical examination must be obtained, and laboratory testing is needed [4].

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Diagnosis & Treatment Algorithm: AUA/SUFU Guideline on Non-Neurogenic Overactive Bladder in Adults



Figure 1. Diagnosis and Treatment Algorithm: AUA/SUFU Guideline on Non-Neurogenic Overactive Bladder in Adult [7].

Understanding that not all patients will require treatment for OAB, it is important to determine the severity and precise symptomatology. The initial evaluation should include a thorough history, physical examination, urinalysis, urine culture, and bladder diary (Figure 1). Since OAB symptoms can be early signs of underlying and/or remediable conditions, special attention should be focused on detecting them. The most common diagnosable causes of OAB are neurogenic bladder, prostatic obstruction in men, and urethral obstruction from pelvic organ prolapse and prior prolapse and incontinence surgery in women [5,6].

While guidelines clearly define different methods of investigations for OAB, there are reasons to believe that these guidelines reflect more of a standard model that may not be appropriate for use in all patients. The study aimed to elucidate the complex and advanced multidisciplinary methods of investigation of OAB patients.

Methods

This review of literature was conducted following the PRISMA guidelines, to investigate the methods of diagnosis of OAB in women. PubMed, ScienceDirect, Cochrane Library, and Google Scholar databases were used to search for scientific publications from 2013 to 2023 using relevant keywords and phrases. We used the keywords ‘overactive bladder’, ‘diagnosis’, ‘urodynamics’, ‘investigation’, ‘women’, and ‘autonomic nervous system’. Inclusion criteria were formed using the population, intervention, comparison, outcomes, and study designs. The population of the study included female patients > 18 years of age with OAB. Filters were applied to limit the search to articles published in the last decade and in English, and only high-quality publications were selected based on their relevance to the research objectives. Duplicate data were removed, and the findings were analyzed and synthesized to provide a detailed and coherent overview of the topic.

Results

The PubMed, ScienceDirect, Cochrane Library, and Google Scholar searches yielded a total of 708

articles. A diagram showing the flow of information through the different phases of review is given in figure 2. Studies included methods of diagnosis of OAB patients. These include quality of life assessment by specialized questionnaires, medical history and physical examination, voiding diary, clinical questionnaires, laboratory and paraclinical investigations, urodynamic studies, and the assessment of the autonomous nervous system. The characteristics of the included scientific publications are listed in tables I-VI.

Quality-of-life assessment

OAB is a common condition that greatly impacts the quality of life, and evaluation of the patient should start with an assessment of the degree to which the condition impacts the patient’s daily life. Standardized quality-of-life questionnaires are available for use in evaluation [9].

Health-related quality of life is assessed using questionnaires that allow the quantification of morbidity and the evaluation of treatment efficacy, as well as being a measure of how lives are affected, and coping strategies adopted [10].

Generic questionnaires, such as the Short Form 36, are general measures of QoL and are therefore applicable to a wide range of populations and clinical conditions, whilst disease-specific questionnaires, such as the King’s Health Questionnaire, are designed to focus on lower urinary tract symptoms [10].

Medical history

Qualitative methods are used in health services research to generate research questions, rather than test tightly formed hypotheses. The method fosters discovering and developing analytical and conceptual constructions of the topic in question, in this case, OAB [11].

The history should include information on the woman’s baseline physical functional level as well as current symptoms that impede functioning [4]. It begins with a detailed account of the precise nature of patient symptoms. The patient should be asked how often s/he urinates during the day and night, how long can comfortably go between urinations, and how long micturition can be postponed once a patient gets the urge.

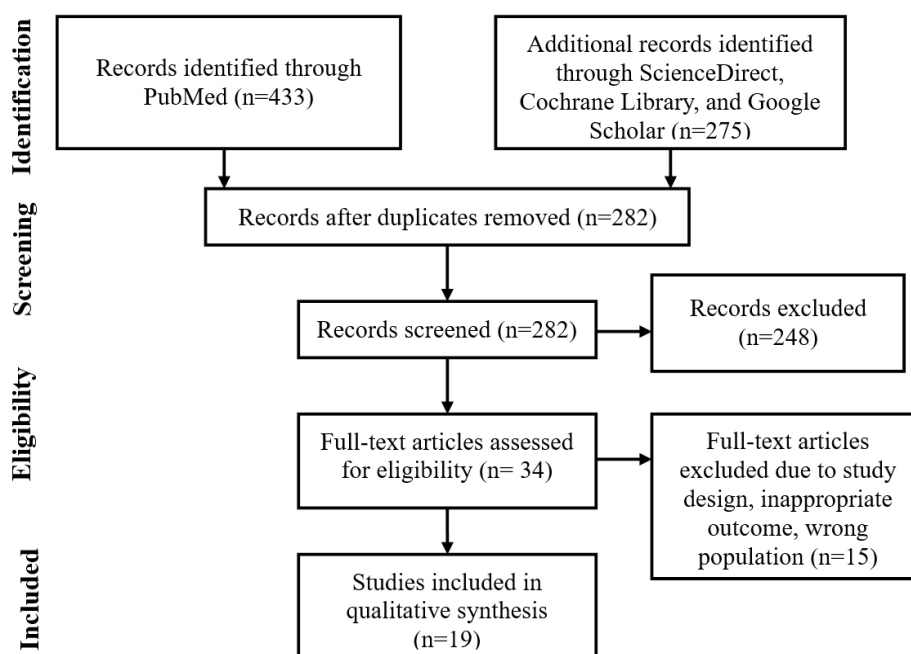


Figure 2. Flow diagram of study selection process adapted from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [8].

It should be determined why the patient voids often. Is it because of urgency, or is it merely out of convenience or an attempt to prevent incontinence? If incontinence is present, is it stress (occurs during coughing, sneezing, rising from a sitting to standing position, or exercise), urge, or mixed? Is the patient aware of the incontinence or just finds himself or herself wet? The severity of incontinence should be graded. Are protective pads worn? Do they become saturated? How often are they changed? Is there difficulty initiating the stream, requiring pushing, or straining to start? Is the stream weak or interrupted? Has the patient ever been in urinary retention? [5].

The duration of symptoms, amount of total daily fluid intake, intake of bladder irritants (e.g., carbonated drinks, artificial sweeteners, caffeine, and alcohol), and the use of medications such as diuretics should also be documented [6]. A key component of the health history is the woman's oral fluid intake. Both excessive and limited fluid intake can lead to frequency and urgency symptoms, although there is no consensus on the quantity of fluid women should drink to maintain ideal hydration. Women should also be asked to complete a food diary to quantify the amount of food, fluid, and caffeine they consume [4].

Other symptoms, such as hematuria, dysuria, dyspareunia, pelvic organ prolapse, neurologic deficits, and pelvic pain, should also be assessed. In addition, all comorbidities and prescribed and over-the-counter medications should be reviewed, as they can also contribute to OAB symptoms [4].

A review of the medical history of women for endocrine conditions is very important (e.g., levels of estrogen, diabetes mellitus, or diabetes insipidus). Additional pelvic floor symptoms (e.g., bowel dysfunction, or dyspareunia) may also be present and co-managed [6]. In women, it is important to ask about symptoms of pelvic organ prolapse (vaginal mass or pressure, sacral backache, or difficulty defecation) [5]. The presence of pelvic pain or dyspareunia usually points away from the diagnosis of OAB, and more towards a diagnosis of pelvic floor tension myalgia, large muscle group dysfunction (hip/paraspinal), interstitial cystitis/painful bladder syndrome, or other causes of pelvic pain, such as endometriosis. Many of these women may have concomitant urinary symptoms due to underlying pelvic floor muscle response/spasm [6] (Table I).

A detailed history is extremely important and can highlight possible risk factors for OAB. Aspects related to pre-existing conditions or surgery (especially urinary tract, but also systemic disorders, important for differential diagnosis), eating habits, and medication that interferes with urinary function are crucial [12]. Regarding prior pelvic surgeries, particular attention should be paid to previous anti-incontinence procedures (e.g., urethral slings, urethral bulking agent injection, or retropubic suspensions), and the use of transvaginal mesh or other pelvic organ prolapse surgeries [6]. A history of vaginal surgery or previous surgical repair of incontinence should suggest the possibility of urethral obstruction. Radiation therapy may cause a small capacity, low compliance bladder, or radiation cystitis [5].

Table I. Characteristics of the included scientific publications.

Author, Year [ref.]	Aim of the study	Results
Raju et al, 2020 [6]	Review of the clinical evaluation and management of OAB in women	A thorough history is the initial step to the evaluation of OAB.
Scarneciuc et al, 2021 [12]	Overactive bladder: A review and update	A detailed history is extremely important and can clearly highlight possible risk factors for OAB.
Fontaine et al, 2021 [5]	Update on the management of overactive bladder (review)	A focused history is paramount in diagnosing OAB.
Nitti et al, 2021 [11]	Diagnosis and management of overactive bladder: A review	The initial evaluation should involve a thorough symptom history, including an assessment of fluid intake, because voiding patterns from excess fluid intake may resemble OAB.

Table II. Characteristics of the included scientific publications.

Author, Year [ref.]	Aim of the study	Results
White et al, 2016 [9]	Review Medical and Advanced Surgical Management of Pelvic Floor Disorders	Physical examination can elucidate underlying medical conditions contributing to symptoms.
Raju et al, 2020 [6]	Review of the clinical evaluation and management of OAB in women	An abdominal, genitourinary, and general evaluation of cognitive function, and the neurologic system including sacral neural pathways examination should be performed.
Scarneciuc et al, 2021 [12]	Overactive bladder: A review and update	A focused clinical examination is imperative, as it can highlight risk factors and pre-existing conditions.
Fontaine et al, 2021 [5]	Update on the management of overactive bladder (review)	Physical examination should include the genitourinary system, as well as digital rectal examination and assessment of prostate in men and vaginal examination in women.

The patient should be specifically queried about neurological symptoms (double vision, muscular weakness, paralysis or poor coordination, tremor, numbness, and tingling), and neurological conditions that are known to affect bladder and sphincter function, such as stroke, multiple sclerosis, spinal cord injury, lumbar disc disease, myelodysplasia, diabetes, and Parkinson's disease [6].

Physical examination

A focused clinical examination is imperative, as it can highlight risk factors and pre-existing conditions. It should include abdominal examination, vaginal examination in women (important to highlight hormonal status, degree of vaginal mucosal estrogenization, presence of prolapse, and cough testing for the presence of leakage, pelvic masses, including urethral diverticulum, vesical or intestinal distension), which are useful for the differential diagnosis from other pathologies showing a symptomatology like OAB [6,9,12].

In women, a vaginal examination should be performed with both an empty bladder (to check the pelvic organs) and a full bladder (to check for incontinence and prolapse) [5]. The examination and evaluation for lower extremity edema should also occur [4].

In women with neurologic disease (multiple sclerosis, Parkinson's disease, or dementia, for example),

a neurologic examination of the genital region should be considered to determine the impact of the disease on the functioning of the lower urinary tract [5]. The examination begins by observing the patient's gait and demeanor as he or she first enters the office. A slight limp or lack of coordination, an abnormal speech pattern, facial asymmetry, or other abnormalities may be subtle signs of a neurological condition [5]. Spinal cord segments S2 to S4 are involved in micturition and should be evaluated accordingly [5,9]. The sacral dermatomes are evaluated by assessing anal sphincter tone and control, perianal sensation. A lax or weakened anal sphincter or the inability to voluntarily contract and relax are signs of neurological damage [5] (Table II).

Because of the strong association between obesity and OAB, the woman's BMI should be calculated; in overweight and obese women, metabolic syndrome screening should occur as well [5].

Voiding diary

A voiding diary is one of the most important tools to assess lower urinary tract symptoms, as it provides quantifiable, objective data that are also useful to analyze the disease severity and/or evolution after the prescription of treatment [13] (Table III).

Table III. Characteristics of the included scientific publications.

Author, Year [ref.]	Aim of the study	Results
Raju et al, 2020 [6]	Review of the clinical evaluation and management of OAB in women	Bladder diaries may be used to evaluate the volume and timing of fluid intake and voids (including the volume and circumstance of incontinence episodes) to document baseline symptoms and assess treatment response.
Scarneciu et al, 2021 [12]	Overactive bladder: A review and update	The use of voiding diaries is recommended as it shows the patient's daily urination habits.
Robinson et al, 2019 [10]	Review the initial clinical assessment and management of women complaining of OAB.	All patients should complete a bladder diary to evaluate fluid intake and voiding patterns.
Truzzi et al, 2016 [13]	A comprehensive review of the literature related to the evolution of the concept, epidemiology, diagnosis, and management of OAB was conducted.	Voiding diary is one of the most important tools to assess the lower urinary tract symptoms, as it provides quantifiable, objective data that are also useful to analyze the evolution after the prescription of treatment

The use of voiding diaries is recommended as it shows the patient's daily urination habits. It is a simple tool, easy to apply, which can highlight urinary volume, frequency, pattern of voiding, and incontinence episodes and can assess the severity of symptoms (sometimes underestimated by the patient or overestimated by the doctor). It is estimated that 3 days of a bladder diary provides very important information about the patient [12].

The voiding frequency and the volume at each void are the main elements of the diary, which allow distinguishing asymptomatic patients and OAB patients (including the volume and circumstance of incontinence episodes). A three-day voiding diary containing the time and volume of each void and avoiding the inclusion of other information (such as liquid intake) that adds few relevant data and makes patient adherence more difficult is enough to assess the lower urinary tract symptoms in the clinical practice [6,13,14].

A voiding diary can be of particular use in evaluating nocturia, as nocturia may be due to factors other than bladder function, such as excessive night-time urine production (nocturnal polyuria), cardiovascular disease, sleep apnea, or other parasomnias. The volume voided is normal or large in nocturnal polyuria, in contrast to the low voiding volumes in OAB [6].

In addition, all patients should complete a bladder diary to evaluate fluid intake and voiding patterns. As well as the number of voids and incontinence episodes, the mean volume voided over 24 hours can also be calculated as well as the diurnal and nocturnal urine volumes [10].

Clinical Questionnaires

Questionnaires that evaluate OAB patients are critical measuring tools when conducting scientific studies. They may be didactically classified as specific questionnaires, urinary incontinence questionnaires, quality-of-life questionnaires, and questionnaires on the impact of urinary incontinence on the quality of life. Among the several questionnaires available worldwide, the following show the highest applicability: ICIQ-OAB, OAB-SF, OAB V-8,

and ICIQ-OABqol. However, these questionnaires should not be regarded as definitive diagnostic tools. They are designed to standardize and enable data comparison in clinical trials and more objectively measure the impact of the symptoms on patients' quality of life. It should also be stressed that questionnaires need to be validated in the country language before being applied [14].

Symptom questionnaires should be used especially to highlight the impact of the condition on quality of life and to determine whether the patient should undergo treatment. There are numerous validated questionnaires, useful in highlighting the progression of treatment, but not currently widely used [12].

Because of the prevalence of OAB in women, they should be routinely screened for symptoms. The International Consultation on Incontinence Modular Questionnaire, a validated four-item screening tool for clinicians and researchers, is available at <https://iciq.net/iciq-oab> [4].

Symptom severity and response can also be evaluated using validated symptom questionnaires for OAB, such as the Overactive Bladder Symptom Score [6].

Urgency is now generally regarded as being the driving symptom of OAB and is known to play an important role in the development of daytime frequency, nocturia, and urgency incontinence. Several validated urgency scoring systems (Patient Perception of Intensity of Urgency Score, Urgency Perception Score, Indevus Urgency Severity Scale) have been developed to attempt to measure urgency severity and these may be used in conjunction with frequency volume charts in clinical practice [10] (Table IV).

Laboratory tests

The initial laboratory evaluation of uncomplicated OAB is a urinalysis. Due to its low cost and non-invasive nature, urinalysis is requested for virtually all patients with OAB symptoms. In the presence of nitrites or leukocyte esterase in the urinalysis or clinical suspicion of a urinary tract infection, a urine culture should be performed [6,9].

Table IV. Characteristics of the included scientific publications.

Author, Year [ref.]	Aim of the study	Results
Raju et al, 2020 [6]	Review of the clinical evaluation and management of OAB in women	Symptom severity and response can also be evaluated using validated symptom questionnaires for OAB, such as the Overactive Bladder Symptom Score.
Scarneci et al, 2021 [12]	Overactive bladder: A review and update	Symptom questionnaires should be used especially to highlight the impact of the condition on quality of life and to determine whether the patient should undergo treatment.
Robinson D, et al, 2019 [10]	Review the initial clinical assessment and management of women complaining of OAB.	Several validated urgency scoring systems (Patient Perception of Intensity of Urgency Score, Urgency Perception Score, Indevus Urgency Severity Scale) have been developed to attempt to measure urgency severity and these may be used in conjunction with frequency volume charts in clinical practice.
Truzzi et al, 2016 [13]	A comprehensive review of the literature related to the evolution of the concept, epidemiology, diagnosis, and management of OAB was conducted.	Questionnaires that evaluate overactive bladder patients are critical measuring tools when conducting scientific studies.

For most patients, once urinary infection and hematuria are ruled out, treatment may be initiated. UTI and chronic irritative bladder conditions can present like OAB [9]. The presence of microscopic hematuria may suggest the existence of a urinary tract neoplasm or other pathologies, and it deserves additional investigation [14].

Urine culture is recommended for all patients to rule out other associated pathologies that may cause OAB-type symptoms. Blood tests can provide additional information including levels of creatinine and glycosylated hemoglobin (HbA1C) [12].

Ultrasound investigation

The ultrasound of the urinary tract is not recommended for the initial evaluation of OAB patients; however, it may be useful for a differential diagnosis. In addition, it allows measuring the post-voiding residual volume in a non-invasive mode, and through this, indicating the existence of infravesical obstruction or detrusor failure [14].

Measurement of post-void residual volume (PVR) (typically <150 mL) can help rule out overflow incontinence [4,9]. PVR should be obtained in patients with obstructive symptoms (e.g., weak stream, urinary hesitancy, or intermittency), a history of anti-incontinence surgery, suspicion for undiagnosed neurologic disease, and at the provider’s discretion. A PVR should also be assessed before starting antimuscarinic drugs in patients at high risk for urinary retention (e.g., those with a prior anti-incontinence surgery, subjective weak or slow urinary stream or other obstructive symptoms, sensation of incomplete bladder emptying, or neurologic diagnosis) [6].

For women with a complex medical history, additional testing, including urodynamic evaluation, cystoscopy, and upper genitourinary tract imaging, can be used to differentiate between OAB and other etiologies [4].

Urodynamic tests

Urodynamics refers to the study of storage, voiding,

and function of the lower urinary tract. It involves assessing a patient’s bladder, sphincters, and urethra to provide detailed information about their storage and release of urine. Most urodynamic tests focus on the bladder’s ability to hold urine and empty the bladder steadily and completely. Urodynamic tests can also show whether involuntary contraction of the detrusor muscle is causing urine leakage [15].

While the diagnosis of OAB is essentially clinical, there is a lot of discussion on the use of urodynamic exams in evaluating the diagnosis of the syndrome. Despite being considered the gold standard for the evaluation of low urinary tract symptoms, its invasive nature, and the fact that it places a risk of urinary infection usually make the urodynamic exam indicated for refractory patients to the conservative treatments of OAB [13].

Another limiting factor to its routine use is the low correlation of urinary symptoms with urodynamic findings in many cases. This was well demonstrated in a review by Digesu, in which the urodynamic results and the clinical diagnosis of OAB matched in 21% of patients only. Few guidelines, like the one from France, recommend urodynamic testing for the initial evaluation of patients with low urinary tract symptoms [16]. On the other hand, the Italian and UK guidelines only recommend the urodynamic investigation in patients at risk of renal complications. The urodynamic testing should be performed following good medical practice criteria when symptoms do not allow for a clear diagnosis when empirical treatment fails, or in cases where more invasive treatments are considered [14].

Urodynamic testing starts with uroflowmetry (measuring flow rate and voiding time) followed by cystometry to assess bladder storage function during filling through a catheter to objectively diagnose detrusor overactivity (DO) as evidenced by uninhibited bladder contractions associated with urgency, and pressure/flow voiding studies.

Table V. Characteristics of the included scientific publications.

Author, Year [ref.]	Aim of the study	Results
Raju et al, 2020 [6]	Review of the clinical evaluation and management of OAB in women	Urodynamics, although not performed for initial evaluation of uncomplicated OAB, may be performed in complicated cases), when there are refractory OAB symptoms despite previous therapies, and before more advanced OAB treatment options.
Scarneci et al, 2021 [12]	Overactive bladder: A review and update	In more complicated situations or in patients refractory to treatment may be performed urodynamic evaluation.
Robinson et al, 2019 [10]	Review the initial clinical assessment and management of women complaining of OAB.	Women with refractory OAB or complex symptoms may benefit from urodynamic investigations.
Truzzi et al, 2016 [13]	A comprehensive review of the literature related to the evolution of the concept, epidemiology, diagnosis, and management of OAB was conducted.	The urodynamic testing should be performed following good medical practice criteria when symptoms do not allow for a clear diagnosis, when empirical treatment fails, or in cases where more invasive treatments are considered
White et al, 2016 [9]	Review Medical and Advanced Surgical Management of Pelvic Floor Disorders	Urodynamic testing may be indicated to further investigate overactive bladder symptoms in patients with refractory symptoms, previous pelvic reconstructive surgery including anti-incontinence operations, neurologic diseases, or voiding dysfunction.
Digesu et al, 2003 [16]	The aim of our study was to determine whether the urodynamic diagnosis is useful in the management of women with symptoms of an overactive bladder (OAB).	The urodynamic results and the clinical diagnosis of overactive bladder matched in 21% of patients only.
English et al, 2020 [15]	Determine whether performing a urodynamic study (UDS) resulted in a change in either patient diagnosis or treatment offered in women with uncomplicated urinary incontinence.	Diagnosis and management are unlikely to change after UDS in patients presenting with uncomplicated OAB.

In women with any concern for an underlying neurologic cause for OAB, electromyography (EMG) can be useful to evaluate the activity of the external striated urethral sphincter muscles. EMG can evaluate whether a patient demonstrates coordination between the external sphincter which should relax when the detrusor muscle contracts and failure to do so may represent dyssynergic activity, indicating a possible upper motor neuron process [6,9]. Patients with refractory symptoms may also benefit from a further investigation using videocystourethrography or ambulatory urodynamics [10].

To initiate investigations for OAB, when conservative management strategies have not been successful, it might be necessary to refer the patient to a urologist, gynecologist, or urogynecologist. At this stage, urodynamics is commonly undertaken as a diagnostic test to assess bladder pressures and confirm idiopathic DO. It is often assumed that patients with symptoms of OAB will have idiopathic DO; however, urodynamics is necessary to confirm or refute this diagnosis [15].

Idiopathic DO differs from OAB in that it is a medical diagnosis, made based on urodynamic testing. Urodynamics will either confirm a diagnosis of idiopathic DO or refute it, in which case the patient will be diagnosed with sensory urgency OAB [15] (Table V).

Cystourethroscopy

Although cystoscopy does not help diagnose OAB,

it may be used to exclude other causes for the symptoms associated with OAB. Cystourethroscopy should be considered in all women complaining of 'red flag' symptoms such as hematuria, painful bladder syndrome, suspected bladder tumor, bladder calculus, recurrent urinary tract infections, and recurrent incontinence [10].

Its indication is limited to cases where there is a suspicion of bladder cancer or in a patient's refractory to treatment. For example, in the study by Ryan, only 4.1% (14/340) of bladder cancer patients experienced exclusively overactive bladder-related symptoms, with carcinoma in situ being the one with the highest positive correlation (21%) [12,14,17].

The presence of hematuria on urinalysis with microscopy (not urine dipstick) in the absence of a benign underlying etiology should prompt additional testing including cystoscopy and upper urinary tract imaging. Likewise, in uncomplicated cases, routine cystoscopy or urine cytology is not recommended [6].

New perspectives for the diagnosis of overactive bladder

The identification of lower urinary tract functional disorder biomarkers, such as for OAB, faces several limitations. To date, no biomarkers have been demonstrated to be effective as a tool for use in daily practice. Yet, some biomarkers have been considered useful as potential tools for diagnosis and therapeutic monitoring [14].

OAB biomarkers may contribute to understanding urinary storage symptoms such as neurotrophins, adenosine triphosphate (ATP), prostaglandins, C-reactive protein (RCP), and cytokines. Other biomarkers may be assessed through the measurement of bladder wall-related events, such as wall thickness and oxyhemoglobin and deoxyhemoglobin concentration. [13,14].

The neuronal growth factor (NGF) modulates the release of neurotransmitters and reduces the sensitivity threshold of nociceptive fibers; therefore, its neutralization diminishes the hyperreflexia in an animal model of spine injury. The NGF is produced in the urothelium and vesical smooth musculature. Clinical and experimental data have shown a direct association between the increased NGF expression in the vesical tissue and in the urine [13,14,18].

Urinary prostaglandins (PGE₂) and cytokines were also proposed as OAB markers. According to the study by Kim et al., the PGE₂ levels were lower in a subgroup of OAB and detrusor hypocontractility patients – as demonstrated in the urodynamic testing – than in OAB patients without detrusor hypercontractility. Other cytokines were also high in the urine of OAB patients, including monocyte chemoattractant protein-1 and the soluble fraction of the CD40 ligand [14]. However, their exclusive association with OAB symptoms is not well established now and cannot be used as a unique and sure investigation of OAB.

The autonomic nervous system (ANS) controls the lower urinary tract, which involves a complex interplay between various centers and pathways. When the autonomic system is not regulated properly, it can lead to urinary bladder dysfunction, resulting in a range of symptoms such as urgency, incontinence, hesitancy, and incomplete bladder emptying. Idiopathic OAB without DO may be associated with sympathetic dysfunction, while sensory urgency could be linked to the same dysfunction [19].

Patients with OAB may experience bladder dysfunction due to autonomic nervous system disorder. Multiple studies have evaluated ANS activity using neurophysiological diagnostic methods to test this hypothesis [20–27]:

1. Cardiovascular sympathetic tests of the autonomic nervous system: the test of sustained exercises of grasping the hand by evaluating the cardiovascular response to physical exertion, focusing mainly on the sympathetic nervous system and the ability to maintain muscle effort; cold pressure test by which the body's response to cold stimulus is measured, being used to evaluate the function of the peripheral nervous system and providing information about the sensitivity and response of blood vessels to temperature changes.

2. Parasympathetic cardiovascular tests of the autonomic nervous system: heart rate response to deep breathing (a physiological respiratory sinus arrhythmia induces a tachycardia during inspiration and bradycardia during exhalation, which is exclusively under

parasympathetic control); ratio 30:15 (a physiological tachycardia exists on the 15th beat after standing, followed by bradycardia on the 30th beat).

3. Mixed tests: Valsalva maneuver (forced breathing that reveals abnormalities of the autonomic nervous system by evaluating changes in heart rate, continuous ECG, and blood pressure during and after the Valsalva maneuver); blood pressure response to standing (changing body position from lying down to standing by measuring heart rate variation); assessment of heart rate variability, a noninvasive measure of autonomic modulation of heart rate.

Choi et al. showed that heart rate variability parameters differed in women with OAB compared to those in the control group, also they observed a decrease in heart rate variability indices in women presenting with OAB compared to those in healthy women. Differences in autonomic nervous system function have also been demonstrated in OAB patients from the onset of emergency and minutes after urination [25,28]. Similarly, Ben-Dror et al. (2012) resulted in low levels of HRV in patients with OAB. These results suggest that the autonomic nervous system in patients with OAB is altered and may be a factor in bladder function disorder, but further study is needed in OAB patients to clarify this possible change in the autonomic nervous system [21,28].

Assessing the balance between the sympathetic and parasympathetic systems can be done by examining the pupillary light reflex. If the pupils remain constricted for a long time and take longer to dilate, it could be an indication of increased parasympathetic activity. Amplitude and contraction velocity are the most reliable parameters for detecting parasympathetic activity [29].

Aydogmus et al. evaluated pupillary functional changes by dynamic pupillometric measurement and determined that significantly smaller initial, minimum, and mean pupil diameters are present in OAB patients compared to controls. They concluded that smaller pupil diameters involve increased parasympathetic tone in the “sphincter pupil” muscle and may be a relevant tool for evaluating the ANS in patients with OAB [30].

Ates et al. demonstrated disrupted sympathetic function with OAB based on the skin sympathetic response test to assess sudomotor activity and function of thin unmyelinated sympathetic nerve fibers in the bladder and bladder neck [24,31].

A contemporary approach to studying the activity of the ANS involves recording cutaneous evoked sympathetic potentials (PEVc). This method allows for the assessment of autonomic indices at both segmental and suprasedgmental levels, both qualitatively and quantitatively [32]. Studies have shown that the recording of cutaneous evoked sympathetic potentials from the suprapubic skin region, which is associated with the iliohypogastric nerve, can reflect the sympathetic activity of the bladder neck and the internal urethral sphincter [33].

Table VI. Characteristics of the included scientific publications.

Author, Year [ref.]	Aim of the study	Results
Ben-Dror et al., 2012 [28]	To characterize autonomic dysfunctions in patients with an overactive bladder (OAB), they compared their heart rate variability (HRV) with the HRV of a normal population.	Low levels of HRV in patients with OAB.
Aydogmus et al., 2017 [30]	To evaluate pupillary functional changes by dynamic pupillometric measurement	Significantly smaller initial, minimum, and mean pupil diameters are present in OAB patients compared to controls
Ates et al., 2016 [31]	To investigate the effects of autonomic sympathetic dysfunction in the etiology of overactive bladder (OAB) in women, by assessing the sympathetic skin response (SSR).	Disrupted sympathetic function with OAB based on the skin sympathetic response test to assess sudomotor activity and function of thin unmyelinated sympathetic nerve fibers in the bladder and bladder neck.
Drake et al., 2016 [34]	Neurogenic lower urinary tract dysfunction: Clinical management recommendations of the Neurologic Incontinence committee of the fifth International Consultation on Incontinence 2013.	PEVc is not only used to evaluate the functional state of peripheral autonomic fibers but also to assess the functional state of brain centers involved in evoked potentials in patients with OAB.
De Wachter et al., 2003 [35]	To determine the influence of technique-related factors on bladder electrical thresholds in order to establish more standardisation in electrical sensory testing in the lower urinary tract (LUT).	A technique called cutaneous evoked sympathetic potentials by electrical stimulation of the urethral mucosa has been developed to assess the integrity of autonomic pathways in the bladder area.
Thomas et al., 2017 [38]	To evaluate the usefulness of somatosensory evoked potential as a screening tool for spinal pathologies in patients with treatment-refractory overactive bladder	In patients with treatment refractory OABs, PEVs is an important tool for screening related pathologies of the spinal cord.

The absence of such potentials can indicate severe organic damage to autonomic nerve fibers or a complete interruption of autonomic nerve pathways, which may be caused by trauma, surgery, tumors, and so on. The latency and amplitude of evoked sympathetic potentials are both diagnostically significant. Physicians have detected prolonged latency and reduced amplitude in patients with OAB syndrome, specifically in the urogenital region [31].

A technique called cutaneous evoked sympathetic potentials by electrical stimulation of the urethral mucosa has been developed to assess the integrity of autonomic pathways in the bladder area [34,35]. Studies have shown that PEVc indices are more stable and informative compared to viscerosensory evoked potentials. Nowadays, PEVc is not only used to evaluate the functional state of peripheral autonomic fibers but also to assess the functional state of brain centers involved in evoked potentials in patients with OAB [34].

Patients who suffer from cortical cerebellar atrophy or cerebellar stroke may experience urinary dysfunction and detrusor hyperactivity [36]. Studies conducted on both animals and humans indicate that the cerebellum, specifically the fastigial nucleus, is involved in a complex sensory-motor visceral program that aids in controlling the micturition reflex [37].

Thomas et al. aimed to evaluate the usefulness of somatosensory evoked potential as a screening tool for spinal pathologies in patients with treatment-refractory overactive bladder and established that in patients with treatment-refractory OABs, PEVs is an important tool for

screening related pathologies of the spinal cord. In this very specific group of patients, those with normal PEVs may not require further MRI investigation [38] (Table VI).

Discussion

This review of literature provides an evaluation of the current publications on the different methods of diagnosis of overactive bladder by specifically examining the investigation of the autonomic nervous system. This review subdivides each evaluation of the patients which may help healthcare providers when making decisions on which method to choose to determine further treatment tactics.

In this review of the literature, the use of a combination diagnosis of LUTS by managing the urodynamic studies and cutaneous evoked sympathetic potentials by electrical stimulation could provide more information about the stage and severity of OAB because sympathetic dysfunction in the genital area may be linked to OAB. Thus, early detection of OAB could be aided by examining PEVc. Ertekin et al. emphasized the importance of monitoring PEVc changes in identifying autonomic dysfunction in the pelvic region [31].

During the 10-year search period for this review, there were no studies identified evaluating the autonomous nervous system in combination with urological clinical and paraclinical investigation, even though none of the guidelines specify the methods of diagnosis of autonomous nervous system.

The autonomic nervous system plays a crucial role

in the regulation of various bodily functions, including bladder function. Evaluating the autonomic nervous system in patients with overactive bladder can provide insights into the underlying mechanisms and potential treatment approaches.

It's important to note that while these methods can provide valuable information, no single test is definitive for evaluating the entire autonomic nervous system. Combining multiple assessments may offer a more comprehensive understanding of autonomic function in OAB patients.

The feasibility of these evaluations depends on factors such as the availability of specialized equipment, expertise, and the specific characteristics of the patient population. Additionally, the choice of assessment methods should consider the individual patient's needs and the goals of the evaluation. Consulting with a healthcare professional, such as a urologist or a neurologist specializing in autonomic disorders, can help determine the most appropriate evaluation strategy for a given patient.

The importance of employing various methods of investigation in OAB patients cannot be overstated. Each method serves a specific purpose in diagnosing, characterizing, and guiding the treatment of OAB. A comprehensive approach that combines medical history, physical examination, specialized tests, and patient-reported data ensures that healthcare providers can tailor treatments to individual patients, ultimately improving their quality of life and helping them manage OAB effectively.

Conclusions

New opportunities for diagnosing overactive bladder have emerged. By understanding the autonomic nervous system's role in urinary bladder dysfunction and using advanced diagnostic techniques like urodynamics and cutaneous evoked sympathetic potentials, healthcare professionals can better diagnose and treat overactive bladder. Early detection can also prevent the condition from progressing and improve the quality of life for affected patients.

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