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DEPARTMENT OF UROLOGY AND SURGICAL NEPHROLOGY

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OVERACTIVE URINARY BLADDER

Methodical guide for medical students

For 4th – year students

of the Faculty of Medicine

Urology and andrology

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LIST OF ABBREVIATIONS

ACh - acetylcholine
ATP - adenosine triphosphate
BACH - Boston Area Community Health
BCG - Bacillus Calmette-Guerin
BMI - body mass index
BoNT botulinum toxin
BOO - bladder outlet obstruction
CHAMP - Collaborating to Heal Opioid Addiction and Mental Health in Primary Care
CNS - central nervous system
CRF - corticotropin releasing factor
CT - computed tomography
DM - diabetes mellitus
DNA - deoxyribonucleic acid
DO - detrusor overactivity
EPIC - European Prospective Investigation into Cancer and Nutrition
EpiLUTS - Epidemiology of Lower Urinary Tract Symptoms
FDA - Food and Drug Administration
FES - functional electrical stimulation
HRQoL - health-related quality of life
IBS - irritable bowel syndrome
ICS - International Organization for Standardization
OABSS - overactive bladder symptom score
IDO - idiopathic detrusor overactivity
I-QOL - incontinence quality of life measure
L - lumbar
LUTS - lower urinary tract symptoms
M - muscarinic
NCBI - National Center for Biotechnology Information
NDO - neurogenic detrusor overactivity
NOBLE - National Overactive Bladder Evaluation
OAB - overactive bladder
OAB-q - overactive bladder questionnaire
OABS - overactive bladder syndrome
PNE - percutaneous nerve evaluation
PTNS - posterior tibial nerve stimulation
PX 2 - ramipexole Dihydrochloride
QOL - quality of life
RCT - randomised controlled trial
SNM - sacral modulation
SUI - stress urinary incontinence
TRPV1 - transient receptor potential cation channel subfamily V member 1
UI - urinary incontinence
Uris 24 - Urge Impact Score 24
UTI - urinary tract infection
UUI - urge urinary incontinence

INTRODUCTION

1.1. Definition

The “clinical syndrome of overactive bladder” (“overactive bladder syndrome”) is defined by the occurrence of urgency with or without urinary incontinence, usually associated with pollakiuria or nocturia in the absence of urinary tract infection or obvious local organic pathology (tumor, infection, calculus) [1].

By definition, the patient micts more than 8 times/day and at least 2 times/night. The symptoms occur without any proven pathological changes in the urinary tract. A local, metabolic, endocrine or neurological pathology must therefore be ruled out beforehand. This also includes pretreatment of the bladder (e.g. using chemotherapy, BCG instillation and radiation), which must be critically evaluated. The key symptom of OAB is the urge to urinate; it is therefore an exclusively symptomatic diagnosis. The presence of urge incontinence is optional (OAB “wet/dry”) [2].

Urgency (“urgency”, synonym urge urination) is defined by the sudden, overwhelming, and frequently irrepressible desire to urinate. It is a need which is abnormal in its brutality and intensity. It is often accompanied by only a moderate or even small amount of urine. It is different from the normal progression of urge from a feeling of a full bladder to a feeling of wanting to urinate with a full bladder. Indeed, the normal physiological need is the warning sign of urination that it is possible to postpone for a certain time to satisfy social conveniences and environmental constraints. Urinary incontinence is the involuntary leakage of urine. Urge urinary incontinence (UUI) is an involuntary leakage of urine accompanied or immediately preceded by urgency. Pollakiuria is an increase in the frequency of urination during the day or at night. Nocturia is the need to urinate waking up the patient. Nocturia must be differentiated from nocturnal pollakiuria and nocturnal polyuria (production of an abnormally high volume of urine during sleep). We speak of OAB “wet” (“wet overactive bladder”) when there is an UUI and OAB “dry” (“dry overactive bladder”) in the absence of UUI [3, 4].

1.2. Epidemiology and risk factors

1.2.1. Prevalence of OAB

The prevalence of OAB is 14 percent. It's more noticeable in women (sex ratio of 1.4) and gets worse as people get older [5]. In addition, only a third of people with OAB see a doctor for this reason. Four key international studies have reported the prevalence of

OAB worldwide. These are the EPIC studies NOBLE, EpiLUTS and MILSOM [6, 7, 8]. The data in this epidemiological study is sometimes inconsistent. Significant variation in prevalence estimations can explain the disparity in prevalence estimates. Methods of symptom assessment, exclusion criteria, and case studies definitions (some studies employed a symptom ranking) intensity, while some did not), and during the time when the occurrence of symptoms was looked into. However, these studies reported some common results. First and foremost, OAB is a prevalent disease that affects both men and women. While both sexes have a comparable overall prevalence, there are some gender disparities. As a result, UTI affects more women than men. Furthermore, isolated symptoms are uncommon in OAB. Pollakiuria is the most usually reported symptom, but it is much more typical to have a combination of symptoms.

In both sexes, the prevalence of OAB symptoms and other filling phase symptoms rises with age. According to the EPIC study, 51 percent of men and 56 percent of women between the ages of 40 and 59 experienced signs of the filling phase [5, 9]. These symptoms were reported by 38% of men and 49% of women under the age of 39. In the NOBLE trial, UUI rose with age in both sexes, from 2% to 19% in women after 44 years and from 0.3 to 9% in males after 64 years, with a notable rise after 64 years [6]. As a result, whereas the prevalence of OAB with UUI grew with age in women throughout their lives, the substantial increase in the prevalence of OAB with UUI in men occurred only after the age of 65. Men, on the other hand, had a considerably larger age-related increase in the incidence of OAB without UUI than women.

Indeed, it was 8.5 percent in men under the age of 45 and 21.8 percent in those over the age of 55. After a progressive rise, the incidence of OAB without UUI in women reached a plateau after 44 years. However, the elderly were frequently left out of these studies. Previous findings from studies of OAB incidence in Europe and the United States were also discovered in Asia. Indeed, a study of 8,284 people over the age of 40 in China, Taiwan, and South Korea found that the overall prevalence of OAB was 20.8 percent (women 22.1 percent, men 19.5 percent) and that the prevalence increased significantly with age, from 10.8 percent in 40-44 year olds to 27.9 percent in over 60 year olds ($p = 0.001$) [10]. Furthermore, the presence of comorbidities (such as neurological disease or diabetes) was linked to a significantly higher OAB prevalence. Only 10% of individuals who did not have OAB reported seeing a doctor for lower urinary tract problems, compared to 64% of those who had severe OAB symptoms.

These findings are an indirect reflection of the considerable discomfort that OAB sufferers endure.

1.2.2. Incidence of OAB

While the above mentioned longitudinal research have proven that OAB prevalence rises with age, other investigations have established that OAB is a disease "scalable" [11, 12]. The number of women with OAB with UUI grew from 6% to 16% in a study conducted in Goteborg (Sweden) between 1991 and 2007, but the proportion of women with OAB without UUI did not change appreciably (11 percent versus 10 percent). In 1991, 23 percent of women with OAB without UUI stayed "dry", 28 percent progressed to OAB with UUI, and almost half reported OAB remission in 2007. Women with OAB without UUI had a greater rate of OAB (49%) than those with UUI (26 percent). OAB's "dynamic" nature is supported by these findings. Other Australian and Japanese research [12, 13] support this conclusion. Remission of OAB symptoms without medical or surgical intervention was observed in 1 in 3 men in the CHAMP research, which included more than 1,705 men over the age of 70 residing in Sydney [13]. Similarly, the OAB incidence rate was 12 percent and the remission rate was 30 percent in a longitudinal study of nearly 4000 men and women in the Japanese society aged 65 and up [12].

1.2.3. Risk factors for OAB

Various OAB risk factors have been mentioned, with some research contradicting each other:

The way of life. As a result, soft drink consumption could be a risk factor for the beginning of OAB [14]. The role of tea, coffee, or alcohol consumption, on the other hand, has not been clearly established [15, 16]. In a study of women, it was discovered that OAB was three times more common in current smokers and twice as common in former smokers compared to never smokers in Finnish women aged 18 to 79. Furthermore, OAB and the intensity of smoking had a dose-response connection [12]. Other studies, on the other hand, have not found a link between smoking and cancer [11, 13]. When it comes to exercise, studies are likewise contradictory [10, 17].

• **Race and ethnicity.** There is little evidence that ethnicity plays a factor in the frequency of OAB. In a small Taiwanese study [18], Aboriginal women were shown to have a greater prevalence of OAB (7.7% versus 4.3 percent, $p = 0.02$) than non-

Aboriginal women. OAB was substantially more common in participants in the EpiLUTS study [19] in the United States, according to multivariate analysis.

Hispanic (OR 1.7, p 0.001) and African American (OR 2.0, p 0.001). Despite a huge range in crude prevalence (27 percent for Asian women, 43 percent for whites, 46 percent for African Americans, and 42 percent for Hispanics), the authors found no statistically significant difference in women after multivariate analysis.

• **Psychological distress.** Urgency and nocturia were linked to previous experiences of sexual, physical, and emotional violence in the BACH survey [20], which included both sexes and all ethnic groups. In a German study, 31 percent of women with OAB reported physical or sexual violence twice as often as women without the virus, according to the findings.

• **The differences in women's and men's disorders.**

Obesity, functional colopathy, childhood enuresis, constipation, anxiety, depression, menopause, neurological illnesses, spinal pathologies, sleep apnea syndrome, asthma, chronic bronchitis, diabetes, and high blood pressure have all been linked to the condition. Surprisingly, only 12% of persons with OAB do not have any comorbidities [5].

1.3. Pathophysiology

OAB is defined as a symptom syndrome that excludes urinary tract infections and other diseases, implying that it is primarily idiopathic. Detrusor instability is more common in overactive bladder patients with incontinence (OAB wet) than in patients without incontinence (OAB dry) (90 percent of males and 58 percent of women with incontinence; without incontinence, 69 percent of men and 44 percent of women). It has been shown to have improved afferent signals In contrast, it is currently unknown to what extent urgency symptoms/the need to urinate occur peripherally or centrally. The results include hypotheses involving (A) increased afferent activity and (B) mechanisms of abnormal afferent signal processing. Hormonal and psychological factors (C) have also been suggested [21].

Brading's groundbreaking research suggests that DO-induced urgency is primarily caused by myogenic dysfunction caused by denervation-related supersensitivity. Detrusor overactivity (DO), according to Drake et al., may be caused by histological alterations in the detrusor, which lead to aberrant electrical coupling of smooth muscle

cells, causing physiological micromotions to synchronize into active involuntary detrusor contraction [22].

Other evidence suggests that urothelial/suburothelial dysfunction causes increased afferent signaling, which may contribute to unregulated detrusor contractions [23].

Only conservative therapy and vaginal application of oestradiol, antimuscarinics, sacral neuromodulation (SNM), or intradetrusor botulinum toxin injections are supported by level 1 evidence in patients with urodynamically confirmed DO among the current treatment options [24].

1.3.1. Urotheliogenic hypothesis: urgency originating from the bladder urothelium/suburothelium

The urothelial hypothesis discusses functional changes in urothelial receptors, as well as the sensitivity and coupling of suburothelial myofibroblasts, all of which contribute to higher afferent signal activity. Reinforced afferent signals increase the early triggering of micturition by causing a premature urge to urinate. The urothelium/suburothelium reacts to local chemical and mechanical stimuli, increasing the activity of nearby afferent neurons, according to the urothelium-based hypothesis [25, 26] (Fig. 4), which causes the micturition reflex to be activated and the urge to urinate to be perceived prematurely [27]. ATP is produced in response to stretching or chemical stimulation of the urothelium, and it acts on P2X receptors to modulate the excitability of surrounding afferent neurons. In patients with neurogenic (NDO) and idiopathic detrusor overactivity (IDT), increased neuronal ATP release from the urothelium has been found [28]. Furthermore, acetylcholine (ACh) from the urothelium can bind to nicotinic or muscarinic ACh receptors (M2, M3), which are implicated in afferent impulse production [29, 30].

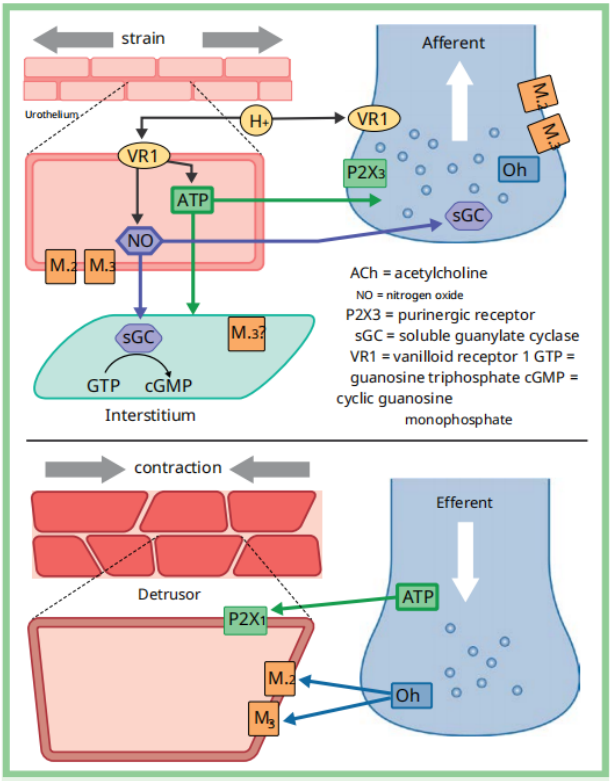

Fig. 4 Overview of the ultrastructure of the urinary bladder. above: neuro-Transmitters of the urothelium are transmitted to the bladder afferents via the interstitium. Bottom: Faulty efferent signals produce involuntary detrusor contractions.

1.3.2. Supraspinal hypothesis urgency originating from the brain and brainstem

Over the last few decades, the central neuronal control of micturition has been widely explored [31], and the decreased capacity to functionally integrate afferent information or reduced supraspinal inhibitory control on the micturition reflex has been suggested since the late 1990s as a possible pathophysiological mechanism of OAB with the emergence of functional brain imaging [32]. A number of studies have demonstrated the concept of two separate subtypes of "brain OAB": one with DO and the other without [33]. The insula (lower bladder volumes) and anterior cingulate gyrus/supplementary motor area (greater volumes) may be neurological features of urgency without DO, whereas deactivation in the prefrontal cortex appears to be the neural hallmark of DO [33]. Tadic et al. [34] verified the difference in supraspinal activity between OAB patients with and without DO, showing that in patients with DO, older age and a greater burden of white matter injury are related with more severe functional urinary impairment. Several studies have shown that this "white matter

illness" may be the structural foundation for the brain aetiology of OAB in people with DO, possibly due to frontal hypoperfusion [35].

As recently demonstrated by Griffiths et al. [36], behavioral therapies appear to be suited for treating "brain OAB" by affording the potential of retraining the supraspinal network to function normally. These researchers discovered two types of brain responses to bladder filling and were able to predict whether a person would respond to biofeedback or not [36]. SNM has been demonstrated to alter activity in various brain areas involved in micturition regulation, as well as stimulate neuroplastic cortical activity reorganization [37]. According to some data, posterior tibial nerve stimulation (PTNS) can also cause plastic reorganization of the cerebral network that controls micturition [38].

1.3.3. Detrusor underactivity

Over the last few years, the urological community has made significant efforts to characterize underactive bladder symptom complex as a distinct clinical entity [39]. While OAB is considered the clinical correlate of urodynamically defined detrusor underactivity, the voiding symptomatology of detrusor underactivity has been shown to overlap with OAB, and urgency has been reported to be the most common symptom in patients with urodynamically proven detrusor underactivity (seen in over 50% of patients) [40]. During the last few years, the urological community has made significant efforts to characterize underactive bladder symptom complex as a distinct clinical entity [39].

In a survey-based epidemiological investigation involving 977 patients, underactive bladder symptoms were found to be related with an increased prevalence of urgency, UUI, and nocturia [41]. Urinary urgency can also be attributed to the well-known DO/impaired contractility relationship [42], which is no doubt associated to increased postvoid residuals and, as a result, reduced functional bladder capacity in patients with DO. UTIs secondary to persistent urinary retention [43] or the influence of such retention on the urinary microbiota might also contribute to detrusor underactivity. Detrusor underactivity may be caused by urothelial/suburothelial dysfunction (urotheliogenic theory) and/or detrusor muscle dysfunction (myogenic hypothesis) based on current evidence [44]. Despite promising preliminary data on cholinesterase inhibitors, no treatment has yet been proven clinically effective in restoring detrusor contractility [45], so clean intermittent self-catheterization remains the standard of care

for these patients, despite the fact that the effectiveness of catheterization alone in relieving storage lower urinariy tract infection (LUTS) in such patients has not been clearly assessed [46]. SNM has been shown to be helpful in patients with detrusor underactivity and OAB symptoms, especially in those with some residual detrusor contractility and DO [43]. Future treatments such as procontractile drugs or stem cell therapy are currently under investigation but remain hypothetical, and SNM has been shown to be helpful in patients with detrusor underactivity and OAB symptoms, especially in those with some residual detrusor contractility and DO.

Phenotyping according to pathophysiological cofactors:

- Metabolic syndrome:

Many studies have found a relationship between metabolic syndrome and OAB, particularly between obesity and OAB [47, 48]. While it was once considered that this link was due to benign prostatic hyperplasia/chronic prostatic inflammation [48], growing evidence has indicated that OAB occurs equally in men and women with metabolic syndrome [47, 48]. In patients with metabolic syndrome, OAB may have its own pathophysiology, involving increased mechanical load stimulating sensory afferents of the trigone and bladder neck, as well as oxidative stress, systemic inflammation, and insulin resistance, all of which promote chronic pelvic ischaemia and urothelial dysfunction [47, 49]. Most commonly used OAB treatments, such as antimuscarinics, SNM, and botulinum toxin, have been shown to be less successful in patients with metabolic syndrome, or at least less effective than in other patient groups [49, 50, 51]. In contrast, the b3-adrenoreceptor agonist mirabegron, which was originally developed as an antiobesity medicine [52], has been proven to be equally efficacious in both obese and nonobese OAB patients [53], and may be well suited for this patient population [54]. Daily low-dose tadalafil was reported to be an effective and well-tolerated treatment for OAB in the first RCT to date investigating the role of PDE inhibitors in female patients [55]. Phosphodiesterase inhibitors may become a noteworthy therapeutic option in patients with metabolic syndrome and OAB, as evidenced by a rising number of animal model studies and exploratory clinical trials [56]. Treatments for obesity, such as weight reduction programs and bariatric surgery, may be considered the most successful therapeutic alternatives based on the current literature, operating on the many mechanisms outlined above, with cure rates for UUI as high as 19 percent and 79 percent, respectively [57, 58, 59].

- Affective disorders:

While OAB may predispose people to anxiety and depression, some research suggests that emotional stress and a history of anxiety/depression are risk factors for the development of OAB in women [60]. This is not surprising given the limbic region of the brain's central processing of afferent impulses. Recent research has revealed the impact of emotional stress and affective disorders on the natural history of OAB [60], as well as a complete assessment of the temporal link between these symptoms. As a result, there may be a bidirectional relationship between affective disorders and OAB, with common biological pathways causing both illnesses to co-occur. Corticotropin releasing factor (CRF) has been looked into as a probable shared pathophysiological component to OAB and anxiety/depression [61].

A recent animal model investigation found a concurrent decrease in serum CRF levels and improvement of depression-induced OAB using a CRF receptor type 1 antagonist, confirming this proposed mechanism and suggesting a potential treatment approach for social stress-induced OAB [62]. Serotonin depletion has been proposed as a common pathophysiological candidate for anxiety/depression and OAB, as its role in affective disorders is well established, and several experimental studies have shown that lowering serotonin levels in the CNS is associated with urinary frequency and DO [63, 64]. Increased reactivity of nociceptive neurons in the CNS to normal or subthreshold afferent input has recently been proposed as the final common pathophysiological component of anxiety/depression and OAB [67]. Many of the foregoing pathophysiological pathways may be shared by social stress-induced OAB and functional gastrointestinal disorders/pelvic organ cross-talk OAB phenotypes [68].

- Sex hormone deficiency:

With oestrogen and progesterone receptors found in the urethra, bladder, and pelvic floor muscles, the influence of sex hormone insufficiency on the lower urinary tract in female patients has been convincingly proven [70]. The involvement of sex hormone insufficiency in the aetiogenesis of LUTS has been corroborated by epidemiological research, with up to 70% of women linking the onset of urine incontinence to their final menstruations [70]. Increased detrusor contractility via the Rho-kinase pathway, increased acetylcholine release, alterations in urothelial afferent signaling, or increased connexin-43 expression are some of the processes that could explain the involvement of oestrogen deficiency in the development of urinary urgency [70, 71]. OAB is frequently associated with UTIs in these patients, as well as vulvovaginal symptoms such vaginal dryness, itching, and dyspareunia, which have recently been characterized

as a symptom complex known as the genitourinary syndrome of menopause [72]. According to a recent Cochrane meta-analysis, using vaginal oestrogen to treat urinary incontinence, particularly UUI [73], can help, while the utility of this strategy in women who do not have vaginal atrophy may be questioned. In an RCT, Nelken et al. [74] found that utilizing a vaginal oestradiol ring or oral oxybutynin had equal results in postmenopausal women with OAB, but oxybutynin had greater adverse effects, reinforcing the hypothesized importance of local oestrogen in these individuals. Except for mirabegron, where a recent prospective research found no effect of sex hormone levels on the clinical efficacy of the b3 agonist [75], the impact of menopausal status on the success of typical OAB treatments has not been investigated.

In contrast to women, there is little evidence that sex hormone deficiency is a cause of OAB in men. However, experimental studies suggest that testosterone may reduce detrusor excitability [76], improve bladder wall fibrosis [77], and influence urothelial mediator release [78], suggesting that androgen deficiency may play a role in the aetiogenesis of OAB. Unfortunately, without a full investigation of storage symptoms, testosterone replacement has been proven to ameliorate LUTS in male patients [79].

- Urinary microbiota:

Recent findings showed that the human urinary system contains microbial communities known as the urinary microbiota, contradicting the previous orthodoxy that urine is normally sterile [80, 81] as a result of breakthroughs in culture methods. The urine microbiota may play a role in the development of OAB, according to preliminary research [81], while the mechanisms behind the causal link, as well as its potential therapeutic implications, remain unknown. In individuals with UUI, bacterial DNA [82, 83] and a larger bacterial load [84] are more frequently found, suggesting a decrease in urine microbiome diversity [82, 84, 85, 86]. Lactobacillus spp. (e.g., Lactobacillus crispatus) may be markers of a healthy female bladder, with a decreased Lactobacillus load in UUI patients [82, 84]. Lactobacillus spp., which produce acid, may protect the lower urinary tract by inhibiting the growth of more pathogenic bacteria that cannot survive in an acidic environment. While Lactobacillus probiotics given intravaginally have showed potential in preventing recurrent UTIs, no research have looked into the impact of Lactobacillus probiotics in OAB [82]. Several preliminary studies have suggested that the urinary microbiome has a significant impact on the outcomes of various OAB treatments such as antimuscarinics or intradetrusor botulinum toxin injection [83, 84, 87], with responders in some of these studies having fewer bacteria

and a less diverse community at baseline [84]. Although data from the three trials available are conflicting [87], this supports the hypothesis that urinary microbiota-related OAB may not be treated well by standard OAB treatments. An atypical urinary microbiome with less diversity was found to be positively correlated with higher levels of depression and anxiety in a recent study [86], implying that urinary microbiota may have the same potential to communicate with the brain as gut microbiota, notably eliciting central sensitisation. As a result, a brain-bladder-microbiota axis may exist, similar to the well-known brain-gut-microbiota axis. Whether this axis could involve the same bidirectional communication mechanisms (neurotransmitter release, immune system stimulation, etc.) and be integrated as part of a larger brain-gut-bladder microbiota axis through central sensitization requires more research, but it could help us better understand OAB syndrome. In addition, it is evident that UTIs are generally accompanied by considerable bladder storage symptoms in clinical practice.

- Functional gastrointestinal disorders:

The bladder and the colorectum share a common embryological origin, both developing from the cloaca, and thus share spinally derived neural pathways with dichotomized afferents innervating both organs and converging at a single dorsal ganglion root, allowing cross-talk mechanisms between the bladder and the colon [88]. Cross-sensitisation is defined as sensitisation of afferent nerves of one of the pelvic organs due to an acute insult in the other [88]. These similar neural pathways may also be the drivers of cross-sensitisation. The pelvic organ cross-talk and cross-sensitization mechanisms are assumed to be at least partly responsible for the co-occurrence of urological and gastrointestinal functional problems documented in multiple studies [88, 89].

Several studies have demonstrated that OAB and faecal incontinence or constipation have a bidirectional relationship [88, 89]. Irritable bowel syndrome (IBS) [88, 89, 90], with a prevalence of 33.3 percent in patients with OAB [91], is the gastrointestinal condition most frequently linked to OAB [88, 89, 90], with both disorders characterized by increased frequency of visceral emptying due to increased sensation (urgency for OAB; pain and discomfort for IBS) [92]. The possibility of central sensitisation playing a role in the cooccurrence of functional urological and gastrointestinal illnesses has piqued researchers' curiosity in recent years [67]. This central sensitisation could be induced by pelvic organ cross-sensitization, with peripheral neural pathways activation leading to signal amplification in the spinal cord and brain [89]. However, some authors

have recently proposed that central sensitisation, as part of a brain-gut-bladder axis, could be a main dysfunction affecting the co-occurrence of both gastrointestinal and urological functional problems, as well as affective disorders (ie, anxiety and depression) [67, 68].

Stress from either psychological (e.g., a previous traumatic incident) or physical (i.e., internal/external physical threat) elements could cause this putative braingut-bladder axis-OAB phenotype. While infection is a well-known internal physical hazard that can produce stress, the gut and bladder microbiota could theoretically be engaged as causal factors via peripheral and central sensitization, supporting the concept of a brain-gut-bladdermicrobiota axis [67, 68]. Treatments that target the bladder or colorectum have been shown to alleviate or worsen functional abnormalities in the other organ [88, 89], which may encourage the use of treatments that target both the bladder and the bowel in this OAB phenotype, like SNM or PTNS [93, 94]. Recent research has suggested that SNM/PTNS may be useful in treating IBS in individuals with affective disorders [95], and some evidence also suggests that SNM/PTNS may be useful in treating social stress-induced OAB [65, 99]. Duloxetine, through targeting central sensitisation, could be a potential treatment option in the therapy of individuals with “brain-gut-bladder axis-OAB”.

Transient receptor potential cation channel subfamily V member 1 (TRPV1) receptor antagonists or a1-adrenoreceptor antagonists, which interfere with neurogenic inflammation driving pelvic organ cross-sensitisation, could be attractive therapeutic methods to test in this population.

- Autonomic nervous system dysfunction:

Sympathetic, parasympathetic, and somatic nerves are well-known determinants of lower urinary tract physiological functioning [23, 97], and they are altered in a number of neurological diseases linked to lower urinary tract dysfunction (e.g., Parkinsonism, multiple sclerosis) [98]. Blanc et al. [99] were the first to suggest that "idiopathic" OAB could be caused by subclinical autonomic nerve system dysfunction. Choi et al. [100] corroborated the idea of an autonomic imbalance in OAB a few years later. Hubeaux et al. [101] used heart rate variability during filling cystometry to gain a more comprehensive understanding of this autonomic balance deficit. They found a prevalence of parasympathetic activity when the bladder was empty and a preponderance of sympathetic activity at the conclusion of bladder filling in women

with OAB [101], suggesting that bladder filling causes a global sympathetic response in OAB women.

Surprisingly, the same research team launched a second investigation, which found that sympathetic dysfunction may predominate over parasympathetic dysfunction in OAB patients, and that OAB patients with autonomic dysfunction are less likely to have DO on urodynamics [102]. While other investigations have found similar changes in sympathetic activity in OAB patients [103], there has also been evidence of a link between OAB and greater parasympathetic activation [104]. Antimuscarinics have been shown in a recent trial to reduce parasympathetic dysfunction while relieving OAB symptoms in these patients [104]. In contrast, a recent study revealed that sympathetic dysfunction in OAB patients could predict a poor response to antimuscarinics, and that b3 agonists could help restore defective sympathetic efferent pathway activity, which would result in detrusor muscle inhibition [105]. The different autonomic testing technologies that are available could then be used to help design first-line treatment for OAB patients.

1.4. Diagnosis

Overactive bladder is a common ailment that has a significant influence on quality of life, thus the patient's evaluation should begin with an assessment of how much the condition affects the patient's daily life. For evaluation, standardized quality-of-life questionnaires are available. In order to fully comprehend an individual patient's experience with OAB, a thorough medical and surgical history, as well as a thorough examination of drugs, is required.

1.4.1. Anamnesis

Structured questionnaires can be useful in this situation [106].

The Kings Health Questionnaire, Urge Impact Score (Uris 24), Incontinence Quality of Life Measure (I-QOL), and OAB Questionnaire (OAB-q) might all be useful for documenting quality of life impairment [107, 108, 109, 110].

The primary diagnosis consists mostly on a comprehensive anamnesis. This should include a focused and organized query of the parameters listed below: symptoms currently present (including onset, duration and severe straights), the frequency of urination (day and night), the presence of a strong need to urinate/urine loss, The amount of water consumed, the volume of urine produced each micturition, and the frequency of micturition are all factors to consider, hematuria is present, infections of

the genital tract, descent complaints, underlying neurological and endocrinological disorders, trauma, prior surgeries, history of medication, height and weight, history of birth, menstrual cycle and sexual history.

1.4.2. Physical examination

The physical examination should involve an examination of the external genitalia and perineum, as well as a vaginal speculum and vaginal/rectal palpation examination, as well as documentation and assessment of the other characteristics. Examination of the external genitalia and the urethral meatus, including vaginal under search; examination of the pelvic floor and potential defects, anal sphincter tone, and pelvic floor activity; rectal digital palpation (examination of the prostate, anal processes, coprostasis, etc.); assessment of changes in the position of the genitals at rest and when pressing, including searching for descent phenomena (cystocele, rectocele); bimanual examination to rule out lower abdominal malignancies; urinalysis, which includes a urine culture, is performed to screen out urinary tract infection and metabolic problems (glucosuria, proteinuria); sonographic examination of the upper urinary tract, including determination of residual urine (exclusion of a urinary tract disorder/urolithiasis); gross neurological examination, including search for neurological abnormalities (tremor, gor, paralysis, spasticity), as well as examination of the bulbocavernosus and anal reflex; incontinence tests (possibly pad tests); exclude the possibility of a fistula.

1.4.3. Urination diary

A micturition diary allows the frequency and volume of micturition to be quantified. Furthermore, the severity of the urgent urine symptoms, the number of incontinence episodes that may exist, the intake of the template, and the amount of water consumed can all be noted. The urinary diary should be kept for at least 2 to 5 days when explaining the OAB [111, 112, 113].

A thorough anamnesis and physical examination can immediately distinguish the symptoms indicated from other issues. The fundamental diagnostics comprise not just differentiating urine tests to rule out a urinary tract infection, but also maintaining a micturition journal for at least two days, noting individual drinking and emptying quantities as well as probable incontinence events. This allows us to objectify the symptoms and identify a habitual polydipsia as the origin of the OAB, as well as a nocturia caused by a nocturnal polyuria [114].

1.4.4. Sonography, uroflowmetry and determination of residual urine

Clinical investigations have found a 20-74 percent incidence of non-neurogenic detrusor overactivity in the context of a bladder outlet blockage/bladder outlet obstruction (BOO) [115]. The micturition evaluation is measured using uroflowmetry. A residual urine volume more than 15% of functional bladder capacity generally suggests "local pathology" and might be a contraindication to anticholinergic treatment for OAB. Furthermore, the residual urine determination conducted sonographically, which should be done first on the full bladder and subsequently on the empty bladder, gives further information regarding the architecture of the bladder wall and surrounding pelvic organs. Ultrasound can detect urethral diverticula, myomas, and cysts in the vaginal wall, allowing additional diagnostics to be carried out. Bladder diverticula, bladder cancers, and foreign bodies in the bladder are all examples of this [116]. This method can also be used to detect prevesical ureteral stones, which frequently cause urgency symptoms.

An ultrasound of the urinary tract is typically required to rule out or identify chronic inflammatory or malignant alterations in the urinary bladder [114].

1.4.5. Urethrocystoscopy

Urethrocystoscopy and retrograde pylography are used to determine if micro- or macrohematuria exists. A urethral calibration and urine cytology can also be conducted. As urethrocystoscopy to rule out or detect overflow symptoms. [114].

1.4.6. Urodynamic examination

The presence of urodynamically detectable detrusor overactivity can also be indicated by the symptom complex of OAB [117]. During the filling phase, detrusor hyperactivity is defined by involuntary detrusor contractions that occur spontaneously or involuntarily. There is a distinction made between phasic and terminal detrusor hyperactivity, with the latter leading to uncontrollable urination. Incontinence with detrusor overactivity occurs when there is a loss of urine as a result of detrusor overactivity. Depending on the origin of the discovered detrusor overactivity, it can be classified as neurogenic or non-neurogenic (idiopathic). There is no known etiology for non-neurogenic detrusor overactivity. This word has taken the place of the term "detrusor instability". Incontinence with non-neurogenic detrusor overactivity occurs when there is a loss of urine. There is always a neurological correlation when there is urodynamically proven neurogenic detrusor hyperactivity. Incontinence with neurogenic detrusor hyperactivity, which is intended to replace the previous term reflex

incontinence, occurs when urine is lost [118]. Urodynamic exams have typically been used to identify urinary incontinence. However, in recent years, the value of urodynamic clarity, particularly in OAB, has been the topic of heated debate. Some writers believe that the management of OAB is mostly determined by the underlying etiology, and that only a knowledge of the typical urodynamic results can assure proper therapy. Other authors disagree, believing that a urodynamic examination is unnecessary when patients should be treated conservatively at first [119]. Patients who have had failed medication therapy or prior procedures/radiation in the pelvic region are an exception. Furthermore, if the patient is scheduled for invasive therapy, a neurogenic condition is present, or a dubious diagnosis is established, a complete assessment of bladder function with the use of urodynamic exams is always essential.

Urodynamic procedures are often the most objective way to examine the lower urinary tract. It should be noted, however, that detrusor overactivity is a urodynamic finding of unknown clinical importance [120]. The diagnosis and treatment of overactive bladder in senior people are impacted by a number of variables. Age-related alterations in the lower urinary tract, neurological and cardiovascular disorders, diabetes mellitus, psychological changes, and musculoskeletal ailments linked with reduced mobility are among them. In this case, a basic examination is generally adequate, with extensive and costly diagnostic procedures being the exception [121].

1.5. Differential diagnosis

OAB symptoms affects an estimated 9% to 16% of the general adult population [122, 123].

OAB is defined as “urgency, with or without urge incontinence, usually with frequency and nocturia” and “in the absence of infection or other proven etiology” [124].

However, patients with OAB symptoms frequently have other proven aetiologies. BPE, prostatic obstruction, neurogenic bladder, infection, bladder carcinoma, bladder stone, sphincteric incontinence, and postoperative causes are examples of concomitant pathological conditions [123, 125, 126, 127, 128, 129].

The etiology and prevalence of these pathological conditions in OAB patients are less well understood. The average age of the 122 men who met the OAB selection criteria was 70 years (median 67, range 28 to 90). In 99 men, urodynamics revealed detrusor hyperactivity (79 percent). The differential diagnoses are listed in Table 1. In 13 patients with neurogenic bladder, the diagnosis was cerebrovascular accident in six, myelopathy in four, Parkinson's disease in one, and multiple sclerosis in two. Traumatic hemiparesis, transient ischemic attack, and stroke are all examples of cerebrovascular accident. Viral myelopathy, spinal stenosis, and surgical trauma all contributed to the myelopathy.

Table 1. *OAB differential diagnoses*

Differential Diagnosis	No. Pts (%)
BPE	40 (32)
Benign prostatic obstruction	27 (22)
Prostate Ca treatment complications	25 (20)
Neurogenic bladder	13 (11)
Urethral stricture	7 (6)
Idiopathic OAB	6 (5)
Bladder stone	2 (2)
Bladder Ca	1 (1)
Bladder diverticulum	1 (1)
Total	122 (100)

Patients with a UTI may exhibit irritative bladder symptoms similar to those seen in OAB (Table 2). However, the onset of symptoms is usually very different, with symptoms associated with UTI being acute and those associated with OAB being chronic. UTIs are distinguished from OAB by the presence of pain with urination (dysuria), costovertebral angle tenderness/pain, and possibly an elevated temperature, as OAB is not usually associated with pain [130]. Acute onset pain may also be caused by the presence of kidney stones, which should be confirmed by an imaging study [usually a non-contrast computed tomography (CT) scan, ultrasound, or intravenous pyelogram] if suspected. Patients who present with dysuria and irritative bladder symptoms may have a lower UTI, in which case a urinalysis is recommended. If there was evidence of leucocyte esterase, nitrates, or blood in the urine dipstick test or white blood cells with or without red blood cells on microscopic examination of urine sediment, a urine culture would be appropriate. A history of UTIs may be a useful predictor of a current infection. Women are especially vulnerable to UTIs, and approximately 20% of women with a history of UTIs can expect a second infection,

with a further 30% of these patients experiencing a third infection [131]. Urine culture is diagnostic, but it is likely that less than half of patients with irritative bladder symptoms will have a positive result [132, 133]. Patients who present with symptoms of UTI and white blood cells on microscopic examination of urine (pyuria) and whose first culture is negative may require a second culture to test for Mycoplasma or Chlamydia infection. OAB is a high probability diagnosis for patients who present with irritative bladder symptoms but no associated pain, as well as a history of unconfirmed UTI and a gradual rather than acute onset of symptoms. UTIs can occur in people who have OAB. These patients typically present with a worsening of their OAB symptoms and dysuria. It is also important to note that a positive culture, or the presence of bacteria on microscopic examination, in the absence of pyuria does not represent bacterial cystitis and is not usually the cause of OAB symptoms.

In the presence of irritative bladder symptoms, haematuria is the defining diagnostic feature, prompting further evaluation and a high level of clinical suspicion. Gross haematuria necessitates a comprehensive and detailed diagnostic evaluation [134, 135], but it does not always predict a diagnosis of bladder cancer, as kidney stones and urinary tract infections (UTIs) are also known to cause gross haematuria. Although the aetiology of microscopic haematuria is often benign, urological evaluation is required to rule out underlying treatable pathology or malignancy**.** While studies have shown that only 1% of asymptomatic patient's microscopic haematuria are likely to have a bladder carcinoma [136, 137], microhaematuria in the presence of OAB symptoms warrants further investigation. Upper tract imaging, urine cytology, and endoscopic bladder evaluation are all part of a comprehensive microscopic haematuria workup. Flexible cystoscopy is a minimally invasive office procedure that allows the urologist to confidently rule out bladder cancer in cases where there is a high level of suspicion. Once identified and referred for evaluation, the presence of microscopic haematuria does not preclude treatment for OAB symptoms. The haematuria associated with bladder cancer can be variable and is usually painless, though blood clots can form and cause pain or obstruct the flow of urine in some cases. Cancer is extremely rare in patients who have two negative tests. In one study of over 300 adult males, only 0.82 percent developed non-invasive bladder tumours, and none developed invasive bladder tumours 9 months after a negative dipstick test (daily testing for 14 days) [138, 139]. Given the ease of a urinalysis or dipstick test, it is probably prudent to retest such patients as part of their annual review.

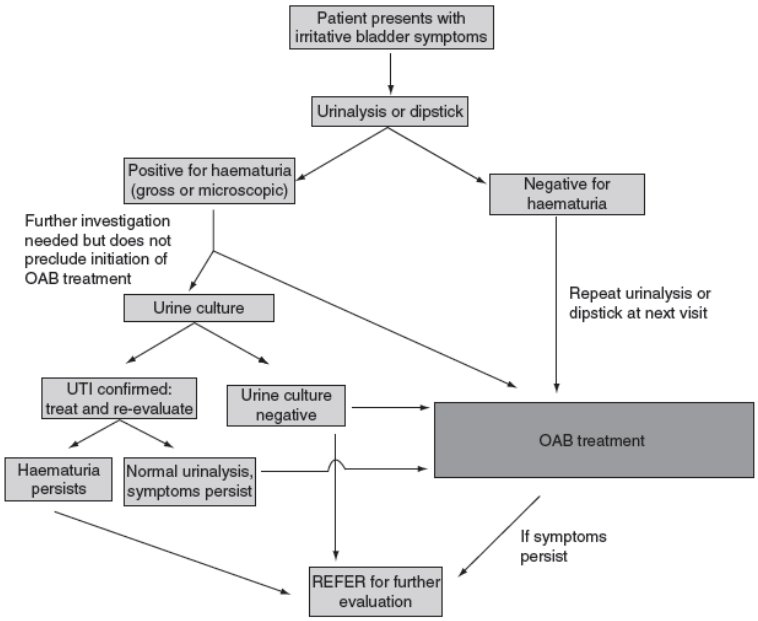

Figure 2 Diagnostic algorithm for the differential diagnosis of overactive bladder (OAB) when bladder cancer is suspected

1.6. Treatment and prognosis

When compared to individuals who have no symptoms or only minor symptoms, men and women with OAB symptoms report lower quality of life (QOL) in terms of health and work productivity, as well as higher levels of worry and despair (no inconvenience) [140].

As a result, the major goal of treatment is to enhance QOL, and patients can usually obtain satisfactory results by combining behavioral therapy with pharmacological treatment [141]. New therapeutic approaches, on the other hand, that strike a good balance between efficacy and tolerability while also improving patient outcomes are needed.

A few basic points are used to make a systematic diagnosis of OAB [142, 143, 144]:

1. A comprehensive medical history.
2. A thorough physical examination.
3. A urinalysis.
4. The voiding diary and symptom questionnaires should be examined.
5. Measurement of voiding residue and urine culture may be required in some cases.

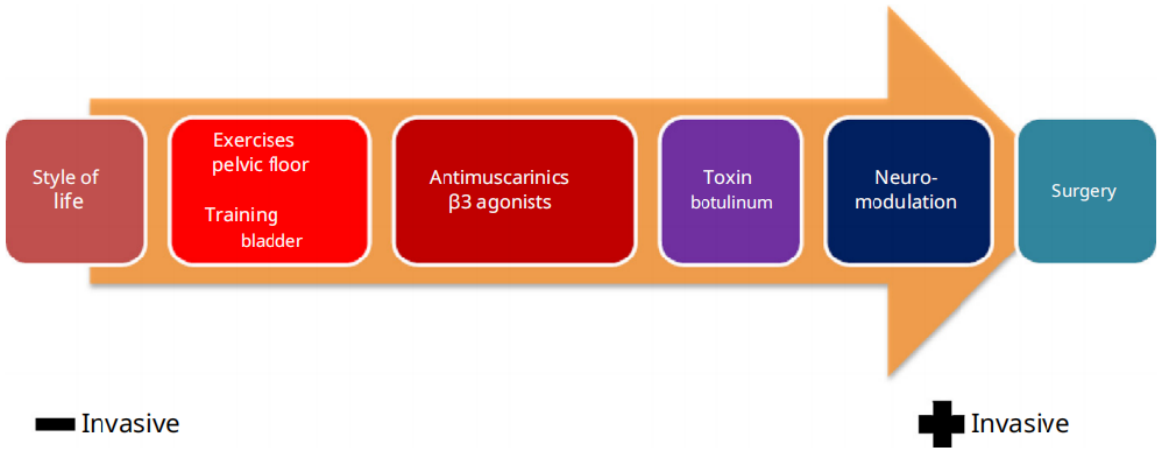

Figure 3 Treatment options in OAB.

Figure 3. Treatment for OAB should be done in stages, beginning with the least invasive procedures and progressing to more aggressive choices based on the therapeutic response [144]

1.6.1. Recommendations for a healthier lifestyle

Non-pharmacological treatment of OAB should be considered first in all patients, and no other therapeutic approaches should be considered until this first level of intervention has been completed [144].

To successfully develop and implement this conservative treatment, it is necessary to understand the patient's medical characteristics, urinary symptoms (urgency, frequency, nocturia, urine leakage) and their severity and impact on their QOL, the functional situation (physical and mental), as well as the degree of motivation and availability of family members and/or caregivers, as well as their level of involvement in addressing the problem [144].

It is important to note that OAB treatment must be thorough and multidisciplinary, involving a combination of non-pharmacological and pharmacological approaches in the vast majority of cases, but palliative treatment is regrettably the only option in certain extremely deteriorated patients [144].

This comprehensive treatment should be approached in a personalized and realistic manner, with the goals of improving QOL, reducing the severity of incontinence or the number of leaks, and regaining continence where possible [144].

Different conservative measures are included in nonpharmacological treatment [142, 143, 144, 145, 146]:

Advice on basic actions that people with OAB can do to assist ease their symptoms is beneficial to all of them. Many patients drink excessively and should be told to restrict their fluid intake to between 1 and 1.5 liters per day [147] and to avoid tea, coffee, and alcohol if these increase their issue. Furthermore, there is growing research that suggests losing weight can help with urine incontinence symptoms [148].

- ***Weight loss:*** Several epidemiological studies have identified obesity as a risk factor for urinary incontinence (UI). According to scientific evidence, the prevalence of UUI rises in direct proportion to one's body mass index. Obese women with a significant weight decrease (> 5%) have been proven to have improved UI. Obese persons with diabetes mellitus who lose weight had a lower risk of acquiring UI [142, 143, 144, 145, 146].
- ***Caffeine depletion:*** Caffeine deficit can relieve symptoms of urgency and frequency, but not UI [142, 143, 144, 145, 146].
- ***Fluid intake control:*** Lowering fluid intake can help to minimize the frequency and urgency of OAB. It's important to remember that reducing fluid intake can lead to problems including UTIs, dehydration, and constipation. The causes of excessive fluid intake should be investigated in the patient's medical history [142, 143, 144, 145, 146].
- ***Treating constipation:*** A history of constipation has been linked to the development of UI. Although there is no evidence that treating constipation helps UI, it is prudent to advise people with UI on how to cure it if it is present [142, 143, 144, 145, 146].
- ***Smoking cessation:*** While there is no conclusive scientific proof that smokers (especially those who smoke more than 20 cigarettes per day) have a higher risk of UI, it has been noticed that it is linked to severe UI. Despite the lack of proof that quitting smoking improves UI symptoms, it is advised that all patients with OAB who smoke be told to stop [142, 143, 144, 145, 146].

1.6.2. Behavior modification programs

They have been shown to alleviate UI symptoms, albeit their effectiveness fades once the program is completed. Patients' needs and talents can be adapted to behavior modification programs. They have nothing to do with the drug's side effects, but they do necessitate the patient's direct participation as well as the physician's effort and time. The use of a mix of behavior modification therapy and oral pharmaceutical treatment could be beneficial [142].

The following are some of the behavior modification programs available [142]:

- Bladder exercise: The training's objective Bladder training aids the patient in regaining bladder control and enhancing their capacity to lessen incontinence episodes and urination frequency. It is based on scheduling urination according to their voiding system (as determined by the voiding diary), advising urination before they detect the desire to void, and identifying emergency leaks. The time between urinations is gradually increased in half-hour increments until urination is spaced between 3 and 4 hours. The times are lowered if there are leaks. Although it takes the patient's willingness and cooperation, as well as a high level of physical and mental capacity to carry out this program, it has been shown to have a positive effect in the management of OAB and has no side effects.

- Pelvic floor exercises (Kegel exercises): Performing these exercises for at least three months has been shown to be a safe and effective treatment for SUI, UUI, and mixed urinary incontinence. There have been no known side effects, and just a few people have stopped using the medication.

For a period of 15 to 20 weeks, it is recommended to execute a series of 15 contractions three or four times a day and monitor the clinical response. Although it does not provide any additional benefit to the completion of Kegel exercises, the use of various gadgets (vaginal cones or Chinese balls) can increase knowledge and compliance with this approach.

- Biofeedback (biofeedback): This approach is based on the ability to reinforce a biological function, in this case urination, through the use of a tactile, visual, or aural signal. The patient sees the signal and learns to regulate and change it through self-control, which can be helpful in strengthening or relaxing the perineal muscles and controlling bladder instability. Muscle, bladder, and vesicosphincter biofeedback are the three forms. This technique necessitates good functional capacity and a high level of teamwork, as well as therapist intervention, which limits its usage in elderly patients.

1.6.3. Pharmacological therapy

While a conservative approach is justified at first, medication therapy is still important in the treatment of people with OAB, and there are a variety of antimuscarinic medicines as well as the newer b3 agonist, mirabegron.

- Anticholinergics (antimuscarinergics)

Anticholinergic therapy for OAB aims to normalize detrusor function and diminish detrusor overactivity, resulting in a reduction in clinical symptoms. The efferent

innervation of the urine bladder is blocked to achieve this. Cholinergic receptors (M receptors) govern detrusor activity, which is overmuscarinic. There are five types of M receptors (M1-M5). M2 and M3 receptors predominate in the urinary bladder, with M3 receptors being primarily implicated in the contraction of the bladder detrusor [149].
The distribution pattern of the M-receptors helps explain the typical side effects, which include constipation and dry mouth, as well as visual or cardiac arrhythmias (Tab. 1). A distinction must be made between selective and non-selective anticholinergics in the case of active drugs used today in the treatment of OAB and urge incontinence (Tab. 2). If the clinical improvement is insufficient or if adverse effects arise, just changing the formulation may be effective.

Tab. 1 Occurrence and function of muscarinic receptors. (According to [4])

region	M receptor type	function
bladder	M2> M3 (3: 1)	M3: detrusor contraction
Salivary glands	M1, M3	M1: lubrication, M3: salivation
Gastrointestinal tract	M2> M3 (4: 1)	M3: stimulation of motility
brain	M1 (-M5)	Higher cognitive functions
eye	M1-M5	Iris sphincter contractions
heart	M2	Heart rate, AV conduction, contractility

Tab. 2 Overview of selective and nonselective anticholinergics

Active ingredient	Trade name	Art
Oxybutynin	E.g. Dridase®	Nonselective
Propiverine	E.g. Mictonorm®	Nonselective
Trospium chloride	E.g. Spasmex®	Nonselective
Tolterodine	Detrusitol®	Nonselective
Fesoterodine	Toviaz®	Nonselective
Solifenacin	Vesikur®	Selective M3
Darifenacin	Emselex®	Selective M3

Because M receptors are so common, it's important to utilize anticholinergics that are as selective as possible or compounds that can't pass the blood-brain barrier to reduce adverse effects. Anticholinergic medicine can considerably limit cognitive capacities in older patients, hence M3-specific preparations (e.g. darifenacin) or preparations that do not pass the blood-brain barrier (e.g. fesoterodine) should be utilized as much as possible in this group of patients [150].
When using oral anticholinergics, oxybutynin can be given intravenously as a conventional anticholinergic if there are significant systemic side effects.

- Beta-3 sympathomimetics

Over the last ten years, pathophysiological research on OAB have discovered three separate subtypes of receptors [154, 155, 156] in the detrusomusculature and urothelium [151, 152, 153]. The 3 receptor is the most common subtype, and it is also thought to be involved in detrusor relaxation in humans [157]. The smooth detrusor muscles are directly relaxed when this 3 receptor is stimulated. Mirabegron is the first and only FDA-approved 3 receptor agonist for the oral treatment of OAB. It exhibits a high intrinsic activity for the 3 receptor and modest activity for the 1 and 2 receptors at the same time. Mirabegron increases the storage capacity of the urine bladder without affecting bladder contraction during micturition [158]. Mirabegron circulates in the blood plasma largely as an unmodified formulation following oral treatment. The enzyme cytochrome P450 3A (CYP3A) and, to a lesser extent, CYP2D6 metabolize mirabegron [159]. As a result, when taking it, it may cause drug interactions.

Mirabegron was given to over 5,500 patients in phase II and III studies that led to its approval [160, 161, 162, 163, 164, 165]. Patients with OAB syndrome were given daily doses of 25, 50, and 100 mg mirabegron in phase III investigations. The frequency, urgency, and urge incontinence symptoms of OAB patients improved significantly in these investigations. Significant benefits could already be seen after 4 weeks of therapy at the initial observation point, and they could be seen consistently throughout the trial (up to 12 months). In the final evaluation, responder analyses revealed significant improvements in continence rates and the rate of patients with a 50% reduction in incontinence episodes, as well as the proportion of patients with a dose of 50 and 100 mg mirabegron who had less than 8 micturitions per 24 h. Mirabegron's effect was not dependent on the patient's age; patients as old as 65 years old benefited as well. Furthermore, the benefits may be seen in both patients who received mirabegron as "first-line" therapy and patients who received mirabegron as "second-line" therapy after anticholinergic medication had been withdrawn.

Mirabegron was also well tolerated in the 12-month follow-up phase of a long-term study. In clinical trials, arterial hypertension, nasopharyngitis, and urinary tract infections were the most common side events. Dry mouth was at the placebo level, meaning it was 4 to 5 times less common than with Tolterodine 4 mg. Mirabegron is predicted to swiftly become a common medicine in the treatment of OAB syndrome due to its excellent side effect profile. However, based on the available data, it is unclear where Mirabegron will fit into the therapeutic cascade ("first-line" or "second-line").

For sequential or combination therapy with antimuscarinergic medications, more randomized phase III studies are needed.

- Botulinum Neurotoxin A

Since February 2013, botulinum toxin A (BoNT/A) has been approved for the treatment of hyperactive urine bladder in the event of medication therapy failure. Exotoxin produced by Clostridium botulinum causes the degradation of synaptic fusion complex proteins at the presynapse, resulting in a blockage of acetylcholine release at the neuromuscular endplate. After BoNT/A injection, ultrastructural analyses of the human detrusor vesicae revealed a downregulation of muscarinic and purinergic receptors [166]. The striated muscle's regenerative sprouting of new axonal endings could not be replicated in the urine bladder [167]. BoNT/A is thought to have two mechanisms of action, according to animal research [168]:

- Muscarinic receptor chemodenervation or downregulation. The lack of acetycholine causes muscular relaxation.
- Signal transduction inhibition at the level of suburothelial afferents, including bound myofibroblasts, with concomitant reduction in bladder sensitivity [169].

Several research on the therapy of idiopathically overactive bladder have been conducted since 2006. Between July 2005 and July 2008, 313 participants were enrolled in a phase 2 study that was randomized, double-blind, and placebo-controlled. A dose of 100 units was shown to be the most effective in terms of effects and side effects [170]. The risk of urinary tract infection and residual urine production both increased as the dose was increased. Depending on the dose, catheterization occurred up to 16% of the time. The 3rd - 4th week was when leftover urine creation peaked.

In comparison to the preoperative scenario, residual urine levels increased by a maximum of 100ml. The January 2013 approval was based on two phase 3 approval studies conducted between 2010 and 2012. These trials included a total of 557 patients with an average age of 61 years. Antimuscarinic medicine had previously been used to treat all of the patients [171]. 100 units of onabotulinum toxin (Botox®) were administered as botulinum neurotoxin. At week 12, botulinum toxin led in a statistically significant reduction of 51 percent in urinary incontinence episodes compared to baseline. In 46 percent of the instances, urinary incontinence was reduced by 75 percent, and 27.1 percent of the patients were entirely continent.

The number of nocturia events was also 20% lower than in the placebo group (placebo 12 percent). At the end of week 12, 61.8 percent of patients said their symptoms had improved significantly. 28 percent of those in the placebo group agreed. Based on patients' desire for retreatment, the median duration of response after treatment with botulinum toxin (Botox®) was 166 days. The rate of urinary tract infection after 100 units was 15.5 percent, which was substantially greater than the placebo. In 5.4 percent of cases, urinary retention necessitated catheterization. Because of the higher remaining urine, 6.1 percent (17 of 278 patients) relied on occasional self-catheterization to empty the bladder. Intermittent self-catheterization, on the other hand, was typically utilized just for a short time. Treatment terminations were uncommon and had nothing to do with the botulinum toxin injection. The drop-out rate was less than 2%, which was comparable to that of the placebo.

Numerous studies have indicated that onabotulinum toxin injection improves quality of life greatly (Fig. 1) [172, 173]. The efficacy appears to be cumulative [174, 175], as repeated treatment after botulinum toxin injection revealed no changes in the overall safety and effectiveness profile. Nonetheless, after 2–5 years, 25–63 percent of patients stop taking their medication. After the second injection, the majority of patients discontinue treatment, and "dropout" rates are uncommon. Regular interventions are required, as is the loss of effectiveness, recurring urinary tract infections during therapy, and the necessity for catheterization if considerable residual urine production occurs. The majority of patients, on the other hand, stayed in urological care and sought other forms of treatment [176, 177, 178].

- Sacral neuromodulation

Patients with sacral neuromodulation have a viable, minimally invasive therapy option if conservative medication therapy alternatives for the treatment of OAB have been exhausted. Since its approval in the late 1990s, sacral neuromodulation has become a well-established therapy for bladder storage and voiding abnormalities [177, 180]. A two-stage treatment, up to and including definitive neuromodulator implantation, has now shown its worth as a standard. Percutaneous nerve evaluation (PNE) was performed using a quadripolar test electrode. There is a case for permanent neuromodulator implantation if symptoms improve by more than 50%. The advantage of the test phase is that it includes a group of individuals who do not react to neuromodulation. The third, and less frequently the fourth, sacral foraminas are pierced and the electrodes, if possible, ideally positioned on the sacral nerve in the prone

position. The electrodes are then connected to an external pulse generator and lead out through the skin. A noticeable reflex reaction of the perineal reflex or extension of the big toe are used to maintain intraoperative position control. If the treatment will be performed under local anesthetic, the patient can be immediately asked about their stimulus response.

The effectiveness in terms of a 50% reduction in symptoms is about 70%, while complete normalization for OAB has been observed in approximately 30% of cases [181]. However, the mechanism of action is not well understood. The effects of neuromodulation are likely to be felt at the spinal and supraspinal levels, although the amount of afferent nerve fiber neuromodulation has likely been overestimated thus far. The effect appears to be most noticeable in the domain of sensorimotor process inhibition by somatic afferents in the spinal reflex arc [182].

Electrode displacement with subsequent loss of function or pain in the area of the neuromodulator are the most typical side effects.

- Percutaneous tibial nerve stimulation

The tibial nerve is a mixed nerve with L4–S3 fibers that arises from the same spinal cord segments as the bladder and pelvic floor innervation. As a result, peripheral neuro regulation may play a role in urinary symptom control.

The temporary insertion of a needle in the lower leg posterior to the tibia above the medial malleolus is used to perform percutaneous tibial nerve stimulation. Treatment takes place in a clinic once a week for the first 12 weeks, then once a month for maintenance, with each session lasting 30 minutes.

Percutaneous tibial nerve stimulation has been demonstrated to be a safe and effective treatment that is comparable to pharmacotherapy [183].

A recent systematic review and meta-analysis [184] found that the pooled subjective success rate was 61.4 percent (95 percent confidence interval: 57.5–71.8) and the objective success rate was 60.6 percent (95 percent confidence interval: 49.2–74.7). The requirement for recurrent stimulations in treating a chronic illness like OAB is a key disadvantage of percutaneous tibial nerve stimulation, as symptoms decrease after 6–12 weeks [185]. There is a scarcity of long-term data in the literature, with only a few trials looking at treatment for more than a year. percutaneous tibial nerve stimulation therapy has been established in a recent study to be a safe, long-term treatment option for OAB symptom control [186].

- Estrogen in the management of overactive bladder

Although there have been few controlled trials to demonstrate their efficacy, estrogen medication has long been utilized in the treatment of urine urgency and urgency incontinence. Although a double-blind, multicenter investigation on the use of estriol in postmenopausal women complaining of urgency failed to confirm these findings [187], a double-blind, placebo-controlled crossover study using oral estriol in 34 postmenopausal women exhibited subjective improvement in symptoms [188].

Treatment with vaginal 17b-estradiol tablets (Vagifem) may help manage the symptoms of OAB, particularly the sense of urgency [189]. Lower urinary tract symptoms of frequency, urgency, urgency incontinence, and stress incontinence were also considerably improved [190] in a double-blind, randomized, placebo-controlled experiment. However, rather than a direct influence on lower urinary tract function, some of the perceived improvement in these symptoms could simply be due to local estrogenic effects correcting urogenital atrophy. When it came to symptoms of urgency incontinence, frequency, and nocturia, estrogen was found to be superior to placebo in a study of 10 randomized, placebo-controlled studies, whereas vaginal estrogen injection was found to be superior to placebo for the symptom of urgency [191].

- Magnetic stimulation therapy

Magnetic stimulation therapy uses targeted pulsating magnetic fields to stimulate the pelvic floor muscles from the outside. Not only does this stimulation of the pelvic floor help with stress urine incontinence, but it also helps with OAB. The advantage is the ease of application on a clothed patient; however, the downside is that the treatment is spatially limited at the device's location (clinic or practice). In a total of 196 patients, six case-control studies revealed an improvement in subjective and objective indicators [192, 193, 194, 195]. In 74 individuals with various kinds of incontinence, other researchers were unable to find any changes on the success metrics of the urination diary, pad test, or urodynamics [196].

2. DISCUSSION

On a global scale, numerous screening tools are now utilized to diagnose OAB. In this study, OABSS was utilized to diagnose OAB, and it demonstrated to be accurate. If the score is 1 or higher, the respondent has OAB. The increase in OAB and the population-based survey are examined in this paper using the International Continence Society's 2002 definition. According to the findings of this investigation, the significant rise is

27.4 percent OAB. Many more research back it up, with estimates ranging from 10.8 percent to 27.9 percent increase in OAB.

The difference in the rise is most likely related to survey techniques, questionnaire design, research populations, and the definition of OAB dissimilarity.

Some research in the literature attempt to identify the risk factor for OABS. Alcohol intake, parity, marital status, lower educational level, drug usage, hypertension, obesity, and advanced age have all been identified as OABS risk factors. UTI, family history, income, parity, BMI, DM, and age are all linked to OAB risk variables in this study.

Previous researchers thought that a rise in OAB was caused by aging. This increase could be explained by aging processes that resulted in bladder dysfunctions due to neurological and reduced muscular activity, as well as changes in physical state caused by age-related factors such as menopause.

Previous research found a link between OAB and diabetes. One of the late effects of diabetes was peripheral neuropathy. Diabetic neuropathy was caused by metabolic dysregulation of Schwann cells and disrupted axonal transport, which resulted in impaired nerve conduction and segmental demyelination. As a result, peripheral neuropathy may be the cause of detrusor hyperactivity and a substantial risk factor for OAB. Consistent with the literature, diabetes was identified as a substantial risk factor for OAB in the study.

Overactive bladder affects 27.4% of women and is unaffected by gender, hypertension, pelvic surgery, smoking, constipation, or sleep, although it is associated with age, body mass index, diabetes mellitus, income, parity, and urinary tract infections [198].

OAB is a prevalent disorder that is characterized by urine urgency, with or without urgency incontinence, frequency, and nocturia in the absence of any other pathology. The clinical diagnosis is based on the symptoms presented by the patient. There are currently numerous treatments available for the management of OAB. Clinical recommendations recommend a multimodal approach to treatment that includes behavioral therapy and medication and can begin in primary care, with referral to specialist services for individuals who are unresponsive to these treatments. Intradetrusor botulinum A and sacral neuromodulation are both effective and safe treatments for refractory OAB. In a restricted set of patients, percutaneous tibial nerve stimulation and augmentation cystoplasty are still available and effective. Unfortunately, there is still a significant percentage of patient dissatisfaction and treatment cessation in all treatments, therefore there is still a need for new therapies in

the management of OAB. There are currently numerous therapy options available for OAB. It is crucial for both clinicians and patients to recognize OAB as a syndrome with no cure rather than a disease; thus, patient education on therapeutic alternatives, including no therapy, is critical. The vast majority of people with OAB will have persistent symptoms, with varying percentages of remission (3–40%). Those with the most severe UUI, a high BMI, and little physical exercise are more likely to proceed. OAB is a chronic illness, and various treatment choices may alleviate but not cure symptoms, resulting in unhappiness and a high incidence of cessation of all available therapy. When given the option, most patients appear to prefer minimally invasive surgery (i.e. onabotA or SNM), with preoperative preparation associated with better patient outcomes [200].

CONCLUSION

1. OAB has a specified definition. This is a common pathology with serious functional effects and a severe decline in quality of life.

2. It is a common chronic health disease that affects people from all walks of life. In general, population studies reveal that the prevalence of OAB is similar in men and women. Women are more likely to experience incontinence, and it is linked to more symptoms. OAB may have a negative impact on health-related quality of life, productivity, and the risk of depression/anxiety and sexual dysfunction. Patients seek treatment because of urinary incontinence, severe symptoms, and discomfort.

3. Because the pathophysiology of OAB has not been fully elucidated and is still being studied, there are somewhat overlapping hypotheses. Myogenic, urothelial, and neurogenic factors cause muscle, nerve, and connective tissue alterations that are mainly unknown.

4. The OAB is a clinical diagnosis that can be used to guide initial treatment. Lower urinary tract symptoms must therefore be clarified ahead of time. However, a clear diagnosis of OAB is difficult due to the lack of recognized biomarkers. In addition to

further diagnostics and extra procedures, such as urodynamics, sufficient fundamental diagnostics, including a detailed anamnesis, are required.

5. Before initiating therapy, basic diagnostics are required. Lifestyle interventions are recommended as a general basic measure. Functional electrical stimulation (FES), behavioral therapy or medication are possible as initial therapy. Treatment decisions should be based on general condition and patient preference. If primary therapy is unsuccessful, extended diagnostics should be carried out before further treatment. Onabotulinum toxin A or sacral neuromodulation are available as minimally invasive treatment options. The decision for a method depends on the individual patient preference. Invasive surgical methods, such as bladder augmentation or supravesical urinary diversion, are now rarely required in patients with OAB

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