

Postmenopausal overactive bladder

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Abstract

Bladder storage symptoms have a severe impact on many areas as regards the quality of life including health-related, social, psychological and working functions. Pharmacotherapy of lower urinary tract stores (LUTS) has been developed to optimize neural control of the lower urinary tract in pathologic states. The bladder can be overactive or underactive. Overactive bladder (OAB) is highly prevalent and is associated with considerable morbidity, especially in aging population. Therefore, an effective treatment of OAB must result in a meaningful reduction in urinary symptoms. Pharmacotherapy for the OAB must be individualized based on the degree of bother, medication side-effect profile, concomitant comorbidities and current medication regimen. Antimuscarinic agents will continue to represent the current gold standard for the first-line pharmacological management of OAB. Alternatively to antimuscarinic therapy, β_3 -adrenergic receptor agonists, due to their efficacy and favorable adverse event profile, are a novel and attractive option of pharmacological treatment of overactive bladder symptoms. A combination of selective antimuscarinic and β_3 -adrenergic receptor agonists, agents with the different mechanism of action, gives a new treatment option for the patient with OAB according to its harms profile. A number of putative novel therapeutic agents is under clinical evaluations that may ultimately provide alternative or combination treatment options for OAB in the nearest future.

Key words: menopause, aging, overactive bladder, pharmacotherapy.

The lower urinary tract stores and evacuates urine. It is controlled by autonomic, somatic and sensory innervation [1]

Aging is a well-known factor affecting pelvic floor and lower urinary tract (LUT) anatomy and function. With increasing age, pelvic floor disorders increase in frequency, including pelvic organ prolapse, overactive bladder (OAB), urinary incontinence (UI), and sexual dysfunction. Although it is difficult to separate the effects of declining estrogen levels in menopause from aging in general, it is clear that the pelvic organs and their surrounding muscular and connective tissue support are estrogen-responsive, epidemiological studies indicate that the menopause is a major risk factor for the development of pelvic floor disorders, and the urinary symptoms and severity of these disorders increase significantly after the menopause [2].

The age-related changes in the bladder and surrounding tissues and/or in the central nervous system correspond to the high prevalence of lower urinary tract symptoms (LUTS) in elderly women [3].

Lower urinary tract symptoms encompass a range of often comorbid concerns relating to storage symptoms, including urinary incontinence, increased day-

time or night-time frequency, urgency, and/or voiding and post-micturition symptoms as hesitancy, slow stream, intermittency, straining to void, spraying/splitting of stream, leakage, painful urination, and feeling of incomplete bladder emptying (urine retention). Overactive bladder, the most bothersome subset of LUTS, has been defined by the International Continence Society (ICS) as urgency, with or without urgency incontinence, usually with frequency and nocturia. According to this definition, urgency is an essential component for the diagnosis of OAB, and it is the cornerstone symptom that drives all other symptoms of OAB. Lower urinary tract symptoms have been traditionally associated with the prostate in men and OAB in women [1, 3-5] (Fig. 1).

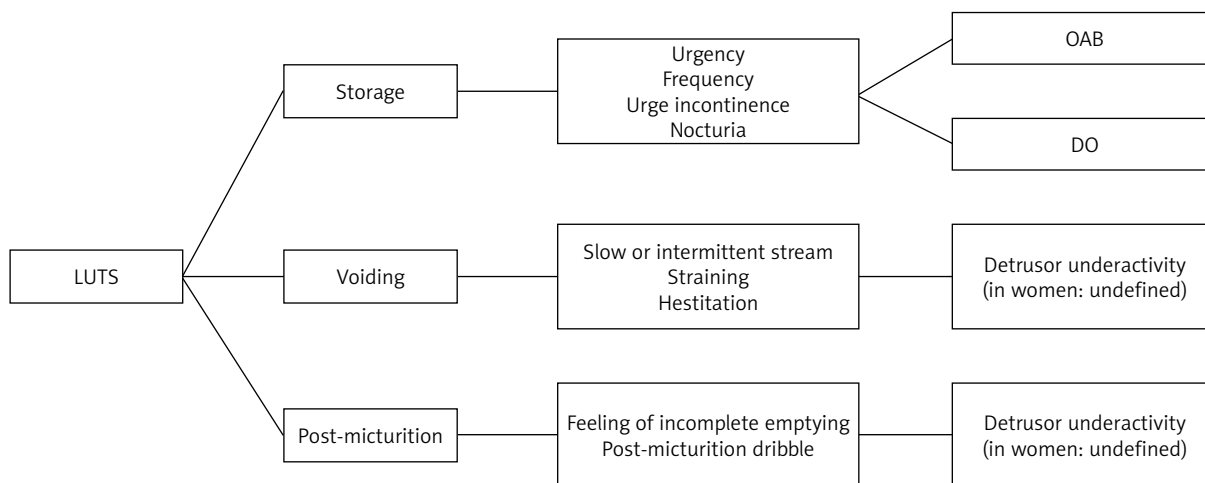
Urinary symptoms are nearly twice as common in women as in men and prevalence steadily increases with aging. Urinary incontinence is reported by between 12% and 47% of middle-aged females and between 17% and 55% of older women, in which group 3-17% reporting daily incontinence. Under half of women aged 48-54 reported stress urinary incontinence (SUI) and about 25% were diagnosed for urge urinary incontinence (UUI). The life time prevalence for experiencing any symptoms was at 30% in women and 20% in men. Moreover, 20% of women and almost 10% of men reported suffering symptoms "often" [6].

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Distribution for LUTS as assessed in the EpiLUTS study indicating overlapping or nonoverlapping symptoms. Storage LUTS include the following symptoms: micturition frequency, nocturia, urinary urgency, and urinary incontinence. Voiding LUTS include slow or weak stream, hesitancy, and terminal dribble. Post-micturition LUTS include sensation of incomplete emptying and post-micturition dribble (n = 15 861 women)

NO LUTS	25.3%
Voiding only	5.2%
Storage only	22.4%
Post-micturition only	0.9%
Voiding and storage	14.8%
Voiding and post-micturition	2.0%
Storage and post-micturition	3.6%
Voiding, storage and post-micturition	26.0%

OAB – overactive bladder, DO – detrusor overactivity

Fig. 1. Lower urinary tract symptoms (LUTS) by type, key symptoms, underlying pathophysiology and relations to disease entity (adapted from [5, 88])

Overactive bladder is not a disease; it is a symptom complex that generally is not a life-threatening condition consisting of urinary urgency described as the sudden compelling desire to void that is difficult to defer, frequency and nocturia (usually), and incontinence (sometimes) (Table I). Patients with OAB do not complain of pain or dysuria. Overactive bladder is often but not al-

ways associated with detrusor overactivity (DO) on urodynamic evaluation. Overactive bladder is a symptom and DO is a urodynamic finding. Approximately 64% of patients with OAB have urodynamically proven DO, while 83% of patients with DO have symptoms suggestive of OAB. Overactive bladder may be idiopathic (other than neurological) or secondary to a neurological cause

Tab. I. Definitions [9]

Overactive bladder	is a clinical diagnosis characterized by the presence of bothersome urinary symptoms. The International Continence Society defines overactive bladder as the presence of “urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infections or other obvious pathology”. Therefore, overactive bladder symptoms consist of four components: urgency, frequency, nocturia and urgency incontinence.
Urgency	is defined by the International Continence Society as the “complaint of a sudden, compelling desire to pass urine which is difficult to defer”. Urgency is considered the hallmark symptom of overactive bladder, but it has proven difficult to be precisely defined or to characterized for research or clinical purposes.
Urinary frequency	can be reliably measured with a voiding diary. Traditionally, up to seven micturition episodes during waking hours has been considered normal, but this number is highly variable based upon hours of sleep, fluid intake, comorbid medical conditions and other factors.
Nocturia	is the complaint of interruption of sleep one or more times because of the need to void. Three or more episodes of nocturia constitutes moderate or major bother. Like daytime frequency, nocturia is a multifactorial symptom which is often due to factors unrelated to overactive bladder (e.g. excessive nighttime urine production, sleep apnea).
Urgency urinary incontinence	is defined as the involuntary leakage of urine, associated with a sudden compelling desire to void. Incontinence episodes can be measured reliably with a diary, and the quantity of urine leakage can be measured with pad tests. However, in patients with mixed urinary incontinence (both stress and urgency incontinence), it can be difficult to distinguish between incontinence subtypes. Therefore, it is common for overactive bladder treatment trials to utilize total incontinence episodes as an outcome measure.

(e.g. multiple sclerosis, spinal cord injury). Idiopathic OAB may be due to bladder outlet obstruction, or have no discernible cause. Overactive bladder is subclassified as “OAB wet” if associated with urinary incontinence or “OAB dry” without incontinence. Involuntary DO due to a neurogenic or myogenic cause is often found on urodynamic evaluation of “OAB wet” [7-10].

When the bladder is healthy, voiding frequency depends on fluid intake and bladder capacity. Most agree that the normal micturition rate is less than 8 per day and 1 or fewer voids per night. Women tend to void more frequently and at lower volumes than men. The number of daytime/night-time voids increases with age. Women with increased daytime (more often than every 2 hours) and night-time (more than 2 times) frequency are significantly older and significantly more bothered by their bladder than those with normal daytime and night-time voiding frequency [3].

Overactive bladder symptoms (frequency, urgency and urgency incontinence) may occur only at night, causing a single symptom of nocturia. The differential diagnosis of nocturia includes nocturnal polyuria (production of greater than 20-33% of total 24-hour urine output during the period of sleep, which is age-dependent with 20% for younger individuals and 33% for elderly individuals), low nocturnal bladder capacity or both. In nocturnal polyuria, nocturnal voids are frequently normal or large volume as opposed to the small volume voids commonly observed in nocturia associated with OAB. Sleep disturbances, vascular and/or cardiac disease and other medical conditions are often associated with nocturnal polyuria. As such, it is often age-dependent, increasing in prevalence with aging and with poorer general health. Overactive bladder also must be distinguished from other conditions such as polydipsia. In OAB, urinary frequency is associated with many small volume voids. Frequency that is a result of polydipsia and resulting polyuria may mimic OAB; the two can only be distinguished with the use of frequency-volume charts. In polydipsia, urinary frequency occurs with normal or large volume voids and the intake is volume matched. In this case, the frequency is appropriate because of the intake volume and the patient does not have OAB. Frequency due to polydipsia is physiologically self-induced OAB and should be managed with education, with consideration of fluid management. Similarly, diabetes insipidus (DI) also is associated with frequent, large volume voids and should be distinguished from OAB. Other causes of urgency should be excluded prior to assigning a diagnosis of OAB [11] (Table II).

Urinary symptoms may exact a heavy toll on quality of life (QoL), and in severe cases may lead to complete social isolation. Incontinence is a particularly embarrassing and potentially disabling condition that may lead to depression, social isolation, and worsening general health. Objective studies on female sexuality report

Tab. II. Common pathologies which can cause urgency [7, 8]

Urogenital atrophy
Bladder stones
Bladder pathology (e.g. cancer)
Acute bacterial cystitis
Recurrent urinary tract infection
Interstitial cystitis
Diabetes insipidus
Diabetes mellitus
Habitual polyuria due to polydipsia
Chronic urinary retention
Nocturnal polyuria
Diuresis due to excessive fluid intake, impaired urine concentrations, or medication (e.g. diuretics)
Anxiety
Caffeine
Prolapse
Fibroids
Pelvic mass
Urethral syndrome
Urethral stricture

relatively high prevalence of female sexual dysfunction in women with OAB. Overactive bladder and incontinence in elderly women are associated with increased morbidity and disability and poor self-assessment, sleep quality, emotional well-being and have been demonstrated to have a greater negative effect on health-related quality of life than diabetes mellitus, hypertension, asthma or depression. Patients aged more than 70 years demonstrated OAB symptoms significantly more often when over-weighted, currently drinking and with depression. Advancing age is associated with decreased bone mineral density and an increased risk of osteoporosis, for which fractures are serious complications. Among elderly women, OAB, urge urinary incontinence and nocturia are associated with an increased risk of falls and fractures what is often caused by rushing to the toilette. Lower urinary tract symptoms or OAB is an embarrassing problem to many older women and thus its presence may be significantly underreported or underdiagnosed and is associated with constipation, musculoskeletal disease, urinary tract infections (UTI), skin infections as well as skin irritations [3, 6, 8].

Between 11% and 73% of women suffer from some urinary symptoms. Among subjects with OAB, urgency incontinence, frequency, and nocturia were reported by 24%, 37% and 37% of women, respectively. How-

Tab. III. Prevalence (%) of overactive bladder by age of women [15]

Age (years)	Prevalence (%)
18-29	5.9
30-39	4.2
40-49	8.5
50-59	11.8
60-69	12.3
70-79	15.6
Age-standardized	8.6

ever, only 33% of women with frequency and 31% with nocturia reported OAB. Nearly half of the women who reported symptoms of OAB also reported urinary incontinence. Overactive bladder symptoms severity tend to increase with age and was most often reported by peri- or postmenopausal women but there are relatively little epidemiological data on the prevalence of OAB syndrome in the elderly (Table III). Studies on overactive bladder have reported a prevalence of OAB rates range from 7% to 27% in men, and 9% to 43% in women. The National Overactive BLadder Evaluation (NOBLE) study found that more than 34 million Americans have OAB. Overall, there was a similar prevalence in men (16.0%) and women (16.9%); however, there were substantial differences in symptom severity between sexes. An overall prevalence of OAB wet was of 9.6% in women over 18 years of age, rising from 5% in those aged 18-44 to 19% in those over 65. In a European, population-based, prevalence study conducted before the 2002 ICS definition was adopted, 17.4% of women aged > 40 years reported symptoms of frequency, urgency, urge incontinence, alone or as any combination, and the prevalence of frequency, urgency, and urge incontinence increased in the elderly. The Leicestershire MRC Incontinence Study found an overall prevalence of OAB in women aged 40 and over of 21.4%. It has been estimated that, while not all may need or want help, 20.4% of people aged 40 years and over, representing around 5 million people in the UK, have a healthcare requirement. In women aged 40 and over this figure increases from 20.5% aged 40-49 up to 35.6% at age 80 and over. In Spain, the EPIC study carried out in specific population groups shows that the prevalence of OAB, previously estimated in adults \geq 40 years in 21.5%, was 5.9% for women between 25 and 64 years and 38.5% for institutionalized persons over 65 years old. A 2011 prevalence study estimated that 10.7% of the 2008 worldwide adult population was affected by OAB, and this is expected to increase to 20.1% by 2018 [8-24].

On the other hand, it is possible that OAB is less common than previously reported. The EPIC study found that approximately 11% of men and 13% of women in four European countries and Canada reported OAB symptoms. Prevalence of OAB for women was only 8.6% in a questionnaire population survey performed on 6000 randomly selected Finns aged 18-79 years. In another study based on ICS definitions a 1-yr incidence rate of OAB was reported on 8.8% compared with 5.4% reported by a study that did not use ICS nomenclature. The Epidemiology of Lower Urinary Tract Symptoms study, also based on ICS definitions, found that the prevalence of urge urinary incontinence was higher in women than men but the global incidence of OAB was low (3.1%) [12, 19, 20, 25, 26].

Wennberg *et al.* reported a 16-yr cumulative incidence of OAB in Swedish women on 20% (average annual incidence: 1.25%). Authors found evidence supporting a dynamic progression of OAB symptom severity over time. Over a 16-yr period the proportion of women with OAB without UII (OAB dry) did not differ significantly (11% vs. 10%) however, the number of women with OAB with UII (OAB wet) increased from 6% to 16%. Among women with OAB dry, 23% remained OAB dry and 28% reported symptom progression to OAB wet after 16 years' period of follow-up. Among women who were OAB wet, 53% remained OAB wet and 21% reported symptom regression to OAB dry at the end of the last year of observation. The rate of complete remission of OAB symptoms was greater for women who were OAB dry (49%) compared with those who were OAB wet (26%) [27].

Donaldson *et al.* reported that the severity of OAB increased with age for respondents between 40 and 49 years of age, reached a plateau for those who are 50-59 years old, increased steeply for those between 60 and 69 years old, continued to rise for those 70-79 years old, and reached a plateau for those over than 80 years old [23].

In a recent geriatric cohort study with 75-year-old patients and urinary symptoms, Wehrberger *et al.* were able to identify that nocturia was the most bothersome symptom for women, with higher patients' complaint than urgency and urge incontinence [28].

Relatively few studies have assessed risk factors for the progression and remission/regression of OAB symptoms. Based on prevalence measurements, factors associated with OAB have been shown to include gender, age, race and ethnicity, parity, dietary and lifestyle factors and comorbid conditions including constipation diabetes and obesity. A proportion of OAB cases (37-39%) remit during a given year, but the majority of patients have symptoms for years [29].

Many women who suffer from anterior or/and posterior vaginal wall descent or prolapse complain of symptoms of OAB and is directly correlated to OAB

severity. It has been suggested that this may be due to descent of the trigone into the anterior vaginal wall prolapse or obstruction of the urethra due to vaginal prolapse causing urethral kinking. Therefore, the first-line treatment of these women is not clear, and the effect of vaginal surgery on concomitant OAB symptoms is still not clear [30].

There have now been a number of surgical trials evaluating the effect of age on surgical outcome for SUI and OAB symptoms. The SISTER trial investigated the effect of age on both perioperative and postoperative outcome in 659 women. The older women (mean age: 69.7 years) were compared with a younger group (mean age: 49.4 years). Urinary incontinence at follow-up was more commonly reported in the older-age group and was likely to have less subjective improvement in both stress and urge symptoms, and was more likely to require redo surgery [31].

In another study, the incidence of persistent OAB after intravaginal slingplasty was similar in both elderly and younger women (68% and 62%, respectively), but symptoms of *de novo* OAB was higher in the elderly group (11.9% vs. 4.7%) [32].

The pathophysiology of OAB explained myogenic theory and neurogenic or urothelial hypothesis. In the first, partial denervation of the detrusor muscle is thought to increase excitability. Changes in central nervous system pathways that inhibit bladder activity and over-sensitivity of the sensory nerve endings in the suburothelial layer of the bladder wall are the basis of the second. In both theories, the outcome is over activity of the detrusor muscle. The motor nerve supply to the bladder is via the parasympathetic nervous system, which affects detrusor muscle contraction. This is mediated by acetylcholine acting on muscarinic receptors (M_1 , M_2 and M_3) subtypes at the level of the bladder activity. Pharmacotherapy relies on the use of drugs with anticholinergic properties. The rationale for using anticholinergic drugs in the treatment of overactive bladder syndrome is to block the parasympathetic acetylcholine pathway and thus abolish or reduce the intensity of detrusor muscle contraction. Action via the sensory pathway allows the anticholinergic agent to modulate afferent innervations in the urothelium, thereby altering sensory feedback during filling phase. A potential secondary mechanism of action has been proposed whereby antimuscarinics exhibit a direct local effect on subtype M_2 of the muscarinic receptor in the urothelium, in addition to the indirect effect brought about the sensory nerve pathways. On the other hand, there is some evidence to suggest that the use of vaginal estrogens leads to changes in autonomic and sensory vaginal innervation density within the vagina and may reverse urothelial damage, inflammatory cells infiltration, and bladder muscular atrophy. Estrogens may inhibit the function of Rho-kinas in bladder smooth

muscle, and hence effect smooth muscle contraction, whilst having no effect on its expression [33-36].

Pharmacotherapy of LUTS has been developed to optimize neural control of the lower urinary tract in pathologic states. The bladder can be overactive or underactive. There is no effective pharmacotherapy for underactive bladder [1].

Several treatment options are available for OAB including bladder and behavioral training, pelvic floor muscle training, pharmacologic treatment, and surgical therapies (Table IV).

Pharmacotherapy for the OAB must be individualized based on the degree of bother, medication side-effect profile, concomitant comorbidities and current medication regimen [1].

Oral antimuscarinics or β_3 -adrenergic receptor agonists represent the mainstay of pharmacologic treatment for the management of OAB (Table V and VI).

Anticholinergics dampen the amplitude of bladder contractions, improving bladder capacity and reducing involuntary detrusor contractions, urgency, and frequency. The mechanism of action and side effect profile of these drugs relate to their pharmacology. Anticholinergic medications inhibit the effects of the neurotransmitter acetylcholine in the peripheral and central nervous system by blocking either nicotinic or muscarinic receptors. Five types of muscarinic receptors have been identified (M_{1-5}), with varying distribution in tissues. Muscarinic receptors are distributed in the cardiac muscle, smooth muscle, the CNS, on presynaptic autonomic nerves, and at autonomic ganglia. Activation of the muscarinic receptors inhibits the release of noradrenalin from the nerve terminal. Due to their mechanism of action, anticholinergics should be used with caution or may be contraindicated in patients with urinary retention, gastric stasis or other conditions with severe impairment of intestinal motility, and uncontrolled narrow-angle glaucoma [7].

Selective anticholinergics have relatively more affinity for M_2 and M_3 muscarinic receptors, which are the most prevalent in the bladder, reducing side effects in the other body systems (Table VI) [37-40].

All of anticholinergics are recognized to be effective in the improvement of OAB symptoms and have an acceptable safety profile. Objective efficacy of anticholinergic drugs for OAB showed similar benefits. Antimuscarinics provide better efficacy in OAB treatment compared with placebo, but no clear differences in efficacy between antimuscarinics were found. A systematic review and meta-analysis of 83 studies ($n = 30\ 699$ women) and six different drugs (fesoterodine, oxybutynin, propiverine, solifenacin, tolterodine and trospium), has demonstrated the overall efficacy of antimuscarinic medication, favoring active treatment over placebo (RR from 1.3 to 3.5). Antimuscarinic therapy has been demonstrated to be statistically sig-

Tab. IV. Overactive bladder: treatment options [9]

First-line treatments:

- Clinicians should offer behavioral therapies (e.g. bladder training, bladder control strategies, pelvic floor muscle training, fluid management) as first-line therapy to all patients with overactive bladder. *Standard (Evidence Strength Grade B)*
- Behavioral therapies may be combined with pharmacologic management. *Recommendation (Evidence Strength Grade C)*

Second-line treatments:

- Clinicians should offer oral anti-muscarinics or oral β_3 -adrenoceptor agonists as second-line therapy. *Standard (Evidence Strength Grade B)*
- If an immediate release (IR) and an extended release (ER) formulation are available, then ER formulations should preferentially be prescribed over IR formulations because of lower rates of dry mouth. *Standard (Evidence Strength Grade B)*
- Transdermal (TDS) oxybutynin (patch [now available to women aged 18 years and older without a prescription]* or gel) may be offered. *Recommendation (Evidence Strength Grade C)*
- If a patient experiences inadequate symptom control and/or unacceptable adverse drug events with one antimuscarinic medication, then a dose modification or a different antimuscarinic medication or a β_3 -adrenoceptor agonist may be tried. *Clinical Principle*
- Clinicians should not use antimuscarinics in patients with narrow-angle glaucoma unless approved by the treating ophthalmologist and should use antimuscarinics with extreme caution in patients with impaired gastric emptying or a history of urinary retention. *Clinical Principle*
- Clinicians should manage constipation and dry mouth before abandoning effective antimuscarinic therapy. Management may include bowel management, fluid management, dose modification or alternative antimuscarinics. *Clinical Principle*
- Clinicians must use caution in prescribing antimuscarinics in patients who are using other medications with anti-cholinergic properties. *Expert Opinion*
- Clinicians should use caution in prescribing antimuscarinics or β_3 -adrenoceptor agonists in the frail overactive bladder patient. *Clinical Principle*
- Patients who are refractory to behavioral and pharmacologic therapy should be evaluated by an appropriate specialist if they desire additional therapy. *Expert Opinion*

Third-line treatments:

- Clinicians may offer intradetrusor onabotulinum toxin A (100 U) as third-line treatment in the carefully-selected and thoroughly-counseled patient who has been refractory to first- and second-line overactive bladder treatments. The patient must be able and willing to return for frequent post-void residual evaluation and able and willing to perform self-catheterization if necessary. *Standard Option (Evidence Strength Grade B C)*
- Clinicians may offer peripheral tibial nerve stimulation (PTNS) as third-line treatment in a carefully selected patient population. *Recommendation (Evidence Strength Grade C)*
- Clinicians may offer sacral neuromodulation (SNS) as third-line treatment in a carefully selected patient population characterized by severe refractory overactive bladder symptoms or patients who are not candidates for second-line therapy and are willing to undergo a surgical procedure. *Recommendation (Evidence Strength Grade C)*
- Practitioners and patients should persist with new treatments for an adequate trial in order to determine whether the therapy is efficacious and tolerable. Combination therapeutic approaches should be assembled methodically, with the addition of new therapies occurring only when the relative efficacy of the preceding therapy is known. Therapies that do not demonstrate efficacy after an adequate trial should be ceased. *Expert Opinion*

Additional treatments:

- Indwelling catheters (including transurethral, suprapubic, etc.) are not recommended as a management strategy for overactive bladder because of the adverse risk/benefit balance except as a last resort in selected patients. *Expert Opinion*
- In rare cases, augmentation cystoplasty or urinary diversion for severe, refractory, complicated overactive bladder patients may be considered. *Expert Opinion*

Follow-up:

- The clinician should offer follow-up with the patient to assess compliance, efficacy, side effects and possible alternative treatments. *Expert Opinion*

nificantly more effective in reducing the incidence of incontinence episodes, micturitions and urgency episodes per day and demonstrated notably higher return to continence. Cochrane review of 61 trials including 11 956 patients, agreed with these findings and there was a significantly greater cure or improvement rate in the antimuscarinic group when compared with placebo (RR = 1.39). There was also a significant improvement in QoL suggesting that these findings had clinical significance [41, 42].

Extended-release formulations offered advantages in terms of efficacy and safety compared with immediate release formulations. There was no clinically relevant difference in efficacy between treatments, and

that in terms of adverse events, high dosages of oxybutynin and propiverine were associated with a greater risk of adverse events [41, 43-45].

Of the 7 244 501 patients over 45 years old with an OAB diagnosis, a quarter of these were treated; 75.6% went untreated. About 75% of those treated were women [46].

In 2009, adult women made 516.8 million outpatient office visits in the USA. Of these, 8.1 million (1.6%) were associated with an OAB anticholinergic medication (annual rate 68 per 1000 women). Women who used anticholinergics were predominantly insured (61.0%) and were older than those not using anticholinergic medications (70.0 vs. 53 years old). Tolterodine

(33.8%) and oxybutynin (33.1%) were the most commonly reported medications, followed by solifenacin (19.5%), darifenacin (9.3%), and trospium (4.4%). Long-acting anticholinergics were used more often than short-acting medications (53.8% vs. 46.3%) [47].

Despite efficacy of anticholinergics, some patients do not respond optimally to overactive bladder treatment. The incidence of antimuscarinic-induced adverse events is relatively high. Dry mouth, dry eyes, constipation, impaired cognition and blurred vision are the most commonly reported adverse events and for these reasons many patients often discontinue anticholinergic therapy. For a patient to persist under treatment, she must be satisfied with it, so a proper balance between tolerability, efficacy, and cost is required. Therefore persistence rates with antimuscarinic therapy are low, with lack of efficacy and adverse events among the most frequent reasons for discontinuation. A study based on prescription data from the United Kingdom estimated that discontinuation rates at 12 months for OAB patients on antimuscarinics ranged between 65% and 86% [37-40] (Table VII).

Castro *et al.* reported that in patients with intolerance of antimuscarinics (77% of women, mean age 61.1 ± 11.2 years) in 69% of cases it was decided by the physician and in 31%, it was patient's decision to switch therapy. Reasons for switching were lack of clinical benefit (60%), side effects (24%), patient's request (8%), non-compliance (6%) and other (2%). About half of reviewed complied with the new treatment. Over 65% showed improvement with respect to their previous treatment, 60% were quite/very satisfied with current treatment, 91% preferred it to their previous treatment and 93% reported that their symptoms had improved [13].

The choice of anticholinergic therapy should be considered by an individual patient taking into account comorbidities and the harms profile. Combination therapy does not have a clear advantage over one therapy alone. Dose escalation does not improve objective parameters and causes more anticholinergic adverse effects, however it is associated with improved subjective outcomes. To decrease side effects, switching to a lower dose or using an extended release formulation or a transdermal delivery mechanism should be always considered [48, 49].

Estrogen has been used for decades in treatment of OAB and UUI, yet much of the evidence to support this use has come from uncontrolled observational studies utilizing a wide range of estrogen preparations, doses, and routes of administration. We have strong evidence that long-term oral estrogen therapy found to improve subjective and objective symptoms of urgency and mixed urinary incontinence over placebo. Secondary analysis of the HERS trial showed no difference in daytime frequency or nocturia between users and non-

Tab. V. Current US Food and Drug Administration (FDA) approved medications for overactive bladder treatment [82]

Medication	FDA approval
Oxybutynin ER	June 1999
Tolterodine tartrate ER	December 2000
Transdermal oxybutynin	March 2004
Trospium chloride IR	May 2004
Solifenacin	November 2004
Darifenacin	December 2004
Trospium chloride ER	August 2007
Fesoterodine	October 2008
Oxybutynin chloride gel 10%	January 2009
Oxybutynin chloride gel 3%	July 2011
Mirabegron	June 2012
Onabotulinum toxin A	January 2013

ER – extended release, IM – immediate release

users of systemic HRT. Currently, the literature does not support the use of systemic estrogen to treat OAB. Therefore, systemic estrogen therapy should not be recommended for the treatment of postmenopausal overactive bladder syndrome or stress urinary incontinence given the lack of evidence of therapeutic benefit – effects of hormonal replacement therapy are comparable to placebo. There is growing evidence to recommend using topical vaginal estrogen in postmenopausal women suffering from vaginal atrophy and symptoms of overactive bladder. Topical vaginal estrogen therapy was associated with statistically significant improvements in all outcome variables including diurnal and nocturnal frequency, urgency, number of incontinence episodes, first sensation to void and bladder capacity. It was documented that using CEE 0.625 mg vaginal cream significantly reduced the incidences of urinary frequency and nocturia, but made no significant change in urge incontinence. Intravaginal deposit of estradiol or estriol caused a subjective improvement in symptoms of overactive bladder. Estriol was found to significantly reduce urinary urgency, but not frequency or nocturia in women with de novo symptoms of overactive bladder after surgical treatment of stress incontinence. There is also evidence from randomized, controlled trials that using 17β-estradiol 25 mg vaginal tablet daily for 12 weeks significantly reduced the number of women with uninhibited bladder contractions, sensory urgency, but not frequency or nocturia, in postmenopausal women compared to placebo. There were net benefits to estrogen application after vaginal surgery, with decreased prevalence or severity of urinary frequency and urgency and other objective signs of atrophy. Therefore, vaginal

Tab. VI. Selected medications used for therapy of overactive bladder and their effects on various body systems/organs [7]

Anticholinergics										
Medication	Dosage and administration	Muscarinic receptor affinity					Main side effects			
		M ₁	M ₂	M ₃	M ₄	M ₅	Dry mouth	Constipation	Cognitive	Other
Oxybutynin IR	2.5-5 mg bid/tid	+	+	+	+	+	+++	++	++	
Oxybutynin ER	5-30 mg/day	+	+	+	+	+	++	++	++	
Oxybutynin patch	1 patch/twice weekly (3.9 mg/day) Rotate application site	+	+	+	+	+	+	+	No effect	
Oxybutynin gel	1 g/skin/daily (abdomen, thighs or upper body) Rotate application site and cover with clothing to avoid transfer	+	+	+	+	+	+	+	No effect	Skin irritation
Solifenacin	5-10 mg/day				+		+	+	No effect	
Darifenacin	7.5-15 mg/day				+		+	+/++	No effect	
Fesoterodine	4-8 mg/day	+	+	+		+	+	+	No effect	
Propiverine IR	15 mg/bid	+	+	+	+	+	+	++	Limited data	
Propiverine ER	30 mg/day	+	+	+	+	+	+	++	Limited data	
Tolterodine IR	1-2 mg/bid	+	+	+		+	+	+	No effect	Prolonged Qt interval (dose > 8 g/day)
Tolterodine ER	2-4 mg/day	+	+	+		+	+	+	No effect	
Trospium	IR: 20 mg/bid ER: 60 mg/day (take on empty stomach 1 hr before meal)	+	+	+	+	+	++	+	No effect	
Non-antimuscarinic treatment for overactive bladder										
Medication	Dosage and administration	Mechanism/site of action				Main side effects				
Mirabegron	25-50 mg/day	β ₃ -adrenergic receptor antagonist				Low incidence: • Hypertension • Tachycardia • Headache • Urinary tract infections • Constipation or diarrhea • Nasopharyngitis				
Botulinum toxin A	100-200 U (idiopathic OAB) 200-300 U (neurogenic OAB)	Presynaptic motor neuron				• Urinary retention • Clean intermittent catheterization (occasionally) • Hematuria • Urinary tract infections				
Tricyclic antidepressant	Starting dose: – Imipramine 10 mg/bid – Amitryptiline 10-20 mg/day	Multiple receptors in CNS Direct action on detrusor muscle				• Anticholinergic like side effects (dry mouth, blurred vision, constipation, urinary retention) • Tremor • Arrhythmia • Nausea				
Desmopressin	0.1-0.2 mg/day	Renal collecting ducts Aquaporin-2-mediated				• Hyponatremia • Cardiac failure • Hypertension				

estrogen may be recommended for the management of urinary urge incontinence for subjective improvements in overactive bladder syndrome symptoms in postmenopausal women and vaginal atrophy [30, 49-53].

The synergistic value of topical estrogen therapy with an anticholinergic agent for the treatment of OAB symptoms is unclear. For women with OAB, both the vaginal estradiol ring and an immediate-release

Tab. VII. Persistence (%) with prescribed antimuscarinic therapy for overactive bladder – one year’s observation [7, 40]

	Anticholinergics								
	Solifenacin	Darifenacin	Tolterodine IR	Tolterodine ER	Propiverine	Oxybutynin IR	Oxybutynin ER	Trospium	Flavoxate
Treatment persistence at 3 months	58	52	46	47	47	40	44	42	28
Treatment persistence at 12 months	35	17	24	28	27	22	26	26	14

oral anticholinergic (oxybutynin 5 mg by mouth twice daily) similarly improved urinary urgency, frequency, or urgency urinary incontinence, although the oral anticholinergic demonstrated a higher rate of side effects (constipation, dry mouth, blurry vision) and discontinuation compared with vaginal estrogen. Nelken *et al.* reported that women who received oxybutynin had a mean decrease of 3.0 voids per day as compared to a decrease of 4.5 voids per day in a group using the estradiol ring although the difference between the study groups was not significant. In women with OAB treated with tolterodine alone or with tolterodine and vaginal estrogen combined therapy (tolterodine 2 mg twice a day was used in both groups, vaginal estrogen was administered twice weekly), antimuscarinic and vaginal estrogen showed more improvement in mean daytime frequency, voided volume, and QoL as compared to the tolterodine arm patients. Whilst there was a trend to improvement in symptoms of nocturia, urgency and urgency incontinence, these findings were not significantly different between the groups. However, another study comparing tolterodine ER 4 mg daily to tolterodine ER 4 mg daily plus daily estriol application showed no difference in efficacy of treatment between groups after a 12-week period. Interestingly, those women who were subsequently found to have a urodynamic diagnosis of detrusor overactivity were found to have an overall poorer outcome in terms of efficacy suggesting that some of the improvement in symptoms may simply be due to improving urogenital atrophy [7, 54-57].

Antimuscarinic therapy may act synergistically with conservative therapy. There was more subjective improvement of overactive bladder symptoms when anticholinergics were compared with bladder training alone, and anticholinergics combined with bladder training were compared with bladder training alone. A Cochrane review of 13 trials including 1770 patients has demonstrated that symptomatic improvement is more common among patients who are on antimuscarinic therapy compared with bladder retraining (RR = 0.73). Combined therapy correlated with higher levels of improvement than bladder training alone (RR = 0.55) In addition, a larger improvement was observed with an antimuscarinic therapy/bladder retraining combination compared with

antimuscarinic therapy alone (RR = 0.81), but the difference was not statistically significant [58-60].

The anticholinergics have been suggested in theory to induce angle-closure glaucoma by narrowing the angle of the anterior chamber, by pupillary dilatation, and by forward movement of the iris-lens diaphragm. Although they can precipitate angle closure glaucoma by a pupillary block mechanism, they are not contraindicated in open-angle glaucoma or in angle-closure glaucoma that has already been treated. A 4-week course of solifenacin succinate treatment in women with OAB seemed to have no clinically significant effect on intraocular pressure, but further larger studies are needed to determine the effect of anticholinergics on anterior chamber parameters and to evaluate their safety in glaucoma patients [61, 62].

Another major concern over OAB treatment of elderly patients is the risk of cognitive side effects due to the pharmacologic treatment with anticholinergic drugs. Older people may be more vulnerable to the effects of antimuscarinic agents because of age-related reductions in cholinergic receptors. The rationale for this is the aging brain characteristic of presenting an overall deficiency in cholinergic neurotransmission – a mechanism necessary for multiple cognitive processes involved in short-term memory [63].

Some individual drug characteristics can influence the possible cognitive impairment in elderly patients as the drug affinity for the muscarinic receptor in the central nervous system, the permeability of the blood-brain barrier, individual ability for drug metabolism and elimination, and simultaneous use of medical therapy for other conditions with antimuscarinic properties. Elderly patients are at a higher risk in the need to use multiple medications for different health conditions. Many medications present an associated antimuscarinic property and should be carefully evaluated when treating these patients in order not to exacerbate the effect and so augment the risk of adverse cognitive events. The most commonly used medications by the elderly population with this property are antiparkinsonian medications, antidepressants (especially the tricyclic ones), antihistamines, bronchodilators, antispasmodics, and antiarrhythmic medications. The permeability of the blood-brain barrier increases with age, Alzheimer’s dis-

ease, diabetes, and multiple sclerosis, increasing the potential for CNS effects of antimuscarinic agents. Some of the cognitive effects that patients can develop are usually impaired attention, delayed memory, altered visuo-spatial orientation, dizziness and somnolence. Among antimuscarinic drugs available for treatment of OAB patients it is well established that oxybutynin has significant potential for adverse effects on cognition in the cognitively intact older patient. Oxybutynin has a high propensity to cross the blood-brain barrier, and has been associated with cognitive impairment in the elderly, most likely as a result of central anticholinergic activity mediated mainly via M_1 and M_2 receptors in the CNS. The newer drugs (solifenacin, darifenacin, trospium, fesoterodine and tolterodine) have not been associated with this kind of adverse event in this specific population, having been demonstrated to be effective and safe. Solifenacin had no detectable effect on cognition and may be an adequate anticholinergic choice for elderly overactive bladder syndrome patients and patients with pre-existing mild cognitive dysfunction or impairment, however, many clinicians are therefore wary of prescribing antimuscarinics to elderly patients, despite their documented efficacy [49, 63, 64].

Although older patients do complain more from drug treatment side effects and the fact that drug treatment for OAB demonstrates a low persistence rate, elderly patients were found to be more compliant to medical treatment and medication for OAB symptoms than younger ones [40].

Management of OAB in vulnerable elderly people, defined as individuals aged more than 65 years who are at risk for the increased functional decline or death over a 2-year period, can be difficult because of the altered bladder function that impacts drug processing and the increased polypharmacy associated with concomitant conditions, which increases with advancing age. In addition, management is confounded with concomitant conditions, including neurological diseases wherein inherent bladder differences appear. Therefore, the choice of treatment in elderly people should take into account the risks of drug-drug interactions, metabolic changes and the potential for adverse effects [3].

Intravesical botulin toxin injection and sacral nerve and posterior tibial nerve stimulation are alternative therapeutical options for patients with overactive bladder syndrome unresponsive to conservative options, anticholinergics, or vaginal estrogen [49].

Mirabegron

Pharmacotherapy for OAB has been predominantly focused on blocking the postsynaptic muscarinic receptors on the detrusor muscle, to decrease involuntary detrusor contractions. Their use may be limited by efficacy, tolerability, and long-term compliance. The an-

ticholinergics are generally comparable regarding efficacy and have a similar core side effect profile relating to their mechanism of action [7].

Subsequent numerous anticholinergic formulations have been developed to improve compliance/persistence by reducing the required dosing frequency and minimizing the side effect profile (Table V).

Unfortunately, the median time for persistence with the first line anticholinergic treatment was 6.53 ± 3.84 months. More than half of the OAB patients were not satisfied with their first line treatment anticholinergic treatment. Persistence was significantly higher in patients treated with anticholinergic medication with an extended-release formulation than in patients treated with immediate-release anticholinergics. The most common reasons for termination of treatment were healing/resolution of symptoms (35.9%), low effectiveness (30.9%) and side-effects (23.7%) [65].

Lee *et al.*, in a prospective, multicentre and randomized study which included 558 patients with the objective of evaluating symptom change after discontinuation of antimuscarinic therapy and retreatment rate, found that after 3 months of drug discontinuation there was a significant rise in urinary frequency, urgency, and incontinence episodes, with symptom scores starting to deteriorate significantly after one month from stopping drug intake. The study demonstrated that after 3 months without the antimuscarinic drug, 65% of the patients request retreatment [66].

Schneider *et al.* found in a study with 5,821 patients with multiple age ranges that the dose of antimuscarinic necessary to treat is probably higher with higher ages and also that the response to treatment was found to be lower in the older patients [67].

In the search for alternative OAB treatments with a novel target and an improved efficacy/tolerability profile to existing treatments, several classes of drugs with differing modes of action are under investigation in overactive bladder syndrome, based on an improved understanding of the complexity of bladder filling and emptying [68, 69].

The urinary bladder is innervated by both sympathetic and parasympathetic nervous systems. Activation of sympathetic nerves contributes to urine storage by relaxing the detrusor muscle through activation of β -adrenergic receptor (β -AR) [70].

Partial denervation of the detrusor (myogenic basis for OAB) might alter the properties of smooth muscle (denervation supersensitivity), leading to local contractions of small units of the detrusor (micromotion). It has been shown that these local contractions in the bladder wall precipitate a feeling of urgency and detrusor overactivity. Thus, β_3 -AR agonists might suppress myogenic local contractions through β_3 -AR in the detrusor, which eventually improve the symptom of urgency [70].

β_3 -adrenoceptor agonists (mirabegron, amibegron, solabegron) have emerged as a promising class of drugs;

the first novel OAB medication for many years. These agents avoid anticholinergic side effects by their alternative mechanism of action. Recent advances in the understanding of the physiopathology of OAB have identified three subtypes of β -adrenoceptor (β_1 , β_2 , and β_3) in the detrusor muscle and urothelium; β_3 -adrenoceptors predominate, accounting for 97% of total β -adrenoceptor messenger RNA [68, 69].

Mirabegron, the first β_3 -adrenoceptor agonist to enter clinical practice, shows high intrinsic activity for β_3 -adrenoceptors and very low intrinsic activity for β_1 - and β_2 -adrenoceptors. Compared with the anticholinergics, mirabegron causes a dose-dependent relaxation of the detrusor muscle during bladder filling, inhibits detrusor overactivity, improves the bladder storage capacity without impairing bladder contraction during voiding with no change in micturition pressure and residual urine volumes [7, 69].

β_3 -adrenoceptor agonists may offer an alternative to antimuscarinic therapy, while at the same time avoids or offers a better side-effect profile compared to anticholinergic agents. In addition, the introduction of a new class of drugs may offer the possibility of a combination therapy, which may minimize adverse events while maximizing efficacy [71, 72].

Several studies evaluated mirabegron in comparison to a placebo group and/or an active control group (tolterodine ER 4 mg) in a total of 9310 patients, over half of these were patients taking mirabegron. Inclusion criteria were similar across studies, generally requiring older patients (55.4-61 years) to have OAB symptoms for ≥ 3 months, ≥ 8 voids per day, and at least three urgency episodes over a three-day period. All studies focused on voids per day and incontinence episodes. Some studies also reported urge urinary incontinence, urgency episodes, and nocturia. Most studies included some measure of QoL [9, 68-71, 73-83].

The safety, tolerability, and superior efficacy compared with placebo was demonstrated with all three doses of mirabegron (25, 50 and 100 mg). Mirabegron 50 mg and 100 mg demonstrated statistically significant improvements compared with placebo in the mean number of incontinence episodes, voids per day, incontinence episodes and urgency episodes per 24 hours, mean micturition volume, and QoL outcomes. Improvements in UUI, urgency episodes, and QoL measures were not as consistently statistically significant. Among studies with an active control group administered tolterodine ER 4 mg/daily, mirabegron generally performed similarly to tolterodine. Rates of adverse events were similar with the exception of dry mouth, which was higher for the tolterodine ER 4 mg group. Changes in blood pressure and pulse rate were minor and comparable between agents, although pulse rate increases were dose-dependent across the mirabegron groups (from 0.6 to 2.3 beats per minute with increasing dose

vs. tolterodine 1.0 to 2.1 beats per minute). Rates of tachycardia were similar for mirabegron and tolterodine and comparable to those observed in the placebo group [9, 68-71, 73-83].

Mirabegron was well tolerated, and the overall rates of treatment-related adverse events were similar across all doses of mirabegron (25 mg, 50 mg, and 100 mg), placebo, and tolterodine-ER 4 mg. Mirabegron appears to be similar in efficacy to the antimuscarinics. The most common adverse events observed with mirabegron in clinical trials of up to 12 months were hypertension, headache, nasopharyngitis, and urinary tract infection, which were of comparable incidence with placebo and tolterodine. Bothersome anticholinergic side effects, such as dry mouth, in the mirabegron group were comparable with those in the placebo group and fivefold less frequent than for tolterodine extended release 4 mg group. Since dry mouth is the most bothersome AE associated with antimuscarinic drugs and often a reason for treatment discontinuation, mirabegron may be a valuable treatment option for these patients. Mirabegron may produce lower rates of constipation than some of the anti-muscarinics. This lower incidence of bothersome adverse events may provide a selection of medications for patients who already present with dry mouth and/or constipation or for patients who experience efficacy from the antimuscarinics but cannot tolerate these adverse events. The benefit of mirabegron in doses 50 or 100 mg was also evident in patients 65+ years of age, and in both treatment-naïve patients and those who previously discontinued antimuscarinic therapy. Assessment of measures of health-related quality of life and treatment satisfaction showed that patients perceived treatment with mirabegron as meaningful [9, 68-71, 73-83] (Table VIII).

Additional useful information is provided by a report of the National Institute for Health and Care Excellence in that it evaluated the mirabegron. National Institute for Health and Care Excellence (NICE) experts concluded that all medications, including mirabegron, have similar efficacy to reduce frequency. With regard to incontinence episodes, mirabegron and other medications also were similar with the exception of solifenacin (5 and 10 mg), which was statistically significantly more effective. In general, mirabegron has similar efficacy to the other antimuscarinics [73].

Mamman *et al.* found that solifenacin 10 mg ranked first in various analyses, in terms of efficacy (micturition, incontinence), among other antimuscarinics. Mirabegron 50 mg has similar efficacy against micturition, incontinence, and UUI compared with most of the approved OAB drugs used in Europe. Only solifenacin 10 mg showed a significantly superior efficacy (100% more effective) in the improvement of micturition and UUI episode frequency compared with mirabegron 50 mg. The improvement in the daily number of incontinence episodes with mirabegron 50 mg was not sig-

Tab. VIII. Adverse events (AEs) associated with antimuscarinic agents: incidence with mirabegron, placebo and tolterodine ER (4 mg). **A)** Data from SCORPIO, ARIES and CAPROCORN pooled analysis [69]. **B)** Summary of mirabegron clinical safety in two phase III studies [71, 79]. **C)** Selected AEs from 12 months mirabegron trial [58]

A)

Adverse event	Placebo	Mirabegron				Tolterodine ER (4 mg)	Systematic therapy and meta-analysis	
	n = 1380	n = 432	n = 1375	n = 929	n = 2736	n = 495	Antimuscarinic therapy	Placebo
%								
Any adverse event	47.7	48.6	47.1	43.3	46.0	46.7	53.4	39.9
Dry mouth	2.1	1.9	1.7	2.5	2.0	10.1	29.6	7.9
Pruritus	0.4	0/2	0.2	0.3	0.3	1.4	15.4	5.2
Constipation	1.4	1.6	1.6	1.6	1.6	2.0	7.7	3.9
Erythema	0.1	0	0.1	0.1	0.1	0.2	6.9	2.0
Vision blurred	0.2	0	0.1	0.4	0.2	0	3.8	2.6
Fatigue	1.0	1.4	1.2	0.8	1.1	1.8	1.6	0.6
Urinary retention	0.4	0	0.1	0	<0.1	0.6	1.1	0.2

B)

Phase III studies	Adverse events	Placebo	Mirabegron		Tolterodine ER (4 mg)
			50 mg	100 mg	
%					
European-Australian study	Dry mouth	2.6	2.8	2.8	10.1
	Constipation	1.4	1.6	1.6	2.0
	Hypertension	7.7	5.9	5.4	8.1
	Headache	2.8	3.7	1.8	3.6
	Urinary tract infections	1.4	1.4	1.8	2.0
	Any adverse events	43.3	42.8	40.1	46.7
American study	Dry mouth	1.5	0.5	2.1	
	Constipation	1.8	1.4	1.6	
	Hypertension	6.6	6.1	4.9	
	Headache	2	3.2	3.0	
	Urinary tract infections	1.8	2.7	3.7	
	Any adverse events	50.1	51.6	46.9	

C)

Adverse event	Mirabegron		Tolterodine ER (4 mg)
	50 mg	100 mg	
%			
Any adverse event	59.7	61.3	62.6
Hypertension	11.0	10.1	10.6
Cardiac arrhythmia	3.9	4.1	6.0
Corrected QT interval prolongation	0.4	0.2	0.4
Constipation	2.8	3.0	2.7
Dry mouth	2.8	2.3	8.6
Urinary tract infections	5.9	5.5	6.4
Dizziness	2.7	1.6	2.6

nificantly different from improvements with tolterodine 4 mg, oxybutynin 10 mg, darifenacin 7.5 mg and 15 mg, and fesoterodine 4 and 8 mg. Mirabegron 50 mg was statistically superior to placebo with a mean difference estimated at 0.493 incontinence episodes per day. Solifenacin 5 mg had a probability of 97% of being more effective in reducing the number of incontinence episodes compared with mirabegron. An equal probability was estimated for solifenacin 10 mg. Mirabegron 50 mg was significantly less efficacious than solifenacin 10 mg and did not differ significantly from other antimuscarinics. Mirabegron 50 mg had an incidence of dry mouth reported by patients similar to placebo. All antimuscarinics were associated with a significantly higher risk of dry mouth compared with mirabegron 50 mg. The OR for the occurrence of dry mouth with antimuscarinics compared with mirabegron 50 mg ranged from 4.213 with solifenacin 5 mg to 40.702 with oxybutynin IR 15 mg. Mirabegron and tolterodine had similar effects on micturition and incontinence, but mirabegron was well tolerated with an incidence of dry mouth comparable with placebo and lower than tolterodine. This is an important finding because dry mouth has been reported to be a frequent cause of treatment discontinuation. The incidence of constipation associated with mirabegron 50 mg was comparable with placebo. Other antimuscarinics except darifenacin 15 mg, fesoterodine 8 mg, solifenacin 5 mg, solifenacin 10 mg, and trospium 60 mg had similar incidences of constipation. These five treatments were associated with significantly greater risks of constipation compared with mirabegron 50 mg with ORs ranging from 1.91 with fesoterodine 8 mg to 4.23 with solifenacin 10 mg. Blurred vision is a relatively rare adverse event, and no significant difference in risk of developing blurred vision was found between treatments [84] (Table IX).

There are limited data on the use of mirabegron in patients with significant comorbidities, such as cognitive impairments, glaucoma, or uncontrolled hypertension [9].

Mirabegron has two other safety advantages over antimuscarinic drugs. First, the most commonly observed central nervous system AEs in patients receiving antimuscarinic drugs are headache, somnolence, and cognitive impairment, which explain the expression of all five muscarinic receptor subtypes (M_1 - M_5) in brain tissue and the possibility of blood-brain barrier penetration. Therefore, mirabegron could be helpful in cognitively impaired patients. Mirabegron decreases the frequency of rhythmic bladder contractions during the filling phase without suppressing amplitude during micturition. Therefore, it could also be useful for treating OAB symptoms associated with bladder outlet obstruction (BOO), with a lower risk of voiding difficulty than with antimuscarinic agents. The favorable efficacy/tolerability ratio of mirabegron suggests that this new therapeutic class could be considered as first-line treatment of OAB, specifically in cognitively impaired and OAB

patients with symptoms associated with postvoiding residual volume due to bladder outlet obstruction [74].

The recommended starting dose of mirabegron is 50 mg once daily in Japan and Europe; in the USA, the recommended starting dose is 25 mg once daily, which can be increased to 50 mg on an individual basis depending on efficacy and tolerability. The lower dose of 25 mg is recommended to patients with severe renal impairment (glomerular filtration rate 15 to 29 ml/min/1.73 m²), moderate hepatic impairment. Caution should be exercised in patients with bladder outlet obstruction and in those receiving concurrent anticholinergic therapy for overactive bladder, due to the potential risk of urinary retention [7].

Mirabegron 50 mg/day is likely to be cost effective compared with tolterodine ER 4 mg/day for adult patients with OAB from a UK NHS perspective. Total 5-year costs per patient were 1,645.62 British pounds for mirabegron 50 mg/day and 1,607.75 British pounds for tolterodine ER 4 mg/day (additional quality-adjusted life years treatment costs for mirabegron comes to up 37.88 British pounds) [85].

In the treatment of OAB, low-cost generic treatments are not necessarily more cost-effective than branded drugs, primarily because of a better efficacy and tolerability balance improves both symptom control and persistence. In a three-line sequence trial including two generic (oxybutynin first line and tolterodine extended-release second line) and one branded drug (solifenacin 5 mg third line) results in patient outcomes at costs similar to a sequence of branded drugs (mirabegron first line, solifenacin 5 mg second line, solifenacin 10 mg third line). Nazir *et al.* found that annual treatment costs per patient were similar for generic and branded antimuscarinic agents (1299 vs. 1385 British pounds), with no meaningful differences in incontinence episodes (103.6/1000 vs. 123.7/1000). Moreover it was observed that there was no significant differences in the number of patients with micturition lower than eight (228.7/1000 vs. 262.1/1000) [86].

Combining a β_3 -adrenoceptor agonist with an antimuscarinic agent may improve efficacy in OAB treatment. Combinations with reduced doses may deliver an improved tolerability profile compared with monotherapy, without compromising efficacy. Compared with solifenacin 5 mg monotherapy, all combinations with solifenacin 5 or 10 mg significantly improved mean micturition volume voided, with adjusted differences ranging from 18.0 ml to 26.3 ml. Combination therapy with solifenacin/mirabegron significantly reduced micturition frequency, and urgency compared with solifenacin 5 mg monotherapy. All combinations were well tolerated, without increasing bothersome adverse effects associated with antimuscarinic therapy compared with mirabegron or solifenacin monotherapy, with the possible exception of constipation [87].

Tab. IX. Antimuscarinics versus mirabegron (50 mg) comparison: change from baseline in the number of micturitions, incontinence episodes, urgency urinary incontinence episodes, occurrences of dry mouth and constipation [84]

Antimuscarinics versus mirabegron 50 mg (Credibility interval 1.0)				
Mean change from baseline	More effective than mirabegron		Less effective than mirabegron	
	Medication and dosage	Credibility interval	Medication and dosage	Credibility interval
Micturitions (24 hrs)	Solifenacin 5 mg	-0.24	Tolterodine 4 mg	0.15
	Solifenacin 10 mg	-0.58	Darifenacin 7.5 mg	0.07
	Oxybutynin 10 mg	-0.05	Darifenacin 15 mg	0.16
	Trospium 60 mg	-0.13	Fesoterodine 4 mg	0.07
			Fesoterodine 8 mg	0.14
26 studies 22 040 patients			PLACEBO:	0.70
Incontinence episodes (24 hrs)	Solifenacin 5 mg	-0.23	Tolterodine 4 mg	0.09
	Solifenacin 10 mg	-0.24	Darifenacin 7.5 mg	0.13
			Darifenacin 15 mg	0.09
			Fesoterodine 4 mg	0.10
			Fesoterodine 8 mg	0.22
17 studies 13 101 patients			Oxybutynin 10 mg	0.14
			PLACEBO:	0.50
Urge urinary incontinence episodes (24 hrs)	Fesoterodine 4 mg	-0.08	Tolterodine 4 mg	0.09
	Fesoterodine 8 mg	-0.22	Darifenacin 15 mg	0.04
	Oxybutynin 10 mg	-0.28		
	Solifenacin 5 mg	-0.3		
	Solifenacin 10 mg	-0.4		
18 studies 16 044 patients			PLACEBO:	0.44
	Medication and dosage	Odds ratio	Medication and dosage	Odds ratio
Dry mouth	None		Tolterodine ER 4 mg	4.23
			Tolterodine IR 4mg	7.3
			Darifenacin 7.5 mg	5.20
			Darifenacin 15 mg	8.4
			Fesoterodine 4 mg	4.6
			Fesoterodine 8 mg	9.98
			Oxybutynin ER 5 mg	4.22
			Oxybutynin ER 10 mg	7.05
			Oxybutynin ER 15 mg	8.16
			Oxybutynin IR 10 mg	14.63
			Oxybutynin IR 9 mg	11.17
			Solifenacin 5 mg	4.21
			Solifenacin 10 mg	10.30
			Trospium 40 mg	5.97
		Trospium 60 mg	4.85	
44 studies 27 309 patients			PLACEBO:	1.34
Constipation			Tolterodine ER 4 mg	1.10
			Tolterodine IR 4mg	1.02
			Darifenacin 7.5 mg	1.72
			Darifenacin 15 mg	3.15
			Fesoterodine 4 mg	1.06
			Fesoterodine 8 mg	1.91
			Oxybutynin ER 5 mg	2.45
			Oxybutynin ER 10 mg	1.01
			Oxybutynin ER 15 mg	2.16
			Oxybutynin IR 10 mg	1.55
			Oxybutynin IR 9 mg	0.99
			Solifenacin 5 mg	2.38
		Solifenacin 10 mg	4.24	
		Trospium 40 mg	1.69	
41 studies 25 257 patients			PLACEBO:	0.73

Conclusions

Overactive bladder is a common disorder affecting the quality of life of millions of women worldwide; unfortunately it is often easier to diagnose than to treat. Our improved understanding of the complex nature of the lower urinary tract functional unit enables us to develop appropriate therapies. Antimuscarinic drugs still are the mainstay of the pharmacological treatment for OAB. Knowledge about pharmacological properties of drugs used in treatment of OAB allows for tailoring therapy to each individual patient. Selective anticholinergics (e.g. solifenacin, darifenacin) have been introduced, increasing the therapeutic options available, and further improvements of antimuscarinics pharmacological profile are possible in the near future with novel

compounds and formulations. β_3 -adrenoreceptor agonist mirabegron may represent a new era in the treatment of patients with OAB. Moreover, it is expected that the class of β_3 -adrenergic receptor agonists will expand with the discovery and clinical development of novel agents. Short- and long-term therapeutic efficacy of solifenacin and mirabegron, modern and up to date option for treatment of OAB, was confirmed in numerous high reliability clinical trials. Good tolerance, elastic range of single therapeutic dose and high level of patient's acceptance gives the specialist a powerful and efficient tool for management of overactive bladder symptoms. A combination of solifenacin and mirabegron, agents with the different mechanism of action, gives a new treatment option for patients with OAB due to its favorable adverse event profile (Box 1).

Box 1. Selected overactive bladder treatment recommendation (NICE Guidelines; 2013) [73]

General principles when using overactive bladder drugs

- When offering antimuscarinic drugs to treat overactive bladder always take account of:
 - the woman's coexisting conditions (for example, poor bladder emptying)
 - use of other existing medication affecting the total anticholinergic load
 - risk of adverse effects
- Before overactive bladder drug treatment starts, discuss with women:
 - the likelihood of success and associated common adverse effects, and
 - the frequency and route of administration, and
 - that some adverse effects such as dry mouth and constipation may indicate that treatment is starting to have an effect, and
 - that they may not see the full benefits until they have been taking the treatment for 4 weeks
- Prescribe the lowest recommended dose when starting a new overactive bladder drug treatment
- If a woman's overactive bladder drug treatment is effective and well-tolerated, do not change the dose or drug

Choosing overactive bladder drugs

- Do not use flavoxate, propantheline and imipramine for the treatment of urinary incontinence or overactive bladder in women
- Do not offer oxybutynin (immediate release) to frail older women (with multiple comorbidities, functional impairments such as walking or dressing difficulties and any degree of cognitive impairment)
- Offer one of the following choices first to women with overactive bladder or mixed urinary incontinence:
 - oxybutynin (immediate release), or
 - tolterodine (immediate release), or
 - darifenacin (once daily preparation)
- If the first treatment for overactive bladder or mixed urinary incontinence is not effective or well-tolerated, offer another drug with the lowest acquisition cost (solifenacin, fesoterodine, oxybutynin (extended release), oxybutynin (transdermal), oxybutynin (topical gel), propiverine, propiverine (extended release), tolterodine (extended release), trospium and trospium (extended release))
- Offer a transdermal overactive bladder drug to women unable to tolerate oral medication
- For guidance on mirabegron for treating symptoms of overactive bladder, refer to Mirabegron for treating symptoms of overactive bladder (NICE technology appraisal guidance 290)

Reviewing overactive bladder drug treatment

- Offer a face-to-face or telephone review 4 weeks after the start of each new overactive bladder drug treatment. Ask the woman if she is satisfied with the therapy:
 - If improvement is optimal, continue treatment
 - If there is no or suboptimal improvement or intolerable adverse effects, change the dose, or try an alternative overactive bladder drug, and review again 4 weeks later
- Offer review before 4 weeks if the adverse events of overactive bladder drug treatment are intolerable
- Offer referral to secondary care if the woman does not want to try another drug, but would like to consider further treatment
- Offer a further face-to-face or telephone review if a woman's condition stops responding optimally to treatment after an initial successful 4-week review
- Review women who remain on long-term drug treatment for urinary incontinence or overactive bladder annually in primary care (or every 6 months for women over 75)
- Offer referral to secondary care if overactive bladder drug treatment is not successful
- If the woman wishes to discuss the options for further management (non-therapeutic interventions and invasive therapy) refer to the MDT and arrange urodynamic investigation to determine whether detrusor overactivity is present and responsible for her overactive bladder symptoms:
 - If detrusor overactivity is present and responsible for the overactive bladder symptoms, offer invasive therapy
 - If detrusor overactivity is present but the woman does not wish to have invasive therapy, offer advice as described in...
 - If detrusor overactivity is not present, refer back to the MDT for further discussion concerning future management

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