

# Diagnosis and Non-Surgical Management of Urinary Incontinence – A Literature Review with Recommendations for Practice

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**Abstract:** Urinary incontinence (UI) is a bothersome symptom with population studies suggesting a prevalence of 13.1% in women and 5.4% in men. While a significant cohort of patients with this complaint may ultimately require surgical management to achieve complete continence, a number of non-surgical measures exist to improve symptoms and quality of life. A range of guidelines exist on this topic, including those published by the European Association of Urology (EAU), the International Continence Society (ICS), the American Urological Association (AUA) and the UK's National Institute for Health and Care Excellence (NICE). The aim of our study is to provide an overview of the initial assessment of patients with UI including history taking, examination and basic investigations. Our review outlines non-surgical management strategies for UI, including conservative measures, behavioral and physical therapies and drug treatment. We shall also examine the above guidelines and present a narrative overview of the literature surrounding the diagnosis and non-surgical management of urinary incontinence.

**Keywords:** urinary incontinence, conservative, non-surgical, behavioral, physical, drug treatment

## Introduction

Urinary incontinence (UI) is the complaint of any involuntary leakage of urine. It is a common condition, which may have a significant negative impact on an individual's quality of life. Population studies suggest a prevalence of 13.1% in women and 5.4% in men.<sup>1</sup> UI may affect any individual of any age but most commonly affects men and women sixty years or older.<sup>1</sup> While there are an extensive range of potential etiologies in all age groups, our review shall specifically focus on non-neurogenic urinary incontinence affecting adult patients.

A number of guidelines exist, including those published by the European Association of Urology (EAU),<sup>2</sup> the International Continence Society (ICS),<sup>3</sup> the American Urological Association (AUA)/Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU)<sup>4-6</sup> and the UK's National Institute for Health and Care Excellence (NICE)<sup>7</sup> on the diagnosis and non-surgical management of non-neurogenic incontinence. Our goal is to provide a broad overview of the key components of the assessment and initial management of these patients.

UI may be classified in a number of ways based on the predominant symptom constellation and underlying pathophysiology. UI may be classified as stress UI,

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urgency UI or mixed UI, which contains symptoms of both stress and urgency UI. Other categories of UI include overflow incontinence, nocturnal enuresis, post-micturition dribble, continuous incontinence (as is often experienced with a vesicovaginal fistula), or insensible incontinence, where an individual may be unaware of how it occurred.

## Methods

A search of the Medline/PubMed electronic database was performed for dates up to February 2021. The search terms used included “urinary incontinence” and “diagnosis” or “non-surgical management” or “conservative management” or “drug treatment” or “behavioral therapy” or “physical therapy”. Further studies were chosen on the basis of manual searches of reference lists and review papers and from meetings of the European Association of Urology (EAU), the American Urological Association (AUA), the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) and the International Continence Society (ICS). Various guideline organizations were also searched for existing practice guidelines and systematic reviews on diagnosis and non-surgical management of urinary incontinence.

## Results

### History

History taking remains an integral component in elucidating possible underlying etiologies for and impact on the quality of life of an individual's UI. Details of a patient's UI should include duration and onset of UI and severity of symptoms (including impact on quality of life). It is critical to enquire about predisposing and aggravating factors, which may point towards etiology and guide initial conservative management by modifying reversible factors.

Predisposing factors include:

1. Female gender
2. Genetic predisposition
3. Race (The EPI study [Establishing the Prevalence of Incontinence] found that the prevalence of UI was significantly higher in white women than black women [33.1% vs 14.6%])<sup>8</sup>
4. Anatomical disorders (vesicovaginal fistula, urethral diverticulum, urethral fistula, bladder exstrophy or epispadias)
5. Diabetes mellitus

6. Pregnancy
7. Childbirth (increasing parity, assisted vaginal delivery including ventouse or forceps extraction)
8. Connective tissue disorders including Ehlers-Danlos syndrome
9. Pelvic, perineal or prostate surgery
10. Pelvic radiotherapy

Aggravating factors include:

1. Ageing
2. Cognitive deficits and poor mobility
3. Poor nutritional status
4. Increased fluid or excessive caffeine intake<sup>9</sup>
5. Obesity<sup>10</sup>
6. Smoking (may cause chronic cough and subsequent raised intra-abdominal pressure)<sup>11</sup>
7. Urinary tract infection (UTI)
8. Estrogen deficiency
9. Medications (including antipsychotics, diuretics and alpha-blockers, especially in women)<sup>12</sup>

It is important to enquire about “red flag” symptoms, which require further investigations, such as pain, hematuria, recurrent UTI or significant voiding or obstructive symptoms as these may indicate issues such as underlying malignancy, as well as to ask about bowel function and symptoms of sexual dysfunction and pelvic organ prolapse in women. In patients with cognitive deficits, it is imperative to obtain a collateral history from caregivers to identify potential risk factors for UI as outlined above.

### Questionnaires

It can be helpful to utilize a validated patient-completed questionnaire to assess initial symptoms and subsequently to monitor patient-reported outcomes following intervention. The most commonly used questionnaires in clinical practice are the ICIQ-UI short form for men and women to assess symptom score and quality of life. The ICIQ-FLUTS and ICIQ-MLUTS assess symptoms in female and male patients, respectively. Advantages of the ICIQ questionnaires are that they are validated across a range of populations and available in a number of different languages.<sup>13</sup> It should be remembered, however, that many health questionnaires and patient-reported outcome measures were developed and tested in patients with lower urinary tract symptoms, not specifically for UI, and should therefore be used with some caution in these populations.<sup>7</sup>

## Physical Examination

A chaperoned physical examination is a crucial component of the assessment of the patient with UI. Patients should be weighed and their body mass index recorded. In the supine position, an abdominal examination should be performed, particularly assessing for a palpable bladder or any abdominal masses.

In women, a pelvic examination should be performed initially in the supine position. It is important to inspect the introitus to glean whether it is well estrogenised or whether there is evidence of atrophic vaginitis. Ask the patient to cough or perform a Valsalva maneuver to elicit potential stress urinary incontinence. Pelvic tone may also be assessed and graded using the Oxford grading system.

The patient should then be asked to turn to the left lateral position, and the chaperone can assist in lifting the upper leg. A warm, lubricated Sim's speculum should be introduced into the vagina to assess pelvic organ prolapse. If a urinary tract fistula is suspected, it may be possible to palpate a defect or see urine pooling in the vagina.

Neurological examination in both sexes should include assessment of gait, anal tone, perineal sensation and lower limb function. Men should have a digital rectal examination performed to assess the prostate.

"Red flag" signs in either gender that require further investigation include urethral, bladder, or pelvic masses, hematuria, new neurological deficit and suspected fistula.

## Basic Investigations

UTI may exacerbate or cause UI. As such, a urinalysis should be performed on all patients presenting with UI and patients reassessed for UI symptoms following treatment of infection. Patients with persistent non-visible hematuria should also be assessed with cystoscopy and upper tract imaging. However, treating asymptomatic bacteriuria has not been shown to improve symptoms of UI in older nursing home residents.<sup>14</sup>

A bladder or voiding diary typically records the type and volume of fluid intake, incontinence episodes and number of pads used along with a recorded chart of urinary frequency and voided urine volume (ie functional bladder capacity). EAU guidelines recommend the use of a voiding diary of at least 3 days duration to reliably measure 24 hour and night-time urine volumes, day- and night-time frequency, urgency, UI episodes and mean voided volume.<sup>2</sup>

Post void residual volume (PVR) assessment can be considered in selected cases if there is concern about overflow incontinence in men with bladder outflow obstruction

or voiding dysfunction. EAU guidelines suggest there is no evidence to support the assessment of PVR in all patients with UI.<sup>2</sup>

Additional investigations that may be considered include perineal pad testing to quantify urine loss or urodynamic studies. Urodynamics may be considered for patients who have persistent UI or bothersome symptoms despite the non-surgical measures outlined below. They should also be performed if a neurological cause for the UI is suspected. The ICS standard urodynamic protocol includes clinical history, including symptom and bother score(s), examination, 3-day voiding chart/diary, representative uroflowmetry with post-void residual, and cystometry with pressure-flow study.<sup>15</sup> EAU guidelines suggest that urodynamic studies should be performed if the findings may change the choice of invasive treatment, and is not recommended in the evaluation of uncomplicated isolated urgency or stress incontinence.<sup>2</sup>

## Non-Surgical Management of Urinary Incontinence

### Conservative Management

Conservative management should be the starting point for any patient with UI. Conservative therapies are recommended as they can be effective and well tolerated and are usually associated with the least risk of harm. A stepwise approach to treatment of incontinence is typically recommended, beginning with addressing underlying medical issues and lifestyle modifications.

In patients with mixed incontinence, conservative management should be directed towards the most bothersome component of the patient's symptoms.

### Treatment of Co-Morbidities

Many elderly patients will suffer from multiple medical conditions that can be associated with lower urinary tract symptoms, including UI. By addressing and optimizing these underlying diseases, it is possible that urinary tract symptoms may improve. In patients with multiple co-morbidities, an individualized approach should be taken as it can be difficult to identify which condition is responsible for their symptoms. Some diseases that can impact on lower urinary symptoms are listed in the section above.

### Constipation

There is a strong association between constipation and UI.<sup>16,17</sup> A large observational study comparing women with UI and pelvic organ prolapse to controls found that

constipation was associated with both prolapse and UI.<sup>18</sup> In elderly patients, multimodal interventions, such as assisted toileting and managed fluid intake have been associated with a reduction in the occurrence of both UI and constipation.<sup>19</sup> Despite this clear association, however, there is no consistent evidence that treatment of constipation alone improves UI.

### Containment

When considering conservative management options, containment devices are an option, especially in patients who have failed or refused active treatment or who may not be suitable for the same. A wide variety of different containment devices are available including absorbent pads, urinary catheters, external collection devices, intravaginal devices for women and penile clamps for men. A useful resource for patients and health care professionals can be found at [www.continenceproductadvisor.org](http://www.continenceproductadvisor.org).

The type of containment device used can vary depending on patient preference and their degree of incontinence. A number of randomized controlled trials (RCTs) and systematic reviews (SRs) have been carried out to assess the various different containment devices on offer and are discussed below.

A SR by Brazzelli and colleagues compared different types of pads and found that pads with superabsorbent filling were superior to standard pads.<sup>20</sup> A two-week crossover RCT in men with UI showed that quality of life was better when using a condom sheath catheter compared to pads.<sup>21</sup>

McMurdo and associates compared pads to indwelling urethral catheters in elderly women and found that there was no difference in skin integrity score or dependency level at six months.<sup>22</sup> Saint et al carried out a randomized control trial in hospitalized men comparing condom and indwelling catheters and highlighted that there were no differences in rates of bacteriuria or symptomatic urinary tract infection. However, patients did find the condom catheter more comfortable and less painful.<sup>23</sup> A Cochrane review identified and summarized three RCTs comparing long-term indwelling catheters and showed no evidence that any one catheter type or material was superior to another.<sup>24</sup> A SR of non-randomized studies identified no difference in urinary tract infection outcomes between patients using suprapubic or urethral catheters, and as might be expected, patients with suprapubic catheters were less likely to suffer from urethral complications.<sup>25</sup>

The role of antibiotic prophylaxis in adults with catheters (indwelling or intermittent) has been investigated and

a Cochrane review summarizing some of these trials found that prophylaxis reduced the incidence of symptomatic UTI.<sup>26</sup> However, a further multicenter RCT highlighted the risk of the development of antibiotic resistance.<sup>27</sup>

Penile clamps can be effective in men with UI. A RCT found hinge type clamps to be more effective than circular clamps and they were also preferred by the participants.<sup>28</sup> A Cochrane review summarized seven trials comparing mechanical devices in women. This reported limited evidence that UI was reduced by intravaginal devices and that there was no difference in control of UI between intravaginal and intra-urethral devices.<sup>29</sup>

### Lifestyle Factors

Various lifestyle factors are associated with incontinence and modification of these factors may help improve symptoms. These include caffeine intake,<sup>9</sup> obesity,<sup>10</sup> smoking,<sup>11</sup> diet, and physical activity.

#### Caffeine Intake

Excessive consumption of caffeinated drinks, such as tea, coffee and cola, has anecdotally been associated with worse lower urinary tract symptoms. Despite this, a number of studies investigating this topic have shown that caffeine reduction does not improve incontinence. However, a recent review of 14 interventional and 12 observational studies has shown that a reduction in caffeine can reduce symptoms of frequency and urgency.<sup>30</sup>

#### Fluid Intake

Modification of fluid intake is commonly recommended to people with UI to help relieve their symptoms, but there is conflicting evidence to support this. A number of RCTs investigating this topic show inconsistent results.<sup>31,32</sup> An RCT by Hashim and colleagues showed that a reduction in fluid intake by 25% improved symptoms in patients with OAB but had minimal impact on UI.<sup>33</sup>

In general, advice should be based on 24-hour intake and output measurements with patients counselled to drink sufficient amounts to avoid thirst. Patients should be advised of the possibility of worsening constipation as a result of fluid restriction. Further investigation should be carried out in patients with low or high 24-hour urine output.<sup>2</sup>

#### Weight Loss

A number of epidemiological studies have shown that being overweight or obese is a significant modifiable risk factor for urinary incontinence.<sup>10,34,35</sup> The prevalence of

both stress and urgency urinary incontinence increases proportionally with a rising body mass index.<sup>36</sup> A number of studies highlight that weight loss improves UI.<sup>10,34,35</sup> Surgical weight loss is associated with a significant improvement in UI – at least two prospective studies have revealed that bariatric surgery was associated with a substantially reduced rate of UI at 11 months and 3 years.<sup>36,37</sup> Weight loss should be recommended as a first-line therapy for any overweight or obese patient with UI, particularly those with stress UI.

### Physical Exercise

Lower levels of UI have been seen in women who undertake moderate exercises, such as walking or swimming; however, it remains unclear whether regular exercise can prevent the development of UI.<sup>38,39</sup> Strenuous physical exercise such as running has been shown to increase the risk of stress UI during physical activity<sup>40,41</sup> and indeed, the presence of UI may prevent some women from exercising.<sup>42</sup> Three RCTs in the elderly, however, have shown that exercise, when used as a component in a multifactorial regime including pelvic floor exercises and weight loss can help improve UI.<sup>19,43,44</sup>

### Smoking

Smoking is often proposed as a risk factor for UI as it can increase coughing episodes. However, there is very weak evidence to suggest that smoking cessation improves urinary incontinence.<sup>45</sup> Despite this, smoking cessation is a general public health measure and should be recommended to patients.<sup>40,46</sup>

## Behavioral and Physical Therapies

The International Continence Society (ICS) defines behavioral therapy as a type of psychotherapy that attempts to modify observable maladjusted patterns of behavior by substituting a new response or set of responses to a given stimulus.<sup>47</sup> This method of treatment requires a self-motivated patient who is open to implementing re-training techniques in conjunction with an allied health professional. These behavioral and physical modifications have a role in almost all cases of UI and can be used alongside and in conjunction with other treatments.<sup>48</sup>

First-line treatment approaches include bladder training (BT), prompted voiding (PV), and pelvic floor muscle training (PFMT). Second- or third-line therapies such as electrical and magnetic stimulation (ES and EM,

respectively), percutaneous tibial nerve stimulation (PTNS) and acupuncture may also be considered.

### Bladder Training (BT)

This method seeks to regain continence by encouraging patients to progressively extend the time between voiding. BT may help individuals who are physically and mentally engaged, but it may take months to achieve symptom improvements. A Cochrane review including BT did not find enough rigorous evidence to prove its benefit but suggested that BT may be helpful in improving UI.<sup>49</sup> NICE guidelines advise maintaining treatment for a minimum of 6 weeks and using the therapy in combination with drugs if frequency is a troublesome symptom.<sup>7</sup>

### Prompted Voiding (PV)

Often part of a toileting program, this term implies that carers, rather than the patient, initiate the decision to void at scheduled intervals.<sup>50</sup> It can improve urinary continence in older adults and individuals with and without physical and cognitive impairments but requires extensive and continuous staff management techniques. The most responsive individuals are those who can maintain high levels of urinary continence between two and four hourly prompted voids.<sup>51</sup> EAU guidelines recommend offering PV to cognitively impaired adults with UI.<sup>50</sup>

### Pelvic Floor Muscle Training (PFMT)

This treatment classically involves sequential contraction and relaxation of the pelvic floor musculature with the goal of strengthening these supports and thus improving UI. NICE guidelines advise that PFMT programs should comprise at least 8 contractions performed 3 times per day.<sup>7</sup>

PFMT can cure or improve SUI and all other types of UI in women.<sup>52</sup> One RCT found that a high-intensity program of PFMT is superior at improving SUI in elderly women compared to BT alone.<sup>53</sup> There is some evidence that improving pelvic floor function may inhibit bladder contractions in patients with OAB.<sup>54</sup> The effect in mixed UI is lower than in women with pure SUI, but it may be augmented by combining the techniques with biofeedback.<sup>2</sup>

EAU guidelines point out that there are greater benefits seen with the addition of biofeedback and supervised high-intensity regimes. However, benefits are not maintained at fifteen-year follow-up.<sup>50</sup> NICE guidelines recommend offering a trial of supervised PFMT for at least 3 months as first-line treatment for women with SUI and continuing with an exercise program if it is beneficial.<sup>7</sup>



Regarding UI in men undergoing radical prostatectomy, a meta-analysis within a Cochrane review suggested that PFMT may speed recovery mainly between the third and sixth postoperative months but is unlikely to do so beyond 12 months after surgery.<sup>55</sup> A meta-analysis has suggested that there is no benefit derived from additional preoperative PFMT.<sup>56</sup>

To summarize, EAU guidelines strongly recommend offering supervised, intensive PFMT, lasting at least 3 months, as a first-line therapy for all women with SUI or MUI (including the elderly and post-natal) as well as instruction on PFMT for men undergoing radical prostatectomy to speed recovery from UI.<sup>50</sup>

## Electric Stimulation

ES with non-implanted devices using surface electrodes (skin, vaginal, anal) aims to inhibit contractions of the detrusor muscle, potentially reducing urinary frequency and urgency. The details and methods of delivery of ES vary considerably.

A 2016 Cochrane Review indicated that ES was better than PFMT, drug treatment and placebo or sham treatment at improving OAB symptoms of urinary frequency and urgency, but it was unclear if ES was more effective than placebo/sham for UI. The trials included were deemed to be of low quality.<sup>7</sup>

EAU and NICE guidelines do not recommend routinely offering ES alone for the treatment of SUI but advise that it can be considered for women who have difficulty contracting pelvic floor muscles to aid motivation and adherence to therapy.<sup>7,50</sup>

## Electrical Stimulation of the Posterior Tibial Nerve (PTNS)

PTNS delivers electrical stimuli to the sacral micturition center via the S2-S4 sacral nerve plexus. The technique requires the insertion of a fine needle, just above the medial aspect of the ankle. Treatment cycles typically consist of twelve weekly treatments of 30 minutes. Available evidence from two SRs shows that PTNS in isolation may improve the urgency of UI compared with sham and other treatments.<sup>58,59</sup>

## Acupuncture

This traditional Chinese technique is purported to improve UI by reinforcing qi (the vital substance constituting the human body) and promoting recovery of bladder function. The most commonly used acupoints are located above the

first, second and third sacral foramina, which lie over the first, second and third sacral nerve roots, respectively, and correspond to the segmental innervation of the parasympathetic nerve supply to the bladder.<sup>60</sup>

A Cochrane review demonstrated that acupuncture for SUI in adults might be beneficial, but sufficient evidence to determine whether acupuncture was more effective than drug treatment was lacking.<sup>61</sup> A recent study showed that electroacupuncture (EA) was effective in reducing SUI compared with sham electroacupuncture, and the effect persisted 24 weeks after treatment.<sup>62</sup>

In a systematic review with a meta-analysis of 10 RCTs including 794 patients, the authors reported that acupuncture may be effective in reducing OAB symptoms compared to sham treatment.<sup>63</sup> The studies were of low quality and compared EA to sham acupuncture, or EA plus tolterodine vs tolterodine alone. Nevertheless, acupuncture is comparatively well tolerated with few adverse reactions and is safe. In the future, studies with high methodological quality and larger sample sizes are required.

## Drug Treatment Estrogens

Estrogen receptors are widely distributed throughout the lower urinary tract, being present in the bladder, urethra, vagina, and pelvic floor musculature.<sup>64</sup> Estrogens influence female urinary continence mechanisms by increasing the density of the periurethral tissues, which account for one-third of urethral pressure.<sup>65</sup>

A Cochrane review published in 2012 found that significantly more women who received local (vaginal) estrogen for UI reported that their symptoms improved compared to placebo. The same review reported that trials investigating systemic estrogen administration found that women reported worsening of their urinary symptoms.<sup>66</sup>

## Antimuscarinics

Bladder function and detrusor contractility are primarily regulated by the acetylcholine signaling pathway via muscarinic receptors.<sup>67</sup> Among the 5 known subtypes of muscarinic receptors, only M2 and M3 subtypes are found in the bladder. Anticholinergic drugs competitively inhibit binding of acetylcholine to the muscarinic receptor and increase bladder storage capacity.<sup>68</sup>

Currently available antimuscarinics include oxybutynin, solifenacin, tolterodine, darifenacin, trospium chloride and fesoterodine. There is a lack of direct comparative

trials that could assist in selecting one antimuscarinic over another. Studies comparing short-acting oral oxybutynin with short-acting oral tolterodine demonstrated that the former is slightly more effective in controlling incontinence, but the latter has fewer anticholinergic side effects and is better tolerated.<sup>69</sup> EAU guidelines suggest that dose escalation of antimuscarinic drugs may be adequate in selected patients to cure or improve UI but with a higher risk of side effects. They also suggest that immediate-release formulations tend to be associated with more side effects compared with extended-release formulations and that the latter should be chosen where possible.<sup>2</sup>

A Cochrane review demonstrated that anticholinergics, as a class, are superior to placebo for treating urgency UI but was unable to demonstrate that any one agent was superior to another.<sup>70</sup> Similarly, Ouslander et al concluded that all of the anticholinergic drugs have similar efficacy.<sup>71</sup>

Since muscarinic receptors have a broad distribution throughout the body, administration of anticholinergic drugs can result in undesirable systemic side effects.<sup>68</sup> These can be immediate (confusion, delirium, headache, blurred vision, dizziness and hallucinations) or delayed (memory loss).<sup>72</sup> Different types of anticholinergics can have different side effects based on pharmacokinetic properties. For example, smaller molecules, neutral in charge and lipophilic, can easily traverse the blood–brain barrier leading to central nervous system side effects.

Concerns have been raised in more recent years about the reversibility of the cognitive effects of long-term anticholinergic use. Gray et al assessed 3434 patients aged 65 and older with no dementia at study entry who were treated with various anticholinergic medications including bladder antimuscarinics, first-generation antihistamines and tricyclic antidepressants. They demonstrated that higher cumulative anticholinergic medication use was associated with an increased risk of dementia.<sup>73</sup> It is imperative to warn younger patients in particular of this risk when prescribing bladder antimuscarinics.

A Cochrane Review of 5 of the 6 available anticholinergic drugs demonstrated that anticholinergics lead to statistically significant improvements in overactive bladder symptoms with fewer leakage episodes and voids compared to placebo.<sup>70</sup>

Discontinuation rates for anticholinergic drugs are high. D' Souza et al demonstrated that among patients treated with oxybutynin and tolterodine ER and IR, 1 year persistence rates were only 13.2%, with a median time to discontinuation of 31 days.<sup>74</sup> A large US survey of

>5000 patients demonstrated that the main reasons for drug withdrawal are typically tolerability of their symptoms or unmet treatment expectations, switching to a new antimuscarinic agent or adverse effects.<sup>75</sup>

Patients with past depressive disorder, urinary infection and polypharmacy have increased odds of early discontinuation.<sup>76</sup>

Absolute contraindications for anticholinergic use include urinary retention, gastric retention, uncontrolled narrow angle glaucoma, and known hypersensitivity to the individual drugs or any of their ingredients.

## Mirabegron

The beta-adrenoceptors (AR) are classified into beta(1), beta(2), and beta(3) subtypes. The predominant adrenoceptors in bladder tissue are  $\beta$ -3 adrenergic receptors ( $\beta$ -3 AR).<sup>77</sup> Beta3-AR mediates relaxation of human detrusor muscle and increases bladder capacity without influencing bladder contraction. Mirabegron is currently the only available  $\beta$ 3 agonist, which acts on beta<sub>3</sub>-adrenergic receptors to relax the detrusor.

Mirabegron was originally developed as a treatment for diabetes and in 2012 was approved by the FDA as a new class of drug used to treat overactive bladder symptoms.<sup>78</sup>

Mirabegron leads to one to two less incontinence episodes per day, similar to sustained-release tolterodine.<sup>79</sup> A systematic review with nearly 6000 patients demonstrated that mirabegron was effective in treating overactive bladder, with a greater decrease in incontinence episodes as well as reduced episodes of micturitions and urgency compared to placebo.<sup>80</sup> Compared to antimuscarinic agents, mirabegron as monotherapy has a similar efficacy with less side effects, which may explain the improved adherence and treatment longevity with mirabegron. Mirabegron may also be useful in men with both voiding and storage symptoms due to bladder outlet obstruction. In the RCT, Nitti et al found that mirabegron did not adversely affect voiding urodynamics compared with placebo after 8 weeks of treatment.<sup>81</sup>

The side effects of mirabegron are generally mild and well tolerated. The most frequent adverse events associated with mirabegron are nausea, diarrhea, constipation, dizziness, and headache. A less common adverse event of mirabegron is elevation in blood pressure and hence mirabegron should not be used in patients with uncontrolled hypertension. The effects of mirabegron on cognitive functions, pharmacokinetic interactions with other drugs, and long-term adverse events need to be further evaluated.<sup>82</sup>

## OAB Treatment in Elderly Patients

Since anticholinergics have similar efficacy, patient comorbidity is the main factor influencing the choice of medication. Elderly patients receiving anticholinergic drugs are at higher risk of confusion, falls and fractures, and therefore anticholinergics should be avoided in patients with dementia, cognitive dysfunction or delirium.<sup>82</sup>

Oxybutynin may worsen cognitive function in elderly patients, but solifenacin, darifenacin, fesoterodine and trospium have not been shown to cause cognitive dysfunction in elderly people in short-term studies.<sup>2</sup> As such, EAU guidelines advise that long-term antimuscarinic treatment should be used with caution in elderly patients, especially those who are at risk of, or have, cognitive dysfunction.<sup>2</sup>

Mirabegron may be considered in the elderly as an alternative to antimuscarinics. A meta-analysis by Wagg et al demonstrated that Mirabegron at a dose of 25 mg and 50 mg was effective and well tolerated in OAB patients aged  $\geq 65$  and  $\geq 75$  years.<sup>83</sup>

## Combination of Antimuscarinic and Beta-3 Agonist

The BESIDE study investigated improvements in OAB symptoms and refractory UI comparing mirabegron 50 mg plus solifenacin 5 mg versus solifenacin 5 or 10 mg alone. They demonstrated that significantly more patients treated with the combination of mirabegron and solifenacin achieved clinically meaningful improvements in incontinence and micturition frequency compared to solifenacin monotherapy alone, at either dose.<sup>84</sup>

## Duloxetine

Duloxetine is a potent serotonin (5-hydroxytryptamine, 5-HT) and noradrenaline re-uptake inhibitor with little or no affinity for cholinergic receptors. Duloxetine increases the levels of serotonin and norepinephrine in the pudendal motor nucleus and thereby increases bladder capacity and striated urethral sphincter activity.<sup>85</sup> Duloxetine increases urethral pressure and maximum urethral closure pressure and sphincter width after 8 weeks of treatment.<sup>86</sup>

Duloxetine was initially developed for use in patients with major depressive disorder and chronic pain. In 2004, duloxetine became the first medication approved for the treatment of women with moderate-to-severe stress urinary incontinence. Duloxetine is administered at 40 mg twice daily for up to 8 weeks, with minimal safety concerns for this duration.

However, no evidence is available on maintenance regimens. Cure rates of 10% may be achieved with doses of 80mg/d.<sup>2</sup>

EAU guidelines advise that duloxetine should be offered in selected patients with symptoms of SUI when surgery is not indicated. They also advise that duloxetine should be initiated and withdrawn using dose titration because of the high risk of adverse events, including GI upset and reports of suicidal ideation.<sup>50</sup>

## Desmopressin

Desmopressin is a synthetic analog of vasopressin, aka antidiuretic hormone. It is widely used in the treatment of diabetes insipidus and nocturnal enuresis. Vasopressin is produced by the posterior pituitary gland and secreted in states of hypovolemia and hyperosmolality, which facilitates the urine concentrating mechanism through interaction with vasopressin type 2 receptor.<sup>87</sup>

There has been growing interest in the use of desmopressin for the treatment of nocturia for whom nocturnal polyuria is prevalent. Desmopressin is available in formulations for oral, parenteral and nasal administration. Men usually benefit from a minimum of 50  $\mu$ g, whereas a dosage of 25  $\mu$ g orally disintegrating sublingual desmopressin appears to be ideal for women. Increasing doses of desmopressin reduces the number of nocturnal voids and voided volumes, as well as increasing the duration of the first sleep period.<sup>88</sup> In one study, desmopressin resulted in more than an hour of additional sleep before the first void and 0.72 fewer voids per night than those on placebo.<sup>89</sup>

Typical adverse effects of desmopressin include headache, hyponatremia, insomnia, dry mouth, hypertension, abdominal pain, peripheral edema and nausea. Among these, hyponatremia is the only potential life-threatening complication and therefore vasopressin is contraindicated in patients with baseline level of sodium less than 130 mmol/L. Since hyponatremia is usually encountered in individuals  $>65$  years old, particular attention should be paid when considering vasopressin in these patient populations.

## Conclusion

UI is a bothersome and distressing symptom, which can have a significant impact on patients, families and carers. Conservative and non-invasive measures are often effective in improving symptoms and should be tried in all cases in the first instance. Ideally, the combined use of these therapies should be utilized as part of a comprehensive and individualized treatment program for UI.



## Disclosure

The authors report no conflicts of interest in this work.

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