# Urinary incontinence in women

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## ABSTRACT

Urinary incontinence affects women of all ages. History, physical examination, and certain tests can guide specialists in diagnosing stress urinary incontinence, urgency urinary incontinence, and mixed urinary incontinence. First line management includes lifestyle and behavior modification, as well as pelvic floor strength and bladder training. Drug therapy is helpful in the treatment of urgency incontinence that does not respond to conservative measures. In addition, sacral neuromodulation, intravesical onabotulinumtoxinA injections, and posterior tibial nerve stimulation can be used in select patient populations with drug refractory urgency incontinence. Midurethral synthetic slings, including retropubic and transobturator approaches, are safe and efficacious surgical options for stress urinary incontinence and have replaced more invasive bladder neck slings that use autologous or cadaveric fascia. Despite controversy surrounding vaginal mesh for prolapse, synthetic slings for the treatment of stress urinary incontinence are considered safe and minimally invasive.

## Introduction

Urinary incontinence in women is a common and costly problem. Many treatment options are available, from simple lifestyle modifications to invasive surgery. This review describes the most common types of urinary incontinence, appropriate clinical investigations, and the treatment options available. Recent advances, including new pharmacologic and surgical therapies, have reshaped the treatment of incontinence. Overall, level I evidence supports the use of these treatments, and clinicians have a wide range of treatment options to choose from.

## Epidemiology and prevalence

The International Continence Society defines urinary incontinence as any involuntary leakage of urine.[1][2] Urinary incontinence is estimated to affect 200 million people worldwide.[3] The prevalence of urinary incontinence in women is variable in the literature, but it is reported to be as high as 55%.[4] This number may be an underestimate, because up to half of women may fail to report urinary incontinence to their healthcare provider.[5] This may be due to embarrassment, lack of knowledge about treatment options, or a belief that urinary incontinence is a normal inevitable part of aging.[6]

According to the 2010 International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report, stress urinary incontinence is defined as voluntary loss of urine on effort, physical exertion, or on sneezing or coughing.[2] Depending on age, the prevalence of stress incontinence ranges from 29% to 75%, with a mean of 48%.[7] The prevalence of daily stress urinary incontinence is 10% in community dwelling middle aged women.[8] A third of women with stress urinary incontinence report leakage weekly.[8]

Urgency urinary incontinence is defined as the involuntary loss of urine associated with urgency.[2] Urgency incontinence is part of a larger symptom complex known as overactive bladder syndrome, which is defined as urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious disease.[2] The National Overactive Bladder Evaluation (NOBLE) study, in which investigators conducted telephone interviews with more than 5000 adults, with a follow-up nested study, found the prevalence of overactive bladder syndrome to be 16.9% in women and 16% in men.[9] People with overactive bladder syndrome-dry (without leakage) have frequency and urgency without leakage, whereas people with overactive bladder syndrome-wet (with leakage) experience overactive bladder syndrome with urgency urinary incontinence. The overall prevalence of urgency urinary incontinence is estimated at 7-33%.[7] Women are more likely to experience urgency urinary incontinence (overactive bladder syndrome-wet) than men, with 9.3% of women experiencing this

condition versus 2.6% of men.[9] The prevalence of mixed urinary incontinence (both stress urinary incontinence and urgency urinary incontinence) ranges from 14% to 61%.[7]

## Socioeconomic burden

The burden of urinary incontinence is high in both human and financial terms.[10] Urinary incontinence has a negative impact on health related quality of life (HRQOL),[11] and it contributes to depression,[12 13] falls,[14] and admission to a nursing home.[15] The adjusted risk of nursing home admission with urinary incontinence is 2.0 for women and 3.2 for men.[15] The total annual cost of urinary incontinence in the United States is estimated to be as high as $32bn (£18.7bn; €23.5bn).[16] Furthermore, costs for women over the age of 65 years are twice those for their younger counterparts.[17] The cost of overactive bladder syndrome in the US alone has been estimated at $65.9bn.[18] Although costs of care include medical care and treatment, the largest contributor for urinary incontinence is the cost of pads, diapers, and bedding.[10 17]

## Risk factors

Established risk factors vary by type of urinary incontinence.

### Pregnancy and childbirth

Pregnancy and childbirth are established risk factors for stress urinary incontinence.[19] Although vaginal delivery and caesarean delivery increase the risk of stress urinary incontinence, the risk is higher in women who deliver vaginally. In a study of more than 15 000 women, the prevalence of urinary incontinence among nulliparous women was 10.1%, versus 15.9% in the caesarean delivery group and 21% in the vaginal delivery group.[20] This may be due to a combination of injury to the pelvic floor musculature and connective tissue, as well as nerve damage as a result of pregnancy and labor.

### Hysterectomy

Hysterectomy has been associated with the development of urinary incontinence,[21 22] particularly stress urinary incontinence.[19] Hysterectomy may damage the muscles of the pelvic floor and lead to incontinence, although this is poorly understood. Stress urinary incontinence has also been associated with vaginal prolapse, including cystocele (prolapse of the bladder), rectocele (prolapse of the rectum),[23] uterine prolapse,[24] and vaginal vault prolapse after hysterectomy, probably from the common risk factor of the weakening of the pelvic floor muscles. Weakening of the structures of the pelvic floor can contribute to both prolapse and incontinence, and the two problems may be inter-related because they often share a common cause.[25]

### Other risk factors

Recurrent urinary tract infection is independently associated with urgency urinary incontinence and is a readily treatable cause of this condition.[26] Higher body mass index[21 24] and advancing age[27] are associated with both stress and urgency urinary incontinence. Family history is important because women whose mothers or older sisters are incontinent are more likely to develop stress and mixed urinary incontinence.[28]

Smoking has been associated with urgency urinary incontinence in women,[29] possibly because of the irritative effects on the bladder. Smoking is also associated with chronic cough, which can contribute to stress urinary incontinence.[30] Caffeine has a diuretic effect and may also play a role in urgency urinary incontinence.[31] A cross sectional national survey of more than 4300 women found that daily caffeine intake of greater than 204 mg (roughly the amount of caffeine in one cup of coffee) was associated with a prevalence of 40% of any type of incontinence, most commonly stress urinary incontinence.[32] Many other factors increase the risk of urinary incontinence, and box 1 provides a summary of the levels of evidence for all established risk factors.

## Evaluation

Because of the lack of self reporting and the high incidence of urinary incontinence and bother, it could be argued that all women presenting to their primary care physician should be screened for symptoms of urinary incontinence.[34] However, professional organizations, such as the US Preventive Services Task Force (USPSTF) and the American Urological Association (AUA), provide no specific screening recommendations, and many women experience leakage that is infrequent and do not seek medical attention. Hence, screening for urinary incontinence is likely to be of maximum benefit to women whose quality of life is affected by urinary incontinence (box 2).

## History

The investigation of a patient with urinary incontinence should begin with a specific history. Associated urinary symptoms such as frequency, urgency, hematuria, recurrent urinary tract infections, and nocturia should be elucidated and explored. To tailor treatment to the individual, it is necessary to determine whether symptoms of stress, urgency, or both types of incontinence are present.[34] Symptom severity can be assessed by inquiry about daily pad usages, including pad size (pantiliner *v* menses pad *v* incontinence pads or diapers). It is important to ask about fluid intake because many women exacerbate symptoms by drinking six to eight glasses of water a day, regardless of thirst.[34] Symptoms of a vaginal bulge may indicate pelvic organ prolapse, which is highly associated with stress urinary incontinence and can also contribute to urgency urinary incontinence.[25]

## Questionnaires

Several validated tools are available to assess the severity of urinary incontinence and measure condition specific HRQOL. The urogenital distress inventory (UDI-6) and the incontinence impact questionnaire (IIQ-7) encompass the urinary domain components of the pelvic floor distress inventory-short form (PFDI-20) and the pelvic floor impact questionnaire short form (PFIQ-7). They are popular questionnaires among specialists and measure symptom severity and impact on HRQOL, respectively.[36]

Although no specific questionnaires are endorsed by professional societies in the US, the National Institute for Health and Care Excellence (NICE) recommends the use of:

- The international consultation on incontinence questionnaire (ICIQ)
- The Bristol female lower urinary tract symptoms questionnaire (BFLUTS)
- The incontinence quality of life questionnaire (I-QOL)
- The stress and urge incontinence and quality of life questionnaire (SUIQQ)
- The urinary incontinence severity score (UISS)
- The stress-related leak, emptying ability, anatomy, protection, inhibition, quality of life, mobility and mental status quality of life index (SEAPI-QMM)
- The incontinence severity index (ISI)
- The king's health questionnaire (KHQ).[35]

A systematic review by the symptom and quality of life committee of the International Consultation on Incontinence confirms the use of these questionnaires, all with a grade A recommendation.[37]

## Bladder diary

A bladder diary can be useful for quantifying symptoms and recording the number and type of episodes of urinary incontinence, and these diaries are recommended by both the AUA and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU).[38][39] A bladder diary will also record the voiding times and exact voided volumes (recorded by a "hat" placed in the toilet).[40] NICE guidelines also recommend the use of bladder diaries in the initial assessment of women with urinary incontinence or overactive bladder syndrome.[35] Women should complete the diary for a minimum of three days to cover variations in their daily activities, although a two day diary may be more feasible for patients to complete.[35] However, bladder diaries are not always needed when the severity and type of urinary incontinence are readily ascertained from the history.

## Physical examination

Pelvic examination will identify the presence of associated pelvic organ prolapse, as well as a woman's ability to initiate voluntary contraction of her pelvic floor muscles (the "Kegel" exercise).[34] The ability to contract the pelvic floor muscles should be confirmed on pelvic examination before initiating pelvic floor muscle training for treatment.[35] This can be done by asking the patient to squeeze her vaginal muscles around the examining finger.

A cough stress test with a comfortably full bladder will identify the presence of stress urinary incontinence in most cases. The stress test is performed by asking the patient whose bladder is comfortably full to cough in the supine or lithotomy position. The test is positive if clinical stress leakage—defined as involuntary leakage from the urethra synchronous with effort or physical exertion, or on sneezing or coughing—is observed.[2] If leakage is not seen on a supine stress test, it may be repeated in the standing position. However, this test is limited, because 34% of women with genuine stress incontinence have a negative stress test at the time of evaluation.[41]

It is also important to identify lower extremity edema (to determine possible sources of polyuria in a patient with nocturia) and overall cognitive status, and to perform a neurologic examination. Urine analysis should be performed in all patients to assess for microhematuria, glucose, protein, leucocytes, and nitrites, and to rule out infection as an acute cause.[35] When indicated, a urine culture is performed. Uroflow (measured flow rate), commonly performed in urologists' and urogynecologists' offices, is useful only for women with signs of voiding dysfunction.[34] Measurement of post-void residual volume, by ultrasound or catheterization, will assess a patient's ability to empty the bladder, and should be performed in women presenting with voiding difficulty or recurrent urinary tract infection.[34][35]

## Cystometry

Patients with uncomplicated stress or urgency urinary incontinence generally do not require cystometry before starting conservative treatment, including drugs, unless they have microhematuria or other complicating factors, such as previous incontinence surgery or recurrent urinary tract infections. A multicenter randomized non-inferiority trial of 630 women showed no benefit of performing urodynamics over office evaluation alone in patients with straightforward stress incontinence before sling surgery.[42] Treatment was successful in 76.9% of the urodynamic testing group versus 77.2% of the office evaluation group, with a non-inferiority margin of 11%.[42] Treatment success was defined as a 70% or more reduction in the baseline score of the urogenital distress inventory and a patient global impression of improvement response of "much better" or "very much better" at 12 months.[42] However, women with a history of anti-incontinence surgery, planned surgery for pelvic organ prolapse, urge predominant incontinence, and neurologic disease were excluded, which limits the generalizability of the study results to patients with more complex needs.

A second multicenter diagnostic cohort non-inferiority randomized controlled trial (RCT) of 126 women with urodynamic findings discordant with clinical assessment randomized women to immediate surgery or tailored treatment based on urodynamics.[43] It concluded that urodynamics should not be routinely used before midurethral sling surgery because immediate surgery was non-inferior to treatment based on urodynamic findings, with non-inferiority defined as less than a five point difference on the urogenital distress inventory.[43]

Urodynamics should not be performed in women with untreated symptoms or urgency incontinence who have no evidence of neurologic disease or voiding dysfunction.[34] AUA/SUFU guidelines discourage the use of urodynamics in the initial workup of the uncomplicated patient.[38] However, it is often helpful in patients with mixed symptoms who

could benefit from further specific delineation of the cause of their urinary incontinence.

Cystometry is also useful before starting more invasive treatment for drug refractory overactive bladder syndrome. NICE guidelines advocate the use of filling and voiding cystometry in women with suspected detrusor overactivity, voiding dysfunction, anterior prolapse, or in those who have had surgery for stress incontinence.[35] If the diagnosis is still unclear, video urodynamics can be considered.[35] Many specialists prefer video urodynamics as part of routine urodynamics because it provides important anatomic information about the appearance of the bladder and bladder neck (often open in women with stress urinary incontinence).

### Initial management

Urinary incontinence can successfully be managed initially at the primary care level in most patients. Referral to a specialist is usually indicated when conservative measures fail to improve symptoms. Specialists include urologists and gynecologists with experience in treating urinary incontinence. A visual summary of treatment options is shown on page 6.

### Lifestyle interventions

Women with all types of urinary incontinence can be advised to decrease their intake of fluids, caffeine, and carbonated drinks.[44] Women are taught, by both the media and the medical establishment, that it is necessary and optimal to drink eight glasses of water daily. Many women do not understand that the recommended six to eight glasses (240 mL each) of water a day includes the water present in food, which contributes substantially to overall total fluid intake.[45] Hence, re-education is appropriate for women with symptoms of overactive bladder syndrome who admit to excessive fluid intake, unless otherwise medically indicated.

Further behavioral modification includes timed voiding, with a goal of reducing voiding frequency to every two to three hours. Women who are unable to wait this long begin by voiding at a set interval (such as an hour) and then increase the time interval by 15-30 minutes each week until the desired interval is reached.[46] According to both AUA/SUFU and NICE guidelines, women with urgency or mixed urinary incontinence should be offered bladder training as a first line treatment.[35][38]

Constipation should be managed and avoided because this contributes to urinary incontinence and voiding dysfunction.[47] Women with a body mass index greater than 25 should be advised to lose weight if they present with new or worsening symptoms,[34] because weight loss significantly reduces symptoms of urinary incontinence.[48] A randomized trial of weight loss versus no intervention in 347 obese women with 10 or more episodes of urinary incontinence a week found a 65% reduction in stress urinary incontinence in the weight loss group versus 47% in controls at 12 months (P<0.001).[48]

### Pelvic floor muscle training

Pelvic floor muscle training consists of strengthening the muscles of the pelvic floor (to reduce stress urinary incontinence) and contracting them in isolation to inhibit detrusor contractions (and reduce urgency urinary incontinence). More commonly known as Kegel exercises, these should be done several times a day and need to be performed consistently over time for benefit to be sustained. A systematic review of patients with urgency, stress, and mixed incontinence found that pelvic floor muscle training was more effective than placebo or no treatment at all and should be included as first line management for urinary incontinence.[49]

AUA/SUFU guidelines recommend pelvic floor muscle training as a first line treatment for overactive bladder syndrome.[38] NICE guidelines recommend offering a trial of pelvic floor muscle training for three months, with eight contractions being performed three times a day, as first line treatment for women with both stress and mixed urinary incontinence.[35] In a study of 22 women with pure stress incontinence, 32% were cured after three months.[50]

When properly performed, these exercises may be more effective than pharmacologic management.[51] An RCT of 197 women with urgency urinary incontinence randomized to behavioral treatment, oxybutynin, or placebo found an 80.7% reduction of urinary incontinence episodes with behavioral treatment versus a 68.5% reduction with drug treatment and a 39.4% reduction with placebo (P=0.04).[51]

### Drug treatments for urgency urinary incontinence and overactive bladder syndrome

#### Anticholinergic drugs

Anticholinergic agents are the mainstay of drug treatment for urgency urinary incontinence and overactive bladder syndrome that does not respond to behavioral modification and pelvic floor exercises. Several agents are currently available, including oxybutynin, tolterodine, fesoterodine, trospium, solifenacin, and darifenacin. Propiverine is also available in the United Kingdom. All have been shown to be safe and effective in the treatment of overactive bladder. Most differences are related to the adverse effects of the various drugs, not the efficacy of these agents. A systematic review showed that patients taking tolterodine were less likely than patients taking oxybutynin to withdraw from studies because of adverse effects such as dry mouth (relative risk 0.52, 95% confidence interval 0.40 to 0.66).[52] However, withdrawal is less likely when extended preparations of either drug are used.[52]

Common adverse effects include constipation, impaired cognition, sedation, and blurred vision.[53] These agents should not be used in patients with narrow angle glaucoma because they can increase intraocular pressure. The incidence of angle closure glaucoma caused by anticholinergic agents in patients with overactive bladder syndrome is unknown. Although these drugs can be safely used in open angle glaucoma and in patients with narrow angle glaucoma treated with laser iridotomy, physicians prescribing anticholinergics should warn patients about the symptoms of an attack, such as eye pain and visual loss. These drugs should be used with caution in patients at high risk or with known narrow angle glaucoma.[54]

AUA/SUFU guidelines recommend exercising caution in prescribing anticholinergics to frail patients because these drugs can cause cognitive changes.[38] Specifically, NICE guidelines state that immediate release oxybutynin should

not be offered to frail older women, defined as women with multiple medical comorbidities, functional impairments in activities of daily living, or any cognitive impairment.[35] These changes are more likely with tertiary amines, such as oxybutynin, and less likely with trospium, a quaternary ammonium compound that is potentially less likely than oxybutynin to cross the blood-brain barrier and cause central nervous system side effects.[55]

Many women are unable to tolerate anticholinergic drugs, and 30-91% stop taking them by one year.[56 57] Physicians are advised to start by prescribing the lowest recommended dose of any anticholinergic drug, and should offer a transdermal route to patients who cannot tolerate the oral formulation.[35] Transdermal routes in both a patch (transdermal oxybutynin, now available without a prescription) and gel formulation (oxybutynin chloride, available in the US) have fewer adverse effects than oral drugs, but may cause a rash or skin irritation.

Although more studies are needed to determine the clinical benefit of using a quaternary amine rather than a tertiary amine, an RCT of trospium and placebo in 327 patients with overactive bladder syndrome reported similar somnolence in both groups.[58] Trospium has been shown to be undetectable in human cerebrospinal fluid and there is evidence to support fewer cognitive deficits with agents that have minimal penetration of the blood-brain barrier, such as trospium.[59]

*Choice of agent*

A meta-analysis of more than 20 formulations of anticholinergics in more than 38 000 patients compared efficacy and adverse events. It found that 40 mg trospium, 100 mg/g oxybutynin gel daily, and 4 mg fesoterodine daily had the best efficacy, whereas higher doses of oral oxybutynin and propiverine had the least favorable profile in terms of efficacy versus adverse events.[60] The review concluded that differences between the various anticholinergic drugs require a patient centered approach to tailor individual treatment algorithms.[61]

NICE guidelines recommend physicians to advise patients that they may not experience the full benefit of these drugs until after four weeks of treatment.[35] AUA/SUFU guidelines recommend four to eight weeks of treatment before pursuing another treatment course.[38] For women with overactive bladder syndrome or mixed urinary incontinence, once daily oxybutynin, tolterodine, or darifenacin should be offered as first line agents.[35] If the first choice is not effective or is poorly tolerated, it is reasonable to offer another drug, preferably the least expensive.[35] Anticholinergic drugs should not be offered to women with symptoms of isolated stress urinary incontinence in the absence of symptoms of overactive bladder syndrome.[34] All women who are prescribed anticholinergic agents should be counseled about the need for concurrent behavioral therapy,[34] because these drugs are more effective in combination with behavioral therapy than with either treatment modality alone.[3]

In 2012, the US Food and Drug Administration approved mirabegron for overactive bladder syndrome. This drug works by relaxing the bladder detrusor muscle through activation of β3 adrenoceptors, thus decreasing the incidence of traditional adverse effects seen with anticholinergics. A placebo controlled RCT found that patients taking once daily mirabegron had 1.1 (−1.35 to −0.91) fewer daily episodes of urinary incontinence with placebo, compared with 1.5 (−1.69 to −1.25) for 50 mg mirabegron, and 1.6 (−1.86 to −1.40) with 100 mg mirabegron, from a baseline of 2.4 episodes daily.[61] Adverse effects were uncommon, with dry mouth and constipation reported in less than 2% of all patients. In addition, a pooled phase III clinical trial showed no significant increase in hypertension (<1 mm Hg) with mirabegron versus placebo.[62]

## Treatment of drug refractory urgency urinary incontinence and overactive bladder symptoms

If patients do not respond to an adequate trial of two different anticholinergic drugs after four weeks each, minimally invasive treatment options are available. Patients should be made aware that overactive bladder syndrome and urgency urinary incontinence, especially when severe, are chronic conditions that can be improved, but are unlikely to be cured.[63] Success is more likely if patients play an active role in managing their symptoms.
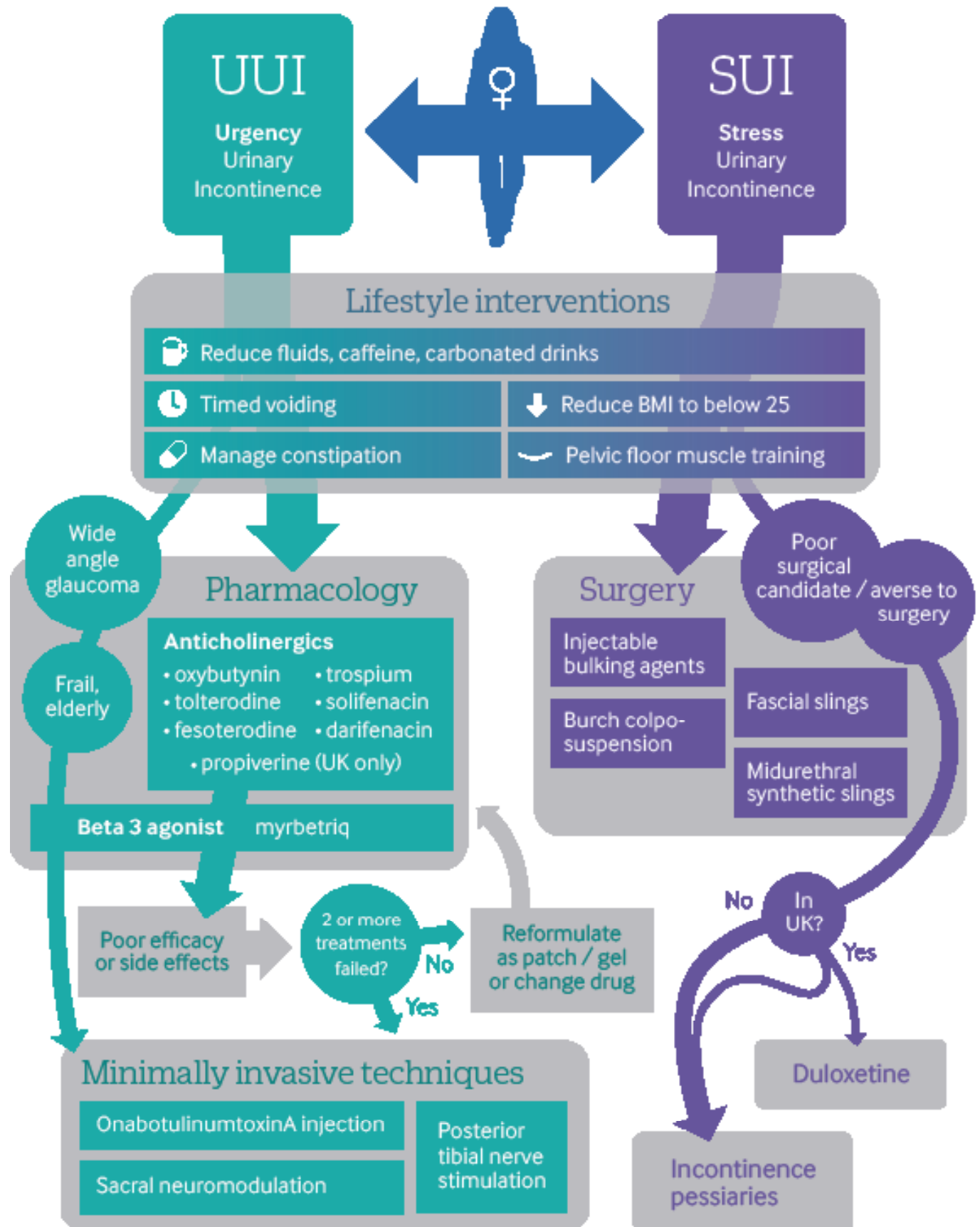
### OnabotulinumtoxinA

OnabotulinumtoxinA is available for office based intravesical injection under local anesthesia. It was approved by the US FDA for use in adults with overactive bladder in January 2013 and by European regulators for use in 14 countries in the European Union in 2011. A multicenter double blind RCT found that onabotulinumtoxinA significantly improved HRQOL and severity of overactive bladder syndrome symptoms. In a study of 548 patients randomized to 100 units of onabotulinumtoxinA versus placebo, a decrease of three urgency urinary incontinence episodes a day (−3.23 to −2.38) was seen at 12 weeks with onabotulinumtoxinA compared with one episode for placebo (−1.16 to −0.48; P<0.001).[64] This RCT showed that onabotulinumtoxinA is an effective treatment for patients who have not responded to more conservative measures, such as anticholinergic drugs.[64] A systematic review of 23 articles, including three RCTs, found that patients treated with intravesical onabotulinumtoxinA had 3.9 fewer urinary incontinence episodes a day than those on placebo (−6.15 to −1.62).[65]

Another RCT of 275 patients with neurogenic detrusor overactivity from spinal cord injury and multiple sclerosis showed that this treatment reduces urinary incontinence and improves urodynamic parameters and quality of life.[66]

Before treatment, patients should be adequately counseled about the risks of onabotulinumtoxinA injections, which include urinary retention (albeit temporary) and urinary tract infections usually associated with incomplete emptying. Retention requires an indwelling catheter or the need to self catheterize temporarily. Patients treated with onabotulinumtoxinA have a nearly ninefold increased risk of a post-void residual complication, such as urinary retention.[65] When a dose of only 100 U is used, retention requiring catheterization is about 5%.[67]

AUA/SUFU guidelines advocate the use of onabotulinumtoxinA 100 U as a third line treatment for women with overactive bladder syndrome who are willing to perform self catheterization if necessary.[38] By contrast, NICE guidelines recommend that 200 U should be injected, unless the woman is worried about retention and is willing to accept

# Treating female urinary incontinence

## UUI
**Urgency** Urinary Incontinence

♀

## SUI
**Stress** Urinary Incontinence

### Lifestyle interventions

- 🥤 Reduce fluids, caffeine, carbonated drinks
- 🕐 Timed voiding
- ⬇ Reduce BMI to below 25
- 💊 Manage constipation
- 〜 Pelvic floor muscle training

Wide angle glaucoma

Frail, elderly

### Pharmacology

**Anticholinergics**
- oxybutynin
- trospium
- tolterodine
- solifenacin
- fesoterodine
- darifenacin
- propiverine (UK only)

**Beta 3 agonist**  myrbetriq

### Surgery

- Injectable bulking agents
- Burch colpo-suspension
- Fascial slings
- Midurethral synthetic slings

Poor surgical candidate / averse to surgery

Poor efficacy or side effects

2 or more treatments failed? **No**

**Yes**

Reformulate as patch / gel or change drug

**No**  In UK?  **Yes**

Duloxetine

### Minimally invasive techniques

- OnabotulinumtoxinA injection
- Posterior tibial nerve stimulation
- Sacral neuromodulation

Incontinence pessiaries

a lower success rate, in which case 100 U is acceptable.[35] However, a recent phase III RCT of 557 patients found that a dose of 100 U produced a clinically significant improvement in overactive bladder syndrome symptoms and HRQOL, with fewer side effects and comparable efficacy to 200 U.[67] Specifically, patients experienced 2.7 fewer incontinence episodes versus 0.9 with placebo from a mean of 5.3 episodes (P<0.001), and 22.9% of patients were completely continent compared with 6.5% with placebo (P<0.001).[67] A systematic review of onabotulinumtoxinA for both neurogenic and idiopathic detrusor overactivity supported a level A recommendation for its use in these patients.[68] Women receiving onabotulinumtoxinA injections should be willing and able to perform clean intermittent catheterization or tolerate an indwelling catheter temporarily.[35]

### Sacral neuromodulation

Sacral neuromodulation has shown efficacy in controlling symptoms of overactive bladder.[69 70] A systematic review including evidence from four RCTs found that 67-80% of patients achieve continence or greater than 50% improvement in urgency urinary incontinence symptoms with sacral nerve stimulation compared with controls awaiting implantation.[70]

Stimulation occurs through electrodes placed into the S3 nerve foramen. There are two techniques for placing the device. In the percutaneous technique, a temporary lead is placed under local anesthesia in the office setting. If successful after a short trial period of three to five days, a permanent lead and implantable pulse generator ("battery") are placed surgically. Alternatively, the two-stage technique involves first placing a permanent lead in the operating room, which is connected to a temporary external battery. If successful after one week (usually defined by ≥50% clinical improvement), a permanent subcutaneous battery is placed in a second surgical procedure. If the trial is unsuccessful, the lead is surgically removed. The formal two stage approach has a higher rate of proceeding to battery implantation than percutaneous testing (50.9% v 24.1%) because the permanent lead is more stable than the percutaneous wire, which can migrate easily.[71] However, around a third of patients who undergo battery placement require surgical revision, most commonly for pain, lead migration, replacement or explantation of the pulse generator, or wound problems.[70] This treatment is an excellent option for women who are unwilling to accept the risk of temporary urinary retention after onabotulinumtoxinA injection.[35] In addition, most women do well for the duration of the battery, which lasts up to five years.

### Posterior tibial nerve stimulation

Posterior tibial nerve stimulation is an office procedure consisting of 12 weekly visits of about 30 minutes each. A small needle is placed posterior and superior to the medial malleolus to stimulate the posterior tibial nerve peripherally and modulate the sacral nerve plexus through the S2-S4 nerves. A multicenter RCT found that 79.5% of patients were subjectively cured or had improvement of overactive bladder symptoms at 12 weeks with percutaneous tibial nerve stimulation, compared with 54.8% of patients taking tolterodine (P=0.01).[72] The second phase of this study found a significant improvement in symptoms of overactive bladder syndrome at

12 months, with patients receiving maintenance treatment an average of once every three weeks. Specifically, patients experienced 2.8 fewer voiding episodes a day (P<0.001), 1.6 fewer urgency incontinence episodes a day (P<0.001), and 3.7 fewer moderate to severe urgency episodes a day, with a 77.9% reduction in these episodes at 12 months (P<0.01).[73] This demonstrates the durability of this treatment option as a long term therapy.[73] A systematic review of RCTs and both retrospective and prospective observational studies reported success rates of 54-93%, although the definitions of success varied.[74] Although initial results are promising, the limited data available, short duration of follow-up, and inconsistency in reporting of the control groups led to the conclusion that more research is needed to support its use in all women with overactive bladder syndrome.[74]

AUA/SUFU guidelines recommend percutaneous posterior tibial nerve stimulation as a third line therapy for highly motivated patients who are willing to comply with the frequent office visits required.[38] Similarly, NICE guidelines recommend offering percutaneous posterior tibial nerve stimulation only if there has been a multidisciplinary team review, conservative management with drugs for overactive bladder syndrome has been unsuccessful, and the patient does not want onabotulinumtoxinA or sacral neuromodulation.[35]

In the past, augmentation cystoplasty, in which a segment of stomach or intestine is patched on to the bladder to increase capacity, was used to treat overactive bladder syndrome refractory to medical therapy. However, since less invasive options such as onabotulinumtoxinA and sacral neuromodulation have entered the armamentarium for overactive bladder syndrome, this procedure is now reserved almost exclusively for urgency urinary incontinence with a neurogenic cause, such as spinal cord injury. In these patients, lifelong follow-up is needed and they should be counseled about the small potential risk of bladder cancer after bladder augmentation.[35]

### Treatment of stress urinary incontinence
#### Non-surgical options

In the US, no drugs are FDA approved for the treatment of stress urinary incontinence that does not respond to Kegel exercises. However, duloxetine, an antidepressant, is available in the UK. A systematic review and meta-analysis of RCTs of duloxetine versus placebo showed that 52.5% of women treated with duloxetine had at least a 50% decrease in the frequency of incontinence episodes, compared with 33.7% of those taking placebo (1.46 to 1.66; P<0.00001).[75] Adverse events such as dry mouth, nausea, constipation, and fatigue were common in the duloxetine treated group, with 62.7% of patients in the treated group reporting side effects versus 45.3% of the placebo group (1.26 to 1.49; P<0.00001).[75] However, current NICE guidelines recommend offering duloxetine only as treatment to women who are not surgical candidates or those who prefer drugs to surgery.[35]

#### Incontinence pessaries

Incontinence pessaries are rubber devices that are placed transvaginally, similar to a birth control diaphragm. They function by applying pressure to the anterior vaginal wall, thus supporting the urethra or even pinching it closed. In an RCT of 446 women randomized to incontinence pessary,

behavioral treatment, or combination therapy, 49% of women who received behavioral therapy reported no bothersome urinary incontinence symptoms versus 33% of women with a pessary (P=0.006).[76] Seventy five per cent of women were satisfied with behavioral therapy versus 63% of women with a pessary (P=0.02).[76] These results persisted only up to three months, and by 12 months success declined in both groups and no difference was seen.[76] Combination therapy was no more effective than either treatment alone.[76] At three months, 40% of women with a pessary reported that their symptoms were "much better" or "very much better," although this was not statistically significant.[76] Therefore, incontinence pessaries are modestly effective and are best used for women who are poor surgical candidates or who choose not to have surgery. However, their use is not supported by the NICE guidelines because limited high quality evidence is available.[35] No guidelines are available regarding the use of pessaries in the US.

### Minimally invasive and surgical options

For women in whom Kegel exercises are ineffective and who desire definitive surgery, five procedures are endorsed by the American Urological Association—the use of injectable bulking agents, laparoscopic suspensions (laparoscopic "Burch" colposuspension), midurethral slings, pubovaginal slings, and open retropubic suspensions.[77] However, midurethral slings are by far the most popular slings used today, owing to their good long term efficacy and minimally invasive approach.

#### *Injectable bulking agents*

Bulking agents are injectable materials placed at the bladder neck to improve continence. Several different bulking agents are available including silicone particles, carbon beads, calcium hydroxyapatite, ethylene vinyl alcohol copolymer, porcine dermal implants, and a hydrogel composed of water and cross-linked polyacrylamide.

Two to three injections are often needed to achieve a durable result. Few comparative data on the different bulking agents are available. In a prospective randomized trial of 45 women with stress urinary incontinence that compared pubovaginal slings with transurethral silicone particles, 81% of the women in the sling group versus only 9% of those in the bulking agent group were objectively cured at six months (P<0.001).[78] Although less effective than surgery, these agents are a reasonable option for women with multiple comorbidities who are poor surgical candidates and desire short term symptomatic relief.[79] Bulking agents can also help women who have already had surgery (such as a sling), yet still have some residual incontinence, achieve complete continence.[80] They may be considered in women who have not improved with conservative management for stress urinary incontinence. However, patients should be counseled that repeat injections may be necessary, efficacy decreases over time, and slings are more efficacious.[35]

#### *Burch colposuspension and fascial slings*

For years the Burch colposuspension and autologous fascial slings were considered the gold standard operations for the treatment of stress urinary incontinence. The Burch procedure involves suspending the anterior vaginal wall to the

ileopectineal (Cooper's) ligament. The autologous sling procedure entails harvesting a strip of rectus fascia, placing it transvaginally, and securing it superiorly to the rectus fascia.

A multicenter randomized trial conducted by the Urinary Incontinence Treatment Network compared outcomes between the pubovaginal sling using autologous rectus fascia and Burch colposuspension. In women with stress urinary incontinence, success rates were higher for those in the pubovaginal sling group (66% *v* 49%; P<0.001).[81] Satisfaction was also higher in the sling group,[81] and this persisted to five year follow-up.[82] However, morbidity was higher in the sling group—postoperative urinary tract infections, voiding dysfunction, and urgency incontinence were more common.[81] Rigorous criteria were used and it was determined that continence rates in the Burch group and sling group were 24.1% (18.5 to 29.7) and 30.8% (24.7 to 36.9), respectively, at five years after surgery.[82] However, the satisfaction rate was more than 73% for all patients at five years, indicating that treatment success and patient satisfaction may not be directly correlated.[82]

In addition to autologous fascial slings, biologic slings may be used from human donor tissue or animal tissue. However, outcomes of slings that apply these allografts and xenografts are less well established than those of the traditional autologous option.[35]

#### *Midurethral synthetic slings*

In recent years, midurethral synthetic slings have replaced pubovaginal slings as the gold standard for surgical correction of stress urinary incontinence.[83] Midurethral slings are thought to be successful because of the "hammock" hypothesis. This describes the urethra as being compressed against a hammock-like supportive layer to assist in the urethral closure mechanism during an increase in intra-abdominal pressure, such as during a cough.[84] This theory originated with the work of Petros and Ulmsten, who described how alterations in connective tissue may cause laxity in the vagina and its supporting ligaments and lead to incontinence.[85]

The placement of a sling is minimally invasive and is usually performed in an outpatient setting. They can be placed either retropubically, as in the classic tension-free vaginal tape procedure, or through the transobturator tape approach (figure). The Trial Of Mid-Urethral Slings (TOMUS) was a multicenter randomized trial by the Urinary Incontinence Treatment Network that showed equivalence between the two approaches by subjective and objective criteria.[86] This trial of 597 women that compared retropubic versus transobturator midurethral slings and a two year follow-up study of adverse events found a significantly higher rate of bladder perforation and voiding dysfunction in the retropubic group and more neurologic symptoms, such as leg weakness or groin numbness, in the transobturator group.[86] [87] Most neurologic symptoms resolved over six weeks.[87] Overall, urinary tract infection was the most common adverse event in both groups.[87]

Success rates of midurethral slings range from 84% to 99%.[83] [88] [89] Risks of surgical correction include bleeding, pain, infection, de novo urgency, urinary retention, and failure of treatment. The best long term data exist for the tension-free vaginal tape procedure. An 11 year prospective follow-up showed a 90% objective cure rate with a negative

Diagram showing the positioning of the retropubic midurethral and transobturator slings
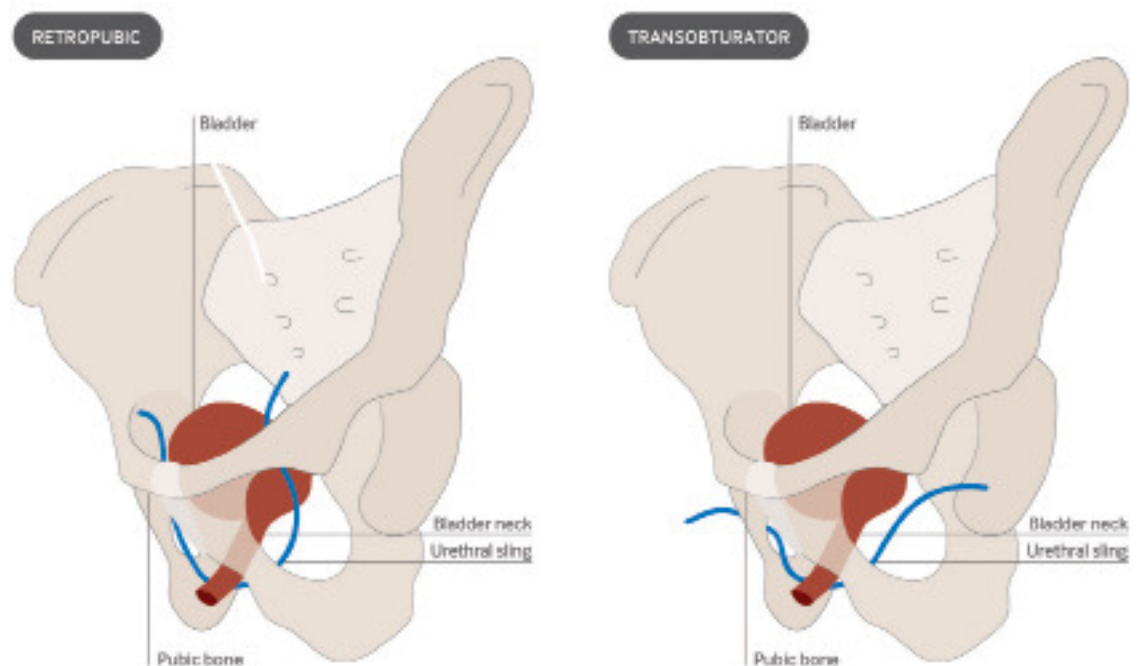


stress test and pad weight and a 77% subjective cure with no long term adverse effects, indicating that this procedure is safe and effective after 10 years.[90]

*Choice of sling*

A systematic review and meta-analysis of sling surgery for stress urinary incontinence recommends the use of either tension-free vaginal tape or transobturator tape slings for objective and subjective cure (level 1A evidence). The decision can be based on adverse events of concern to the patient.[91] The 49 RCTs included in this meta-analysis compared midurethral slings with open or laparoscopic Burch colposuspension, and the review recommends either, depending on adverse events of concern to the patient (level 1A evidence).[91] Pubovaginal slings are recommended over Burch procedures to maximize cure (level 1A evidence).[91] Midurethral slings are recommended over pubovaginal slings for better subjective cure (level 2C evidence).[91]

Single incision mini-slings have gained popularity as an option with potentially fewer complications. However, some preliminary studies suggest that mini-slings have lower subjective and objective cure rates and higher reoperation rates when compared with traditional midurethral slings.[92] Because data vary by the specific mini-sling used, level 1 data are needed to compare the efficacy of mini-slings with that of retropubic and transobturator slings.

*Vaginal mesh*

Mesh for the surgical correction of stress incontinence and in midurethral synthetic slings is safe and effective. In 2008, the FDA issued a statement cautioning against the use of vaginal mesh in the surgical correction of pelvic organ prolapse and incontinence. After adverse events reported to the FDA exceeded 3874, an updated FDA warning in 2011 stated that most mesh related complications were associated with vaginally placed mesh for prolapse, and that there

were insufficient data to recommend against using mesh for stress urinary incontinence procedures. In January 2014, the American Urogynecologic Society (AUGS) and SUFU issued a joint statement that strongly supported the use of polypropylene mesh for midurethral sling surgery. The statement recognized the procedure as the safe, effective, worldwide standard of care for the treatment of women with stress urinary incontinence. In a study of adverse events over two years after a sling procedure, only 4% of women experienced mesh related complications and most of these did not require surgical intervention.[87]

## Looking ahead

As healthcare systems seek increased value at a lower cost, urinary incontinence is an area where costs can be considerably reduced through minimizing the use of diagnostic testing. Quality of care indicators are a means to measure the care provided to women with urinary incontinence and can be used as an algorithm for the investigation and treatment of urinary incontinence, regardless of provider specialty. This method is useful for areas in which the level of evidence is limited.[34 93]

The application of these algorithms can improve incontinence care at the generalist level and thereby reduce the need for specialty care, while algorithms applied to specialist care can help reduce costly, and sometimes unnecessary, testing.

Further research is needed to improve our understanding of the physiology underlying overactive bladder syndrome. In addition, the prevention of lower urinary tract symptoms is an exciting area of research that has the potential to reduce the burden of urinary incontinence. Urinary biomarkers are an ongoing area of research, and several clinical trials are under way to identify the role of urinary nerve growth factor, prostaglandin E2, ATP, and others as potential biomarkers for overactive bladder syndrome to identify at risk patients and predict responsiveness to treatment (see clinicaltrials.gov).

## FUTURE RESEARCH QUESTIONS

What is the ideal treatment algorithm for patients in whom conservative management of overactive bladder syndrome has been unsuccessful? Should a patient be considered first for onabotulinumtoxinA, tibial nerve stimulation, or sacral nerve modulation? Which patients will best respond to which types of treatment?

What is the long term efficacy and safety of suburethral mini-slings and midurethral slings?

In the era of mesh related complications, are midurethral slings still safe?

What is the surgical outcome of repeat sling surgery after initial sling surgery has been ineffective?

The Pelvic Floor Disorders Network is currently conducting several innovative clinical trials, including Anticholinergics versus Botox Comparison (ABC), a randomized trial of onabotulinumtoxinA versus drugs for reducing urgency urinary episodes of incontinence. The network is also comparing the effectiveness of onabotulinumtoxinA with that of sacral neuromodulation for the treatment of refractory urgency urinary incontinence in a randomized active control trial known as Refractory Overactive Bladder: Sacral NEuromodulation v BoTulinum Toxin Assessment (ROSETTA). These two trials will offer exciting information on the most efficacious treatments for urgency urinary incontinence and will help the clinician decide on the most appropriate treatment for patients with overactive bladder syndrome.

### Conclusion

Urinary incontinence affects a large number of women and results in a substantial socioeconomic burden. Minimally invasive treatment measures can readily be initiated by primary care providers, with referral to a specialist when conservative management is not effective. Many minimally invasive and efficacious treatment options are available for both stress and urgency urinary incontinence. Despite the high rate of mesh related complications after vaginally placed mesh for prolapse, midurethral mesh slings for stress urinary incontinence have an acceptably low complication rate with durable efficacy. Newer treatments for overactive bladder syndrome and urgency urinary incontinence, including mirabegron and intravesical botulinum injection, have greatly changed the landscape of treatment, providing a wide range of treatment options to patients with overactive bladder syndrome that is refractory to traditional anticholinergic drugs.

1    Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Urology 2003;61:37-49.
2    Haylen BT, de Ridder D, Freeman RM, Swift SE, Berghmans B, Lee J, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Int Urogynecol J 2010;21:5-26.
3    Norton P, Brubaker L. Urinary incontinence in women. Lancet 2006;367:57-67.
4    Thom D. Variation in estimates of urinary incontinence prevalence in the community: effects of differences in definition, population characteristics, and study type. J Am Geriatr Soc 1998;46:473-80.
5    Branch LG, Walker LA, Wetle TT, DuBeau CE, Resnick NM. Urinary incontinence knowledge among community-dwelling people 65 years of age and older. J Am Geriatr Soc 1994;42:1257-62.
6    Cheater FM, Castleden CM. Epidemiology and classification of urinary incontinence. Baillieres Best Pract Res Clin Obstet Gynaecol 2000;14:183-205.
7    Hunskaar S, Arnold EP, Burgio K, et al. Epidemiology and natural history of urinary incontinence. In: Abrams P, Khoury S, Wein A, eds. Incontinence—first international consultation on incontinence. Plymbridge Distributors, 1999:199-226.
8    Nygaard IE, Heit M. Stress urinary incontinence. Obstet Gynecol 2004;104:607-20.
9    Stewart WF, Van Rooyen JB, Cundiff GW, Abrams P, Herzog AR, Corey R, et al. Prevalence and burden of overactive bladder in the United States. World J Urol 2003;20:327-36.
10   Anger JT, Saigal CS, Madison R, Joyce G, Litwin MS, Urologic Diseases of America Project. Increasing costs of urinary incontinence among female Medicare beneficiaries. J Urol 2006;176:247-51; discussion 51.
11   Hunskaar S, Vinsnes A. The quality of life in women with urinary incontinence as measured by the sickness impact profile. J Am Geriatr Soc 1991;39:378-82.
12   Melville JL, Delaney K, Newton K, Katon W. Incontinence severity and major depression in incontinent women. Obstet Gynecol 2005;106:585-92.
13   Nygaard I, Turvey C, Burns TL, Crischilles E, Wallace R. Urinary incontinence and depression in middle-aged United States women. Obstet Gynecol 2003;101:149-56.
14   Brown JS, Vittinghoff E, Wyman JF, Stone KL, Nevitt MC, Ensrud KE, et al. Urinary incontinence: does it increase risk for falls and fractures? Study of Osteoporotic Fractures Research Group J Am Geriatr Soc 2000;48:721-5.
15   Thom DH, Haan MN, Van Den Eeden SK. Medically recognized urinary incontinence and risks of hospitalization, nursing home admission and mortality. Age Ageing 1997;26:367-74.
16   Levy R, Muller N. Urinary incontinence: economic burden and new choices in pharmaceutical treatment. Adv Ther 2006;23:556-73.
17   Wilson L, Brown JS, Shin GP, Luc KO, Subak LL. Annual direct cost of urinary incontinence. Obstet Gynecol 2001;98:398-406.
18   Ganz ML, Smalarz AM, Krupski TL, Anger JT, Hu JC, Wittrup-Jensen KU, et al. Economic costs of overactive bladder in the United States. Urology 2010;75:526-32, 32 e1-18.
19   Peyrat L, Haillot O, Bruyere F, Boutin JM, Bertrand P, Lanson Y. Prevalence and risk factors of urinary incontinence in young and middle-aged women. BJU Int 2002;89:61-6.
20   Rortveit G, Daltveit AK, Hannestad YS, Hunskaar S, Norwegian ES. Urinary incontinence after vaginal delivery or cesarean section. N Engl J Med 2003;348:900-7.
21   Parazzini F, Chiaffarino F, Lavezzari M, Giambanco V, Group VS. Risk factors for stress, urge or mixed urinary incontinence in Italy. BJOG 2003;110:927-33.
22   Brown JS, Sawaya G, Thom DH, Grady D. Hysterectomy and urinary incontinence: a systematic review. Lancet 2000;356:535-9.
23   Samuelsson E, Victor A, Svardsudd K. Determinants of urinary incontinence in a population of young and middle-aged women. Acta Obstet Gynecol Scand 2000;79:208-15.
24   Van Oyen H, Van Oyen P. Urinary incontinence in Belgium; prevalence, correlates and psychosocial consequences. Acta Clin Belg 2002;57:207-18.
25   Zargham M, Alizadeh F, Moayednia A, Haghdani S, Nouri-Mahdavi K. The role of pelvic organs prolapse in the etiology of urinary incontinence in women. Adv Biomed Res 2013;2:22.
26   Bortolotti A, Bernardini B, Colli E, Di Benedetto P, Giocoli Nacci G, Landoni M, et al. Prevalence and risk factors for urinary incontinence in Italy. Eur Urol 2000;37:30-5.
27   Sampselle CM, Harlow SD, Skurnick J, Brubaker L, Bondarenko I. Urinary incontinence predictors and life impact in ethnically diverse perimenopausal women. Obstet Gynecol 2002;100:1230-8.
28   Hannestad YS, Lie RT, Rortveit G, Hunskaar S. Familial risk of urinary incontinence in women: population based cross sectional study. BMJ 2004;329:889-91.
29   Bump RC, McClish DK. Cigarette smoking and urinary incontinence in women. Am J Obstet Gynecol 1992;167:1213-8.
30   Fuganti PE, Gowdy JM, Santiago NC. Obesity and smoking: are they modulators of cough intravesical peak pressure in stress urinary incontinence? Int Braz J Urol 2011;37:528-33.
31   Riesenhuber A, Boehm M, Posch M, Aufricht C. Diuretic potential of energy drinks. Amino Acids 2006;31:81-3.
32   Gleason JL, Richter HE, Redden DT, Goode PS, Burgio KL, Markland AD. Caffeine and urinary incontinence in US women. Int Urogynecol J 2013;24:295-302.
33   Wein AJ, Kavoussi LR, Novick AC, Partin AM, Peters CA. Urinary incontinence and pelvic prolapse: epidemiology and pathophysiology. In: Wein AJ, ed. Campbell-Walsh urology. 10th ed. Elsevier Saunders, 2012:1871-95.
34   Anger JT, Scott VC, Kiyosaki K, Khan AA, Weinberg A, Connor SE, et al. Development of quality indicators for women with urinary incontinence. Neurourol Urodynam 2013;32:1058-63.
35   National Institute for Health and Care Excellence. Urinary incontinence: the management of urinary incontinence in women. CG171. 2013. www.nice.org.uk/Guidance/CG171.
36   Uebersax JS, Wyman JF, Shumaker SA, McClish DK, Fantl JA. Short forms to assess life quality and symptom distress for urinary incontinence in women: the incontinence impact questionnaire and the urogenital distress inventory. Continence Program for Women Research Group. Neurourol Urodynam 1995;14:131-9.

37 Avery KN, Bosch JL, Gotoh M, Naughton M, Jackson S, Radley SC, et al. Questionnaires to assess urinary and anal incontinence: review and recommendations. *J Urol* 2007;177:39-49.

38 Gormley EA, Lightner DJ, Burgio KL, Chai TC, Clemens JQ, Culkin DJ, et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline. *J Urol* 2012;188(6 suppl):2455-63.

39 Scientific Committee of the First International Consultation on Incontinence. Assessment and treatment of urinary incontinence. *Lancet* 2000;355:2153-8.

40 Fonda D, Resnick NM, Colling J, Burgio K, Ouslander JG, Norton C, et al. Outcome measures for research of lower urinary tract dysfunction in frail older people. *Neurourol Urodynam* 1998;17:273-81.

41 Haylen BT, Sutherst JR, Frazer MI. Is the investigation of most stress incontinence really necessary? *Br J Urol* 1989;64:147-9.

42 Nager CW, Brubaker L, Litman HJ, Zyczynski HM, Varner RE, Amundsen C, et al. A randomized trial of urodynamic testing before stress-incontinence surgery. *N Engl J Med* 2012;366:1987-97.

43 Van Leijsen SAL, Kluivers KB, Mol BJ, in 't Hout J, Milani AL, Roovers JPWR, et al. Value of urodynamics before stress urinary incontinence surgery a randomized controlled trial. *Obstet Gynecol* 2013;121:999-1008.

44 Khan IJ, Tariq SH. Urinary incontinence: behavioral modification therapy in older adult. *Clin Geriatr Med* 2004;20:499-509, vii.

45 Valtin H. "Drink at least eight glasses of water a day." Really? Is there scientific evidence for "8 × 8"? *Am J Physiol Regul Integr Comp Physiol* 2002;283:R993-1004.

46 Wyman JF, Burgio KL, Newman DK. Practical aspects of lifestyle modifications and behavioural interventions in the treatment of overactive bladder and urgency urinary incontinence. *Int J Clin Pract* 2009;63:1177-91.

47 Kinnunen O. Study of constipation in a geriatric hospital, day hospital, old people's home and at home. *Aging* 1991;3:161-70.

48 Wing RR, West DS, Grady D, Creasman JM, Richter HE, Myers D, et al. Effect of weight loss on urinary incontinence in overweight and obese women: results at 12 and 18 months. *J Urol* 2010;184:1005-10.

49 Dumoulin C, Hay-Smith J. Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. *Cochrane Database Syst Rev* 2010;1:CD005654.

50 Benvenuti F, Caputo GM, Bandinelli S, Mayer F, Biagini C, Sommavilla A. Reeducative treatment of female genuine stress incontinence. *Am J Phys Med* 1987;66:155-68.

51 Burgio KL, Locher JL, Goode PS, Hardin JM, McDowell BJ, Dombrowski M, et al. Behavioral vs drug treatment for urge urinary incontinence in older women: a randomized controlled trial. *JAMA* 1998;280:1995-2000.

52 Madhuvrata P, Cody JD, Ellis G, Herbison GP, Hay-Smith EJ. Which anticholinergic drug for overactive bladder symptoms in adults. *Cochrane Database Syst Rev* 2012;1:CD005429.

53 Erdem N, Chu FM. Management of overactive bladder and urge urinary incontinence in the elderly patient. *Am J Med* 2006;119(3 suppl 1):29-36.

54 Kato K, Yoshida K, Suzuki K, Murase T, Gotoh M. Managing patients with an overactive bladder and glaucoma: a questionnaire survey of Japanese urologists on the use of anticholinergics. *BJU Int* 2005;95:98-101.

55 Todorova A, Vonderheid-Guth B, Dimpfel W. Effects of tolterodine, trospium chloride, and oxybutynin on the central nervous system. *J Clin Pharmacol* 2001;41:636-44.

56 Sexton CC, Notte SM, Maroulis C, Dmochowski RR, Cardozo L, Subramanian D, et al. Persistence and adherence in the treatment of overactive bladder syndrome with anticholinergic therapy: a systematic review of the literature. *Int J Clin Pract* 2011;65:567-85.

57 Brostrom S, Hallas J. Persistence of antimuscarinic drug use. *Eur J Clin Pharmacol* 2009;65:309-14.

58 Staskin DR, Harnett MD. Effect of trospium chloride on somnolence and sleepiness in patients with overactive bladder. *Curr Urol Rep* 2004;5:423-6.

59 Chancellor MB, Staskin DR, Kay GG, Sandage BW, Oefelein MG, Tsao JW. Blood-brain barrier permeation and efflux exclusion of anticholinergics used in the treatment of overactive bladder. *Drugs Aging* 2012;29:259-73.

60 Buser N, Ivic S, Kessler TM, Kessels AG, Bachmann LM. Efficacy and adverse events of antimuscarinics for treating overactive bladder: network meta-analyses. *Eur Urol* 2012;62:1040-60.

61 Nitti VW, Auerbach S, Martin N, Calhoun A, Lee M, Herschorn S. Results of a randomized phase III trial of mirabegron in patients with overactive bladder. *J Urol* 2013;189:1388-95.

62 Chapple CR, Cardozo L, Nitti VW, Siddiqui E, Michel MC. Mirabegron in overactive bladder: a review of efficacy, safety, and tolerability. *Neurourol Urodynam* 2014;33:17-30.

63 Anger JT, Nissim HA, Le TX, Smith AL, Lee U, Sarkisian C, et al. Women's experience with severe overactive bladder symptoms and treatment: insight revealed from patient focus groups. *Neurourol Urodynam* 2011;30:1295-9.

64 Chapple C, Sievert KD, MacDiarmid S, Khullar V, Radziszewski P, Nardo C, et al. OnabotulinumtoxinA 100 U significantly improves all idiopathic overactive bladder symptoms and quality of life in patients with overactive bladder and urinary incontinence: a randomised, double-blind, placebo-controlled trial. *Eur Urol* 2013;64:249-56.

65 Anger JT, Weinberg A, Suttorp MJ, Litwin MS, Shekelle PG. Outcomes of intravesical botulinum toxin for idiopathic overactive bladder symptoms: a systematic review of the literature. *J Urol* 2010;183:2258-64.

66 Cruz F, Herschorn S, Aliotta P, Brin M, Thompson C, Lam W, et al. Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomised, double-blind, placebo-controlled trial. *Eur Urol* 2011;60:742-50.

67 Nitti VW, Dmochowski R, Herschorn S, Sand P, Thompson C, Nardo C, et al. OnabotulinumtoxinA for the treatment of patients with overactive bladder and urinary incontinence: results of a phase 3, randomized, placebo controlled trial. *J Urol* 2013;189:2186-93.

68 Chancellor MB, Elovic E, Esquenazi A, Naumann M, Segal KR, Schiavo G, et al. Evidence-based review and assessment of botulinum neurotoxin for the treatment of urologic conditions. *Toxicon* 2013;67:129-40.

69 Starkman JS, Wolter CE, Scarpero HM, Milam DF, Dmochowski RR. Management of refractory urinary urge incontinence following urogynecological surgery with sacral neuromodulation. *Neurourol Urodynam* 2007;26:29-35; discussion 6.

70 Brazzelli M, Murray A, Fraser C. Efficacy and safety of sacral nerve stimulation for urinary urge incontinence: a systematic review. *J Urol* 2006;175(3 pt 1):835-41.

71 Cameron AP, Anger JT, Madison R, Saigal CS, Clemens JQ; Urologic Diseases in America Project. National trends in the usage and success of sacral nerve test stimulation. *J Urol* 2011;185:970-5.

72 Peters KM, Macdiarmid SA, Wooldridge LS, Leong FC, Shobeiri SA, Rovner ES, et al. Randomized trial of percutaneous tibial nerve stimulation versus extended-release tolterodine: results from the overactive bladder innovative therapy trial. *J Urol* 2009;182(3):1055-61.

73 MacDiarmid SA, Peters KM, Shobeiri SA, Wooldridge LS, Rovner ES, Leong FC, et al. Long-term durability of percutaneous tibial nerve stimulation for the treatment of overactive bladder. *J Urol* 2010;183:234-40.

74 Levin PJ, Wu JM, Kawasaki A, Weidner AC, Amundsen CL. The efficacy of posterior tibial nerve stimulation for the treatment of overactive bladder in women: a systematic review. *Int Urogynecol J* 2012;23:1591-7.

75 Li J, Yang L, Pu C, Tang Y, Yun H, Han P. The role of duloxetine in stress urinary incontinence: a systematic review and meta-analysis. *Int Urol Nephrol* 2013;45:679-86.

76 Richter HE, Burgio KL, Brubaker L, Nygaard IE, Ye W, Weidner A, et al. Continence pessary compared with behavioral therapy or combined therapy for stress incontinence: a randomized controlled trial. *Obstet Gynecol* 2010;115:609-17.

77 Dmochowski RR, Blaivas JM, Gormley EA, Juma S, Karram MM, Lightner DJ, et al. Update of AUA guideline on the surgical management of female stress urinary incontinence. *J Urol* 2010;183:1906-14.

78 Maher CF, O'Reilly BA, Dwyer PL, Carey MP, Cornish A, Schluter P. Pubovaginal sling versus transurethral macroplastique for stress urinary incontinence and intrinsic sphincter deficiency: a prospective randomised controlled trial. *BJOG* 2005;112:797-801.

79 Keegan PE, Atiemo K, Cody J, McClinton S, Pickard R. Periurethral injection therapy for urinary incontinence in women. *Cochrane Database Syst Rev* 2007;3:CD003881.

80 Lee HN, Lee YS, Han JY, Jeong JY, Choo MS, Lee KS. Transurethral injection of bulking agent for treatment of failed mid-urethral sling procedures. *Int Urogynecol J* 2010;21:1479-83.

81 Albo ME, Richter HE, Brubaker L, Norton P, Kraus SR, Zimmern PE, et al. Burch colposuspension versus fascial sling to reduce urinary stress incontinence. *N Engl J Med* 2007;356:2143-55.

82 Brubaker L, Richter HE, Norton PA, Albo M, Zyczynski HM, Chai TC, et al. 5-year continence rates, satisfaction and adverse events of burch urethropexy and fascial sling surgery for urinary incontinence. *J Urol* 2012;187:1324-30.

83 Ogah J, Cody JD, Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. *Cochrane Database Syst Rev* 2009;4:CD006375.

84 DeLancey JO. Structural support of the urethra as it relates to stress urinary incontinence: the hammock hypothesis. *Am J Obstet Gynecol* 1994;170:1713-20; discussion 20-3.

85 Petros PE, Ulmsten UI. An integral theory of female urinary incontinence. Experimental and clinical considerations. *Acta Obstetric Gynecol Scand Suppl* 1990;153:7-31.

86 Richter HE, Albo ME, Zyczynski HM, Kenton K, Norton PA, Sirls LT, et al. Retropubic versus transobturator midurethral slings for stress incontinence. *N Engl J Med* 2010;362:2066-76.

87 Brubaker L, Norton PA, Albo ME, Chai TC, Dandreo KJ, Lloyd KL, et al. Adverse events over two years after retropubic or transobturator midurethral sling surgery: findings from the Trial of Midurethral Slings (TOMUS) study. *Am J Obstet Gynecol* 2011;205:498 e1-6.

88 Novara G, Ficarra V, Boscolo-Berto R, Secco S, Cavalleri S, Artibani W. Tension-free midurethral slings in the treatment of female stress urinary incontinence: a systematic review and meta-analysis of randomized controlled trials of effectiveness. *Eur Urol* 2007;52:663-78.

89 Latthe PM, Foon R, Toozs-Hobson P. Transobturator and retropubic tape procedures in stress urinary incontinence: a systematic review and meta-analysis of effectiveness and complications. *BJOG* 2007;114:522-31.

90 Nilsson CG, Palva K, Rezapour M, Falconer C. Eleven years prospective follow-up of the tension-free vaginal tape procedure for treatment of stress urinary incontinence. *Int Urogynecol J Pelvic Floor Dysfunct* 2008;19:1043-7.

91 Schimpf MO, Rahn DD, Wheeler TL, Patel M, White AB, Orejuela FJ, et al. Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. *Am J Ostet Gynecol* 2014;211:71.e1-71.e27.

92 Abdel-Fattah M, Ford JA, Lim CP, Madhuvrata P. Single-incision mini-slings versus standard midurethral slings in surgical management of female stress urinary incontinence: a meta-analysis of effectiveness and complications. *Eur Urol* 2011;60:468-80.

93 Min LC, Reuben DB, Adams J, Shekelle PG, Ganz DA, Roth CP, et al. Does better quality of care for falls and urinary incontinence result in better participant-reported outcomes? *J Am Geriatr Soc* 2011;59:1435-43.