Drugs 2006; 66 (5): 591-606
0012-6667/06/0005-0591/$44.95/0

Pharmacological Management of Women with Mixed Urinary Incontinence

Hashim Hashim and *Paul Abrams*

Bristol Urological Institute, Southmead Hospital, Westbury-on-Trym, Bristol, UK

Contents

Abstract

Mixed urinary incontinence (MUI) is a symptomatic diagnosis. It is defined by the International Continence Society as the complaint of involuntary leakage associated with urgency and also with exertion, effort, sneezing and coughing. A search of medical databases revealed that only a small number of limited studies that assess the prevalence, epidemiology and treatment of MUI have been conducted. Most studies have looked separately at either stress urinary incontinence or urgency urinary incontinence. Thus, management of MUI involves a combination of treatments for both stress and urgency incontinence, but should concentrate initially on the most bothersome and/or predominant symptom. Initial management includes an accurate history and examination, which is supplemented by a bladder diary and quality-of-life questionnaire. Once a preliminary diagnosis is established, first-line therapy includes patient education and lifestyle interventions, such as weight loss. This is supplemented by pelvic floor muscle training and bladder training, which help with both components of MUI. Oral pharmacotherapy often acts synergistically with the previous treatments; howev-

er, only very few randomised, placebo-controlled trials have looked at the effects of pharmacotherapy on MUI. The two main classes of drugs are the antimuscarinics, which are effective in urgency incontinence, and the serotonin-norepinephrine re-uptake inhibitors, which are effective in stress incontinence. Combination of these two drug classes is a feasible option but has not been tested in any trials to date. Should these treatments fail, then patients should be referred for cystometry to confirm the diagnosis. Treatment options available following urodynamics include invasive minor and major surgical procedures, which either treat the stress or urgency component of MUI but not both. Surgical procedures carry the risk of infection, haemorrhage and failure.

1. Definition

In 2002, the International Continence Society (ICS) published their standardisation report for lower urinary tract symptoms (LUTS) terminology.[1] Urinary incontinence was defined as "the complaint of any involuntary leakage of urine", with three main types being identified. Urge urinary incontinence, part of the overactive bladder syndrome (OAB), was defined as the complaint of involuntary leakage accompanied or immediately preceded by urgency. It is also known as 'wet' overactive bladder (OAB wet). Urge urinary incontinence will be replaced by the term 'urgency urinary incontinence (UUI)' in the new ICS standardisation report, which is expected to be published in the near future. Stress urinary incontinence (SUI) is the complaint of involuntary leakage on effort or exertion, or on sneezing or coughing. Mixed urinary incontinence (MUI) is the complaint of involuntary leakage associated with urgency and also with exertion, effort, sneezing and coughing. Thus, MUI is a combination of UUI and SUI. These definitions are all based on symptomatic diagnoses rather than urodynamic diagnoses.

If UUI is demonstrated on urodynamics associated with detrusor overactivity (DO) then it is termed detrusor overactivity incontinence (DOI). If SUI is demonstrated on urodynamics it is termed urodynamic stress incontinence (USI), which replaces the older term of genuine stress incontinence. The existence of USI and DOI, or USI and DO but no DOI, has also been defined in some literature as MUI, but in fact it is mixed urodynamic incontinence, which is not an ICS definition.

Since MUI is a mixture of both SUI and UUI, it can probably be subdivided into stress-predominant MUI, urgency-predominant MUI or balanced MUI. However, to date, there are no data that look at the separate prevalence of MUI with SUI or UUI predominance.

2. Prevalence and Incidence

The prevalence of MUI is difficult to quantify and ranges between 11% and 61% with a median of 29%.[2] This is because of the different definitions, population samples, age ranges and questionnaires used. Some studies suggest that SUI is the most prevalent, followed by MUI and then UUI. Others suggest that the prevalence of SUI, UUI and MUI is approximately one-third each. In the National Overactive Bladder Evaluation (NOBLE) programme, 2735 women were recruited. Of these, 34.4% had MUI, 33.8% had SUI and 31.8% had UUI. It was estimated that 17 million women in the USA have urinary incontinence of all types.[3] The prevalence of MUI and UUI tend to increase with age, while that of SUI tends to decrease with age.[4] In one series of women attending a urodynamics tertiary referral centre, 87% of women who were 'OAB wet' had symptoms of SUI, with 52% having USI.[5]

Studies on the incidence of MUI are very scarce, as it depends on the study population, and more trials are encouraged on the incidence of MUI.

3. Aetiology

When discussing the aetiology of MUI, it is important to look at the pathophysiology of both UUI and SUI separately because the pathophysiology of MUI is poorly understood and is probably a combination of both UUI and SUI.

UUI is mainly caused by DO, defined as involuntary detrusor contractions during bladder filling

when performing urodynamics. During the bladder-filling phase, which is when OAB symptoms occur, there is continuous and increasing afferent activity from the bladder.

The myogenic theory[6] suggests that changes in the smooth muscle leading to increased excitability and coupling between cells are a prerequisite for involuntary detrusor contractions. This can happen with ageing. The neurogenic theory[7] suggests that damage to the nerves in the brain and spinal cord can result in changes that trigger DO, as can occur in suprapontine lesions, such as stroke and Parkinson's disease, where there is a loss of inhibition of the micturition reflex leading to neurogenic DO.

SUI occurs because of sphincteric incompetence as a result urethral weakness and/or bladder-neck hypermobility secondary to congenital anomalies, childbirth resulting in pelvic floor weakness and postmenopausal involution of the urethra.[8] For continence to be maintained, there needs to be a functioning intra-urethral striated sphincter, controlled by pudendal innervation, a well vascularised urethral mucosa and submucosa, a properly aligned and functioning intrinsic urethral smooth muscle, and intact vaginal wall support. Failure of any of these can potentially result in SUI.

Vaginal delivery can result in damage to the continence mechanism by direct injury to the levator pelvic floor muscles and/or damage to the motor innervation. Pudendal nerve damage seems to be an important factor in the development of SUI, and damage to it from direct crushing or traction can result from multiparity, forceps delivery, increased duration of the second stage of labour, third-degree perineal tear and high birth weight.[9]

There is some evidence that afferent nerve activity from the pelvic floor and urethra is involved in detrusor inhibition during bladder filling, and therefore suggesting that SUI secondary to pelvic floor deficiency can result in DO due to decreased afferent nerve activity.[10]

4. Economic Costs and Quality of Life

To date, no studies have identified costs of urinary incontinence by type. Costs include routine care costs, such as laundry, pads and medications, loss of productivity and the cost of consequences such as urinary tract infections, falls and fractures. In one study, it was found that patients with MUI can have a 3-fold higher risk of falling than patients without MUI, while SUI and UUI were not significantly associated with falls.[11] The costs associated with urinary incontinence are borne by society, which includes the patient and family, the government and the health providers.

In the US, the direct healthcare costs for urinary incontinence (all types) in 1995 were estimated to be $US16.3 billion per year.[12] This rose to $US19.5 billion in 2000, with $US14.2 billion being borne by community residents and $US5.3 billion by institutional residents.[13]

In the UK, the direct costs of clinically significant storage symptoms in 2000, borne by the health service, were estimated to be £536 million (£233 million for women), and those borne by individuals to be £207 million (£178 million for women). The intangible costs borne by individuals were estimated to be £669 million (£368 million for women). This gives a total annual cost of £1.41 billion, amounting to about 1.1% of the National Health Service expenditure.[14]

There are many studies that assess the effects of SUI and UUI on quality of life (QoL) separately, but very few that assess the effects of MUI on QoL. Urgency is one of the most bothersome lower urinary tract symptoms, and thus, patients with UUI and MUI have worse quality of life than those with only SUI.[15] In a recent study, MUI had the highest impact on quality of life, with UUI and SUI having lower but similar impacts.[16] There is also an increase in symptoms of depression and anxiety in patients with urinary incontinence, as well as degradation in generic quality of life, especially physical, social and emotional functioning. People who have urinary incontinence restrict their exercise, are embarrassed to go out and may become home-bound. Incontinence can also affect relationships, since some women may leak urine during the different stages of intercourse.[17]

5. History, Examination and Basic Assessment

Initial assessment (figure 1) of patients with MUI should include a detailed and accurate history and

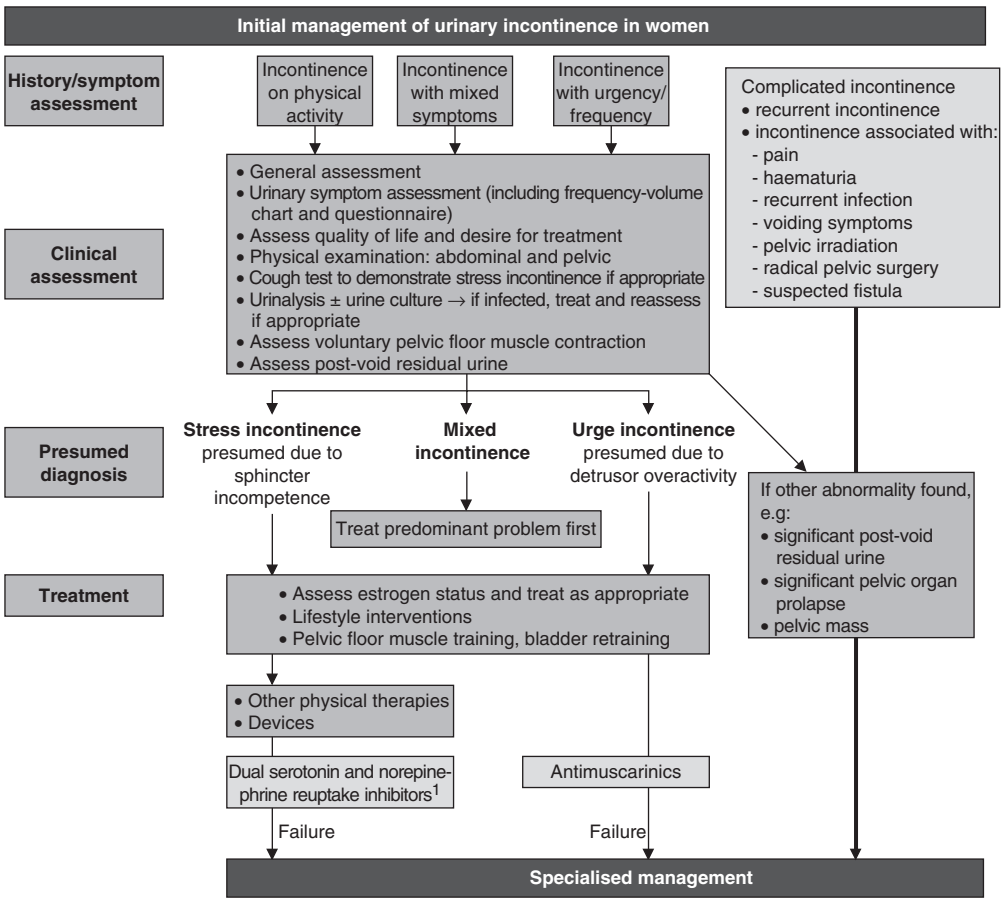

Fig. 1. International Consultation on Incontinence algorithm for initial management of female incontinence (reproduced from Abrams et al.,[18] with permission). **1.** Subject to local regulatory approval.

examination. The history should include inquiry about storage and voiding symptoms. Storage symptoms include frequency, urgency, UUI, SUI, nocturia, bladder sensation and pain. Voiding symptoms include hesitancy, slow stream, interrupted stream, straining and terminal dribbling. The number and type of pads used per day, if any, should also be documented. An important part of the history that is often missed is the relationship of leakage to intercourse and whether it is at penetration or orgasm.

The following questions should be asked:

- Do you leak when you cough, sneeze, laugh, bend or lift heavy objects, etc.?
- Do you leak when you have urgency?

These two questions will help in the diagnosis of SUI, UUI or MUI. If the answer to both questions is 'yes', then the patient probably has MUI. If the answer to the first question is 'yes' and to the second is 'no', the patient probably has SUI. Finally, if the answer to the first question is 'no' and to the second is 'yes', then the patient probably has UUI. A problem arises in those patients who have an urgency episode and trigger a DO wave when coughing or changing position, and therefore have difficulty in differentiating between UUI and SUI. A two-item stress/urgency incontinence questionnaire (S/UIQ), which is based on questions similar to those above but asks patients to recall the number of SUI and UUI episodes experienced during the preceding

week, has recently been validated and can be used as a useful screening tool.[19]

It is important to inquire about the patient's gynaecological and obstetric history, including the number and mode of deliveries, any episiotomies, tears and prolonged labour. The doctor also needs to ask about bowel function and, in particular, faecal incontinence. Previous surgical and gynaecological operations are also important, especially procedures that may have required bladder instrumentation or caused denervation to the pelvic floor.

Medications, including diuretics and α-adrenoceptor antagonists, can cause increased frequency and incontinence, respectively, and it is important to know if the patients are taking them.[20]

The type and amount of fluid that patients drink can have an effect on frequency and urgency, especially caffeinated drinks. It should be remembered that water-containing foods, such as fruits and vegetables, also add to the fluid load. Smoking has also been associated with urinary incontinence, partly as a result of chronic coughing and partly because of possible interference with collagen synthesis.[21,22]

It is also worth inquiring about family history, as there is some evidence that genetics can play a role in both UUI and SUI.[23]

Examination of women with MUI should start with a measurement of height and weight to calculate the body mass index, since there is an association between obesity and SUI.[24] Following that, an abdominal examination should be performed to look for any scars and masses; then a neurological examination of the lower limbs is required to look for evidence of neurological disease; finally, a vaginal and rectal examination should be carried out. During rectal examination, assessment of the anal tone, sensation, reflex and squeeze should be performed.

Vaginal examination should include assessment of estrogen status and pelvic squeeze, and should also look for atrophic vaginitis, pelvic organ prolapse (POP) and leakage during coughing or straining. POP is diagnosed using a Sim's speculum with the patient lying in the left lateral position and then asking the patient to bear down. Quantification of POP can be assessed using the International Continence Society pelvic organ prolapse quantification (ICS POP-Q) test.[25] In simple terms, three types of POP are identified: anterior vaginal wall, posterior vaginal wall and apex of the vagina or vault prolapse. The hymen is used as a reference point to define the degree of prolapse, and six specific vaginal sites are measured in centimetres from that reference point (figure 2), giving four degrees of prolapse.

Following the history and examination, the basic assessment should include urinalysis (dipsticks are adequate for initial assessment) to look for infection (leukocytes and nitrites), blood and glucose. This should be followed by a flow rate and post-void residual volume measurements using either a bladder scanner or 'in/out' catheterisation.

To assess lower urinary tract symptoms more accurately, patients should fill out a frequency/volume chart for at least 4 days.[27] A disease-specific QoL questionnaire, for example International Consultation on Incontinence Modular Questionnaire – urinary incontinence short form (ICIQ-UI SF),[28] should be filled out to assess the impact of MUI. Both these are important in the initial assessment of patients and also in assessing the effects of treatment. It is sometimes useful to quantify objectively the amount of urine lost by means of pad testing, although it is not diagnostic of the type of incontinence.[29]

Imaging of the lower urinary tract by ultrasound or abdominal radiographs is only recommended in patients whose initial evaluation or urinary symptoms suggest a lower urinary tract or pelvic patholo-

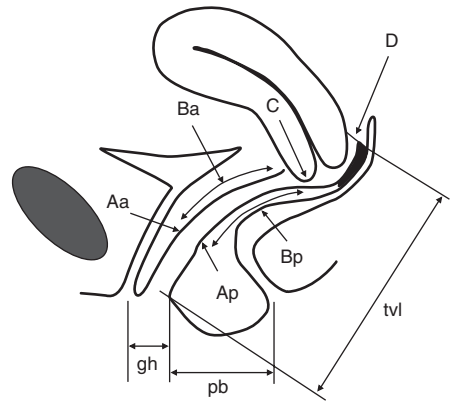

Fig. 2. Six sites (points Aa, Ba, C, D, Bp, and Ap), genital hiatus (gh), perineal body (pb), and total vaginal length (tvl), used for pelvic organ support quantification in the International Continence Society pelvic organ prolapse quantification (POP-Q) test (reproduced from Abrams et al.,[26] with permission).

gy. Similarly, cystoscopy is only recommended in patients whose initial evaluation suggests other pathologies such as 'dipstick' haematuria, raising the possibility of bladder cancer, or when patients suffer with pain or discomfort, suggesting the possibility of an intravesical lesion.[18]

6. Treatment

Once assessment, as described in section 5, has been completed, a preliminary symptomatic diagnosis of MUI can be made. Treatment of MUI is more difficult and complicated because of the existence of both UUI and SUI. These two pathologies and their different treatments should be emphasised and explained to the patient so their expectations are realistic. Time should be spent with the patient to explain that initial treatment will be aimed at the most bothersome and/or predominant symptom, and that one treatment may not cure both pathologies and combination treatment modalities may therefore be required. Treatment is initiated, assuming the patient's willingness, for the most bothersome symptom, i.e. either the UUI component or SUI component of MUI. The most bothersome symptom is usually also the most predominant one, but if they are not the same, then a joint decision between the treating doctor and the patient should be made as to which one should be treated first.

The principles of treatment for both UUI and SUI are aimed at alleviating symptoms and improving quality of life. Medical databases including MEDLINE, EMBASE and Science Direct were searched for treatment options for MUI, which can be divided into five treatment modalities:

1. lifestyle interventions;
2. pelvic floor muscle training (PFMT);
3. bladder training;
4. oral pharmacotherapy;
5. interventional/invasive therapy.

6.1 Lifestyle Interventions

Lifestyle interventions involving bodyweight, exercise, diet and smoking are often recommended by doctors for the treatment of urinary incontinence.

Weight loss is often recommended for women who have SUI, since obesity is an independent risk factor for SUI. However, there is only level 2 evidence that weight loss in morbidly obese women decreases SUI, and scant level 1 evidence that moderately obese women who lose weight have less SUI than those who do not.[30] However, there is also some evidence that weight loss is effective in UUI.[31]

Incontinence is often more exaggerated in some women while exercising, and thus, they may be advised not to exercise in order to stop the leakage. However, there is only level 2–3 evidence to suggest that active women or those involved in heavy lifting are more likely to have SUI than inactive women. There are no trials looking at whether stopping exercise reduces incontinence. On the contrary, exercising may play a role in strengthening the pelvic floor muscles and may be encouraged.[32]

Manipulation of fluid input to restrict carbonated and caffeine-containing drinks, and limiting fluid input to about 1.5–2.0L in 24 hours are also part of lifestyle interventions. The evidence regarding the effect of caffeine on UUI is conflicting with level 2–3 evidence that caffeine intake is associated with UUI, and scant level 1 evidence that decreasing caffeine improves UUI. In a randomised, controlled, crossover trial of 69 women with either USI or DO, it was shown that decreasing fluid intake reduced urinary incontinence episodes in both groups, while the reduction of caffeine had no effect.[33] There also seems to be a reduced risk of UUI with higher consumption of vegetables, bread, chicken, Vitamin D, protein and potassium.[34,35]

The effect of smoking on urinary incontinence is conflicting. It seems to increase the risk of severe urinary incontinence, but there are no data available as to whether stopping smoking reduces urinary incontinence. On the one hand, smokers are more likely to have violent coughing and, therefore, more likely to increase their abdominal pressures causing SUI, while on the other hand, they seem to have stronger urethral sphincters.[30] Nicotine also seems to produce phasic contractions of the detrusor *in vitro* and has been implicated in OAB.[36,37]

Other lifestyle interventions that have been tried include avoiding constipation, since straining may be a risk factor for POP and SUI. Also crossing the legs and bending forwards may decrease SUI. However, there are no trials available to suggest that

reducing constipation or changing posture decrease SUI.

The evidence for lifestyle interventions in the treatment of MUI is not as good as that for other forms of treatment, and implementation of these interventions requires stamina and dedication because the results may take longer to achieve. However, such changes are generally cheap and easy to implement. Lifestyle interventions are often combined with bladder training and pelvic floor exercises.

6.2 Pelvic Floor Muscle Training

PFMT involves voluntary contraction by tightening and squeezing the pelvic floor muscles to prevent leakage. Different mechanisms may be involved by which PFMT prevents SUI. A well timed strong and fast pelvic floor contraction can prevent SUI by squeezing the urethra and increasing the intra-urethral pressure above the intra-abdominal pressure as well as possibly preventing urethral descent and pushing the urethra against the back of the symphysis pubis.[38]

Patients with UUI are taught to tighten the pelvic floor when they get an involuntary detrusor contraction and in situations that can result in urgency, for example when UUI results from a change in posture, such as sitting up from lying down or standing up from a sitting position.

Many different training programmes have been proposed for PFMT and are easily available online or in print from continence foundations. They all seem to be more effective than placebo in the treatment of both SUI and UUI, and thus MUI, but it should be remembered that an intensive and well supervised programme, within service constraints, provides better results than a simple unsupervised programme.[39,40] Unfortunately, well supervised programmes are not available in all healthcare systems, and are mainly available in Scandinavian countries; thus, providing written instructions and regular follow-up with patient motivation is probably a good alternative and may achieve good results in some patients.

6.3 Bladder Training

Bladder training involves a scheduled voiding program with gradual increase of voiding intervals. It aims to regain bladder control by suppressing involuntary detrusor contractions, possibly through increased feedback inhibition and modulation of afferent sensory impulses, thereby increasing the voided volumes and the time interval between voids, and thus improving the voiding pattern by reducing frequency and incontinence episodes. The patients are taught to void regularly every hour on the hour and then asked to increase the duration between voids by 15–30 minutes each week until they feel comfortable with their urinary frequency. Bladder training can be supplemented by relaxation and distraction techniques.[41,42]

There does not seem to be a difference in outcome between patients treated with PFMT or bladder training.[43] However, combining both treatments is more effective in the short term than PFMT alone. From a statistical point of view, this combination benefit may not be sustainable in the long term. However, from the patient's perspective, there also seems to be an improvement in the long term.[38]

Both biofeedback (technique by which information about a normally unconscious physiological process is presented to the patient and/or the therapist as a visual, auditory or tactile signal) and/or electrical stimulation (application of electrical current to stimulate the pelvic viscera or their nerve supply) have been used in the treatment of urinary incontinence. However, they do not seem to provide any additional post-treatment benefits compared with PFMT or bladder training alone.[44,45] However, these methods can be used as adjuncts in patients who are unable to locate their pelvic floor muscles and are unable to contract them voluntarily.

Since PFMT and bladder training are cheap, easy and effective with no adverse effects, they should be used as first-line therapy in the treatment of MUI. However, these treatments need resilience and dedication from both patients and the person treating them, since their therapeutic effects are not immediately apparent. It is advisable to use bladder diaries and QoL questionnaires in the assessment of treatment effects in patients treated with PFMT and bladder training.

If there is no improvement in the patient's perceived symptoms after 1–3 months of treatment, assuming patient compliance, then the patient should be re-evaluated and oral pharmacotherapy considered.

6.4 Oral Pharmacotherapy

Oral pharmacotherapy for the treatment of MUI produces a dilemma for the treating clinician. Most pharmacological drug trials have looked at either SUI or UUI separately with very few trials looking at MUI specifically; this makes it difficult to apply evidence-based medicine to the treatment of MUI.

Pharmacological treatment of SUI aims to increase urethral closure pressure by increasing urethral smooth and striated muscle tone. Treatment of UUI, on the other hand, aims to reduce detrusor contraction and increase bladder capacity. Many drugs have been tried but have been limited by their adverse effects, limited efficacy and availability of randomised, controlled trials. The basis for use of these drugs includes the presence of different types of receptors in the human bladder and urethra. The receptors in the bladder include β_1, β_2 and β_3-adrenoceptors and muscarinic receptors, while in the urethra, the receptors include α- and β-adrenoceptors. Estrogen receptors are present in both the bladder and urethra, and seem to play an important yet unidentified role in the continence mechanism. Serotonergic receptors, in Onuf's nucleus, also appear to play a role.

6.4.1 α-Adrenoceptor Agonists

α-Adrenoceptor agonists such as ephedrine, norephedrine (level 3 evidence), midodrine (level 2 evidence) and methoxamine (level 2 evidence) have been used in the treatment of SUI. These drugs have been limited by their adverse effects, including increased blood pressure, headache, tremor and sleep disturbances.[46] Midodrine has only been licensed in Finland for the treatment of SUI.[47]

6.4.2 β-Adrenoceptor Antagonists

β-Adrenoceptor antagonists, such as propranolol, produce their effects by blocking β-adrenoceptors and enhancing the effects of norepinephrine (noradrenaline) on α-adrenoceptors. These drugs are also limited by their cardiac and pulmonary adverse effects.

6.4.3 β_2-Adrenoceptor Agonists

β_2-adrenoceptor agonists, such as clenbuterol, can increase urethral closure pressure by increasing the contractility of fast-contracting striated muscle fibres through potentiation of acetylcholine at the neuromuscular junction. It was initially developed as a bronchodilator. Clenbuterol was statistically significantly better than placebo in reducing pad weight and frequency of incontinence episodes, and in increasing maximum urethral closure pressure during urodynamics. It has a level 2 evidence for its effects but has only been approved in Japan for treatment of SUI.[48] Its adverse effects include tremor, headache and tachycardia. β_2-Adrenoceptors agonists also have a relaxing effect on the smooth detrusor muscle during bladder filling. In a double-blind study, clenbuterol has shown good therapeutic effects in 15 of 20 women with UUI.[49] Therefore, in theory, it may be effective in MUI; however, further trials are required.

6.4.4 Tricyclic Antidepressants

Imipramine is the main tricyclic antidepressant that has been used in incontinence. Its main use is in nocturnal enuresis in children, but has also been used in the treatment of SUI, UUI and MUI.[50] The mechanism of action of imipramine is not clear, but it does seem to have marked systemic anticholinergic action as well as blockade of the reuptake of serotonin and norepinephrine. Imipramine also has cardiotoxic adverse effects, including orthostatic hypotension and ventricular arrhythmias. There are no randomised controlled trials looking at the effects of imipramine in UUI, SUI or MUI, but some open-label studies have shown some beneficial effects in SUI (level 3 evidence).[51]

6.4.5 Serotonin and Norepinephrine Reuptake Inhibitors

Duloxetine hydrochloride is a balanced and potent dual reuptake inhibitor of serotonin and norepinephrine. Both these neurotransmitters are believed to play key roles in lower urinary tract function. Serotonin suppresses parasympathetic activity and enhances sympathetic and somatic activity, causing bladder relaxation and increasing outlet resistance, thus promoting urine storage. Norepinephrine variably affects lower urinary tract function, depending on the receptor subtype with which

it interacts. Serotonin and norepinephrine amplify the effect of glutamate on urethral striated muscle contraction. Glutamate is an excitatory neurotransmitter in bladder and urethral striated muscle reflex pathways, and plays a role in initiating urethral striated muscle contraction during bladder filling.[52] In the voiding phase, there is suppression of glutamate transmission, which will result in inhibition of sphincter contraction and relaxation of the urethral striated muscle, and thus, bladder emptying.[53]

During bladder filling, duloxetine is thought to act centrally in the nervous system by stimulating sacral pudendal motor neurones α_1-adrenergic and serotonin 5-HT_2 receptors through increasing the concentration of serotonin and norepinephrine in Onuf's nucleus, and thus amplifying the effect of glutamate. The increase in pudendal nerve activity increases striated urethral rhabdosphincter contractility and promotes urethral closure during filling.[54]

This central mode of action through the sacral cord pudendal nerve nucleus implies that the cardiovascular class effect seen with α-adrenergic agents would be reduced with the serotonin and norepinephrine reuptake inhibitors. In fact, in the trials, duloxetine did not affect blood pressure significantly or cause ECG changes.[55]

In four randomised, placebo-controlled, multicentre clinical trials performed worldwide involving nearly 1800 women, duloxetine reduced the number of urinary incontinence episodes by at least 50% in more than half the women with SUI compared with 33% in placebo-treated patients.[56-59] On the basis of an intention-to-treat statistical analysis, duloxetine also seemed to improve quality of life to a clinically relevant extent, as measured by the Incontinence Quality of Life Questionnaire (I-QOL), and made patients feel better about their condition, as measured by the Patient Global Impression of Improvement (PGI-I),[60] compared with placebo. Nausea is the main adverse effect with duloxetine, but it is generally well tolerated, ranging from mild to moderate and lasting between 1 and 4 weeks. One way of reducing the risk of nausea is to start duloxetine treatment with 20mg twice daily for 2 weeks, and then to increase the dose to the recommended 40mg twice daily.[61] Other common adverse events observed in the clinical studies were dry mouth, fatigue, insomnia, constipation, headache, dizziness, somnolence and diarrhoea.

Duloxetine (level 1 evidence) is licensed at 40mg twice daily for the treatment of SUI in the European Union but not in the USA. Interestingly, it has also been licensed as an antidepressant at 60mg once daily.[62] There have been some reports by the FDA of increased suicidal ideation in adults with depression who are taking antidepressants, but none have been reported in the clinical trials on incontinence and most patients in these trials did not have depression to start with.

In a randomised, controlled trial of duloxetine alone, PFMT alone, combined treatment and no active treatment of women with SUI, it was found that combination therapy of duloxetine and PFMT was more efficacious in reducing urinary incontinence episodes than either alone. There was also better improvement of quality of life with combined treatment.[63]

In a sub-analysis of a previous trial conducted with duloxetine, it seems to cause a similar reduction in frequency of urinary incontinence episodes in MUI and SUI.[64] In 2004, a multicentre, multinational trial was completed, which compared the efficacy and safety of duloxetine and placebo in women with symptoms of MUI. Results of that trial should be available in the near future, but in the meantime, it seems reasonable to use duloxetine in women with stress-predominant MUI.

6.4.6 Antimuscarinics

Antimuscarinics form the cornerstone oral pharmacological treatment for patients with OAB and UUI.[65] Currently, there are six main agents marketed and used with different preparations and formulations. These include oxybutynin, tolterodine, propiverine, solifenacin, darifenacin and trospium chloride. Fesoterodine will be available in the near future. Five muscarinic receptor subtypes exist (M_1–M_5) in the detrusor muscle, with the M_2 receptors accounting for about two-thirds and the M_3 receptors for about one-third of these receptors. The M_3 receptors have been found to be predominantly responsible for normal and abnormal detrusor contractions.[66]

Essentially, all the antimuscarinics have a similar mode of action, which is to act on the muscarinic

receptors in the bladder to block the action of acetylcholine and thus reduce detrusor contractions. Their main differences lie in their affinity and selectivity for the muscarinic receptors both in the bladder and other organs in the body, thus producing differing extents of similar adverse effects and treatment results. The main adverse effects include dry mouth, constipation, blurred vision and dizziness.

Many randomised, double-blind, placebo-controlled trials have been conducted with all the antimuscarinic agents and they all have level 1 evidence in reducing UUI episodes compared with placebo.[67] However, only three agents have been examined in trials in the treatment of MUI and these are oxybutynin, tolterodine and solifenacin.

In an 8-week, randomised, double-blind, placebo-controlled, multicentre, multinational trial of 854 adult women with urgency-predominant MUI, tolterodine extended-release (ER) 4mg once daily, was compared to placebo once daily.[68] There were 101 study sites in Europe, with 92% of patients receiving tolterodine and 89% of patients receiving placebo completing the trial. Results, analysed on an intention-to-treat basis, showed that tolterodine produced a statistically significant reduction in weekly UUI episodes as well as daily urgency and frequency episodes, with increase in bladder capacity and improvement in quality of life as measured by the ICIQ-LUTSqol[69] (previously known as the King's Health Questionnaire) compared with placebo. There was no significant difference in either treatment group with regard to response to treatment between patients who experienced UUI first compared with those experiencing SUI first. Both treatment and placebo groups had equal and significant reductions in the number of SUI episodes, suggesting a placebo effect.

This was a well conducted trial that looked at both subjective and objective measures of improvement. However, although the decrease in urinary incontinence was statistically significant, a reduction of four incontinence episodes per week may not be clinically significant. Also, the conclusion states that it would be justified to treat the UUI first, for women whose UUI and SUI episodes occur with equal frequency, but this is not completely accurate because treatment should be aimed at the most troublesome symptom.

The second trial using tolterodine looked at the effects of twice-daily tolterodine for 16 weeks in patients with urgency-predominant MUI and compared them with the effects in patients with UUI alone. This was a single-blind, multicentre trial and patients were analysed on a per-protocol basis. There were significant median changes from baseline in urinary frequency, UUI and nocturia in the two groups, but no significant differences in treatment effects between the two groups; thus, it was concluded that tolterodine is as effective in MUI as it is in UUI. There was no mention of changes or the effects on urgency in the placebo-treated group.[70]

There are no prospective studies to date comparing oral oxybutynin with placebo in MUI. However, in a retrospective study of 25 women with urodynamic mixed incontinence who were treated with various combinations of oxybutynin, imipramine and estrogen, 32% of the patients treated were cured and 28% were markedly improved.[71] In that study, urodynamics did not predict cure or improvement, and the balance of symptoms of UUI and SUI was not discussed.

On the other hand, transdermal (TD) oxybutynin, which is a new formulation of oxybutynin recently marketed in the US and Europe, has been involved in trials that included patients with MUI. In a 12-week randomised, double-blind, placebo-controlled trial of TD oxybutynin, three doses were evaluated in 520 adult men and women with UUI and MUI.[72] This was followed by another 12-week period of open-label dose titration to assess continued safety and efficacy. It was shown that TD oxybutynin 3.9mg was the optimal dose that significantly reduced the median number of weekly urinary incontinence episodes and daily frequency episodes, as well as increasing bladder capacity and significantly improving quality of life as measured by the Incontinence Impact Questionnaire (IIQ).

In another trial, the efficacy and safety of TD oxybutynin 3.9mg and oral tolterodine ER 4mg were compared with that of placebo in patients with UUI and MUI who had previously responded to antimuscarinic therapy.[73] This was a 12-week randomised, double-blind, double-dummy, placebo-controlled trial of 361 adult patients, with a 2-week washout period and 1–2 weeks of bladder diary completion prior to randomisation. Results showed

that both TD oxybutynin and tolterodine ER equally and significantly reduced the median number of daily incontinence episodes compared with placebo, as well as increasing the average voided volume per void and improving quality of life measured by the IIQ. Pruritus was the main adverse effect of the oxybutynin patch, and dry mouth was the main adverse effect of tolterodine ER.

Although the two TD oxybutynin trials showed that there was reduction in urinary incontinence episodes, there was no mention of the effects on MUI or on the SUI component, especially since two-thirds of the women included had concomitant symptoms of SUI.

Solifenacin has not been studied in a trial looking at MUI specifically. However, a subgroup analysis of data pooled from four 12-week phase III trials conducted globally in patients with UUI or urgency-predominant MUI was carried out on an intention-to-treat basis. Patients with stress-predominant MUI were excluded. Patients received solifenacin 5mg or 10mg or matching placebo. There was a statistical reduction from baseline in the symptoms of urgency, frequency and UUI in the groups taking solifenacin 5mg and 10mg compared with placebo. Normalisation of frequency and resolution of urgency and UUI was also compared in this sub-analysis. There was statistically significant resolution of urgency with both active treatment doses in the MUI group, but only a significant resolution of incontinence episodes with the 10mg dose. There was a normalisation of frequency (less than eight micturitions per day) with both treatment doses in the MUI group compared with placebo. Adverse effects were similar to those of other anitmuscarinics, and treatment was well tolerated in both treatment groups as evidenced by the comparable discontinuation rates to placebo.[74]

Therefore, it can be concluded that combination therapy with duloxetine and an antimuscarinic is likely to be suitable for patients with MUI. However, no trial to date has been conducted to look into the safety and efficacy of this combination. It is also reasonable to conclude that other antimuscarinics with similar efficacy to tolterodine and solifenacin can be used safely in MUI. In fact, in clinical practice, antimuscarinics are being used as first-line therapy in the treatment of MUI, irrespective of whether it is stress or urgency predominant.

6.4.7 Estrogens

There are no trials looking at the effect of estrogen in women with MUI. However, for the treatment of SUI, estrogen has been the subject of many trials, but most were not randomised, blinded or placebo controlled. Also, many different dosages and different formulations, including oral and vaginal estrogens, have been used. Two meta-analyses have been conducted, which concluded that estrogen is not objectively efficacious in the treatment of SUI when given alone. However, when combined with other forms of therapy, such as other pharmacological agents or PFMT, it may have a role.[75,76] Some trials have reported that, subjectively, improvement did occur with estrogen when compared with placebo.

The evidence is scarce regarding the efficacy of estrogens in the treatment of UUI. Local administration of vaginal estrogens in postmenopausal women with urogenital atrophy who have urgency, frequency and UUI seems to be beneficial in reducing these symptoms.[77] This may be a result of reversal of the atrophy rather than actual effect on the lower urinary tract. Other trials have concluded that, although estrogens produced subjective and objective improvement in women with UUI, it was not statistically different to placebo.[78] Estrogen has level 2 evidence in the treatment of SUI and UUI.

6.4.8 Antidiuretics

Decreasing urine production by the kidneys would, in theory, prolong bladder-filling time, increasing the time to reach maximum capacity, thus reducing incontinence episodes. Desmoporessin, a synthetic analogue of antidiuretic hormone (vasopressin), can be used to produce antidiuresis. It has been used in the treatment of patients with nocturia, nocturnal enuresis and diabetes insipidus.

In a randomised, double-blind, placebo-controlled, multicentre, multinational proof-of-concept study, desmopressin 40μg was administered nasally to 64 women over 10 days (7 days active drug and 3 days placebo).[79] 57 women completed the trial. Leakage was measured using incontinence pads. The results showed that patients taking desmopressin had a significantly higher mean incidence of

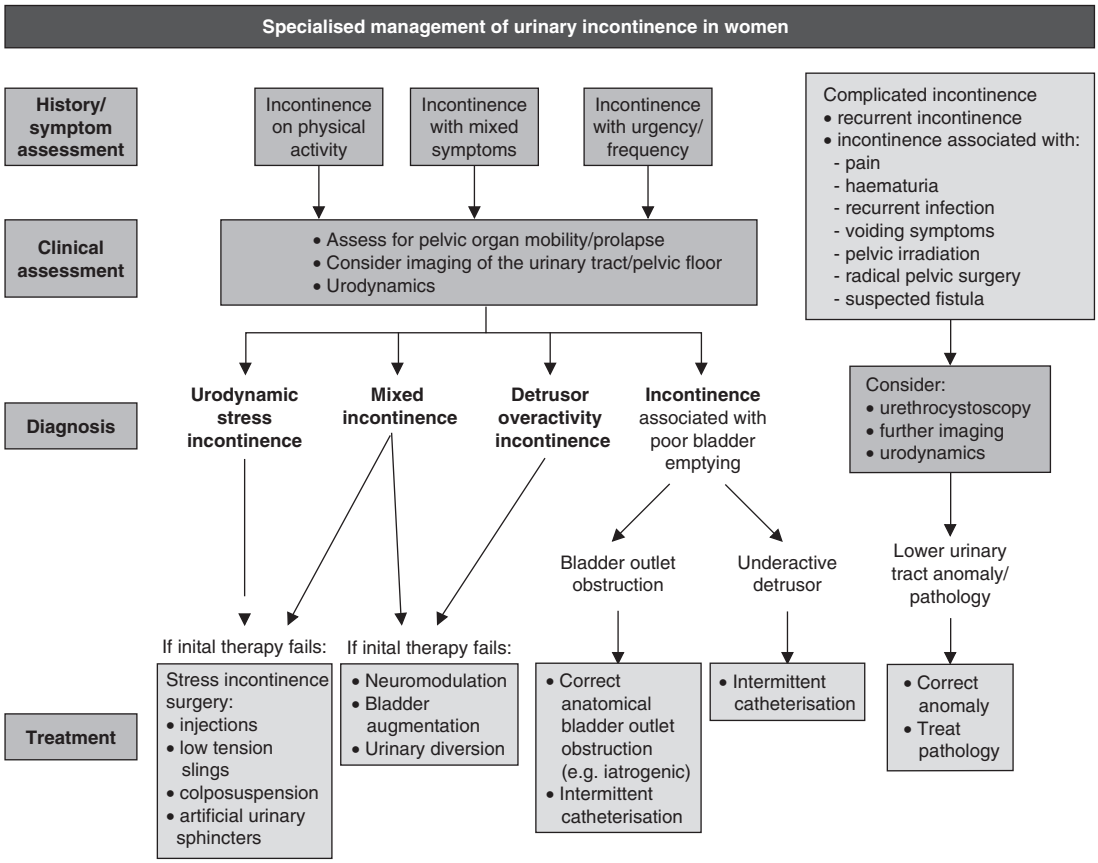

Fig. 3. International Consultation on Incontinence algorithm for specialised management of female incontinence (reproduced from Abrams et al.,[18] with permission).

periods with no leakage during the first 4 hours and 8 hours after taking desmopressin, but a similar incidence thereafter. The volume leaked with desmopressin was less than with placebo and the time to the first incontinence episode was longer. The effect appeared to be the same for all the three types of incontinence (SUI, UUI and MUI).

Desmopressin can cause hyponatraemia and fluid retention, although this was not reported by patients in the trial. The study did not look at the effects of desmopressin on patients' quality of life, but the results on incontinence are very encouraging and antidiuresis could have a future potential role for the treatment of MUI in women.

6.5 Interventional/Invasive Therapy

Most women with MUI gain some improvement with PFMT, bladder training, oral pharmacotherapy and lifestyle interventions. However, there remain some who are not satisfied with the treatment either because of failure of initial management or severe impairment of quality of life. In such instances, referral for specialist management by a urologist with an interest in female urology, or by a urogynaecologist, is highly recommended.

Specialist assessment (figure 3) includes reassessment for POP and urodynamics.[80] Urodynamics helps to confirm the diagnosis, but in some patients it is sometimes difficult to reproduce both stress or urgency incontinence, and ambulatory urodynamics is recommended in those instances.

Urodynamic assessment should include filling and voiding cystometry. Either urethral pressure profilometry to measure maximum urethral closure pressure, or Valsalva leak point pressure to assess urethral function can be used; however their use remains to be debatable because their clinical significance has not been fully established.

Once a diagnosis is established, further treatment can follow one of two paths: treatment of either the UUI or the SUI component of MUI. This will again depend on the most troublesome symptom. Once urodynamic confirmation of symptoms is obtained, the clinical diagnosis of UUI changes to DOI and that of SUI changes to USI.

Treatment of DOI aims to reduce or abolish urgency and incontinence, and to increase bladder capacity. This may initially include intravesical installation of resiniferatoxin or botulinum toxin-A injections into the detrusor muscle. If that is not successful, neuromodulation could be considered. Finally, if DOI persists, surgical options will need to be considered, including bladder augmentation, detrusor myectomy and urinary diversion.[65] Obviously, all these operations carry risks and these must be weighed against the benefit of improvement in quality of life. There are no trials to date looking at the effects of these measures on the SUI component of MUI.

Surgical treatment of USI, on the other hand, aims to reduce or abolish leakage during stress situations, such as coughing and exercise, and until recently, this was the only treatment option for SUI and USI. Surgical treatment of USI includes periurethral or para-urethral injectable agents, such as collagen; low tension slings, such as transvaginal or transobturator tapes; colposuspension; and artificial urinary sphincters.[81] There are many trials looking at the effects of surgery on SUI and USI; however, only a few trials have been conducted to look at the effects of surgery for SUI or USI in MUI, and specifically on the effects of surgery on the UUI or DOI component of MUI.

There is level 3 evidence from retrospective studies that women who had operations for USI and who also had DO or DOI preoperatively will have a less favourable outcome from surgery than those with USI and stable bladders,[82,83] with about 60–80% of them having improvement in OAB symptoms.[84,85] There is also level 3 evidence, in patients with MUI, that the outcome of USI surgery, especially with regards to cure of urgency incontinence, is better in those patients whose SUI symptoms preceded their OAB symptoms than for those with OAB preceding SUI symptoms.[86] However, even then, the good initial cure rates will probably only last about 4 years,[87] with a substantial decrease in cure rates following that.

Many of the surgical trials were retrospective, single-centre, short term and included relatively small numbers. Also, importantly, there was inconsistency in how study populations were defined, in when surgery was performed (either before or after urodynamic diagnosis) and in whether improvement was determined by clinical or urodynamic diagnosis. It would be of interest in the future to look at whether there is a difference between cure rates for low-tension slings and colposuspension.

Before any surgery for stress-predominant MUI, it is important to discuss with all female patients that urodynamic evaluation is a prerequisite before proceeding. They should also be warned that symptoms of urgency and UUI may not improve with surgery, since the diagnosis based on symptoms is not very accurate.[88,89]

7. Conclusion

MUI is a prevalent but difficult condition to manage because it includes symptoms of both stress and urgency incontinence. Management should include a thorough history and examination to exclude other pathologies. The voiding diary and QoL questionnaires form an indispensable part of both diagnosis and treatment. Treatment expectations should be realistic and strike a balance between the patient's expectations and what is actually achievable; the best way to proceed should be a mutual decision between patient and doctor. Initial treatment concentrates on the most troublesome symptom and includes lifestyle interventions and pelvic floor muscle and bladder training. These can be combined with oral pharmacotherapy for optimum results. Many different oral medications are available; however, duloxetine is the only one recommended for treatment of SUI and therefore stress-predominant MUI, and antimuscarinics for treatment of OAB and thus urgency-predominant MUI. Combining these

two drug classes is also a feasible treatment option but, to date, this has not been examined in a randomised controlled trial. If these treatment options fail, further investigation with urodynamics is required to confirm the diagnosis. Once diagnosis is confirmed, there are invasive minor and major surgical procedures available, but none have been evaluated in patients with MUI. It should be emphasised to patients with MUI that cure rates following surgery for SUI may be reduced, and that OAB symptoms will remain and may even worsen.

Assessment of patients with MUI should be continuous, as some patients will improve after conservative and medical treatment of their most predominant symptom, but other symptoms may arise later.

Trials are needed to study the epidemiology and pathophysiology of MUI, and the short- and long-term cure rates of the various conservative, medical and surgical treatments. However, before this can be achieved, there needs to be a standardisation of the terminology used in MUI trials, specifically clinical and urodynamic definitions.

Acknowledgements

Dr Hashim Hashim is or has been an investigator, lecturer and consultant for many pharmaceutical companies producing or developing drugs for lower urinary tract symptoms.

Professor Paul Abrams is or has been an investigator, lecturer and consultant for many pharmaceutical companies producing or developing drugs for lower urinary tract symptoms.

No sources of funding were used in the preparation of this article.

References

1. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002; 21 (2): 167-78
2. Hunskaar S, Burgio K, Clark A, et al. Epidemiology of urinary (UI) and faecal (FI) incontinence and pelvic organ prolapse (POP). In: Abrams P, Cardozo L, Khoury S, et al., editors. Incontinence. Paris: Health Publication Ltd, 2005: 255-312
3. Stewart WF, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the United States. World J Urol 2003 May; 20 (6): 327-36
4. Hannestad YS, Rortveit G, Sandvik H, et al. A community-based epidemiological survey of female urinary incontinence: the Norwegian EPINCONT study. Epidemiology of Incontinence in the County of Nord-Trondelag. J Clin Epidemiol 2000 Nov; 53 (11): 1150-7
5. Hashim H, Abrams P. Is the bladder a reliable witness for predicting detrusor overactivity? J Urol 2006 Jan; 175 (1): 191-5
6. Brading AF. A myogenic basis for the overactive bladder. Urology 1997 Dec; 50 (6A Suppl.): 57-67
7. de Groat WC. A neurologic basis for the overactive bladder. Urology 1997 Dec; 50 (6A Suppl.): 36-52
8. Mostwin J, Bourcier A, Haab F, et al. Pathophysiology of urinary incontinence, fecal incontinence and pelvic organ prolapse. In: Abrams P, Cardozo L, Khoury S, et al., editors. Incontinence. Paris: Health Publication Ltd, 2005: 423-84
9. Rortveit G, Daltveit AK, Hannestad YS, et al. Vaginal delivery parameters and urinary incontinence: the Norwegian EPINCONT study. Am J Obstet Gynecol 2003 Nov; 189 (5): 1268-74
10. Mostwin JL. Pathophysiology: the varieties of bladder overactivity. Urology 2002 Nov; 60 (5 Suppl. 1): 22-6
11. Takazawa K, Arisawa K. Relationship between the type of urinary incontinence and falls among frail elderly women in Japan. J Med Invest 2005 Aug; 52 (3-4): 165-71
12. Wilson L, Brown JS, Shin GP, et al. Annual direct cost of urinary incontinence. Obstet Gynecol 2001 Sep; 98 (3): 398-406
13. Hu TW, Wagner TH, Bentkover JD, et al. Costs of urinary incontinence and overactive bladder in the United States: a comparative study. Urology 2004 Mar; 63 (3): 461-5
14. Turner DA, Shaw C, McGrother CW, et al. The cost of clinically significant urinary storage symptoms for community dwelling adults in the UK. BJU Int 2004 Jun; 93 (9): 1246-52
15. Coyne KS, Zhou Z, Thompson C, et al. The impact on health-related quality of life of stress, urge and mixed urinary incontinence. BJU Int 2003 Nov; 92 (7): 731-5
16. Monz B, Pons ME, Hampel C, et al. Patient-reported impact of urinary incontinence-Results from treatment seeking women in 14 European countries. Maturitas 2005 Nov; 52 Suppl. 2: 24-34
17. Yip SK, Chan A, Pang S, et al. The impact of urodynamic stress incontinence and detrusor overactivity on marital relationship and sexual function. Am J Obstet Gynecol 2003 May; 188 (5): 1244-8
18. Abrams P, Andersson KE, Brubaker L, et al. Recommendations of the International Scientific Committee: evaluation and treatment of urinary incontinence, pelvic organ prolapse and faecal incontinence. In: Abrams P, Cardozo L, Khoury S, et al., editors. Incontinence. Paris: Health Publication Ltd, 2005: 1589-630
19. Bent AE, Gousse AE, Hendrix SL, et al. Validation of a two-item quantitative questionnaire for the triage of women with urinary incontinence. Obstet Gynecol 2005 Oct; 106 (4): 767-73
20. Steele AC, Kohli N, Mallipeddi P, et al. Pharmacologic causes of female incontinence. Int Urogynecol J Pelvic Floor Dysfunct 1999; 10 (2): 106-10
21. Bump RC, McClish DK. Cigarette smoking and urinary incontinence in women. Am J Obstet Gynecol 1992; 167: 1213-8
22. Bump RC, McClish DK. Cigarette smoking and pure genuine stress incontinence of urine: a comparison of risk factors and determinants between smokers and nonsmokers. Am J Obstet Gynecol 1994 Feb; 170: 579-82
23. Mushkat Y, Bukovsky I, Langer R. Female urinary stress incontinence: does it have familial prevalence? Am J Obstet Gynecol 1996 Feb; 174 (2): 617-9
24. Bai SW, Kang JY, Rha KH, et al. Relationship of urodynamic parameters and obesity in women with stress urinary incontinence. J Reprod Med 2002 Jul; 47 (7): 559-63
25. Bump RC, Mattiasson A, Bo K, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. Am J Obstet Gynecol 1996 Jul; 175 (1): 10-7

26. Staskin D, Hilton P, Emmanuel A, et al. Initial assessment of incontinence. In: Abrams P, Cardozo L, Khoury S, et al., editors. Incontinence. Paris: Health Publication Ltd, 2005:
27. Schick E, Jolivet-Tremblay M, Dupont C, et al. Frequency-volume chart: the minimum number of days required to obtain reliable results. Neurourol Urodyn 2003; 22 (2): 92-6
28. Avery K, Donovan J, Peters TJ, et al. ICIQ: a brief and robust measure for evaluating the symptoms and impact of urinary incontinence. Neurourol Urodyn 2004; 23 (4): 322-30
29. Abrams P, Blaivas JG, Stanton SL, et al. The standardisation of terminology of lower urinary tract function. The International Continence Society Committee on Standardisation of Terminology. Scand J Urol Nephrol Suppl 1988; 114: 5-19
30. Hannestad YS, Rortveit G, Daltveit AK, et al. Are smoking and other lifestyle factors associated with female urinary incontinence? The Norwegian EPINCONT Study. BJOG 2003 Mar; 110 (3): 247-54
31. Subak LL, Whitcomb E, Shen H, et al. Weight loss: a novel and effective treatment for urinary incontinence. J Urol 2005 Jul; 174 (1): 190-5
32. Bo K, Borgen JS. Prevalence of stress and urge urinary incontinence in elite athletes and controls. Med Sci Sports Exerc 2001 Nov; 33 (11): 1797-802
33. Swithinbank L, Hashim H, Abrams P. The effect of fluid intake on urinary symptoms in women. J Urol 2005 Jul; 174 (1): 187-9
34. Dallosso HM, McGrother CW, Matthews RJ, et al. Nutrient composition of the diet and the development of overactive bladder: a longitudinal study in women. Neurourol Urodyn 2004; 23 (3): 204-10
35. Dallosso HM, McGrother CW, Matthews RJ, et al. The association of diet and other lifestyle factors with overactive bladder and stress incontinence: a longitudinal study in women. BJU Int 2003 Jul; 92 (1): 69-77
36. Hisayama T, Shinkai M, Takayanagi I, et al. Mechanism of action of nicotine in isolated urinary bladder of guinea-pig: involvement of tachykinin(s) released by nicotine in the drug's sympathomimetic effect. Arch Int Pharmacodyn Ther 1989 Sep; 301: 277-84
37. Koley B, Koley J, Saha JK. The effects of nicotine on spontaneous contractions of cat urinary bladder in situ. Br J Pharmacol 1984 Oct; 83 (2): 347-55
38. Wilson PD, Berghmans B, Hagen S, et al. Adult conservative management. In: Abrams P, Cardozo L, Khoury S, et al., editors. Incontinence. Paris: Health Publication Ltd, 2005: 855-964
39. Millard RJ. Clinical efficacy of tolterodine with or without a simplified pelvic floor exercise regimen. Neurourol Urodyn 2004; 23 (1): 48-53
40. Nygaard IE, Kreder KJ, Lepic MM, et al. Efficacy of pelvic floor muscle exercises in women with stress, urge, and mixed urinary incontinence. Am J Obstet Gynecol 1996 Jan; 174 (1 Pt 1): 120-5
41. Publicover C, Bear M. The effect of bladder training on urinary incontinence in community-dwelling older women. J Wound Ostomy Continence Nurs 1997 Nov; 24 (6): 319-24
42. Roe B, Williams K, Palmer M. Bladder training for urinary incontinence in adults. Cochrane Database Syst Rev 2000; (2): CD001308
43. Yoon HS, Song HH, Ro YJ. A comparison of effectiveness of bladder training and pelvic muscle exercise on female urinary incontinence. Int J Nurs Stud 2003 Jan; 40 (1): 45-50
44. Burgio KL, Robinson JC, Engel BT. The role of biofeedback in Kegel exercise training for stress urinary incontinence. Am J Obstet Gynecol 1986 Jan; 154 (1): 58-64
45. Bo K, Talseth T, Holme I. Single blind, randomised controlled trial of pelvic floor exercises, electrical stimulation, vaginal cones, and no treatment in management of genuine stress incontinence in women. BMJ 1999 Feb; 318 (7182): 487-93
46. Alhasso A, Glazener C, Pickard R, et al. Adrenergic drugs for urinary incontinence in adults. Cochrane Database Syst Rev 2005; (3): CD001842
47. Weil EH, Eerdmans PH, Dijkman GA, et al. Randomized double-blind placebo-controlled multicenter evaluation of efficacy and dose finding of midodrine hydrochloride in women with mild to moderate stress urinary incontinence: a phase II study. Int Urogynecol J Pelvic Floor Dysfunct 1998; 9 (3): 145-50
48. Ishiko O, Ushiroyama T, Saji F, et al. beta(2)-adrenergic agonists and pelvic floor exercises for female stress incontinence. Int J Gynaecol Obstet 2000 Oct; 71 (1): 39-44
49. Gruneberger A. Treatment of motor urge incontinence with clenbuterol and flavoxate hydrochloride. Br J Obstet Gynaecol 1984 Mar; 91 (3): 275-8
50. Hunsballe JM, Djurhuus JC. Clinical options for imipramine in the management of urinary incontinence. Urol Res 2001 Apr; 29 (2): 118-25
51. Lin HH, Sheu BC, Lo MC, et al. Comparison of treatment outcomes for imipramine for female genuine stress incontinence. Br J Obstet Gynaecol 1999 Oct; 106 (10): 1089-92
52. Thor KB. Targeting serotonin and norepinephrine receptors in stress urinary incontinence. Int J Gynaecol Obstet 2004 Jul; 86 Suppl. 1: S38-52
53. Michel MC, Peters SL. Role of serotonin and noradrenaline in stress urinary incontinence. BJU Int 2004 Jul; 94 Suppl. 1: 23-30
54. Thor KB. Serotonin and norepinephrine involvement in efferent pathways to the urethral rhabdosphincter: implications for treating stress urinary incontinence. Urology 2003 Oct; 62 (4 Suppl. 1): 3-9
55. Mariappan P, Ballantyne Z, N'dow J, et al. Serotonin and noradrenaline reuptake inhibitors (SNRI) for stress urinary incontinence in adults. Cochrane Database Syst Rev 2005; (3): CD004742
56. Dmochowski RR, Miklos JR, Norton PA, et al. Duloxetine versus placebo for the treatment of North American women with stress urinary incontinence. J Urol 2003 Oct; 170 (4 Pt 1): 1259-63
57. Millard RJ, Moore K, Rencken R, et al. Duloxetine vs placebo in the treatment of stress urinary incontinence: a four-continent randomized clinical trial. BJU Int 2004 Feb; 93 (3): 311-8
58. Norton PA, Zinner NR, Yalcin I, et al. Duloxetine versus placebo in the treatment of stress urinary incontinence. Am J Obstet Gynecol 2002 Jul; 187 (1): 40-8
59. Van KP, Abrams P, Lange R, et al. Duloxetine versus placebo in the treatment of European and Canadian women with stress urinary incontinence. BJOG 2004 Mar; 111 (3): 249-57
60. Yalcin I, Bump RC. Validation of two global impression questionnaires for incontinence. Am J Obstet Gynecol 2003 Jul; 189 (1): 98-101
61. Bump R, Yalcin I, Voss S. The effect of duloxetine dose escalation and tapering on the incidence of adverse events (AE) in women with stress urinary incontinence (SUI) [abstract no. 116]. Neurourol Urodyn 2005 Sep; 24 (5/6): 582-3
62. Burt VK, Wohlreich MM, Mallinckrodt CH, et al. Duloxetine for the treatment of major depressive disorder in women ages 40 to 55 years. Psychosomatics 2005 Jul; 46 (4): 345-54
63. Ghoniem GM, Van Leeuwen JS, Elser DM, et al. A randomized controlled trial of duloxetine alone, pelvic floor muscle training alone, combined treatment and no active treatment in women with stress urinary incontinence. J Urol 2005 May; 173 (5): 1647-53
64. Bump RC, Norton PA, Zinner NR, et al. Mixed urinary incontinence symptoms: urodynamic findings, incontinence severity, and treatment response. Obstet Gynecol 2003 Jul; 102 (1): 76-83

65. Hashim H, Abrams P. Drug treatment of overactive bladder: efficacy, cost and quality-of-life considerations. Drugs 2004; 64 (15): 1643-56

66. Sellers DJ, Yamanishi T, Chapple CR, et al. M3 muscarinic receptors but not M2 mediate contraction of the porcine detrusor muscle in vitro. J Auton Pharmacol 2000 Jun; 20 (3): 171-6

67. Andersson KE, Appell R, Cardozo L, et al. Pharmacological treatment of urinary incontinence. In: Abrams P, Cardozo L, Khoury S, Wein A, editors. Incontinence. Paris: Health Publication Ltd, 2005: 809-54

68. Khullar V, Hill S, Laval KU, et al. Treatment of urge-predominant mixed urinary incontinence with tolterodine extended release: a randomized, placebo-controlled trial. Urology 2004 Aug; 64 (2): 269-74

69. Abrams P, Avery K, Gardener N, et al. ICIQ Advisory Board. The International Consultation on Incontinence modular questionnaire: www.iciq.net. J Urol 2006 Mar; 175 (3 Pt 1): 1063-6; discussion 1066

70. Kreder KJ, Brubaker L, Mainprize T. Tolterodine is equally effective in patients with mixed incontinence and those with urge incontinence alone. BJU Int 2003 Sep; 92 (4): 418-21

71. Karram MM, Bhatia NN. Management of coexistent stress and urge urinary incontinence. Obstet Gynecol 1989 Jan; 73 (1): 4-7

72. Dmochowski RR, Davila GW, Zinner NR, et al. Efficacy and safety of transdermal oxybutynin in patients with urge and mixed urinary incontinence. J Urol 2002 Aug; 168 (2): 580-6

73. Dmochowski RR, Sand PK, Zinner NR, et al. Comparative efficacy and safety of transdermal oxybutynin and oral tolterodine versus placebo in previously treated patients with urge and mixed urinary incontinence. Urology 2003 Aug; 62 (2): 237-42

74. Kelleher C, Cardozo L, Kobashi K, et al. Solifenacin: as effective in mixed urinary incontinence as in urge urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunt 2005 Nov; 8: 1-7

75. Moehrer B, Hextall A, Jackson S. Oestrogens for urinary incontinence in women. Cochrane Database Syst Rev 2003; (2): CD001405

76. Fantl JA, Cardozo L, McClish DK. Estrogen therapy in the management of urinary incontinence in postmenopausal women: a meta-analysis: First report of the Hormones and Urogenital Therapy Committee. Obstet Gynecol 1994 Jan; 83 (1): 12-8

77. Cardozo L, Lose G, McClish D, et al. A systematic review of the effects of estrogens for symptoms suggestive of overactive bladder. Acta Obstet Gynecol Scand 2004 Oct; 83 (10): 892-7

78. Robinson D, Cardozo L. Oestrogens and the lower urinary tract. BJOG 2004 Dec; 111 Suppl. 1: 10-4

79. Robinson D, Cardozo L, Akeson M, et al. Antidiuresis: a new concept in managing female daytime urinary incontinence. BJU Int 2004 May; 93 (7): 996-1000

80. Dwyer PL. Differentiating stress urinary incontinence from urge urinary incontinence. Int J Gynaecol Obstet 2004 Jul; 86 Suppl. 1: S17-24

81. Balmforth J, Cardozo LD. Trends toward less invasive treatment of female stress urinary incontinence. Urology 2003 Oct; 62 (4 Suppl. 1): 52-60

82. Colombo M, Zanetta G, Vitobello D, et al. The Burch colposuspension for women with and without detrusor overactivity. Br J Obstet Gynaecol 1996 Mar; 103 (3): 255-60

83. Osman T. Stress incontinence surgery for patients presenting with mixed incontinence and a normal cystometrogram. BJU Int 2003 Dec; 92 (9): 964-8

84. Segal JL, Vassallo B, Kleeman S, et al. Prevalence of persistent and de novo overactive bladder symptoms after the tension-free vaginal tape. Obstet Gynecol 2004 Dec; 104 (6): 1263-9

85. Rezapour M, Ulmsten U. Tension-free vaginal tape (TVT) in women with mixed urinary incontinence: a long-term follow-up. Int Urogynecol J Pelvic Floor Dysfunct 2001; 12 Suppl. 2: S15-18

86. Scotti RJ, Angell G, Flora R, et al. Antecedent history as a predictor of surgical cure of urgency symptoms in mixed incontinence. Obstet Gynecol 1998 Jan; 91 (1): 51-4

87. Holmgren C, Nilsson S, Lanner L, et al. Long-term results with tension-free vaginal tape on mixed and stress urinary incontinence. Obstet Gynecol 2005 Jul; 106 (1): 38-43

88. Sand PK, Hill RC, Ostergard DR. Incontinence history as a predictor of detrusor stability. Obstet Gynecol 1988 Feb; 71 (2): 257-60

89. Weidner AC, Myers ER, Visco AG, et al. Which women with stress incontinence require urodynamic evaluation? Am J Obstet Gynecol 2001 Jan; 184 (2): 20-7

Correspondence and offprints: Dr *Hashim Hashim*, Bristol Urological Institute, Southmead Hospital, Westbury-on-Trym, Bristol, BS10 5NB, UK.
E-mail: hashim@doctors.org.uk