Recent advances in urinary incontinence management

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Urinary incontinence affects almost half the world’s population and is most common among women. This article reviews some key points and recent developments in the management of urinary incontinence and stresses the importance of classifying the type of incontinence prior to treatment.

Urinary incontinence (UI), defined as involuntary leakage of urine, is a common symptom affecting women of all ages, that varies in nature and severity. In 2008, the 4th International Consultation on Incontinence estimated that 46 per cent of the world’s adult population (age ≥20 years) experience lower urinary tract symptoms (LUTS). Incontinence may profoundly influence the psychological, social and physical wellbeing of affected individuals. Prior to commencing any treatment it is important to classify the type of incontinence (see Table 1).

Women experience more UI than men, and incidence increases with age. Contributory factors include pregnancy, childbirth, menopause and increasing age. UI may also occur due to congenital defects, neurological damage, iatrogenic causes such as surgery and radiotherapy. Prior to commencing any treatment it is important to classify the type of incontinence (see Table 1).

Assessment
Assessment includes obtaining a full history for the type and severity of incontinence, along with a complete background medical history. Abdominal and vaginal examination should be performed routinely and rectal examination if required to exclude abdominal and/or pelvic masses or constipation. Urine analysis and measurement of postvoid residual is advisable, along with a three-day bladder diary to rule out urinary tract infection, voiding dysfunction and assess frequency, total intake and output and, other issues such as nocturia and nocturnal polyuria. It is also vital to assess the impact of symptoms on quality of life and desire for treatment to help predict treatment adherence. Urodynamics can be considered when there is mixed UI, symptoms suggestive of voiding dysfunction or evidence of anterior vaginal wall prolapse and who fail to respond to conservative therapies like physiotherapy, bladder retraining and/or pharmacological treatment. Cystoscopy should not be performed as initial management of UI, but can be considered when there are symptoms of recurrent cystitis and/or voiding dysfunction. Patient’s medication should be reviewed as some drugs increase LUTS (see Table 2).
Overactive bladder (OAB) is a symptom complex of urgency, with or without urgency incontinence, usually with frequency and nocturia; this is further classified into OAB-wet (with leakage) and OAB-dry (without leakage). It is a common condition, affecting more than 10 per cent of the global population. Management options include lifestyle and behavioural modification, pharmacological options and surgical management. NICE recommendations on management are outlined in Table 3.

Anticholinergics are the mainstay of treatment. They inhibit the binding of acetylcholine at muscarinic receptors in the detrusor muscle, thereby reducing involuntary detrusor contractions. The available anticholinergics and their side-effects are listed in Table 4. Intravaginal oestrogens should be offered for the treatment of OAB symptoms in postmenopausal women with vaginal atrophy. Some of the treatment options are as follows:

### Botulinum toxin type A (BTX-A)

BTX-A (Botox) is a neurotoxin that blocks acetylcholine release at the neuromuscular junction, causing muscle weakness. It is licensed for the treatment of refractory detrusor overactivity. Recent data from two trials suggest that 100 units may be as effective as 150 or 200 units, but with a lower rate of adverse events and a particularly low rate of urinary retention (5–10 per cent with 100 units and 15–20 per cent with 200 units). It is not yet entirely clear whether this comes at a cost of more rapid return of symptoms away from a research environment. Thus, there is not a fully defined algorithm to recommend a starting dose, nor when or in whom a higher dose should be administered. Higher dose of 300 units was initially used in neurogenic detrusor overactivity, however 200 units is now the usual recommended starting dose.

Risks include recurrent urinary tract infections (UTIs), urinary retention requiring self-catheterisation (20–30 per cent) with 200 units dosage, and rarely transient muscle weakness. There is no clear evidence for the optimal dose of botulinum toxin and the safety or number of repeated injections in the treatment of idiopathic detrusor overactivity (IDO). Other BTX-A

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**Table 1. Types of urinary incontinence**

**Overactive bladder**

Overactive bladder (OAB) is a symptom complex of urgency, with or without urgency incontinence, usually with frequency and nocturia; this is further classified into OAB-wet (with leakage) and OAB-dry (without leakage). It is a common condition, affecting more than 10 per cent of the global population. Management options include lifestyle and behavioural modification, pharmacological options and surgical management. NICE recommendations on management are outlined in Table 3.

**Table 2 Drugs and substances – effects on the lower urinary tract**

<table>
<thead>
<tr>
<th>Drug/substance</th>
<th>Effect</th>
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<tbody>
<tr>
<td>ACE inhibitors</td>
<td>Diuresis; cough with relaxation of the pelvic floor leading to SUI</td>
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<tr>
<td>Alcohol</td>
<td>Diuretic effect leading to urgency and frequency</td>
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<tr>
<td>Alpha-adrenergic agonists</td>
<td>Increased urethral resistance causing postvoid dribble, straining and urinary retention</td>
</tr>
<tr>
<td>Alpha-blockers</td>
<td>Urethral relaxation and decreased urethral resistance, causing SUI</td>
</tr>
<tr>
<td>Anticholinergics (H1 antihistamines, antiparkinsonian agents)</td>
<td>Urinary retention with symptoms of postvoid dribbling, straining, hesitancy in urine flow, overflow incontinence, faecal impaction</td>
</tr>
<tr>
<td>Antipsychotics/sedatives, hypnotics</td>
<td>Sedative effect, causing confusion; may relax detrusor muscle leading to urinary retention and overflow incontinence</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Urinary retention</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Urinary retention, faecal impaction</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Polyuria, bladder irritation</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Polyuria resulting in urgency and frequency</td>
</tr>
<tr>
<td>Neuroleptics (thioridazine, chlorpromazine)</td>
<td>Anticholinergic effect, sedation</td>
</tr>
<tr>
<td>Opioids</td>
<td>Urinary retention, sedation, faecal impaction, delirium</td>
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preparations like abobotulinumtoxinA are also used for OAB, whereas incobotulinumtoxinA is not.

**Sacral nerve stimulation (SNS)**
SNS is a recognised albeit invasive and expensive treatment for OAB and UI. It uses an implanted device (initially test and then permanent) that stimulates the S3 nerve root. Current evidence on its safety and efficacy appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance.2 It can be offered when conservative therapy has failed or when patients are unable to perform clean intermittent self-catheterisation. Issues such as need for test stimulation and its probability of success, risk of failure, adverse effects such as infection and haematoma, need for revision and a long-term commitment must be discussed with patients.2 Determining whether unilateral or bilateral stimulation renders better results need further research.12

**Posterior tibial nerve stimulation (PTNS)**
PTNS is a minimally invasive, outpatient neuromodulation procedure13 with insufficient evidence for its routine use to treat OAB. It involves intermittent (weekly) stimulation of the tibial nerve at the ankle with no permanent lead or stimulator implanted. This can be offered to woman declining BTX-A or SNS in selected centres that offer it.2

**Surgical treatments**
Surgical treatments employed for IDO include augmentation cystoplasty and urinary diversion. These are reserved for the most severe cases of refractory IDO, as they are associated with significant risk of complications. Regarding urinary diversion, regenerative medicine together with tissue engineering techniques gives hope for artificial urinary conduit construction de novo without affecting the ileum.14 For augmentation cystoplasty, preoperative counselling for the woman or her carer should include discussion of common and serious complications: bowel disturbance, metabolic acidosis, mucus production and/or retention in the bladder, UTI and urinary retention. The small risk of malignancy occurring in the augmented bladder and need for life-long follow-up should be discussed.2 With the effectiveness and low-risk profile of botulinum toxin in comparison to the former, these options are infrequently used.

**New medical therapy**
Mirabegron (Betmiga) is a beta3-agonist that causes detrusor relaxation and increased stability during bladder storage. Its efficacy for the treatment of OAB has been demonstrated in five randomised, placebo-controlled trials.15 The side-effect profile is much lower than anticholinergic medication but side-effects include: hypertension, urinary and upper respiratory tract infections, headache, constipation, arthralgia, diarrhoea, tachycardia and abdominal pain. With current evidence, mirabegron represents a reasonable alternative to anticholinergics for treating OAB. Recent studies have demonstrated significant improvements in symptoms using combination therapy with mirabegron and solifenacin having similar safety and acceptability.16,17

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**Table 3. NICE recommendations on the management of OAB**

<table>
<thead>
<tr>
<th>Future treatment possibilities</th>
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<tbody>
<tr>
<td>Preliminary studies have shown promising results for new treatments like vitamin D3-receptor antagonists and neurokinin-1-receptor antagonists as alternatives to anticholinergics in the treatment of OAB.18,19</td>
</tr>
</tbody>
</table>

**Stress urinary incontinence**
Stress urinary incontinence (SUI) is a widespread condition in women that is caused by urethral hypermobility due to weakened pelvic floor support and/or intrinsic sphincter deficiency.20 Both occur appreciably more commonly, but not solely, following pregnancy.

**Treatment options** include pelvic floor exercises, electrical stimulation, pharmacotherapy and surgery. Despite renewed interest in conservative therapies and many reports demonstrating mixed results for efficacy and safety of several oral agents, surgery remains the stronghold of treatment for most women.

**Conservative treatment**
This involves pelvic floor muscle training, with lifestyle modifications like fluid management, weight loss, and treatment of chronic conditions like cough and constipation. A recent Cochrane review suggests that pelvic floor muscle training is superior to no treatment or placebo in women with mixed UI or SUI, with insufficient evidence for its efficacy over other treatments.21

Duloxetine is an oral medication licensed for the treatment of moderate to severe SUI. It is a balanced serotonin and nor-
A recent meta-analysis demonstrated its efficacy in treating SUI. However, side-effects, including abdominal discomfort, are common and it is often reserved for women unfit for or awaiting surgery, who decline surgery or are yet to complete their family.

Surgical treatments
With more women reporting bothersome symptoms of SUI and the widespread availability of mid-urethral tape (MUT) procedures, larger numbers of surgical treatments are being performed worldwide. There are different surgical procedures such as Burch colposuspension, needle suspension (eg Pereyra, Stamey, Gittes and Raz) and MUTs. Although single incision MUT procedures have been developed in the treatment of SUI, a recent Cochrane review has demonstrated its inferiority to standard MUTs.

Autologous fascial pubovaginal sling (AF-PVS)
A recent prospective study has demonstrated that despite higher rates of retention and need for repeat operation, AF-PVS after failed MUS is an acceptable treatment option with no difference in success as compared to patients undergoing initial AF-PVS placement.

Bulking agents
Bulking agents placed cystoscopically or blindly at the bladder neck are designed to partially occlude the bladder neck. Many urethral bulking agents are available, such as bovine glutaraldehyde cross linked (GAX) collagen, polydimethylsiloxane elastomer (silicone), carbon coated zirconium beads, polytetrafluoroethylene (Teflon), hyaluronic acid/dextranomer, and autologous tissues such as cartilage and fat. The overall reported success rate of perirethral bulking agents is 48–75 per cent, and repeat injections are usually required.

Artificial urinary sphincter (AUS)
In view of the associated morbidity, the use of an artificial urinary sphincter should be considered for the management of stress UI in women only if previous surgery has failed. Life-long follow-up is recommended. In a recent study robot-assisted laparoscopic approach for AUS implantation has been shown to allow improved dexterity and visibility compared to traditional laparoscopy, with complete continence rate of 88 per cent.

Newer therapies
A recent Cochrane review showed that use of artificial sphincters in the management of SUI was questionable and larger trials were needed to determine their role in the management of SUI. Preliminary studies using stem cells for strengthening the urethral sphincter have shown promise. In particular, mesenchymal stem cells and CD34(+) cells have shown great assurance to differentiate into muscular and vascular components, respectively. Evidence supporting the use of cytokines and growth factors such as hypoxia-inducible factor 1-alpha, vascular endothelial growth factor, basic fibroblast growth factor, hepatocyte growth factor and insulin-like growth factor further increase the feasibility and direction of differentiation. Bridging the benefits of stem cells and growth factors involves the use of synthetic scaffolds like poly (1,8-octanediol-co-citrate; POC) thin films. POC scaffolds are synthetic, elastomeric polymers that serve as substrates for cell growth, and upon degradation, release growth factors to the microenvironment in a controlled, predictable fashion.

Table 4. Available anticholinergics, authors’ recommended doses and common side-effects

<table>
<thead>
<tr>
<th>Anticholinergic</th>
<th>Dosage</th>
<th>Common side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxybutinin</td>
<td>7.5–15mg (divided doses)</td>
<td>Dry mouth, constipation, nausea, blurred vision, somnolence, urinary retention</td>
</tr>
<tr>
<td>Oxybutynin patches</td>
<td>3.9mg twice weekly</td>
<td>Pruritus, erythema, reduced dry mouth</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>5–10mg daily</td>
<td>Dry mouth, constipation, blurred vision, increased sweating</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>2–4mg daily (divided doses)</td>
<td>Dry mouth, constipation, nausea, blurred vision</td>
</tr>
<tr>
<td>Tolterodine m/r</td>
<td>4mg daily (divided doses)</td>
<td>Dry mouth, constipation, nausea, blurred vision</td>
</tr>
<tr>
<td>Darifenacin</td>
<td>7.5–15mg daily</td>
<td>Constipation</td>
</tr>
<tr>
<td>Fesoterodine</td>
<td>4 and 8mg daily</td>
<td>Constipation, fatigue</td>
</tr>
<tr>
<td>Trospium</td>
<td>20mg twice daily</td>
<td>Constipation, less/no anticholinergic cognitive side-effects</td>
</tr>
<tr>
<td>Trospium m/r</td>
<td>60mg daily</td>
<td>Constipation, dry mouth, less/no anticholinergic cognitive side-effects</td>
</tr>
<tr>
<td>Propiverine</td>
<td>30 or 45mg daily</td>
<td>Dry mouth, constipation, nausea, blurred vision, somnolence,</td>
</tr>
<tr>
<td>Propiverine m/r</td>
<td>20 or 30mg daily</td>
<td>Constipation, nausea, blurred vision, somnolence</td>
</tr>
</tbody>
</table>

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Nocturnal enuresis

Many women with IDO experience nocturnal enuresis, with management principles being similar to IDO. Desmopressin may also be considered to reduce bothersome nocturia, but caution should be exercised in women with cystic fibrosis, those aged over 65 or those with cardiovascular disease (eg hypertension). Serum sodium should be checked on day 3 and 5 of treatment due to the side-effects of fluid retention and hyponatraemia. A recent systematic review showed that the initial dose should be 50–100µg with caution at higher doses. Although unlicensed for this indication, tricyclic antidepressants (amitriptyline or imipramine) are also helpful in nocturnal enuresis but have systemic anticholinergic effects. These drugs should be used cautiously in the elderly due to cardiac side-effects and an increased risk of falls.

Overflow incontinence

Overflow incontinence can be caused by constipation and pelvic pathology such as large fibroids and ovarian cysts leading to voiding difficulties. Voiding dysfunction leading to incomplete emptying may result in overflow incontinence. Voiding dysfunction may also result from detrusor sphincter dyssynergia, urethral stricture or an underactive bladder. Women with persistent mobility (due to surgery, frailty and poor cognition), and is 

to give women the most appropriate management options. Treatment choices are available, additional research is ongoing to identify and address the causes is the main principle of management. There are devices and aids to support toileting needs, eg commodes, easily removed clothing. Prompted-voiding programmes are advisable. In intractable cases of functional incontinence, long-term catheterisation may be offered.

Conclusion

While numerous conservative, pharmacological and surgical treatment choices are available, additional research is ongoing to give women the most appropriate management options to achieve maximal efficacy with least side-effects. In this molecular and regenerative medicine age, future research in incontinence care is aimed at directing us to innovative arenas, hopefully providing evidence based preventative and curative therapy.

References

2. NICE guidelines [CG171]. Published September 2013.
Prescription review

In 2014, GPs in England wrote 6.3 million prescriptions for drugs for urinary frequency and incontinence at a total cost of £137 million. This was an increase of 10 per cent in volume and 6 per cent in spending compared with 2013.

Three drugs account for over 80 per cent of prescribing volume: solifenacin (37 per cent), oxybutynin (28 per cent) and tolterodine (18 per cent) and a similar proportion of costs, with solifenacin taking a disproportionate share of spending (53 per cent).

Average costs per prescription (equating to about one month’s treatment) fall into three categories. Least expensive are fluvoxate, oxybutynin and tolterodine (£6–£17); at about £20 are trospium and propiverine; the most expensive, at £27–£31, are darifenacin, fesoterodine, duloxetine, mirabegron and – the most expensive overall as well as the most frequently used – solifenacin.

Although it is now marginally cheaper per prescription than in 2010, the use of solifenacin has increased by 94 per cent since then, with an increase in spending of 86 per cent. By contrast, prescribing of oxybutynin increased by 33 per cent with no change in total spending and a 25 per cent fall in average cost over the same period. Prescribing of tolterodine has changed little but the advent of generic alternatives helped to lower total spending by 57 per cent and average cost by 61 per cent.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Volume (000s)</th>
<th>NIC (£000)</th>
<th>Mean NIC/scr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darifenacin</td>
<td>34</td>
<td>928</td>
<td>27.14</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>167</td>
<td>4920</td>
<td>29.47</td>
</tr>
<tr>
<td>Fesoterodine</td>
<td>251</td>
<td>7061</td>
<td>28.18</td>
</tr>
<tr>
<td>Fluvoxate</td>
<td>30</td>
<td>257</td>
<td>8.62</td>
</tr>
<tr>
<td>Mirabegron</td>
<td>236</td>
<td>7137</td>
<td>30.20</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>1748</td>
<td>16,700</td>
<td>9.55</td>
</tr>
<tr>
<td>Propiverine</td>
<td>47</td>
<td>999</td>
<td>21.25</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>2347</td>
<td>73,397</td>
<td>31.28</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>1171</td>
<td>19,429</td>
<td>16.60</td>
</tr>
<tr>
<td>Trospium</td>
<td>305</td>
<td>6446</td>
<td>21.11</td>
</tr>
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