Management of overactive bladder syndrome

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Overactive bladder (OAB) syndrome is the term used to describe the symptom complex of urinary urgency with or without urge incontinence, usually with frequency and nocturia. Drug treatment continues to have an important role in the management of women with OAB. Other treatment options include conservative management with lifestyle interventions, modification of fluid intake, and physiotherapy including bladder retraining. Surgery remains the last resort in the treatment and is usually reserved for intractable detrusor overactivity, as it is associated with significant morbidity. This article reviews the management of the overactive bladder with specific focus on newer developments in the medical treatment of OAB in women.

that only 18.2% women continued drug treatment for more than 6 months, partly due to the side effects of anticholinergic therapy.⁷ The current approaches to improving the treatment of OAB include delayed release formulations of existing oral agents, new pharmaceutical agents with greater specificity/selectivity, and alternative routes of administration. The purpose of this article is to review the management of the overactive bladder, with specific focus on newer developments in the medical treatment of OAB in women.

CONSERVATIVE MANAGEMENT

A conservative approach is often justified, especially if symptoms are only mild, or easily manageable.

Lifestyle interventions

The frequency–volume chart, or urinary diary, is an important tool in the investigation of patients with lower urinary tract symptoms and voiding dysfunction.⁸ This facilitates history taking regarding frequency, nocturia and volume voided, and has been shown to be valuable and reliable for the assessment of micturition patterns.⁹ There is poor correlation between subjective estimates of diurnal and nocturnal urinary frequency and objective charted measurements.¹⁰ Moderation of fluid intake to 1–1.5 litres per day reduces urine production and can ease symptoms. Alcohol, caffeine, and medication such as diuretics are major causes of acute incontinence, especially in the elderly.¹¹ Drug regimens avoiding diuretics, control of chronic cough and constipation, cessation of smoking, exclusion or treatment of urinary tract infection, and weight reduction are desirable.

Physiotherapy

Behavioural therapy for detrusor overactivity was first reported by Jeffcoate and Francis who, in the 1960s, advocated the practice of voiding “by the clock” for urge incontinence.¹² Treatment frequently consists of bladder re-training by “bladder drill”, to re-learn the cortical inhibition of detrusor contractions. This may be time consuming and frustrating—correct diagnosis is necessary to ensure maximum patient compliance with treatment. Behavioural modification improves central control of bladder function, avoiding the mortality and morbidity of surgery, and the side-effects of drug treatment. However, this type of treatment requires high levels of motivation and encouragement, and suffers from high relapse rates.

Studies of “bladder drill” lack consistency in their nomenclature and methodology. However, in a review of the randomised clinical trials of conservative treatments, Berghams *et al*¹³ showed

Overactive bladder (OAB) syndrome is the term used to describe the symptom complex of urinary urgency with or without urge incontinence, usually with frequency and nocturia.¹ Recent epidemiological studies have reported an overall prevalence of OAB in women of 16.9%, suggesting that there could be 17.5 million women in the USA who suffer from this condition. The prevalence increases with age, from 4.8% in women under 25 years to 30.9% in those over the age of 65 years.² This is supported by prevalence data from Europe in which 16 776 interviews were conducted in a population based survey.³

The symptoms of OAB are primarily due to involuntary contractions of the detrusor muscle during the filling phase of the micturition cycle. These involuntary contractions, when observed during urodynamic studies, are termed detrusor overactivity and are mediated by acetylcholine-induced stimulation of bladder muscarinic receptors.⁴

Drug treatment continues to have an important role in the management of women with OAB, although many of the agents used have not been subjected to controlled clinical trials.⁵ From the number of preparations studied it is clear that there are no ideal drugs and very often the clinical results have been disappointing, this being due to both poor efficacy and side effects.⁶ Comparison of drug treatments for OAB is hampered by a placebo effect of 30–40%; since the response to any drug is only in the region of 60%, any differences detected are likely to be small, thus requiring large-scale studies to demonstrate an effect. In addition, anticholinergic treatment is associated with significant side effects. A questionnaire follow up study of women with detrusor overactivity showed

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strong evidence that bladder drill is more effective than no treatment, and weak evidence that bladder drill is better than drug treatment. There is insufficient evidence, though, of the efficacy of bladder drill with drug treatment, bladder drill with pelvic floor exercises and biofeedback, or biofeedback and behavioural therapy, due to inadequate clinical trials.

DRUG TREATMENT

Oxybutynin

Oxybutynin is a tertiary amine that undergoes extensive first-pass metabolism to an active metabolite, N-desmethyl oxybutynin,¹⁴ which occurs in high concentrations¹⁵ and is thought to be responsible for a significant part of the action of the parent drug. It has a mixed action consisting of both an antimuscarinic and a direct muscle relaxant effect, in addition to local anaesthetic properties. The latter is important when given intravesically but probably has no effect when given systemically. Oxybutynin has been shown to have a high affinity for muscarinic receptors in the bladder¹⁶ and has a higher affinity for M₁ and M₃ receptors over M₂.¹⁷

The effectiveness of oxybutynin in the management of patients with detrusor overactivity is well documented.

Extended release oxybutynin

More recently a controlled release oxybutynin preparation using an osmotic system (OROS) has been developed which has been shown to have comparable efficacy to immediate release oxybutynin, although associated with fewer adverse effects.¹⁸ These findings are in agreement with a further study of controlled release oxybutynin (Ditopan XL, Lyrinel XL) which reported the incidence of moderate to severe dry mouth to be 23%, with only 1.6% of participants discontinuing the medication due to adverse effects.¹⁹ A recent study, however, has also found that use of extended release oxybutynin in elderly subjects may impair recent memory.²⁰

Transdermal oxybutynin

In order to maximise efficacy and minimise adverse effects, alternative delivery systems are currently under evaluation. An oxybutynin transdermal delivery system (Kentera) has recently been developed and compared with extended release tolterodine in 361 patients with mixed urinary incontinence. Both agents significantly reduced incontinence episodes, increased volume voided and led to an improvement in quality of life when compared to placebo. The most common adverse event in the oxybutynin patch arm was application site pruritis in 14%, although the incidence of dry mouth was reduced to 4.1% compared to 7.3% in the tolterodine arm.²¹

Oxybutynin gel is also a new development currently being pursued.

Propiverine

Propiverine has been shown to combine anticholinergic and calcium channel blocking actions²² and is the most popular drug for detrusor overactivity in Germany, Austria and Japan. Open label studies in patients with detrusor overactivity have demonstrated a beneficial effect²³; in a double blind placebo-controlled trial of its use in neurogenic detrusor overactivity it has been shown to increase bladder capacity and compliance significantly in comparison to placebo. Dry mouth was experienced by 37% in the treatment group as opposed to 8% in the placebo group, with dropout rates being 7% and 4.5%, respectively.²⁴

Tolterodine

Tolterodine is a competitive muscarinic receptor antagonist with relative functional selectivity for bladder muscarinic receptors²⁵; while it shows no specificity for receptor subtypes

it does appear to target the bladder over the salivary glands.²⁶ The drug is metabolised in the liver to the 5-hydroxymethyl derivative, which is an active metabolite with a similar pharmacokinetic profile and is thought to contribute to the therapeutic effect.²⁷

Tolterodine is also available as an extended release once daily preparation, Detrusitol XL. A recent double blind multicentre trial of 1235 women compared extended release tolterodine to immediate release tolterodine and placebo and found that the extended release preparation was found to be significantly more effective.²⁸ In addition to increased efficacy, extended release tolterodine has been shown to have better tolerability. In a double-blind, multicentre, randomised placebo controlled trial of 1529 patients, extended release tolterodine was found to be 18% more effective in the reduction of episodes of urge incontinence while having a 23% lower incidence of dry mouth.²⁹

Comparative randomised controlled trials such as the OPERA (Overactive bladder: Performance of Extended Release Agents),³⁰ OBJECT (Overactive Bladder: Judging Effective Control and Treatment)³¹ and ACET (Antimuscarinic Clinical Effectiveness Trial) study³² have confirmed its effectiveness.

Several randomised, double-blind, placebo controlled trials, both on patients with idiopathic detrusor overactivity and neurogenic detrusor overactivity, have demonstrated a significant reduction in incontinent episodes and micturition frequency.^{33–35} Further studies have confirmed the safety of tolterodine, and at the recommended daily dosage the incidence of adverse events was no different to that in patients taking placebo.³⁶

In addition, the safety and efficacy of tolterodine has also been compared to that of oxybutynin. These have suggested that although clinical efficacy is comparable for both drugs, oxybutynin was associated with higher withdrawal rates and a higher incidence of adverse events, notably dry mouth.^{37 38}

More recently tolterodine has also been developed as an extended release once daily preparation, Detrusitol XL.

Trospium

Trospium chloride is a quaternary ammonium compound which is non-selective for muscarinic receptor subtypes, and shows low biological availability.³⁹ It crosses the blood-brain barrier to a limited extent and hence would appear to have few cognitive effects.⁴⁰ In a recent placebo-controlled, randomised, double-blind, multicentre trial trospium chloride produced significant improvements in maximum cystometric capacity and bladder volume at first involuntary contraction. Clinical improvement was significantly greater in the group receiving trospium and the frequency of adverse events was similar in both groups.⁴¹ Trospium chloride has also been compared to oxybutynin in a randomised, double-blind, multicentre trial. With both agents there was a significant increase in bladder capacity, a decrease in maximum voiding detrusor pressure, and a significant increase in compliance although there were no statistically significant differences between the two treatment groups. Those taking trospium had a lower incidence of dry mouth (4% vs 23%) and were also less likely to withdraw (6% vs 16%) when compared to the group receiving oxybutynin.⁴²

Solifenacin

Solifenacin is a potent M₃ receptor antagonist that has selectivity for the M₃ receptors over M₂ receptors and has much higher potency against M₃ receptors in smooth muscle than it does against M₃ receptors in salivary glands. Despite solifenacin expressing a higher potency than darifenacin in a model of inhibition of M₃ receptor mediated calcium ion mobilisation in guinea pig colonic smooth muscle cells,⁴³ it has been shown to be 40-fold less potent than oxybutynin and

79-fold less potent than tolterodine in its inhibition of salivary secretion⁴⁴ as well as being more selective for the M₃ receptor.

The clinical efficacy of solifenacin has been assessed in several multicentre, randomised trials at the dose of 5 mg and 10 mg once daily in patients with overactive bladder.^{45–47}

These studies suggest that solifenacin appears to be an effective treatment for OAB, with the most commonly reported adverse events being dry mouth, constipation and blurred vision.

Darifenacin

Darifenacin is a tertiary amine with moderate lipophilicity and is a highly selective M₃ receptor antagonist, which has been found to have a fivefold higher affinity for the human M₃ receptor relative to the M₁ receptor.⁴⁸ Darifenacin is equipotent with atropine in the ileum and bladder and six times less potent at inhibiting muscarinic receptors in the salivary gland. Salivary responses are inhibited at doses 6–10-fold higher than those required to inhibit bladder responses.

The efficacy of darifenacin has been investigated in multicentre studies.^{49–50} The most common adverse events were mild-to-moderate dry mouth and constipation with a central nervous system (CNS) and cardiac safety profile. Darifenacin was significantly superior to placebo for improvements in micturition frequency, bladder capacity, frequency of urgency, severity of urgency, and number of incontinence episodes leading to a change in clothing or pads. However, there was no significant reduction in nocturia.

Darifenacin has been launched in Europe and North America, and has just been licensed for use in the UK. Since it is the most M₃ specific of the newer anti-muscarinic agents, may offer a better balance between efficacy and unwanted effects.

Botulinum toxin (Botox)

There are seven immunologically distinct antigenic subtypes of botulinum toxin, of which type A is the most widely used. Botulinum toxin A (Botox) is a purified neurotoxin complex, which blocks the release of acetylcholine and other transmitters from presynaptic nerve endings. This results in decreased muscle contractility and muscle atrophy at the injection site. The produced chemical denervation is reversible as axons are regenerated in about 3–6 months. Botox cannot cross the blood–brain barrier and hence has no CNS side effects.

The minimal invasiveness of Botox-A toxin injection in the bladder makes it attractive in the treatment of refractory detrusor overactivity. Studies have shown success rates between 26–80%.^{51–53} Data are lacking on dose, concentration, site, and number of injection and long term efficacy and side effects. A recent prospective, non-randomised, ongoing study has evaluated the efficacy and safety of botulinum-A toxin injections in the detrusor muscle to treat patients with idiopathic overactive bladder resistant to conventional treatment.⁵⁴ Eighty-eight per cent of the patients showed significant improvement in bladder function in regard to subjective symptoms, quality of life and urodynamic parameters ($p < 0.001$). Urgency disappeared in 82% of the patients and incontinence resolved in 86% within 1–2 weeks after botulinum-A toxin injections. There were no severe side effects except temporary urine retention in four cases. Mean (SD) efficacy of duration was 6 (2) months.

Calcium channel blocking agents

Contractile activity in bladder smooth muscle is activated by the movement of extracellular calcium into the cell. Spontaneous and evoked contractile activity is mediated by membrane depolarisation and the movement of calcium into the smooth muscle cell through L-type Ca²⁺ channels.⁵⁵ The inhibition of

the entrance of extracellular calcium with L-type Ca²⁺ blocking agents, such as nifedipine, can prevent spontaneous and evoked contractile activity.⁵⁶

Nifedipine has been shown to reduce the frequency and amplitude of detrusor contractions,⁵⁷ although these findings were not confirmed in a further study which found there was no significant effect on detrusor contractions.⁵⁸ Similar contradictory findings have been reported regarding the use of flunarizine.^{6–9} Diltiazem has also been shown to significantly increase bladder capacity, lower bladder pressure and decrease the number of episodes of incontinence.⁶⁰

At present there is insufficient evidence to suggest that calcium channel blocking agents are effective in the treatment of detrusor overactivity, although the development of a selective calcium channel blocking agent which eliminates spontaneous contractions without affecting micturition may prove to be of use in the treatment of detrusor overactivity.

Other

Imipramine and other tricyclic antidepressants have been shown to have systemic anticholinergic effects⁶¹ and blocks reuptake of serotonin. Some authorities have found a significant effect in the treatment of patients with detrusor overactivity⁶² although others report little effect.⁶³ Their role in detrusor overactivity remains of uncertain benefit, although they are often useful in patients complaining of nocturia and bladder pain. These must be used with caution in the elderly due to possible cardiac effects and an increase in falls.

Desmopressin (DDVP)—synthetic vasopressin—has a potent antidiuretic effect, being used in the management of diabetes insipidus and nocturnal enuresis. More recently it has been shown to be effective in reducing nocturia in patients with both neuropathic and non-neuropathic bladders.⁶⁴ Recent studies have also demonstrated benefit in daytime urinary frequency and urinary incontinence.⁶⁵

Intravesical instillations of capsaicin, a neurotoxin extracted from red chilli peppers,⁶⁶ have significant effect over placebo in the treatment of neurogenic detrusor overactivity. Its analogue resiniferatoxin⁶⁷ has been shown to have fewer side effects, with an increase in bladder capacity. However, the place of these neurotoxins in clinical practice is still uncertain.

NEW DEVELOPMENTS

Potassium channel opening agents

The opening of K⁺ ion channels in the membrane of the detrusor muscle cell results in an increase in K⁺ movement out of the cell, resulting in membrane hyperpolarisation.⁶⁸ This reduces the opening probability of ion channels involved in membrane depolarisation and hence excitability is reduced.⁶⁹ Three types of potassium channels have been identified in the detrusor muscle: ATP sensitive channels, calcium-dependent large conductance channels; and calcium-dependent large conductance channels.³² At present the relationship between each of these types of channels and the myogenic, neurogenic and micturition forms of detrusor contraction has not been determined. To date cromakalim, nicorandil and pinacidil have been investigated, although newer agents are currently under development.⁷⁰

Potassium channel openers are thought to be active during the bladder filling phase and, while abolishing spontaneous detrusor contractions, are not thought to affect normal bladder contractions. However, their clinical usefulness is limited by significant cardiovascular effects, with cromakalim and pinacidil being found to be up to 200 times more potent as inhibitors of vascular preparations than of detrusor muscle.⁷¹ In clinical trials assessing the use of these drugs in patients with detrusor overactivity, no bladder effects have been found at doses which already lower blood pressure.⁷² More recently

National guidelines from NICE

The National Institute for Health and Clinical Excellence (NICE) has recently published guidelines on the management of urinary incontinence in women. This can be downloaded from www.nice.org.uk/CG040. The guidelines for management of OAB are summarised below:

- **Assessment and investigation**—At initial clinical assessment, incontinence should be categorised based on the patient's symptoms and treatment should be directed towards the predominant symptom. Bladder diaries should be used in the initial assessment with a minimum of 3 days of the diary. The use of urodynamics is not recommended before conservative treatment.
- **Conservative management**—Bladder training for a minimum of 6 weeks should be offered as first line treatment.
- **Drug treatment**—Immediate release non-proprietary oxybutynin should be offered as first line drug treatment if bladder training has been ineffective. If this is not well tolerated, darifenacin, solifenacin, tolterodine, trospium or an extended release or transdermal formulation of oxybutynin should be considered as alternatives. Women should be counselled about the side effects of antimuscarinic drugs.
- **Surgical management**—Sacral nerve stimulation is recommended for women who have detrusor overactivity not responsive to conservative or medical treatment.
- **Competence of surgeons performing operative procedures for incontinence in women**—Surgery for incontinence should only be undertaken by surgeons who have received appropriate training in the management of incontinence and associated disorders or who work within a multidisciplinary team with this training and who regularly carry out this form of surgery.

newer drugs with K_{ATP} channel opening properties have been described,⁷³ which may be useful for the treatment of bladder overactivity; however, at present, there is no evidence to suggest that K^+ channel openers represent a viable treatment alternative. A recent randomised double-blind study also failed to show any beneficial effect of potassium channel openers over placebo in patients with overactive bladder.⁷⁴ Hence, more work is needed to establish the role of this form of therapy in OAB.

α -Adrenoceptor antagonists

While it is well known that α -adrenoceptor antagonists are useful in the treatment of benign prostatic hyperplasia in men,⁷⁵ there are no clinical trials showing their efficacy in OAB. In addition, in women these drugs may exacerbate or result in stress incontinence.⁷⁶

β -Adrenoceptor agonists

There is evidence that β -adrenoceptor agonists increase bladder capacity in man.⁷⁷ In a double-blind study, clenbuterol was shown to have a good therapeutic effect in women with detrusor overactivity.⁷⁸ Other studies have shown no effect in the elderly with detrusor overactivity⁷⁹ or in the young with neurogenic detrusor overactivity.⁸⁰

Neurokinin antagonists

Neurokinins are widely distributed neuropeptides in both the central and peripheral nervous system. Some studies have confirmed the presence of NK2 receptors in human detrusor

Useful websites

- www.continence-foundation.org.uk
- www.incontact.org
- www.promocon.co.uk

muscle.⁸¹ NK2 receptors may play a role in the pathophysiology of OAB, and NK2 receptor antagonists have been shown to reduce the frequency and amplitude in animal studies.⁸² Hence these neurokinin antagonists may prove to be useful in the treatment of detrusor overactivity.

Surgery

Many different surgical treatments have been tried in the management of detrusor overactivity, but few are still in regular use today. Abandoned procedures include bladder distension, vaginal denervation, bladder transection, and sacral neurectomy. Their demise was caused by an unacceptably high rate of complications and limited efficacy.

Surgical solutions for detrusor overactivity include sacral neuromodulation, detrusor myectomy, augmentation cystoplasty, or urinary diversion.

Sacral neuromodulation

Stimulation of the S3 nerve root by an implanted electrical pulse generator can provide effective relief from frequency-urgency symptoms. In a prospective randomised trial of sacral neuromodulation versus delay, incontinence episode frequency (IEF), severity, and pad use were all reduced in the active arm ($p < 0.0001$); 47% were dry, and 29% reported a reduction in IEF of more than 50% at 6 months.⁸³ Neuromodulation is, however, very expensive. Patients need expert assessment, and management—although it is not suitable for routine use, sacral neuromodulation appears to be useful for a selected minority. The stimulator is a small electrical pulse generator, approximately the same size as a cardiac pacemaker, and is commonly implanted in the upper outer quadrant of the buttock. Complications most commonly reported are generator site pain (15.9%) and implant site pain (19.1%). Lead migration may occur in up to 7%. The surgical revision of technical failures and complications was 32.5%. This may be expected to reduce in the future as the technological development of generators and implant leads progresses.

Clam augmentation cystoplasty

Augmentation cystoplasty is used to increase the size of the urinary reservoir and render the bladder less contractile. It is indicated in patients who lack adequate bladder capacity or detrusor compliance; who manifest debilitating frequency-urgency symptoms, with urge incontinence, urinary tract infections; who have failed to derive benefit from medical treatment; whose lifestyle is severely limited; or with high pressure urine storage endangering the upper renal tracts.

The operation most frequently used is the "clam" cystoplasty. In this procedure,^{84, 85} the bladder is bisected almost completely and a patch of gut (usually ileum) equal in length to the circumference of the bisected bladder (about 25 cm) is sewn in place. This often cures the symptoms of detrusor overactivity⁸⁶ by converting a high-pressure system into a low-pressure system, although inefficient voiding may result. Patients have to learn to strain to void, or may have to resort to clean intermittent self-catheterisation, sometimes permanently. In addition, mucus retention in the bladder may be a problem, but this can be partially overcome by ingestion of 200 ml of cranberry juice each day⁸⁷ in addition to intravesical mucolytics

such as acetylcysteine. The chronic exposure of the ileal mucosa to urine may lead to malignant change.⁸⁸ There is a 5% risk of adenocarcinoma arising in ureterosigmoidostomies, where colonic mucosa is exposed to N-nitrosamines found in both urine and faeces, and a similar risk may apply to enterocystoplasty. Biopsies of the ileal segment taken from patients with "clam" cystoplasties show evidence of chronic inflammation of villous atrophy, and diarrhoea caused by disruption of the bile acid cycle is common.⁸⁹ This may be treated using cholestyramine. In addition, metabolic disturbances such as hyperchloremic acidosis, B12 deficiency and occasionally osteoporosis secondary to decreased bone mineralisation may occur.

Detrusor myectomy

Detrusor myectomy offers an alternative to clam cystoplasty by increasing functional bladder capacity without the complications of bowel interposition. In this procedure the whole thickness of the detrusor muscle is excised from the dome of the bladder, thereby creating a large bladder diverticulum with no intrinsic contractility.⁹⁰ While there is a reduction in episodes of incontinence there is little improvement in functional capacity and thus frequency remains problematic.⁹¹⁻⁹²

Urinary diversion

As a last resort for those women with severe detrusor overactivity or neurogenic detrusor overactivity who cannot manage clean intermittent catheterisation, it may be more appropriate to perform a urinary diversion. Usually this will utilise an ileal conduit to create an abdominal stoma for urinary diversion. An alternative is to form a continent diversion using the appendix (Mitrofanoff) or ileum (Koch pouch) which may then be drained using self-catheterisation.

CONCLUSION

Pharmacological treatment, in addition to bladder retraining, remains important in the management of women with symptoms of the OAB syndrome. While tolerability has previously limited compliance, the development of long acting agents with a better adverse event profile has improved this dramatically. The development of new M₃ specific and bladder selective muscarinic antagonists may also improve efficacy and compliance while limiting adverse effects. Intravesical injection of Botox A toxin has a role in refractory detrusor overactivity, although there are still concerns regarding long term efficacy and side effects. The development of calcium antagonists and potassium channel opening agents may offer alternatives to anti-muscarinic treatment, although at present there are no clinically useful drugs available. The potential role of α -adrenoreceptor antagonists, β -adrenoreceptor agonists and neurokinin antagonists remains to be elucidated. Surgery remains the last resort in management of intractable detrusor overactivity.

Ultimately, perhaps a better understanding of the causes and pathophysiology of overactive bladder syndrome may result in the development of new treatments for such a common and distressing condition.

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