Treatment options for the overactive bladder syndrome

Hashim Hashim[†] *& Paul Abrams*

[†]*Author for correspondence*
Bristol Urological Institute, Southmead Hospital, Westbury on Trym, Bristol, BS10 5NB, UK
Tel.: +44 117 959 5690
Fax: +44 117 950 2229
hashim@doctors.org.uk

Urgency is the cornerstone symptom of overactive bladder (OAB) syndrome. It affects millions of people worldwide and has considerable effects on society. Most previous studies concentrated on urinary incontinence and it wasn't until 2002, when the new definition of OAB was published, that interest in this condition began to increase. Unfortunately, the cause of OAB is not clearly established, thus all available treatments are aimed at alleviating symptoms rather than cure. Management is based on making an accurate diagnosis by excluding other pathologies and treating the symptoms conservatively and/or pharmacologically. Treatments are based on the assumption that OAB is due to involuntary detrusor contractions typical of detrusor overactivity. Antimuscarinic agents form the mainstay of medical therapy. There have been many recent developments in antimuscarinic drug therapy for OAB, which have gained more interest, particularly with the introduction of the term 'bladder selectivity', and it is hoped that these newer agents will provide a wider variety of drugs that could help in the management of OAB. Should medical treatment fail and symptoms become unbearable, surgical treatment is the last resort. However, recently neuromodulation and possibly botulinum toxin have attempted to bridge the gap between oral pharmacologic and operative treatment.

Keywords: antimuscarinics, detrusor overactivity, neuromodulation, overactive bladder, quality of life, surgery

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The International Continence Society (ICS) defined the overactive bladder as a syndrome consisting of urgency, with or without urgency incontinence, usually with frequency and nocturia (**Table 1**), if there is no proven infection or other obvious pathology [1]. It is suggestive of urodynamically demonstrable detrusor overactivity (DO). This definition is based on a clinical diagnosis and complements previous definitions that were based on detrusor function during the filling phase of urodynamics.

The bladder has been termed the 'unreliable witness' [2] and not all patients with overactive bladder (OAB) symptoms will have detrusor overactivity, nor will all patients with DO have OAB symptoms. The most important thing to remember is that the two terms should not be used interchangeably and that OAB is a clinical diagnosis, while detrusor overactivity is a urodynamic diagnosis. In fact, in one series, 69% of men and 44% of women, with symptoms of urgency alone, had DO [3].

Prevalence

Until recently, little was known about the prevalence of OAB, as most previous studies concentrated on urgency urinary incontinence (UUI) or did not use the new definition of OAB. Studies have shown that prevalence of OAB increases with age and is more common in women than men, with the prevalence of UUI ranging between 3 and 43% depending on the definition used [4].

In a European population-based telephone survey of men and women aged 40 years and older, it was found that the overall prevalence of OAB was 16.6%, being slightly lower in men (15.6%) than women (17.4%), but increased with age in both groups [5]. Approximately 49 million in Europe are probably affected, of whom only 60% consulted a medical practitioner and 27% received treatment.

Similar OAB prevalence results were obtained in the USA as part of the National Overactive BLadder Evaluation (NOBLE) program [6]. The overall prevalence of OAB was 16.6%, and only slightly higher in women (16.9%), compared with men (16.0%). This equates to approximately 33 million sufferers in the USA.

A telephone survey of adults, aged 35 years and older, was also conducted in Canada, and it was found that the overall prevalence of OAB was 18.1% [7]. It was lower in men (14.8%) than in women (21.2%). Dry OAB (no urgency incontinence) was assessed to be the highest subtype, with a rate of 13.6% (11.7% in men and 15.6% in women). The prevalence of wet OAB (with urgency incontinence) was

Table 1. Definition of overactive bladder symptoms and detrusor overactivity.

Symptom	Definition
Urgency	Complaint of a sudden compelling desire to pass urine which is difficult to defer
Urgency urinary incontinence	Complaint of involuntary leakage accompanied by or immediately preceded by urgency
Nocturia	Complaint that the individual has to wake up at night one or more times to void
Increased daytime frequency	Complaint by the patient who considers that he/she voids too often by day
Detrusor overactivity	Urodynamically demonstrable involuntary detrusor contractions during the filling phase of cystometry, which may be spontaneous or provoked

estimated to be 2.3% (2% in men; 2.6% in women). Dry OAB increased with age in both men and women; wet OAB was markedly higher in both men and women over the age of 75 years.

Quality of life & economic costs

Not only is OAB a prevalent condition, it can also have significant effects on an individual's quality of life (QoL), with significant cost to society. In sufferers, OAB can significantly affect all aspects of QoL including social, psychologic, occupational, domestic, physical and sexual aspects. Unfortunately, many sufferers do not present to the healthcare provider, thus OAB remains underreported, despite increased awareness and improved diagnosis and treatment [8,9]. In fact, it has been found that OAB has a greater impact on QoL than diabetes [10–12].

It has been estimated that, in the USA, OAB in 2000 was costing approximately US$12.6 billion per year, ranking fifth after arthritis, incontinence, pneumonia/influenza and osteoporosis. This cost is comparable to the costs of asthma and osteoporosis, but less than that of urinary incontinence (US$19.5 billion) [13,14]. Patients with OAB also tend to visit the toilet more often, have an increased risk of urinary tract infections and twice the odds of being injured in a fall with increased risk of fractures, especially in the elderly, who may have to rush to the toilet to void when they suffer an urgency episode and on the way to the toilet, end up falling and fracturing a limb [15]. Overall, patients with UUI have a 30% increased risk of falls and 3% increased risk of fractures [16].

Most of these costs are direct ones, such as those associated with treatment, diagnosis, routine care and the consequences of the disease. It is also important to consider indirect costs of lost wages and productivity (and intangible costs associated with pain, suffering and decreased QoL) which are difficult to measure, but would increase the total costs even further [17].

Since OAB has severe consequences on QoL and society, it is important that doctors diagnose and treat it appropriately.

Causes of overactive bladder

In order to treat and cure a condition properly it is important to find the cause. Unfortunately, the actual cause of OAB is still unknown, although three main theories have been proposed.

The first theory is the myogenic or muscle-related theory, which suggests that smooth muscle changes are necessary for the production of an involuntary detrusor contraction. Thus, partial denervation of the detrusor may alter the properties of smooth muscle, leading to increased excitability and coupling between cells. A local contraction occurring in any part of the detrusor will spread throughout the bladder wall resulting in a coordinated myogenic contraction of the whole bladder [18].

The neurogenic or nerve-related theory is the second theory, and it suggests that damage to central inhibitory pathways in the brain or spinal cord, or sensitization of peripheral afferent terminals in the bladder can unmask primitive voiding reflexes that trigger DO [19].

The third theory is the autonomous bladder theory, which is a new hypothesis and suggests that during normal bladder filling there is autonomous activity, nonmicturition contractions and phasic sensory discharge. These basic mechanisms can become modified in pathologic conditions, thus leading to inappropriate augmentation of autonomous activity, excessive excitatory inputs or failure of inhibiting inputs. This abnormal nonmicturition activity could underlie DO [20].

The true cause of OAB and DO may differ between individuals, and may include one or more of the above three theories, and possibly other mechanisms as yet undescribed. Until the true cause, or causes, are found, treatment should be aimed towards the relief of symptoms, improvement of QoL and reduction of overall costs.

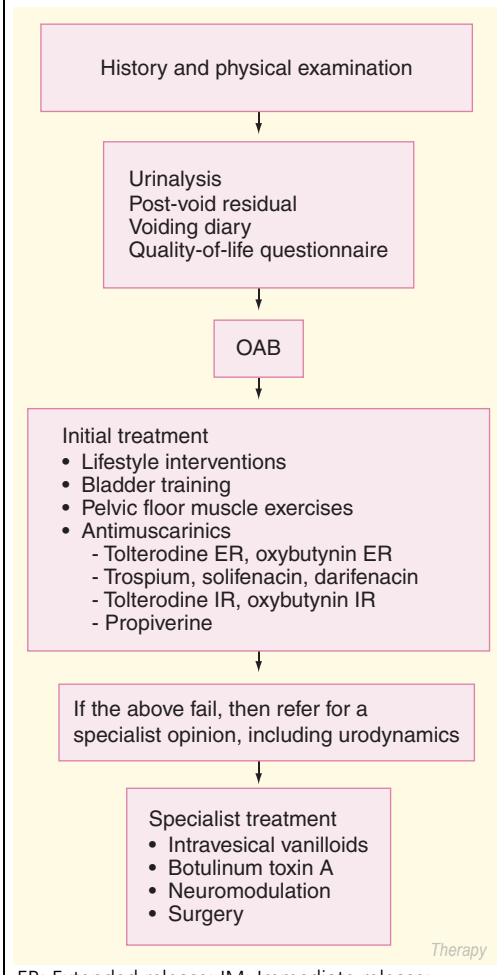
Diagnosis of overactive bladder

Accurate diagnosis of OAB should include a thorough history of urologic symptoms and examination of the abdomen and genitalia including a digital rectal examination in men and vaginal examination in women. Urinalysis should be carried out to exclude any pathology such as urinary tract infections, glucosuria and hematuria. A urine free-flow rate and postvoid residual urine needs to be performed to look for any evidence of bladder outlet obstruction.

Following history and examination, it is important to ask the patient to fill out a voiding diary for at least 4 days [21] to be able to quantify exactly how many frequency episodes occur, quantify fluid input and output, estimate bladder capacity and exclude global polyuria (for example due to diabetes insipidus) and nocturnal polyuria. The voiding diary is an invaluable tool in the management of OAB and should not be omitted, as it gives a better picture regarding the pattern of voiding than can be obtained from symptoms alone [22,23]. Ideally the diary should be completed before the patient comes for consultation.

Since OAB affects QoL, it is also important to have a baseline measure of QoL. Many questionnaires exist for this purpose, but most are generic (such as the SF-36) rather than disease specific such as ICI-QoL, KHQ [24,25]. The aim is to use a single, simple questionnaire, that is disease specific for OAB such as ICI-OABq [26,27]. Once a diagnosis of OAB is made, treatment can be initiated.

Figure 1. OAB treatment algorithm.



ER: Extended release; IM: Immediate release; OAB: Overactive bladder.

Treatment

The principles of treatment are to increase voided volume, decrease urgency and to reduce UUI episodes since, in almost all OAB groups, no curative treatment can be offered (**Figure 1**).

Treatment strategies for OAB include:

- Lifestyle interventions
- Bladder training and pelvic floor muscle exercises (PFME)
- Oral pharmacotherapy
- Intravesical therapy
- Neuromodulation
- Surgery

Lifestyle interventions

Lifestyle interventions must include patient and partner or caregiver education. General advice on fluid intake is important, although the evidence is conflicting regarding fluid manipulation as a means of controlling OAB symptoms. Some physicians advise patients to reduce their fluid input, thus reducing the amount of urine voided and controlling frequency.

Caffeine has been cited in the literature as a mild diuretic, causing increased urinary frequency. It also antagonizes adenosine receptors in the renal system therefore having a direct effect on increasing bladder muscle activity [28], although no laboratory research has been cited in the literature on this. However, patients are normally advised to reduce their caffeine intake by either switching to decaffeinated drinks, which have reduced amounts of caffeine, or to bland fluids to see if that helps.

Patients who suffer with nocturia are normally advised not to drink after six in the evening and to empty their bladders before going to bed. Patients should also be reminded that water-containing foods such as vegetables

and fruits should be avoided in the evening. Advice on emptying the bladder before going out should also be given.

In women, there seems to be an increased risk of onset of OAB associated with obesity, smoking and consumption of carbonated drinks and a reduced risk with higher consumption of vegetables, bread and chicken [29]. Intake of Vitamin D, protein and potassium seem to be protective of OAB and associated with decreased risks of onset [30].

In men, there seems to be a negative association between beer intake and subsequent OAB onset, with reduced risk at all levels of intake compared with those who seldom/never drank beer, suggesting that beer may have a protective role in the development of OAB, although the possible mechanism remains to be defined. Unlike in women, none of the food groups studied were associated with OAB onset, with the possible exception of potatoes, which showed an increased risk of onset at the highest level of consumption. Physical activity, smoking and obesity were not significantly associated with OAB either [31]. Results of this survey suggest that prevention is better than cure and thus, lifestyle modifications may be important for preventing and treating OAB: however, the results of this epidemiologic work need to be corroborated by further studies.

Bladder training & pelvic floor muscle exercises

The lifestyle interventions described above, may be enough to control the symptoms of OAB and improve QoL, however, they probably work better when combined with bladder training and PFMEs.

Bladder training aims to regain bladder control by suppressing involuntary detrusor contractions through increased feedback inhibition, thereby increasing the voided volumes and the time interval between voids and improving the voiding pattern by reducing frequency [32]. Bladder training consists of a scheduled toileting regime whereby patients are taught to void regularly every hour, on the hour, and then asked to increase the duration between voids by 10 or 15 min each week until they feel comfortable with their urinary frequency. Bladder training is usually supplemented by PFME (Kegel exercises), where the patients are taught to tighten the pelvic floor when they get an involuntary contraction and also when sitting up from lying down and standing up from a sitting position – these are both situations which can result in urgency and urgency incontinence due to an involuntary detrusor contraction.

Reports regarding the use of biofeedback [1] (technique by which information about a normally unconscious physiologic process is presented to the patient and/or the therapist as a visual, auditory or tactile signal) and/or electrical stimulation [1] (application of electric current to stimulate the pelvic viscera or their nerve supply) suggest that they do not seem to provide any additive effect, in terms of efficacy, in providing better results, compared with bladder training alone [33]. They can however be used as an adjunct to bladder training in patients who are unable to locate their pelvic floor muscles and are unable to contract them voluntarily [34].

Lifestyle interventions, bladder training and PFME, although time consuming, are cheap and effective methods of reducing the symptoms of OAB. Also, being the least invasive and least dangerous treatments for the patients, they should be considered as first-line therapy for OAB [35]. The voiding diary should be used to assess success and compliance during these treatments.

Should the above treatments fail, then pharmacotherapy should be initiated. Actually, it is more efficacious to combine conservative treatments, especially bladder training, with pharmacotherapy [36].

Oral pharmacotherapy

The detrusor smooth muscle is supplied by the parasympathetic system nerves (S2, 3 and 4). Acetylcholine (ACh) is the main neurotransmitter at the nerve endings, acting on the muscarinic receptors in the bladder and resulting in detrusor contraction. It would be logical to think that by blocking these receptors with antimuscarinic drugs, during bladder filling, DO could be reduced.

The situation is not as simple as it sounds because Ach is a transmitter in many other organs in addition to the bladder and acts on five subtypes of muscarinic receptors (M_1–M_5) variously distributed throughout the body organs. Therefore, blocking the action of Ach is likely to affect other organs in the body.

All five subtypes of muscarinic receptors have been demonstrated on the detrusor. The M_2 receptor is the predominant subtype accounting for two-thirds of the receptors. M_3 receptors make up the other third and have been found to be predominantly responsible for normal and abnormal

detrusor contractions [37]. ACh acting on M_3 receptors stimulates phospholipase C, generating inositol triphosphate and releasing calcium ions. ACh acting on M_2 receptors stimulates inhibitory adenyl cyclase with reduction of the intracellular content of cAMP. The M_2 and M_3 receptors have also been demonstrated on afferent nerves, urothelial cells, suburothelial cells and interstitial cells, while M_4 receptors have been demonstrated on the presynaptic nerve terminals [38]. Although there is no activity in the cholinergic nerves during bladder filling, ACh can be released from the urothelium or may leak from efferent nerves, to act on M receptors [38]. Unfortunately, M_3 receptors are also present in smooth muscle, salivary glands, the eyes and brain, and thus blocking them in these organs can cause constipation, dry mouth, blurred vision and dizziness, respectively. The M_2 receptors are also present in the heart and their blockade causes tachycardia. This is why it has been difficult to develop bladder-selective antimuscarinic drugs.

Nevertheless, antimuscarinic drugs form the cornerstone and mainstay of medical pharmacologic treatment for OAB [39] that, although effective, may be poorly tolerated with little long-term data on their use in clinical practice [40]. These drugs aim to reduce the symptoms of OAB due to DO, without significantly depressing detrusor contraction during voiding, thus resulting in clinical and QoL improvements.

Over the past couple of years there has been increasing interest from the pharmaceutical industry in OAB and new drugs have been introduced to the market with a few others in the production pipeline. Currently, there are six main drugs, namely: oxybutynin, tolterodine, propiverine, trospium, solifenacin and darifenacin (**Table 2**). Level 1, Grade A evidence has been given to all these drugs by the International Consultation on Incontinence, which follows the evidence-based medicine principles defined in collaboration with the Oxford and the Cochrane groups (**Table 3**).

Oxybutynin chloride

Oxybutynin was the first antimuscarinic used for the treatment of OAB. It was licensed in 1972 and is still being used in many centers across the world in its generic form. Oxybutynin is a tertiary amine that has a short half-life with high affinity for the muscarinic receptors of the bladder and parotid gland with higher affinity for M_1 and M_3 receptors [41] and 12-times more selective for M_3 over M_2 receptors [42]. Its active metabolite, *N*-desethyloxybutynin (NDO), has

Table 2. Drugs used for OAB treatment and cost for 28-day treatment [201].

Generic name	Trade name (UK)	Available doses	Mode of delivery	Frequency	Cost (GBP£)
Oxybutynin	Ditropan	IR: 2.5mg	Oral	t.i.d.	6.86
		IR: 5mg	Oral	t.i.d.	13.34
	Lyrinel XL	ER: 5mg	Oral	o.d.	11.51
		ER: 10mg	Oral	o.d.	23.03
	Kentera	36mg/patch (3.9mg/d)	Transdermal	b.i.d	27.20
Tolterodine	Detrusitol	IR: 1mg	Oral	b.i.d.	29.03
		IR: 2mg	Oral	b.i.d.	30.55
	Detrusitol XL	ER: 4mg	Oral	o.d.	29.03
Trospium	Regurin	20mg	Oral	o.d.	24.26
Propiverine	Detrunorm	15mg	Oral	b.i.d.	30.55
Solifenacin	Vesicare	5mg	Oral	o.d.	25.77
		10mg	Oral	o.d.	33.51
Darifenacin	Emselex	7.5mg; 15mg	Oral	o.d.	NA

b.i.d.: Twice daily; ER: Extended release, IR: Immediate release; NA: Not yet available; OAB: Overactive bladder; o.d.: Once daily; t.i.d: Three times daily.

Table 3. Oxford guidelines for levels of evidence and grades of recommendation [38].

Level	Evidence
1	Systematic reviews, meta-analysis, good-quality randomized, controlled trials
2	Less good-quality randomized, controlled trials, good-quality prospective cohort studies
3	Case-control studies, case series
4	Expert opinion
Grade	**Recommendation**
A	Based on Level 1 evidence (highly recommended)
B	Consistent Level 2 and 3 evidence (recommended)
C	Level 3 studies or "majority evidence" (optional)
D	Evidence inadequate and/or conflicting (no recommendation possible)

similar properties to the parent drug, thus contributing to oxybutynin's pharmacologic effects [43]. Oxybutynin also has musculotropic, smooth muscle-relaxant [44] and local anesthetic effects [45]. It is currently available in three formulations:

- Oral tablet immediate release (OXY-IR)
- Oral tablet extended release (OXY-ER)
- Topical transdermal patch (OXY-TD)

OXY-IR undergoes extensive hepatic first-pass metabolism and acts within 30 to 60 min of administration, with peak effects within 3 to 6 h of administration. It is recommended that treatment is started at the lower dose of 2.5 mg three-times daily and increased gradually after 7 days, with a maximum allowed dosage of 30 mg/day.

OXY-ER was approved by the US Food and Drug Administration (FDA) in 1999. It is administered once daily, using the oral-release osmotic system (OROS), which allows controlled release of medication, based on the permeability of the agent encapsulating the medication and osmotic pressure. Plasma concentration increases within 4 to 6 h and is maintained at a fairly constant concentration over 24 h.

OXY-ER seems to be as effective as OXY-IR, compared with placebo in reducing UUI but is better tolerated with less side effects [46,47]. There is less dry mouth due to the reduction in the peak concentration and a decrease in the number of peaks associated with each dose thus reducing the fluctuations between trough and peak levels. Constipation occurs less often with OXY-ER, since the tablet is absorbed in the large intestine rather than the stomach [48] and is not affected by gastric pH, intake of food or time of dosing [49,50]. It improves QoL [51] and probably increases compliance, since it is taken once rather than three-times daily [52].

Oxybutynin is the first, and only, antimuscarinic to be marketed as a transdermal patch (OXY-TD). It was approved in the USA by the FDA in March 2003 and in Europe by the European Agency for the Evaluation of Medicinal Products (EMEA) in December 2004. The patch is applied twice weekly to the abdomen, hips or buttocks.

OXY-TD achieves higher plasma concentrations of oxybutynin relative to NDO, with a lower daily dose and less inhibition of saliva production than oral oxybutynin as it avoids first-pass metabolism, which results in the production of the active metabolite of oxybutynin [53]. It also appears to be as efficacious as OXY-IR in reducing UUI with a favorable systemic side-effect profile [54].

Compared with long-acting tolterodine, OXY-TD appears to be as effective in patients with urgency and mixed incontinence by reducing the average number of incontinence episodes, increasing the voided volume and improving QoL [55]. Peak plasma concentration is reached in 36 h with less side effects such as dry mouth and constipation, but causes skin irritation with pruritis and erythema [56].

The rectal and intravesical routes have also been used in the administration of oxybutynin to avoid hepatic first-pass metabolism. These routes should only be used in patients who cannot tolerate oral or transdermal routes, or in which other treatments have failed.

Rectal oxybutynin suppositories have been shown in a small retrospective trial to have some benefit in a selected group of patients [57]. Conversely, the intravesical route has been subjected to some randomized, placebo-controlled trials, especially in patients with neurogenic DO who were shown to reduce urinary frequency [58,59,60]. However, the intravesical route is inconvenient unless the patient already performs intermittent self-catheterization to achieve bladder emptying.

Tolterodine tartrate

Tolterodine is a synthetic tertiary amine that was launched in 1998 and is administered orally either as an immediate-release (TOLT-IR) or extended-release form (TOLT-ER).

It is a competitive specific muscarinic receptor antagonist with greater selectivity for the bladder over salivary glands, *in vivo* in a feline model [61]. Its active 5-hydroxymethyl metabolite (DD 01) exhibits antimuscarinic activity similar to that of tolterodine [62]. *In vitro*, the relative binding affinity of tolterodine at the bladder muscarinic receptors is similar to that of oxybutynin. However, tolterodine only shows about four times the selectivity for the M_3 over M_2 receptor subtype [63].

Tolterodine undergoes extensive first-pass metabolism in the liver. Peak serum concentrations of the drug usually occur within 1 to 2 h after administration of a dose of TOLT-IR or 2 to 6 h after TOLT-ER. The half-life is 3 h for extensive metabolizers and 10 h for poor metabolizers of the drug.

TOLT-IR has been shown to decrease urinary frequency and UUI episodes with an increase in volume voided per void up to 12 months of treatment when compared with placebo [64]. It was well tolerated with improvement in QoL and discontinuation rates similar to placebo [65]. Side effects were mainly antimuscarinic in nature.

TOLT-ER has been shown to be more effective than placebo and TOLT-IR in relieving symptoms of urinary frequency, urgency and UUI with a decrease in pad usage, improvement in mean voided volume per void and QoL in patients with OAB symptoms [66,67]. Gender does not seem to affect the efficacy of TOLT-ER but there is a slight decrease in efficacy with advanced age [68]. TOLT-ER showed improved efficacy after 1 week of treatment but maximum benefit after 4 weeks of treatment [69], with good tolerability and safety over a 12-month period [70]. It causes less dry mouth than TOLT-IR [66].

Two trials compared TOLT-IR with OXY-IR and showed that both drugs equally reduced frequency, UUI episodes and increased voided volume per void in 24 h and both where better than placebo in all three parameters. However, tolterodine caused less dry mouth and fewer adverse events, and thus was better tolerated, allowing patients to continue treatment for longer periods [71,72].

The Overactive Bladder: Judging Effective Control and Treatment (OBJECT) trial showed that OXY-ER was significantly more effective in reducing the number of weekly UUI episodes, total incontinence episodes and micturition frequency episodes compared with TOLT-IR. Side effects, including dry mouth and CNS effects, occurred with similar frequencies in both groups and both drugs were equally tolerated, resulting in similar discontinuation rates [73].

The Overactive bladder: Performance of Extended Release Agents (OPERA) trial compared TOLT-ER with OXY-ER. It showed that both patient groups had similar improvements in weekly UUI episodes and total incontinence episodes. Oxybutynin was statistically more effective in reducing mean weekly micturition frequency and in producing total dryness (no incontinence episodes) in the last 7-day 24-h voiding diary. Dry mouth, although mild, was significantly more common with oxybutynin. Other side effects, including CNS effects, had similar frequencies, with both drugs resulting in comparable tolerability. There were also similar discontinuation rates [74].

The Antimuscarinic Clinical Effectiveness Trial (ACET) compared TOLT-ER with OXY-ER in an open-label study. It showed that a significantly lower proportion of patients withdrew from the trial when on TOLT-ER compared with OXY-ER, due to poor tolerability. Also, the patients on TOLT-ER had a significantly better degree of perceived improvement in their bladder symptoms, with less severe dry mouth than OXY-ER [75].

The different, and sometimes conflicting, results of these trials are mainly due to the fact that different drug formulations, different study populations and differnet inclusion criteria are used and also due to design of the trials.

Propiverine

Propiverine is a tertiary amine antimuscarinic with calcium channel-blocking action *in vitro* and with neurotropic and musculotropic effects on the urinary bladder smooth muscle [76]. It is administered orally and undergoes extensive first-pass metabolism, has several active metabolites, reaches peak plasma levels in about 2.5 h and is eliminated in the urine, bile and feces [77].

In one trial, propiverine reduced the number of micturitions and the number of urgency episodes within 24 h compared with placebo with an increase in the mean volume voided per void. It was judged efficacious, but did not improve QoL much more than placebo. Although it had good tolerability, dry mouth was the most frequently reported adverse event followed by 'eye problems'. Gastrointestinal disorders and nervous system disorders were the most frequent adverse events leading to withdrawal from the study [78].

One study compared propiverine with TOLT-IR [79]. It demonstrated that propiverine is comparable to tolterodine in terms of efficacy, tolerability and improvement in QoL. Compared with oxybutynin, dry mouth is reported as less common and less severe. Propiverine improved urodynamic measurements including cystometric bladder capacity at first desire to void and mean maximal cystometric capacity, as effectively as oxybutynin [80].

Solifenacin succinate

Solifenacin is a new, bladder-selective antimuscarinic. It was launched in August 2004 in Europe and approved by the FDA in the USA in November 2004.

Solifenacin is administered orally, and primarily cleared by hepatic metabolism but there is also some urinary excretion. *In vitro*, in monkeys and rats, solifenacin displayed tissue selectivity towards the bladder smooth muscle cells over salivary glands and higher bladder selectivity compared with tolterodine, oxybutynin and darifenacin [81,82]. It is approximately 12-times more selective for the M_3 than the M_2 receptor subtype [63] and reaches maximum plasma concentration in 3 to 8 h, with an elimination half-life of 45 to 68 h, thus offering good bioavailability [83].

Solifenacin significantly reduces the mean number of urgency and UUI episodes in 24 h and the mean number of voids per 24 h including nocturia and increases the mean volume voided per void compared with placebo. The most common side effects are dry mouth, constipation and blurred vision [84,85,86].

Tolterodine 2 mg twice daily has been used as a third arm in some of the trials involving solifenacin, where both were compared with placebo but not to each other. It was shown that tolterodine did not reduce urgency or incontinent episodes significantly in those patients; however, there was a decrease in urinary frequency and an increase in voided volume per void. Dry mouth in tolterodine was higher than the 5 mg dose of solifenacin, but lower than the 10 mg dose [85]. Interestingly; however, from the pooled data analysis of four trials, both tolterodine and solifenacin significantly improved the above symptoms except nocturia, which was only improved by solifenacin [87]. QoL also improved, with further improvement at 1 year of administration suggesting that it is well tolerated with a favorable therapeutic index and a low discontinuation rate [88,89]. A 'head-to-head' trial comparing solifenacin with TOLT-ER was completed in 2004 [90]. Solifenacin was used in a flexible-dose regimen with TOLT-ER as an active comparator in a double-blind, placebo-controlled, randomized trial. Solifenacin, with a flexible dosing regimen, showed superior efficacy to TOLT-ER in reducing urgency, UUI and pads used, with an increase in bladder capacity. In addition, solifenacin was not inferior to TOLT-ER in improving nocturia or daytime frequency. However these results were the combined effects of both the 5 and 10 mg doses of solifenacin and what is really needed is the comparison of each separately with respect to TOLT-ER. Side effects were mainly mild-to-moderate with higher constipation and dry mouth rates with solifenacin compared with TOLT-ER but no p-values for statistical significance were provided. Discontinuation rates were comparable in both groups. The main question that remains to be answered is: which is more important – clinical efficacy or side effects?

Darifenacin hydrobromide

Darifenacin is also an M_3 receptor antagonist [92]. The European Commission approved darifenacin in October 2004 and the FDA in December 2004. It was launched in the first half of 2005 in Germany and the USA with further launches in other countries expected in the second half of 2005 and early 2006. It is administered orally once daily, with an elimination half-life of approximately 3 to 4 h [92]. Darifenacin was the first selective M_3 receptor antagonist and is 59-times more selective for the M_3 over the M_2 receptor subtype [63].

Clinical trials have shown that darifenacin has a rapid onset of action with significant reduction in micturition frequency and median number of urgency and UUI episodes and increase in bladder capacity at both doses,compared with placebo within 2 weeks of beginning treatment [93]. Darifenacin also significantly increased warning time and reduced nocturia in patients with OAB [94,95]. There was a higher incidence of dry mouth and constipation compared with placebo, no blurred vision was reported and CNS and cardiac adverse events were comparable with placebo. It has long-term safety for up to 1 year, is well tolerated in the elderly, with no effect on cognitive function and improves QoL [96,97].

Oxybutynin was used as a third arm in one trial using darifenacin [98]. Both darifenacin and OXY-IR produced significant improvement in number and severity of urgency episodes/day and

number of incontinence episodes/week compared with placebo. However, neither produced any significant differences in the frequency of micturitions compared with placebo. Oxybutynin was associated with a significantly higher rate of dry mouth compared with either darifenacin or placebo. Blurred vision and dizziness were only reported by patients receiving oxybutynin.

Trospium chloride

Trospium chloride (TCL) has been used in Europe for more than 20 years but was approved in the USA by the FDA in July 2004. TCL, unlike the previous antimuscarinics, is a hydrophilic quaternary amine and, in theory, does not cross the blood–brain barrier, as may the tertiary amines which are lipophilic. This means that CNS and cognitive performance side effects such as dizziness should be minimal with trospium [99]. It is a competitive inhibitor of ACh at muscarinic receptors with almost equal selectivity for the M_3 and M_2 receptors [63].

TCL reaches peak plasma concentration after 4 to 6 h, but is poorly absorbed from the upper gastrointestinal tract: 80% is excreted in the stool as the active parent compound [100,101]. Compared with placebo, TCL decreased urgency severity, daytime frequency and UUI episodes, while increasing volume voided per micturition, all within 1 week of starting treatment, and decreased nocturia within 4 weeks of starting treatment [102,103]. TCL also increases maximum cystometric capacity and urinary volume at first involuntary detrusor contraction [103]. It is well tolerated by patients without causing CNS effects or sleepiness [105].

To date, there are no trials comparing TCL with TOLT or OXY-ER; however, it appears to be as effective as OXY- and TOLT-IR in reducing micturition frequency but more effective than TOLT-IR at reducing incontinence episodes and better tolerated than OXY-IR [106,107].

Fesoterodine

Fesoterodine is a novel bladder-selective antimuscarinic that has undergone Phase II trials and finished Phase III trials in 2004. It appears to be effective and well tolerated [108], with possible availability on the market in 2006. It is extensively metabolized in the liver to its active metabolite which is a specific but nonsubtype-selective antimuscarinic with maximum plasma levels reached after approximately 5 h and a terminal half-life of 7 h [109].

Other oral pharmacologic agents

Other oral pharmacologic agents have been used for the treatment of OAB; however, the level of evidence available is not sufficient for them to be used generally, although some physicians continue to use and prescribe them. These include:

- Estrogens (Level 2, Grade C): Local estrogens were better than systemic estrogens and are effective in relieving frequency, nocturia, urgency and incontinence episodes especially in postmenopausal women [110,111]
- Flavoxate (Level 2, Grade D): Nonanticholinergic antispasmodic which has gone out of favor in the developed world [112]
- Imipramine (Level 3, Grade C): Antidepressant and nonsubtype selective antimuscarinic with possible effects on arginine vasopressin release and renal proximal sodium and water absorption [38]
- Propantheline (Level 2, Grade B): Quaternary amine with low bioavailability. It is nonsubtype selective with a short half-life of less than 2 h [38]
- α-antagonists such as tamsulosin (Level 3, Grade C): May be effective in selected cases, such as neurogenic DO to decrease maximum detrusor pressure and increase maximum flow rate
- β-agonists such as terbutaline (Level 3, Grade C): These drugs have a relaxant effect but need controlled trials to confirm their effect in OAB
- Prostaglandin synthesis inhibitors such as flurbiprofen, indomethacin (Level 3, Grade C): Limited drugs tested and may have side effects
- Calcium antagonists have been found not to be effective

Which oral agent to use?

When choosing an antimuscarinic drug, a balance must be reached between efficacy and side effects. It is important to remember that, with all the medications mentioned above, the national drug formulary may need to be consulted to look for contra-indications and cautions. When prescribing, enquiries about concomitant diseases should be made, in particular renal failure and hepatic failure as they can affect the metabolism and elimination of antimuscarinic drugs.

Physicians should be careful when prescribing antimuscarinics to elderly patients, as the elimination time of the drug may be increased

(e.g., oxybutynin) and also because elderly patients are more likely to be taking other drugs, giving rise to potential drug interactions. Elderly individuals are more likely to experience adverse drug reactions that are far more serious and prolonged.

The decision to choose one drug over the other is very difficult and is probably governed by which drug is licensed by national and local drug authorities, availability at the local hospital or in the community and the cost of the drug, especially in countries where medications are not subsidized by the government.

Based on the current evidence, both OXY-ER and TOLT-ER are better than IR formulations and should be used as first-line medications due to efficacy and better compliance. In the elderly and those that operate machinery, it would probably be better to use TCL. Although both solifenacin and darifenacin have good quality data, their use will remain to be second-line until more clinical experience is gained in community-dwelling patients. Once that is established they may become first-line treatments.

What if oral pharmacotherapy treatment fails?

Although conservative and oral pharmacotherapy are the mainstays of treatment of OAB, they sometimes fail. Patients who fail initial therapy and want further therapy, should be referred for urodynamics to confirm the diagnosis of DO. Once the diagnosis is confirmed, treatment options include intravesical therapy, neuromodulation or surgery.

Intravesical pharmacotherapy

Sometimes oral pharmacotherapy fails to control symptoms and there is a need for other treatment modalities to be tried: intravesical oxybutynin was discussed above.

Botulinum-A toxin

Botulinum A toxin (BTA) has been used to treat strabismus and spasmodic torticollis for many years. It selectively blocks the release of ACh from nerve endings and has therefore been used by some urologists as second-line treatment for neurogenic DO, with good results in nonrandomized trials [113]. 300 U in neurogenic DO and 200 U in idiopathic DO of BTA toxin are injected at 20 to 30 different sites into the detrusor muscle, sparing the trigone [114]. This can be performed as a day case under local anesthesia with a flexible cystoscope [115,116]. In a retrospective study, BTA toxin increased mean cystometric capacity and mean infused volume at first detrusor contraction while decreasing mean voiding pressure in neurogenic patients [117]. Subjective and objective assessments in patients has shown significant improvements for at least 6 months and up to 14 months [118].

In a multicenter, randomized, controlled trial, it was found that both 200 U and 300 U of BTA are effective in reducing UUI in patients with neurogenic DO by allowing the bladder to hold and retain more urine [119]. There is also some evidence to show that BTA toxin may be beneficial in idiopathic DO however to date, there has been no study published comparing BTA toxin with placebo in idiopathic DO [120].

Resiniferatoxin

Resiniferatoxin (RTX) is an ultrapotent analog of capsaicin and belongs to a group of substances known as vanilloids [121]. These compounds act selectively on vanilloid receptor subtype-1 to desensitize unmyelinated afferent C-fibers [122]. These fibers are responsible for detecting noxious stimuli and initiating painful sensations in the bladder of normal individuals. In neurogenic patients, the C-fiber afferents are activated and provide an additional afferent pathway in the micturtion reflex [123]. Capsaicin has been used previously and shown to be useful in neurogenic DO, although it causes bladder irritation. Resiniferatoxin intravesically seems to be as effective as capsaicin, with less irritation to the bladder, in neurogenic DO [124], but none of the trials have compared resiniferatoxin or capsaicin with placebo in neurogenic DO. Resiniferatoxin was compared to placebo in idiopathic DO and both significantly improved parameters such as daytime frequency, number of incontinence episodes, nocturia, patient perception of improvement, functional and maximal cystometric capacity with no statistical difference between the placebo and resiniferatoxin groups [125].

Neuromodulation

Sacral nerve stimulation (SNS) and percutaneous tibial nerve stimulation (PTNS) are new modalities that have been used in some centers worldwide and will probably help bridge the gap between pharmacotherapy and major surgery [126].

The FDA has approved SNS for OAB and voiding difficulties. SNS is minimally invasive and involves inserting a lead through the third

sacral foramina to lie close to the third sacral nerve (S3) under local anesthesia, with the subsequent implantation of a neurostimulator in the buttock, if an initial trial period of stimulation is successful. This sends electric impulses to the sacral nerves and helps control OAB symptoms. SNS appears to be successful in reducing frequency, UUI episodes and nocturia as well as increasing bladder capacity and bladder volume at both first bladder sensation and normal desire to void [127]. It also improves QoL of patients [128].

PTNS is less invasive than SNS and has been approved by the FDA and European authorities. It involves inserting a needle electrode proximal to the medial malleolus. This modulates the sacral nerve plexus via the peripheral nervous system by stimulating the afferent nerve fibres of the tibial nerve and thus controls the symptoms of OAB. The treatment is carried out in 30-min sessions for 12 sessions and then repeated as required. PTNS appears to be effective in reducing daytime and night-time frequency and UUI episodes with an improvement in QoL [129].

Surgery

Surgery should be the last resort in the treatment of intractable OAB after failure of all the above treatments. Surgical options tried in the past included bladder distension, bladder transection and transvaginal denervation. These techniques had short-term results and high recurrence rates and sometimes high complication rates. Surgical rhizotomy is another procedure but is limited to patients with spinal cord injuries because of its effects on the motor and sensory nerves.

Surgical options that currently exist aim to abolish urgency and UUI by increasing functional bladder capacity and thus reducing detrusor pressure at this capacity. These include augmentation cystoplasty, which aims to increase functional bladder capacity, detrusor myectomy, which removes part of the bladder smooth muscle, and finally urinary diversion where all else fails [130]. These techniques appear to offer better results than the previous procedures but like any operation, have their own complication rates such as recurrent infections and bowel obstruction.

Expert commentary & outlook

The bladder has a complex signaling mechanism and several hypotheses have been proposed regarding mechanisms participating in the activation of bladder contraction. Many new drugs, with central and peripheral nervous system targets, are undergoing research to look for new ways of treating OAB and, it is envisaged that over the next 5 to 10 years, more drugs will be available for the treatment of OAB with fewer side effects. Drugs which are under investigation include [131]:

- Neuromuscular junction inhibitors of ACh release from cholinergic nerve terminals such as BT
- Serotonin norepinephrine reuptake inhibitors such as duloxetine. Serotonin deficiency and urinary incontinence seem to be linked and activation of central serotonergic systems by serotonin 5HT reuptake inhibitors as well as serotonin $5HT_{1A}$ and $5HT_2$ agonists seem to increase bladder volume and decrease detrusor contraction
- Opioid receptors seem to be involved in micturition control. It has been found that in animal studies tramadol can inhibit DO through α-receptor agonism and amine reuptake inhibition
- γ-aminobutyric acid (GABA) receptors present in the brain and spinal cord have been shown in animal studies to be involved in micturition. Increasing endogenous levels of GABA in the CNS may improve micturition control. Gabapentin used in patients with neurogenic DO appears to improve symptoms and urodynamic parameters. This will need to be explored in randomized, controlled trials
- Potassium channel openers offer a theoretical treatment potential through hyperpolarisation of the detrusor. They cause an efflux of potassium ions which leads to a decrease in influx of calcium ions resulting in inhibition of contraction during the filling phase of the bladder, abolishing DO with no effect on normal micturition [38]
- Drugs in development include bladder-selective antimuscarinics, purinergic receptor antagonists, vanilloids/afferent nerve inhibitors and β3-specific agonists
- Desmopressin has been used in the treatment of nocturia and recently, in a pilot study, has been shown that it can be used in the treatment of daytime urgency incontinence [132]. This is a new concept and may in the future be used to treat OAB

Hopefully the cause of OAB can also be found and thus treatment aimed at cure rather than relief of symptoms.

Highlights

- Overactive bladder (OAB) is a prevalent condition affecting millions of people worldwide, which has significant economic costs.
- The cause(s) of OAB is unknown and therefore treatment is aimed at relieve of symptoms rather than cure.
- History, examination, voiding diaries and quality of life questionnaires are very important in the assessment of patients with OAB.
- Conservative treatment including lifestyle interventions, bladder training and pelvic floor muscle exercises are the first line treatments.
- Antimuscarinics are the mainstay of pharmacotherapy.
- Best treatment option includes combining conservative treatment with oral drug therapy.
- Nonsurgical treatments can be initiated before urodynamics.
- If oral drug therapy fails then options include intravesical pharmacotherapy, neuromodulation and surgery.

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Affiliations

Hashim Hashim, MBBS, MRCS,
Urology Research Registrar
Bristol Urological Institute,
Southmead Hospital,
Westbury on Trym, Bristol, BS10 5NB, UK
Tel.: +44 117 959 5690
Fax: +44 117 950 2229
hashim@doctors.org.uk

Paul Abrams, MD, FRCS,
Professor of Urology
Bristol Urological Institute,
Southmead Hospital,
Westbury on Trym, Bristol, BS10 5NB, UK
Tel.: +44 117 959 5690
Fax: +44 117 950 2229
paul_abrams@bui.ac.uk