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Drug Treatment of Overactive Bladder

Efficacy, Cost and Quality-of-Life Considerations

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Abstract

Overactive bladder (OAB) syndrome has been recognised by the International Continence Society as an important symptom syndrome that affects millions of people worldwide. Quality of life is affected in most people with OAB; however, the aetiology is unknown. Some researchers suggest that it is because of a damage to central inhibitory pathways or sensitisation of peripheral afferent terminals in the bladder, others suggest that it is a bladder muscle problem; the reality is probably a spectrum encompassing these two main explanations. Therefore, treatment is difficult and is aimed at alleviating symptoms (being those of urgency, with or without urge incontinence, usually with frequency and nocturia) rather than treating the cause. A thorough patient history and physical examination are required to establish a possible diagnosis. Frequency/volume charts form an important aid to the diagnosis. Once a presumptive diagnosis is made, conservative management forms the first line of treatment and includes lifestyle modifications, bladder training and pelvic floor exercises. If this fails, pharmacotherapy, in the form of anticholinergic drugs, is initiated.

There are many antimuscarinic drugs, for example oxybutynin, tolterodine and trospium chloride. Each has a different specificity to bladder muscarinic receptors, thus producing different adverse effect profiles (e.g. dry mouth, blurred vision and constipation). Different individuals experience these adverse effects to different extents. New anticholinergic drugs, that have undergone phase III trials and are more specific to the muscarinic M_3 human bladder receptor, are being introduced to the market in 2004 (e.g. solifenacin succinate and darifenacin). In addition to adverse effect profile, cost and improvement in quality of life are

important factors in choosing treatment. Further research is being conducted on other types of drugs and different administration modalities, for example intravesical botulinum toxin A. Sacral nerve neuromodulation is emerging as a potential treatment, but if all treatments fail then surgery is the last resort.

1. Definition

Overactive bladder (OAB) has been defined by the Standardisation Subcommittee of the International Continence Society (ICS) as urgency, with or without urge incontinence, usually with frequency and nocturia, if there is no proven infection or other obvious pathology.[1] This definition complements the previous ICS definitions which were based on the assessment of detrusor function during the filling phase of cystometry. Table I defines these terms.

OAB has been recognised as a symptom syndrome suggestive of the lower urinary tract dysfunction, detrusor overactivity. Synonyms include urge syndrome and urgency-frequency syndrome. Although urgency is the key symptom of OAB, it is important to realise that we still do not have an adequately validated tool to measure urgency.

2. Prevalence and Cost

Most previous studies concentrated on urinary incontinence and, until recently, little was known about the prevalence of OAB. In six European countries (France, Germany, Italy, Spain, Sweden and the UK) 16.6% of the population aged more than 40 years had symptoms of 'OAB' (single or in combination), frequency being the most commonly (85%) reported symptom followed by urgency (54%) and urge incontinence (36%).[2] The prevalence increases with age and it was estimated that 22 million people have OAB in these six European countries, of whom only 60% had consulted a medical practitioner and 27% were receiving treatment, and probably over 49 million throughout the whole of Europe have OAB. There were some differences in prevalence between countries, ranging from 12% in France and Italy to 22% in Spain. Although chronic frequency was the most commonly reported symptom in the study, it is important to realise that this survey was conducted before the new definition of OAB was published in 2002. The new definition states that urgency is the cornerstone of OAB; thus, the study will have overestimated the prevalence of OAB, which by the new definition is probably closer to 10–12%.[3]

In the US, a recent study was conducted using the new definition of OAB as part of the National Overactive Bladder Evaluation (NOBLE) programme: 16.5% of the population (16% of men and 16.9% of women) aged >18 years had the symptoms of OAB.[4] This would equate to about 34 million people in the US.

OAB affects all aspects of quality of life including physical, social, psychological, occupational, domestic and sexual functioning, and has a greater impact on quality of life, as measured by 36-item Short Form (SF-36), than type 2 diabetes mellitus, but less than depression.[5-8]

Patients with OAB have to visit the toilet more often because of urgency, and it has been estimated that in patients with urinary incontinence there is a 30% increased risk of falls and 3% increased risk of fractures.[9,10] OAB also has a significant economic impact on society in general.[11] In the US, for the

Table I. Definitions of symptoms of overactive bladder

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

year 2000, the cost of OAB was about $US12.6 billion, which is comparable with the costs of asthma and osteoporosis, but less than that of urinary incontinence ($US19.5 billion).[12] Most of these costs were direct costs including treatment, diagnosis, routine care and consequences (e.g. skin infection/irritation).[13] However, other important costs include indirect ones, such as lost wages, and intangible costs associated with decreased quality of life. These are difficult to measure and, thus, the overall economic burden is difficult to assess.

3. Theories of Overactive Bladder

OAB is associated with involuntary contractions of the detrusor muscle, defined as detrusor overactivity, which occur as the bladder fills. In normal function the bladder should be relaxed as urine fills the bladder. The cause of this is unknown; however, two main theories of detrusor overactivity have been proposed. The myogenic theory[14] suggests that partial denervation of the detrusor results in alterations in the properties of the detrusor muscle cells leading to increased excitability, thus producing involuntary pressure rises. The neurogenic theory[15] suggests that damage to central inhibitory pathways or sensitisation of peripheral afferent terminals in the bladder can unmask primitive voiding reflexes that trigger detrusor overactivity. A third theory, the autonomous bladder hypothesis, has been proposed recently. It suggests that detrusor overactivity is a consequence of inappropriate activation or modulation of phasic activity.[16] Detrusor overactivity is said to be idiopathic if there is no defined cause or neurogenic if there is a relevant neurological condition, for example multiple sclerosis, spinal cord lesion, etc.

4. Management

The general practitioner/primary care physician is usually the first point of contact for symptomatic patients who decide to seek help. The most important aspect of the consultation is for the physician to explain to the patient that this condition is very common and the patient has to be made comfortable to talk about his/her symptoms.

To diagnose OAB, like all other medical problems, patients should undergo a thorough history and good physical examination as they form the basis for diagnosis, investigations and treatment, and serve to exclude medical problems that may mask or present in a similar way to OAB.

By applying evidence-based medicine, the aim is to provide a clear and concise algorithm for the management of patients with OAB (figure 1), taking into consideration different treatment modalities, their characteristics, cost and effects on quality of life.

4.1 Patient History

In the history of patients with OAB, it is important to establish what urinary symptoms the patients have, how long the symptoms have been ongoing and which are the most bothersome symptoms. The average number of symptom episodes (urgency, urge incontinence, frequency, nocturia) and the number of pads used, if any, should be estimated, but must also be recorded more accurately using a voiding diary.

A medical and drug history is also very important to exclude causes that may be aggravating the symptoms (e.g. patients with heart failure on diuretics). Surgical history is also important, especially operations related to the genitourinary tract or those that may cause denervation (e.g. spinal or pelvic surgery). Inquiry of bowel function is important as there have been reports of association between OAB and irritable bowel syndrome.[17]

In females, a gynaecological and obstetric history is very important, including the mode and number of deliveries, symptoms during intercourse (especially incontinence) and a history of pelvic organ prolapse or gynaecological surgery.

The impact of OAB on quality of life is important and, therefore, the perceived impact on everyday life should be documented (e.g. reduced social activity and physical exercise).

Alcohol (ethanol) and caffeine are known to irritate the bladder[18] and exacerbate symptoms of OAB; therefore, the physician needs to enquire about the average quantity of tea, coffee and alcohol consumed per day as the diuretic effect of these substances can be responsible for worsening symptoms.

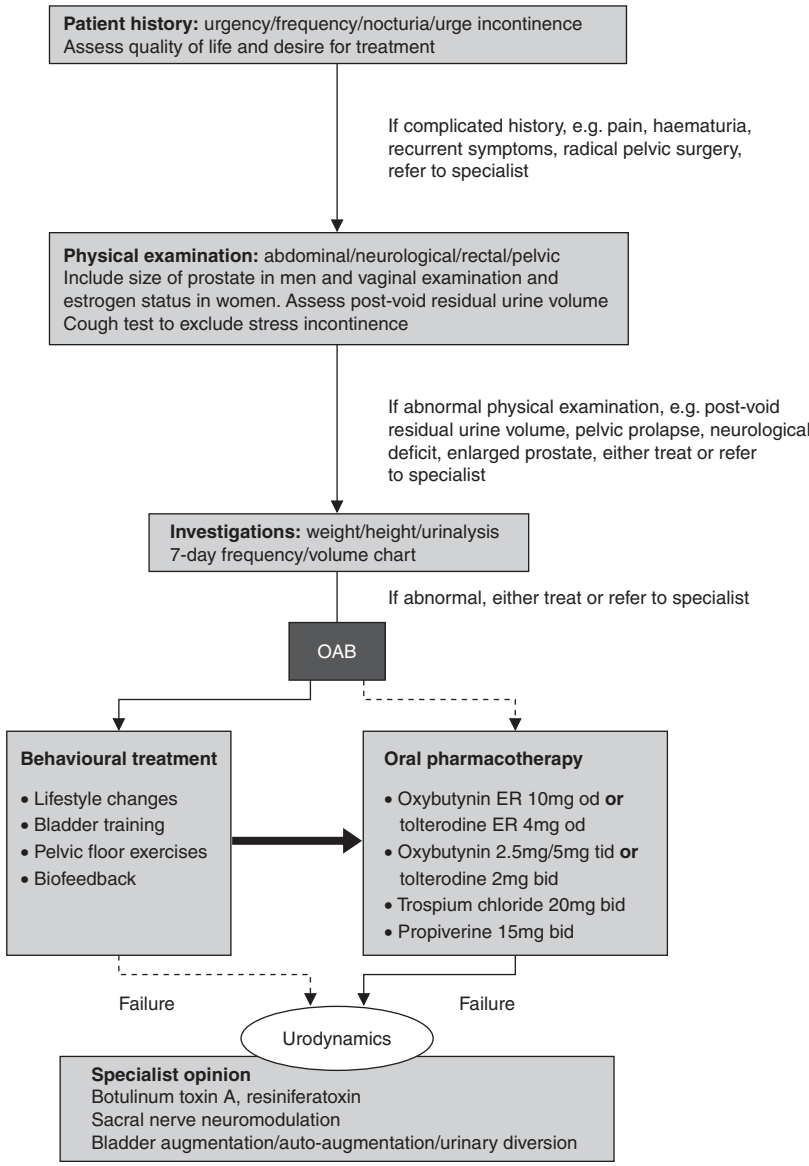

Fig. 1. Algorithm for the management of overactive bladder (OAB) syndrome. **bid** = twice daily; **ER** = extended release; **od** = once daily; **tid** = three times daily.

4.2 Physical Examination

Following patient history taking, physical examination should concentrate on abdominal examination to look for a palpable bladder, followed by a neurological examination of the lower limbs looking at tone, power, reflexes and sensation. In men, digital rectal examination should be performed to assess the prostate and check for constipation as well as anal tone, sensation and pelvic squeeze.

In women, the perineum needs to be inspected to look for atrophic vaginitis and pelvic organ prolapse, and to check for leakage during coughing or straining. Although it is useful to assess anal tone in females, a pelvic examination is also required to

assess pelvic floor strength. A detailed examination for pelvic organ prolapse is performed using a Sims speculum with the patient lying in the left lateral position, and the patient asked to 'bear' down (strain).

4.3 Investigations

Simple bedside tests such as weight, height and urinalysis are important. The weight and height are used to calculate the body mass index to advise on weight loss. Urinalysis, by looking at the urine using a clear glass container[19] and/or urine dipstick, is used to exclude urinary tract infections by looking for leucocytes and nitrites, glucosuria and haematuria. Bladder scanning by ultrasound (if available) or an 'in/out' catheterisation can be used to measure post-void residual urine volume accurately.

After patient history, physical examination and investigations the physician will be in a better position to make a provisional diagnosis and advise on further management.

At this point the primary care physician has two main routes to follow: (i) continue with any further investigation, if indicated, and initiate treatment; or (ii) send the patient to a urologist.

As a result of healthcare systems and hospital specialists being under-resourced, there is a trend in the UK to move patient care towards the general practitioner in the community; therefore, we recommend the first pathway for initial management. Referral to a specialist is necessary if the patient history or physical examination is complex (e.g. a neurological cause for the patient's symptoms, haematuria, large residual volume of urine) or if there is failure of initial treatment by the general practitioner.

The next step in reaching a diagnosis is to ask the patient to complete a voiding diary. Voiding diaries give a better picture regarding the pattern of voiding than can be obtained from symptoms alone. There are three main types of charts,[1] depending on the information required.

1. Micturition time chart: records only the times of micturitions for at least 24 hours.
2. Frequency/volume chart (FVC): records the voided volume and the time of each micturition, day and night, for at least 24 hours.
3. Bladder diary: records the time of micturitions, voided volume, incontinence episodes, pad usage, urgency episodes and fluid intake.

The duration that the patient is asked to keep a chart for depends on how much information is required. This can range from 1 to 14 days, with 7 days being the average: at least 3 days are needed in order not to compromise the diagnostic value of the FVC.[20] A 4-day diary seems to give the same information as a 7-day diary.[21] However, it is the practice of the authors to use a 7-day bladder diary, but without the documentation of urgency episodes (figure 2).

Quality of life, in relation to OAB, can also be assessed in primary care using standardised validated questionnaires such as the International Consultation on Incontinence Questionnaire – Short Form (ICIQ-SF) and the International Continence Society Male Questionnaire (ICSmale).[19,22,23] Assessment of renal function, by a blood test looking at serum/plasma urea, creatinine and electrolytes is only recommended in specific situations, for example, patients with urinary incontinence and a high probability of renal impairment or prior to surgical procedures.[19]

4.4 Treatment

Once patient assessment is complete, the physician can initiate treatment. In almost all OAB groups no curative treatment can be offered. The principles of treatment are to increase voided volume, decrease urgency and reduce urinary urge incontinence episodes. Treatment includes:

- lifestyle interventions;
- bladder training and pelvic floor exercises;
- pharmacotherapy; and
- surgery.

The first three treatments can be started by the primary care physician. If they fail, then a specialist opinion should be sought.

4.4.1 Lifestyle Interventions

Lifestyle interventions include patient and carer education about the condition, general and lifestyle measures, including stopping caffeine (which acts as a mild diuretic and stimulant to the detrusor muscle)[18] and alcohol intake, not drinking fluids after 6:00pm and voiding before going to bed, if

Name _____

Date	Time of getting up for the day	Time Volume (mL) Daytime (from waking up to going to bed)	Time of going to bed	Night-time (from going to bed to getting up)	Number of pads used in 24h period

Average intake of tea/coffee per day (in cups/mugs) = _____

Average intake of other fluids (excluding alcohol) per day (in cups/mugs/glasses) = _____

Average alcohol intake per week (in glasses/pints) = _____

Fig. 2. Frequency/volume chart.

nocturia is a problem. Some specialists advise restricting fluid intake to about 1.5L per day; however, this is still a matter of debate and there have been no randomised controlled trials to assess whether patients with OAB should drink more or less fluid to help with symptom control.

4.4.2 Bladder Training and Pelvic Floor Exercises

Bladder training[24] aims to help regain bladder control by suppressing involuntary detrusor contractions through feedback inhibition, thereby increasing the voided volumes and the time interval between voids. The patients are taught to void regularly every hour on the hour and then asked to increase the duration between voids by 15 minutes each week until they feel comfortable with their urinary frequency. Bladder training is usually supplemented by pelvic floor exercises (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 urge incontinence because of an involuntary detrusor contraction.[25]

Biofeedback[1] (a technique by which information about a normally unconscious physiological process is presented to the patient and/or the therapist as a visual, auditory or tactile signal) and/or electrical stimulation[1] (application of an electrical current to stimulate the pelvic viscera or their nerve supply) do not seem to provide any additive effect in terms of efficacy in providing better results compared with bladder training alone.[26,27] However, these methods of treatment can 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.[28]

During bladder training and pelvic floor exercises the FVC should be used to assess success and compliance. These treatments are inexpensive and effective methods of reducing symptoms of OAB and can be easily initiated by primary care physicians.[29]

Some specialist departments produce leaflets that explain these exercises to patients and these can be easily supplied to general practitioners in the local area. These exercise instructions are also available on the Internet (e.g. http://www.continence-foundation.org.uk).

4.4.3 Pharmacotherapy

The detrusor muscle is supplied by the parasympathetic system nerves (S2, S3 and S4 spinal segments). In simple terms, the normal micturition reflex is activated by myelinated Aδ-fibres which ultimately lead to an increase in efferent nerve impulses resulting in detrusor contraction. The main neurotransmitter at the nerve endings on the detrusor smooth muscle is acetylcholine acting on the muscarinic M_3 receptors in the bladder. It would make sense that by blocking these receptors detrusor overactivity could be reduced. The problem lies in the fact that acetylcholine is not only a neurotransmitter in the bladder but also in many other organs. The situation is made more complex by the fact that there are five subtypes of muscarinic receptors (M_1–M_5) distributed throughout the body organs. Therefore, blocking the action of acetylcholine could have effects all over the body.

In the detrusor, the predominant muscarinic receptor is M_2, which accounts for two-thirds of the receptors. M_3 receptors make up the other one-third but it is the M_3 receptor subtype that has been found to be predominantly responsible for the detrusor contraction.[30] Facilitatory M_1 receptors and inhibitory M_4 receptors have also been demonstrated on the cholinergic nerve endings of the detrusor. The M_3 receptors are also present in smooth muscle, salivary glands, the eyes and brain.[31] This is why it has been difficult to develop bladder-selective anticholinergic drugs. The ubiquitous nature of the M_3 receptor might give the adverse effects of constipation, dry mouth, blurred vision and drowsiness by drugs blocking these receptors. The other important receptors are M_2 receptors, which are present in the heart and cause parasympathetically induced bradycardia through their stimulation, and the M_1 receptors found in the brain and said to facilitate memory.[32] Therefore, blockage of the M_2 and M_1 receptors can lead to tachycardia and to memory loss, respectively.

The recommendation for first-line medical treatment of OAB is the use of anticholinergic drugs[33] which, although effective, may be poorly tolerated. There is little long-term data on their use in clinical practice.[34] These drugs aim to decrease leakage episodes and the number of voids per day, resulting in clinical and quality of life improvements. However, they lack selectivity for the bladder receptors and, therefore, have a number of adverse effects that some patients find intolerable (e.g. dry mouth, blurred vision, dizziness and constipation). When choosing an anticholinergic drug the balance has to be between efficacy and adverse effects.

It is important to remember that with all the medications mentioned in the following sections the national drug formulary may need to be consulted to look for contraindications 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 anticholinergic drugs.

Physicians should be careful when prescribing anticholinergic drugs 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 poten-

tial drug interactions. Elderly individuals are more likely to experience adverse drug reactions that are far more serious and prolonged.

Oxybutynin

Oxybutynin is the first anticholinergic drug that was used for OAB. It was approved by the US FDA in 1975 and has been used since then for symptoms of OAB, including urge incontinence. It has been only in the past few years that new drugs have been developed that act in a similar way.

Oxybutynin is a tertiary amine with anticholinergic effects on smooth muscle, including the bladder, and antispasmodic effects on the detrusor muscle. It is usually administered orally and undergoes extensive hepatic first-pass metabolism. The metabolite, N-desethyloxybutynin, has similar properties to the parent drug.[35]

In its immediate-release (IR) form, oxybutynin is manufactured as tablets in strengths of 2.5mg, 3mg and 5mg. It can also be used as syrup (2.5mg in 5mL). The onset of action is within 30–60 minutes of administration with peak effects within 3–6 hours of administration. It is recommended that treatment is started at the lower dose and increased gradually after 7 days: 2.5mg three times daily increasing to 5mg three times daily if the patient tolerates the increase. The maximum allowed dosage is 30 mg/day.[36]

A modified, once-a-day extended-release (ER) formulation of oxybutynin is also available on the market (approved in 1999 by the US FDA) in 5mg, 10mg and 15mg tablets. We recommend the use of this rather than the IR formulation as this increases compliance with the medication and it seems to be as effective,[37,38] but better tolerated with fewer adverse effects such as dry mouth.[39] There is also less constipation since the absorption is in the large intestine rather than the stomach.

The advantages of the ER formulation are due to a reduction in the peak concentration with each dose and a decrease in the number of peaks associated with multiple dose administrations. These reduce the fluctuations between trough and peak concentrations. Oxybutynin also improves the quality of life of patients over 3–12 months of therapy.[40]

Two other modes of delivery for oxybutynin are the intravesical and transdermal routes. Both of these routes seem to produce fewer systemic adverse effects than the oral route because they avoid the first-pass metabolism that results in the production of the active metabolite of oxybutynin. The transdermal route achieves a higher plasma concentration of oxybutynin with a lower daily dose and less inhibition of saliva production.[41] Further studies will need to be done to look at the efficacy of this route, patient compliance and the effect on symptoms compared with the oral route. An adverse effect of the transdermal route is skin irritation in some patients. Transdermal oxybutynin seems to have comparable effects with long-acting tolterodine in patients with mixed and urge incontinence.[42] It has recently been marketed in the US as an 39 cm^2 patch in a dose of 36mg per patch (3.9 mg/day). Oxybutynin is delivered consistently over 3–4 days.

The intravesical route may be effective in those patients with OAB in which other treatments, for example oral treatment, have failed or cannot be tolerated because of the systemic adverse effects of oral treatment.[43] However, this route may be inconvenient unless the patient already performs intermittent self-catheterisation to achieve bladder emptying.

Tolterodine

Tolterodine is a synthetic tertiary amine and a competitive specific muscarinic receptor antagonist with a greater selectivity for the bladder over salivary glands, *in vivo*. Its active 5-hydroxymethyl metabolite (DD 01) exhibits antimuscarinic activity similar to that of tolterodine. *In vitro*, the relative binding affinity of tolterodine at the muscarinic receptors in the bladder is similar to that of oxybutynin. It undergoes extensive first-pass metabolism in the liver. It was launched in 1998, is administered orally and made in an IR form (1mg or 2mg) and an ER form (2mg or 4mg). Initial adult dosage of tolterodine is 2mg twice daily as IR tablets or 4mg once daily as ER capsules. Peak serum concentrations of the drug usually occur within 1–2 hours after administration of a dose of IR tablets or 2–6 hours after ER capsules.[36] The half-life is 3 hours for extensive metabolisers and 10 hours for poor metabolisers of the drug. The dosage can be reduced according to individual clinical response and toler-

ance.[44] Tolterodine ER is more effective than placebo in relieving urinary symptoms (e.g. urinary frequency, urgency, urge incontinence) in patients with OAB.[45] In addition, in several studies, patients' perceptions concerning improvement of symptoms were substantially greater using the higher dosage of tolterodine.

In a 12-week comparative, randomised, double-blind, placebo-controlled study in patients with OAB, treatment with tolterodine ER capsules (4mg once daily), tolterodine IR tablets (2mg twice daily) and placebo resulted in mean decrease in the number of voluntary micturitions per 24 hours, mean increase in the volume of urine voided per micturition, mean decrease in the number of incontinence episodes per week and decrease in number of pads used per 24 hours, in the drug (both formulations) groups compared with the placebo group.[46]

Three important published trials were the Overactive Bladder: Judging Effective Control and Treatment (OBJECT),[47] Overactive Bladder: Performance of Extended Release Agents (OPERA)[48] and Antimuscarinic Clinical Effectiveness Trial (ACET).[49]

The OBJECT[47] trial compared oxybutynin ER 10mg once daily with tolterodine IR 2mg twice daily, with men and women taking the tablets for 12 weeks. It showed that oxybutynin ER was significantly more effective in reducing the number of weekly urge incontinence episodes, total incontinence episodes and micturition frequency episodes compared with tolterodine IR. Adverse 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. However, a problem with this trial was that it compared two different formulations and there was no data on the effect on quality of life and the patient's perception of their bladder condition.

The OPERA[48] trial compared tolterodine ER 4mg once daily with oxybutynin ER 10mg once daily in women taking the tablets for 12 weeks. It showed that both patient groups had similar improvements in the weekly urge urinary incontinence 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-hour voiding diary. Dry mouth, although mild, was significantly more common with oxybutynin. Other adverse effects, including CNS effects, had similar frequencies with both drugs resulting in comparable tolerability. There were also similar discontinuation rates. Although this trial offers a comparison of the two drugs in a certain group of patients, it is important to realise that it has limitations: it involved only women with severe urge incontinence episodes (21–60 per week) and, thus, cannot be generalised, for example, to include men with only urgency.

In ACET,[49] tolterodine ER 2mg and 4mg once daily was compared with oxybutynin ER 5mg and 10mg once daily. This was an open-label trial for 8 weeks involving men and women with urinary frequency and urgency with or without urge incontinence. It showed that a significantly lower proportion of patients withdrew from the trial when receiving tolterodine ER 4mg compared with the other drugs because of poor tolerability. Also, the patients receiving tolterodine ER 4mg had a significantly better degree of perceived improvement in their bladder symptoms, with less severe dry mouth than the oxybutynin ER 10mg group. The main limitation of this trial was that it was a non-randomised, open-label study, thus subject to bias and confounding.

The decision to choose one drug over the other is very difficult and is probably governed by which drug is licensed and available at the local hospital or in the community. Cost[36] (table II) is another factor in deciding which drug to use. Although both drugs are known to improve quality of life, there are no

Table II. Cost of anticholinergic drugs based on 28-day treatment at standard dosage[36]

Drug (UK trade name)[a]	Cost in £ (2004 value)
Oxybutynin IR (Ditropan®) 2.5mg bid	4.57
Oxybutynin IR (Ditropan®) 5mg bid	8.89
Oxybutynin ER (Lyrinel® XL) 5mg od	8.86
Tolterodine IR (Detrusitol®) 2mg bid	30.56
Tolterodine ER (Detrusitol® XL) 4mg od	29.03
Trospium chloride (Regurin®) 20mg bid	24.27
Propiverine (Detrunorm®) 15mg bid	30.56

a The use of trade names is for product identification purposes only and does not imply endorsement.

bid = twice daily; **ER** = extended release; **IR** = immediate release; **od** = once daily.

'head to head' trials comparing the effects of both drugs on quality of life.

Other trials have looked at combining pharmacotherapy with bladder training or pelvic floor exercises. One study looked at the effects of a combination of bladder training and pharmacotherapy, compared with drug treatment alone, on the symptoms of OAB. It showed that combination therapy seems to be more effective in reducing voiding frequency episodes and increasing volume voided per void; however, there was no statistically significant difference in reduction of urgency and urge incontinence episodes in both groups.[50] Another study compared the effects of pharmacotherapy alone versus drug treatment with a simplified pelvic floor exercise regimen.[51] There was significant reduction in frequency, urgency and urge incontinence episodes in both groups; however, there was no statistically significant difference between the groups suggesting that the addition of a simple written pelvic floor exercise regimen to a drug treatment is not beneficial and that a more intense programme may be required.

Trospium Chloride

Trospium chloride is a quaternary ammonium derivative of nortropan (plant alkaloid). It is a competitive inhibitor of acetylcholine at muscarinic receptors. It is hydrophilic and, in theory, does not cross the blood-brain barrier, as may the tertiary amines discussed earlier (oxybutynin and tolterodine) which are lipophilic. This means that CNS and cognitive performance adverse effects such as dizziness should be minimal with trospium chloride. Trospium chloride reaches peak plasma concentration after 4–6 hours but is poorly absorbed from the gastrointestinal tract: 80% is excreted in the faeces as the active parent compound.[36] It is available as 20mg tablets and the usual recommended dosage is 20mg twice daily.

Trospium chloride has been used in Europe for more than 20 years and has undergone trials in the US recently. It will be launched in 2004 in the US.

The drug seems to be well tolerated by patients, improves symptoms within 1 week of starting treatment, and also causes less dry mouth than oxybutynin IR.[52] Trospium chloride increases maximum cystometric bladder capacity and urinary volume at first involuntary detrusor contraction.[53] There is also improvement in the quality of life of patients and reduction in costs per patient.[54] There are no trials to date comparing trospium chloride with the ER formulations of tolterodine or oxybutynin; however, it appears to be as effective as oxybutynin and tolterodine IR formulations in reducing micturition frequency, but more effective than tolterodine IR at reducing incontinence episodes and better tolerated than oxybutynin IR.[55]

Propiverine

Propiverine is a tertiary amine anticholinergic with calcium channel antagonising action *in vitro*, and with neurotropic and musculotropic effects on the urinary bladder smooth muscle.[56] It undergoes extensive first-pass metabolism, has three active metabolites, reaches peak plasma levels in about 2.5 hours and is eliminated in urine, bile and faeces. It is usually given in a dosage of 15mg twice or three times daily with a maximum of four times daily.[36]

Few randomised controlled studies have been published comparing propiverine with either oxybutynin or tolterodine. A randomised, double-blind, multicentre trial comparing propiverine 15mg twice daily with tolterodine IR 2mg twice daily found that propiverine is comparable with tolterodine in terms of efficacy, tolerability and improvement in quality of life.[57] Compared with oxybutynin, dry mouth is reported as less common and less severe, and propiverine improved urodynamic measurements including cystometric bladder capacity at first desire to void and mean maximal cystometric capacity as effectively as oxybutynin.[58]

Solifenacin Succinate and Darifenacin

Solifenacin succinate is a new, bladder-selective M_3 receptor antagonist, which is primarily cleared by hepatic metabolism, but there is also some urinary excretion. *In vitro*, in monkeys and rats, solifenacin succinate displayed tissue selectivity towards the bladder smooth muscle cells over salivary glands and higher bladder selectivity compared with tolterodine, oxybutynin and darifenacin.[59]

In a phase IIIa study, solifenacin succinate 5mg and 10mg once daily significantly reduced the mean number of urgency and urge incontinence episodes in 24 hours, reduced the mean number of voids per 24 hours and increased the mean volume voided per

void, compared with placebo. It had a favourable therapeutic index and was well tolerated with a low discontinuation rate that was comparable with placebo.[60] It is expected to be available on the market by the end of 2004.

Darifenacin (7.5mg or 15mg orally) is also a selective M_3 receptor antagonist.[61,62] It has very recently completed a multicentre, double-blind, placebo-controlled phase III trial.[63] The study showed that darifenacin had a rapid onset of action with significant reduction in micturition frequency and median number of urgency and urge incontinence episodes, and increase in bladder capacity, at both 7.5mg and 15mg once daily dosages, compared with placebo. With darifenacin 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. Darifencin seems to improve the symptoms of OAB and some data were presented in a satellite symposium at the ICS October 2003 conference in Florence, Italy, showed significant improvement in many aspects of patients' lives. It is also expected to be available on the market by the end of 2004 or early 2005.

Botulinum Toxin A and Resiniferatoxin

Botulinum toxin A, one of the most potent known biological neurotoxins, is produced by the Gram-positive bacterium *Clostridium botulinum*. It has been used by physicians to treat different medical conditions, including strabismus and spasmodic torticollis. It selectively blocks release of acetylcholine from nerve endings and has, therefore, been used by some urologists as second-line treatment of neurogenic detrusor overactivity, with good results in non-randomised trials.[64,65] Botulinum toxin A 300 units in neurogenic detrusor overactivity and 200 units in idiopathic detrusor overactivity are injected at 20–30 different sites into the detrusor muscle, sparing the trigone. This can be done as a day case under local anaesthesia with a flexible cystoscope.[66] Thus, it may prove helpful in the future for treatment of OAB; however, to date there have been no large randomised controlled trials comparing botulinum toxin A to placebo and no large trials on its use in idiopathic detrusor overactivity.

Resiniferatoxin is an ultra-potent analogue of capsaicin, and belongs to a group of substances known as vanilloids. These compounds act selectively on vanilloid receptor subtype-1 to desensitise unmyelinated afferent C-fibres. These fibres are responsible for detecting noxious stimuli and initiating painful sensations in the bladder of normal individuals.[67] In neurogenic patients the C-fibre afferents are activated. Capsaicin has been used previously and shown to be useful in neurogenic detrusor overactivity, although it causes bladder irritation. Resiniferatoxin, in a dose of 30mL at 10 μmol/L administered for 30 minutes intravesically, seems to be as effective as capsaicin, with less irritation to the bladder.[68,69] As with botulinum toxin A, its usefulness still remains to be established in large randomised controlled trials and in idiopathic detrusor overactivity.

Other Pharmacological Treatments

Other drugs that have been used in the treatment of OAB include flavoxate, imipramine and estrogens. All of these may help; however, there are no large randomised, controlled, double-blind studies that show they are more beneficial than placebo in the treatment of OAB.

With long-term use of antimuscarinics, about 80% of patients with OAB usually stop treatment within 6 months.[70] In another study, 78.4% of patients discontinued anticholinergic drug treatment because of lack of efficacy, adverse effects and poor compliance.[71] These reports indicate that there remains a need for the development of new therapeutic treatments for OAB. New oral treatments under research include calcium channel antagonists and potassium-channel openers. Trials on selective serotonin and norepinephrine reuptake inhibitors, such as duloxetine, are being undertaken on patients with mixed urinary incontinence (stress and urge) which may, in future, be beneficial for OAB patients. Gene therapy may also, in the future, prove to be an important treatment for OAB.

4.4.4 Specialist Referral

If first-line treatment in primary care fails, the patient should be referred for a specialist opinion. The specialist may choose to perform urodynamics to confirm detrusor overactivity in patients with the symptomatic diagnosis of OAB.

If the patient's quality of life is sufficiently affected by his/her OAB symptoms then other treatments should be discussed. A new treatment that seems to be effective is sacral nerve neuromodulation.[72] This may now be positioned between drugs and the major surgery options of urinary diversion, enterocystoplasty or auto-augmentation.[73]

5. Conclusion

OAB syndrome is a very common condition that affects people of all ages and may cause a severe impact on quality of life. Overall, OAB leads to a significant economic burden. The management of OAB involves a thorough patient history and physical examination followed by appropriate investigations. There is no cure for OAB at present and treatment is aimed at minimising the effects of symptoms. The first-line treatments are lifestyle interventions, bladder training, pelvic floor muscle exercises and anticholinergic drugs. If these fail then specialist input is required. There is considerable ongoing research into new drugs and methods of treatment and certainly most, if not all, health authorities worldwide are paying more attention to OAB, particularly because of its heavy financial burden on society.

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