BMJ

BMJ 2012;344:e2365 doi: 10.1136/bmj.e2365 (Published 17 April 2012)

CLINICAL REVIEW

The management of overactive bladder syndrome

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In 2010, the International Continence Society restated the definition of overactive bladder syndrome as a condition with characteristic symptoms of "urinary urgency, usually accompanied by frequency and nocturia, with or without urgency incontinence, in the absence of urinary tract infection or other obvious pathology."[1] In 2009, disease specific total expenditures for this syndrome exceeded $24.9bn (£15.76bn; €19.01bn).[2] However, overactive bladder syndrome remains underdiagnosed and undertreated, despite prevalence estimates in men and women of 17% in the United States (National Overactive Bladder Evaluation study) and 12-17% in six European nations.[2 3] One population based prevalence study found that 60% of older or disabled patients seek treatment but only 27% receive it.[4] The study also showed that overactive bladder syndrome is associated with worse quality of life scores than those in hypertension, depression, diabetes, and asthma. In fact, many patients are unaware that useful medical treatment is available.[4] Retrospective observational studies have shown that the medical and surgical consequences of overactive bladder—particularly in older or disabled patients—include depression, falls, fractures, urinary tract infections, and skin infections.[5] The condition is particularly challenging to screen for, diagnose, and treat because the causes are unknown. We review the diagnosis and management of overactive bladder syndrome drawing on examples from US Preventive Services Task Force levels I-III clinical evidence (box 1).

Who gets it?

Although overactive bladder syndrome is most common in patients over 40 years of age,[4] it can also affect children and young adults. It is important to correct the common assumption that the syndrome is an inevitable part of ageing.[4]

What causes it?

Overactive bladder syndrome is sometimes referred to as "detrusor overactivity." The causes are probably multifactorial. There may be injury to a central inhibitory neural pathway, with or without deregulation of an afferent sensory bladder pathway, which suggests a neurogenic component.[6] A myogenic component is also a possibility because there seems to be potential for partial denervation of the bladder muscle with increased excitability and an involuntary rise in pressure within the bladder.[7] Basic science research and expert opinion have prompted the recent hypothesis that detrusor overactivity results from deregulation of detrusor muscle phasic activity.[8 9]

How are patients with overactive bladder syndrome assessed?

There are usually no clinical signs on examination, so a careful history is essential (box 2). Patients may have urgency, frequency (more than eight voids per 24 hours), or nocturia (two or more voids after falling asleep and a return to sleep after voiding), with or without urge incontinence. There must be an absence of obvious urinary tract disease including urinary tract infections, calculi, and bladder tumours.

Clinicians should ask about caffeine intake and foods that can irritate the bladder, including spicy foods and citrus fruits, both

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Extra material supplied by the author (see http://www.bmj.com/content/344/bmj.e2365?tab=related#webextra)

Web fig 1: Example of a voiding diary
Web fig 2: Overactive bladder questionnaire
Web fig 3: Short form version of the overactive bladder questionnaire
Web references

Summary points

- Patients with overactive bladder syndrome have a frequent and strong desire to urinate (with or without incontinence), which adversely affects quality of life
- The causes of overactive bladder syndrome are probably multifactorial
- Verified patient reported outcome questionnaires help assess the severity of symptoms of urgency, frequency, and nocturia and track their improvement with treatment
- Conservative treatments such as reducing fluid intake, avoiding foods and drinks that irritate the bladder, regulating voiding, and performing pelvic floor muscle exercises regularly may be combined with anticholinergic drugs
- Poor adherence to drug treatment is common but may be improved by managing side effects and finding the most suitable drug for individual patients
- Second line treatments include sacral neuromodulation, tibial nerve stimulation, and intermittent botulinum toxin injection into the detrusor muscle

Sources and selection criteria

We discuss the diagnosis and management of overactive bladder syndrome according to current best evidence as assessed through our clinical and research experience. We searched Medline, PubMed, and the Cochrane Library for the years 1995-2012 with the search terms overactive bladder, overactive bladder syndrome, OAB, urgency, urge incontinence, and frequency. The search identified 49 suitable United States Preventive Services Task Force levels I-III evidence based research studies (box 1).

Box 1 United States Preventive Services Task Force levels of evidence

- Level I: Evidence obtained from at least one properly designed randomised controlled trial
- Level II-1: Evidence obtained from well designed controlled trials without randomisation
- Level II-2: Evidence obtained from well designed cohort or case-control analytical studies, preferably from more than one centre or research group
- Level II-3: Evidence obtained from multiple time series, with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence
- Level III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Box 2 Investigating a patient for overactive bladder syndrome

- Note onset of frequency, urgency, nocturia, and urge incontinence. Record the quality and quantity of these symptoms
- Determine what improves or worsens these symptoms, whether the symptoms have led to any injuries through falls, and whether the patient is restricting himself or herself to the home
- Find out what drugs the patient is currently taking. Diuretics can exacerbate symptoms and α agonists (phenylephrine) can close the bladder neck and lead to overflow incontinence; α blockers can lead to stress incontinence by their relaxing and opening effects on the bladder neck area
- Current and past medical or surgical problems, especially those related to fluid management for heart failure, can increase fluid mobilisation and overwhelm the bladder, potentially leading to overactive bladder symptoms or overflow incontinence. Poorly controlled diabetes with blood sugars >1400 mg/L (kidney threshold) leads to severe osmotic diuresis that cannot be controlled with anticholinergic drugs. Drugs for overactive bladder syndrome will have no effect unless diabetes is more tightly controlled. Once this is accomplished the patient's voiding diary entries should show an improvement. Strokes and neurological diseases can lead to overactive bladder and incontinence. Radiotherapy for uterine, colon, rectal, or prostate cancer can also irritate the bladder wall lining and muscle wall, leading to decreased bladder compliance and capacity
- Surgery such as transurethral resection of the prostate, Burch colposuspension, midurethral slings, and laser prostate therapy can lead to overactive bladder symptoms and can also complicate treatment
- Check for previous treatment for overactive bladder syndrome: obtain old records to verify the procedures and results
- Ask the patient to keep a bladder diary by recording for 2-3 days oral consumption of fluids only (in mL), amount voided, and the severity of the symptoms
- Perform urine analysis and culture
- Perform urine cytology if the patient has microscopic haematuria or symptoms of irritative voiding
- Check for glucose using a urine dipstick and, if positive, measure the patient's glycated haemoglobin to determine the average blood sugar level during the preceding three months. If the value is above normal, a glucose tolerance test is recommended
- Measure post-void residual urine (should be less than 50 mL) with ultrasound or straight catheter. The patient should void immediately before this test if the last void was more than half an hour ago
- If available, perform uroflowmetry before and in sequence with the post-void residual urine. Look for a maximum urinary flow greater than 15 mL/s, with at least 150 mL voided. Values of <150 mL may not accurately reflect the patient's true maximum flow
- Urodynamic testing may be performed by a urologist, obstetrician, or gynaecologist after referral

of which acidify the urine. Other bladder irritants include carbonated drinks, tomato based food products, artificial sweeteners, and processed foods (which contain artificial ingredients, preservatives, and flavourings). Caffeinated and alcoholic drinks are diuretics and can greatly increase urine production.

Symptoms should be considered in the context of the patient's 72 hour voiding diary. The range of frequency in normal healthy patients is four to eight voids per 24 hours, so an increase above this may be important. Nocturia is defined by waking to void, voiding, and returning to full sleep. Without a return to full sleep, subsequent voids are not included in the nocturia count and may suggest a sleep disorder instead. Urge

incontinence—involuntary leakage of urine accompanied by or immediately preceded by urgency—is another useful symptom that is easily documented on voiding diaries.

Objective assessment tools are useful to quantify symptom severity and assess the effects of treatment.[10] Voiding diaries provide information about the amount and time of voiding, severity of urgency, episodes of stress or urgency incontinence, pad usage, and oral intake; patients record data for at least 48-72 hours (web fig 1).[10] The international consultation on incontinence, urinary distress inventory, and incontinence impact questionnaire are patient reported quality of life measurements that have been derived and validated for research and for use by clinicians. Pfizer has developed two disease-specific questionnaires that are now commonly used by general practitioners, urologists, and gynaecologists: the overactive bladder questionnaire and its short form version (web figs 2 and 3). The longer questionnaire has 33 items, which assess social interaction, sleep, concern, and coping skills, whereas the short form has 19 items, which assess "bother" and quality of life measures that may be useful in the consultation to screen for the syndrome.[10]

Referral

Clinical guidelines for when GPs should refer to a specialist are available at the National Institute for Health and Clinical Excellence.[11] Criteria for urgent specialist referral include macroscopic haematuria, microscopic haematuria in patients over 50 years of age, recurrent urinary tract infections associated with haematuria in patients over 40 years, and a suspected malignant genitourinary mass. Less urgent referral criteria include consistent urethral or bladder pain, clinically benign pelvic masses, faecal incontinence, potential neurological pathology, persistent symptoms of voiding difficulty, genitourinary fistula, history of continence surgery, and a history of pelvic cancer surgery or pelvic radiotherapy.[12]

Investigations

Over the course of the first few clinic visits, patients should complete a 72 hour voiding diary (one per visit), have a uroflow assessment (the maximum speed of urination with at least 150 mL voided plus residual urine), and undergo multiple ultrasound post-void residual volume determinations. These assessments will help to discern whether the patient has problems with the storage or emptying of the bladder contents and may need referral to a urologist, gynaecologist, or urogynaecologist.

Patients who are resistant to conservative treatment may need more sophisticated assessments of bladder function, including urodynamics, videourodynamics, and neurophysiological outpatient studies.

Urodynamics may help to assess the underlying cause and to determine the appropriate treatment. For example, some patients whose symptoms are complicated by urinary incontinence cannot differentiate between symptoms of stress and urge incontinence; stress incontinence in these patients with mixed symptoms will often hinder improvements in urgency until the stress incontinence component is identified by urodynamics and dealt with, potentially with minimally invasive surgery including a midurethral sling.

How is overactive bladder syndrome treated?

The European Association of Urology and the Japanese Urological Society have suggested a two part approach to management—initial or first line treatment followed by specialised secondary treatment.[13 14] The core treatment incorporates dietary modifications, bladder retraining, pelvic floor retraining with and without biofeedback, and anticholinergic drugs as first line medical treatment.[13 14] It is best practice to discuss behavioural modification therapy with all patients, although not everyone can adhere to the required actions. The goal of treatment is to attain an adequate improvement in symptoms, as shown by a reduction in total score on a verified standardised overactive bladder syndrome questionnaire in any of the symptoms of urgency, frequency, nocturia, and urge incontinence while minimising the potential side effects of drugs.

Lifestyle modification

Potentially useful dietary measures[15] may include a reduction in the intake of fluids,[16] caffeine,[17] acidic foods, and alcohol, in addition to weight reduction and smoking cessation.[16] In a randomised crossover trial, patients were asked to increase or decrease their fluid intake, following a predetermined fluid regimen. People who reduced their daily intake by 25% had a significant improvement in frequency, urgency, and nocturia. Many participants had difficulty in reducing their oral intake by 50%.

The effects of caffeine have been evaluated in observational studies and other randomised double blind placebo controlled prospective trials.[17] An observational study assessed the effects of caffeine at a dose of 4.5 mg/kg on bladder function by performing uroflowmetry and cystometry before and after each participant drank water with and without caffeine on two separate occasions. Caffeine caused diuresis and a quicker urge to void while increasing the speed of urination and the amount voided. The study concluded that caffeine can promote urgency and frequency, and it is recommended that patients with overactive bladder symptoms carefully manage their caffeine consumption.[17] One prospective cohort study included 123 morbidly obese women who had bariatric surgery.[18] The study monitored improvement in overactive bladder symptoms after surgery and weight loss (patients had a mean body mass index of 47.5 before surgery and 31.0 after surgery) over a mean follow-up of 1.7 years. Patients had a significant reduction in frequency and stress incontinence, and improvement on the urinary distress inventory and incontinence impact questionnaire score.[18] A questionnaire study assessed the effect of smoking status and intensity on overactive bladder symptoms; 3000 questionnaires were mailed to randomly identified patients from the Finnish population register.[19] Smoking was significantly associated with urinary urgency (odds ratio 2.7, 95% confidence interval 1.7 to 4.2 for current smokers and 1.8, 1.2 to 2.9 for former smokers compared with non-smokers) and frequency (3.0, 1.8 to 5.0 and 1.7, 1.0 to 3.1). Smoking was not associated with nocturia or stress incontinence. Compared with light smoking, heavy smoking was associated with a risk of urgency (2.1, 1.1 to 3.9) and frequency (2.2, 1.2 to 4.3).[19] Several single arm prospective studies have shown that reducing night-time fluid intake reduces nocturia and improves quality of life symptom scores.[20 21] However, the resultant concentrated urine can also act as a bladder irritant because of its increased acidity.[22]

Behavioural bladder retraining

A 2000 modified crossover study found that bladder retraining is most effective when combined with oral drugs.[23] Behavioural therapy can be both labour intensive and time intensive because it has multiple components and patients need to be educated as to how to use them all. It is important to communicate to the

patient that treatment requires motivation and patience, without which long term improvements will not be achieved. The main components of bladder retraining are timed and delayed voiding, as well as dietary modifications and pelvic floor muscle rehabilitation, with or without biofeedback. Timed voiding involves urinating at regular set intervals that disregard the normal urge to void.[23] Initially, voiding intervals may be as short as every 30 minutes, with the time between voids being slowly increased over several weeks until the patient can maintain control for periods of three to four hours.[23] This regimen slowly increases the bladder capacity and may reduce the number of episodes of urgency and urgency incontinence. Patients need to keep a written urination log so that they can verify improvement or worsening of symptoms. Expert opinion suggests that this approach is less successful in non-ambulatory patients (who often have comorbidities such as pelvic or leg fractures, obesity, or heart failure) because it is labour intensive for patients, care givers, and other medical staff.[24] The addition of pelvic floor muscle rehabilitation, with or without biofeedback, may improve symptom control for ambulatory patients through improving isolation of the levator ani muscles. However, to gain appropriate muscle control and strength, as well as prolonged symptom improvement, exercises must be completed regularly, preferably daily, but weekly at least.[25]

A bladder diary that records daily frequency, urgency, nocturia, and urge incontinence episodes and their severity will help the patient and doctor to evaluate conservative treatment and to isolate exacerbating factors, such as foods eaten, activities performed, timing of diuretic drugs, and worsening comorbidities.

Drug treatments

Drugs—usually anticholinergics—that suppress symptoms of overactive bladder are the mainstay of current medical management. Anticholinergics (also known as antimuscarinics) improve symptoms via two mechanisms: by competitively inhibiting the binding of acetylcholine to the bladder muscle wall (detrusor muscle) and by potentially inhibiting urothelial sensory receptors and directly decreasing afferent nerve activity. A 2008 meta-analysis of anticholinergic drugs in the treatment of overactive bladder syndrome concluded that these drugs are well studied, safe, tolerable, efficacious, significantly improve certain measures of quality of life, and should remain as first line treatment.[26] A 2006 Cochrane review assessed 61 trials that compared anticholinergic drugs with placebo (42 with parallel group design and 19 crossover trials), with a total of 11 956 patients.[27] At the end of treatment, there was a significantly greater chance of cure or improvement (relative risk 1.39, 1.28 to 1.51; leakage episodes per 24 hours: weighted mean difference −0.54, −0.67 to −0.41; number of voids per 24 hours: −0.69, −0.84 to −0.54). The placebo effect is also important in the treatment of overactive bladder syndrome. A 2009 meta-analysis of randomised placebo controlled studies of antimuscarinic drugs concluded that placebo response is both substantial and heterogeneous with commonly used clinical endpoints, including a reduction in episodes of frequency, urgency, and urge incontinence.[28] At the end of 2011, at least 11 commonly prescribed anticholinergic drugs were commercially available in the US and Europe, many of which have less expensive generic equivalents as well as time release formulations (table⇓).

Many patients fail to adhere to their oral drugs in the first three months of treatment, perhaps because improvement may come slowly and by small degrees or because of side effects. A retrospective cohort study in 2008 showed that patient adherence to anticholinergic drugs is still suboptimal.[w1]

Dry mouth and constipation are the two most common adverse effects of anticholinergic drugs. A prospective observational study found that this may lead to the discontinuation of treatment in 50% of patients.[w2] Constipation may potentiate symptoms, because excessive stool in the rectal ampulla decreases bladder capacity, so recommend fibre and stool softeners early on during treatment if constipation is a problem.[w2]

Antimuscarinics can have serious side effects, such as confusion and cognitive deficits, particularly in older people.[w3] Older patients may experience greater central nervous system toxicity secondary to cerebrovascular disease and other conditions that can affect the permeability of the blood-brain barrier.[w3] The use of agents with reduced blood-brain barrier penetrance (such as trospium and darifenacin) may prevent cognitive side effects in these patients.[w4] Other central nervous system effects include dizziness, somnolence, insomnia, and sedation.[w4] Factors that may increase the adverse events of antimuscarinics in older people include reduced rate of drug metabolism in the liver and kidneys, changes in the numbers of muscarinic receptors in the brain, and the likelihood of polypharmacy.[w4 w5]

Vagolytic action in the cardiovascular system may lead to alternations in heart rate and blood pressure.[w6] An M_3 muscarinic acetylcholine receptor selective agent may be preferable in patients with pre-existing heart disease. Several antimuscarinic drugs are relatively M_3 receptor specific, but it is unclear whether they are better than non-selective ones. Alternative routes of delivery are available for people who have difficulty swallowing or experience side effects from oral drugs. For example, oxybutynin chloride may be used as a patch or gel—a 1 mL/100 mg dose of a 10% gel applied to the upper arm, abdomen, thigh, or shoulder delivers a constant dose of oxybutynin over 24 hours, and this method of delivery may be associated with reduced adverse effects.

Antimuscarinic agents are variably excreted unchanged in the urine. Their therapeutic effect may be partly mediated by direct interaction with the urothelium,[w7] so drugs that are excreted largely unchanged in the urine, such as trospium, might have some advantages over other agents, although this has not been seen in clinical studies.[w5] However, this potential mechanism of action means that these drugs might be able to be directly instilled into the bladder as intravesical therapy.

Because successful treatment of symptoms is related to adherence to drugs, encourage patients to persevere (within reason) and take their drugs as prescribed.[w8] Regular follow-ups are important to monitor treatment effects and adherence. We have found that adherence can be improved by educational initiatives such as recommending reasonable, achievable treatment goals of up to a 50% reduction in urgency, frequency, nocturia, and urge incontinence (as documented by voiding diaries or quality of life measurements); encouraging a bowel regimen to combat constipation; and incorporating the use of reduced glucose or no glucose sweets (for patients with diabetes) or other sialogogues to alleviate dry mouth.

It is also important to discuss contraindications to the use of anticholinergic drugs with patients because they often do not mention all of their medical problems to the specialist. Contraindications include hypersensitivity to these drugs, untreated angle closure glaucoma, partial or complete gastrointestinal obstruction, hiatal hernia, gastro-oesophageal reflux, intestinal atony, paralytic ileus, toxic megacolon, severe colitis, myasthenia gravis, and urinary obstruction. Patients with these conditions may be best managed with other conservative

measures such as timed voiding or pelvic floor retraining; alternatively, they will need clearance for the use of these drugs from the clinician caring for the disorder.

Assessing the success of first line treatment

Complete cures are rare, and—given the variability in lifestyle and fluid intake on a day to day basis—may be short lived. Improvement is measured by a reduction in the number of 24 hour voids and in the number of episodes of frequency, urgency, and urge incontinence. Measurable improvement may take as long as 12 weeks, although it is sometimes seen as early as a week after starting treatment. It is reasonable to allow a four week window for assessing treatment response. After this time, if symptoms have not improved adequately and side effects have not been problematic, the drug can be titrated to a higher dose. We find that patients can see little improvement with one drug but a clinically relevant improvement when switched to a new drug within the same class. Treatment failure with one or even several drugs in the same class does not imply that the entire class will be ineffective for a particular patient, and persistence is needed.[w9]

Treatment of recalcitrant overactive bladder syndrome

A few minimally invasive second line treatments can be tried if anticholinergic drugs are unsuccessful.

Direct multiple injection of the detrusor muscle with botulinum toxin via cystoscopy is one such treatment. It is thought that botulinum toxin A selectively blocks the presynaptic release of acetylcholine from nerve endings to result in postsynaptic flaccid paralysis of muscle.[w10-w12] Other afferent effects via sensory and pain fibres have also been proposed. This treatment can be administered in the clinic with local intravesical anaesthesia with viscous lidocaine or similar. A recent randomised placebo controlled trial found that, compared with placebo, botulinum toxin A reduced urgency, frequency, and urge incontinence by 35-50% and significantly improved urodynamic parameters, including increased maximum cystometric capacity (ability to hold urine) and increased volume before first involuntary detrusor contraction.[w12] However, the effects of this treatment begin to diminish at six to nine months and repeat treatments are necessary.[w10-w12] A prospective cohort study reported that the improvement after multiple injections was maintained, although the dropout rate after two injections was 37%.[w13] The most common reasons for discontinuation were insufficient efficacy (13%) and temporary urinary retention (11%).[w13]

Sacral neuromodulation and percutaneous tibial nerve stimulation are the only two second line treatments currently approved by the Food and Drug Administration in the US for the management of recalcitrant overactive bladder syndrome. Sacral neuromodulation was approved in 1997 for the treatment of this syndrome; a mild electrical current is sent unilaterally from a pulse generator (about the size of a cardiac pacemaker) implanted in the buttock to the sacral nerve (S_3) via an implanted neurostimulator electrode lead placed through the S_3 foramen adjacent to the S_3 nerve root. Patients feel the stimulation in the bladder, rectum, perineum, or vagina (or a combination thereof). The exact mechanism by which this treatment works is still being investigated, but one theory is that it restores an equal balance between the inhibitory and excitatory neural voiding control systems. A single centre retrospective cohort study that analysed data on patients with follow-up of one, three, five, and 10 years reported an overall 80% reduction in symptoms.[w14] Potential side effects include late failure (return of symptoms after one year), lead migration, and infection of the implanted pulse generator. The cost of sacral neuromodulation surgery in the United States approaches $90 000 for stage one and two procedures combined.

Posterior tibial nerve neuromodulation was first described in 1983, and a recent review of a retrospective observational study has confirmed a 60-80% success rate for patients with recalcitrant disease.[w15] A small needle is inserted into the lower leg near the ankle, and an external stimulator sends a constant electrical signal through the tibial nerve retrograde to the sacral plexus, which regulates bladder and pelvic floor function. Treatment comprises a 30 minute session once a week for 12 weeks. Although the treatment is low risk and not associated with any serious adverse effects, ongoing maintenance treatment may be needed.[w15] Posterior tibial neuromodulation is approved by the FDA for use in overactive bladder syndrome and in Europe is used extensively to treat faecal incontinence.

Level III clinical evidence shows that surgery to augment the size of the bladder by adding to its intraluminal surface area with the interposition of a 10-15 cm loop of small bowel or stomach—referred to as an augmentation enterocystoplasty—is also of benefit to patients with recalcitrant disease. These large scale operations require many hours of surgery, days of hospital stay, and weeks of convalescence. A few retrospective cohort studies have shown that these operations reduce urgency, but at the potential cost of incomplete emptying of the new bladder, which may necessitate clean intermittent catheterisation on a temporary to permanent basis. It cannot be predicted preoperatively which patients will succumb to this potential complication. An observational retrospective study assessed 10 augmentation enterocystoplasties in women with recalcitrant urgency symptoms with a mean follow-up of 29 months. Eight of 10 patients were cured of urgency symptoms and eight of 10 were also able to void spontaneously, while one used self catheterisation once daily and the other an indwelling Foley catheter.[w16] Expert opinion suggests that several options exist for patients with recalcitrant urgency, so the use of augmentation has probably decreased, although it can still be used as a successful third line intervention.[w17] An eight year prospective cohort study assessed bowel problems after augmentation cystoplasty in 116 patients, 30 of whom had recalcitrant overactive bladder symptoms.[w18] It found that 59% of patients had troublesome diarrhoea, 50% of whom were managed with daily antidiarrhoeal drugs; 47% had faecal incontinence, 41% with faecal urgency and nocturnal bowel movements (18%). These complications affected work (36%), social function (50%), and sexual activity (43%).

Might new oral drugs be available in the future?

Drugs under study target specific receptors or other bladder muscle or nerve physiological processes at the Rho-kinase pathway, in addition to neurokinin 1 antagonists and calcitonin gene related protein receptor antagonists, which act at the level of the spine. Two new anticholinergic drugs studied in phase II trials include PSD-506, an M_2 and M_3 selective agent, and SMP-986, a β_3 adrenoceptor agonist that reduces bladder muscle contraction.[w19] Other β_3 adrenoceptor agonists in trial include KUC-7483, YM-178, and GW-427353. Cizolirtine citrate, a calcitonin gene related product,[w19] and substance P, which together antagonise the neurokinin 1 and calcitonin gene related protein spinal receptors, is also in phase II clinical trials. Similar drugs in phase II trials include TA-5538 and SSR-240600. Rho A pathway inhibitors currently under investigation in phase III trials include a vitamin D_3 analogue, Elocalcitol.[w20] This may

reduce bladder muscle wall stiffness commonly seen in overactive bladder and pelvic organ prolapse, theoretically increasing bladder capacity and potentially reducing frequency and urgency.

Conclusion

Anticholinergics remain the most effective drugs to treat the complex symptoms of overactive bladder. Their efficacy, potency, and side effects have been well studied and recently confirmed by a large scale meta-analysis. Surgery is the second line approach for medically recalcitrant patients. Well researched minimally invasive approaches including botulinum A toxin have proved to be effective, with a low complication rate, although they are more costly than conservative drug treatments. Newer drugs that target different physiological pathways may soon replace these treatments, but it is too early to comment on their future usefulness.

Contributors: SPM helped with the writing, research, editing, and illustrations; RMM and SLS helped with the writing and editing; ESR helped with the writing, editing, organisation, and content; CMM and LMG helped with the writing, editing, and illustrations; SPM and ESR are guarantors.

Funding: None received.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Accepted: 20 February 2012

Cite this as: *BMJ* 2012;344:e2365

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Additional educational resources for patients

Pfizer sponsored link (www.overactivebladder.com/)—Excellent presentation on overactive bladder syndrome, including definition, treatment, and patient profile

WebMD (www.webmd.com/urinary-incontinence-oab.com)—Website that keeps its content up to date with slide presentations, videos, and discussions; easy to read and understand

National Association for Continence (www.nafc.org/bladder-bowel-health/types-of-incontinence/urge-incontinence/)—Useful pdfs that are easy to read and store

eMedicine (www.emedicinehealth.com/overactive_bladder/article_em.htm)—Another well organised website with good quality material

Tips for the general practitioner

Useful information

Ask the patient about urgency and frequency and whether the problem needs treatment

If treatment is requested start with a two to three day voiding diary

Normal voiding is five to eight times in 24 hours

Nocturia with one nightly episode is normal from age 40-80 and twice thereafter

Consider fluid reduction or pelvic floor exercises (or both) for three months in patients with two or more urgency episodes during the voiding diary (as long as they are not taking diuretics and they do not have poorly controlled diabetes with glycosuria)

If these two treatment options do not work start treatment with the lowest dose of any of the anticholinergic drugs listed in the table

Remember to increase the dose as necessary

When to refer to a urologist, gynaecologist, or urogynaecologist

When conservative measures, including reduced fluid consumption and pelvic floor exercises, have not been successful

Patients who have tried the full dose of two or more drugs without clinically significant improvement or those in whom treatment has been discontinued because of side effects

Table

Table 1| Useful information for the most commonly prescribed overactive bladder drugs (worldwide)

Drug; annual cost*	Date of FDA approval	Dose	Frequency	Half life (hours)	Time to peak (days)	Side effects
Oxybutynin chloride gel 10% (M_3 and M_1 selective); £244	January 2009	1 g of 100 mg/g or 1.14 mL	Once daily	64 at steady state	Steady state by 7 days	Dry mouth 7.5%, constipation 1.3%, application site reaction 5.4%
Fesoterodine (non-selective); £336 (4 mg), £418 (8 mg)	October 2008	4 mg or 8 mg	Once daily	7-8	5	Dry mouth 18.8% and 34.6%, constipation 4.2% and 6.0%, insomnia 1.3% and 0.4%
Trospium chloride XR (non-selective); £302	August 2007	60 mg	Once daily, 1 hour before breakfast	36	5	Dry mouth 10.7%, constipation 8.5%, dry eyes 1.6%
Darifenacin (M_3 selective); £366 (7.5 mg), £451 (15 mg)	December 2004	7.5 or 15 mg	Once daily	7-20	5-8	Dry mouth 20.2% and 35.3%, constipation 14.8% and 21.3% dizziness 0.9% and 2.1%
Solifenacin (M_3 and M_1 selective); £357 (5 mg), £458 (10 mg)	November 2004	5 mg or 10 mg	Once daily	45-68	3-8	Dry mouth 10.9% and 27.6%, constipation 5.4% and 13.4%, blurred vision 3.8% and 4.8%, dizziness 1.9% and 1.8%
Trospium chloride immediate release (non-selective); £337	May 2004	20 mg	Twice daily, 1 hour before meals	18	5-6	Dry mouth 10.7%, constipation 9.6%, headache 4.2%
Transdermal oxybutynin (M_3 and M_1 selective); £376	March 2004	36 mg patch delivers 3.9 mg/day	Change patch twice weekly	7-8	10-48	Dry mouth 9.6%, constipation 3.3%, pruritis 16.8%, erythema 5.6%
Tolterodine tartrate long acting (non-selective); £399	December 2000	4 mg	Once daily	7-18	2-6	Dry mouth 23%, constipation 6%, headache 6%, dizziness 2%, blurred vision 1%
Oxybutynin extended release (M_3 and M_1 selective); £321 (10 mg)	June 1999	5-30 mg	Once daily	12-13	3-6	Dry mouth 34%, constipation 16.8%

*Costs of one year's supply and review by the general practitioner (£1=€1.2=$1.6).

FDA=Food and Drug Administration.

Voiding Diary

Name: _____

Date and Time	Liquid Intake Type and Amount	Voluntary Void Y/N	Urgency-related Void (void secondary to compelling need to void for fear of leakage) Y/N	Leakage Associated With Need to Void Y/N	Volume of Urine Leakage Small, Moderate, Large
4/16, 6 am	Coffee, 2 cups	Y	N	N	Large

OAB-q

This questionnaire asks about how much you have been bothered by selected bladder symptoms during the past 4 weeks. Please place a ✓ or ✗ in the box that best describes the extent to which you were bothered by each symptom during the past 4 weeks. There are no right or wrong answers. Please be sure to answer every question.

During the past 4 weeks, how bothered were you by. . .	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**A great deal**	**A very great deal**
1. Frequent urination during the daytime hours?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
2. An uncomfortable urge to urinate?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
3. A sudden urge to urinate with little or no warning?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
4. Accidental loss of small amounts of urine?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
5. Nighttime urination?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
6. Waking up at night because you had to urinate?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
7. An uncontrollable urge to urinate?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
8. Urine loss associated with a strong desire to urinate?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

The above questions asked about your feelings about individual bladder symptoms. For the following questions, please think about your overall bladder symptoms in the past 4 weeks and how these symptoms have affected your life. Please answer each question about how often you have felt this way to the best of your ability. Please place a ✓ or ✗ in the box that best answers each question.

During the past 4 weeks, how often have your bladder symptoms . . .	None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
9. Made you carefully plan your commute?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
10. Caused you to feel drowsy or sleepy during the day?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
11. Caused you to plan “escape routes” to restrooms in public places?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
12. Caused you distress?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
13. Frustrated you?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
14. Made you feel like there is something wrong with you?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
15. Interfered with your ability to get a good night’s rest?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
16. Caused you to decrease your physical activities (exercising, sports, etc.)?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
17. Prevented you from feeling rested upon waking in the morning?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
18. Frustrated your family and friends?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
19. Caused you anxiety or worry?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
20. Caused you to stay home more often than you would prefer?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
21. Caused you to adjust your travel plans so that you are always near a restroom?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
22. Made you avoid activities away from restrooms (i.e., walks, running, hiking)?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
23. Made you frustrated or annoyed about the amount of time you spend in the restroom?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
24. Awakened you during sleep?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

During the past 4 weeks, how often have your bladder symptoms . . .	None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
25. Made you worry about odor or hygiene?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
26. Made you uncomfortable while traveling with others because of needing to stop for a restroom?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
27. Affected your relationships with family and friends?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
28. Caused you to decrease participating in social gatherings, such as parties or visits with family or friends?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
29. Caused you embarrassment?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
30. Interfered with getting the amount of sleep you needed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
31. Caused you to have problems with your partner or spouse?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
32. Caused you to plan activities more carefully?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
33. Caused you to locate the closest restroom as soon as you arrive at a place you have never been?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

OAB-q short form symptom bother

This questionnaire asks about how much you have been bothered by selected bladder symptoms during the past 4 weeks. Please place a ✓ or ✗ in the box that best describes the extent to which you were bothered by each symptom during the past 4 weeks. There are no right or wrong answers. Please be sure to answer every question.

During the past 4 weeks, how bothered were you by. . .	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**A great deal**	**A very great deal**
1. An uncomfortable urge to urinate?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
2. A sudden urge to urinate with little or no warning?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
3. Accidental loss of small amounts of urine?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
4. Nighttime urination?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
5. Waking up at night because you had to urinate?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
6. Urine loss associated with a strong desire to urinate?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

For the following questions, please think about your overall bladder symptoms in the past 4 weeks and how these symptoms have affected your life. Please answer each question about how often you have felt this way to the best of your ability. Please place a ✓ or ✗ in the box that best answers each question.

During the past 4 weeks, how often have your bladder symptoms . . .	**None of the time**	**A little of the time**	**Some of the time**	**A good bit of the time**	**Most of the time**	**All of the time**
1. Caused you to plan "escape routes" to restrooms in public places?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
2. Made you feel like there is something wrong with you?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
3. Interfered with your ability to get a good night's rest?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
4. Made you frustrated or annoyed about the amount of time you spend in the restroom?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
5. Made you avoid activities away from restrooms (i.e., walks, running, hiking)?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
6. Awakened you during sleep?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
7. Caused you to decrease your physical activities (exercising, sports, etc.)?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
8. Caused you to have problems with your partner or spouse?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
9. Made you uncomfortable while traveling with others because of needing to stop for a restroom?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
10. Affected your relationships with family and friends?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
11. Interfered with getting the amount of sleep you needed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
12. Caused you embarrassment?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
13. Caused you to locate the closest restroom as soon as you arrive at a place you have never been?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6