Management of the overactive bladder: a review of pharmacological therapies and methods used by the urological specialist

Elizabeth Waine, MD, Hashim Hashim, MD, Paul Abrams, MD

Bristol Urological Institute, Southmead Hospital, Westbury on Trym, Bristol, United Kingdom

WAINE E, HASHIM H, ABRAMS P. Management of the overactive bladder: a review of pharmacological therapies and methods used by the urological specialist. The Canadian Journal of Urology. 2007;14(2):3478-3488.

Overactive bladder is a common urological diagnosis, which is often untreated as patients fail to seek help for this embarrassing problem. This disorder causes significant lifestyle limitations for the patient and is also expensive as it reduces national productivity and therefore affected patients should be treated. It is simple for primary care providers to make a working diagnosis in this disorder and they should be carrying out simple investigations in order to make the diagnosis. Commencement of therapy should start with conservative measures such as lifestyle modifications including pelvic floor exercises and bladder drill followed by the introduction of pharmacological treatments if necessary. The patient should be fully educated about their disorder and about the potential side effects of the medication they are given in order to improve compliance. There are a number of antimuscarinics available on the market for the treatment of overactive bladder but it is often difficult to decide which is the best form of management for these patients. In this review we address the necessary investigations that need to be carried out as well as providing an overview of the different non-surgical and medical treatments for this common problem. Should these therapies fail, then the referral to a urological specialist should be made prior to invasive therapy.

Key Words: overactive bladder, antimuscarinics, detrusor overactivity neuromodulation, detrusor myectomy, augmentation cystoplasty

Introduction

Overactive bladder (OAB) was defined in 2002 by the Standardization Subcommittee of the International Continence Society (ICS) as the presence of urgency with or without urge incontinence, accompanied by urinary frequency, and nocturia, but in the absence of urinary tract infection or other pathology.[1] Overactive bladder is a symptomatic diagnosis and in order to make a diagnosis of detrusor overactivity, which is the usual pathophysiological cause of OAB, urodynamics is essential.

Accepted for publication January 2007

Address correspondence to Dr. Paul Abrams, Bristol Urological Institute, Southmead Hospital, Westbury on Trym, Bristol, BS10 5NB, United Kingdom

Since the definition of overactive bladder has changed it is difficult to find the true prevalence of the disorder worldwide. Prior to the change in definition of OAB a study carried out in six European countries estimated that 16.6% of the population aged 40 or above had symptoms of OAB, frequency being most commonly reported (85%), whilst urgency (54%), and urge incontinence (36%)were the next most commonly reported symptoms.[2] Of these populations in Europe 60% had sought medical consultation and 27% were receiving treatment. A recent study in Japan by way of a questionnaire has showed an estimated prevalence of OAB of 12.4% in a population over the age of 40 years and prevalence rates of 6.4% having urgency incontinence and 6.0% without incontinence.[3] The questionnaire also assessed health-related quality of life (HRQol) and found that 53% of the respondents had some change in the HRQoL and of these 23% had

had medical input for their symptoms (23% men, 8% women). Following the introduction of the new definition of OAB, the National Overactive Bladder Evaluation (NOBLE) programme estimated that 16.5% of the US population (16% of men and 16.9% of women) over the age of 18 had the symptoms of OAB.[4]

The economic costs are also important when considering OAB. Not only do we need to think about the medical costs but because OAB can be so debilitating, we must also include lost productivity. A study carried out by the University of Michigan reported that OAB, and more notably urinary urgency incontinence occurred in 37% of the responders, when questionnaires were sent to women between 18 and 60 years of age. Of those with severe symptoms 88% reported a reduction in concentration, performance of physical activities, self-confidence or the ability to complete tasks without interruption.[5] The overall cost of OAB in the United States in 2000 was estimated at between US $9.1 billion[6] and US $12.6 billion[7] although this is still less than the financial burden of all urinary incontinence which costs US $19.5 billion.[7]

The precise cause of OAB is unknown although the main mode of action of pharmacological therapy for OAB is at the synaptic junctions. It is therefore important to understand the basic neurophysiology of bladder function, Figure 1. Afferent innervation within the urothelium of the bladder responds to pressure rather than bladder volume once the bladder has undergone its initial stage of filling.[8] This sensory information is carried by pressure-volume fibers within the pelvic nerves to the spinal cord segments S2-4, where a small number synapse with preganglionic parasympathetic cell bodies, whilst the majority cross the midline and ascend in the lateral funiculus to the pontine micturition centre.

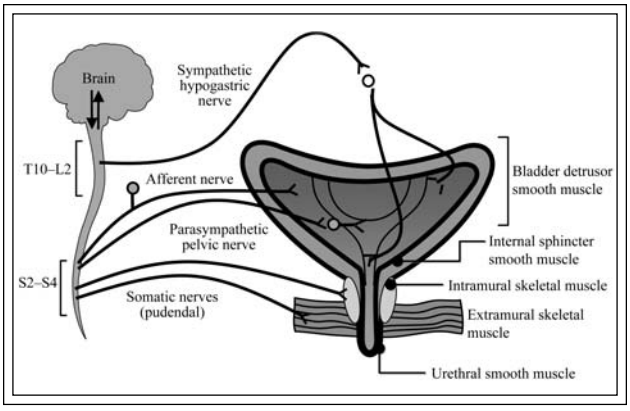

Figure 1. Sensory and motor control of micturition. Adapted from Wein AJ.[13]

A few fibers allow conscious awareness of bladder filling by continuing to the cerebral cortex. There are a small number of nociceptors found in the trigonal area which are stimulated by the over distension of the bladder.[9] These impulses are projected in the hypogastric nerve to T10-L2 from where they ascend to the pons via the contralateral lateral column. The pontine micturition centre is the point of control of the bladder's storage and voiding capabilities. The afferent impulses synapse at nuclei within the dorsolateral region of the pons. There are also synapses with the higher centres such as the cerebellum, extrapyramidal system and the brainstem, which partly explain the conscious, emotional and psychological influences upon micturition, although the exact mechanism of their function is still poorly understood.[10] Efferent signals descend from the pons within the lateral columns and synapse with the preganglionic bodies of the parasympathetic nerves within the intermediolateral column of S2-S4. The nerves then run as the nervi erigentes and synapse with postganglionic parasympathetic nerves, which have their nerve endings within the detrusor muscle and urethra. There are impulses that pass from the pons to Onuf's nucleus that controls the striated muscle of the sphincter and via the pudendal nerve from S2-4 to the levator ani. De Groat has worked upon the theory of inhibitory interneurones that prevent the onward transmission of impulses from afferent nerves to postganglionic parasympathetic nerves until a frequency threshold is reached.[11] As the frequency of afferent signals reaches this threshold it leads to postganglionic parasympathetic outflow that results in coordinated contraction and relaxation of the smooth and striated muscle elements of the lower urinary tract.[12]

There are three theories as to why the condition of overactive bladder occurs. During filling the bladder should be in a relaxed state however in OAB the detrusor muscle contracts involuntarily (detrusor overactivity). The first hypothesis for this phenomenon is the myogenic theory, which suggests that partial denervation of the detrusor muscle results in an alteration in the excitatory function of the detrusor muscle cells. This then leads to involuntary detrusor contractions, and thus a rise in intravesical pressures.[14] There is also a suggestion that there is a neurological basis to the overactive bladder where there has been an insult to the central inhibitory pathways or sensitization of the peripheral afferent terminals in the bladder, thus leading to the stimulation of the detrusor muscle.[15] The final theory behind detrusor overactivity is that there is inappropriate activation of the phasic activity of the detrusor.[16]

Assessment of the patient with OAB symptoms

Patients often seek the advice of their primary care physician and in order to correctly diagnose and manage a patient with OAB the physician must first take a careful and detailed history as well as a thorough physical examination. Figure 2. If the general practitioner is at all worried they should refer to the urological outpatients for further assessment. Once in the outpatient department the urologist should repeat the history and examination. The history should include a thorough examination of the patients symptoms, for example if a patient has urgency are there triggers, for example caffeine.[17] If they are experiencing incontinence how severe is that incontinence? How many pads are they using per day and is the patient having to change outer clothing because of the incontinence? It is of great importance to assess the patient's symptoms when they are in different environments, for example at night, at work or on holiday. Questioning should also include whether there is any presence of hematuria or infection. There must also be a detailed past medical history, which includes previous surgical interventions and also a comprehensive drug history including non-proprietary drugs, and if the patient is female, a full obstetric and gynecological history should be taken. Quite often a review of systems may elucidate the presence of co-morbidities such as untreated congestive cardiac failure, which may aggravate, or irritable bowel syndrome which is associated with the symptoms of OAB.[18] Other avenues that should be explored during questioning are smoking and occupational history as well as daily fluid management, as there may be identifiable lifestyle changes that can be made to alleviate symptoms.

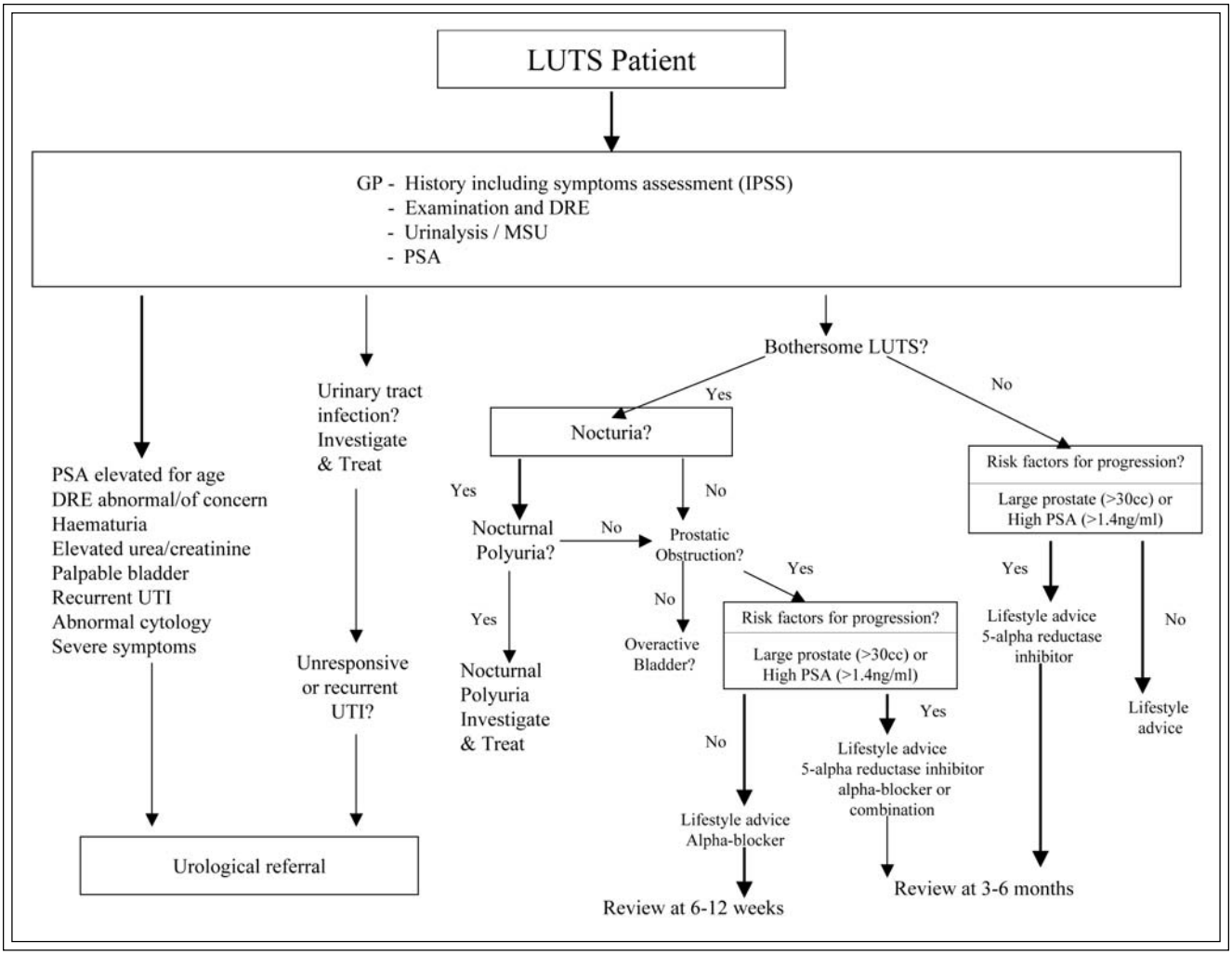

Figure 2. Algorithm for the evaluation of a patient in the primary care setting. After thorough assessment following the algorithm allows patients to receive the appropriate treatment for their symptom profile.

Physical examination commences with a full abdominal examination to assess for the presence of a palpable bladder, and careful note made of surgical scars. There should always be a full neurological examination and a record made of lower limb tone, power, reflexes and sensation. A digital rectal examination should also include assessment of neurological deficits as well as the presence of fecal loading or of an enlarged and/or abnormal prostate. In a female patient, a pelvic examination using a Simms speculum is included in the consultation, and observation of simple disorders such as atrophic vaginitis, anterior or posterior vaginal or uterine prolapse should also be made.

In addition to the history and examination a number of simple outpatient and laboratory tests can be carried out to distinguish between the differential diagnoses. A mid stream urine specimen should be tested and if necessary sent for microscopy, and culture. As well as ruling out infection, urine testing will assess for the presence of hematuria, alerting the health care professional to the possibility of intravesical lesions such as stones or tumors. If PSA is performed, after appropriate counseling, an elevated level may suggest the presence of benign prostatic obstruction or even prostate cancer, which may account for symptoms. Those with a palpable bladder should have urea and electrolytes checked in order to treat any resultant renal failure. Patients with severe symptoms, which are having significant impact on their daily lives, should have further investigation. Assessment tools such as a frequency volume chart, or modules from the International Consultation Incontinence Questionnaires[19] can also assist the physician in the assessment of a patient's symptoms and also the severity with which they interrupt activities of daily living. In addition to these questionnaires, OAB specific questionnaires have been developed and are reliable tools in assessing the impact that a patient's symptoms are having on their quality of life.[20] Bladder diaries can be used to document the time of micturition, voided volumes, episodes of urgency and incontinence, the number of incontinence pads used and how wet they are, as well as documentation of fluid intake. Recent studies have shown that a 3-day diary is as effective as a 7-day diary in assessing patients' symptoms. Also it improves accuracy, as it reduces the use of memory in filling in gaps in a 7-day diary.[21]

Management of the overactive bladder

Conservative measures

Management of the overactive bladder can be divided into four main areas and the primary care physician can initiate most of these therapies. Initially conservative measures should be tried. Educating the patient about lifestyle changes and diet as well as the effects of drug therapy and the impact they have upon symptoms is important to gain compliance.[22] Fluid management is extremely important and many patients will be able to control their symptoms by simple measures such as eliminating caffeine from their fluid intake. A simple explanation of the effect of caffeine has by acting as a diuretic and stimulant of the detrusor[17] will have a reinforcing effect on the patient. Other areas of fluid management are the educating the patient in the understanding the fluid component of their daily food intake, cessation of any fluid intake after 6.00 pm and ensuring that they void before bed may reduce or eradicate nocturia.

Bladder training and pelvic floor exercises are useful non-pharmacological measures to enable the patient to gain control of their symptoms. Educating the patient about their symptoms and active bladder management therapies such as pelvic floor exercises, bladder drill and biofeedback mechanisms have been shown to be as effective as pharmacological therapy.[23] Bladder training leads to a reduction in voiding frequency as well as increasing voided volumes. The patient is taught to void each hour on the hour, and then asked to increase the interval by 15 minutes each week until they are satisfied with their voiding frequency. In addition to this the patient is also taught pelvic floor exercises to be carried out when they experience a bladder contraction, or when they rise from lying or sitting as these situations have been identified as triggers for involuntary detrusor contractions.[24] The community continence advisors can improve compliance by reinforcing the importance of these self-help therapies.

Drug therapy

Pharmacological treatments for over active bladder are numerous, each having its own profile of bioavailability, side effects and dose regimen. First line pharmacological treatment should be using of one of the many antimuscarinic preparations.[25] These drugs aim to reduce the frequency of voiding and the number of incontinent episodes, thus improving the quality of life for the patient. However, these dugs are not "bladder specific", resulting in often quite distressing side effects such as dry mouth, blurred vision, dizziness and constipation. They may also cause confusion in the elderly and this is often more obviously seen in patients with dementia. However, by using the range of preparations available, with

different dosing schedules and modes of delivery, it is usually possible to find an acceptable balance for symptom control and tolerability of side effects.

Oxybutynin

Oxybutynin was the first commercially available antimuscarinic drug and has been on the United States market since 1975. Oxybutynin is a tertiary amine that undergoes hepatic first pass metabolism that produces the metabolite N-desethyloxybutynin, which along with its parent compound has very good antispasmodic effects on the detrusor muscle as well as relaxation of smooth muscle.[26] The original oral preparation, immediate release (IR) formula, can be taken up to three times a day with a maximum total dose of 30 mg per day. Its onset of action is 30-60 minutes from administration with its peak effect 3-6 hours after oral intake. Because of its side effect profile oxybutynin should be given initially at its lowest dose possible (2.5 mg) and patients should be warned about the side effects in order to maintain compliance.[27] This formulation of drug can be titrated to ensure that the minimum dose is given to provide adequate control. In an effort to reduce non-compliance, a single dose modified release (ER) preparation was developed and gives equal symptom control,[28] but because it is a modified release preparation, the side effects of dry mouth, constipation and blurred vision can be reduced.[29] The reduction in side effects is due to the reduction in peak serum concentrations and better control of symptoms is a consequence of the reduced peak and trough effect, resulting from a slow constant release. Oxybutynin ER has been shown to improve patient's quality of life over 3-12 months of therapy.[30]

An alternative method of delivering oxybutynin is via a transdermal patch, which prevents first pass metabolism within the liver, and thus reduces the production of the active metabolite N-desethyloxybutynin, and therefore prevents the side effect of dry mouth. There is an increase in plasma concentration of oxybutynin for a lower dose via this administrative route.[31] The transdermal patch can cause local skin irritation, but a trial which compared it with a daily oral dose of slow release tolterodine or placebo in patients with urgency and mixed incontinence showed that it had a comparable effect with tolterodine but with fewer side effects.[32] It is also possible to deliver oxybutynin via an intravesical route although this is not convenient unless the patient is already carrying out intermittent self-catheterization.

Tolterodine

Tolterodine is another commonly utilized anticholinergic drug, which is a tertiary amine with an active metabolite, 5-hydroxymethyl, brought about by hepatic metabolism. Unlike oxybutynin, tolterodine and its metabolite are more selective agonist of the bladder muscarinic receptor than those found in the salivary gland.[33] It is again an oral preparation that can be given as an immediate release (1 mg or 2 mg) twice daily or as an extended release once daily formula (2 mg or 4 mg) that achieves peak plasma concentrations within 1-2 hours or 2-6 hours respectively after administration.[27] It does have a very variable half-life of 3-10 hours, depending upon the ability of an individuals to metabolize the drug. Therefore it does require careful titration of dose depending upon the individuals metabolic response.[34] The use of tolterodine has been shown to be effective in relieving the symptoms of urinary frequency, urgency and urge incontinence, that are seen in patients with overactive bladder.[35]

There are three important clinical trials that have compared the different preparations of tolterodine and oxybutynin in patients with the symptoms of overactive bladder.

The first of these trials was the Overactive Bladder: Judging Effective control and Treatment (OBJECT).[36] This trial compared the use of oxybutynin ER 10 mg once daily with tolterodine IR 2 mg twice daily over 12 weeks in both men and women. This trial showed that oxybutynin ER was significantly more effective in reducing the number of both urge incontinent and total incontinence episodes as well as urinary frequency. It also showed that there was no overall difference in the frequency of adverse side effects including dry mouth and CNS effects. The main problem with this trial is that the authors have compared different preparations of the drugs and thus have compared medications with different metabolic profiles. The authors also failed to measure the effects on quality of life of the drug treatments.

The next important trial was the OPERA study (Overactive Bladder: Performance of Extended Release Agents). This trial did compare like with like, using the extended release formula for tolterodine 4 mg and oxybutynin 10 mg in females for 12 weeks. This trial did show a statistically significant difference in the clinical effectiveness of oxybutynin, which reduced the frequency of micturition as well as reducing the weekly urge and total urinary incontinence episodes. It also produced "total dryness" (no incontinent episodes) in the last 7 days of the 24-hour voiding diary. However not surprisingly oxybutynin brought about a greater frequency of dry mouth, although the other side effects

of the antimuscarinics were seen in equal frequencies with both drugs. The drawback of this trial is that it only compared a single group of patients who had severe symptoms and therefore cannot be generalized to include men who may only have urgency.[37]

The Antimuscarinic Clinical Effectiveness Trial (ACET)[38] compared tolterodine ER 2 mg and 4 mg with oxybutynin ER 5 mg and 10 mg once daily in an open label trial lasting 8 weeks. It included both men and women with a diagnosis of overactive bladder. A significantly lower proportion of patients withdrew from the trial when taking tolterodine ER 4 mg when compared with the other drug regimens. These patients were also found to have better symptom control as well as less dry mouth than the patients receiving oxybutynin 10 mg. Since this was an open labeled trial it was subject to bias. Whilst these trials compare clinical effects these two popular antimuscarinics, there are no trials to compare quality of life, therefore making it difficult to determine the best method of treatment. Cost, local policy and availability of the drug also play a part in deciding which method of treatment to use.

Trospium chloride

Trospium chloride is a quaternary ammonium derivative from the plant alkaloid nortropan. It binds competitively to the muscarinic receptors and its advantage is that, unlike the other antimuscarinics, which are lipophilic, it is hydrophilic. This means that it should not cross the blood brain barrier, theoretically reducing the CNS and cognitive side effects, and is theoretically the safest drug to use in the elderly or confused patient. Trospium chloride is inefficiently absorbed by the gastrointestinal tract, as 80% of its active compound is excreted in the feces, and the absorption is further reduced if taken with food. It is also slow to reach its peak plasma concentration taking 4-6 hours,[27] and has a half-life of 10 hours. The drug is metabolized by the kidney and therefore adjustments to the dose should be made in patients with renal insufficiency.[39] However it is a well-tolerated drug that improves symptoms within 1 week[40] of commencing treatment. It causes less dry mouth when compared with oxybutynin IR preparations.[41] As a result of the meta-analysis by Frohlich et al,[42] trospium chloride was shown to be very effective in neurological and idiopathic detrusor overactivity. Trospium chloride was shown to produce significant improvements in 'maximum cystometric bladder capacity' and 'urinary volume at first unstable contraction' when compared with placebo. It was also reported to have a similar adverse reaction profile as placebo. As yet there are no head to head trials of trospium chloride and the other anticholinergics.

Propiverine hydrochloride

Propiverine hydrochloride is a tertiary amine with both anticholinergic and calcium channel antagonistic properties and therefore has been shown to have an effect on the muscarinic receptors of the detrusor smooth muscle but also has the theoretical advantage of working directly upon the detrusor muscle itself, via calcium channel antagonism.[43] Propiverine undergoes first pass metabolism bringing about the production of several active metabolites, M-5, M-6 and M-14. It has been shown that the parent compound and these metabolites affect detrusor contraction but only propiverine and the metabolite M-14 have any effect on the calcium channels.[44] Propiverine reaches its peak plasma levels in 2.5 hours. It is excreted in bile, urine and feces. It is a twice-daily preparation with a better side effect profile than oxybutynin, and its effect upon cystometric bladder capacity at first desire to void and mean maximal bladder capacity is comparable to oxybutynin.[45] It has also been put head to head with tolterodine 2 mg twice-daily preparation and it has been shown to have a comparable efficacy, tolerability and improvement in quality of life.[46]

Solifenacin succinate

Solifenacin succinate is a once daily antimuscarinic that has recently been approved in the United States, Europe and now Canada. It selectively binds to the M_3 receptor and has been shown to select the M_3 receptors within the bladder rather than the salivary glands with a higher affinity than other antimuscarinic treatments in monkeys.[47] Solifenacin has been shown to be effective in the management of OAB in patients who have no incontinence. It significantly reduced daily urgency episodes, urinary frequency and increased voided volumes when compared with placebo.[48] The STAR trial, which was a comparison of solifenacin 5 mg and 10 mg with tolterodine 4 mg, found that with a flexible dosing regimen was found to be superior to tolterodine ER. This was because it significantly reduced the number of urgency episodes as well as urge incontinence and overall incontinence. It also enabled a larger proportion of incontinent patients to be continent by the end of the study. However the trial design allowed up titration of solifenacin but not tolteridine.[49]

Darifenacin

Darifenacin is a once daily selective M_3 receptor antagonist, with theoretical reduction of the adverse affect of dry mouth.[50] It has undergone safety trials compared with oxybutynin and placebo and been shown to have a similar effect on incontinent episodes

TABLE 1. **Drugs used in the treatment of detrusor overactivity: assessments according to the Oxford System (modified).[54]**

	Level of evidence	Grade of recommendation
Anti muscarinic drugs		
Tolterodine	1	A
Trospium	1	A
Darifenacin	1	A
Solifenacin	1	A
Propantheline	2	B
Atropine, hyocymaine	2	D
Drugs with mixed action		
Oxybutynin	1	A
Propiverine	1	A
Dicyclomine	4	C
Flavoxate	4	D

1 = Randomized controlled clinical trials; 2 = Good quality prospective studies; 3 = Retrospective "case-control" studies;
4 = Case series; A = Based on level 1 evidence (= highly recommended); B = Consistent level 2 or 3 evidence (= recommended);
C = Level 4 studies or "majority evidence" (= recommended with reservation);
D = Evidence inconsistent inconclusive (= not recommended)

as well as urgency, as oxybutynin 5 mg t.d.s. Darifenacin was found to produce less dry mouth, however the two drugs had similar incidence of constipation.[51] Darifenacin was also found to be safe in an elderly population (≥ 65 years) with OAB and produced significant improvements in all major symptoms of OAB, with the main adverse events of dry mouth and constipation being reported as only mild or moderate when compared to placebo.[52] It has also been shown to increase urgency free time in patients with OAB.[53]

In order to compare the pharmacological treatments available for overactive bladder the third International Consultation on Incontinence, held in Monaco in 2004 looked at the available trials and literature and ranked the treatments based upon the evidence.[54] Table 1.

There are a group of patients who provide urologists and primary care physicians with a perceived problem; these are the men with mixed bladder outlet obstruction and overactive bladder. This is because there is a theoretical risk of acute urinary retention with antimuscarinic treatment in men with BOO. So which pharmacological treatment is safe for these men? Abrams and Feneley showed that 42% of a population of 318 men with symptoms to suggest bladder outlet obstruction had urodynamic detrusor overactivity as well as obstruction.[55] A recent study using tolterodine versus placebo in men with OAB and BOO was performed to evaluate its safety in such men. Men > 40 years with BOO and confirmed detrusor overactivity were randomized to 12 weeks double blind treatment with tolterodine immediate release or placebo at a ratio of 2:1. There were significant treatment differences in volume to first detrusor contraction and maximum cystometric capacity, favoring tolterodine over placebo. Change in PVR was significantly greater among patients treated with tolterodine than placebo. There were no significant between-group differences in the incidence of adverse events. One patient reported urinary retention that had been treated with placebo.[56] This study postulates that the fears of treating men with OAB have been over emphasized.

Therapy for OAB if non-surgical treatment fails

Botulinum toxin

Botulinum toxin type A (BTX-A) is one of the neurotoxins released by the soil dwelling bacterium *Clostridium botulinum*. It acts at the neuromuscular junction by proteolysis of the intracellular proteins that aid in the exocytosis of the pre-synaptic vesicles containing acetylcholine.[57] The result of which is a failure of the post-synaptic depolarization and propagation of contraction within the muscle fiber served by that synapse. It has therapeutic indications throughout the field of medicine and has been extensively used by plastic surgeons in cosmetic surgery and in patients with hyperhydrosis.[58] It has also been utilized with

success in the treatment of anal fissures, chronic neuropathic pain and in children with spastic limb deformities.[59-61] Over the last few years it has become a widely used treatment modality for patients with OAB, who have failed to respond to treatment with antimuscarinic medication. The toxin is injected intravesically via a cystoscope into the detrusor muscle at 20-30 sites. Dosing regimes vary from 200 to 1000 units of BTX-A. The higher dose regimens have only been used in trials in patients with neurogenic OAB. Ruffion et al used the higher doses and found that these had a prolonged effect when compared with the lower doses however the higher doses exposed the patients to a higher risk of neurological side effects.[62] When used in patients with refractory idiopathic OAB, it appears that a dose of 300 units provides an immediate improvement in urgency and frequency, it increases volume at first desire to void, and increases cystometric capacity. The improvement in quality of life was maintained for 24 weeks.[63] Unfortunately this trial like many others is only a small series of patients with refractory idiopathic OAB and further evaluation is needed to adequately assess the safety and efficacy of this technique.

Neuromodulation

Sacral nerve stimulation often referred to as neuromodulation is approved in the USA for the treatment of urinary urge incontinence, voiding difficulties and urgency-frequency syndrome. Urinary urge incontinence results from an imbalance in the control system often causing detrusor overactivity, this then leads to incontinence during the filling phase of micturition.[64] Neuromodulation readjusts this imbalance by its actions on the sacral nerves.[64] It works by inhibiting the sensory processing in the spinal cord, and stimulating voiding reflexes by inhibiting of guarding reflex pathways.[65] Its efficacy and safety have been demonstrated by multicentre trials and have shown that compared to control groups patients with neuromodulation have a significant reduction in the frequency of voids, have an increase in voided volumes and reduction in urgency, and a reduction in incontinent episodes. One study showed that there was a return to baseline symptoms with deactivation of the neuromodulator.[66,67] By 2003 > 600 urologists and urogynecologists were using neuromodulation for the management of urinary urge incontinence. The use of neuromodulation should be considered before the use of invasive surgical procedures.[68]

Detrusor myectomy

The technique of detrusor myectomy was first described by Snow and Cartwright in 1989.[69] The detrusor muscle is excised from the dome of the bladder leaving the underlying bladder urothelium intact. This leaves a large epithelial bulge to act as an "autoaugmentation" by increasing the storage capacity of the bladder. The initial studies of this technique were carried out in six dogs but the technique was then used in seven children aged 4-17years. The initial study had variable results with complications including vesico-ureteric reflux, and extravasation from the bladder, which resolved with continued catheterization. Five of the seven children had improvements in their symptoms after this procedure.[70] Several other authors have produced series of up to 30 patients with variable results.[71-73] Long term follow up (28-142 months) from our institution showed that 80% of the patients had an increase in cystometric capacity of the bladder, 60% had a reduction in the maximum detrusor pressure at maximum flow ($pdetQ_{max}$) and the bladder contractility index ($pdetQ_{max}+5Q_{max}$) decreased in 78%.[73]

Augmentation cystoplasty

Augmentation cystoplasty aims to increase the functional capacity and lower the end filling pressure of an overactive bladder by introducing a segment of bowel. Different intestinal segments have been used including jejunum, ileum, cecum and sigmoid colon. The most commonly used segment is still the ileum as jejunum has the problem of high water reabsorption.[74] Sigmoid colon tends to be used if the small bowel mesentery is short. Detubularized ileum has the advantage of producing a reservoir with lower pressures and better compliance.[75] Post operatively the patients must learn to void by abdominal straining and /or by the use of clean intermittent self-catheterization.

Patients should be counseled preoperatively about the common complications associated with augmentation cystoplasty, which include voiding mucous, and infections, although some series have reported a lowering in the incidence of infections post operatively.[76] There are also the risks of metabolic disturbances, such as hyperchloremic acidosis, although the disturbances tend to be mild.[77] Patients may also experience bowel dysfunction, which is believed to be due to an interruption in the normal enterohepatic circulation. Hematological surveillance should also be carried out on a regular basis as the use of ileum can reduce vitamin B_{12} deficiency.[78] They must also be warned that there is a risk of bladder perforation and also a risk of urinary tract stones.[79] Lifelong follow up of patients with regular inspection of the mucosa is

necessary as there are case reports of delayed malignancy occurring within the ectopic bowel.[80,81]

Conclusions

Overactive bladder is a common urological diagnosis with far reaching economical and personal consequences. The diagnosis is easily made and the primary care physician can initiate treatment. To make a correct diagnosis there should be a thorough history and examination to assess the severity of symptoms and the impact that the symptoms are having on the daily life of the individual. Commencement of treatment should always begin with lifestyle modifications such as fluid and dietary changes, pelvic floor exercises and bladder drill. If these measures fail to control symptoms then it is fair to give the patient a trial of pharmacological treatment. It may take a trial of a few different preparations and dosing regimens to find a drug that it suitable for the patient. If after a trial of medication the symptoms persist then referral to a urological specialist is required to assess the suitability of that patient for more invasive treatment modalities. There is increasing evidence that the use of botulinum toxin and neuromodulation may bring about control of symptoms without the need for more invasive procedures. □

References

1. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, van Kerrebroeck P, Victor A, Wein A. Standardisation Sub-committee of the International Continence Society. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn* 2002;21(2):167-178.
2. Milsom I, Abrams P, Cardozo L, Roberts RG, Thuroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU Int* 2001;87(9):760-766.
3. Homma Y, Yamaguchi O, Hayashi K. Neurogenic Bladder Society Committee. An epidemiological survey of overactive bladder symptoms in Japan. *BJU Int* 2005;96(9):1314-1318.
4. Stewart WF, Van Rooyen JB, Cundiff GW, Abrams P, Herzog AR, Corey R, Hunt TL, Wein AJ. Prevalence and burden of overactive bladder in the United States. *World J Urol* 2003;20(6):327-336.
5. Fultz N, Girts T, Kinchen K, Nygaard I, Pohl G, Sternfeld B. Prevalence, management and impact of urinary incontinence in the workplace. *Occup Med (Lond)* 2005;55(7):552-557.
6. Getsios D, El-Hadi W, Caro I, Caro JJ. Pharmacological management of overactive bladder: a systematic and critical review of published economic evaluations. *Pharmacoeconomics* 2005;23(10):995-1006.
7. Hu TW, Wagner TH, Bentkover JD, Leblanc K, Zhou SZ, Hunt T. Costs of urinary incontinence and overactive bladder in the United States: a comparative study. *Urology* 2004;63(3):461-465.
8. Iggo A. Tension receptors in stomach and urinary bladder. *J Physiol* 1955;128:593-607.
9. Learmonth JR. A contribution to the neurophysiology of the urinary bladder in man. *Brain* 1931;54:147-176.
10. Dietrichs E, Haines DE. Possible pathways for cerebellar modulation of autonomic responses: micturition. *Scand J Urol Nephrol* 2002;(210 Suppl):16-20.
11. De Groat WC. Nervous control of the urinary bladder in the cat. *Brain Res* 1975;87:201-211.
12. De Groat WC. Physiology of urinary bladder and urethra. *Ann Intern Med* 1980;92:312-315.
13. Wein AJ. Expert Opinion. *Invest Drugs* 2001;10:65-83.
14. Brading AF. A myogenic basis for the overactive bladder. *Urology* 1997;50(6A Suppl):57-67.
15. de Groat WC. A neurologic basis for the overactive bladder. *Urology* 1997;50(6A Suppl):36-52.
16. Gillespie JI. Modulation of autonomous contractile activity in the isolated whole bladder of the guinea pig. *BJU Int* 2004;93(3):393-400.
17. Creighton SM, Stanton SL. Caffeine: does it affect your bladder? *Br J Urol* 1990;66(6):613-614.
18. Cukier JM, Cortina-Borja M, Brading AF. A case-control study to examine any association between idiopathic detrusor instability and gastrointestinal tract disorder, and between irritable bowel syndrome and urinary tract disorder. *Br J Urol* 1997;79(6):865-878.
19. Abrams P, Avery K, Gardener N, Donovan J; ICIQ Advisory Board. The International Consultation on Incontinence Modular Questionnaire: www.iciq.net. *J Urol* 2006;175(3 Pt 1):1063-1066.
20. Coyne K, Revicki D, Hunt T, Corey R, Stewart W, Bentkover J, Kurth H, Abrams P. Psychometric validation of an overactive bladder symptom and health-related quality of life questionnaire: the OAB-q. *Qual Life Res* 2002;11(6):563-574.
21. Dmochowski RR, Sanders SW, Appell RA, Nitti VW, Davila GW. Bladder-health diaries: an assessment of 3-day vs 7-day entries. *BJU Int* 2005;96(7):1049-1054
22. Herschorn S, Becker D, Miller E, Thompson M, Forte L. Impact of a health education intervention in overactive bladder patients. *Can J Urol* 2004;11(6):2430-2437.
23. Burgio KL. Current perspectives on management of urgency using bladder and behavioral training. *J Am Acad Nurse Pract* 2004;16(10 Suppl):4-7.
24. Burgio KL. Influence of behavior modification on overactive bladder. *Urology* 2002;60(5 Suppl 1):72-76.
25. Andersson KE. Antimuscarinics for treatment of overactive bladder. *Lancet Neurol* 2004;3(1):46-53.
26. Hughes KM, Lang JC, Lazare R, Gordon D, Stanton SL, Malone-Lee J, Geraint M. Measurement of oxybutynin and its N-desethyl metabolite in plasma, and its application to pharmacokinetic studies in young, elderly and frail elderly volunteers. *Xenobiotica* 1992;22(7):859-869.
27. Haymarkey Publishing Ltd. eMIMS:monthly index of medical specialities: the definitive prescribing information system [on-line]. Available from URL:http://www.eMIMS.net
28. Gleason DM, Susset J, White C, Munoz DR, Sand PK. Evaluation of a new once-daily formulation of oxbutynin for the treatment of urinary urge incontinence. Ditropan XL Study Group. *Urology* 1999;54(3):420-423.
29. Anderson RU, Mobley D, Blank B, Saltzstein D, Susset J, Brown JS. Once daily controlled versus immediate release oxybutynin chloride for urge urinary incontinence. OROS Oxybutynin Study Group. *J Urol* 1999;161(6):1809-1812.
30. Diokno A, Sand P, Labasky R, Sieber P, Antoci J, Leach G, Atkinson L, Albrecht D. Long-term safety of extended-release oxybutynin chloride in a community-dwelling population of participants

with overactive bladder: a one-year study. *Int Urol Nephrol* 2002;34(1):43-49.
31. Appell RA, Chancellor MB, Zobrist RH, Thomas H, Sanders SW. Pharmacokinetics, metabolism, and saliva output during transdermal and extended-release oral oxybutynin administration in healthy subjects. *Mayo Clin Proc* 2003;78(6):696-702.
32. Dmochowski RR, Sand PK, Zinner NR, Gittelman MC, Davila GW, Sanders SW; Transdermal Oxybutynin Study Group. Comparative efficacy and safety of transdermal oxybutynin and oral tolterodine versus placebo in previously treated patients with urge and mixed urinary incontinence. *Urology* 2003;62(2):237-242.
33. Maruyama S, Oki T, Otsuka A, Shinbo H, Ozono S, Kageyama S, Mikami Y, Araki I, Takeda M, Masuyama K, Yamada S. Human muscarinic receptor binding characteristics of antimuscarinic agents to treat overactive bladder. *J Urol* 2006;175(1):365-369.
34. Jonas U, Hofner K, Madersbacher H, Holmdahl TH. Efficacy and safety of two doses of tolterodine versus placebo in patients with detrusor overactivity and symptoms of frequency, urge incontinence, and urgency: urodynamic evaluation. The International Study Group. *World J Urol* 1997;15(2):144-151.
35. Appell RA. Clinical efficacy and safety of tolterodine in the treatment of overactive bladder: a pooled analysis. *Urology* 1997;50(6A Suppl):90-96.
36. Appell RA, Sand P, Dmochowski R, Anderson R, Zinner N, Lama D, Roach M, Miklos J, Saltzstein D, Boone T, Staskin DR, Albrecht D; Overactive Bladder: Judging Effective Control and Treatment Study Group. Prospective randomised controlled trial of extended-release oxybutynin chloride and tolterodine tartrate in the treatment of overactive bladder: results of the OBJECT Study. *Mayo Clin Proc* 2001;76(4):358-363.
37. Diokno AC, Appell RA, Sand PK, Dmochowski RR, Gburek BM, Klimberg IW, Kell SH; OPERA Study Group. Prospective, randomised, double-blind study of the efficacy and tolerability of the extended-release formulations of oxybutynin and tolterodine for overactive bladder: results of the OPERA trial. *Mayo Clin Proc* 2003;78(6):687-695.
38. Sussman D, Garely A. Treatment of overactive bladder with once-daily extended-release tolterodine or oxybutynin: the antimuscarinic clinical effectiveness trial (ACET). *Curr Med Res Opin* 2002;18(4):177-184.
39. Doroshyenko O, Jetter A, Odenthal KP, Fuhr U. Clinical pharmacokinetics of trospium chloride. *Clin Pharmacokinet* 2005;44(7):701-720.
40. Rudy D, Cline K, Harris R, Goldberg K, Dmochowski R. Multicenter phase III trial studying trospium chloride in patients with overactive bladder. *Urology* 2006;67(2):275-280.
41. Halaska M, Ralph G, Wiedemann A, Primus G, Ballering-Bruhl B, Hofner K, Jonas U. Controlled, double-blind, multicentre clinical trial to investigate long-term tolerability and efficacy of trospium chloride in patients with detrusor instability. *World J Urol* 2003;20(6):392-399.
42. Frohlich G, Bulitta M, Strosser W. Trospium chloride in patients with detrusor overactivity: meta-analysis of placebo-controlled, randomised, double-blind, multi-center clinical trials on the efficacy and safety of 20 mg trospium chloride twice daily. *Int J Clin Pharmacol Ther* 2002;40(7):295-303.
43. Madersbacher H, Murtz G. Efficacy, tolerability and safety profile of propiverine in the treatment of the overactive bladder (non-neurogenic and neurogenic). *World J Urol* 2001;19(5):324-335.
44. Wuest M, Hecht J, Christ T, Braeter M, Schoeberl C, Hakenberg OW, Wirth MP, Ravens U. Pharmacodynamics of propiverine and three of its main metabolites on detrusor contraction. *Br J Pharmacol* 2005;145(5):608-619.
45. Madersbacher H, Halaska M, Voigt R, Alloussi S, Hofner K. A placebo-controlled, multicentre study comparing the tolerability and efficacy of propiverine and oxybutynin in patients with urgency and urge incontinence. *BJU Int* 1999;84(6):646-651.
46. Junemann KP, Halaska M, Rittstein T, Murtz G, Schnabel F, Brunjes R, Nurkiewicz W. Propiverine versus tolterodine: efficacy and tolerability in patients with overactive bladder. *Eur Urol* 2005;48(3):478-482.
47. Kobayashi S, Ikeda K, Miyata K. Comparison of in vitro selectivity profiles of solifenacin succinate (YM905) and current antimuscarinic drugs in bladder and salivary glands: a Ca2+ mobilization study in monkey cells. *Life Sci* 2004;74(7):843-853.
48. Abrams P, Swift S. Solifenacin is effective for the treatment of OAB dry patients: A pooled analysis. *Eur Urol* 2005;48(3):483-487.
49. Chapple CR, Martinez-Garcia R, Selvaggi L, Toozs-Hobson P, Warnack W, Drogendijk T, Wright DM, Bolodeoku J; for the STAR study group. A comparison of the efficacy and tolerability of solifenacin succinate and extended release tolterodine at treating overactive bladder syndrome: results of the STAR trial. *Eur Urol* 2005;48(3):464-470.
50. Alabaster VA. Discovery & development of selective M3 antagonists for clinical use. *Life Sci* 1997;60(13-14):1053-1060.
51. Zinner N, Tuttle J, Marks L Efficacy and tolerability of darifenacin, a muscarinic M3 selective receptor antagonist (M3 SRA), compared with oxybutynin in the treatment of patients with overactive bladder. *World J Urol* 2005;23(4):248-252.
52. Foote J, Glavind K, Kralidis G, Wyndaele JJ. Treatment of overactive bladder in the older patient: pooled analysis of three phase III studies of darifenacin, an M3 selective receptor antagonist. *Eur Urol* 2005;48(3):471-477.
53. Zinner N, Susset J, Gittelman M, Arguinzoniz M, Rekeda L, Haab F. Efficacy, tolerability and safety of darifenacin, an M(3) selective receptor antagonist: an investigation of warning time in patients with OAB. *Int J Clin Pract* 2006;60(1):119-126.
54. Andersson K-E, Appell R, Cardozo L, et al; 3rd International Consultation on Incontinence. Pharmacological treatment of urinary incontinence. In: Abrams P, Cardozo L, Khoury S, Wein A, eds. Incontinence. Volume 2. Plymouth, UK: Health Publication Ltd, 2005;809-855.
55. Abrams P, Feneley RCL. The significance of the symptoms associated with bladder outflow obstruction. *Urol Int* 1978;33:171-174.
56. Abrams P, Kaplan S, De Koning Gans HJ, Millard R. Safety and tolerability of tolterodine for the treatment of overactive bladder in men with bladder outlet obstruction. *J Urol* 2006;175(3):999-1004.
57. Dolly O. Synaptic transmission: inhibition of neurotransmitter release by botulinum toxins. *Headache* 2003;43(Suppl 1):S16-S24.
58. Farrugia MK, Nicholls EA. Intradermal botulinum A toxin injection for axillary hyperhydrosis. *J Pediatr Surg* 2005;40(10):1668-1669.
59. Brisinda G, Maria G, Bentivoglio AR, Cassetta E, Gui D, Albanese A. A comparison of injections of botulinum toxin and topical nitroglycerin ointment for the treatment of chronic anal fissure. *N Engl J Med* 1999;341(2):65-69.
60. Argoff CE. A focused review on the use of botulinum toxins for neuropathic pain. *Clin J Pain* 2002;18(6 Suppl):S177-S181.
61. Munin MC, Navalgund BK, Levitt DA, Breisinger TP, Zafonte RD. Novel approach to the application of botulinum toxin to the flexor digitorum superficialis muscle in acquired brain injury. *Brain Inj* 2004;18(4):403-407.
62. Ruffion A, Capelle O, Paparel P, Leriche B, Leriche A, Grise P. What is the optimum dose of type A botulinum toxin for treating neurogenic bladder overactivity? *BJU Int* 2006;97(5):1030-1034.
63. Rajkumar GN, Small DR, Mustafa AW, Conn G. A prospective study to evaluate the safety, tolerability, efficacy and durability of response of intravesical injection of botulinum toxin type A into detrusor muscle in patients with refractory idiopathic detrusor overactivity. *BJU Int* 2005;96(6):848-852.
64. Fall M, Lindstrom S. Electrical stimulation. A physiologic approach to the treatment of urinary incontinence. *Urol Clin North Am* 1991;18(2):393-407.

65. Schmidt RA, Senn E, Tanagho EA. Functional evaluation of sacral nerve root integrity. Report of a technique. *Urology* 1990;35(5):388-392.
66. Hassouna MM, Siegel SW, Nyeholt AA, Elhilali MM, van Kerrebroeck PE, Das AK, Gajewski JB, Janknegt RA, Rivas DA, Dijkema H, Milam DF, Oleson KA, Schmidt RA. Sacral neuromodulation in the treatment of urgency-frequency symptoms: a multicenter study on efficacy and safety. *J Urol* 2000;163(6):1849-1854.
67. Schmidt RA, Jonas U, Oleson KA, Janknegt RA, Hassouna MM, Siegel SW, van Kerrebroeck PE. Sacral nerve stimulation for treatment of refractory urinary urge incontinence. Sacral Nerve Stimulation Study Group. *J Urol* 1999;162(2):352-357.
68. Abrams P, Blaivas JG, Fowler CJ, Fourcroy JL, Macdiarmid SA, Siegel SW, Van Kerrebroeck P. The role of neuromodulation in the management of urinary urge incontinence. *BJU Int* 2003;91(4):355-359.
69. Cartwright PC, Snow BW. Bladder autoaugmentation: partial detrusor excision to augment the bladder without use of bowel. *J Urol* 1989;142(4):1050-1053.
70. Cartwright PC, Snow BW. Bladder autoaugmentation: early clinical experience. *J Urol* 1989;142(2 Pt 2):505-508.
71. Stohrer M, Kramer G, Goepel M, Lochner-Ernst D, Kruse D, Rubben H. Bladder autoaugmentation in adult patients with neurogenic voiding dysfunction. *Spinal Cord* 1997;35(7):456-462.
72. Swami KS, Feneley RC, Hammonds JC, Abrams P. Detrusor myectomy for detrusor overactivity: a minimum 1-year follow-up. *Br J Urol* 1998;81(1):68-72.
73. Kumar SP, Abrams PH. Detrusor myectomy: long-term results with a minimum follow-up of 2 years. *BJU Int* 2005;96(3):341-344.
74. Gough DC. Enterocystoplasty. *BJU Int* 2001;88(7):739-743.
75. Radomski SB, Herschorn S, Stone AR. Urodynamic comparison of ileum vs. sigmoid in augmentation cystoplasty for neurogenic bladder dysfunction. *Neurourol Urodyn* 1995;14(3):231-237.
76. Krishna A, Gough DC. Evaluation of augmentation cystoplasty in childhood with reference to vesico-ureteric reflux and urinary infection. *Br J Urol* 1994;74(4):465-468.
77. Nurse DE, Mundy AR. Metabolic complications of cystoplasty. *Br J Urol* 1989;63(2):165-170.
78. Steiner MS, Morton RA, Marshall FF. Vitamin B12 deficiency in patients with ileocolic neobladders. *J Urol* 1993;149(2):255-257.
79. Woodhouse CR, Robertson WG. Urolithiasis in enterocystoplasties. *World J Urol* 2004;22(3):215-221.
80. Ali-El-Dein B, El-Tabey N, Abdel-Latif M, Abdel-Rahim M, El-Bahnasawy MS. Late uro-ileal cancer after incorporation of ileum into the urinary tract. *J Urol* 2002;167(1):84-88.
81. Radomski SB, Herschorn S, Stone AR. Urodynamic comparison of ileum vs. sigmoid in augmentation cystoplasty for neurogenic bladder dysfunction. *Neurourol Urodyn* 1995;14(3):231-237.