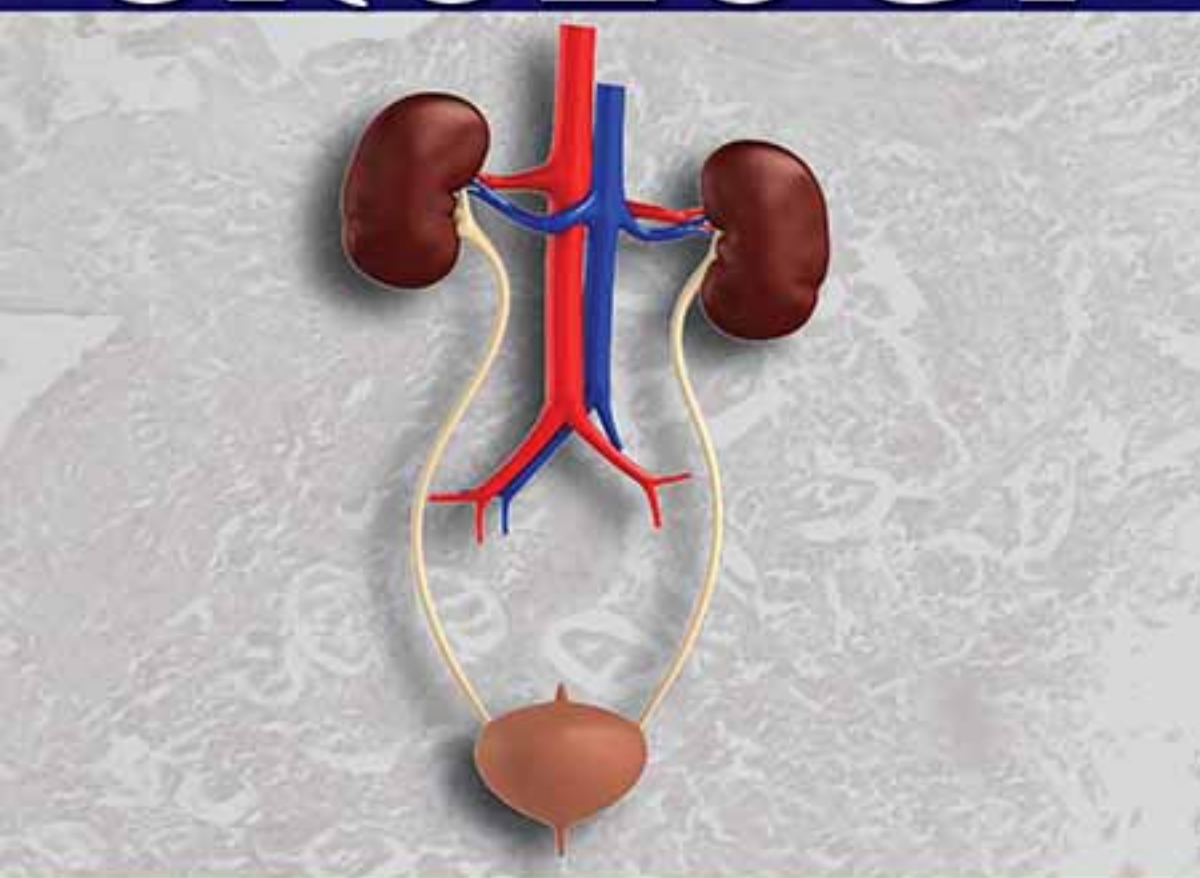
Manual of Medical Treatment *in* UROLOGY



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Foreword
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CHAPTER

4

Medical Treatment of Urinary Incontinence

Ayman Mahdy, Ismaila A Mungadi

INTRODUCTION

As defined by the International Continence Society, urinary incontinence (UI) is "the complaint of any involuntary leakage of urine."[1] Many types of UI have been defined with the most common being stress urinary incontinence (SUI), urge urinary incontinence (UUI), and mixed urinary incontinence (MUI). SUI is the complaint of involuntary leakage on effort or exertion, or on sneezing or coughing. UUI is the complaint of involuntary leakage accompanied by or immediately preceded by urgency. MUI, however, is the complaint of involuntary leakage associated with urgency and also with exertion, effort, sneezing, or coughing.[1] UI is a major health problem that affects both men and women with higher prevalence in women and among aging populations. UI significantly affects patients' quality of life with possible subsequent stigmatization.[2]

CONTROL OF MICTURITION

The parasympathetic (S_2-S_4) efferent is excitatory to the detrusor muscle and passes through the pelvic splanchnic nerves to reach the bladder via the inferior hypogastric plexus. The sympathetic (T_{12}-L_2) efferent passes through hypogastric plexus. The sympathetic nerves stimulate α-adrenergic receptors concentrated in the trigone, bladder neck, and urethra. The striated external sphincter is innervated by pudendal nerves. The afferents pass through similar pathways to the spinal cord. Bladder afferent consists of myelinated (A-δ) and unmyelinated (C) fibers. These afferents monitor bladder tension and volume. Silent C fibers become recruited as mechanoreceptors in response to various chemical stimuli.

Normal continence is promoted by spinal guarding reflex. This is brought during sympathetic stimulation caused by bladder distension during filling. The outlet smooth muscles and urethral sphincter contract while

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the parasympathetic bladder muscular activity is inhibited. Intense bladder activity activates the pontine micturition center and micturition is initiated by inhibition of this guarding reflex. Micturition can be voluntarily aborted by contracting periurethral sphincter that also reflexly inhibits detrusor contraction.

EVALUATION OF URINARY INCONTINENCE PATIENTS

Starting with the patient history, a thorough evaluation should detect all aspects of the patients' condition. History should identify the type of UI, severity (number of pads, diapers, or other protection methods used per day), impact on quality of life using certain validated questionnaires, age at onset, previous treatment trials, associated medical conditions (especially gastrointestinal, neurological, and/or mental). History might also help identifying certain reversible causes of UI. Associated storage and/or emptying urinary tract symptoms should be addressed.

HOW CAN WE PREVENT URINARY INCONTINENCE?

The first and most important step in treating disease conditions is prevention. Although it seems difficult, prevention of UI has been a potential project for many health organizations including the National Institute of Health (NIH).[3] Proper recognition of the risk factors for the condition is an important step during the prevention process. The risk factors for UI include advanced age, gender (females more than males), diabetes, neurological diseases, pregnancy and childbirth, smoking, obesity, urinary tract infections (UTIs), history of UI during childhood, positive family history of UI, physical inability, use of other medications, pelvic organ prolapse (POP), cognitive diseases, as well as menopause in women and prostate diseases in men. Lifford et al.[4] have summarized the potential target populations for urine incontinence prevention. Those populations included the following:

1. *Pregnant women*: Pelvic floor muscle training (PFMT) during pregnancy and the postpartum period has been shown to decrease the UI rates during late pregnancy and postpartum.
2. *Post-prostatectomy incontinence*: Pre- and postoperative PFMT was shown to decrease the prevalence of SUI in this group of patients.[5]
3. *Elderly population*: Diokno et al.[6] have reported that combined bladder training and PFMT have doubled the continence rate in the studied elderly women 55 to 80 years of age.
4. *Diabetic patients*: Prevention of diabetes mellitus type 2 could prevent almost half of severe incontinence conditions.

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URINARY INCONTINENCE MANAGEMENT OPTIONS

Many lines of treatment have been studied in the literature. The approach is usually a combination of different therapies. A list of the medical management options is summarized below:

1. *No treatment*: The "no treatment" approach is considered after underlying medical conditions (tumors, cancer, urinary retention, urinary obstruction etc.) have been excluded. A second important factor that affects the "no treatment" decision is the patient choice.
2. *Conservative management*: This includes bladder retraining, toilet training, timed voiding, PFMT, general advice (fluids, diet, and bowel management), medication review, management of bowel dysfunction (constipation/fecal impaction), improving access to toilet facilities, and improving mobility and use of pads/continence aids and other supplies:
   a. *Bladder retraining*: is considered the first-line treatment for UI.[7] Through this approach, the patient is taught how to suppress the urgency "wave." There are few strategies the patient can follow; these include distraction (thinking of something different from the sensation of urgency), repeated pelvic floor muscle contractions (rapid and intense 5–6 contractions within 2–3 seconds), toe pressure, and perineal pressure (patients may sit on their heel). This increases the scheduled interval between voiding by 30 minutes.
   b. *PFMT* is prescribed as first-line treatment for SUI, UUI. or MUI, particularly in cases with no concomitant POP.[8] It is based on "Kegel" exercise and consists of repetitive contractions of the PFM. It is taught by a health care provider. Midwives can be responsible for postpartum rehabilitation using this technique as well. Voluntary contraction of the PFM helps to increase the urethral pressure, improves SUI, and also suppress detrusor muscle contraction and hence improves UUI.

The first step is to help the patient identify the correct muscles. The patient is asked to act as if he or she is trying to prevent passing gas. Another way is for the patient to insert her finger in the vagina and try to squeeze it using her vaginal muscles. The patient should feel the pressure over her finger and also the sensation in her vagina. Men can be taught in a similar fashion with a finger in the rectum.

Once recognition of the "correct" group of muscles is assured, PFMT sessions can be started. There are many PFMT protocols that are proved to be successful. A number of studies including one by Siu et al.,[9] have demonstrated a considerable success using a program of 30 contractions repeated 3 times daily. During the session, the patient is asked to perform few flicks or 2-to3-second contractions, followed by one sustained (5 second or more) contraction,

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followed by relaxation of at least 10 seconds. As part of urge control process, and as the patient feels the urge to urinate, the patient is instructed to relax his/her body, start five short PFM contractions, and focus on these muscles. This suppresses the feeling of urgency and the patient has enough time to reach the bathroom while walking in a normal pace. PFMT needs lifelong patient compliance in order to maintain good outcome.

Use of absorbent products (pantiliners, pads, diapers, etc.): This is the first management option for UI in frail, elderly population with other physical and cognitive impairments. It is also a good choice for patients with occasional leakage of small amounts of urine. These products come in variety of sizes and different materials. Some have ingredients that turn to gel when wet, adding more protection. Others have built in deodorants to minimize urine smell. The main purpose is to keep the patient's body dry, avoid urine–skin contact–related complications and makes the urine leakage undetectable by others, and hence minimizes the UI-related emotional and psychological complications.

ROLE OF PHARMACOTHERAPY

Drug Therapy

The major role of drug therapy in UI is in treatment of UUI and MUI. So far, there are no available FDA-approved medications that assure urethral closure and can treat SUI. The most commonly used medications in treatment of UI include the following:

Antimuscarinic Medications

These act by blocking the action of Ach. These medications affect the muscarinic receptors in the bladder as well as other organs resulting in a variety of side effects with constipation and dry mouth being the most common. There are six currently available antimuscarinic medications in the United States. Namely, Oxybutinin, Tolterodine, Trospium, Fesoterodine, Darifenacin, and Solifenacin. They are thought to work through inhibition of bladder sensory innervations as well as detrusor contraction. These medications have proved 70–80% UUI reduction rates. For the best outcome, the use of antimuscarinic medications should be accompanied with behavioral therapy.

There are five different muscarinic receptors (M1-5).[10] M2 and M3 are predominant in the bladder smooth muscle and M3 are considered by Scarpero et al.[11] more important in detrusor contraction; hence, they are thought to be responsible for detrusor overactivity and bladder emptying. M1 receptors are cognition receptors, M2 receptors have a role in heart rate regulation, M3 receptors mediate salivary secretion and bowel movement, M4 receptors are mainly found in the brainstem while their function is unknown, and M5 receptors have a role in accommodation. Antimuscarinics' side effects

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will be related to their effects on these different receptors. Drugs which can cross the blood brain barrier and affect M1 receptors will induce cognitive impairment, those which block M2 receptors will have a negative impact on the heart rate. Antimuscarinics that block M3 receptors will cause dry mouth and constipation as their main side effects.[12]

Response to antimuscarinic treatment is very subjective. There is no cut-off definition for successful outcome. Success depends mainly on patient perception of symptoms' improvement. Treatment outcome is affected by other confounders that should be considered when counseling patients. These confounders include type of incontinence (UUI vs. MUI), patient lifestyle (amount of fluid the patient drinks every day), associated medical condition (e.g. congestive heart failure), and other medications (e.g. diuretics, bladder irritants, and alpha agonists).

Patient compliance for the medication markedly affects the outcome. Many factors affect patient compliance and should be taken in consideration at time of drug prescription. Factors that affect patient compliance include drug tolerance, cost (along with insurance regulations), mode of delivery, dose frequency, patient age, other comorbidities, severity of symptoms, and treatment outcome. For best results, an open and detailed discussion should be initiated between the physician and the patient before starting treatment. In a survey of 5,392 patients with OAB, 24.5% reported discontinuing 1 antimuscarinic prescription medication or more during the prior 12 months. Survey responses of those who discontinued showed that the most frequently reported reason for discontinued medication was "didn't work as expected."[13] Hence, patients should be counseled that improvement of symptoms is usually perceived 2–3 weeks after initiation of the therapy. Cost and insurance issues should be addressed before drug prescription. Patients other comorbidities should be also considered.

Based on their chemical structure, the antimuscarinics are divided to two major subgroups; tertiary and quaternary amines. All antimuscarinics, except for Trospium are tertiary amines. Tertiary amines are readily absorbable while quaternary amines have lower gastrointestinal absorption and therefore need be taken on an empty stomach. Trospium is the considered the safest in polypharmacy patients because it has the least potential for drug–drug interaction. Trospium and darifenacin have lower tendency for CNS side effects.

β3 agonists (Mirabegron)

Mirabegron is a β3-adrenoceptor agonist which has recently been approved by the FDA for treatment of OAB. The medication acts through a different mechanism of action from that of the antimuscarinic medications. It activates the β3 (the most potent of the β) receptor sin the bladder wall). This results

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in detrusor muscle relaxation. The medication has also been approved in Japan, Canada and Europe, for the treatment of OAB symptoms. The treatment can be initiated with a starting dose of 25 mg which can be increased to 50 mg daily according to patient response and tolerability.[14]

Estrogen Therapy

This is a well-known treatment strategy for menopause-associated symptoms including hot flashes, vaginal dryness, and night sweats. In menopausal and postmenopausal women, estrogen deficiency has been also proposed as a cause for UTIs, POP, urgency, frequency, and UUI.[15] Estrogen and progesterone receptors are found in vaginal epithelium as well as urethra and bladder trigone.[16] It has been stated by the American College of Obstetricians and Gynecologists that "for genitourinary symptoms associated with menopause, estrogen and progestin have been shown to be beneficial." A recent Cochrane review, however, concluded that treatment with estrogen alone was associated with perceived improvement or cure compared with placebo but that larger trials were needed.

In a recent large, randomized clinical trial by Hendrix et al.[17] estrogen therapy was not found beneficial for treating UI. On the contrary, it was found to precipitate UI in continent women who used estrogen therapy versus placebo. For lower genitourinary only symptoms, local (vaginal) estrogen therapy is preferable. The vaginal estrogen delivery forms available in the United States include estradiol creams (Estrace and Premarin), estradiol vaginal tablets (Vagifem), and estradiol vaginal rings (Estring). The effect is perceived within 4–6 weeks (2–3 weeks for vaginal rings).

Side effects of local estrogen therapy include vaginal discharge, headache, sexual changes, leucorrhea, breast tenderness, vaginal spotting, abdominal pain, nausea, and vomiting. Contraindications for estrogen therapy include hypercoagulable states, history of cardiovascular disease (deep vein thrombosis, strokes, and pulmonary embolism), breast cancer, and/or endometrial cancer. Estrogen should be also used with caution in elderly population because of risk of dementia. Proper instructions should be given to patients regarding risks, benefits, and side effects. Modes of drug delivery (better written) instructions should be also provided.

Other Medical Therapies

Desmopressin Acetate (DDAVP)

These can be used with caution for treatment of nocturia and nocturnal enuresis.[18] Hyponatremia is a major side effect and sodium level should be monitored during therapy.

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Tricyclic Antidepressants

These are thought to have anticholinergic and alpha adrenergic properties. Imepramine is usually used for treatment of nocturnal enuresis in both children and adults. However, no studies are available about its use in adults. Furthermore, its use in adults is not FDA approved for treating nocturnal enuresis.

Alpha Agonists

These propose to increase the bladder outlet resistance through activation of the alpha receptors at the urethral smooth muscles and hence improving SUI. The use of these medications is associated with multiple cardiovascular side effects related to their alpha receptor stimulating properties.

Use of Absorbent Products (Pantiliners, Pads, Diapers, etc.)

This is the first management option for UI in frail, elderly population with other physical and cognitive impairments. It is also a good choice for patients with occasional leakage of small amounts of urine. These products come in variety of sizes and different materials. Some have ingredients that turn to gel when wet adding more protection. Others have built in deodorants to minimize urine smell. The main purpose is to keep the patient's body dry, avoid urine-skin contact–related complications and makes the urine leakage undetectable by others and hence minimizes the UI-related emotional and psychological complications.

OUTLINE OF SOME PHARMACOTHERAPEUTIC AGENTS[19,20]

Antimuscarinic and Musculotropic Drugs

Propantheline (Pro-Banthine)

Properties: Propantheline is a nonselective (M_1, M_2, and M_3) muscarinic receptor antagonist. It competitively blocks acetylcholine binding to neuroeffector site on detrusor muscle and other muscarinic receptors sites including ganglia.

Indications: Overactive bladder, adult enuresis.

Side effects: Dry mouth, constipation, abdominal discomfort, palpitation, and arrhythmias, CNS stimulation including convulsion, reduced sweating, difficulty micturition and urinary retention, photosensitivity, and allergic reaction.

Contraindication: Glaucoma, urinary retention, bladder outflow obstruction, gastrointestinal atony, and abstruction, ulcerative colitis.

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Caution: Cardiac, renal, and hepatic impairment; hyperthyroidism; elderly, reflux esophagitis; pregnancy; breastfeeding.

Interaction: Wide interaction with drugs having parasympathomimetic and antimuscarinic actions. Please determine interaction with any concomitantly administered drug.

Dosage: Propantheline (Pro-Banthine)—15 mg 3 times daily and 30 mg at bed time adjusted according to response to a maximum of 120 mg daily.

Preparation: Oral.

Oxybutinin

Properties: An antimuscarinic drug with high affinity for M_1 and M_3 receptors. It is indicated in patients with urinary frequency, bladder overactivity, bladder instability, nocturnal enuresis, and postoperative bladder spasms.

Side effect: See propantheline.

Contraindications: See propantheline.

Caution: See propantheline.

Dosage: Oxybutinin hydrochloride, oral 2.5 mg 2 to 4 times daily. Elderly 2.5 mg twice daily to a maximum of 5 mg twice daily.

Preparations: Oral—immediate release.

Oral–modified (extended) release for daily doing, transdermal and intravesical.

Propiverine

Properties: This drug is an antimuscarinic and calcium antagonist. It is indicated in patients with frequency, overactive bladder, neurogenic bladder instability, and postoperative bladder spasms.

Side effects: See propantheline.

Contraindications: Children, also see propantheline.

Caution: See propantheline.

Interaction: See propantheline.

Dosage: Propiverine hydrochloride—15 mg 1–3 times daily

Preparation: Oral

Tolterodine

Properties: Tolterodine is a nonselective antimuscarinic agent. Tolterodine and its metabolites do not cross blood-brain barrier and the drug has low CNS system toxicity. It is indicated in patients with urinary frequency, overactive bladder, and postoperative bladder spasms.

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Side effects: See propantheline. Also, fatigue, chest pain, peripheral edema, xerophthalmia, and paresthesia.

Contraindications: See propantheline, children.

Caution: See propantheline

Interaction: See propantheline

Dosage: Oral, 2 mg twice daily may reduce to 1 mg twice daily to minimize side effects.

Preparation: Oral, tolterodine tartrate immediate release.
– Oral modified (extended)—release for once daily dosing.

Trospium Chloride

Properties: This quaternary amine is a nonselective muscarinic antagonist. It is as effective as oxybutinin with better tolerability. It does not cross blood-brain barrier. Its profile of side effects, contraindications, and interactions are similar to tolterodine.

Dosage: Oral trospium chloride 20 mg twice daily.

Darifenacin

Properties: An antimuscarinic drug with high affinity for M_3 receptors. It is indicated in patients with urinary frequency, bladder overactivity, bladder instability, nocturnal enuresis, and postoperative bladder spasms.

Dosage: Adult over 18 years: 7.5 mg twice daily.

Botulinum A Toxin (Botox)

Properties: Botulinum toxin A blocks acetylecholine release at cholinergic synapses. Inhibition lasts from weeks to 3 to 4 months. The nerves recover only following sprouting. It is indicated in neurogenic detrusor overactivity.

Side effects: Distant muscle jitter, misplaced injection site, muscle paralysis, distant muscles paralysis, injection site burning sensation, allergic reaction, formation of antibodies to Botulinum A toxin, and fever.

Contraindication: Pregnancy, breastfeeding, and disorders of muscle activity

Interaction: Effect enhanced by aminoglycosides and nondepolarizing muscle relaxants.

Dosage: Botulinum A toxin injections, cystoscopic, at 20–30 sites within detrusor but excluding the trigone. Please see manufacturers guide for details.

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Desmopressin (DDAVP)

Properties: Desmopressin or 1-deamino-8-D-arginine vasopressin (DDAVP) is an antidiuretic peptide. It acts on V_2 receptors causing water conservation. Desmopressin is indicated for primary nocturnal enuresis in children. This peptide is quickly inactivated by trypsin on oral administration (only 0.15% absorbed).

Side effects: Desmopressin has little V_1-receptor-mediated vascular pressor or gastrointestinal side effects. Its major V_2-receptor-mediated side effect is water intoxication. Other side effects are headache, abdominal pain, nausea, and local effects on nasal passages (edema, rhinorrhea, epistaxis rhinitis, and ulceration) flowing nasal administration.

Contraindications: Renal failure, cardiac insufficiency, and other medical conditions requiring diuresis.

Caution: Excessive fluid intake, elderly, children below 7 years.

Interaction: Diuretic effect potentiated by carbamazepine, chlorpropamide, morphine, NSAIDs, and attenuated by ethanol.

Dosage: Oral: Desmopressin, oral—100–200 μg at bed time starting with lower doses and increasing only if not effective. Withdraw for one week and reassess after 3 months.

Intranasal: Desmopressin, intranasal 10–20 μg at bed time, also withdraw for 1 week and reassess following 3 months of treatment.

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Manual of Medical Treatment *in* UROLOGY

Manual of Medical Treatment in Urology is a product of many years of dedication by the contributors and the editors to avail the reading public with a concise guide to the uses of drugs in the treatment of afflictions in this surgical specialty–Urology.

The book is expected to serve as a manual to readers on various aspects of medical therapy for urological conditions, and will also provide accessible and handy office reference on drug choice, side effects and dosing.

Due to the dynamic nature of drug therapy, readers are advised to verify pharmacotherapeutic information from current evidence-based protocols and manufacturers' guide.



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Professor Mbibu authored over one hundred articles in peer-reviewed journals. He also served on the Editorial Boards of the Annals of the African Medicine and Nigerian Journal of Surgical Research.

He was examiner at both the Primary and Part II Final, in Urology, of the Faculty of Surgery of West African College of Surgeons. Until his death, Professor Mbibu was the head of Department of Surgery, Ahmadu Bello University and a visiting Consultant Urologist to Usmanu Danfodiyo University Teaching Hospital, Sokoto and Armed Forces Hospital, Nigeria.



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