Medical management of overactive bladder

Sidney B. Radomski, MD,[1] Jack Barkin, MD[2]

[1]University of Toronto, Toronto Western Hospital, Toronto, Ontario, Canada

[2]University of Toronto, Humber River Regional Hospital, Toronto, Ontario, Canada

RADOMSKI SB, BARKIN J. Medical management of overactive bladder. Can J Urol 2012;19(Suppl 1): 2-9.

Overactive bladder (OAB) with or without urinary incontinence is a common condition in both men and women. OAB has a significant impact on quality of life for most patients. In most cases, sophisticated testing is not required for a primary care physician to diagnose OAB and start treating a patient. Management of OAB requires behavioral modification and, if necessary, pharmacotherapy may be added. If a patient does not respond to treatment initiated by a primary care physician, then he or she should be referred to a specialist in OAB to undergo further investigations and treatments.

Key Words: pharmacotherapy, overactive bladder, behavioral modification

Introduction

Overactive bladder (OAB) may be defined as urgency—that is, a sudden, compelling, difficult-to-defer desire to pass urine —usually accompanied by frequency and nocturia and possibly accompanied by incontinence.[1] Frequency can be defined as a patient's perception that he or she is voiding too often during the day; nocturia can be defined as waking up one or more times a night to void; and urge incontinence is involuntary urine leakage immediately after or along with urgency.[1]

OAB can have a neurological cause, such as multiple sclerosis, or a non-neurogenic cause, such as lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH). It can be subdivided into "OAB dry" (with no incontinence) or "OAB wet" (with incontinence).[2] The prevalence of OAB in the general population is approximately 16%, according to two large studies.[2,3] These studies also reported that men had a higher prevalence of OAB dry and women had a higher prevalence of OAB wet.[2,3] OAB wet is often related to bladder instability or involuntary detrusor contractions of neurogenic or myogenic origin. In urodynamic testing, this can be seen as an unwanted or uncontrollable bladder contraction. The prevalence of OAB increases with age in both men and women, but this age-related increase is more pronounced in women.[2,3] Both types of OAB have a significant impact on quality of life.[4] The impact on quality of life from OAB appears to be the same as or even greater than that from diabetes.[4-6]

Clinical assessment and diagnosis

Many other diseases have symptoms that mimic those of OAB, so other causes of LUTS, such as urinary tract infections (UTIs), need to be excluded before making

Address correspondence to Dr. Sidney B Radomski, Toronto Western Hospital (University Health Network), 399 Bathurst Street, MP8-304, Toronto, Ontario M5T 2S8 Canada

TABLE 1. **Causes of lower urinary tract symptoms other than overactive bladder**

- Urinary tract infection (recurrent)
- Interstitial cystitis
- Bladder cancer
- Excessive fluid intake and output
- Urinary retention
- Benign prostatic hyperplasia
- Urethral strictures
- Bladder stones
- Chronic prostatitis
- Constipation
- Medications

a diagnosis of OAB, see Table 1.[7] The clinician needs to determine the presence (or absence), frequency, severity, bother, and effect on quality of life of OAB symptoms in a patient.[8] A basic patient evaluation for OAB includes taking a history, performing a physical exam, and making appropriate clinical investigations, see Table 2.[9] The clinical investigations should at least include a urinalysis and an assessment of bladder emptying, which can be done by either palpating or doing an ultrasound scan of the lower abdomen.[8] A simple voiding diary, in which a patient lists the number of voids, time of day, and general fluid intake, for about 3 days, can be very helpful to assess daytime and nighttime voiding frequency.

In practical terms, voiding frequency is considered abnormal if an individual voids more than seven or eight times a day. However, according to the International Continence Society (ICS) guidelines, voiding frequency is considered abnormal if a patient feels he or she voids too often during the day.[1] Nocturia is generally considered abnormal if the patient voids more than once a night. Fluid intake has a significant impact on frequency and nocturia. Increasing fluid intake after supper may increase nighttime voids.

TABLE 2. **Basic evaluation of overactive bladder**

- History (duration, severity, degree of bother, fluid and caffeine intake, medications, etc.)
- Physical exam (abdominal, pelvic, rectal exam)
- Urinalysis and urine culture
- Post-void residual urine volume
- Simple voiding diary

Patient history

Urgency and urge incontinence are relatively easy for the physician to assess. The physician can ask a patient questions such as "When you get the urge to void, can you easily put it off?" or "When you have the urge to void, can you make it to the bathroom in time or do you have urine leakage?" Urine leakage may also occur without warning or urgency, and the physician should ask about this. It is unclear why patients have no sensation of this type of urine leakage, but it is common. In many instances, OAB wet may be confused with stress incontinence. Stress incontinence is urine leakage that is directly associated with an increase in intraabdominal pressure, which can be caused, for example, by straining or heavy lifting. Urgency may coexist with stress incontinence.[8] About a third of patients with OAB have both conditions.[8]

In some cases, physical activity may provoke urgency incontinence due to an unstable bladder or due to a bladder contraction caused by an increase in abdominal pressure. This unwanted bladder contraction can be mistaken for stress incontinence, and at times it can be difficult to differentiate the two conditions. For example, in some patients, walking briskly, or just getting out of bed in the morning and putting their feet on the floor can provoke bladder contractions that can be mistaken for stress incontinence.

Physicians need to assess the duration of symptoms, and, if applicable, the type of leakage protection and number of pads/diapers that a patient uses per day. This can vary due to cost, patient preference, etc. Intake and timing of all fluids, especially caffeinated beverages (tea, coffee, hot chocolate) and alcohol, also needs to be assessed. If an individual has nocturia, then limiting fluid intake after dinner or before bed can be helpful.

Physicians also need to ask patients about other medical problems and medications that may be associated with urinary frequency, see Table 3. These include diabetes, blood sugar control, congestive heart failure, diuretic use, constipation, neurologic conditions, medications used to treat dementia, and interstitial cystitis.

If a patient is diabetic, good blood sugar control is important, since elevated blood sugar may cause diuresis and hence frequency. Patients, especially elderly ones, may be taking therapies for constipation that have anticholinergic effects and thus impact OAB.

Neurological conditions such as stroke, multiple sclerosis, or Parkinson's disease can affect the lower urinary tract. It is important to ask men about BPH or

TABLE 3. **Medical problems and medications that may lead to urinary frequency, urgency, retention or other signs of voiding dysfunction**

- Poor blood sugar control in diabetes
- Congestive heart failure
- Diuretic use
- Constipation
- Medications such as antihistamines, antidepressants, anticholinergics
- Neurological conditions (stroke, multiple sclerosis, Parkinson's disease)
- Benign prostatic hyperplasia, prostate cancer, pelvic prolapse
- Urinary tract infections, hematuria, lower urinary tract symptoms
- Interstitial cystitis

prostate cancer, and to ask women about gynecological surgery or obstetrical procedures. The physician also needs to assess patients for symptoms of or surgery for pelvic prolapse. He or she also needs to ask patients about any history of urinary tract infections (UTIs), hematuria, or other lower urinary tract symptoms or problems.

Medications used to treat dementia may affect the lower urinary tract and be in direct conflict with anticholinergics used to treat OAB. Furthermore, if a patient has any cognitive impairment or dementia, OAB medications may worsen his or her mental status.

An excellent mnemonic, DIAPERS, can be used to assess causes of transient incontinence, and this mnemonic is especially useful for elderly patients, see Table 4.[10]

OAB needs to be distinguished from a less common disorder, interstitial cystitis (IC), also called painful bladder syndrome (PBS). IC/PBS is characterized by suprapubic pain related to bladder filling, which is accompanied by other symptoms such as urinary frequency or nocturia, in the absence of any other disorder.[8] The main distinguishing feature in IC/PBS is the significant pain associated with urgency. IC/PBS is less common than OAB, and it is difficult to accurately diagnose this condition.

TABLE 4. **Causes of transient incontinence: "DIAPERS"**[10]

- **D**elirium
- **I**nfection (urinary)
- **A**trophy (vagina/urethra)
- **P**harmaceuticals
- **E**xcess urine output
- **R**estricted mobility
- **S**tool impaction

Physical examination

In patients with OAB, an examination of the lower abdomen should detect a distended bladder. Women should have a pelvic examination that is performed when they are in a supine position, and which looks for genitourinary atrophy, prolapse, and movement of the bladder and urethra (that occurs with straining and coughing, and causes leakage). Stress incontinence is best assessed when a patient has a comfortably full bladder, is in the standing position, and then coughs and strains. Lastly, a rectal exam should be performed in men to assess prostate size, consistency, and other rectal pathology and constipation.

Clinical investigations

Blood and urine tests

If renal dysfunction is suspected, patients should have blood drawn to determine serum creatinine and blood urea nitrogen levels. Drug dosage may need to be adjusted if the patient has severe renal failure.[11] A fasting serum glucose level should be obtained if a patient may have diabetes. Urinalysis and urine culture should be done at baseline to rule out UTI, hematuria, and proteinuria. Men may need to have a serum prostate-specific antigen (PSA) test.

Voiding diary and voiding questionnaires

A voiding diary, in which patients list the type, time, and volume of fluid they ingest, as well as the time of voiding and leakage events, can be very helpful. Either a simple or detailed voiding diary can be used, depending on the patient.

Patients can also fill in a validated questionnaire, such as the International Consultation on Incontinence Questionnaire (ICIQ) or the Overactive Bladder Questionnaire (OABq).[12] These can be used to assess the degree of symptom bother and the impact on

health-related quality of life from OAB. A patient can fill in this type of questionnaire in his or her physician's waiting room.

Imaging studies

In general, in OAB, imaging is only used to assess post-void residual (PVR) urine volume. Most urologists have a portable bladder scanner in their offices. Other physicians can generally easily order a pelvic ultrasound to assess PVR urine volume. Caution is needed when performing pelvic ultrasounds and PVR urine volume studies. Overfilling the bladder prior to a pelvic ultrasound can make it difficult for many individuals to empty their bladders completely, and hence, the test can give a false positive PVR urine volume. We recommend that patients be "comfortably full" for ultrasound tests to determine PVR urine volume. Generally, imaging the upper urinary tract is not necessary for patients with OAB, unless there is concern because the patient has hematuria, urinary retention, or possibly a "high pressure bladder." A "high pressure bladder" may occur in neurological conditions such as spinal cord injury, and it may cause hydronephrosis, renal scarring, or atrophy.

Other diagnostic tests

Cystoscopy: This test allows direct examination of the urethra and bladder with a thin, lighted telescope. Cystoscopy is not necessary for an initial patient work up for OAB or for the management of OAB. It is helpful when a patient has hematuria, or may have BPH, IC, a urethral stricture, a bladder stone, or a bladder tumor. This test is usually requested by a urologist or urogynecologist.

Urodynamic testing: This testing involves inserting small catheters into the bladder and rectum to assess bladder function upon filling and voiding, after instilling saline or, for video urodynamics, after instlling contrast material. It is the most sophisticated testing available to assess bladder function. For the initial patient work up and management of OAB, urodynamic testing is not necessary. It too is generally requested by a urologist, urogynecologist, or geriatrician. It is often performed in patients who do not respond to therapy for OAB and in patients with complex cases of incontinence (for example, mixed incontinence or a history of previous incontinence that was treated and has now recurred) or with prolapse surgery or radiation to the pelvis.

Management of OAB

The recommended initial management of OAB is conservative therapy with or without pharmacotherapy. If a patient fails to respond to this type of treatment that is initiated by a primary care physician, then, in general, he or she should be referred to a specialist such as a urologist, urogynecologist, or geriatrician who specializes in the treatment of OAB or voiding dysfunction.

Conservative management

Physicians should start by correcting processes that can be corrected: they should assess and treat a patient's UTI, elevated fasting blood sugar, constipation, and congestive heart failure. They should also instruct patients to avoid or limit consumption of caffeine (in food or drinks), alcohol, and salty foods. Excessive caffeine intake is an independent risk factor for detrusor overactivity, and the relationship may be dose dependent.[13] Fluid intake should not be excessive unless it is medically necessary (for example, if the patient has kidney stones). A 25% reduction in fluid intake has been shown to significantly reduce urgency, frequency, and nocturia, while increasing fluid intake has been shown to worsen frequency.[14] In general, consuming 2 to 2.5 liters of fluid per day is adequate. Keep in mind that fluids also include fruits, vegetables, salads, soups, cereal with milk, etc. The timing of fluid consumption is important if a patient has nocturia. Reducing consumption of fluids and caffeine after dinner will be helpful. Diuretics taken at bedtime will increase nocturia. Timed voiding (i.e., voiding every 3 to 4 hours) may also help prevent urgency and urge incontinence. Voiding every 3 to 4 hours and not delaying when the urge is present can reduce urine leakage due to urgency. However, when timed voiding is excessive, that is, every 1 to 2 hours, this can be just as bothersome for the patient. Lastly, weight loss in moderately and morbidly obese women has been shown to decrease incontinence.[15]

Bladder retraining

This includes two techniques: pelvic floor rehabilitation with biofeedback, and bladder drill techniques. The first technique involves using strengthened pelvic floor muscles to improve bladder control. A nurse or physiotherapist teaches patients how to do this. This therapy is often most effective in cases of stress incontinence, but it has been effective in cases of OAB.[15]

Bladder drill is a technique, a patient intentionally increases the length of time between urinating despite the need to void. This method attempts to retrain the bladder to lessen urgency and lengthen the time intervals between voids. In some cases, this may be helpful.

The benefit of bladder retraining is that it is relatively harmless. The disadvantages are that it is time consuming, there are no set protocols, results can be variable, trained therapists are often not readily available, and it can be costly.

Pharmacotherapy

In all instances, pharmacotherapy should be added to conservative and behavioral treatment. The best results occur when both pharmacotherapy and behavioral treatment are initiated.[16]

The main first-line medications for the treatment of OAB are anticholinergics (antimuscarinics). Hormone replacement therapies, tricyclic antidepressants, desmopressin, alpha blockers, and Botox injections have been used in certain cases.

Anticholinergics (antimuscarinics)

These are the mainstays of OAB treatment. The recommendations for their use are based on level 1, grade A evidence.[17] Numerous randomized placebo-controlled trials have confirmed the effectiveness of these drugs for OAB.[18-26] Most anticholinergics have very similar side effects, which include dry mouth, constipation, and dry eyes, see Table 5. Cognitive impairment is also of concern with some anticholinergic medications. Trospium (Trosec), solifenacin (Vesicare), and darifenacin (Enablex) do not appear to affect cognitive function.[24,27,28] Immediate-release and long-acting forms of oxybutynin have been shown to cause cognitive impairment.[29,30]

Cognitive effects of tolterodine appear to be low, due to the relatively low lipophilicity of this drug, which suggests that it has a limited, though small ability to penetrate into the CNS.[31] Thus it should be used with caution in elderly patients who have any cognitive deficit. Fesoterodine (Toviaz) also appears to have little effect on cognition in the elderly.[32] Both fesoterodine and tolterodine (Detrol) are metabolized to the active metabolite 5-hydroxymethyl tolterodine (5-HMT). However, tolterodine undergoes this conversion in the liver, whereas fesoterodine is converted by serum esterases, bypassing the liver. Thus, more reliable, consistent, and tighter therapeutic blood levels can be achieved with fesoterodine. The two drugs have virtually identical side-effect profiles at dosages of 4 mg. However, whereas in patients who do not respond to 4 mg of fesoterodine, dosages can be safely and effectively escalated to 8 mg, doubling the tolterodine dosage is contraindicated.[33]

In addition to the above-mentioned anticholinergics, which are in pill form, a long-acting oxybutynin topical gel (Gelnique) is now available. Because it is topical, it is not first metabolized through the liver, so it is safer in individuals who have any liver deficiency. In a 1 week randomized controlled study in healthy older adults, oxybutynin topical gel did not have any clinically meaningful effect on recent memory or other cognitive functions.[34] As well, the topical form has been reported to be associated with a lower incidence of dry mouth and constipation.

For more information about these newer anticholinergic therapies—fesoterodine and mirabegron (a selective, human beta- 3 adrenoreceptor agonist)—see the "Emerging Therapies" article by Barkin in this supplement.[35]

The effect of combining anticholinesterase drugs used for cognitive impairment with anticholinergic drugs for OAB is currently unclear.[36] The combination should be used with caution. The use of anticholinergics in older men with OAB is a special situation, since BPH may play a role. Good evidence suggests that the use of an alpha blocker and an anticholinergic can significantly improve LUTS in men with BPH.[37] However, it is important to make sure these men empty their bladders more completely and effectively, since urine retention, although not as common as once believed, can occur in older men who are taking anticholinergics.

Hormone replacement therapy

The use of hormone replacement therapy (including estrogen in oral or cream form) should be considered for women with genitourinary atrophy, but this therapy has little effect on decreasing incontinence.[38]

Tricyclic antidepressants

These have been used to treat OAB, but they are not first-line therapies. The exact mechanism by which they affect the bladder is unclear.[39] They are effective and have been used extensively to treat bedwetting in children.[40] They should be used with caution in the elderly, since they can cause confusion, drowsiness, and arrhythmias.[41,42]

Desmopressin

This oral, synthetic antidiuretic hormone, has been extensively used in children for nocturnal enuresis.[43] Desmopressin works to reduce urine production by increasing water reabsorption in the renal collecting ducts for up to an average of 10 hours. It is not first-line therapy for nocturia in adults, but it can be used to treat some adults. In elderly patients, however, the drug can cause hyponatremia that leads to congestive heart failure.[44,45] Therefore, the use of desmopressin is not generally recommended in the elderly.

TABLE 5. **Antimuscarinic medications for overactive bladder**

Name (Brand name)	Dosage and adjustments	Main side effects*,†
Darifenacin (Enablex)	7.5 mg-15 mg daily Dose should not exceed 7.5 mg in moderate hepatic impairment. Avoid use in severe hepatic insufficiency. Dose should not exceed 7.5 mg in those on potent CYP3A4 inhibitors.‡ Use with caution with other substrates of CYP2D6 that have a narrow therapeutic window (e.g., trycyclic antidepressants), since their clearance may be reduced	Dry mouth, constipation, low rate of cognitive impairment
Fesoterodine (Toviaz)	4 mg-8 mg daily Doses should not exceed 4 mg in severe renal impairment (CrCl < 30 mL/min) and those on potent CYP3A4 inhibitors;‡ should not be used in severe hepatic impairment	Dry mouth, constipation, dry eyes, low rate of cognitive impairment
Oxybutynin ER (Ditropan XL, Uromax)	5 mg-30 mg daily Not studied in renal or hepatic impairment	Dry mouth, constipation, blurred vision/dry eyes, and cognitive impairment
Oxybutynin gel 10% (Gelnique)	1 gram applied to skin daily Apply to abdomen, thighs or upper arms/shoulders. Rotate application sites. Not studied in renal or hepatic impairment	Skin irritation or pruritus, low incidence of dry mouth and constipation
Oxybutynin IR (Ditropan)	5 mg bid-qid Use with caution in patients with renal or hepatic disease	Significant dry mouth, constipation, and cognitive impairment
Oxybutynin transdermal patch (Oxytrol)	1 patch applied twice weekly (delivers 3.9 mg/day) Rotate application sites. Use with caution in patients with renal or hepatic impairment	Skin irritation or pruritus, low incidence of dry mouth and constipation
Solifenacin (Vesicare)	5 mg-10 mg daily Doses should not exceed 5 mg in severe renal impairment (CrCl < 30 mL/min) or moderate hepatic impairment, and those on potent CYP3A4 inhibitors;‡ should not be used in severe hepatic impairment	Dry mouth, constipation, blurred vision/dry eyes, low rate of cognitive impairment
Tolterodine (Detrol)	1 mg-2 mg bid Doses should not exceed 1 mg bid in patients with impaired hepatic function or renal impairment, and those on potent CYP3A4 inhibitors.‡	Dry mouth, constipation, blurred vision/dry eyes, and lower rate of cognitive impairment. Reports of worsening dementia when initiated in patients taking cholinesterase inhibitors for dementia
Tolterodine ER (Detrol LA)	2 mg-4 mg daily Doses should not exceed 2 mg daily in patients with impaired hepatic function or renal impairment, and those on potent CYP3A4 inhibitors.‡	Dry mouth, constipation, blurred vision, and lower rate of cognitive impairment Reports of worsening dementia when initiated in patients taking cholinesterase inhibitors for dementia
Trospium (Trosec [Canada], Sanctura and Sanctura XR [US])	20 mg bid, must be taken on an empty stomach (at least 1 hour before meals). Dose should not exceed 20 mg hs in patients ≥ 75 yrs or those with severe renal impairment (CrCl 15-30 mL/min). Not studied in moderate or severe hepatic dysfunction, or severe renal impairment with CrCl < 15 mL/min. Dose for extended release formulation [Sanctura XR; US only] is 60 mg daily (at least 1 hour before meals)	Dry mouth, constipation, blurred vision/dry eyes, possible lower rate of cognitive impairment

bid = twice a day; CrCl = creatinine clearance; ER = extended release; hs = at bedtime; IR = immediate release; qid = four times a day
*See individual product monographs for a complete list of side effects
†Cognitive impairment (confusion, dementia, delerium, etc.) more commonly observed in elderly patients
‡Examples of potent CYP3A4 inhibitors include ketoconazole, clarithromycin, erythromycin, ritonavir, verapamil, and others

Alpha blockers

These may be used to treat LUTS (including OAB) in men without obstruction due to BPH. This form of therapy may relieve many OAB symptoms without the need for anticholinergics.

Botox injection of the bladder wall

This has been successfully used in neurogenic OAB and non-neurogenic OAB.[46,47] Recently, Botox injections into the bladder have been approved by both the US Food and Drug Administration and Health Canada for patients with neurogenic OAB associated with multiple sclerosis or spinal-cord injury. Botox injection has drawbacks, including loss of effectiveness after 3 to 9 months, possible spread of the toxin effects, and cost. Tachyphylaxis does not appear to be a concern with Botox.

Other therapy

Neuromodulation, in the form of peripheral posterior tibial nerve stimulation and sacral neuromodulation, has been used in patients who have intractable OAB.[48-51]

Conclusion

OAB is common and affects both men and women. Patients can have OAB dry or OAB wet. In most cases, a patient history including a short voiding diary, a physical examination, and some simple blood and urine tests are all that are needed to diagnose a patient with OAB and begin treatment for this condition. A combination of behavioral therapy plus medication (an anticholinergic agent), which is easily and appropriately initiated by the primary care physician, is the best initial treatment. If this treatment fails, then the patient should be referred to a urologist, urogynecologist, or geriatrician who specializes in OAB. At that point, more sophisticated tests such as cystoscopy or urodynamics may be considered, and patient management may require more advanced treatments.

Disclosure

Dr. Sidney B. Radomski is on advisory boards for Astellas, Pfizer, Allergan and Lilly.
Dr. Jack Barkin has been a clinical investigator, speaker and medical advisory board member and consultant for Abbott, Lilly, Bayer, Paladin, Watson Pharma, Bayer, AstraZeneca , Astellas, Solvay, Pfizer and Triton. □

References

1. Abrams P, Cardozo L, Fall M et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Subcommittee of the International Continence Society. *Neurourol Urodyn* 2002;21(2):167-178.
2. Stewart WF, Van Rooyen JB, Cundiff GW et al. Prevalence and burden of overactive bladder in the United States. *World J Urol* 2003; 20(6):327-336.
3. 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;87:760-766.
4. McGhan WF. Cost effectiveness and quality of life considerations. *Am J Manag Care* 2001;7(Suppl 2):S62-S75.
5. Komaroff AL, Fagioli LR, Doolittle et al. Health status in patients with chronic fatigue syndrome and in general population and disease comparison groups. *Am J Med* 1996;101(3):281-290.
6. Kobelt G. Economic consideration and outcome measurement in urge incontinence. *Urology* 1997;50(suppl 6A):100-107.
7. Abrams P, Cardozo L, Khoury S, Wein A. Incontinence. The Third WHO International Consultation on Incontinence, Health Publications, 2005.
8. Abrams P, Drake M. Overactive Bladder. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, ed. Campbell-Walsh Urology 9th edition, Philadelphia: Saunders Elsevier, 2007: 2079-2090.
9. Barkin J. Overactive bladder. *Can J Urol* 2011;18(Suppl 1):8-13.
10. Resnick NM: Voiding dysfunction in the elderly. In: Yalla SV, McGuire EJ, Elbadawi A, Blaivas JG, ed. Neurourology and Urodynamics: Principles and Practice, New York: Macmillan Publishing Company; 1988:303-330.
11. Herschorn S, Bruschini H, Comiter C et al. Surgical treatment of stress incontinence in men. *Neurourol Urodyn* 2010;29(1):179-190.
12. Coyne K, Revicki D, Hunt T et al. 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.
13. Arya LA, Myers DL, Jackson ND. Dietary caffeine intake and the risk for detrusor instability: a case-control study. *Obstet Gynecol* 2000;96(1):85-89.
14. Hashim H, Abrams P. How should patients with an overactive bladder manipulate their fluid intake? *BJU Int* 2008;102(1):62-66.
15. Abrams P, Cardozo L, Khoury S, Wein A (editors). Incontinence. 4th International Consultation on Incontinence, Paris July 5-8, 2008. Paris: Health Publication Ltd, 2009.
16. Burgio K L, Locher JL, Goode PS. Combined behavioral and drug therapy for urge incontinence in older women. *J Am Geriatr Soc* 2000;48(4):370-374
17. Andersson K-E, Wein AJ. Pharmacologic Management of Storage and Emptying Failure. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, ed. Campbell-Walsh Urology 9th edition, Philadelphia: Saunders Elsevier, 2007: 2091-2123.
18. Zinner N, Gittelman M, Harris R, Trospium Study Group et al. Trospium chloride improves overactive bladder symptoms: a multicenter phase III trial. *J Urol* 2004;171(6 Pt 1):2311-2315.
19. van Kerrebroeck P, Kreder K, Jonas U et al. Tolterodine once daily: superior efficacy and tolerability in the treatment of overactive bladder. *Urology* 2001;57(3):414-421.
20. Andersson KE, Appell R, Awad S et al. Pharmacological treatment of urinary incontinence. In: Abrams P, Khoury S, Wein A, ed. Incontinence, 2nd International Consultation on Incontinence, Plymouth, UK: Plymbridge Distributors; 2002: 479-511.
21. Andersson KE, Appell R, Cardozo L et al. Pharmacological Treatment of Urinary Incontinence. In: Abrams P, Cardozo L, Khoury S, Wein A, ed. Incontinence, 3rd International Consultation on Incontinence, Plymouth, UK: Health Publications; 2005.

22. Chapple C, Steers W, Norton P et al. A pooled analysis of three phase III studies to investigate the efficacy, tolerability and safety of darifenacin, a muscarinic M3 selective receptor antagonist, in the treatment of overactive bladder. *BJU Int* 2005;95(7):993-1001.
23. Cardozo L, Lisec M, Millard R et al. Randomized, double-blind placebo controlled trial of the once daily antimuscarinic agent solifenacin succinate in patients with overactive bladder. *J Urol* 2004;172(5 Pt 1):1919-1924.
24. Haab F, Cardozo L, Chapple C, Ridder AM, Solifenacin Study Group. Long-term open-label solifenacin treatment associated with persistence with therapy in patients with overactive bladder syndrome. *Eur Urol* 2005;47(3):376-384.
25. Diokno AC, Appell RA, Sand PK, OPERA Study Group et al. Prospective, randomized, 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.
26. Dmochowski RR, Sand PK, Zinner NR, Transdermal Oxybutynin Study Group et al. 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.
27. Lipton RB, Kolodner K, Wesnes K. Assessment of cognitive function of the elderly population: effects of darifenacin. *J Urol* 2005;173(2):493-498.
28. Todorova A, Vonderheid-Guth B, Dimpfel W. Effects of tolterodine, trospium chloride, and oxybutynin on the central nervous system. *J Clin Pharmacol* 2001;41(6):636-644.
29. Katz IR, Sands LP, Bilker W, DiFilippo S, Boyce A, D'Angelo K. Identification of medications that cause cognitive impairment in older people: the case of oxybutynin chloride. *J Am Geriatr Soc* 1998;46(1):8-13.
30. Kay G, Crook T, Rekeda L et al. Differential effects of the antimuscarinic agents darifenacin and oxybutynin ER on memory in older subjects. *Eur Urol* 2006;50(2):317-326.
31. Zinner NR, Mattiasson A, Stanton SL. Efficacy, safety, and tolerability of extended-release once-daily tolterodine treatment for overactive bladder in older versus younger patients. *J Am Geriatr Soc* 2002;50(5):799-807.
32. Paguria D, O'Conner RC, Guralnick ML. Antimuscarinic drugs: review of the cognitive impact when used to treat overactive bladder in elderly patients. *Curr Urol Rep* 2011;12(5):351-357.
33. Herschorn S, Swift S, Guan Z et al. Comparison of fesoterodine and tolterodine extended release for the treatment of overactive bladder: a head-to-head placebo-controlled trial. *BJU Int* 2010;105(1):58-66.
34. Kay GG, Staskin DR, Macdiarmid S, McIlwain M, Dahl NV. Cognitive effects of oxybutynin chloride topical gel in older healthy subjects: a 1-week, randomized, double-blind, placebo- and active-controlled study. *Clin Drug Investig* 2012;32(10):707-714.
35. Barkin J, Folia. Emerging therapies. *Can J Urol* 2012;19(Suppl 1): 49-53.
36. Wagg A, Verdejo C, Molander U. Review of cognitive impairment with antimuscarinic agents in elderly patients with overactive bladder. *Int J Clin Pract* 2010;64(9):1279-1286.
37. Kaplan SA, Roehrborn CG, Rovner ES, Carlsson M, Bavendam T, Guan Z. Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder: a randomized controlled trial. *JAMA* 2006;296(19): 2319-2328.
38. Hendrix SL, Cochrane BB, Nygaard IE et al. Effects of estrogen with and without progestin on urinary incontinence. *JAMA* 2005; 293(8):935-948.
39. Andersson KE. Treatment of overactive bladder: other drug mechanisms. *Urology* 2000;55(5A Suppl 1):51-57.
40. Glazener CM, Evans JH, Peto RE. Tricyclic and related drugs for nocturnal enuresis in children. *Cochrane Database Syst Rev* 2003;3: CD002117.
41. Resnick NM. Urinary incontinence. *Lancet* 1995;346(8967):94-99.
42. Resnick NM, Yalla SV. Geriatric Incontinence and Voiding dysfunction. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, ed. Campbell-Walsh Urology 9th edition, Philadelphia: Saunders Elsevier, 2007:2305-2321.
43. Norgaard JP, Rittig S, Djurhuus JC. Nocturnal enuresis: an approach to treatment based on pathogenesis. *J Pediatr* 1989;114(4 Pt 2):705-710.
44. Robson WL, Norgaard JP, Leung AK. Hyponatremia in patients with nocturnal enuresis treated with DDAVP. *Eur J Pediatr* 1996; 155(11):959-962.
45. Schwab M, Ruder H. Hyponatraemia and cerebral convulsion due to DDAVP administration in patients with enuresis nocturna or urine concentration testing. *Eur J Pediatr* 1997;156(8):668.
46. Herschorn S, Gajewski J, Ethans K et al. Efficacy of botulinum toxin A injection for neurogenic detrusor overactivity and urinary incontinence: a randomized, double-blind trial. *J Urol* 2011;185(6):2229-2235.
47. Dmochowski R, Chapple C, Nitti VW et al. Efficacy and safety of onabotulinumtoxinA for idiopathic overactive bladder: a double-blind, placebo controlled, randomized, dose ranging trial. *J Urol* 2010;184(6):2416-2422.
48. Peters KM, Macdiarmid SA, Wooldridge LS et al. Randomized trial of percutaneous tibial nerve stimulation versus extended-release tolterodine: results from the overactive bladder innovative therapy trial. *J Urol* 2009;182(3):1055-1061.
49. Vandoninck V, Van Balken MR, Finazzi Agró E et al. Posterior tibial nerve stimulation in the treatment of urge incontinence. *Neurourol Urodyn* 2003;22(1):17-23.
50. Schmidt RA, Jonas U, Oleson KA et al. Sacral nerve stimulation for treatment of refractory urinary urge incontinence. Sacral Nerve Stimulation Study Group. *J Urol* 1999;162(2):352-357.
51. van Kerrebroeck PE, van Voskuilen AC, Heesakkers JP et al. Results of sacral neuromodulation therapy for urinary voiding dysfunction: outcomes of a prospective, worldwide clinical study. *J Urol* 2007;178(5):2029-2034.