



Pharmacologic Therapy of Lower Urinary Tract Dysfunction

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Introduction

Pharmacologic therapy, a primary treatment of urinary urge incontinence and detrusor overactivity, is also important in the treatment of other urinary disorders including stress incontinence, nocturnal enuresis and nocturia, and voiding dysfunction. The purpose of this chapter is to highlight the role that pharmacotherapy plays in the treatment of patients with lower urinary tract dysfunction.

Pharmacologic agents often produce statistically significant changes in urodynamic parameters; however, this may not always translate into clinically significant improvement.¹ In most drug trials, a significant placebo effect is seen. Therefore, when evaluating the efficacy of pharmacologic agents for the treatment of incontinence and other urogynecologic disorders, it is important to rely most heavily on evidence from random-

ized placebo-controlled trials. Other shortcomings of some currently available data, including small numbers of patients, short follow-up, variable outcome measures, and non-generalizable study populations, must be kept in mind when evaluating the effectiveness of pharmacologic treatment of urogynecologic conditions.

Estrogen

Given that many women first notice urinary incontinence in their 40s and 50s, there has been considerable interest in exploring the link between estrogen depletion related to menopause and urinary symptoms. There is ample biologic plausibility for such a link. In the embryo, the female urinary and genital systems develop from a common urogenital sinus. The urethra, bladder, trigone, and pubococcygeus muscle are richly supplied with estradiol receptors. Clinical studies have found that estrogen positively influences surrogate outcomes that are thought important in improving urinary symptoms. For example, estrogen improves the maturation

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tion index in the vagina and urethra, and raises the sensory threshold of the bladder during urodynamic investigations. In addition, estrogen affects collagen synthesis and degradation, and stimulates blood supply to the urethra. Further, several early uncontrolled studies found that estrogen improved bladder symptoms including leakage, nocturia, urgency, and frequency.²

However, the early promise of estrogen's therapeutic impact on the lower urinary tract has not been borne out by randomized, placebo-controlled trials. In a randomized double-blind placebo-controlled study of 83 hypoestrogenic women with either stress or urge incontinence, Fantl and colleagues found no differences in either objective or subjective treatment outcomes after cyclic estrogen replacement (conjugated equine estrogens and medroxyprogesterone in a cyclic fashion) versus placebo.³ After 3 months, there were no differences between the groups with regard to the number of incontinence episodes, volume of urine loss, standardized quality of life outcomes, or the patient's perception of clinical improvement. Similarly, Jackson and coworkers found equal improvement in 57 women with stress or mixed incontinence treated with estradiol valerate versus placebo.⁴

A large randomized trial of estrogen replacement therapy versus placebo in women with heart disease provided a look at the effect of estrogen plus progesterone on urinary incontinence.⁵ Of 1525 women with incontinence at baseline, the proportion of women whose incontinence improved after 4 years of estrogen (21%) was similar to that of women receiving placebo (26%). However, significantly more women receiving estrogen plus progesterone had worsened incontinence than did women receiving placebo (39% versus 27%, respectively).

Estrogen given locally, without progesterone, may have different effects. To date, there are no methodologically sound studies that carefully assess this question.

Of interest, there is emerging evidence that selective estrogen receptor modulators

(SERMs) may impact pelvic floor dysfunction in varying ways. In 6,926 women randomly assigned to either raloxifene or placebo, women receiving the SERM were less likely to undergo surgery for prolapse during the 3-year study period than women receiving placebo (0.7% versus 1.5%, respectively).⁶ In contrast, enrollment in an investigational study of levomefloxiene, a different type of SERM, was halted after 10 months. In the 2,924 women already enrolled, there was a marked increase in the incidence of urinary incontinence (17% in the study group, compared with 4% in the placebo group) and pelvic organ prolapse (7% versus 2%, respectively).⁷

Urge Incontinence

Motor innervation to the detrusor is via the parasympathetic nervous system, whose fibers travel in the pelvic nerve to the bladder wall. The primary receptors in the bladder are muscarinic type 2 and type 3 receptors. Pharmacologic agents that block the parasympathetic input to the detrusor have long been the mainstay of therapy for what is now called neurogenic and non-neurogenic detrusor overactivity (formerly known as detrusor instability) and urge urinary incontinence. Unfortunately, because muscarinic type 2 and type 3 receptors are not located exclusively in the bladder, antimuscarinic agents frequently cause side effects, which may preclude long-term use.

In a comprehensive review of the diagnosis and management of detrusor instability, Wall noted that belladonna was first proposed in 1936 as an agent to control urgency and frequency.⁸ Atropine was the first anticholinergic medication introduced, but because of its potency, severe side effects occurred, which led to the development of synthetic quaternary ammonium analogs.

Oxybutynin chloride is a tertiary amine that has multiple effects, including antispasmodic, local anesthetic, anticholinergic, and antihistaminic characteristics.⁸ When taken by mouth, oxybutynin is rapidly absorbed

and metabolized. In several randomized controlled trials of middle-aged patients, immediate-release oxybutynin was superior to placebo, reducing incontinence frequency by 15% to 56% over placebo rates.⁹ Immediate-release oxybutynin continues to be one of the most widely prescribed anticholinergic medications for the treatment of urge incontinence in the United States. While side effects with this medication are common, dangerous or irreversible side effects are not. In a review of 192 patients prescribed oxybutynin, 76% of patients noted side effects.¹⁰ The most common side effect was dry mouth, but dysphagia (difficulty in swallowing), stomach ulcers, blurred vision, diarrhea, constipation, abdominal distension, nausea, headache, dizziness, and drowsiness were also reported. Twenty-three percent of patients had side effects so unpleasant that they stopped taking the drug.

Some evidence suggests that oxybutynin may be less effective in elderly patients. In a short-term study, 24 incontinent, elderly, institutionalized patients with detrusor instability were randomly assigned in a double-blind fashion to placebo or oxybutynin, 5 mg per day.¹¹ This study found no clinically significant difference between either group. Side effects were also approximately equal between the two groups. A study that examined the efficacy of immediate-release oxybutynin in conjunction with bladder retraining for incontinent nursing home patients found that bladder retraining alone reduced the mean percentage of 2-hour checks that were wet from 43% to 32%; however, the addition of either placebo or oxybutynin did not result in any further reduction.¹²

In an attempt to decrease systemic side effects of the immediate-release form, oxybutynin has been administered as an intravesical agent. However, Kasabian et al found that half of the patients did not complete the study because of side effects (eg, dry mouth, flushing, recurring infections), or because of the inconvenience of catheter-

ization that was required for instillation of the agent.¹³ Conversely, in another study that randomized 52 women with frequency, nocturia, and urgency to either intravesical oxybutynin or placebo once daily for 12 days, the bladder was stable on cystometrogram in 82% of women that received oxybutynin, compared with no women in the placebo group.¹⁴ The women that received intravesical oxybutynin also had significantly fewer episodes of urinary frequency, both during the day and at night. In this study, the incidence and severity of side effects was minimal in patients treated with oxybutynin.

It is clear that side effects are a limiting factor in the effectiveness of anticholinergic medications. Tolterodine, introduced in 1998, is a "bladder selective" agent that shows a propensity for binding to muscarinic receptors in the bladder over those in the salivary gland. In women with overactive bladder, tolterodine was as effective as oxybutynin but was better tolerated.¹⁵ Tolterodine is available in immediate-release and extended-release formulations. The extended-release formulation is a once-daily capsule using a drug delivery system of soluble microspheres. As the outer layer of the microsphere dissolves, the drug is slowly released, resulting in a stable serum concentration over 24 hours. In a multicenter, double-blind, randomized, placebo-controlled trial in which extended-release tolterodine was compared with immediate-release tolterodine and placebo, there was 71% median reduction in urge incontinent episodes with the extended-release formulation, compared with 60% reduction with tolterodine immediate-release and 33% reduction with placebo.¹⁶ The incidence of dry mouth in this study was 23% for the extended-release formulation and 30% for the immediate-release.

An extended-release formulation of oxybutynin has been developed utilizing a unique osmotic delivery system. The OROS™ System (ALZA Corp., Mountain View, CA) consists of a semi-permeable

membrane enclosing a two-layer core. One layer contains oxybutynin chloride and the other, an osmotically active agent. As water from the gastrointestinal tract enters the capsule, the oxybutynin is hydrated to form a suspension. At the same time, the osmotic agent is also hydrated, and as it expands, it pushes the oxybutynin out of the capsule at a controlled rate through a tiny, laser-drilled orifice in the capsule membrane.¹⁷ This time-release formulation results in more of the oxybutynin released in the distal small intestine and colon. In a multicenter randomized study,¹⁸ 378 patients were randomly assigned to receive either extended-release oxybutynin 10 mg per day or immediate-release tolterodine 4 mg per day in 2 doses. In the patients on extended-release oxybutynin, the weekly number of urge incontinent episodes decreased from 25.6 to 6.1 episodes, whereas on immediate-release tolterodine, the number decreased from 24.1 to 7.8 episodes. There were no significant differences in dry mouth or other side effects.

Anticholinergic and antimuscarinic agents are relatively contraindicated in patients with narrow-angle glaucoma, as these agents may cause an increase in intraocular pressure, or in patients with significant cardiac arrhythmias.⁸

There has been some interest in using calcium channel blockers to treat detrusor instability. Calcium channel blockers have had extensive experimental use, but with the exception of terodiline hydrochloride, not wide clinical use. Terodiline is a secondary amine with both anticholinergic and calcium-antagonist properties. It initially looked like a promising agent for the treatment of detrusor instability and it was approved for sale in Europe.¹⁹ However, before its release in the United States, it was found to have a significant incidence of cardiac side effects, some of which resulted in death. Terodiline has been withdrawn from the market.

Other drugs infrequently used for detrusor instability include emepronium bromide

and flavoxate chloride. In scant studies, neither had substantial benefit over placebo.⁹ Ouslander and Sier conducted a review of drug trials for the treatment of geriatric incontinence over a 20-year period between 1965 and 1985.²⁰ These authors found that most of the studies used emepronium bromide and randomized double-blind placebo-controlled studies were few. Overall, the data were decidedly mixed. Three studies showed no improvement in symptoms when active drug was used, while in three other studies, some improvement was seen, albeit small.

Tricyclic antidepressants, such as imipramine, have multiple effects on the bladder, which may be beneficial in some patients. These agents possess variable antimuscarinic and anticholinergic properties, and block reuptake of amines at central nerve terminals. Imipramine does not have significant anticholinergic activity on bladder muscle.⁸ Thus, it appears that imipramine may exert its effect on the bladder primarily by direct antispasmodic and local anesthetic activity. In addition to the previously discussed anticholinergic side effects, tricyclic agents may also cause sedation, confusion, and drowsiness; therefore, use in older patients may be limited.

Lepor and Theune conducted a randomized double-blind study to determine whether terazosin (an alpha-blocker) was more effective than placebo in treating women with urinary urgency and frequency.²¹ There was no difference in the primary outcome measure, the American Urologic Association symptom score, between the 2 groups.

Giggle incontinence is most commonly seen in children and teenagers, although occasionally it may occur in adults. Classically, it has been thought to be a type of urge incontinence and therefore has been treated primarily with anticholinergic medications. However, Sher and Reinberg observed that laughter precipitated an alteration of muscle tone and suggested that giggle incontinence has a functional relationship to cataplexy

(abrupt attacks of muscular weakness and hypotonia triggered by an emotional stimulus such as mirth, anger, fear, or surprise).²² Cataplexy is a component of the narcoleptic syndrome complex, which sometimes responds to stimulant medication. These authors found that seven children (mean age 10.9 years) who were treated with methylphenidate reported complete resolution of their giggle incontinence.

Surprisingly few studies have addressed how well pharmacologic therapy for urge incontinence works long-term, outside of clinical trial settings. In a 5-year follow-up study of 50 women with detrusor instability, 12% were reported as cured at the time of follow-up; however, 129 changes in drug therapy had been made.²³ In another study that used symptom questionnaires, the medium-term efficacy of anticholinergic therapy (mostly oxybutynin) was evaluated in 256 women 6 months after initiation.²⁴ Only 18.2% continued drug treatment more

than 6 months, while 5.5% were “cured of symptoms.”

It is not clear whether this poor treatment effectiveness is a result of side effects, difficulty adhering to dosing schedules, lack of follow-up, cost, limited efficacy of the drugs themselves, or a combination of factors. It is thought that the newer, longer-acting medications discussed above may overcome some of these limitations, given that they are administered once daily and may be associated with fewer side effects. Indeed, in a small prospective cohort of women prescribed tolterodine, 20 of 28 women continued to take the medication 9 months after initiating therapy.¹⁸ However, a retrospective analysis of a pharmacy claims database found less adherence: only 32% of patients were still obtaining tolterodine refills 6 months after the first prescription.²⁵

Table 1 summarizes commonly used drugs and dosages used to treat urge incontinence.

TABLE 1. Commonly Used Medications for Urge Incontinence

Drug Generic and Brand Names	Oral Dose Range
Oxybutynin	
Ditropan ¹	2.5–5 mg three or four times a day (immediate release)
Ditropan syrup	1 tsp = 5 mg
Ditropan XL ²	5, 10 or 15 mg each day (extended release)
Hyoscyamine	
Levsin ³	0.125–0.25 mg 4 times a day
Levbid, Levsinex	1–2 twice a day
Levsin elixir	1 tsp = 0.125 mg
Levsin/SL	sublingual pill
Cystospaz ⁴	0.15–0.3 mg 4 times a day
Cystospaz-M	1 twice a day
Dicyclomine	
Bentyl ¹	20 mg 4 times a day
Propantheline	
Pro-Banthine ⁵	15–30 mg 4 times a day
Tolterodine	
Detrol	1–2 mg twice a day (immediate-release)
Detrol LA ⁶	4 mg each day (extended-release)

¹ Hoeschst Marion Rouseel, Kansas City, MO

² Alza Corporation, Mountain View, CA

³ Schwartz Pharma, Inc., Milwaukee, WI

⁴ PolyMedica Pharmaceuticals, Woburn, MA

⁵ Roberts Pharmaceutical Corp., Eatontown, NJ

⁶ Pharmacia & Upjohn, Kalamazoo, MI

Stress Incontinence

Most attempts at the pharmacologic treatment of stress incontinence have aimed to increase the alpha-adrenergic input to the urethra. As with other studies of pharmacologic therapy, results tend to be better in nonrandomized studies than in controlled trials. To date, pharmacologic therapy for stress incontinence appears more effective in women with milder degrees of stress incontinence. In a double-blind, placebo-controlled trial, women with mild to moderate stress incontinence treated with phenylpropranolamine (50 mg twice a day) had an increase in maximal urethral closure pressure and a decrease in the number of leaking episodes, compared with placebo.²⁶ Although the frequency of incontinence episodes in the treatment group decreased by 50%, no patients became completely continent. Adverse reactions in this group were few. However, because of recent reports of severe side effects including cardiac events, phenylpropranolamine is no longer marketed in the United States. While seemingly effective for mild degrees of stress incontinence, it is no longer part of our treatment recommendations.

In a small, double-blind, placebo-controlled crossover trial of norephedrine, Ek and colleagues found that symptoms of stress incontinence improved and the maximal urethral pressure and closure pressure increased.²⁷ Objective and subjective measures of improvement correlated well. While on norephedrine, 2 patients became completely continent while 12 patients reported reduced leakage. Nine women in the study reported no difference between medication and placebo.

Imipramine, discussed above for the treatment of urge incontinence, has also been used to treat stress incontinence. Unfortunately, prospective randomized controlled trials validating the apparent success rates of several small uncontrolled series are not available, and anecdotal clinical experi-

ence suggests that the success rate is significantly lower than reported.

Given that estrogen may enhance the sensitivity of alpha-adrenergic receptors in the bladder neck and urethra, several investigators have examined the clinical utility of combined estrogen and alpha-adrenergic therapy for the treatment of stress incontinence. Most studies of combination therapy show an improvement in symptoms; however, objective findings such as increases in urethral pressure are less consistent. Ahlström and coworkers treated 29 postmenopausal women with stress incontinence in a prospective trial with either estriol alone or combination therapy with estriol and phenylpropranolamine.²⁸ Overall, patients on combination therapy reported an improved clinical response compared with those on estriol alone. The group that received combination therapy had objective findings of higher maximum urethral closure pressure and increased vaginal cellular maturation. Similarly, Ek et al noted that patients treated with a combination of norephedrine and estradiol improved significantly more than patients on single-agent therapy.²⁹ Although in this trial the urethral closure pressure increased with combination therapy, it did not increase more than with norephedrine alone, nor did it increase significantly with estradiol alone. Conversely, Beisland and colleagues found that in an open, randomized crossover trial, estriol and phenylpropranolamine both acted individually to increase maximum urethral closure pressure.³⁰ However, the observed pressure transmission ratio did not change significantly. The findings reported in the previously mentioned studies generally note that combination therapy with estrogen and alpha-adrenergic agents provide symptomatic improvement, although the physiologic mechanism for this improvement is less well defined.

While the medications described previously have not had a major role in the treatment of stress incontinence both because of limited effect and unacceptable side effects, new serotonin and norepinephrine reuptake

inhibitors show promise. A large, randomized, placebo-controlled trial assessed the impact of duloxetine on stress incontinence in women.³¹ Five hundred fifty-three women between the ages of 18 and 65 years were randomly assigned to placebo or to 3 different doses of duloxetine. After 12 weeks, the median number of incontinent episodes decreased in all groups, with the greatest reduction in women taking the highest dose, 80 mg per day. In this group, the median incontinence frequency decreased by 64%, compared with 41% in women taking placebo. Five percent of women taking placebo discontinued treatment, compared with 15% of those receiving the highest dose of medication.

This substantial improvement rate noted in women taking placebo mimics that reported in other randomized trials of drug therapy. While this is in part due to the placebo factor itself, it also demonstrates the therapeutic effect of keeping a voiding diary, in itself an intervention as well as an outcome measure.

Nocturnal Enuresis and Nocturia

Medications that treat nocturia and nocturnal enuresis generally have one of three aims: to reduce nighttime urine output, to increase bladder capacity and reduce unstable bladder contractions, and to act centrally on sleep and micturition centers.

DDAVP (desmopressin) is an analog of arginine vasopressin and has been used extensively to treat children with nocturnal enuresis. Some studies suggest that it may also be useful in adults. DDAVP is available both as a nasal spray and as an oral preparation. The dose required when taken orally is approximately ten times greater because of the increased bioavailability of the nasal preparation. Complications associated with the DDAVP, although rare, include hyponatremia, particularly in patients with excessive fluid intake. Therefore, it is reasonable in

high-risk patients to measure serum sodium levels periodically.

In a double-blind, randomized multicenter study, patients between the ages of 12 and 45 years were given oral DDAVP in dosages of 200 and 400 μg per day.³² Reported side effects were minimal, occurring in only four patients, and included dizziness, edema, mood changes, and headache; there were no instances of hyponatremia. The authors noted that while some patients had an initial response to the 200 μg dose, many required an increase to 400 μg to maintain their response.

Valiquette et al evaluated the short-term use of DDAVP in a double-blind crossover trial of 17 patients with multiple sclerosis.³³ Patients maintained nighttime voiding diaries for the duration of the 6-week trial. DDAVP reduced the percentage of nights with nocturia from 97% to 66%. The average number of nocturia episodes decreased from 2.35 to 1.09 episodes, which resulted in an increase in maximal uninterrupted sleep hours from 3.74 to 5.77 hours. However, four of the seventeen patients stopped participation after developing hyponatremia.

Few clinical trials specifically investigate the use of anticholinergic medications to treat nocturia and nocturnal enuresis. Anecdotal experience supports a trial of a long-acting or extended-release form of an anticholinergic, taken approximately 1 hour before bedtime.

The most extensively studied medications for the treatment of nocturnal enuresis are tricyclic antidepressants, particularly imipramine. Proposed theories to explain the mechanism of action of tricyclic agents are alteration of sleep mechanism, anticholinergic effect, antidepressant effect, and effect on antidiuretic hormone excretion. The typical starting dose of imipramine is 25 mg at bedtime, which may be increased to 75 mg. In the elderly, imipramine should be used cautiously, as it increases the risk of hip fracture, presumably related to the side effect of orthostatic hypotension.³⁴

Hunsballe et al investigated the effect of imipramine on nocturnal urine output in patients between the ages of 15 and 37 years who complained of nocturnal enuresis.³⁵ Patients with enuresis had less concentrated urine than controls. In six of fifteen patients, imipramine exerted a marked antidiuretic effect, manifested by decreased urine output, reduced urine osmolality, lower excretion of sodium and potassium, and increased renal tubular reabsorption of urea. Based on these studies, the authors concluded that imipramine has a vasopressin-independent antidiuretic effect, which can be attributed primarily to increased alpha-adrenergic stimulation in the proximal renal tubules.

In a randomized, placebo-controlled trial comparing nighttime doses of placebo and 1 mg of bumetanide (a loop diuretic), bumetanide decreased nocturia episodes by 25% compared with placebo.³⁶

Table 2 demonstrates common medications for nocturia and nocturnal enuresis.

Voiding Dysfunction

Voiding dysfunction in women, albeit rare, may be caused by obstruction (either postoperative or secondary to prolapse), impaired detrusor contractility, or impaired urethral sphincter relaxation. Patients with voiding dysfunction require an in-depth evaluation before attempting therapy. At-

TABLE 2. Medications for Nocturia and Nocturnal Enuresis

Drug Generic and Brand Name	Bedtime Dose
Imipramine Tofranil ¹	25–75 mg
Doxepin Sinequan ²	50–75 mg
Desmopressin (DDAVP ³) Nasal spray (10 mcg per spray) Oral tablet ⁴	20–40 mcg 200–400 mcg

¹ Ciba Geneva Pharmaceuticals, Summit, NJ

² Pfizer Inc., New York, NY

³ Rhône-Poulenc Rorer Pharmaceuticals Inc., Collegeville, PA

⁴ FDA approved for central diabetes insipidus only

tempts at treating voiding dysfunction using pharmacologic therapy have met with inconsistent results.

Urinary retention is common, both postoperatively and postpartum. Bladder overdistention may damage the elastic properties of the bladder, creating voiding dysfunction. A number of medications have been used to treat this problem to decrease the duration of time that patients require catheterization. Agents used have included parasympathomimetic agents, which stimulate detrusor contraction, and alpha-adrenergic blockers, which decrease urethral resistance.

Tammela compared patients randomly assigned to receive phenoxybenzamine, carbachol, or placebo for postoperative urinary retention.³⁷ In the group that received phenoxybenzamine, only 17% of patients had persistent retention, compared with 49% in the carbachol group and 57% in the placebo group.

Stanton et al reported a minimal decrease in the time to resumption of spontaneous voiding following colposuspension in a group of 40 women treated with phenoxybenzamine, intravesical prostaglandin E₂, or bethanechol chloride.³⁸ However, oral diazepam, given as a nighttime sedative from the day before surgery until spontaneous voiding occurred, was effective in decreasing the time until spontaneous voiding from 12.2 to 10.2 days. Given that most recent case series of various anti-incontinence surgeries report a much shorter duration of dysfunctional voiding without pharmacologic therapy, the generalizability of this study to current practice is low.

References

- Wein AJ. Pharmacologic treatment of incontinence. *J Am Geriatr Soc.* 1990;38:317–325.
- Griebing TL, Nygaard IE. The role of estrogen replacement therapy in the management of urinary incontinence and urinary tract infection in postmenopausal women. *Endocrinol Metabol Clin North Am.* 1997;26:347–360.

3. Fantl JA, Bump RC, Robinson D, et al. Efficacy of estrogen supplementation in the treatment of urinary incontinence. The Continence Program for Women Research Group. *Obstet Gynecol.* 1996;88:745–749.
4. Jackson S, Shepherd A, Brookes S, et al. The effect of oestrogen supplementation on post-menopausal urinary stress incontinence: a double-blind placebo-controlled trial. *Br J Obstet Gynaecol.* 1999;106:711–718.
5. Grady D, Brown JS, Vittinghoff E, et al. The HERS Research Group. Postmenopausal hormones and incontinence: the Heart and Estrogen/Progesterone Replacement Study. *Obstet Gynecol.* 2001;97:116–120.
6. Goldstein SR, Neven P, Zhou L, et al. Raloxifene effect on frequency of surgery for pelvic floor relaxation. *Obstet Gynecol.* 2001;98:91–96.
7. Goldstein SR, Nanavati N. Adverse events that are associated with the selective estrogen receptor modulator levomefloxiene in an aborted phase III osteoporosis treatment study. *Am J Obstet Gynecol.* 2002;187:521–527.
8. Wall LL. Diagnosis and management of urinary incontinence due to detrusor instability. *Obs Gyn Surg.* 1990;45(Supp 11):1s–47s.
9. Haeusler G, Letitch H, van Trotsenberg M, et al. Drug therapy of urinary urge incontinence: a systematic review. *Obstet Gynecol.* 2002;100:1003–1016.
10. Baigrie RJ, Kelleher JP, Fawcett DP, et al. Oxybutynin: is it safe? *Br J Urol.* 1988;62:319–322.
11. Zorzitto ML, Jewett MAS, Fernie GR, et al. Effectiveness of propantheline bromide in the treatment of geriatric patients with detrusor instability. *Neurourol Urodyn.* 1986;5:133–140.
12. Ouslander JG, Blaustein J, Connor A, et al. Habit training and oxybutynin for incontinence in nursing home patients: a placebo-controlled trial. *J Am Geriatr Soc.* 1988;36:40–46.
13. Kasabian NG, Vlachiotis JD, Lais A, et al. The use of intravesical oxybutynin chloride in patients with detrusor hypertonicity and detrusor hyperreflexia. *J Urol.* 1994;151:944–945.
14. Enzensberger H, Helmer H, Kurz CH. Intravesical instillation of oxybutynin in women with idiopathic detrusor instability: a randomized trial. *Br J Obstet Gynaecol.* 1995;102:929–930.
15. Abrams P, Freeman R, Anderstrom C, et al. Tolterodine, a new antimuscarinic agent: as effective but better tolerated than oxybutynin in patients with an overactive bladder. *Br J Urol.* 1998;81:801–810.
16. Van Kerrebroeck P, Kreder KJ, Jonas U, et al for the Tolterodine Study Group. Tolterodine once-daily: superior efficacy and tolerability in the treatment of overactive bladder. *Urology.* 2001;57:414–421.
17. Portera SG, Lipscomb GH. Pharmacologic therapy for urinary incontinence and voiding dysfunction. *Clin Obstet Gynecol.* 1998;41:691–701.
18. Appell RA, Sand P, Dmochowski R, et al. Prospective randomized 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;76:358–363.
19. Fischer-Rasmussen W. Evaluation of long-term safety and clinical benefit of terodiline in women with urgency/urge incontinence. A multicentre study. *Scand J Urol Nephrol Suppl.* 1984;87:35–47.
20. Ouslander JG, Sier HC. Drug therapy for geriatric urinary incontinence. *Clin Geriatr Med.* 1986;2:789–807.
21. Lepor H, Theune C. Randomized double-blind study comparing the efficacy of terazosin versus placebo in women with prostatism-like symptoms. *J Urol.* 1995;154:116–118.
22. Sher PK, Reinberg Y. Successful treatment of giggle incontinence with methylphenidate. *J Urol.* 1996;156:656–658.
23. Aitchison M, Carter R, Paterson P, et al. Is the treatment of urgency incontinence a placebo response? Results of a five-year follow-up. *Br J Urol.* 1989;64:478–480.
24. Kelleher CJ, Cardozo LD, Khullar V, et al. A medium-term analysis of the subjective efficacy of treatment for women with detrusor instability and low bladder compliance. *Br J Obstet Gynaecol.* 1997;104:988–993.
25. Lawrence M, Guar DR, Benson SR, et al. Immediate-release oxybutynin versus tolterodine in detrusor overactivity: a popu-

- lation analysis. *Pharmacotherapy*. 2000;20:470-475.
26. Collste C, Lindskog M. Phenylpropanolamine in the treatment of female stress urinary incontinence. Double-blind placebo controlled study in 24 patients. *Urology*. 1987;30:398-403.
 27. Ek A, Andersson KE, Gullberg B, et al. The effects of long-term treatment with norephedrine on stress incontinence and urethral closure pressure profile. *Scand J Urol Nephrol*. 1978;12:105-110.
 28. Ahlström K, Sandahl B, Sjöberg B, et al. Effect of combined treatment with phenylpropanolamine and estriol, compared with estriol treatment alone, in postmenopausal women with stress urinary incontinence. *Gynecol Obstet Invest*. 1990;30:37-43.
 29. Ek A, Andersson KE, Gullberg B, et al. Effects of oestradiol and combined norephedrine and oestradiol treatment on female stress incontinence. *Zentralbl Gynakol*. 1980;102:839-844.
 30. Beisland HO, Fossberg E, Moer A, et al. Urethral sphincteric insufficiency in postmenopausal females: treatment with phenylpropanolamine and estriol separately and in combination. A urodynamic and clinical evaluation. *Urol Int*. 1984;39:211-216.
 31. Norton PA, Zinner NR, Talcin I, et al. Duloxetine versus placebo in the treatment of stress urinary incontinence. *Am J Obstet Gynecol*. 2002;187:40-48.
 32. Janknegt RA, Zweers HM, DeLaere KP, et al. Oral desmopressin as a new treatment modality for primary nocturnal enuresis in adolescents and adults: a double-blind, randomized, multicenter study. *J Urol*. 1997;157:513-517.
 33. Valiquette G, Herbert J, Maede-D'Alisera P. Desmopressin in the management of nocturia in patients with multiple sclerosis. A double-blind cross-over trial. *Arch Neurol*. 1996;53:1270-1275.
 34. Ray WA, Griffin MR, Schaffner W, et al. Psychotropic drug use and the risk of hip fracture. *N Engl J Med*. 1987;316:363-369.
 35. Hunsballe JM, Rittig S, Pedersen EB, et al. Single dose imipramine reduces nocturnal urine output in patients with nocturnal enuresis and nocturnal polyuria. *J Urol*. 1997;158:830-836.
 36. Pedersen PA, Johansen PB. Prophylactic treatment of adult nocturia with bumetanide. *Br J Urol*. 1988;62:145-147.
 37. Tammela T. Prevention of prolonged voiding problems after unexpected postoperative urinary retention: comparison of phenoxybenzamine and carbachol. *J Urol*. 1986;136:1254-1257.
 38. Stanton SL, Cardozo LD, Kerr-Wilson R. Treatment of delayed onset of spontaneous voiding after surgery for incontinence. *Urology*. 1979;13:494-496.