Treating Urge Incontinence:

The Role of the New Pharmacologic Agents

Angela C. Cafiero, PharmD, CGP, Martin Rosenberger, RPh, and Emily R. Hajjar, PharmD, BCPS

Urge incontinence (UI), an increase in urinary urgency and frequency which results in an involuntary loss of urine from the bladder,[1] is a common problem in the elderly. Chronic incontinence can predispose older AL residents to health risks—such as falls or skin problems—and/or social embarrassment.

Fortunately, this condition usually is reversible, and there is much that can be done to address UI and help seniors who have this problem to enjoy better health and quality of life. Ideal management of UI includes a combination of nonpharmacological and pharmacological strategies.

Why Worry about UI in ALFs?

Recognition and treatment of UI is important in assisted living facilities since it can lead to financial, social, and medical problems. Total costs of urinary incontinence not only include the direct costs of undergarments, catheters, and medications but also the indirect cost of nursing care. The cost of nursing care includes time spent changing incontinent elders, as well as medications administration costs. A 2001 study by the American College of Obstetricians and Gynecologists estimated direct costs due to incontinence in the United States at $16.3 billion. Nursing home admissions resulting in part from incontinence accounted for $2.4 billion in these direct costs.[2]

Socially, UI can cause residents to fear leaving their rooms or apartments and render them socially isolated. Medically, incontinence can lead to falls, infections such as urinary tract infections or skin infections, and the development of ulcers. Finally, UI can financially, socially, and medically impact residents and even necessitate them leaving the ALF for a nursing facility or other setting.

Physiology of the Bladder

Micturation is controlled by the autonomic nervous system and the parasympathetic and sympathetic nervous systems. These systems influence the detrusor muscle and sphincters of the bladder. A malfunction of these systems is a major contributor to UI. As the bladder fills and internal urine pressure increases past a certain threshold, reflex parasympathetic (cholinergic) nerve pathways are stimulated.[3] Acetylcholine is released by parasympathetic nerve fibers activating nicotinic and muscarinic receptors. There are at least five sub-classes of muscarinic receptors.[4] It is the stimulation of M3 muscarinic receptors on the detrusor muscle that leads to its contraction of the bladder and subsequent opening of the internal urethral sphincter. The M3 receptors also are located in the salivary glands and intestinal tract. The M2 receptors may be important in detrusor muscle contraction under certain pathologic conditions. Stimulation of the other muscarinic receptors is associated with the anticholinergic adverse effects. An ideal anticholinergic agent would be selective for the M3 receptors of the bladder.

In healthy individuals, sympathetic nerve fibers and/or voluntary signals from the central nervous system can prevent this automatic micturation reflex from occurring.[3] In AL residents with UI, the detrusor muscle becomes overactive due to abnormal neurologic stimulation. Certain disorders such as Parkinsonism, multiple sclerosis, stroke, dementia or other central nervous system disorders can lead to an overactive contractility of the detrusor muscle.[5] As a result, these residents feel a frequent need to void and may be unable to stop the leakage of urine.

Introduction to the Pharmacological Agents

Although non-pharmacological therapies such as lifestyle modifications, undergarments, and bladder training are an option in elders with UI, pharmacological therapy can be extremely beneficial in reducing the incidence of incontinence episodes. Due to the overstimulation of the cholinergic system on the detrusor muscle, anticholinergic agents have been the treatment of choice for UI. By antagonizing the acetylcholine responding muscarinic receptors, the detrusor muscle relaxes, thus decreasing involuntary urine loss. There are several anticholinergic agents available that vary in their affinity for the types of muscarinic receptors. The two older anticholinergic agents, oxybutynin and tolterodine, now are joined by darifenacin, solifenacin, and trospium in the class.

Table 1.
Anticholinergic Drugs

Drug	Dose (max dose)	Comments
Oxybutynin (Ditropan)	5mg BID-TID (20mg/day)	
Oxybutynin XL	5mg QD (30mg/day)	
Oxybutynin (Oxytrol)	1 patch (3.9mg/day) twice a week	replace patch every 3-4 days
Tolterodine (Detrol)	2mg BID (4mg/day)	dose reduction in moderate hepatic & renal impairment (2mg/day)
Tolterodine LA	4mg QD (4mg/day)	
Darifenacin (Enablex)	7.5mg QD (15mg/day)	dose reduction in moderate hepatic impairment (7.5mg/day)
Solifenacin (Vesicare)	5mg QD (10mg/day)	dose reduction in moderate hepatic & severe renal impairment (5mg/day)
Trospium (Sanctura)	20mg BID (20mg/day)	dosing interval should be daily in patients with Clcr <30mL/min

Anticholinergic agents vary in their incidence of adverse effects.

All of the anticholinergic agents have been proven to be effective in placebo-controlled trials. However, the agents vary in their incidence of adverse effects. They have been shown to decrease episodes of urge incontinence and the average number of micturitions per day and increase the volume voided per micturition. Comparison studies between the agents are limited, so superiority of one agent can vary between individuals. Table 1 details the anticholinergic agents.

Typical anticholinergic adverse effects seen with all the anticholinergic

agents include dry mouth, constipation, nausea, headache, blurred vision, dizziness, drowsiness, and dyspepsia. The new anticholinergic agents, darifenacin and solifenacin, are reported to be more selective to the muscarinic receptors of the bladder, therefore theoretically decreasing their incidence of adverse effects. Trospium also has less central nervous system effects as it is a quaternary amine which prevents its penetration into the CNS. The incidence of dizziness and drowsiness depends on the selectivity of the agent to the bladder and the ability of the agent to penetrate the blood-brain barrier. Oxybutynin appears to be less selective to the bladder and thus has the highest incidence of CNS adverse effects.[6,7] The occurrence of adverse effects can be increased with the addition of another medication that has anticholinergic properties.

All of the anticholinergic agents are susceptible to drug interactions but by different mechanisms. Oxybutynin, solifenacin, tolterodine, and darifenacin are metabolized by the cytochrome (CYP P450) liver enzyme system. Oxybutynin and solifenacin are metabolized by CYP 3A4, tolterodine primarily by CYP 2D6 (and by CYP 3A4 when CYP 2D6 is depleted) and darifenacin by both. These agents are prone to the drug interactions by inhibitors, which increase the anticholinergic levels (for example: ketoconazole, erythromycin). Because tolterodine and darifenacin have the potential to be metabolized by both P450 3A4 and P450 2D6, dose reduction may be necessary with concomitant 3A4 inhibitors. Trospium is metabolized through hydrolysis and, thus, does not have any drug interactions mediated by the CYP P450 system. However, it is excreted renally and can be susceptible to other drugs that compete for renal tubular secretion (for example, digoxin, metformin, morphine).

All of the anticholinergic agents are contraindicated in patients with urinary retention, gastric retention, uncontrolled narrow-angle glaucoma or a known hypersensitivity to the agent. These agents must be used with caution in patients with bladder outflow obstruction, gastrointestinal obstructive disorders or motility disorders, hepatic impairment, blurred vision, dizziness, drowsiness or in patients at risk of heat prostration.[8,9,10,11] All of the anticholinergic agents except darifenacin have a precaution or dose reduction in patients with renal impairment. Specific precautions are addressed under the individual agents.

Oxybutynin (Ditropan®, Ditropan XL®, Oxytrol®)

Oxybutynin, the first anticholinergic agent available for the treatment of UI, has played a key role in the treatment of this condition. Due to its non-specific anticholinergic binding to the muscarinic receptors, it has a high incidence of central and peripheral adverse effects. Because of its short half life, the immediate-release formulation is dosed several times a day. Therefore, an extended-release formulation was created.

Although non-pharmacological therapies such as lifestyle modifications, undergarments, and bladder training are an option in elders with UI, pharmacological therapy can be extremely beneficial in reducing incidence of incontinence episodes.

The extended-release formulation still resulted in anticholinergic adverse effects but much less than the immediate-release formulation. Its benefit lies in its reduced adverse effects and its convenience of once daily dosing. A large multicenter study comparing the efficacy and side effects of immediate-release oxybutynin with controlled-release oxybutynin found the incidence of xerostomia to be 87% and 68% respectively (p=0.04).[12] The researchers postulated that a "slower increase in plasma oxybutynin concentrations" or the "maintenance of even plasma concentrations" may reduce the occurrence of dry mouth in the extended release formulation.

In 2003, the Food and Drug Administration (FDA) approved a transdermal formulation of oxybutynin (Oxytrol®). This agent can be worn 3-4 days before changing the patch. The application site should be rotated during each application amongst the abdomen, hip or buttock. Unlike the other anticholinergic agents, the transdermal patch may have application site adverse effects (pruritus, erythema). In ALFs, the transdermal oxybutynin patch can be advantageous for residents with dysphagia and those unable to tolerate the xerostomia. The patch formulation also minimizes the administration cost for daily medications. However, the transdermal formulation costs significantly more than generic immediate-release oxybutynin.

Tolterodine (Detrol®, Detrol LA®)

Tolterodine is the second anticholinergic medication FDA approved for UI. It appears to have a greater specificity for muscarinic receptors of the urinary bladder, thus reducing the amount of peripheral adverse effects such as dry mouth and constipation. Although tolterodine may be more specific for the bladder, patients may still experience anticholinergic side effects. It is available as an immediate-release and long-acting formulation. The long-acting formation has a lower

incidence of dry mouth as compared to the immediate-release formulation. Dose reduction to a daily dose of 2 mg is necessary in elders with moderate hepatic and renal impairment. The discovery of this agent with a decreased adverse effect profile allowed for another option in the treatment of UI.

Darifenacin (Enablex®)

In 2004, the FDA approved darifenacin, which has a high affinity and selectivity for M3 receptors. Although there is data indicating that darifenacin may be more selective to the bladder than to the salivary glands, dry mouth has been reported in 19% of patients taking 7.5 mg daily and 31% of patients taking 15 mg daily.[13] Darifenacin may have an increased occurrence of constipation over placebo. One study showed constipation in 15% of patients taking 7.5 mg daily and 21% in patients taking 15 mg daily. Darifenacin is administered once daily without regard to meals. Elders with moderate hepatic impairment need a dose reduction to a maximum dose of 7.5 mg a day. It is available as an extended-release tablet that may not be cut or crushed. This may be a disadvantage to those elders receiving their medications through a gastric tube. Darifenacin is less likely to cause dizziness and drowsiness since it is less able to penetrate the CNS due to its high selectivity for the M3 receptors.

Solifenacin (Vesicare®)

Solifenacin succinate is a non-selective muscarinic antagonist that appears, from animal studies, to have higher bladder selectivity than oxybutynin, tolterodine and darifenacin. Solifenacin is an extended-release agent that cannot be cut or crushed and is administered once daily without regard to meals. Dose reduction to 6 mg a day is necessary in elders with moderate hepatic impairment and severe renal impairment. Unlike other anticholinergic agents, solifenacin has the potential for prolongation of the QT interval of the electrocardiogram. Although this may be unlikely, elders should use solifenacin with caution because of the increased risk of QT prolongation or if they are concomitantly taking medications that prolong the QT interval such as fluoroquinolones.

Trospium (Sanctura®)

Although trospium is newly FDA approved agent in 2004 in the United States, it has been widely used in Europe for years. It has the highest affinity for all of the muscarinic receptors; however, its unique chemical structure provides an advantage. The trospium chemical structure is a hydrophilic, quaternary amine with a positive charge which prevents it from crossing the blood-brain barrier and allows it to be slowly absorbed from the gastrointestinal tract. This would be beneficial to elders who suffer from anticholinergic induced cognitive impairment. The quaternary structure avoids metabolism by the P450 enzyme system. Trospium is administered twice daily one hour before meals or on an empty stomach since food significantly reduces absorption. Trospium has a potential advantage over the other anticholinergic agents because it has fewer central and peripheral anticholinergic effects and drug interactions.

Unfortunately, the cost associated with treating a complication from untreated UI is more than the cost of the medication, so pharmacologic treatment often is used.

Selection of an Anticholinergic Medication for ALF Patients

The overall cost of the treatment of UI in ALF can be quite considerable given the increasing medication and administration costs. Unfortunately, the cost associated with treating a complication from untreated UI is more than the cost of the medication, so pharmacologic treatment often is used. The older anticholinergic agents are available generically, which can decrease the medication cost. Immediate-release oxybutynin and tolterodine are available generically and, thus, lend a cost savings option to treatment. Generic immediate-release oxybutynin ranges approximately 15% to 30% of the cost of the brand name products.[14]

In ALF, the cost of medication administration by the nurses must be taken into consideration. Medications given once daily can decrease nursing-assisted administration labor needed compared to more frequently dosed medications. Oxybutynin XL, tolterodine LA, darifenacin, and solifenacin are available as once daily agents. These agents enhance compliance for those elders who administer the medication themselves. The use of the transdermal oxybutynin patch decreases administration costs. However, the agent itself is estimated to cost approximately $100 per month.[14]

The selection of an anticholinergic agent can be based on the health care providers' experience, cost of the medication, compliance with therapy, adverse effect profile, and previous trial of an agent. Elders respond differently to some agents, so lack of efficacy of one agent does not necessarily mean failure of the entire class of anticholinergics.

Conclusion

Anticholinergic agents have been proven to be efficacious for the treatment of UI. The differences

(continued on page 30)

activity and structured routines, recreational therapists address psychosocial issues and adjustment as well.

Do these interventions really work? Research has demonstrated clear benefits and positive outcomes in improved physical, cognitive, social, communication, and emotional functioning, as well as in leisure involvement. Recreational therapy interventions have been shown to improve levels of active engagement and interaction and increase quality of life.

In the areas of physical functioning, the benefits of recreational therapy include fall and injury reduction; improved balance, endurance, and posture; and increased flexibility, strength, range of motion, and ambulation. As for cognitive functioning, this type of therapy has been shown to enhance memory, attention span, awareness of surroundings, and alertness. Recreational therapy also has been demonstrated to result in improved mood, decreased feelings of loneliness, increased relaxation and coping strategies, reduced symptoms of depression, and reduced agitation and disturbing behaviors in demented residents.

It is important to note that recreational therapy is not covered by Medicare in assisted living. However, it can be written into HMO and other health care/long term care insurance contracts. ALFs also may want to consider including a fee for such services in their costs to residents/families. The plus side of this is that they can promote these services in their marketing materials. By explaining how recreational therapy benefits residents and enables them to age in place, facilities can distinguish themselves from the competition.

Even if residents/families or facilities have to pay for recreational therapy services, the benefits far outweigh the costs. By maximizing independence and functioning, these interventions result in decreased nursing and caregiving time. By preventing and/or reducing falls and wandering, recreational therapy services also can help avoid injuries and hospitalizations. At the same time, by documenting the recreational therapy services they utilize, facilities gain a valuable risk management tool that can help reduce or eliminate litigation and liability costs.

To find a recreational therapist in your region or to learn more about recreational therapy, check out these Web sites: nctrc.org, atra-tr.org, and recreationtherapy.com. ALC

Dawn De Vries, MPA, CTRS, is Director of Continuing Education and Research at the American Therapeutic Recreation Association in Alexandria, VA.

Urge Incontinence

(continued from page 23)

between the agents lie in their specificity to the muscarinic receptors and their adverse effect profile. If the efficacy of an individual agent is insufficient or adverse effects become intolerable, utilization of another anticholinergic agent is reasonable. The ideal agent is patient specific but can be selected on its administration, medication costs, and adverse effect profile.

In the ALF environment, treatment of UI outweighs the risks of suffering adverse effects from anticholinergic therapy; and the results of treatment are positive. Residents are happier, more independent, and confident enough to be active and involved in the facility. And staff members are less stressed and have more time to interact with and help residents in other areas of care. ALC

Angela C. Cafiero, PharmD, CGP, is Assistant Professor of Clinical Pharmacy at the University of the Sciences in Philadelphia and the Philadelphia College of Pharmacy. Martin Rosenberger, RPH is a Doctor of Pharmacy student at the Philadelphia College of Pharmacy. Emily R. Hajjar, PharmD, BCPS, is Assistant Professor of the Sciences in Philadelphia and Philadelphia College of Pharmacy.

References

1. Abrams P, Cardozo L, Fall M, et al. Standardisation sub-Committee of the International Continence Society. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. *Urology.* 2003; 61(1):37-49.

2. Wilson L, Brown JS, Shin GP, et al. Annual direct cost of urinary incontinence. *Obstet Gynecol* 2001;98(3):398-406.

3. Vander AJ, Sherman JH, Luciano DS. The kidneys and regulation of water and inorganic ions. In: Prancan KM, Bradley JW, editors. *Human Physiology.* 6th ed. New York: McGraw-Hill, Inc.;1994.

4. Kershen RT, and Hsieh M. Preview of new drugs for overactive bladder and incontinence: darifenacin, solifenacin, trospium and duloxetine. *Current Urology Reports.* 2004;5:359-367.

5. Newman DK, Giovannini D. The overactive bladder: a nursing perspective. *Am J Nursing* 2002;102(6):36-46.

6. Ditropan XL (oxybutynin) Package insert. Ortho-McNeil Pharm.2004.

7. Hussar DA and Cafiero-Moroney, AC. Anticholinergic agents for overactive bladder. *The Drug Advisor.* 2005;4(3):1-12.

8. Sanctura (trospium). Package insert. *Esprit Pharm.*2006

9. Detrol (tolterodine) Package insert. Pharmacia & Upjohn Pharm.2003.

10. Enablex (darifenacin) Package insert. Novartis Pharm.2004

11. Vesicare (solifenacin) Package insert. Astellas Pharm.2005.

12. Harvey MA, Baker K, Wells GA. Tolterodine versus oxybutynin in the treatment of urge urinary incontinence: a meta-analysis. *Obstet and Gynecol* 2001;185(1):56-61.

13. Haab F, Stewart L, Dwyer P. Darifenacin, an M3 selective receptor antagonist, is an effective and well-tolerated once-daily treatment for overactive bladder. *Eur Urol.* 2004; 45(4): 420-9.

14. Dull P. Transdermal oxybutynin (oxytrol) for urinary incontinence. *Am Fam Physician* 2004;70(12):2351-2356.