Anticholinergic Treatment Options for Urinary Incontinence

James Kilgus, RPh
FL ASCP meeting
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Defining Urinary Incontinence (UI)

- Urge incontinence
  - Associated with the urge to urinate
  - A subset of overactive bladder (OAB)
- Stress incontinence
  - Urinary leakage with increased bladder pressure related to coughing, sneezing, laughing
- Mixed incontinence
  - Combination of urge and stress incontinence
- Overflow incontinence
  - An overfilling of the bladder
- Functional
  - Incontinence caused by factors unrelated to storage or outlet of urine, eg, dementia

NIH Clinical Practice Guidelines: Urinary Incontinence in Adults: Acute and Chronic Management. *Clinical Practice Guidelines.* Number 2 (1996 update). AHCPR Publication No. 96-0682; March 1996.
Nitti VW. *Rev Urol.* 2002;4(suppl 4):S2-S6.

Urinary Incontinence Impact on LTC

—Second major reason for placement in LTC [1]
—An estimated 50% of residents have UI [2]
—Incontinence may develop after admission [3]
—Associated with significant morbidities [4]
- Pressure ulcers, UTI's, falls and fractures

1. Newman, D, et al. Managing and Treating Urinary Incontinence, Baltimore: Health Professions, 2002: In Press
2. Palmer MH, *J Wound Ostomy Continence Nurs.* 2002; .29: 4-5
3. Palmer MH, et al. *Res Nurs Health.* 1991: 14:405-412
4. Resnick NM. *Ger Urol.* 1996; 23:55-74

Costs of UI in Patients Over Age 65

• Diagnosis and treatment (behavioral, Rx, surgery)	$ 1.12 billion	4.4%
• Routine care (pads, reusable briefs, laundry, catheters)	$11.41 billion	44.5%
• Consequences (skin irritation, UTI, falls)	$ 4.7 billion	18.3%
• Additional hospital/institution	$ 8.4 billion	32.8%
Total direct costs	$ 25.6 billion	
• Indirect costs (loss of wages, etc)	$ .70 billion	
Total costs	$26.3 billion	

Wagner TH, Hu TW. *Urology.* 1998;51:355-361.

Economic Cost to LTC Facilities

- More than $5.7 billion in long-term care costs annually (1998 dollars)
- More than $5,400/patient-year 75% ($4,100) for routine care per patient-year (supplies, laundry)
- Annual cost ~ $714,000/100-bed facility

Wagner & Hu. *Urology.* 1998;51(suppl 3):355-361.

Importance of Managing UI

- Medical complications
  - Falls and fractures
  - Depression
  - Skin care issues, including pressure ulcers
  - UTI
- Quality of life (QOL)
  - Affects social interaction, self-esteem, and life satisfaction
  - Caregiver and family stress and burden

Lekan-Rutledge D. *Urol Nurs.* 2004;24:281-302.

Importance of Managing UI (cont)

- Medico-legal risk
  - Causal or presumptive connection of falls and fractures possibly contribute to "undermanaged" UI
- Regulatory issues
  - Section H of the Minimum Data Set
  - Quality Indicators
  - F-Tags
  - Resident Assessment Protocols (RAPs) for UI
  - State and federal survey issues

Prochoda KP. *JAMA*. 2002;3(Suppl 1):511-515.

Risk Factors for Residents With Incontinence

- Lifestyle
  - Morbid obesity
  - Smoking
  - Excessive fluid intake
- Transient causes
  - Drugs
  - Infection
  - Fecal impaction
  - Delirium
  - Psychological
  - Impaired mobility
- Neurological disorders
  - Stroke
  - Parkinson's disease
  - Dementia
  - Spinal cord

Crespi Lofton J. *J Am Pharm Assoc*. 2001;41(suppl 2):S3-S17. Newman DK. *The Urinary Incontinence Sourcebook*. Chicago, Ill: Lowell House. 1999:19-25.

Comorbidities Associated With Incontinence

- Multiple sclerosis
- Spinal cord injury
- Stroke
- Parkinson's disease
- Alzheimer's disease
- Diabetes
- Congestive heart failure
- Urinary retention
- Enlarged prostate
- Pelvic organ prolapse
- Tumors
- Bladder cancer
- Prostate cancer

DuBeau CE. *Urol Clin North Am*. 1996;23:11-18. Stewart WF et al. *World J Urol*. 2003;20:327-336. Merkelj I. *South Med J*. 2001;94:952-957. Dmochowski RR et al. *J Urol*. 2002;168:580-586.

Approaches to Drug Therapy Selection

- Define the type of urinary incontinence
  - Urge vs stress vs mixed vs overflow
  - Available agents FDA approved for urge incontinence
- Determine barriers to success within the facility
  - Caregiver/provider burden
  - Facility resources
- RAP Guidelines
  - Recommended therapies within the facility
- Determine patient characteristics and preferences
  - Comorbid conditions
  - Dysphagia or other swallowing disorders

Lee SY et al. *Geriatrics*. 2000;55(11):65-71. Thompson DL. *Urol Nurs*. 2004;24(4):305-313.

Goals of Urinary Incontinence Management

- Reduce wetting episodes
- Improve ADLs
- Reduce complications
- Reduce caregiver burden
- Reduce cost of direct and indirect continence care

Goals should be individualized based on underlying disease states and disabilities

Lekan-Rutledge D. *Urol Nurs*. 2004;24(4):281-302. Lekan-Rutledge D. *Am J Nursing*. 2003;103(3):36-46. Wagner TH, Hu TW. *Urology*. 1998;51:355-361.

Approved Pharmacological Options for Urge Incontinence

- Oral
  - —Oxybutynin
    - Ditropan - 5 mg
    - Ditropan XL - 5, 10, 15 mg
  - —Tolterodine
    - Detrol - 1, 2 mg
    - Detrol LA - 2, 4 mg
  - —Trospium (Sanctura) - 20 mg
  - —Solifenacin (Vesicare) - 5, 10 mg
  - —Darifenacin (Enablex) – 7.5, 15 mg
- Transdermal
  - —Oxybutynin (Oxytrol®) - 3.9 mg twice a week

Oral Agents

Oxybutynin Efficacy

	OXY-IR (n = 115)	OXY-ER (n = 111)
Incontinence episodes		
—No./wk	*19.5*	*18.9*
—Mean change from baseline	*-13.8*	*-14.5*

The difference between oxybutynin IR and oxybutynin ER fulfilled the criteria for comparable efficacy

* Ditropan XL (oxybutynin) prescribing information 2000

Oxybutynin ER* Adverse Events (%)

Dry mouth	60.8
Constipation	13.1
Headache	9.8
Somolence	11.9

* Ditropan XL (oxybutynin) prescribing information 2000

Tolterodine* Efficacy

	TOL-IR (n = 514) 2mg BID	TOL-CR (n = 507) 4mg QD
Incontinence episodes		
—No./wk	*23.2*	*22.1*
—Mean change from baseline	*-10.6*	*-11.8*
Micturitions		
—No./d	*11.1*	*10.9*
—Mean change from baseline	*-1.7*	*-1.8*
Void volume		
—mL	*137*	*141*
—Mean change from baseline	*+29*	*+34*

* Detrol (tolterodine) prescribing information 2002; Detrol LA (tolterodine) prescribing information 2004

Tolterodine* Adverse Events (%)

	TOL-IR (n = 986) 2mg BID	TOL-CR (n = 505) 4mg QD
Dry mouth	*35*	*23*
Constipation	*7*	*6*
Dizziness	*5*	*2*
Somnolence	*3*	*3*
Headache	*7*	*6*

* Detrol (tolterodine) prescribing information 2002; Detrol LA (tolterodine) prescribing information 2004

Trospium* Efficacy

	Placebo (n = 256)	Trospium (n = 253)
Urinary frequency/24 hours		
—Mean baseline	*12.9*	*12.7*
—Mean change from baseline	*-1.3 (0.2)*	*-2.4 (0.2)*
Urge incontinence episodes/week		
—Mean baseline	*30.1*	*27.3*
—Mean change from baseline	*-13.9 (1.2)*	*-15.4 (1.1)*
Void volume		
—Mean baseline	*156.6*	*155.1*
—Mean change from baseline	*7.7 (3.1)*	*32.1 (3.1)*

All p values < 0.05

* Sanctura (trospium) prescribing information 2004

Trospium* Adverse Events (%)

	Placebo	Trospium
Dry mouth	5.8	20.1
Constipation	4.6	9.6
Headache	2.0	4.2
Urinary retention	0.3	1.2

* Sanctura (trospium) prescribing information 2004

Solifenacin* Efficacy

	Placebo	5 mg/d	10 mg/d
Micturitions			
—Baseline	12.2	12.1	12.3
—Mean reduction/day	1.2	2.2	2.6
Incontinence episodes			
—Baseline	2.7	2.6	2.6
—Mean reduction/day	0.8	1.4	1.5
Void volume			
—Baseline	143.8	149.6	147.2
—Mean increase (mL)	7.4	32.9	39.2

* VESIcare (solifenacin) Prescribing Information. Yamanouchi, November 2004.

* P < 0.05 vs placebo

Solifenacin* Adverse Events (%)

	Placebo	Solifenacin 5 mg/d	Solifenacin 10 mg/d
Dry mouth (%)	4.2	10.9	27.6
Constipation	2.9	5.4	13.4
Blurred vision	1.8	3.8	4.8

*VESIcare (solifenacin) Prescribing Information. Yamanouchi, November 2004.

Darifenacin* Efficacy

	Placebo (n=164)	Darifenacin 7.5 mg/d (n=229)	Darifenacin* 15 mg/d (n=115)
Incontinence episodes			
—Median baseline	16.6	16.3	17.0
—Median change from baseline	- 7.6	- 9.0	- 10.4
Micturitions			
—Median baseline	10.1	10.1	10.1
—Median change from baseline	- 0.8	- 1.6	- 1.7
Void volume			
—Median baseline (ml)	162.4	160.2	151.8
—Median change from baseline	7.6	14.9	30.9

* P < 0.05 vs placebo

*Enablex (darifenacin) Prescribing Information. Novartis, December 2004.

Darifenacin* Adverse Events (%)

	Placebo (n = 388)	Darifenacin 7.5 mg/d (n = 337)	Darifenacin 15 mg/d (n = 334)
Dry mouth (%)	8.2	20.2	35.3
Constipation	6.2	14.8	21.3
Dyspepsia	2.6	2.7	8.4

* Enablex (darifenacin) Prescribing Information. Novartis, December 2004.

Possible Limitations of Oral Agents in Population

Elderly may have difficulty using oral medications

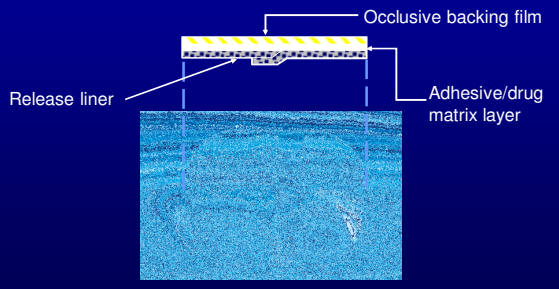
- May be at higher risk for dysphagia due to pathophysiological changes
- Dementia may reduce ability to chew and swallow when required
- Gastrointestinal disorders may limit bioavailability of medication

Zagaria MAE. *US Pharm.* 2005;1:30-39.

Transdermal Oxybutynin

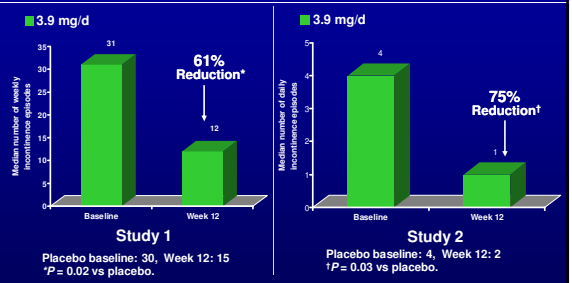
Oxybutynin Transdermal Delivery System (TDS)

3.9 mg/day, twice weekly



OXYTROL™ (oxybutynin transdermal system) Prescribing Information. February 2003.

Transdermal Oxybutynin Efficacy



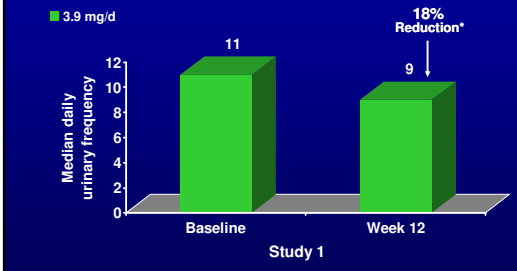
Placebo baseline: 30, Week 12: 15
*P = 0.02 vs placebo.

Placebo baseline: 4, Week 12: 2
†P = 0.03 vs placebo.

- 49% of subjects studied were aged 65 years or older
- 19% of patients studied were aged 75 years or older
- 50% reduction in placebo groups for both studies

OXYTROL® (Oxybutynin Transdermal System) Prescribing Information. February 2003. Dmochowski RR et al. *J Urol.* 2002;168:580-586.

Transdermal Oxybutynin Efficacy



Placebo baseline: 11
Week 12: 10
*P = 0.0313 vs placebo.

OXYTROL® (Oxybutynin Transdermal System) Prescribing Information. February 2003.

Transdermal Oxybutynin Safety

	Study 1		Study 2	
	TDS% (n = 125)	Placebo, % (n = 132)	TDS % (n = 121)	Placebo, % (n = 117)
App. site pruritus	16.8	6.1	14.0	4.3
Dry mouth	9.6	8.3	4.1	1.7
App. site erythema	5.6	2.3	8.3	1.7
Constipation	–	–	3.3	–
Diarrhea	3.2	2.3	–	–
Abnormal vision	–	–	2.5	–
App. site vesicles	3.2	–	–	–
App. site macules	–	–	2.5	–
App. site rash	–	–	3.3	0.9
Dysuria	2.4	–	–	–

†Number (%) of adverse events occurring in ≥ 2% of OXYTROL®-treated patients and greater in OXYTROL® group than in placebo group.

OXYTROL® (Oxybutynin Transdermal System) Prescribing Information. February 2003.

Patch Placement

- One patch (3.9 mg/d) twice a week
- Apply on the abdomen, hip, or buttock—absorption is bioequivalent
- Put patch on a clean, dry, and smooth area
- Do not put patch on areas that have been treated with oils, lotions, or powders
- Choose a new site with each application
- Avoid reapplication to the same site within 7 days

OXYTROL® (Oxybutynin Transdermal System) Patient Information Leaflet. December 31, 2003.

Application-Site Reactions: Treatment Options

- Rotate patch application site
- Use a moisturizer to maintain quality of skin
  - Do not apply to the application site immediately before patch application
- If necessary, the short-term use of a mild topical corticosteroid is suggested
- In the event of a severe reaction, the patch should be discontinued

Bárány E. In: *Dry Skin and Moisturizers: Chemistry and Function*. Boca Raton, Fla: CRC Press LLC; 1999:389. Orth DS, Appa Y. In: *Dry Skin and Moisturizers: Chemistry and Function*. Boca Raton, Fla: CRC Press LLC; 1999:225. Habif TP. *Skin Disease: Diagnosis and Treatment*. St. Louis, Mo: Mosby; 2001:10-59. DiNardo A, Wertz P. In: *Skin Moisturization*. New York, NY: Marcel Dekker Inc; 2002:175. Dermatologic disorders. Contact dermatitis. In: *The Merck Manual of Diagnosis and Therapy*. 17th ed. New York, NY: John Wiley & Sons; 1999:786-787.

Pharmacological Management

Implementing Effective Pharmacological Management

- Full work-up to identify type of UI
- Reverse potentially reversible factors
- Use as adjunct to behavioral management—a multifactoral approach
- Evaluate resident comorbities and limitations, such as the ability to swallow
- Manage drug-induced adverse effects

Jones DH et al. *Geriatrics*. 2002;1(suppl 1):S1-S11. DeBeau CE et al. *Ann Long-Term Care*. 2003;11(12):2-11.

Use of Anticholinergic Agents in Residents With Dementia/AD

- Cholinergic system is damaged with dementia and AD
- Residents with dementia/AD are sensitive to cognitive impairment induced by drugs with anticholinergic properties
- Adverse effects related to:
  - Total anticholinergic "load"
  - Baseline cognitive function
  - Individual pharmacokinetic and pharmacodynamic variability
- When appropriate, the goal of therapy is to eliminate the use of anticholinergic agents or substitute with an agent that has less anticholinergic effects

Tune LE. *J Clin Psychiatry*. 2001;62(suppl 21):S11-S14. Roe CM et al. *J Am Geriatr Soc*. 2002;50:836-842. Carnahan RM. *J Am Geriatr Soc*. 2004;52:2082-2087.

Commonly Used Medications With Anticholinergic Effects

- Captopril
- Cimetidine
- Codeine
- Digoxin
- Furosemide
- Isosorbide
- Nifedipine
- Ranitidine
- Theophylline
- Triamterene and hydrochlorothiazide
- Warfarin

Pollock BG. *ElderCare*. 2004;4(2):5-7. Lu C, Tune LE. *Am J Geriatr Psychiatry*. 2003;11:458-461.

Summary

- Different types of urinary incontinence can be diagnosed based on signs, symptoms, and clinical evaluation
- Significant medical, QOL, legal, regulatory, and economic implications are associated with UI
- Specific individualized management goals should be defined before initiating treatment
- Management options include nonpharmacologic and pharmacologic approaches

Summary

- All drug therapies have shown efficacy when compared to placebo
- All oral drug therapies have shown anticholinergic adverse events when compared to placebo
- Anticholinergic load should be monitored when drug therapy is used to manage urge incontinence in residents with dementia or AD
- When appropriate, agents with none or little anticholinergic activity should be utilized in residents with dementia or AD