

[연수강좌]

개원의가 반드시 알아야 할 배뇨장애 질환

- 과민성방광(OverActive Bladder, OAB)-

김 준 철

가톨릭의대 비뇨기과

배뇨장애 (Lower Urinary Tract Symptom)

• Storage, voiding and post micturition symptoms

Storage	Voiding	Post micturition
Frequency	Hesitancy	Incomplete emptying
Urgency	Poor stream	Terminal dribble
Urge incontinence	Straining	
Nocturia	Intermittency	



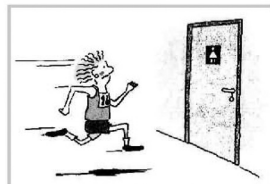
Overactive bladder, OAB

Overactive bladder (OAB) : Symptom syndrome

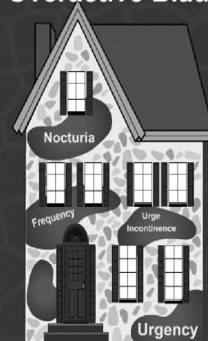
Urgency, with or without urge incontinence, usually with frequency and nocturia

Urgency

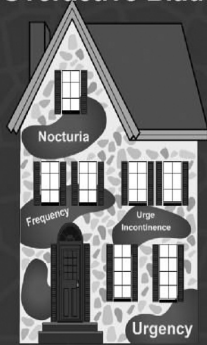
A strong and sudden desire to urinate
Difficult to defer



Urgency Is the Cornerstone Symptom of Overactive Bladder



Urgency Is the Cornerstone Symptom of Overactive Bladder



Frequency

Going to the toilet often (more than eight times in a 24-hour period)



Urge Incontinence

Urge incontinence occurs when there is a very strong urge to pass urine and which cannot be held back, resulting in the person wetting himself on the way to the toilet

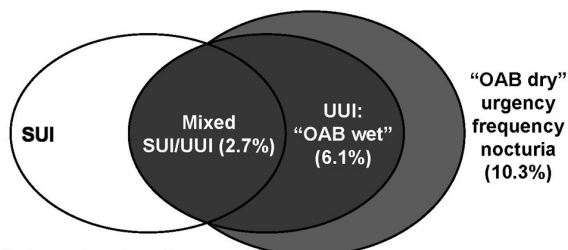


Nocturia

- Wake at night 1 or more times to void

Storage Symptoms and Incontinence

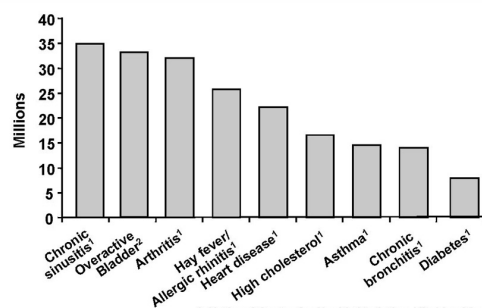
In a recent US survey (n = 5204), 16.5% of individuals in the general population met the criteria for OAB



SUI: stress urinary incontinence
UII: urge urinary incontinence

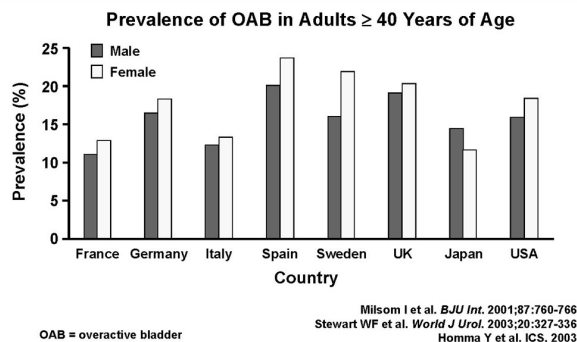
Stewart W et al. *World J Urol*. 2002. Available at: <http://link.springer.de/link/service/journals/00345>.

OAB is Nearly as Common as Arthritis and Sinusitis

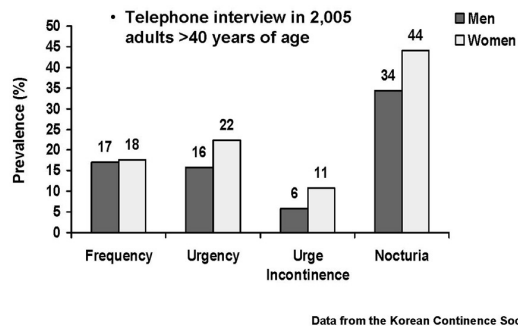


1. National Center for Health Statistics. Vital health stat 10;1994.
2. Stewart W et al. *World J Urol*. 2002. Available at: <http://link.springer.de/link/service/journals/00345>.

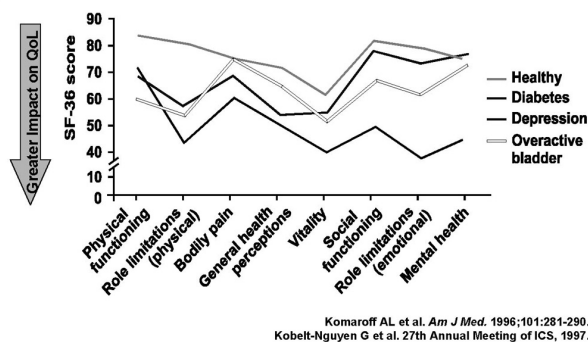
OAB Affects 11% to 22% of Adults



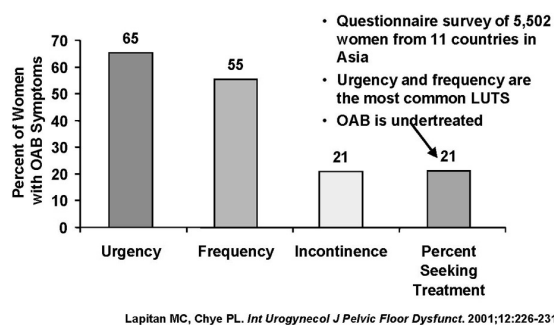
Prevalence of OAB Symptoms in Korea



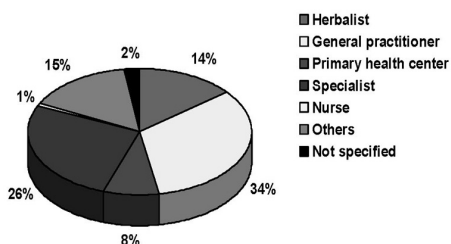
OAB Has a Greater Impact on Quality of Life Than Diabetes



53% of Asian Women Have Symptoms of OAB



Whom Do Asian Women Consult for OAB?



Causes of Overactive Bladder

- In the majority of cases, the underlying cause is unknown.
- Many conditions that can cause or contribute to OAB symptoms

How Can The Physician Diagnose OAB?

- Effective treatment of OAB symptoms
: Necessitates a targeted diagnostic evaluation
- Diagnostic evaluation
: Should be obtained to rule out other conditions

Conditions that can cause or contributes to OAB Symptoms

- Lower urinary tract conditions
- Neurologic conditions
- Systemic conditions
- Functional and behavioral conditions
- Side effects of medication

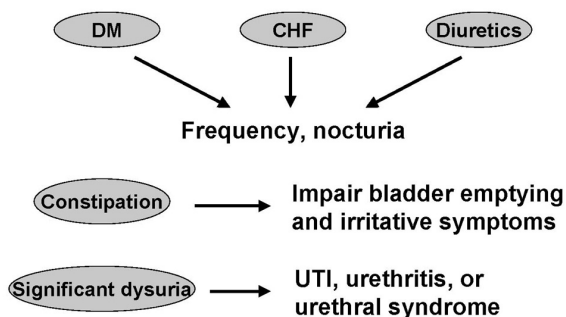
Diagnostic Evaluation of OAB

- History
- Physical examination
- Voiding diary
- Laboratory test (U/A and urine culture)
- Urinary flow rate with residual urine
- Cystoscopy
- Urodynamic study

Diagnostic Evaluation : History

- Focus on medical, neurologic, and genitourinary symptoms
- Review voiding patterns and symptoms
- voiding diary
- Review medications
- Evaluate functional and mental status

Diagnostic Evaluation : History



Specific Conditions have OAB

Urethral syndrome

- Frequency, urgency, voiding difficulty, dysuria, and pain (less common)
- Pathogenesis : poorly understood
- Diagnosis of exclusion
- bacteriuria(-) or lower urinary tract conditions(-)
- U/A & U/C, urethral and cervical culture, cystoscopy, urodynamic study

Specific Conditions have OAB

Interstitial cystitis

- Etiology : poorly understood
- Frequency, urgency in addition to suprapubic pain and discomfort
- Diagnosis
 - Urodynamic study : low compliance, capacity
 - Cystoscopy : glomerulation

Symptom Assessment

- 하루 24시간 동안 몇 번 화장실에 가십니까?
- 낮 시간 동안 얼마나 자주 화장실에 가십니까?
- 취침 중에 화장실에 가기 위하여 몇 번 깨십니까?
- 얼마나 자주 소변이 갑자기 마려워 참기 힘들십니까?
- 소변이 마려울 때 화장실에 도착하기 전에 속옷을 적시는 경우가 있으십니까? 그리고 그 양은 얼마나 되십니까?
- 웃거나, 기침이나 제재기시 또는 줄넘기를 하거나 달리기할 할 때 요실금이 있으십니까?

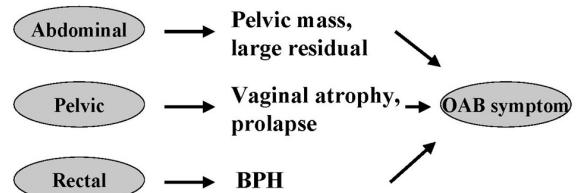
Diagnostic Evaluation : Physical examination

- General, abdominal (including bladder palpations), and neurologic examinations
- Pelvic and rectal examinations in women and rectal examination in men
- Observe for urine loss with stress (eg, cough, Valsalva, etc.)



Diagnostic Evaluation : Physical examination

- Abdominal, pelvic, rectal examination



Diagnostic Evaluation : Physical examination

- Neurologic examination
 - : Simple neurologic examination (S2 to S4)
 - Evaluate underlying neurologic deficit



Consider UDS

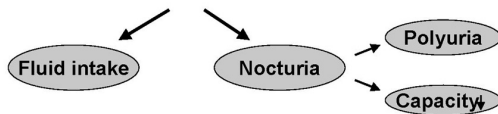
Diagnostic Evaluation : Voiding diary

- ◆ Patients record of bladder symptoms, type/amount of drinks taken, time/amount of urine passed

성명:				연령:	
날짜	배뇨시간	소변량	음료량 및 시간	요실금 발생시간	연관활동 및 증상

Diagnostic Evaluation : Voiding diary

- Can be helpful in determining the frequency, volume, and pattern of voiding
- Providing clues to underlying causes and contributing factors



Diagnostic Evaluation : Voiding diary

- Voiding diary provide information on cause of nocturia
- Nocturia can be the result of
 - Nocturnal polyuria
 - Abnormal lower urinary tract function
 - Combination of these two elements

Diagnostic Evaluation : Laboratory Tests

- Urinalysis
 - to rule out hematuria, pyuria, bacteriuria, glucosuria, proteinuria
- Blood work as appropriate
 - glucose
 - prostate serum antigen
 - others



Urinary Tract Infection

- 50% of women will develop a UTI during their lifetime
 - Recurrent infection : 12 – 27%
 - Recurrent lower UTI, irritation & bladder pain
 - Cystoscopy & biopsy
- ↓
- Differentiate IC, CIS, calculi & Tbc

Diagnostic Evaluation : Uroflow and residual

- Should be considered in selected patients
- Screening method of ruling out obstruction in older men
- Voiding difficulty with large residual
 - produce OAB symptom
 - anticholinergics may worsen voiding difficulties
- Performed in patients with risk factors for urinary retention (diabetes, spinal cord disease, BPH)

Diagnostic Evaluation : Cystoscopy

- Performed in patients with sterile hematuria or risk factors for bladder cancer
- Their urine should be sent for cytology
- Indicated in patients with a history of recurrent urinary tract infection
- Cystoscopy in OAB symptom : uncertain

Diagnostic Evaluation : Urodynamic Study

- Controversial
- It is appropriate to treat lower urinary tract symptoms based upon history and physical exam alone

Indication of Urodynamic study

- persistence despite appropriate therapy
- potential hazards of therapy
- incontinence
- outflow obstruction
- neurogenic bladder
- nonspecific symptom
- for more accurate diagnosis

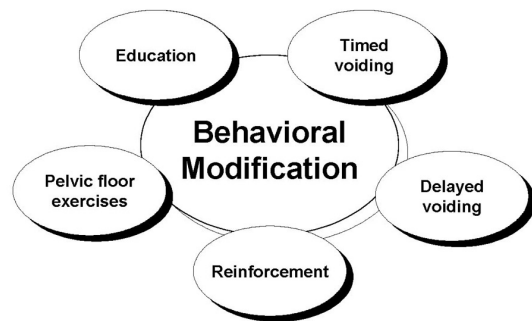
Wein A. In: Campbell's Urology, Philadelphia, Pa: WB Saunders; 2002; 8th ed: 905-908.

Treatment of Overactive Bladder : What is Best?

Treatment Options

- Behavioral therapy
- Pharmacotherapy
- Modulatory/surgical therapies

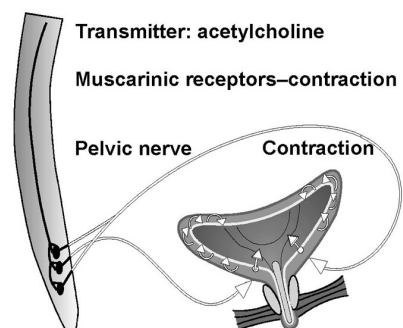
Behavioral Modification



Pharmacologic Therapy

- Antimuscarinic agents are currently the mainstay for treating OAB
- OAB symptoms are relieved by
 - inhibition of involuntary bladder contractions
 - increased bladder capacity

Parasympathetic Innervation and Receptors



Recommended drugs for the treatment of OAB

3rd International Consultation Meeting on Incontinence,
Monaco, 2004

Antimuscarinic	Tolterodine Trospium Solifenacin Darifenacin
Drugs with mixed action	Oxybutinin Propiverine
Vasopressin analogues	Desmopressin

Oxybutynin

- Potent muscarinic receptor antagonist
- Local anesthetic as well as smooth muscle relaxant effects at higher dose
- Frequently causes side effects
: Lower doses used to improve tolerability profile

Broadley, Kelly. *Molecules*. 2001;6:142-193.

Propiverine

- Currently used in Korea and Japan; lower doses used in both countries
- Muscarinic receptor antagonist + calcium channel blocker
- Long half-life
 - tablet taken qd, only good for 12 hours
 - need to monitor liver function for long-term use

Siegmund et al. *Pharmazie*. 1990;45:67-67.
Madersbacher, Mürtz. *World J Urol*. 2001;19:324-335.

Trospium Chloride

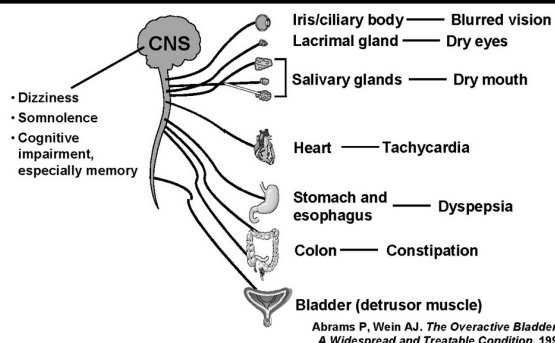
- Nonselective muscarinic antagonist
- Quaternary ammonium compound
 - minimal penetration of the blood-brain barrier
- Variable absorption from GI tract
 - no significant hepatic metabolism (<5%)
 - dose reduction in renal failure
 - excreted 80% unchanged in urine

Tolterodine

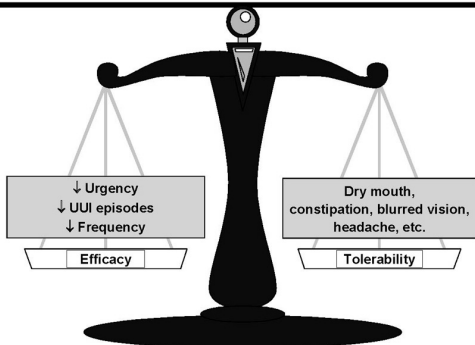
- Developed specifically for overactive bladder
- Muscarinic receptor antagonist nonselective for the M₁ to M₅ receptors
- Organ selective for bladder over salivary glands
- Available worldwide since 1997; 7 million patients treated to date
- Once daily, sustained-release formulation available in many countries since 2000

Nilvebrant L et al. *Life Sci*. 1997;60:1129-1136.
Abrams P et al. *Br J Urol*. 81:801-810.

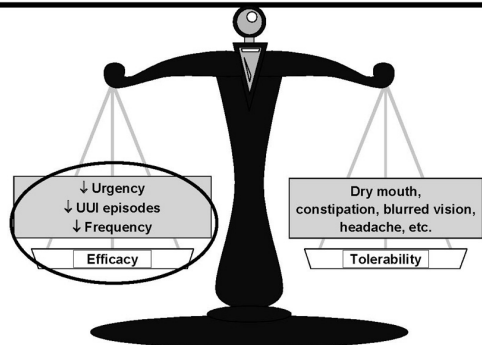
Muscarinic Receptor Distribution



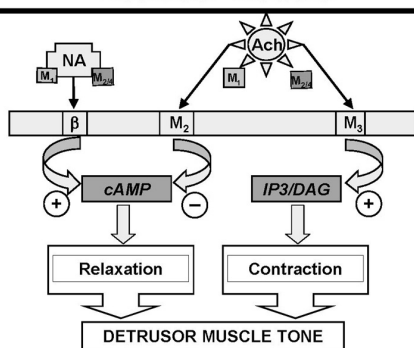
Antimuscarinic Therapy: Balancing Efficacy and Tolerability



Antimuscarinic Therapy: Balancing Efficacy and Tolerability



Neurophysiology of the Detrusor Muscle



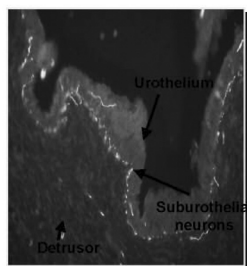
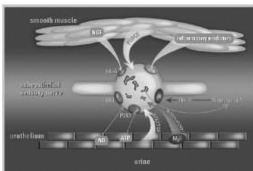
M₂ Receptors and Contractility

- M₂ participation suggested in a variety of pathologic states
 - outflow obstruction
 - denervation
 - aging
 - diabetes
- Afferent role for muscarinic receptors in the lower urinary tract?

Braverman AS et al. *Am J Physiol*. In press.

Afferent Nerves in the Bladder

- Greater density of all muscarinic receptors in the bladder urothelium versus the detrusor
- M₂ muscarinic receptor subtype is prominent in the bladder urothelium



Andersson K. *Urology*. 2002;59:45.

Tolterodine Has the Ability to Block Both the Sensory and Motor Arms

Antagonist	K _i (nM)*				
	M ₁	M ₂	M ₃	M ₄	M ₅
Tolterodine	3.0	3.8	3.4	5.0	3.4
Oxybutynin	2.5	6.7	0.7	2.0	11

Lower number = greater affinity for receptor

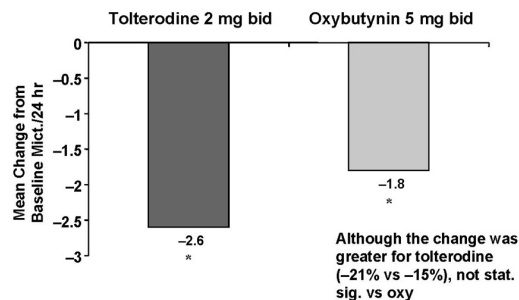
Chapple C. *Urology* 2000;55 (Suppl. 5A).
Gillberg PG et al. *Eur J Pharmacol*. 1998;349:285-292.
*CHO cells expressing human muscarinic receptors
Webrant L et al. *Eur J Pharmacol*. 1997;327:195-207.

The Use of Tolterodine for OAB in Korean Patients

- **Background**
 - a comparison of tolterodine IR (2 mg bid) and oxybutynin IR (5 mg bid)
- **Methods**
 - double blinded, randomized, multicenter, parallel group study
 - end points measured were micturition diaries, patient's perception of benefit, compliance, and tolerability data

Lee J et al. *Int J Urol*. 2002;9:247-252.

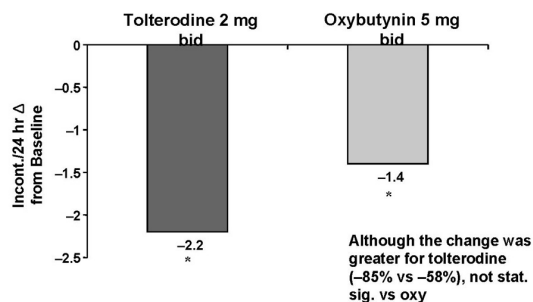
The Use of Tolterodine for OAB in Korean Patients: Δ in Micturition (8 weeks)



*P = 0.0001 vs baseline.

Lee J et al. *Int J Urol*. 2002;9:247-252.

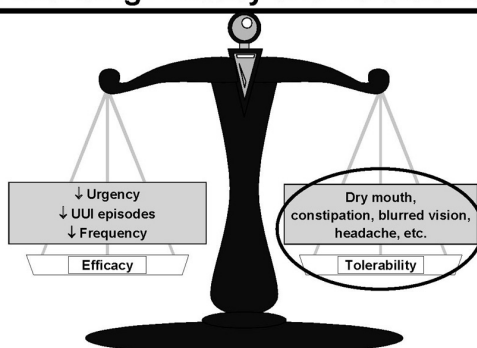
The Use of Tolterodine for OAB in Korean Patients: Δ in Incontinence Episodes Results (8 weeks)



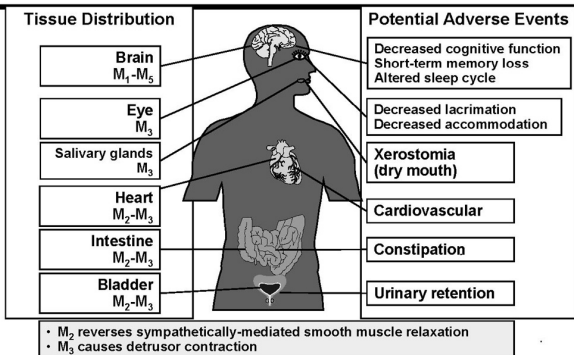
*P = 0.0001 vs baseline.

Lee J et al. *Int J Urol*. 2002;9:247-252.

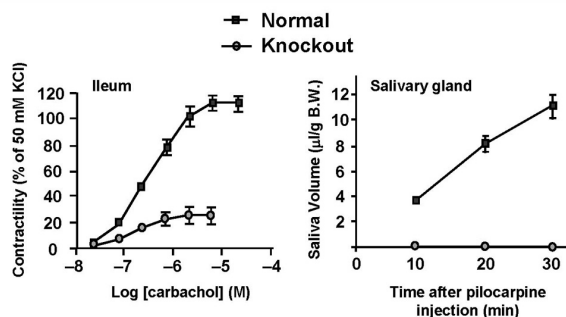
Antimuscarinic Therapy: Balancing Efficacy and Tolerability



Muscarinic Receptor Distribution and Potential Adverse Events With Antagonist Use



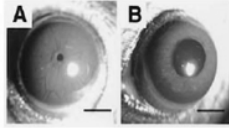
Role of M₃ Receptor in GI Contraction and Salivation



Matsui M et al. *PNAS*. 2000;97:9579-9584.

Role of M₃ Receptor in Pupillary Constriction

Decreased pupillary constriction
in response to light



Normal

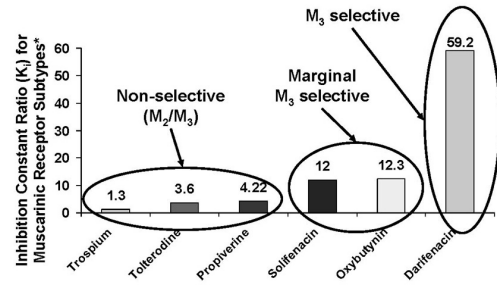
KO

Increased illumination

KO = Knockout

Matsui M et al. PNAS. 2000;97:9579-9584.

Receptor Profiles of Available Antimuscarinic Agents



Chapple ICS 2003 *Animal models Napier C et al. Proc ICS. 2002;445 [Abstract] Heading CE. Curr Opin CPNS Inves Drugs. 2000;3:321-325

Meta-analysis of Clinical Trials of Antimuscarinic Agents for OAB: Relative Risk of Selected Adverse Events

Intervention and Daily Dose	Blurred Vision	Constipation	Dizziness	Dry Mouth	Dyspepsia	Urinary Retention*
Tolterodine IR 2 mg	NS	NS	NS	2.4	NS	NS
Tolterodine IR 4 mg	NS	NS	NS	3.6	NS	NS
Tolterodine ER 4 mg	NS	NS	NS	2.9	NS	NS
Oxybutynin IR 5-7.5 mg	NS	NS	NS	3.3	NS	5.6
Oxybutynin IR 8.8-15 mg	1.7	NS	NS	3.3	NS	NS
Oxybutynin TDS 3.9 mg	NS	NS	NS	NS	NS	NS
Darifenacin 7.5 mg	2.2	NS	NS	2.2	NS	NS
Darifenacin 15 mg	2.4	NS	NS	2.9	3.2	NS
Solifenacin 5 mg	NS	2.9	NS	3.0	NS	NS
Solifenacin 10 mg	2.4	4.4	NS	5.8	NS	NS
Trospium 40 mg	NS	2.1	NS	3.2	NS	NS
Propiverine IR 30 mg	NS	NS	NS	3.5	NS	NS
Propiverine IR 45 mg	1.9	NS	NS	NS	NS	NS

*All cells with data show significant relative risk ratios favouring placebo
ER = extended release; IR = immediate release; NS = no statistical significance compared with placebo; TDS = transdermal system

Chapple CR et al. Eur Urol. 2005

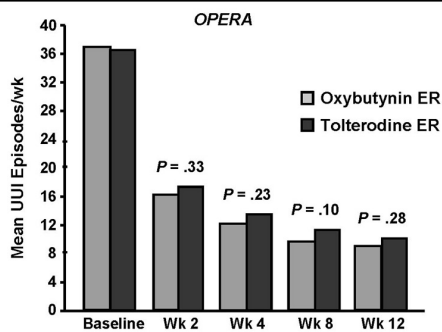
Meta-analysis of Clinical Trials of Antimuscarinic Agents for OAB: Relative Risk of Withdrawal

Intervention and Daily Dose	Total Withdrawals	Withdrawals Due to Adverse Events
Tolterodine IR 2 mg	NS	NS
Tolterodine IR 4 mg	NS	NS
Tolterodine ER 4 mg	0.7	NS
Oxybutynin IR 5-7.5 mg	NS	NS
Oxybutynin IR 8.8-15 mg	1.4	1.8
Oxybutynin TDS 3.9 mg	NS	NS
Darifenacin 7.5 mg	NS	NS
Darifenacin 15 mg	NS	NS
Solifenacin 5 mg	NS	NS
Solifenacin 10 mg	NS	NS
Trospium 40 mg	NS	NS
Propiverine IR 30 mg	NS	NS
Propiverine IR 45 mg	NS	NS

*All cells with data show significant relative risk ratios favouring placebo
NS = no statistical significance compared with placebo

Chapple CR et al. Eur Urol. 2005

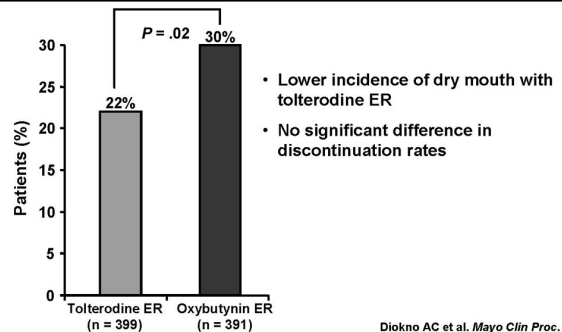
Tolterodine ER Versus Oxybutynin ER: No Statistical Difference in Primary Efficacy End Point



UII = urge urinary incontinence.

Diokno AC et al. Mayo Clin Proc. 2003;78:687-695.

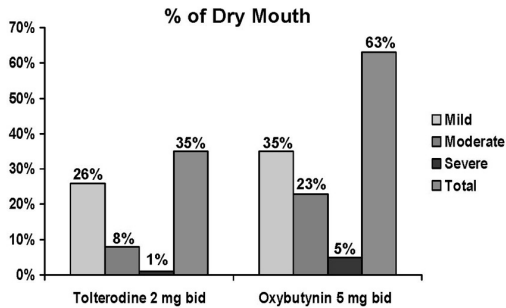
Tolterodine ER Versus Oxybutynin ER: OPERA Trial



- Lower incidence of dry mouth with tolterodine ER
- No significant difference in discontinuation rates

Diokno AC et al. Mayo Clin Proc. 2003;78:687-695

The Use of Tolterodine for OAB in Korean Patients: Safety and Tolerability Results



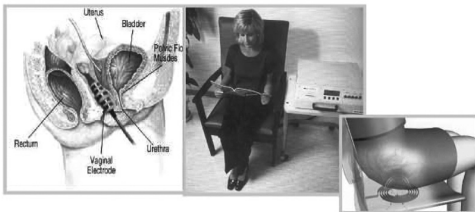
Lee J et al. *Int J Urol*. 2002;9:247-252.

Surgical/Modulatory Therapies

- Denervation
 - ✓ Central
 - ✓ peripheral and perivesical
- Electrical/magnetic stimulation
- Neuromodulation
- Augmentation cystoplasty

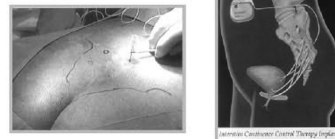
Electrical/Magnetic Stimulation

- One of neuromodulating therapy

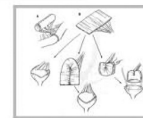


Surgical Therapy

- Sacral neuromodulation



- Bladder augmentation



Reasons to Refer Patients to Specialists

- Symptoms do not respond to initial treatment within 2–3 months
- Hematuria without infection on urinalysis
- Recurrent symptomatic urinary tract infection
- Symptoms suggestive of poor bladder emptying
- Pelvic bladder urethral pain

Abrams P, Wein AJ. *The Overactive Bladder—A Widespread and Treatable Condition*. 1998.

Reasons to Refer Patients to Specialists (cont.)

- Evidence of unexplained neurologic or metabolic disease
- Failed previous incontinence surgery
- Elevated PVR
- Radical pelvic surgery
- Symptomatic prolapse
- Prostate problems
- Surgery planned (2nd opinion)

Abrams P, Wein AJ. *The Overactive Bladder—A Widespread and Treatable Condition*. 1998.

Summary

- OAB symptom : Common, disabling, affecting the QOL
- OAB symptoms may be caused by myriad factors
- Other conditions that can cause OAB symptom : Must be excluded before diagnosing OAB

Summary

- Treat based on history and physical exam
- Urodynamics can be useful in some patients
- Treatment options : behavioral therapy, pharmacotherapy, and surgery

Summary

- Antimuscarinic agent can be regarded as the drug of first choice to treat OAB
- We should consider balance between efficacy and tolerability