Drug Class Review

Agents for Overactive Bladder

Final Update 4 Report
Evidence Tables

March 2009

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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The medical literature relating to the topic is scanned periodically (see http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm for scanning process description). The Drug Effectiveness Review Project governance group elected to proceed with another update of this report based on the information contained in the scan. Please see timeline on the DERP website for details on the date of its release. Prior versions of this report can be accessed at the DERP website.

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Immediate Release vs Immediate Release (IR vs IR)			
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Leung 2002	RCT Multicenter Hong Kong	Women, age ≥18, urodynamically confirmed diagnosis of overactive bladder (phasic detrusor contraction with an amplitude ≥15 cm water, urinary frequency (≥8 voids/24h), urgency or urge incontinence (≥1 incontinence episode/24h))	Diagnosis of stress incontinence, clinically significant voiding difficulty, UTIs, require catheterization, uninvestigated hematuria or bladder cancer, currently on treatment for overactive bladder or on anticholinergic drugs, presence of psychiatric disease or cognitive impairment, contraindications for antimuscarinic drugs. Patients underwent Mini Mental Status Exam and Electrocardiograph testing to rule out psychiatric or cardiovascular disease.
Lee 2002	RCT Multicenter South Korea	Male or female, 18+ yrs, with overactive bladder defined by symptoms of urinary frequency and urgency with or without incontinence.	Significant stress incontinence, any anticholinergic drug treatment within 2 wks, renal or hepatic disease, any contraindication to antimuscarinic therapy, UTI, interstitial cystitis or hematuria, bladder outlet obstruction, behavioral training, any urinary catheterization, and any other treatment started at least 2 months prior to enrollment.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Immediate Release vs Immediate Release (IR vs IR)			
Oxybutynin (Oxy) vs.Tolterodine (Tol)			
Leung 2002	Tol 2mg twice daily x 10 weeks Oxy 5mg twice daily x 10 weeks	None reported	Visual Analog Scale of patient assessment of severity of symptoms at baseline, 4 and 10 weeks, (0 = no effect, 10 = max severity), perceived changes in symptoms before and after treatment assessed at 4 and 10 weeks (+5 = max improvement, -5 = max deterioration). Voiding diary (1 week) at baseline, 4 and 10 weeks. Urinary pad test* at baseline and 10 weeks.
Lee 2002	Tol 2mg twice daily Oxy 5mg twice daily x 8 wks	estrogen allowed.	Micturition diary assessed at 8 wks Patient assessment of treatment benefits as yes/no; with yes further defined as little or much. Compliance assessed by tablet count at 8 wks

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Immediate Release vs Immediate Release (IR vs IR)				
Oxybutynin (Oxy) vs.Tolterodine (Tol)				
Leung 2002	106 enrolled (number per group not stated)	Age range 43-63 yrs Median age 49.5 female	56% postmenopausal, median parity 3	Withdrawals: Tol: 8 Oxy: 9 Number lost to follow-up not reported Number analyzed not clear
Lee 2002	228 enrolled (Tol 112, Oxy 116)	mean age 52 (range 20 to 86) 77% female	Previous drug therapy: Tol 32%, Oxy 22% mean # micturitions/d: 12 % with incontinence: 39%	41 (Tol 15, Oxy 26) Lost to f/u: 2 228 assessed by ITT, 187 by PP

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Author, Year	Outcomes
Immediate Release vs Immediate Release (IR vs IR)	
Oxybutynin (Oxy) vs.Tolterodine (Tol)	
Leung 2002	Diaries Analysis of variance shows NS between groups on any measure, all groups improved. Symptoms Change in overall severity (from baseline) Oxy: 4 and 10 weeks 0.7 Tol: 4 and 10 weeks 0.2 (NS by intention to treat, per protocol not reported) Perceived change in symptom severity (from baseline) Oxy: 4 and 10 weeks 1.0 Tol: 4 and 10 weeks 2.0 (NS at 4 weeks, at 10 weeks p = 0.053 by intention to treat, 0.047 by per protocol)
Lee 2002	ITT analysis: Mean change in Micturitions/d: Tol -2.6 Oxy -1.8 (NS) Mean change in incontinence/d: Tol -2.2 Oxy -1.4 (NS) PP analysis: Patient perception of benefit: Tol 45% much benefit Oxy 46% much benefit (NS)

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Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Immediate Release vs Immediate Release (IR vs IR)	
Oxybutynin (Oxy) vs.Tolterodine (Tol)	
Leung 2002	Xerostomia Questionnaire at 4 and 10 weeks, independent reporting of other side effects. Significant deterioration on all measures of dryness except denture fit, for both drugs. NS between groups. Side effects reported: Oxy 49% Tol 60% (NS) Reported to be mostly abdominal aches, general malaise and urinary retention
Lee 2002	Spontaneously reported adverse events were reported and rated as serious or nonserious and according to intensity, and relationship to study drug. 227 patients assessed Tol: 62 patients reported 101 adverse events Oxy: 94 patients reported 154 adverse events (p = 0.001) Dry mouth: Tol 39 (35%) 72 (63%) (p<0.001) Severe dry mouth: Tol 1 (1%), Oxy 6 (5%) Micturition disorder: Tol 10 (9%), Oxy 16 (14%) Dyspepsia/abdominal pain: Tol 14 (13%), Oxy 12 (10%) Headache: Tol 4 (4%), Oxy 6 (5%)

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Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Immediate Release vs Immediate Release (IR vs IR)		
Oxybutynin (Oxy) vs.Tolterodine (Tol)		
Leung 2002	Unclear. States that most withdrawals not due to side effects, but that patients withdrawing while on Oxy were more likely to have co-existing illnesses (p<0.012).	Compliance measured. Oxy 87.5% (11 to 99.3) Tol 75% (8.9 to 98.8) (NS)
Lee 2002	29 : Tol 11 (6 dry mouth, 55%) Oxy 18 (16 dry mouth, 88%)	

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Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Abrams 1998	RCT Multicenter UK, Ireland and Sweden	Men or women 18+ yrs, urodynamically confirmed bladder overactivity, increased frequency (8 or more micturitions/24hrs), and urge incontinence (1 or more episodes/24hrs) and/or urgency during a 2 week washout/run-in period.	Clinically significant stress incontinence, detrusor hyper-reflexia, hepatic, renal or hematologic disorders, symptomatic or recurrent UTI, bladder outlet obstruction, bladder training or electrostimulation, indwelling or intermittent catheter
Drutz 1999	RCT Multicenter USA/Canada	Age 18+ with evidence of detrusor overactivity on cystometry, along with urinary frequency, and either urge incontinence or urinary urgency.	Clinically significant stress incontinence, renal or hepatic disease, any disease which the investigator thought would make the patient unsuitable, UTI, interstitial cystitis, hematuria, any catheterization, behavioral training within 14d, unstable dose of any drug with anticholinergic side effects, previous serious adverse effects on Oxy, mean voided volume/d >3L, or risk of urinary retention.
Immediate Release vs Immediate Release (IR vs IR)			
Oxybutynin (Oxy) vs Flavoxate (Fla)			

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Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Abrams 1998	Tol 2mg twice daily Dose could be dropped to 1mg during first 2 weeks if not tolerated Oxy 5mg three times daily Dose could be dropped to 2.5mg during first 2 weeks if not tolerated Pl three times daily Subjects >/= 65 yrs in UK and Ireland could start the dose of Oxy at 2.5mg and increase to 5mg during first 2 weeks Total trial duration 12 weeks	None reported	Micturition diary assessed at 2, 4, 8, and 12 weeks Patient assessment of severity of symptoms based on 6-point scale (0 = no problems, 6 = severe problems) Change between baseline and 12 weeks defined as decrease in score of 1 or more points.
Drutz 1999	Tol 2mg twice daily Oxy 5mg three times daily Placebo three times daily x 12 wks Dose reduction to Tol 1mg or Oxy 5mg twice daily allowed during first 2 wks.	None reported	Change in micturitions/d and incontinence episodes/d at 12 wks, assessed by micturition diary.
Immediate Release vs Immediate Release (IR vs IR)			
Oxybutynin (Oxy) vs Flavoxate (Fla)			

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Abrams 1998	Number screened/eligible not stated 293 enrolled (118 Tol, 118 Oxy, 57 Pl)	Age range 19-80 yrs Mean age Tol 55, Oxy 58, Pl 58 76% female	Previous drug therapy: Tol 52%, Oxy 60%, Pl 75% Mean micturitions/24h: 12 Tol, 11 Oxy, 12 Pl Mean incontinence episodes/24h: 2.9 Tol, 2.6 Oxy, 3.3 Pl	37 (10 Tol, 20 Oxy, 7 Pl) reported withdrawing due to adverse effects, no other withdrawals or loss to follow-up reported, but 3 patients missing in 'evaluable patients'.
Drutz 1999	277 enrolled (Tol 109, Oxy 112, Placebo 56)	mean age: Tol 63yrs, Oxy 66 yrs, placebo 62 yrs % female: Tol 81, Oxy 72, Placebo 80 % Caucasian: Tol 87, Oxy 94, Placebo 93	% hyperreflexia: Tol 7, Oxy 7, Placebo 5 % Previous drug therapy: Tol 45, Oxy 45, Placebo 55 % with incontinence: Tol 83, Oxy 92, placebo 89 % Prior Urinary tract surgery: Tol 27, Oxy 45, placebo 34	57withdrew 147 analyzed (70 Tol, 41 Oxy, 36 placebo) 27 excluded due to dose reductions 46 excluded due to protocol violations
Immediate Release vs Immediate Release (IR vs IR)				
Oxybutynin (Oxy) vs Flavoxate (Fla)				

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Abrams 1998	Change in mean number of voids/24 hrs at week 12: -2.7 Tol, -2.3 Oxy, -1.7 Pl (Tol vs. Oxy NS) Change in mean number of incontinence episodes/24 hrs at week 12:(n = 92 Tol, 88 Oxy, 40 Pl) -1.3 Tol, -1.7 Oxy, -0.9 Pl (Tol vs. Oxy NS) Change in subjective assessment of symptoms at week 12: Improved 50% Tol, 49% Oxy, 47% Pl
Drutz 1999	PP analysis: Change in mean micturitions/d: Tol -2.0, Oxy -2.0, placebo -1.1 (NS for Tol vs Oxy) Change in incontinence/d: Tol -1.7, Oxy -1.7, placebo -1.0 (NS for Tol vs Oxy) Other variables: At least 50% reduction in frequency: Tol 63%, Oxy 65% Cure (no incontinence in 7 days prior) Tol 21%, Oxy 22%
Immediate Release vs Immediate Release (IR vs IR)	
Oxybutynin (Oxy) vs Flavoxate (Fla)	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Abrams 1998	All adverse events were recorded and categorized by intensity (mild, moderate, severe). The likelihood of relationship to study drug was evaluated for serious adverse events and patient withdrawn if deemed medically necessary or patient wished withdrawal. At least one adverse event reported: 89% Tol, 97% Oxy, 81% Pl (Tol vs. Oxy p = 0.023) Dry mouth: 50% Tol, 86% Oxy, 21% Pl (Tol vs. Oxy p<0.001) More patients reported dry mouth to be severe on Oxy than on Tol or Pl (numbers not given) 1 serious adverse event (syncope) was considered related to Tol
Drutz 1999	Spontaneously reported adverse events were reported and rated as serious or nonserious and according to intensity, at visits at 2, 4, 8 and 12 wks ITT analysis: % reporting adverse events: Tol 78%, Oxy 90, placebo 75 (p = 0.013 Tol vs Oxy) Dry mouth: Tol 30%, Oxy 69%, placebo 15% (p <0.001 Tol vs Oxy) Moderate to severe dry mouth: Tol 9%, Oxy 44%, placebo 7% Other adverse events reported: headache: Tol 15%, Oxy 10% dizziness: Oxy 11% (others not reported) cardiovascular events: Tol 7%, Oxy 8% Dose reduction: Tol 7%, Oxy 23%, placebo 4% (p<0.001 Tol vs Oxy)
Immediate Release vs Immediate Release (IR vs IR)	
Oxybutynin (Oxy) vs Flavoxate (Fla)	

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Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Abrams 1998	Tol 8%, Oxy 17%, Pl 2% Due to dry mouth: Tol 0.8%, Oxy 13%, Pl 3.5%	Dose reductions requested by 8% Tol, 32% Oxy, 2% Pl (Tol vs. Oxy p<0.001)
Drutz 1999	Tol 7 (6%), Oxy 23 (21%), placebo 4 (7%) (p = 0.002 Tol vs Oxy)	Only Allowed dose reductions in protocol, but then excluded these from analysis. Incomplete reporting of adverse events. 46 excluded from analysis due to protocol violations, but which groups assigned not reported.
Immediate Release vs Immediate Release (IR vs IR)		
Oxybutynin (Oxy) vs Flavoxate (Fla)		

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Milani 1993	RCT, Crossover Multicenter Italy	Females, 18+, with motor or sensory urgency according to the criteria of the International Continence Society.	Severely ill, overt neurological disease, non-compliant, or taking drugs that could affect urinary symptoms.
Zeegers 1987	RCT, Cross-over study Multicenter Netherlands, Austria	Weight 56-85kg Symptoms: frequent voiding, urgency or urge incontinence (patients with neurogenic bladder may have been included)	Kidney, liver or cardiovascular pathology, obstruction or infection, ongoing anticholinergic therapy, glaucoma or Parkinson's disease

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Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Milani 1993	Fla 400mg or Oxy 5 mg x 4wks, then crossover after 7 d washout	not given	Diurnal and nocturnal frequency, incontinence, urgency, dysuria and pad use by diary. Symptoms scored 0,1, or 2 with 0 = best, 2 = worst. Evaluated at baseline at 4wks. Patient assessment of results at 4 wks (cured, improved, no change, worse).
Zeegers 1987	Randomized to either: {Fla 200mg three times daily x 3 weeks, Emp 200mg three times daily x 3 weeks, Pl three times daily x 3 weeks} or {Oxy 5mg three times daily x 3weeks, Emp 200mg three times daily x 3 weeks, Pl three times daily x 3 weeks) with the order of drugs also randomized.	None reported	Patient and physician score at end of each 3 week period; 1 = no effect, 5 = excellent effect.

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Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Milani 1993	50 enrolled	mean age 51 (range 19 to 78) 100% female	23 (46% sensory urge, 54% motor urge.	9 withdrawn: Fla: 3 poor compliance Oxy: 1 poor compliance, 5 side effects 41 analyzed
Zeegers 1987	Number screened/eligible not stated; stated to be consecutive patients 60 enrolled (30 in Fla/Emp/Pl, 30 in Oxy/Emp/Pl)	Age range 16-78 yrs Reported by center and by completer/noncompleter status rather than by treatment group. 70% female	None reported	12 withdrawn due to side effects, 5 lost to follow-up, 2 found to have non-urologic pathology 41 completed entire protocol and were analyzed

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Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Milani 1993	Mean change in scores (0-2): Fla: 0.78, Oxy 0.83 Incontinence: Fla 1.05, Oxy 0.9 Urgency: Fla 0.66, Oxy 0.92 Pads: Fla 0.59, Oxy 0.71 Dysuria: Fla 0.072, Oxy 0.072 Patient assessment (n=38) Fla: 82% cured or improved Oxy: 79% cured or improved (NS) Patient's preference: 61% Fla, 37% Oxy, 2% no preference
Zeegers 1987	NS found between drugs in reduction in urge, instability or incontinence episodes. Patient and Physician scores were combined in results: Average score: 2.25 Pl, 2.28 Emp, 2.02 Fla, 2.95 Oxy (stated Oxy significantly better, no p-value given) Fair/Good/Excellent Score: 41% Pl, 34% Emp, 31% Fla, 61% Oxy

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Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Milani 1993	Adverse events were elicited at 4 wks, and rated as serious or nonserious and according to intensity. By ITT: Fla 11/50 (22%), Oxy 42/50 (84%), plus 5 patients withdrawn due to adverse events. Dry mouth: Fla 2%, Oxy 78% Abdominal or stomach pain: Fla 24%, Oxy 36%
Zeegers 1987	Combined in score 15% Pl, 26% Emp, 8% Fla, 17% Oxy

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Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Milani 1993	5 (10%)	
Zeegers 1987	12 withdrawals: 2 Pl, 8 Emp, 0 Fla, 2 Oxy	Analysis of the effect of the previous treatment on scores for current treatment showed no change in Oxy score. Without prior drug treatment scores are: Pl 29%, Emp 18%, Fla 44%, Oxy 63% with fair/good/excellent response

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Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Extended Release vs. Immediate Release (ER vs IR)			
Oxybutynin ER vs Oxybutynin IR			
Versi 2000	RCT Multicenter USA	Community dwelling adults, 7 to 45 urge incontinence episodes/wk, at least 4 days of incontinence/wk, previous response to treatment with anti-cholinergic drug	clinically significant medical problems, postvoid residual urine volume over 100ml, other conditions in which oxybutynin is contraindicated
Birns 2000	RCT multicenter UK	Age 18 to 76 yrs, outpatients with voiding problems and currently stabilized on and tolerant to treatment with Oxy 5mg twice daily, with bladder sensation, and able to keep a diary chart	other anticholinergic drugs or drugs with anti-cholinergic effects, contraindication to anti-cholinergic therapy, (myasthenia gravis, glaucoma, functional or organic gastric obstruction), UTI, bladder outlet obstruction, only of nocturnal enuresis

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Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Extended Release vs. Immediate Release (ER vs IR)			
Oxybutynin ER vs Oxybutynin IR			
Versi 2000	Oxy ER 5-20mg once daily or Oxy IR 5-20mg/d - schedule not reported doses increased in 5mg/day increments every 7 days doses decreased by 5mg if side effects were intolerable Optimal dose identified and taken for 1 week	none reported	7 day urinary diary after maintenance dose determined
Birns 2000	Oxy ER 10mg once daily or Oxy 5mg twice daily x 6 wks	none reported	Urinary diary (micturition and incontinence episodes) reviewed at visits 2, 3, 4

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Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Extended Release vs. Immediate Release (ER vs IR)				
Oxybutynin ER vs Oxybutynin IR				
Versi 2000	screened 417 eligible/enrolled 226	Mean age 59yrs ER; 60yrs IR % Female: ER 88%, IR 90% Ethnicity: White: 86.5 ER; 90.4 IR Black: 5.4ER; 3.5 IR Asian: 0.9 ER; 0 IR	Urge incontinence episodes/wk: ER 18.6, IR 19.8	withdrawn ER: 6 IR: 9 Lost to f/u ER: 1 IR: 0 analyzed ER 111 IR 115
Birns 2000	162 screened 130 randomized	mean age: 56 yrs % female: 68% (ER 71%, IR 66%)	81% with urge or stress/urge incontinence (ER 78%, IR 84%)	Loss to f/u: 2 (1 each arm) Analyzed: 128 by ITT, 125 by PP

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Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Extended Release vs. Immediate Release (ER vs IR)	
Oxybutynin ER vs Oxybutynin IR	
Versi 2000	Mean change in urge incontinence episodes/wk: -15.7 ER, -15.4 IR (NS)
Birns 2000	Daytime continence at 4 wks ER 53%, IR 58% (NS) Secondary Criteria No of pts with night-time continence at completion of study median change in the no of voluntary daytime voids voluntary night-time voids daytime episodes of incontinence night-time episodes of incontinence No clinically significant difference between treatment groups Exact information not given

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Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Extended Release vs. Immediate Release (ER vs IR)	
Oxybutynin ER vs Oxybutynin IR	
Versi 2000	Reports of adverse effects recorded at each pt visit Dry mouth: ER 48%, IR 59% Kaplan Meier analysis moderate or severe dry mouth reports indicates a significant difference (p = 0.007) in favor of ER
Birns 2000	Assessed during visits every two weeks 78 pts reported adverse events (60%) (ER 55%, IR 67%) Dry mouth: ER 23%, IR 17% Dizziness ER 2%, IR 9% Vision abnormality ER 7%, IR 5% Cough ER 3%, IR 5% Headache ER 0, IR 5%

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Extended Release vs. Immediate Release (ER vs IR)		
Oxybutynin ER vs Oxybutynin IR		
Versi 2000	Overall: 10 (8%) ER: 3 (3%) abdominal pain: 1 nausea/dysphagia: 1 edema/rash: 1 IR: 7 (6%) dry mouth: 1 blurred vision: 1 nausea: 1 impaired urination, edema, blood pressure changes, UTI: 1 gastric obstruction: 1 UTI: 1 edema and pain: 1	Mean duration of treatment/follow-up not stated. Only dry mouth reported in detail.
Birns 2000	1 (considered unlikely due to study drug)	Mixed types of incontinence Study included a run-in phase to establish tolerability, patients with adverse events excluded during run-in

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Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Radomski 2004	Single center Open label pilot crossover trial Canada	Efficacy analysis included all subjects age ≥18 with urodynamically confirmed detrusor instability, frequent micturition (≥ 8/day) and/or urinary incontinence (≥2 incontinence period /day) during washout period. Patients could be on oxybutynin IR prior to study. Safety analysis included all patients receiving at least one dose of medication.	Use of medications other than study meds, primary diagnosis of stress incontinence, allergy to anticholinergics/antispasmodics, conditions contraindicating anticholinergic therapy, large daily fluid intake (>6 liters), hepatic/renal disease, interstitial cystitis, uninvestigated hematuria or hematuria secondary to a malignancy, history of recurrent urinary tract infection, indwelling catheter, bladder training within 14 days of entry, drug/alcohol abuse, recent initiation of estrogen, clinically significant neurological disorder, morbid obesity, pregnant or nursing, child bearing age not using contraceptives
Anderson 1999	RCT multi-center USA	Men or women, community dwelling, in good health with urge incontinence or mixed urge incontinence with primary urge component (6+ urge incontinence episodes/wk)	known treatable cause, greater than 100mL post void residual, prostate symptoms in the past 9 mos, risk for complete urinary retention, taken drugs other than hyoscyamine, oxybutynin, propantheline for incontinence, positive urine drug screen, glaucoma, gastric narrowing or myasthenia gravis
Nilsson 1997	Crossover study Multicenter Finland	Females with a history of urge incontinence and detrusor instability confirmed by cystometry.	Stress incontinence (as measured by questionnaire), use of loop diuretics, prazosin, anticholinergics, or antidepressants with anticholinergic effects.

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Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Radomski 2004	Oxy IR twice daily at dose at discretion of investigator for first two weeks (if on Oxy IR prior same dose continued 3 patients, if deemed obese 5 mg twice daily otherwise 2.5 mg twice daily), followed by two week washout, followed by Oxy CR 15 mg once daily for four weeks	Subjects not permitted to use other medications to alleviate incontinence during the 8 week trial	Satisfaction rating at end of week 2 and week 8 using a four point scale.
Anderson 1999	ER Oxy 5-30mg once daily or IR Oxy 5mg once to four times daily. Doses started at 5mg and adjusted during 4 to 7 day intervals, optimal dose taken for 7 days. dose reductions allowed for adverse effects	not given	7-day voiding diary and incontinence pad use at baseline and after "final dose" achieved Duration of study varied by patient, depending on titration needs.
Nilsson 1997	Oxy ER 10mg once daily Oxy 5mg twice daily 60 days, no washout between arms	none reported	urinary diary, disability questionnaire, and assessment of effect of symptoms on general welfare, work, exercise, urge, symptoms of leakage, and frequency by VAS measured at 7-8 wks

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Radomski 2004	#screened not reported. 12 included for safety analysis. 9 included for efficacy analysis (completed 8 week study)	For efficacy analysis mean age = 69 female 67% For safety analysis mean age not reported, % females same. Ethnicity not reported	Baseline/washout: number of voluntary voids/day 10.4;number of UI episodes/day 2.7. Patients diagnosed for average 10.8 months prior to study entry (SD=6.6).	3/0/9
Anderson 1999	158 screened 105 enrolled 93 analyzed	Mean age: ER 59yrs; IR 60yrs % Female: ER 94%, IR 90%	mean urge incontinence episodes/wk: ER 27.4, IR 23.4 mean voids/wk: ER 48.3, IR 51.5	withdrawn ER 7 IR 6 Lost to F/U not reported analyzed 93 (efficacy analysis)/105 (safety analysis)
Nilsson 1997	17 enrolled	mean age 46yrs (range 37-65) 100% female	none reported	1 "due to the sponsors' request" after first study period 16 analyzed in ER group, 17 in IR group

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Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Radomski 2004	ER reduced UI episodes from baseline 45% (p=0.13) vs IR 7% (p=0.58). Treatment scores differed by 1.0 UI episode/day (p=0.11) favoring ER. ER reduced daily void frequency by 14 % compared to IR 6% (p=0.41). No significant difference in mean satisfaction scores at end of IR and ER phases.
Anderson 1999	mean reduction in number of Urge Incontinence/wk ER: 22.6 IR:20.3 (NS) mean reduction in total incontinence episodes ER: 23.3 IR: 22.5 (NS)
Nilsson 1997	Mean change in micturitions/d: ER: 2.6, IR 2.8 mean change in degree of disability: ER: 5.1, IR 4.6 Mean change in VAS Scores: general welfare: ER 36, IR 39 work ER 33 IR41 exercise ER 31 IR 35 urge ER 32 IR 35 leakage ER 27 IR 35 frequency ER 36 IR 37 No comparisons were statistically significant

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Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Radomski 2004	Adverse events collected during scheduled visits and entered in diary. Mild dry mouth most frequent followed by unspecified pain
Anderson 1999	Spontaneously reported and anti-cholinergic effects assessed at each study visit Dry mouth: ER 68%, IR 87% (p = 0.04) Moderate to severe dry mouth: ER 25%, IR 46% (p = 0.03) Somnolence: ER 38%, IR 40% Blurred vision: ER 28%, IR 17% Constipation: ER 30%, IR 31% Dizziness ER 28%, IR 38%
Nilsson 1997	Patients reported on a questionnaire throughout study, classified as mild, moderate, severe 14/16 on ER, 5/17 on IR reported at least one adverse event Dry mouth: ER 69%, IR 82% Headache ER 44%, 41% Dyspepsia ER 31%, IR 12% fatigue ER 13%, 24% Blurred vision 25%, IR 12% % Severe: ER 17%, IR 14% reported that these were NS, but unclear what data being compared.

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Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Radomski 2004	3 withdrawals due to adverse events--stomach pain (1), mild peripheral edema (1), severe vision distortion	Unusual design--different treatment duration for two drugs and dosing for Oxy may have been low
Anderson 1999	2 (4%) in each group due to anticholinergic adverse events	Previously all pts had responded to IR oxy Very high incidence of adverse events - may reflect the aggressive dose titration Duration of study (mean) not reported, very little data on final dose in either group
Nilsson 1997	none reported	Very high numbers of subjects reporting adverse events

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Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Barkin 2004	RCT Multicenter Canada	Men and women, age ≥18, demonstrated UI (≥ 7 episodes/wk) and urinary frequency (≥8 micturitions/d) during baseline no-treatment period, currently not using any other medication for UI	Post-void residual volume >100mL, unstable dosage of any drug with anticholinergic or diuretic/antidiuretic side effects, allergy or previous life-threatening side effects with anticholinergic/ antispasmodic medications, primary diagnosis of stress UI, conditions contraindicating anticholinergic therapy, daily fluid intake >3L, hepatic/renal disease, diagnosed painful bladder syndrome, uninvestigated voiding difficulty with risk of urinary retention, uninvestigated hematuria or hematuria secondary to malignant disease, UTI or history of recurrent UTI (>3 UTIs/y), in-dwelling catheter or bladder training within 14d of screening, drug/alcohol abuse, untreated psychiatric conditions affecting completion of voiding diaries, bladder outlet obstruction, pregnancy or breast feeding and failure to use reliable contraception in women of childbearing potential

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Barkin 2004	No-treatment baseline period for 3 wks Oxy IR 5mg 3X/day, dose titration in 5mg increments in 2 wks followed by stable-dose phase for 4 wks Oxy ER 15mg 1X/day, dose titration in 5mg increments in 2 wks followed by stable-dose phase for 4 wks	Subjects not permitted to use other medications to alleviate incontinence during the 9 week trial period	24h-patient diary assessed during final 2 wks of treatment, used the Purdue Urgency Questionnaire to assess severity of urgency and frequency of urgency [severity scored on scale or 1 (no urgency or ability to delay voiding) to 5 (≥ 6 episodes of urgency or inability to delay voiding/urine leakage with urge)], used Incontinence Impact Questionnaire (evaluates effect of incontinence on 8 activities of daily living) and the Urogenital Distress Inventory (evaluates distress associated with 8 urinary symptoms) to assess changes in QoL.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Barkin 2004	NR / NR / 125 enrolled (Oxy IR 60, Oxy ER 65)	Of 94 subjects evaluable for efficacy: Oxy ER: 91% women; mean age 58y (range 26-78y), 38% >65y Oxy IR: 90% women; mean age 60.6y (range 26-83y), 44% >65y	41% of patients were taking ≥4 medications at study entry	Withdrawals: Oxy IR:22 (37%); Oxy ER:13 (20%) Lost to follow-up: Oxy IR: 2; Oxy ER:0 Number analyzed for efficacy: 94 defined as completing ≥2 weeks in the stable-dose phase and did not have major protocol violations/ Reported adverse events were analyzed for all randomized patients

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Barkin 2004	Oxy ER vs Oxy IR for all comparisons (endpoint minus baseline): Mean reduction in incontinence episodes/wk: 13.9 vs 16.9 (p=NS) Mean reduction in episodes of voluntary micturition/day: 1.8 vs 2.4 (p=NS) Mean increase in vol. of urine voided/micturition: 25mL vs 40mL (p=NS) Mean score of urgency decrease: 1.0 vs 1.3 (p=NS) Mean severity score decrease (1: no urgency or ability to delay voiding, to 5: ≥6 episodes of urgency or inability to delay voiding): 1.5 vs 1.4 (p=NS) Mean number of pads/day: 0.6 vs 0.5 (p=NS)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Barkin 2004	AE data collected during scheduled visits and in diary. AE data included tolerable/not tolerable questions, # and severity of the events, lab assessments: clinical chemistry and hematological (at baseline and end of study) Oxy ER vs Oxy IR (%) Dry mouth: overall: 68% vs 72%; moderate or severe: 38% vs 45% Pharyngitis (dry throat): 35% vs 40% Dry skin: 17% vs 12% Diarrhea: 14% vs 5% Headache: 12 % vs 22% Urinary tract infection: 12 % vs 18% Dizziness: 11% vs 18% Dyspepsia: 11% vs 17% Rhinitis: 11% vs 15% Abdominal pain: 9% vs 10% Asthenia: 18% vs 15% Constipation: 8% vs 10% Taste perversion: 8% vs 12% Cough increased: 6% vs 13% Dysphagia: 6% vs 13% Dry eyes: 3% vs 15% Nausea: 5% vs 17%

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Barkin 2004	Oxy IR: 12 (20%) Oxy ER: 11 (17%)	sponsored by Purdue Pharma

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Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Extended Release vs. Immediate Release (ER vs IR)			
Tolterodine ER vs Tolterodine IR			
Van Kerrebroeck 2001	RCT Multicenter Multinational	Men or women, age 18+ with urinary frequency (8+ micturitions/24h), urge incontinence (5+ /week), or symptoms of overactive bladder for 6+ months	Stress Incontinence, total daily urine volume 3+ L, contraindications to anticholinergic drugs, hepatic/renal disease, UTI/cystitis, hematuria, bladder outlet obstruction, electrostimulation or bladder training, urinary catheter, taking drugs inhibiting CYP 3A4 liver enzymes,
Swift 2003 Re-analysis of data for women only in Van Kerrebroeck 2001 study (above)	RCT Multicenter International	Subset of above study: women, age 18+ with urinary frequency (8+ micturitions/24h), urge incontinence (5+ /week), or symptoms of overactive bladder for 6+ months	Stress Incontinence, total daily urine volume 3+ L, contraindications to anticholinergic drugs, hepatic/renal disease, UTI/cystitis, hematuria, bladder outlet obstruction, electrostimulation or bladder training, urinary catheter, taking drugs inhibiting CYP 3A4 liver enzymes,

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Extended Release vs. Immediate Release (ER vs IR)			
Tolterodine ER vs Tolterodine IR			
Van Kerrebroeck 2001	Tol ER 4mg once daily or Tol IR 2mg or Placebo twice daily x 12 wks	none reported	micturition diary assessed at baseline and 12 wks 1 week f/u
Swift 2003 Re-analysis of data for women only in Van Kerrebroeck 2001 study (above)	Tol ER 4 mg (n=417) once daily vs. Tol IR 2 mg twice daily (n=408) vs. Pla (n=410) for 12 wks.	Other treatments for OAB not permitted, except estrogen treatment commenced >2 months prior.	micturition diary assessed at baseline and 12 wks 1 week f/u

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Extended Release vs. Immediate Release (ER vs IR)				
Tolterodine ER vs Tolterodine IR				
Van Kerrebroeck 2001	1529 randomized into study Tol ER: 507 Tol IR: 514 placebo: 508	median age 60yrs 81% Female	Mean number incontinence episodes/wk: ER 22, IR 23, Placebo 23 Mean number micturitions/d: ER 11, IR 11, Placebo 11 previous therapy for UI ER: 53%, IR 54%, Placebo 52% poor efficacy ER: 3%, IR 38%, Placebo 41%	187 (12%)
Swift 2003 Re-analysis of data for women only in Van Kerrebroeck 2001 study (above)	Screened NR Eligible NR Enrolled=1235	Mean age=59 All female 95% white 4% black 1% other	Previous drug therapy for OAB=55% Mean number incontinence episodes/wk ER 22, IR 23, Placebo 24 Mean number voluntary micturitions/d: ER 11, IR 11, Placebo 11 previous therapy for UI ER: 56%, IR 54%, Placebo 55%	143 (12%)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Extended Release vs. Immediate Release (ER vs IR)	
Tolterodine ER vs Tolterodine IR	
Van Kerrebroeck 2001	Mean change in incontinence episodes/wk: ER -11.8, IR -10.6, Placebo -6.9 Mean change in number of micturitions/wk: ER -3.5, IR -3.3, Placebo -2.2 Mean change in number of pads used/d: ER -0.5, IR -0.5, Placebo -0.2 Median Percent Change in Incontinence episodes (time period not stated): ER -70%, IR -60%, Placebo -33% (p< 0.05 ER vs IR)
Swift 2003 Re-analysis of data for women only in Van Kerrebroeck 2001 study (above)	Mean change in incontinence episodes/wk: ER -11.8, IR -10.1, Placebo -7.2 (p=0.036 ER vs IR) Mean change in number of voluntary micturitions/wk: ER -1.9, IR -1.7, Placebo -1.2 Mean change in number of pads used/d: ER -0.6, IR -0.5, Placebo -0.2 (all ER and IR vs. Pla statistically significant)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Extended Release vs. Immediate Release (ER vs IR)	
Tolterodine ER vs Tolterodine IR	
Van Kerrebroeck 2001	Spontaneously reported events were categorized and causation assigned dry mouth further categorized Dry mouth: ER 23%, IR 30%, Placebo 8% Constipation: ER 6%, IR 7%, Placebo 4% Headache: ER 6%, IR 4%, Placebo 5%
Swift 2003 Re-analysis of data for women only in Van Kerrebroeck 2001 study (above)	Reporting details NR. Tol ER vs. Tol IR vs. Pla: Dry mouth: 105/415 (25.3%) vs. 127/407 (31.2%) vs. 33/410 (8.0%) Dry skin: 2 (0.5%) vs. 5 (1.2%) vs.1 (0.2%) Dizziness: 7 (1.7%) vs. 7 (1.7%) vs. 4 (1.0%) Somnolence: 12 (2.9%) vs. 11 (2.7%) vs. 8 (2.0%) Abnormal vision: 5 (1.2%) vs. 4 (1.0%) vs. 2 (0.5%) Constipation: 27 (6.5%) vs. 27 (6.6%) vs. 14 (3.4%)

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Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Extended Release vs. Immediate Release (ER vs IR)		
Tolterodine ER vs Tolterodine IR		
Van Kerrebroeck 2001	88 (5.7%) ER: 27 (5.3%) IR: 28 (5.5%) placebo 33 (6.5%)	Dry mouth classified as mild/moderate/severe but data only reported for ER
Swift 2003 Re-analysis of data for women only in Van Kerrebroeck 2001 study (above)	Tol ER 22/417 (5%) vs. Tol IR 20/408 (5%) vs. Pla 26/410 (6%)	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Extended Release vs. Immediate Release (ER vs IR)			
Oxybutynin ER vs. Tolterodine IR			
Appell 2001	RCT Multicenter USA	Overactive bladder between 7 and 50 episodes per week of urge incontinence 10+ voids/24 hr mixed stress and urge incontinence if the majority of accidents were related to urinary incontinence	Other causes of incontinence post void residual volume more than 150ml delivered baby pelvic bladder vaginal or prostate symptoms in past 6 months risk of complete urinary retention clinically important medical problems organ abnormalities hematuria positive urine culture narrow angle glaucoma pelvic organ prolapse gastric conditions anticholin drugs must be discontinued known allergy alcohol or drug abuse (current) unable to follow direction or schedules not able to swallow tablets whole

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Extended Release vs. Immediate Release (ER vs IR)			
Oxybutynin ER vs. Tolterodine IR			
Appell 2001	ER Oxy 10mg once daily Tol 2mg twice daily 12 week study	Not given	Safety monitoring patient reporting at each study visit 2,4,8,12 weeks number of urge incontinence episodes at 12 weeks vs. baseline used 7 day urinary diary

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Extended Release vs. Immediate Release (ER vs IR)				
Oxybutynin ER vs. Tolterodine IR				
Appell 2001	378 randomized (Oxy ER 185, Tol 193) 332 completed (Oxy ER 160, Tol 172)	Mean Age: 59 yrs Female: 83% Ethnicity: White 87% African American 6% Hispanic 4% Asian 2% Other 1%	Drug naïve Oxy ER: 109 Tol: 119	Overall: 46 (21 Tol, 25 Oxy ER) Lost to Follow-up Oxy ER: 3 Tol:3

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Extended Release vs. Immediate Release (ER vs IR)	
Oxybutynin ER vs. Tolterodine IR	
Appell 2001	Mean number of urge incontinence episodes/wk Oxy ER -19.5, Tol -16.3 Mean change in micturition frequency Oxy ER -24.7, Tol -20.1

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Extended Release vs. Immediate Release (ER vs IR)	
Oxybutynin ER vs. Tolterodine IR	
Appell 2001	Patient reported dry mouth occurred in equal proportion in each group both groups had similar rates of dry mouth and other adverse effects

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Extended Release vs. Immediate Release (ER vs IR)		
Oxybutynin ER vs. Tolterodine IR		
Appell 2001	Oxy ER 14 Tol 15	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Sand et al. 2004 OBJECT (subanalysis of women only)	RCT Multicenter USA	see Appell, 2001	see Appell, 2001

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Sand et al. 2004 OBJECT (subanalysis of women only)	Oxy ER 10mg once daily Tol 2mg twice daily 12 week study	see Appell, 2001	Subjects completed 7-day voiding diaries at baseline and 12-weeks

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Sand et al. 2004 OBJECT (subanalysis of women only)	315 women enrolled/ 276 completed study	mean age: Oxy 58.4y and Tol 58.8y 100% female	Naïve to anticholinergics: Oxy 60.5% and Tol 60.7%	see Appell, 2001

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Sand et al. 2004 OBJECT (subanalysis of women only)	see Appell, 2001 Decrease in urge incontinence episodes: Oxy ER: -21.9, Tol: -20.4 Mean decrease in micturition frequency episodes Oxy ER: -23.7, Tol: -20.4 Total decrease incontinence episodes Oxy ER: -17.9, Tol: -15.1

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Sand et al. 2004 OBJECT (subanalysis of women only)	see Appell, 2001 Oxy ER vs. Tol Dry mouth: 28.3% vs 33.7% Constipation: 8.6% vs 6.7% Impaired urination/urinary retention: 4.0% vs 1.2% Blurred vision: 2.6% vs 0.6% Dizziness: 3.9% vs 4.3% Somnolence: 3.3% vs 1.8% Insomnia: 0.7% vs 1.8% Nervousness: 0.0% vs 1.2% Headache: 9.2% vs 10.4% Dyspepsia: 5.3% vs 6.1% Nausea: 3.3% vs 1.8% Vomiting: 2.0% vs 1.8%

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Sand et al. 2004 OBJECT (subanalysis of women only)	withdrawals due to AE: Oxy 11 patients and Tol 12 patients	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Extended Release vs. Immediate Release (ER vs IR)			
Tolterodine ER vs. Oxybutynin IR			
Homma 2003	RCT Multicenter Japan & Korea	Men and women, aged ≥20 with symptoms of urinary urgency, frequency (>/= 8 voids/24h), incontinence (>/= 5 episodes/wk), or overactive bladder for ≥6months.	Demonstrable stress incontinence; total daily urinary volume >3 L, avg volume >200 mL; significant hepatic or renal disease; any contraindication to anticholinergic treatment; symptomatic or recurrent UTI; interstitial cystitis; haematuria or BOO; indwelling catheter or intermittent self-catheterization; electrostimulation or bladder training within 14 days or expected during study.
Homma 2004 subanalysis of HRQoL in Japanese OAB patients	RCT Multicenter Japan & Korea (this subanalysis looked at Japanese pts only)	Men and women, aged ≥20 with symptoms of OAB for ≥ 6 months and urinary urgency, frequency (≥ 8 voids/24h), incontinence (≥ 5 episodes/wk), or overactive bladder for ≥6months.	Korean patients were excluded from analysis due to lack of valid King's Health Questionnaire in Korean language
Darifenacin ER vs. Oxybutynin IR			

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Extended Release vs. Immediate Release (ER vs IR)			
Tolterodine ER vs. Oxybutynin IR			
Homma 2003	Tol ER 4 mg once daily vs. Oxy IR 3 mg three times daily x 12 wks	Not allowed within 14 days of trial: anticholinergic drug or unstable dosage of any drug with anticholinergic side-effects, any drug for OAB (except estrogen started >2months), potent CYP3A4 inhibitors, or any investigational drug.	Voiding diary for 7 days at baseline and wk 12. Primary outcome, change in median number of incontinence episodes. Secondary endpoint, median number and volume of voids, number of incontinence pads used. Subjective assessment by 6-pt perception of bladder condition, 3-pt perception of urgency, and 3-pt assessment of treatment benefit. Quality of life measured by KHQ at baseline and 12 wks
Homma 2004 subanalysis of HRQoL in Japanese OAB patients	Tol ER 4 mg once daily vs. Oxy IR 3 mg three times daily x 12 wks	See Homma 2003	Micturition diary completed during 7 days of run-in (baseline and the last 7days of treatment (week 12) King's Health Questionnaire (KHQ) was used to determine health related quality of life (HRQoL) at baseline and week 12
Darifenacin ER vs. Oxybutynin IR			

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Extended Release vs. Immediate Release (ER vs IR)				
Tolterodine ER vs. Oxybutynin IR				
Homma 2003	Screened NR Eligible NR Enrolled = 608 Tol ER = 240 Oxy IR = 246 Pla = 122	Tol/Oxy grps Age range 26-84, mean age 59.3 Female 70.2% Ethnicity: Japanese 48.2% Korean 51.8%	Previous OAB drug therapy= 23% "Causes severe problems" or "many severe problems"=52%	3 withdrawn before treatment, not included in ITT Total withdrawn: Tol 25 (10.4%) Oxy 57 (23.2%) Analyzed: 605
Homma 2004 subanalysis of HRQoL in Japanese OAB patients	293 enrolled: Tol 114, Oxy 122, Placebo 57	Mean age: 63.4 y Range: 25-88y % female: 66.5% 100% Japanese	prior drug therapy for OAB: 18.4% of total (Tol 19.3%, Oxy 15.6%, Pla 22.8%) % with ≥5 incontinence episodes/wk: 98.6% % with ≥ 8 micturitions/24h: 97.9% % with mean vol. voided ≤ 200ml: 97.6%	see Homma, 2003, not specifically reported in current article
Darifenacin ER vs. Oxybutynin IR				

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Extended Release vs. Immediate Release (ER vs IR)	
Tolterodine ER vs. Oxybutynin IR	
Homma 2003	Diaries percentage change Median incontinence episodes: Tol -78.6% vs. Oxy -76.5% (p=0.4469)) Median number voids: Tol -2.0 vs. Oxy -2.1 (p=0.3132) Pad usage: median change was 0 in all groups. Subjective measures Improvement in bladder condition: Tol 72% vs. Oxy 73% (NS) Deterioration in bladder condition: Tol and Oxy 5% vs Pla 8% Improved ability to hold urine: Tol 49% vs. Oxy 57% Treatment beneficial (much): Tol 42% vs. Oxy 53% (NS) KHQ quality of life Tol vs. Oxy :no statistically significant differences on any domain
Homma 2004 subanalysis of HRQoL in Japanese OAB patients	HRQoL Tol vs Oxy had no significant differences between the amount of improvement compared to each other on these parts of the KHQ: Incontinence impact, Role limitations, Physical limitations, Social limitations, Personal relationships, Emotions, Sleep and energy, Severity (coping) measure+L23, General health perception, and Symptom severity. The improvements were all significantly different from placebo except in Emotions and General health perceptions.
Darifenacin ER vs. Oxybutynin IR	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Extended Release vs. Immediate Release (ER vs IR)	
Tolterodine ER vs. Oxybutynin IR	
Homma 2003	Directly observed and spontaneously reported at visits 3 through 6, rated as mild, moderate or severe. (Tol vs. Oxy) Dry mouth: 80 (33.5%) vs. 131 (53.7%) p<0.001 Severe dry mouth: 0.4% vs 8.2% Dry eyes: 3 (1.3%) vs. 7 (2.9%) Blurred vision: 3 (1.3%) vs. 8 (3.3%) Constipation: 17 (7.1%) vs. 15 (6.1%) Somnolence: 1 (0.4%) vs. 4 (1.6%) Difficulty in micturition: 3 (1.3%) vs. 21 (8.6%)
Homma 2004 subanalysis of HRQoL in Japanese OAB patients	*Tol ER vs Oxy vs Pla* Dry mouth: 36.9% vs 61.5% vs 5.3% (p=0.002 for Tol vs Oxy) Severity of dry mouth: mild: 31.6% vs 45.1% vs 5.3% moderate: 5.3% vs 13.1% vs 0% severe: 0% 3.3% vs 0%
Darifenacin ER vs. Oxybutynin IR	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Extended Release vs. Immediate Release (ER vs IR)		
Tolterodine ER vs. Oxybutynin IR		
Homma 2003	Dry mouth: Tol 0.4% vs. Oxy 9.4% All events: Tol 5.0% vs. Oxy 17.1% p<0.001 Serious event, possibly drug related: 1 Oxy cardiac failure. No deaths and no clinically significant changes in lab or ECG values.	Compliance ≥75% of medication: Tol 98% vs. Oxy 93%
Homma 2004 subanalysis of HRQoL in Japanese OAB patients	See Homma, 2003 for overall withdrawals due to AE. Withdrawals due to AEs in Japanese pts: Oxy: 16.4% Tol: 5.3%	
Darifenacin ER vs. Oxybutynin IR		

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Zinner, 2005	RCT, DB Crossover Multicenter USA	Male or female, 18-85 years with urge incontinence (>4 sig incontinent episodes/week), urinary frequency (>8 voids/day)	Neurogenic bladder or stress incontinence, contraindications to antimuscarinic therapy, previous bladder or prostate surgery, bladder stones, acute or chronic UTI, sig urinary outflow obstruction, clinically sig concomitant disease

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Zinner, 2005	Dar ER 15, 30mg/day Oxy IR 5mg TID	Placebo	Daily paper voiding diaries

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Zinner, 2005	NR/NR/76	Mean age: 59.9 yrs Range: 33-84 yrs 93.4% females Ethnicity: NR	Mean weight (kg): 75.7 Mean # of incontinence episodes/week: 20.4 Mean # of urgency episodes/day: 9.3 Mean severity of urgency episodes (1=mild; 2=moderate; 3=severe): 2 Mean # of micturitions/day: 10.4	16/NR/58

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Zinner, 2005	Mean change from baseline in # of Incontinence episodes/week Dar ER 15: -10.99 vs Dar ER 30: -12.2 vs Oxy IR: -11.57 vs Pla: -6.38 (p<0.05 for each compared to placebo) Mean change from baseline in # of urgency episodes/day Dar ER 15: -1.27 vs Dar ER 30: -1.63 vs Oxy IR: -1.1 vs Pla: -0.51 (p<0.05 for each compared to placebo) Mean change from baseline in # of micturitions/day Dar ER 15: -1.14 vs Dar ER 30: -1.62 vs Oxy IR: -1.23 vs Pla: -0.85 (p<0.05 for Dar ER 30 vs placebo and Dar ER 30 vs Dar ER 15)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Zinner, 2005	Self report by patient Incidence of dry mouth Dar ER 15: 13.1% vs Dar ER 30: 34.4% vs Oxy IR: 36.1% vs Pla: 4.9% (p<0.05 for Dar ER 15 vs Oxy IR and for Dar ER 30 vs Pla and for Oxy IR vs Dar ER 15 for Oxy IR vs Pla) Incidence of constipation Dar ER 15: 9.8% vs Dar ER 30: 21.3% vs Oxy IR: 8.2% vs Pla: 3.3% (p<0.05 for Dar 30 ER vs Pla and Dar ER 30 vs Oxy IR) Incidence of blurred vision Dar ER 15: 0% vs Dar ER 30: 0% vs Oxy IR: 3.3% vs Pla: 0% (NS) Incidence of dizziness Dar ER 15: 0% vs Dar ER 30: 0% vs Oxy IR: 1.6% vs Pla: 0% (NS)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Zinner, 2005	5 withdrew due to AEs	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Extended Release vs. Extended Release (ER vs ER)			
Oxybutynin ER vs.Tolterodine ER			
Sussman 2002	Two RCTs (one open-label Tol ER 2mg vs. 4mg, the other blinded Oxy ER 5mg or 10mg) Multicenter USA	Male or female, 18+ yrs, with overactive bladder defined by symptoms of urinary frequency and urgency with or without incontinence. Inclusion/exclusion criteria identical for both protocols.	Pure stress incontinence, urinary retention, gastric retention or uncontrolled narrow-angle glaucoma, significant hepatic or renal dysfunction, symptomatic or recurrent UTI, use of electrostimulation, bladder training, pelvic floor exercise within 1 week, indwelling or intermittent catheterization and any contraindication to antimuscarinic therapy.
Diokno 2003 OPERA	RCT Multicenter USA	Women, aged ≥18, with documented 21-60 urge urinary incontinence episodes per week and avg ≥10 voids per day.	Treatable genitourinary conditions that could cause incontinence, 2 postvoid residual volumes >150 mL, pronounced risk of developing complete urinary retention, clinically important medical problems that could lead to undue risk of anticholinergic effects, hematuria, uncontrolled narrow-angle glaucoma, obstructive uropathy, reduced gastrointestinal motility, and known hypersensitivity to study medications.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Extended Release vs. Extended Release (ER vs ER)			
Oxybutynin ER vs.Tolterodine ER			
Sussman 2002	Tol ER 2mg or 4mg once daily Oxy ER 5mg or 10mg once daily x 8 weeks No dose adjustments allowed	None reported	Patient assessment of symptoms based on 6-point scale (0 = no problems, 6 = severe problems) at baseline and 8 weeks Patient and Physician rated benefit (No, yes - a little, and yes-very much) at 8 weeks
Diokno 2003 OPERA	Oxy ER 10 mg/day vs. Tol ER 4 mg/day x 12 wks	None reported	Diaries at baseline week, and weeks 2, 4, 8, 12. Outcomes: total incontinence episodes, total incontinence episodes, micturition frequency.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Extended Release vs. Extended Release (ER vs ER)				
Oxybutynin ER vs.Tolterodine ER				
Sussman 2002	Number screened/eligible not stated. 1289 enrolled 669 Tol (333 Tol 2mg, 336 Tol 4mg) 620 Oxy (313 Oxy 5mg, 307 Oxy 10mg)	Mean age 62.6 yrs Female 75% Caucasian 84% Black 10% Hispanic 5%	Prevalence of incontinence symptoms: 62% overall (61% Tol, 64% Oxy) Prior Drug Therapy: 19% overall (17% Tol, 21% Oxy) Majority moderate to severe symptoms	89 patients excluded from analysis (reasons/group assigned not reported) 209 withdrew: 48 Tol 2mg (14%) (of these 2 lost to follow-up) 39 Tol 4mg (12%), (of these 4 lost to follow-up) 59 Oxy 5mg (19%) (of these 0 lost to follow-up) 63 Oxy 10mg (21%) (of these 2 lost to follow-up) Analyzed: 313 Tol 2mg, 316 Tol 4mg, 286 Oxy 5mg, 285 Oxy 10mg
Diokno 2003 OPERA	Screened 1485 Eligible NR Enrolled 790 Oxy ER= 391 Tol ER = 399	Mean age=60 100% female Ethnicity: White 85% Black 8% Hispanic 6%	Prior treatment anticholinergic drugs=47%	Total withdrawn: Oxy 52 (13.3%) Tol 42 (10.5%) Lost to followup: Oxy 13 (3.3%) vs. Tol 3 (0.8%) Sample size at baseline, wk 2,4,8,12: Oxy= 382,380,365,346,336,382 Tol = 393,390,383,370,355,393

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Extended Release vs. Extended Release (ER vs ER)	
Oxybutynin ER vs.Tolterodine ER	
Sussman 2002	Patients reporting improvement in symptoms: Tol 2mg 60%, Tol 4mg 70% Oxy 5mg 59%, Oxy 10mg 60% (p<0.01 for all vs Tol 4mg) Degree of change in symptoms was greater in Tol 4mg vs Oxy 10mg (p<0.01) The peak improvement was 1 point for Tol 4mg and 0 points for Oxy 10mg. Subgroup analysis of patients reporting improvement in symptoms who had moderate to severe symptoms at baseline: Tol 4mg 77%, Oxy 10mg 65% (p<0.01) Subgroup analysis of patients reporting improvement in symptoms who were drug naive at baseline: Tol 2mg 60%, Tol 4mg 69% Oxy 5mg 60%, Oxy 10mg 61% (NS) Subgroup analysis of patients reporting improvement in symptoms who were drug experienced at baseline: Tol 2mg 57%, Tol 4mg 75% Oxy 5mg 59%, Oxy 10mg 54% (NS) No difference between groups on patient or physician assessment of benefit - data not presented
Diokno 2003 OPERA	Mean change in urge incontinence episodes: Oxy -26.3 vs. Tol -25.5 (NS) Mean change in total incontinence episodes: Oxy -31.1 vs. Tol -28.6 (NS) Decrease in mean micturition frequency: Oxy 28.4 vs. Tol 25.2 (p=0.003) No incontinence in last week: Oxy 23.0% vs. Tol 16.8% (p=0.03)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Extended Release vs. Extended Release (ER vs ER)	
Oxybutynin ER vs.Tolterodine ER	
Sussman 2002	Dry mouth evaluated on 100 mm Visual Analog Scale(0 - least problem, 100 - most severe) at baseline and 8 weeks Change in dry mouth severity was dose dependent for both drugs. Tol 2mg vs. Tol 4mg p = 0.09, Oxy 5mg vs. Oxy 10mg p=0.05 Change in severity of dry mouth:(100 point VAS) Tol 2mg 2.3 Tol 4mg 6.0 Oxy 5mg 6.3 Oxy 10mg 11.3 (p=0.03 Tol 4mg vs. Oxy 10mg)
Diokno 2003 OPERA	Data collected at each visit or any time reported by participant, rated as mild, moderate, severe. Dry mouth: Oxy 116/391 (29.7%) vs. Tol 89/399 (22.3%) (p=0.02) mild: oxy 87/391 (22.3%) vs Tol 69/399 (17.3%) mod-severe: Oxy 29/391 (7.4%) vs Tol 20/399 (5%) Constipation: Oxy 25/391(6.4%) vs. 31/399 (7.8%) (NS)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Extended Release vs. Extended Release (ER vs ER)		
Oxybutynin ER vs.Tolterodine ER		
Sussman 2002	Only reported for Tol 4mg (19, 6%) and Oxy 10mg 37 (13%).	Report does not make clear why subjects excluded from intention to treat analysis, does not report all withdrawal reasons, does not report adverse event withdrawals for all doses, reports no side effect data other than change in dry mouth. Clinical significance of change in dry mouth not clear.
Diokno 2003 OPERA	All events: Oxy 20/391 (5.1%) vs. Tol 19/399 (4.8%) Due to dry mount: Oxy 7, Tol 4	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Chu et al, 2005 OPERA Extension (subanalysis of CNS AEs)	RCT, Multicenter, USA	see Diokno 2003	see Diokno 2003
Anderson 2006 OPERA post-hoc analysis based on history of prior anticholinergic treatment	RCT, Multicenter, USA	see Diokno 2003	see Diokno 2003

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Chu et al, 2005 OPERA Extension (subanalysis of CNS AEs)	Oxy ER 10mg/day vs. Tol ER 4mg/day x 12 weeks	see Diokno 2003	Data collected at each visit or anytime reported by participant. AE cited as reasons for withdrawal were specifically identified for analysis. AE were coded the FDA "Coding Symbols for Thesaurus of Adverse Reaction Terms" (COSTART V). Focus on AE that COSTART includes under the CNS classification. For additional information see Diokno, 2003
Anderson 2006 OPERA post-hoc analysis based on history of prior anticholinergic treatment	Oxy ER 10mg/day vs. Tol ER 4mg/day x 12 weeks	see Diokno 2003	Data collected at each visit or anytime reported by participant. AE cited as reasons for withdrawal were specifically identified for analysis. AE were coded the FDA "Coding Symbols for Thesaurus of Adverse Reaction Terms" (COSTART V). Focus on AE that COSTART includes under the CNS classification. For additional information see Diokno, 2003

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Chu et al, 2005 OPERA Extension (subanalysis of CNS AEs)	see Diokno 2003	see Diokno 2003	see Diokno 2003	see Diokno 2003
Anderson 2006 OPERA post-hoc analysis based on history of prior anticholinergic treatment	see Diokno 2003	see Diokno 2003	see Diokno 2003 group 1: prior anticholergic treatment, n=373 Oxy ER (180), Tol ER (193) group 2: no prior anticholergic treatment, n=417 Oxy ER (211), Tol ER (206)	see Diokno 2003 group 1: prior anticholergic treatment, n(%) Oxy ER 15(8.3)/3(1.7)/ITT, Tol ER 17 (8.8)/1(0.5)/ITT group 2: no prior anticholergic treatment Oxy ER 37 (17.5)/10(4.7)/ITT, Tol ER 25 (12.1)/2(1.0)/ITT

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Chu et al, 2005 OPERA Extension (subanalysis of CNS AEs)	COSTART V CNS AEs including dizziness, insomnia, somnolence, anxiety, hypertonia, nervousness, tremor and confusion (reported in mild, moderate or severe categories). Oxy ER (n=391) vs Tol ER (n=399) (p=NS for all comparisons) Any CNS AE: 9.0% vs 8.3% Dizziness: 3.8% vs 2.5% Somnolence: 1.0% vs 2.3% Insomnia: 1.8% vs 0.8% Depression: 1.3% vs 0.8% Hypertonia: 0.5% vs 1.0%
Anderson 2006 OPERA post-hoc analysis based on history of prior anticholinergic treatment	Group 1 VS. Group 2 Mean change in urge incontinence episodes: Oxy -25.4 vs. Tol -24.1 (p=0.306) VS. Oxy -27.2 vs. Tol -26.9 (p=0.663) Mean change in total incontinence episodes: Oxy -28.8 vs. Tol -26.5 (p=0.086) VS. Oxy -33.1 vs. Tol -30.6 (p=0.886) Decrease in mean micturition frequency: Oxy 24.4 vs. Tol 21.8 (p=0.052) VS. Oxy 31.7 vs. Tol 28.5 (p=0.035) No incontinence in last week: Oxy 23.6% vs. Tol 15.1% (p=0.038) VS. Oxy 29.4% vs. Tol 26.4% (p=0.495)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Chu et al, 2005 OPERA Extension (subanalysis of CNS AEs)	Incidence and severity of AEs judged possible or probably related to Oxy ER and Tol ER during OPERA study: All comparisons are for Oxy ER (mild, moderate, severe) vs Tol ER (mild, moderate, severe) Dizziness: (1.8% , 0.8%, 0%) vs (1.5%, 0.5% , 0%) Insomnia: (0.8%, 0.5%, 0%) vs (0%, 0%, 0%) Somnolence: (0.5%, 0.3%, 0%) vs (1.5%, 0.5%, 0%) Anxiety: (0.5%, 0.3%, 0%) vs (0%, 0%, 0%) Hypertonia: (0%, 0.3%, 0%) vs (0%, 0%, 0%) Nervousness: (0%, 0.3%, 0%) vs (0%, 0%, 0%) Tremor: (0.3%, 0%, 0%) vs (0.3%, 0%, 0%) Confusion: (0.3%, 0%, 0%) vs (0%, 0%, 0%) Not judged to be related to treatment: Oxy ER: depression, increased libido, or vertigo. Tol ER: abnormal dreams, anxiety, depression, facial paralysis, hypertonia, insomnia, paresthesia, or vertigo.
Anderson 2006 OPERA post-hoc analysis based on history of prior anticholinergic treatment	Group 1 (n=180) VS. Group 2 (n=193), all nsd except where p value reported Data collected at each visit or any time reported by participant, rated as mild, moderate, severe. n (%) Dry mouth: any degree: 58 (32.3) vs. 37 (19.2), p=0.004 VS 58 (27.5) vs. 52 (25.2) mild: Oxy 44(24.4) vs Tol29 (15.0) VS Oxy 47 (22.3) vs Tol40 (19.4) mod-severe: Oxy 18 (10.0) vs Tol 8 (4.1) VS Oxy 13 (6.2) vs Tol 12 (5.8) Constipation: Oxy 14 (7.8) vs Tol 10 (5.2) VS Oxy 11 (5.2) vs Tol 21 (10.2) Diarrhea: Oxy 14 (7.8) vs Tol 11 (5.7) VS Oxy 17 (8.1) vs Tol 14 (6.8) Headache: Oxy 8 (4.4) vs Tol 10 (5.2) VS Oxy 14 (6.6) vs Tol 14 (6.8)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Chu et al, 2005 OPERA Extension (subanalysis of CNS AEs)	Withdrawals due to CNS AEs: Oxy: 6 (1.5%) Tol: 2 (0.5%)	
Anderson 2006 OPERA post-hoc analysis based on history of prior anticholinergic treatment	Withdrawals due to Aes, Group 1 VS. Group 2: Oxy: 7 (3.9%) vs. Tol: 6 (3.1%) VS Oxy: 13 (6.2%) vs. Tol: 13 (6.3%)	some analysis of non-ITT population that showed significant differences -- not reported here

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Armstong, 2005 OPERA post-hoc analysis for adverse event, dry mouth	RCT, DB Multicenter	Women >18 years, with urinary urge incontinence (21-60 episodes/week), urinary urgency, and frequency (≥10 voids/day)	Treatable genitourinary conditions that could cause incontinence, 2 postvoid residual volumes >150 mL, sig risk of developing complete urinary retention, clinically sig medical conditions that could lead to undue risk of anticholinergic effects, hematuria, uncontrolled narrow-angle glaucoma, obstructive uropathy, reduced gastrointestinal motility, known hypersensitivity to the study medications
Trospium chloride vs oxybutynin			
Halaska 2003	RCT Multi center Europe	Patients with urge syndrome or urge incontinence	Absolute tachycardia, Closed-angle glaucoma, myasthenia gravis, severe arteriosclerosis of the cerebral vessels, stress incontinence, undue frequency of micturition due to heart failure, renal failure or diuretic therapy, bladder outlet obstruction, acute UTI at the beginning of the trial, hiatus hernia in combination with reflux esophagitis, stenosis in the GI tract, megacolon, colonic ulceration, allergy or intolerance towards atropine, Oxy, trospium or other constituents of trial medications, concurrent medication with anticholinergics, tricyclic or tetracyclic antidepressants, alpha-blockers or beta-sympathomimetics within the last 7 days before starting the trial, urological or gynecological operations within the last 3 months before starting the trial, serious illnesses or conditions which would preclude participation in any clinical trial (malignant neoplasms, alcoholism, drug misuse), pregnancy or lactation, participation in any other study

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Armstong, 2005 OPERA post-hoc analysis for adverse event, dry mouth	Oxy ER 10mg/day vs. Tol ER 4mg/day x 12 weeks	None	Adverse events data were collected at end of 2, 4, 8, and 12 weeks; investigator assigned severity levels based on observation and patient report
Trospium chloride vs oxybutynin			
Halaska 2003	Average 54 weeks of treatment with either Oxy 5 mg twice daily or Trospium 20 mg twice daily. Multiple appointments for evaluation through the course of the trial	None	Micturition diaries reported at 0, 2, 26, and 52 weeks. Efficacy also reported by doctor and patient as follows: cured, definite improvement, slight improvement, no improvement or deterioration.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Armstong, 2005 OPERA post-hoc analysis for adverse event, dry mouth	NR/NR/790	Mean age: 60 yrs Range: 18-92 yrs 100% female 84.9% Caucasian	47.2% previously received anticholinergic medication	94 52 in Oxy ER vs 42 in Tol ER
Trospium chloride vs oxybutynin				
Halaska 2003	Screened NR Eligible 358 Enrolled 357	Mean age 53.7 Female 86% Ethnicity NR	Smokers: 13% Previous illnesses: 70% Previous medication: 41% Mean body weight: 71.8 Kg	91 withdrew (Trospium 67, Oxy 24)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Armstong, 2005 OPERA post-hoc analysis for adverse event, dry mouth	Overall incidence of dry mouth Mild: Oxy ER: 21% vs Tol ER: 17% Moderate: Oxy ER: 5.6% vs Tol ER: 4% Severe: Oxy ER: 1.5% vs Tol ER: 0.5% Discontinued due to dry mouth: Oxy ER: 1.8% vs Tol ER: 1%
Trospium chloride vs oxybutynin	
Halaska 2003	Baseline incontinence episodes Trospium: 1.5; Oxy: 2.1. Treatment in both arms resulted in "the frequency of incontinence episodes diminished by about one episode at each follow-up attendance." Frequency of micturition/day at baseline: Trospium:11.4; Oxy:12.5. Assessed at 2, 26, 52 weeks. Reduction for Trospium 1.2, 2.9, 3.5; Oxy 1.5, 3.4, 4.2. Baseline episodes of urgency: Trospium: 10.2 ;Oxy: 11.0. Reduction for Trospium: 1.6, 3.2, 3.5; Oxy: 1.7, 3.2, 3.6. Subjective appraisal of efficacy after 52 weeks of treatment by physicians 29% Trospium rated as "cured", Oxy 17%. Patient ratings "similar."

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Armstong, 2005 OPERA post-hoc analysis for adverse event, dry mouth	Investigator assessed AEs at weeks 2, 4, 8, and 12 or when reported by a patient Investigator assigned severity of AEs based on following definitions Mild: event may be noticeable but does not influence daily activities and usually does not need intervention Moderate: Event may be sufficiently troublesome to make the person uncomfortable; it may influence performance of daily activities; and it may need intervention Severe: Event may cause severe discomfort; it usually interferes with daily activities; it usually needs treatment or intervention; and it may cause the person to discontinue the study
Trospium chloride vs oxybutynin	
Halaska 2003	Follow up appointments at 2, 6, 12, 20, 26, 32, 40, 52 weeks to assess safety and tolerability. 20 item questionnaire used to assess tolerability at 26 and 52 weeks. 4 point scale used to measure severity. Subjective tolerability recorded by doctor and patient using very good, good, satisfactory or poor scale. Overall withdrawal 25% Tros, 26.7% Oxy. Adverse events occurred in 64.8% Tros, 76.7% in Oxy. <u>Tros vs. Oxy</u> Dry Mouth: 33% vs 50% Constipation: 7% vs 4% Visual disturbance: 3% vs 6%

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Armstong, 2005 OPERA post-hoc analysis for adverse event, dry mouth	Withdrawals due to any AE: Oxy ER: 20 (5.1%) Tol ER: 19 (4.8%) Withdrawals due to dry mouth: Oxy ER: 7 (1.8%) Tol ER: 4 (1%)	This study focused only on dry mouth AE, not on effectiveness or efficacy of study medications. Was a subanalysis of bigger OPERA study.
Trospium chloride vs oxybutynin		
Halaska 2003	Trospium 16 (6%) Oxy 9 (10%)	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Madersbacher 1995	RCT Multi center Germany	Patients with spinal cord injuries and detrusor hyper-reflexia	Acute urinary tract infection, glaucoma, known allergy to atropine, Oxy or Trospium, tachycardia, renal, hepatic and/or cardiovascular insufficiency, intake of other anticholinergic drugs, body weight over 90 kg, age below 18 years.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Madersbacher 1995	Initial one week washout followed by 2 weeks of treatment with either Oxy 5 mg three times daily or Trospium 20 mg twice daily. To maintain double blind conditions the Trospium group received a placebo at midday	None	Twenty "well being" items were the subject of direct questioning before and at the end of the trial--specifically dry mouth, blurred/double vision, palpitation, constipation, difficulty in swallowing. Severity graded on 4 point scale.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Madersbacher 1995	Screened NR Eligible NR Enrolled 95 Trospium=52 ; Oxy=43 .	Mean age=`32. Female 50% Ethnicity NR	Type of spinal cord injury not specified. Differences in baseline urodynamic measures for maximum bladder capacity and compliance	10/NR/88

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Madersbacher 1995	Not reported. "Severe" dry mouth present in 4% trospium, 23% Oxy. Withdrawal less in trospium (6%) than Oxy (16%). Overall side effect rate comparable. No change in lab parameters.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Madersbacher 1995	Adverse effects assessed via interview focused on "well being" items. Severity grading done--methodology for grading based on a four point scale. Dry mouth: 56% Oxy vs 54% Trospium. "Severe" dry mouth: in 23% Oxy vs 4% Trospium. Withdrawal less in Trospium (6%) than Oxy (16%). Overall side effect rate comparable. No change in lab parameters.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Madersbacher 1995	Trospium 3 (6%) Oxy 7 (16%)	No information on nature of spinal cord injury or duration of injury. No information on other medications patients on during trial.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Transdermal vs. Immediate Release (TD vs. IR)			
Oxybutynin TD vs. Oxybutynin IR			
Davila 2001	RCT Multicenter USA	Men and women, aged ≥18, with history of urge or mixed urinary incontinence, previously diagnosed, with symptomatic improvement during treatment with oral oxybutynin for ≥6 weeks. During 2-wk washout from current treatment, min. 3 incontinent episodes and increase >30%. Diagnosis of detrusor instability based on symptoms and urodynamic study confirming involuntary bladder contractions.	Allergy to oxybutynin, intolerable of transdermal system, pregnancy or lactation, overflow incontinence secondary to underactive or noncontractile detrusor or outlet obstruction, impaired bladder compliance, including tonic increase in pressure greater than 15 cm during filling cystometry, current medical conditions or therapies that could contribute to UI, or medical conditions that could worsen due to oxybutynin.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Transdermal vs. Immediate Release (TD vs. IR)			
Oxybutynin TD vs. Oxybutynin IR			
Davila 2001	Starting dose assigned depending on prior oral oxybutynin dose of </= 10mg, 11-15mg, or >/= 20mg daily: Oxy TD 2.6mg, 3.9mg, or 5.2mg daily (2, 3 or 4 patches per day), patch applied twice weekly Oxy IR 10 mg, 15mg or 22,5mg total daily x 6 wks Dose titrated up if no side effects after 2 wks	NR	3-day diary of daily incontinence episodes, recorded at prestudy, washout, and wks 2,4,6. Questionnaire of anticholinergic symptoms, VAS for efficacy at wks 2,4,6.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Transdermal vs. Immediate Release (TD vs. IR)				
Oxybutynin TD vs. Oxybutynin IR				
Davila 2001	Screened NR Eligible NR Enrolled 76 Oxy TD = 38 Oxy IR = 38	Mean age 63.5 Female 92% Ethnicity: White 95% Black 5%	NR	2/76 (2.6%) withdrawn before 4 wks

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Transdermal vs. Immediate Release (TD vs. IR)	
Oxybutynin TD vs. Oxybutynin IR	
Davila 2001	Oxy TD vs Oxy IR Reduction in mean incontinence episodes at 6 wks: 4.8/7.2 (66.7%) vs. 4.6/7.2 (63.9%)(NS) Zero incontinence: 8/38 (21%) vs.10/38 (26%) VAS score improvement 5.8 vs 6.0 (p<o.0001)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Transdermal vs. Immediate Release (TD vs. IR)	
Oxybutynin TD vs. Oxybutynin IR	
Davila 2001	Invalidated questionnaire to evaluate titration for presence and severity of 10 symptoms assessed at 2, 4 and 6 wks. Oxy TD vs. Oxy IR Dry mouth: 15 (39%) vs. 31 (82%) (p<0.001) Reduction in severity of dry mouth vs prior treatment: 67% vs. 33% Worse dry mouth: 5% vs. 33% Constipation: 8 (21%) vs. 19 (50%) Somnolence 7 (18%) vs. 14 (37%) Blurred vision: 7 (18%) vs. 9 (24%) Impaired urination: 9 (24%) vs. 9 (24%)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Transdermal vs. Immediate Release (TD vs. IR)		
Oxybutynin TD vs. Oxybutynin IR		
Davila 2001	Oxy IR: 1 (dry mouth) Oxy TD: 1 contact dermatitis due to patch	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Transdermal vs. Sustained Release (TD vs.SR)			
Oxybutynin TD vs. Tolterodine SR			
Dmochowski 2003	RCT Multicenter USA	Men and women, aged ≥18, taking current pharmacologic treatment for overactive bladder with beneficial response (by patient response). Post-washout: >/= 4 urge urinary incontinent episodes, with either pure urge or predominant urge, 24 or more voids, and an average urinary void volume of 350ml or less over 3 days.	History of urinary tract surgery in previous 6 months, diagnosis of interstitial cystitis, urethral syndrome, painful bladder syndrome, or overflow urinary incontinence.
Tolterodine vs. Solifenacin			
Chapple et al. 2004	RCT Multicenter International	Patients ≥18 with OAB symptoms (including urgency, urge incontinence, or frequency) for ≥3 months; post-run-in eligibility included an average frequency of ≥8 voids /24 h and 3 episodes of urgency and/or 3 episodes of incontinence during 3-day voiding period.	Patients with clinically significant BOO, a postvoid residual volume of >200ml, stress incontinence, presence of a neurological cause for detrusor muscle overactivity, evidence of UTI or of bladder stones, previous pelvic irradiation, previous or current malignant disease of the pelvic organs, any medical condition contraindicating the use of antimuscaric medication (including narrow-angle glaucoma and urinary or gastric retention), nonpharmalogical OAB treatment including electrostimulation therapy or start of a bladder training program during the 2 wks before or during the study, diabetic neuropathy, use of drugs intended to treat incontinence, use of any drugs with cholinergic or anti-cholinergic side effects, participation in a clinical trial within 30 days prior to study entry, pregnant or nursing women, women intending to become pregnant during the study, and women not using reliable contraceptive methods.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Transdermal vs. Sustained Release (TD vs.SR)			
Oxybutynin TD vs. Tolterodine SR			
Dmochowski 2003	Oxybutynin transdermal (Oxy TD) 3.9 mg/day (applied twice weekly): n=121 Tolterodine sustained release (Tol SR) 4 mg/day: n=123 Placebo: n=117 12 wk treatment period	Maintain any nonpharmacologic incontinence management program.	Diary of urine volume, urge and incontinence episodes; measured at 0, 2, 6, 12 wks. QOL instrument and VAS "periodically."
Tolterodine vs. Solifenacin			
Chapple et al. 2004	Placebo BID; Tolterodine 2mg BID (Tol); Solifenacin 5 mg QD (Sol 5); Solifenacin 10 mg QD (Sol 10)		Patient-reported voiding diary (episodes of urgency and incontinence, times of voiding, volume voided/void, pad use, and episodes of sleep disturbance) at wks 0,4,8, & 12

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Transdermal vs. Sustained Release (TD vs.SR)				
Oxybutynin TD vs. Tolterodine SR				
Dmochowski 2003	Screened NR Eligible NR Enrolled 361	Mean age 63.5 Female 92.8% White 94.5% Black 3.6% Other 1.9%	Prior treatment median duration >1 yr (range 6 wks to 20 years) Oxy 49.6% Tol 47.4%	41 withdrawn 1 lost to followup 361 analyzed
Tolterodine vs. Solifenacin				
Chapple et al. 2004	1281 enrolled; 1081 randomized; 1033 evaluated	Mean age: Placebo: 57.8; Tolterodine (2 mg): 56.9; Solifenacin (5 mg): 58.1; Solifenacin (10mg): 57.2 25% male >98% white	Mean no. of voids/24 h: 12.07; Urge incontinence only: 653/1033; No incontinence: 67/1033; Mixed stress and urge incontinence: 313/1033; Prior drug therapy: 670/1033; Any non-drug therapy: 348/1033	Withdrawn: 36/1077 (3.6%); Lost to fu: 11/1077 (1.0%)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Transdermal vs. Sustained Release (TD vs.SR)	
Oxybutynin TD vs. Tolterodine SR	
Dmochowski 2003	Mean change in incontinence episodes per day at 12 wks: Oxy -2.9, Tol -3.2, Pla -2 (Oxy vs Tol p=0.5878) Mean decrease in urinary frequency per day: Oxy -1.9, Tol -2.2, Pla -1.4 (Oxy vs Tol p=0.2761) Frequency reduction greater for patients with 14+ micturitions/day; reduction NS for <10/day. Avg urinary volume: Oxy +24 mL, Tol +29 mL vs. Pla +5.5 mL (Oxy vs. Tol p=0.7690) Global Assessment of Disease State scores: Oxy vs. Tol p =0.1861 IIQ (QoL scale): -22 vs -23 (NS) Urogenital distress Inventory: -25 vs -28 (NS)
Tolterodine vs. Solifenacin	
Chapple et al. 2004	Change in mean number of urgency episodes/24 h: **Tolterodine:** -38%, p=0.0511 **Solifenacin:** 5mg once daily: -52%, p<0.001 10mg once daily: -55%, p<0.001 **Placebo:** -33%, no p-value reported.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Transdermal vs. Sustained Release (TD vs.SR)	
Oxybutynin TD vs. Tolterodine SR	
Dmochowski 2003	Method of assessment not reported Application site reactions: Oxy 32/121 (25.4%; 5% severe), Tol 7/123 (5.7%), Pla 8/117 (6.9%) Systemic adverse events: Oxy 23/121 (19%), Tol 29/123, Pla 14/117 (12%) Anticholinergic side effects (% only, numbers NR) Dry Mouth Oxy TD 4.1% vs Tol SR 7.3% Constipation Oxy TD 3.3%, Tol SR 5.7%
Tolterodine vs. Solifenacin	
Chapple et al. 2004	Dry mouth: placebo=13 (4.9%),Sol 5mg=39 (14%),Sol 10mg=57 (21.3%), Tol=49 (18.6%); Constipation: placebo=5 (1.9%), Sol 5mg=20 (7.2%), Sol 10mg=21 (7.8%), Tol=7 (2.6%); Blurred vision: Placebo=7 (2.6%), Sol 5mg=10 (3.6%), Sol 10mg=15 (5.6%), Tol=4 (1.5%)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Transdermal vs. Sustained Release (TD vs.SR)		
Oxybutynin TD vs. Tolterodine SR		
Dmochowski 2003	Oxy TD I= 13/121 (10.7%; 12 due to application site reaction, 1 hot flushes). Tol SR = 2/123 (1.6%; 1 fatigue, 1 dizziness).	
Tolterodine vs. Solifenacin		
Chapple et al. 2004	31/1077 (2.9%) for withdrawals due to all adverse events	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Chapple, et al. 2005 STAR (data from uncorrected proof)	RCT, Europe	Men and women aged ≥18y, OAB Symptoms for ≥ 3m, outpatient, demonstrated UI (≥1 episode/24h) and urinary frequency (≥8 micturitions/d) and ≥1 Urgency episodes/24h during 3-day voiding diary period	Stress Incontinence (SI) or Mixed Incontinence where SI was predominant and neurogenic DO
Chapple et al 2007 STAR post-hoc	RCT Europe	Men and women aged ≥18y, OAB Symptoms for ≥ 3m, outpatient, demonstrated UI (≥1 episode/24h) and urinary frequency (≥8 micturitions/d) and ≥1 Urgency episodes/24h during 3-day voiding diary period	Stress Incontinence (SI) or Mixed Incontinence where SI was predominant and neurogenic DO
Darifenacin vs. Oxybutinin			

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Chapple, et al. 2005 STAR (data from uncorrected proof)	Stable dosing phase: (Weeks 0-4) Solifenacin 5mg once/d Tolterodine ER 4mg once/d Flexible dosing phase: (Weeks 5-12) Solifenacin 5mg once/d (Sol 5) Solefenacin 10mg once/d (Sol 10) Tolterodine ER 4mg once/d (Tol 4)	none reported	3-day micturition diary presented at scheduled visits at wks 4, 8 and 12. Symptoms assessed include: micturition frequency (primary endpoint), episodes of urgency, incontinence with and without urgency, nocturia, pad usage/24h, volume voided per micturition. Health related QoL: validated 6-point categorical scale to assess Perception of Bladder Condition.
Chapple et al 2007 STAR post-hoc	Stable dosing phase: (Weeks 0-4) Solifenacin 5mg once/d Tolterodine ER 4mg once/d No dose increase (NDI) phase: (Weeks 5-12) Solifenacin 5mg once/d (Sol 5) Tolterodine ER 4mg once/d (Tol 4)	none reported	3-day micturition diary presented at scheduled visits at wks 4, 8 and 12. Symptoms assessed include: micturition frequency (primary endpoint), episodes of urgency, incontinence with and without urgency, nocturia, pad usage/24h, volume voided per micturition. Health related QoL: validated 6-point categorical scale to assess Perception of Bladder Condition.
Darifenacin vs. Oxybutinin			

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Chapple, et al. 2005 STAR (data from uncorrected proof)	1355 screened/1200 randomized and enrolled / Full analysis set (FAS): 1177	Mean Age: Sol 5 & 10: 56.5y Tol ER: 56.4y Age range: NR Sol: 85.3% female Tol ER: 88.3% female Sol: 99.3% Caucasian 0.7% Other Tol ER: 99.5 Caucasian 0.5% Other	Sol: 70.8% ≤65y; 29.2% >65y; and 6.7% >75y Tol ER: 70.6% ≤65y; 29.4% >65y; and 6.0% >75y	Withdrawals: Sol: 3.5% Tol ER: 3.0%
Chapple et al 2007 STAR post-hoc	1355 screened/1200 randomized and enrolled / Full analysis set (FAS): 1177 post-hoc: Sol 5 NDI:N=297 Tol ER NDI: n=267	Mean Age: Sol 5: 56.5y Tol ER: 56.9y Age range: NR Sol: 87.5% female Tol ER: 87.1% female Sol: 99.3% Caucasian 0.7% Other Tol ER: 99.3 Caucasian 0.7% Other	Sol: 70.0% ≤65y; 30.3% >65y; and 6.7% >75y Tol ER: 70.6% ≤65y; 30.0% >65y; and 7.0% >75y	Withdrawals: Sol: 3.0% Tol ER: 4.2%
Darifenacin vs. Oxybutinin				

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Chapple, et al. 2005 STAR (data from uncorrected proof)	Primary endpoint: micturition frequency Secondary endpoints: episodes of urgency, incontinence with and without urgency, nocturia, pad usage/24h, volume voided per micturition. Health related QoL: validated 6-point categorical scale to assess Perception of Bladder Condition. Sol (5 & 10 combined) vs Tol ER (reductions are endpoint minus baseline numbers) Mean reduction in number of urgency episodes/24h: 2.85 vs 2.42 episodes Mean reduction in number of urge incontinence episodes/24h: 1.42 vs 0.83 episodes Mean reduction in number of incontinence episodes/24h: 1.60 vs 1.11 episodes Mean reduction in number of pads used/ 24h: 1.72 vs 1.19 pads Mean reduction in number of nocturia episodes/night: 0.71 vs 0.63
Chapple et al 2007 STAR post-hoc	Primary endpoint: micturition frequency Secondary endpoints: episodes of urgency, incontinence with and without urgency, nocturia, pad usage/24h, volume voided per micturition. Health related QoL: validated 6-point categorical scale to assess Perception of Bladder Condition. Sol 5 vs Tol ER (from baseline to 4-weeks) Mean reduction in number of urgency episodes/24h: 1.71 vs 1.47 episodes, ns Mean reduction in number of urge incontinence episodes/24h: 1.22 vs 0.91 episodes, ns Mean reduction in number of incontinence episodes/24h: 1.30 vs 0.90 episodes, p=0.0181 Mean reduction in number of pads used/ 24h: 1.21 vs 0.80 pads, p=0.0089 Mean reduction in number of nocturia episodes/night: 0.51 vs 0.44, ns Sol 5 NDI vs Tol ER (from baseline to 12-weeks) Mean reduction in number of urgency episodes/24h: 2.47 vs 2.49 episodes, ns Mean reduction in number of urge incontinence episodes/24h: 1.46 vs 1.03 episodes, ns Mean reduction in number of incontinence episodes/24h: 1.56 vs 1.23 episodes, ns Mean reduction in number of pads used/ 24h: 1.55 vs 1.40 pads, ns Mean reduction in number of nocturia episodes/night: 0.72 vs 0.69, ns
Darifenacin vs. Oxybutinin	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Chapple, et al. 2005 STAR (data from uncorrected proof)	AE were evaluated at each clinic visit in response to general and non-specific questioning by the investigator or volunteered by patient Comparisons: Sol (mild%, moderate%, severe% AEs) vs Tol (mild%, moderate%, severe% AEs) Dry Mouth: (17.5%, 10.8%, 1.7%) vs (14.8%, 7.7%, 1.5%) Constipation: (3.2%, 2.7%, 0.5%) vs (1.3%, 1.0%, 0.2%) Blurred Vision: (0.7, 0%, 0%) vs. (0.7%, 1.0%, 0%)
Chapple et al 2007 STAR post-hoc	AE were evaluated at each clinic visit in response to general and non-specific questioning by the investigator or volunteered by patient Comparisons: Sol NDI (mild%, moderate%, severe% AEs) vs Tol ER(mild%, moderate%, severe% AEs) Dry Mouth: (6.5%, 10.4%, 0.7%) vs (5.0%, 7.0%, 2.1%) Constipation: (2.0%, 1.7%, 0.3%) vs (1.0%, 1.4%, 0.0%) Blurred Vision: (0.3, 0%, 0%) vs. (0.7%, 1.7%, 0%)
Darifenacin vs. Oxybutinin	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Chapple, et al. 2005 STAR (data from uncorrected proof)	Withdrawals due to AEs: Sol: 3.5% Tol ER: 3.0%	Overall withdrawal rates are unclear. Study funded by Yamanouchi Pharmaceutical Co.
Chapple et al 2007 STAR post-hoc	Withdrawals due to AEs: Sol 5 NDI: 1.3% Tol ER: 2.4%	Study funded by Yamanouchi Pharmaceutical Co. Professor Chapple is a consultant and speaker for Astellas Pharma Inc (Yamanouchi, Pfizer, Novartis and Schwarz and has acted as a consultant to UCB
Darifenacin vs. Oxybutinin		

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Chapple & Abrams 2005	RCT, Crossover, UK	Men and women, age 18-75y, with cystometric detrusor overactivity within previous 6m (included idiopathic and neurogenic) with ≥2 associated symptoms (≥7 Urgency episodes/wk and ≥7 micturitions/day, ≥1 incontinence episode/wk requiring pads or change of clothing	Previous bladder surgery for detrusor overactivity (DO), prostatectomy in the last 6m, bladder stones, treatment with diuretic, antimuscarinics, tricyclic antidepressants or digoxin within past 2 wks, stress and mixed incontinence unless DO was principal urodynamic observation and <1 SI episode/week, pregnancy or breast feeding and inadequate contraception, excessive alcohol intake, starting or modifying bladder training program, anticholinergic therapy contraindications.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Chapple & Abrams 2005	Three Cohorts: 1) Dar IR 2.5mg three times/d or Oxy IR 2.5mg three times/d 2) Dar ER 15mg once/d or Oxy IR 5mg three times/d 3) Dar ER 30mg once/d or Oxy IR 5mg three times/d each treatment period was for 7 days	none reported	Visual Nearpoint measured at baseline, pre-dose and 2 an 4 hours after the final dose on day 7 of each treatment period using a standard instrument, the RAF nearpoint ruler. Symptoms diary for OAB symptoms and adverse events

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Chapple & Abrams 2005	103 screened/ 65 eligible/ 65 enrolled	Age range: 21-75y 67.7% males 7.7% African-American 92.3% white	93.8% idiopathic DO and 6.2% neurogenic DO	6 withdrawals: Dari ER: 3 Oxy IR: 3 lost to fu: NR

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Chapple & Abrams 2005	urodynamic parameters, salivary flow, heart rate and visual nearpoint Mean max. decrease in salivary flow from baseline to day 7: Cohort 1: Dar 2.5 mg tid: -0.90 ml/min; Oxy 2.5 mg tid: -0.88 ml/min Cohort 2: Dar 15 mg QD: -0.98 ml/min; Oxy 5 mg tid: -1.55 ml/min Cohort 3: Dar 30 mg QD: -1.06 ml/min; Oxy 5 mg tid: -1.30 ml/min

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Chapple & Abrams 2005	observed or volunteered AE, serious AEs, and discontinuations, clinical lab tests (haematology, biochemistry, urinalysis and physical examinations) *Cohort 1% (Dar: no. of pts; Oxy: no. of pts) vs. Cohort 2% (D: #; O: #) vs. Cohort 3% (D:#; O:#)* Pts with all AEs: 43% (D:5, O 8) vs 73% (D:16; O;19) vs 98% (D:22; O:24) Pts with treatment-related AEs: 40% (D:4; O:8) vs 68% (D:14; O:19) vs 98% (D:22; O:24) Discontinued due to AEs: 3.3% (D:0; O:1) vs 2.1% (D:1; O:0) vs 6.4% (D:1; O:2) Discontinued due to treatment-related AEs: 0% vs 2.1% (D:1; O:0) vs 4.3% (D:1; O:1) Dry mouth: 40% (D: 4; O:8) vs 62.5% (D:13; O:17) vs 94%(D:21; O:23) Constipation: 6.7% (D:1; O:1) vs 29.2% (D:8; O:6) vs 25.5% (D:10; O:2) Dyspepsia: 3.3% (D:1; O:0) vs 16.7% (D:3; O:5) vs 8.5% (D:2; O:2) Headache: 3.3% (D:1; O:0) vs 8.3% (D:1; O:3) vs 10.6% (D:2; O:3) Abnormal vision: 6.7% (D:1; O:1) vs 8.3% (D:1; O:3) vs 12.8% (D:4; O:2) Somnolence: 3.3% (D:0; O:1) vs 4.2% (D:1; O:1) vs 4.3% (D:2; O:1) Asthenia: 3.3% (D:0; O:1) vs 0% vs 6.4% (D:3; O:1) Pharyngitis: 0% vs 2.1% (D:O; O:1) vs 4.3% (D:2; O:1) Dysphagia: 0% vs 8.3%(D: 1; O:3) vs 0% Pruritus: 0% vs 2.1% (D:O; O:1) vs 4.3% (D:3; O:0) Dry eyes: 0% vs 0% vs 6.4% (D:1; O:3) Urinary tract disorder: 0% vs 6.3%(D: 2; O:1) vs 0% Confusion: 0% vs 0% vs 4.3% (D:3; O:0) Epistaxis: 0% vs 0% vs 4.3% (D:1; O:2) Dysuria: 0% vs 0% vs 4.3% (D:1; O:2)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Chapple & Abrams 2005	Discontinued due to AEs: 3.3% (D:0; O:1) vs 2.1% (D:1; O:0) vs 6.4% (D:1; O:2) Discontinued due to treatment-related AEs: 0% vs 2.1% (D:1; O:0) vs 4.3% (D:1; O:1)	sponsored by Pfizer

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 2. Internal validity

Author, Year	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded
Immediate Release vs Immediate Release						
Leung 2002	Adequate	Not reported	Some differences, Not statistically significant. Menopausal: 45% Oxy, 66% Tol Coexisting illness: 58.5% Oxy, 50.9% Tol Concomitant drugs: 60% Oxy, 72% Tol	Yes	Yes	Yes
Lee 2002	Adequate	Not reported	Some differences, Previously treated with drug for incontinence: Tol 32%, Oxy 22%; stratification of drugs used Not reported.	Yes	Yes	Yes
Malone-Lee 2000	Adequate	Not reported	Similar	Yes	Yes	Yes
Drutz 1999	Not reported	Not reported	Some differences, mean age and % male higher in Oxy group, Oxy group had more patients with incontinence, and significantly more in Oxy group had prior urinary tract surgery,	Yes	Yes	Yes
Abrams 1998	Not reported	Not reported	Some differences, Not statistically significant. Previously treated with drug for incontinence: 52% Tol, 60% Oxy, 75% Pl Some characteristics Not stratified by group, i.e. concomitant disease or drugs, prior urinary tract surgery.	Yes	Not reported (method of blinding in light of dose adjustments and varying schedules not stated)	Not reported (method of blinding in light of dose adjustments and varying schedules not stated)
Milani 1993	Not reported	Not reported	Not reported	Yes	Yes	Yes

Oxy=Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection

Evidence Table 2. Internal validity

Author, Year	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up
Immediate Release vs Immediate Release					
Leung 2002	No	Stated ITT, but actual numbers analyzed not reported	No, of those withdrawing a higher proportion of those on Oxy had coexisting disease or concomitant drugs, were slightly older and had higher mean parity.	Withdrawals reported clearly Cross over Not reported Compliance: Oxy 88% Tol 75%	No
Lee 2002	Yes	Yes	Not clear	Yes	18% withdrew from study, 97% of these due to adverse events with higher number in Oxy group.
Malone-Lee 2000	Yes	Yes	Not clear	Attrition reported clearly, crossovers Not reported, adherence measured but Not reported.	No
Drutz 1999	Yes	Only for adverse events	Not clear	Attrition reported clearly, others Not reported	47% of original patients excluded from analysis, 20% withdrew overall, with 12% of original group withdrawing due to adverse events.
Abrams 1998	Yes	Yes	Not clear	Withdrawals due to adverse effects reported clearly Others Not reported	No
Milani 1993	Yes	No	Not clear	Yes	18% drop out rate, higher in Oxy group due to adverse effects

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Evidence Table 2. Internal validity

Author, Year	Score (good/ fair/ poor)
Immediate Release vs Immediate Release	
Leung 2002	Fair
Lee 2002	Fair (+)
Malone-Lee 2000	Fair
Drutz 1999	Poor
Abrams 1998	Fair
Milani 1993	Poor

Oxy=Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection

Evidence Table 2. Internal validity

Author, Year	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded
Zeegers 1987	Not reported	Not reported	Not clear	Yes	Yes	Yes

Oxy=Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection

Evidence Table 2. Internal validity

Author, Year	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up
Zeegers 1987	Yes	No	Not clear	Withdrawals due to adverse effects reported clearly Others Not reported	Yes, high loss to follow-up in Emp group

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Evidence Table 2. Internal validity

Author, Year	Score (good/ fair/ poor)
Zeegers 1987	Poor

Oxy=Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection

Evidence Table 2. Internal validity

Author, Year	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded
Halaska 2003	3:1 Trospium: Oxy Methodology not reported	Not reported	Similar demographics. Oxy group had somewhat increased frequency of incontinence, micturitions/day and urgency episodes/day	Yes	Yes	Yes
Madersbacher 1995	Not reported	Not reported	Some differences in gender and baseline urodynamic measures	Yes	Yes	Not reported

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Evidence Table 2. Internal validity

Author, Year	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up
Halaska 2003	Yes	Yes	Not clear	Withdrawals due to adverse effects, poor efficacy, poor compliance reported. No crossovers.	Yes, withdrawal rate 25% overall, similar in both arms
Madersbacher 1995	Yes	No	Not clear	Not clear.	Yes. 11% withdrawal overall Oxy 16% Trospium 6%

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Evidence Table 2. Internal validity

Author, Year	Score (good/ fair/ poor)
Halaska 2003	Fair
Madersbacher 1995	Fair

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Evidence Table 2. Internal validity

Author, Year	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded
Immediate Release vs Extended Release						
Van Kerrebroeck 2001	Adequate	Not reported	Yes	Yes	Yes	Yes
Appell 2001	Adequate	Not reported	Yes, stratified randomization based on the severity of urge incontinence	Yes	Yes	Yes
Birns 2000	Yes, Block randomization 2pts/block Hospitals 5 pts/block OP Clinic	Not reported	Patient demographics Not given other than mean age: 56 yo	Yes	Yes	Yes
Versi 2000	Not reported	Adequate - central randomization by phone	Stated no significant differences, but not enough data presented to assess	Yes	Yes	Yes
Nillsson 1997	Non-randomized	Not reported	Not reported	Yes	Not reported (stated ER group took placebo in evening)	Not reported (stated ER group took placebo in evening)
Anderson 1999	Not reported	Not reported	Some differences, mean number urge incontinence episodes/wk higher in ER group (NS).	Yes	Yes	Yes
Homma 2003	Yes	NR	Yes	Yes	NR	yes
Swift 2003	Yes	NR	Yes	Yes	NR	Yes

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Evidence Table 2. Internal validity

Author, Year	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up
Immediate Release vs Extended Release					
Van Kerrebroeck 2001	Yes	Yes	Not clear	Yes 95% compliance	12% overall loss to f/u 6% lost due to adverse events: ER 5%, IR 5^, Placebo 6%
Appell 2001	Yes	repeated measures analysis done, but only p-values reported	Not clear	Yes	Overall = 12% 14% Oxy ER, 11% Tol
Birns 2000	Yes	No	Not clear	Yes	1.5% overall
Versi 2000	Yes	Not clear	Not clear	Yes	7% overall 6% ER, 8% IR
Nillsson 1997	Not reported (stated ER group took placebo in evening)	No	Yes	1 patient withdrawn from study by sponsor, adherence Not reported	No
Anderson 1999	Yes	No	Not clear	Yes 98% compliance	12% overall withdrawal 13% ER, 12% IR group
Homma 2003	Yes	Stated ITT. Actual numbers analyzed NR.	Not clear	Attrition yes, crossovers none, adherence yes	Non ADE withdrawals similar between groups, loss to follow up low, but lowest in Oxy grp
Swift 2003	Yes	Yes, carry forward approach	not clear	Attrition yes; adherence 96% took >75% of prescribed medication	No, 12% overall, distributed fairly evenly.

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Evidence Table 2. Internal validity

Author, Year	Score (good/ fair/ poor)
Immediate Release vs Extended Release	
Van Kerrebroeck 2001	Fair
Appell 2001	Fair
Birns 2000	Fair
Versi 2000	Fair
Nillsson 1997	Poor
Anderson 1999	Fair
Homma 2003	Fair
Swift 2003	Fair

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Evidence Table 2. Internal validity

Author, Year	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded
Radomski 2004	Crossover No randomization	Open label	Crossover. IR Oxy always provided first and only 2 weeks. ER provided 4 weeks	Yes	No	No

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Evidence Table 2. Internal validity

Author, Year	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up
Radomski 2004	No	No for efficacy, yes for adverse events	Not clear. Three withdrawals included in safety analysis.	Yes	3 of 12 withdrew due to adverse events

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Evidence Table 2. Internal validity

Author, Year	Score (good/ fair/ poor)
Radomski 2004	Poor

Oxy=Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection

Evidence Table 2. Internal validity

Author, Year	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded
Barkin, 2004	NR	NR	similar	yes	yes, method NR	yes, method NR
Chapple et al, 2005	yes	NR	similar	yes	NR	NR
Chapple & Abrams, 2005	yes	NR	similar	yes	NR	NR
Chapple, Rechberger et al, 2003	NR	NR	some differences, prior drug therapy: placebo 32%, Sol 5mg 34.9%, Sol 10mg 40.1%, Tol 30.8%, types of incontinence: Tol group had more mixed incontinence than all other groups and placebo has the most UI only.	yes	NR	NR
Zinner, 2005	Yes	Yes	Yes (stated but no details reported)	Yes	Yes	Yes

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Evidence Table 2. Internal validity

Author, Year	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up
Barkin, 2004	yes, method NR	no	not clear	withdrawals reported clearly, crossover not reported, Compliance reported in withdrawal reasons: 2 patients in Oxy group, contamination NR	no
Chapple et al, 2005	yes	yes	not clear	withdrawals reported clearly, crossover not reported, Compliance not reported, contamination NR	NR
Chapple & Abrams, 2005	yes	no	not clear	withdrawals reported clearly, crossover reported clearly, Compliance described but not reported, contamination NR	no
Chapple, Rechberger et al, 2003	NR	yes	not clear	withdrawals reported clearly, other NR	no
Zinner, 2005	Yes	NR	Yes	Withdrawals reported, crossover as planned, compliance NR, contamination NR	No

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Evidence Table 2. Internal validity

Author, Year	Score (good/ fair/ poor)
Barkin, 2004	fair
Chapple et al, 2005	fair
Chapple & Abrams, 2005	fair
Chapple, Rechberger et al, 2003	fair
Zinner, 2005	Fair

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Evidence Table 2. Internal validity

Author, Year	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded
Extended Release vs Extended Release						
Sussman 2002	Not reported Randomization was within drug group - centers were assigned to Tol or Oxy then subjects randomized to dose. Centers blinded to existence of other arm of study.	Not reported	No, some differences: Tol 4mg group had more Caucasians Oxy 10mg group had more patients with prior drug experience, and more men Oxy 5mg group were younger	Yes	Tol arms stated to be open label. Oxy arms Not clear if blinded.	Tol arms stated to be open label. Oxy arms Not clear if blinded.
Diokno 2003	NR	NR	Yes	Yes	Yes	Yes
OPERA						
Armstong, 2005	Yes	Yes	Yes	Yes	Yes	Yes
Transdermal vs. Immediate Release						
Davila 2001	Yes	NR	Yes, except most males (5/6) in Oxy TD group	Yes	NR	NR
Transdermal vs. Extended Release						

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Evidence Table 2. Internal validity

Author, Year	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up
Extended Release vs Extended Release					
Sussman 2002	Tol arms stated to be open label. Oxy arms Not clear if blinded.	Stated to be ITT, to be included patients had to have received at least one dose of study drug AND had a least one post-randomization efficacy assessment. Missing data were imputed by last observation carried forward method.	Not clear	Withdrawals due to adverse effects reported clearly for Tol4mg and Oxy10mg only. Reported loss to follow-up, withdrawal of consent, withdrawal due to lack of efficacy, and due to side effects. Others Not reported	Unable to calculate for Tol 2mg and Oxy 5mg. For Tol 4mg loss to follow-up other than side effects = 6%, for Oxy 10mg = 9%.
Diokno 2003 OPERA	Yes	Yes (using last observation carried forward)	Unclear	Attrition yes Adherence NR	Slightly more loss in Oxy group, including one death. Total loss 104/790 (13.2%)
Armstong, 2005	Yes	NR	Unclear	Attrition yes (12% overall) Crossover NR Adherence NR	No
Transdermal vs. Immediate Release					
Davila 2001	Yes	No, but only 1 drop out from each group	NR		no
Transdermal vs. Extended Release					

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Evidence Table 2. Internal validity

Author, Year	Score (good/ fair/ poor)
Extended Release vs Extended Release	
Sussman 2002	Fair (-)
Diokno 2003 OPERA	Fair
Armstong, 2005	Fair
Transdermal vs. Immediate Release	
Davila 2001	Fair
Transdermal vs. Extended Release	

Oxy=Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection

Evidence Table 2. Internal validity

Author, Year	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded
Dmochowski 2003	NR	NR	Yes, though more male and black patients in oxy TD group	Yes	NR	Yes

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Evidence Table 2. Internal validity

Author, Year	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up
Dmochowski 2003	Yes	Yes	Unclear	Attrition overall 41/361 (11%) Adherence 92%	Unclear, not all withdrawals accounted for

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Evidence Table 2. Internal validity

Author, Year	Score (good/ fair/ poor)
Dmochowski 2003	Fair

Oxy=Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Study Design Setting	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Interventions (drug, regimen, duration)
Flavoxate				
Gruneberger 1984	RCT Single Center Germany	39 enrolled, others not reported	Mean age :Fla 48, Cle 53 100% female Ethnicity: not reported	Fla 200mg or Clenbuterol (Cle) 0.01mg three times daily x 6 weeks
Meyhoff 1983	RCT Crossover	20 enrolled, others not reported	Median age: 51 100% female Ethnicity: not reported	Fla 200 mg, Eme 200 mg;or Pl four times daily x 14 days
Bradley 1970	RCT Single Center USA	46 enrolled, others not reported	18/46(39%) male; 28/46(61%) female Age: not reported Ethnicity: not Reported	Fla 200mg or Pro 30 mg four times daily x 7 days
Herbst 1970	RCT Number of centers not stated USA	43 enrolled, others not stated	Age: 75% over 50 20/43(47%) male; 23/43(53%) female Ethnicity: not reported	Fla 200 mg or Pro15 mg four times daily x 7 days
Oxybutynin				

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Other population characteristics (diagnosis, etc)
Flavoxate	
Gruneberger 1984	Neurogenic cause: Fla 9 (47%), Cle 14 (70%) Mixed incontinence: Fla 3 (16%), Cle 3 (15%)
Meyhoff 1983	Comorbid stress incontinence: 10/20(50%); One or more previous operations: 5/20(25%); detrusor instability: 14/20(70%); unable to suppress voluntarily induced detrusor contraction: 5/20(25%)
Bradley 1970	Urinary Tract Infection: Fla 6(25%), Pro 5(23%); Symptoms only: Fla 4(17%), Pro 2(9%); Cystitis alone or mixed: Fla 10(42%), Pro 12(54.5%); Bladder carcinoma alone or mixed: Fla 2(8%), Pro 0; Benign Prostatic hypertrophy: Fla 1(4%), Pro 1(4.5%); Post-Prostatectomy: Fla 0, Pro 1(4.5%); Enuresis: Fla 0, Pro 1(4.5%); Bladder neck obstruction: Fla 1(4%), Pro 0
Herbst 1970	Cystitis/urethrocystitis: 13/43(30%); Symptoms only : 6/43(14%); Post Prostatectomy: 7/43(16%); Urethral calculus: 6/43(14%); Trigonitis/urethrotrigonitis: 5/43(12%); Prostatitis: 4/43(9%)
Oxybutynin	

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Eligibility criteria	Exclusion criteria
Flavoxate		
Gruneberger 1984	Not Reported	Not Reported
Meyhoff 1983	Rapid fill CO2 cystometry revealing detrusor instability as defined according to definitions of the International Continence Society or was considered present if the patient did not have uninhibited detrusor contractions during filling cystometry but was unable to suppress a voluntarily induced detrusor contraction within 50 sec. once it had started; absent or minimal bladder suspension defect, not requiring incontinence surgery; maximum urinary flow rate <15 ml/s; residual urine volume <50 ml following spontaneous voiding; mid-stream urine culture showing <105 colonies/ml	Patients with detrusor sphincter dyssynergia; bladder stone or bladder tumor; neurological disease; glaucoma or severe heart failure; concomitant use of drugs affecting the autonomic nervous system or smooth muscles
Bradley 1970	Not Reported	Not Reported
Herbst 1970	Not Reported	Not Reported
Oxybutynin		

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Number withdrawn/ lost to fu/ analyzed	Method of outcome assessment and timing of assessment
Flavoxate		
Gruneberger 1984	Withdrawals: Fla 5 (25%) due to little or no efficacy and strong side effects, Cle 1 (5%) due to drug interaction	Subjective assessments (not described)
Meyhoff 1983	1 withdrawal due to unspecified disease unrelated to treatment	Patient-reported drug preferences measured at end of trial; Urinary diary (diurnal and nocturnal micturition patterns, total number of voidings, incontinence)
Bradley 1970	Withdrawals: Fla 2(8%); both due to adverse events Pro 2 (9%); 1 dizziness, 1 lost to follow-up	Subjective assessments: rating scale ranging from 'no change' to 'complete recovery'
Herbst 1970	Not Reported	Not Reported
Oxybutynin		

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Outcomes
Flavoxate	
Gruneberger 1984	Patients assessment: Cured/Improved: Fla 11 (58%), Cle 15 (75%)
Meyhoff 1983	Micturations/24h: Fla +1, Eme -0.5, Pl -1 (NS) Incontinence episodes: Fla -1, Eme -1, Pl -2 (NS) Drug preferences: Fla 3 (16%), Eme 4 (21%), Pl 9 (47%) NS
Bradley 1970	"Complete" improvement in: Frequency: Fla 6(29%), Pro 4(38%); Urgency: Fla 7(35), Pro 2(14%) Nocturia: Fla 4(27%), Pro 1(7%);
Herbst 1970	Good to excellent therapeutic response: Fla 50%, Pro 30% (p-value not reported)
Oxybutynin	

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events
Flavoxate		
Gruneberger 1984	Not clear. Fla: 9 reports of gastric side effects, Cle:4 had trembling and tachycardia, 3 had nervousness	4 withdrew due to gastric complaints, 1 due to severe neurosis, Cle: 1 withdrew due to drug interaction
Meyhoff 1983	Assessment unclear. Total adverse events reported: Fla 34, Eme 26, Pl 16 Dry mouth: Eme 8, Fla 5, Pl 5; Visual disturbances: Eme 2, Fla 3, Pl 1; Nausea/heartburn: Eme 7, Fla 7, Pl 2; Vomiting: Eme 1, Fla 0, Pl 0; Constipation: Eme 3, Fla 0, Pl 0; Dizziness: Eme 4, Fla 1, Pl 1; Headache: Eme 4, Fla 0, Pl 0; Incomplete bladder Emptying: Eme 2, Fla 1, Pl 1; Diarrhea: Eme 2, Fla 3, Pl 1; Depression: Eme 0, Fla 1, Pl 2; Edema: Eme 0, Fla 1, Pl 1; Exanthema: Eme 0, Fla 1, Pl 0; Others: Eme 1, Fla 3, Pl 2	Not Reported
Bradley 1970	Not clear. Fla: Dry mouth 1; Abdominal pain 1; Headache 1 Pro: Dizziness 1; Constipation 1	Fla: 2 withdrew; but not clear due to which adverse events Cle: 1 withdrew due to dizziness
Herbst 1970	Not clear. Dry mouth/throat: Fla 1, Pro 13; Blurred vision: Fla 0, Pro 1; Difficulty in urinating: Fla 0, Pro 1; Drowsiness: Fla 0 Pro 1; Headache: Fla 0 Pro 1 Difficulty in concentrating: Fla 1 Pro 0 Dizziness: Fla 1 Pro 0	Not Reported
Oxybutynin		

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Study Design Setting	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Interventions (drug, regimen, duration)
Holmes 1989	RCT Crossover Single center London	23 enrolled, others not reported	Age: Oxy 39.6, Pro 44.5 100% female Ethnicity: not reported	Oxy 5 mg or Pro 15 mg three times daily 1 month intervention, 1 week washout, then crossover
Madersbacher 1999	RCT Multicenter Austria	366 enrolled; others not reported	Age: Prov 49.6, Oxy 50.3; Pl 47.6 Prov 9(21%) male, 117(79%) female; Oxy 8(22%) male, 113(78%) female; Pl 4(18%) male, 59(82%) female Ethnicity: not reported	Oxy 2.5 mg or Prov 15 mg three times daily x 4 weeks

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Other population characteristics (diagnosis, etc)
Holmes 1989	Daytime frequency: Oxy 38.6 total voids/3 days, Pro 29.1 total voids/3 days; Nocturia: Oxy 5 total voids/3 nights, Pro 7 total voids/3 nights
Madersbacher 1999	Sensory urge (overall) 196(54%); Motor urge (overall): 78(21%) Years of urge incontinence: Prov 2.4, Oxy 2.4, Pl 2.0 Previous treatment or urge incontinence: Prov 32, Oxy 32, Pl 21

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Eligibility criteria	Exclusion criteria
Holmes 1989	Not Reported	Not Reported
Madersbacher 1999	History of urgency or urge incontinence, a maximum cystometric bladder capacity of < or equal to 300 ml.; age 18 or older; body weight 45 kg. or greater	Detrusor hyperreflexia; postoperative incontinence; infravesical obstruction; a postvoid residual urine of > 15% of the maximal cystometric bladder capacity; acute Urinary Tract infections; angina pectoris; glaucoma; megacolon; clinically relevant cardiac, renal or hepatic dysfunctions; tachy/dysrhythmias; frequency or nocturia due to heart or renal insufficiency; overt cerebral sclerosis

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Number withdrawn/ lost to fu/ analyzed	Method of outcome assessment and timing of assessment
Holmes 1989	Unclear	Daytime frequency: measured in total voids over 3 days; Nocturia: measured by total voids over 3 nights range; Incontinence: rated using linear analogue scale
Madersbacher 1999	Unclear	Bladder diary

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Outcomes
Holmes 1989	Mean change in micturations/24h: Oxy -2.5, Pro -1.2 Mean change in Visual Analog Scale of severity of incontinence symptoms: Oxy -22.2, Pro -17.6
Madersbacher 1999	Mean change in frequency per day: Oxy -2.4, Prov -1.9, Pl -1

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events
Holmes 1989	Unclear. Dry mouth: Oxy 29.8, Pro 18.4; Constipation: Oxy 10.1, Pro 9.3; Blurred vision: Oxy 12.1, Pro 16.2	Withdrawals: 3
Madersbacher 1999	Total incidence: Prov 64%, Oxy 72%, Pl 42% Frequency of severe dry mouth: Oxy>Prov (p 0.0093) Visual disturbance: Prov 27%, Oxy 18%, Pl 14% Nausea: Prov 4.1%, Oxy 9.9%, Pl 8.3% Vomiting: Prov 2.1%, Oxy 1.4%, Pl 2.8%	Withdrawals: Pro 13%, Oxy 11%, Pl 9.7

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Study Design Setting	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Interventions (drug, regimen, duration)
Hycoscyamine				
Serels 1998	Unclear Cross-over Single Center USA	34 enrolled; Others not reported	Mean age: 62 yrs Range: 28-91 100% female Ethnicity: NR	Hyoscyamine 0.375 mg bid; Doxazosin 2 mg QHS; Hyo + Dox (combination) Pts got each therapy for a month, unless they were unwilling to cross-over

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Other population characteristics (diagnosis, etc)
Hycoscyamine	
Serels 1998	NR

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Eligibility criteria	Exclusion criteria
Hycoscyamine		
Serels 1998	NR	NR

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Number withdrawn/ lost to fu/ analyzed	Method of outcome assessment and timing of assessment
Hycoscyamine		
Serels 1998	NR	NR

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Outcomes
Hycoscyamine	
Serels 1998	Improvement on AUA symptom score: Hyo = 68%; Dox = 68%; Combination= 77% Mean improvement in American Urological Assoc.(AUA) symptom score over baseline (p value: baseline vs endpoint score): Hyo: 34% (p<0.001) Dox: 30% (p=0.002) combination: 48% (p=0.004) Increased Voiding Pressure: % (n) Hyo: 53%(20), Dox: 66% (15), Combin: 72% (8) Decreased Compliance: Hyo: 53% (9), Dox: 61% (8), Combin: 100%(3)

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events
Hycoscyamine		
Serels 1998	*Percentages are in order: Hyo, Dox, combination* Moderate -to-severe side effects: 19 (61%), 8 (47%), 8 (61%) These percentages are estimated from a graph: Dry mouth: 70 %, 20%, 58% Fatigue: 33%, 31%, 8% Dizziness: 25%, 20%, 23% Headaches: 22%, 8%, 8% Constipation: 26%, 11%, 8% Diarrhea: 10%, 8%, 0% Vaginal dryness: 3%, 0%, 0% Night sweats: 3%, 0%, 0% Leg edema: 0%, 3%, 8%	Not Reported

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 4. Anticholinergic overactive bladder syndrome drugs compared with non-drug therapy

Author, Year	Study Design Setting	Number screened/ eligible/enrolled	Age Gender Ethnicity	Interventions (drug, regimen, duration)
Goode 2002	RCT Single site USA	486 screened, 197 randomized/105 analyzed	Mean age 67	Oxy 2.5mg or Pl 3X daily, increasing by 2.5mg once daily to max 5mg 3X daily Beh: visit 1 = biofeedback to isolate pelvic muscles and teach exercises, visit 2 = teach patients to adapt to urge sensations, if not 50%+ improvement, bladder-sphincter biofeedback with patient contracting pelvic muscles against increasing volumes of fluid, visit 4 = review, encouragement and fine-tune Duration of study: 8 wks
Burgio 2001	RCT Single site USA	468 screened/ 197enrolled	Age Range: 55 to 91 yrs Mean age 68yrs 97% White 3% African American	Oxy 2.5mg or Pl once daily to 5mg three times daily Biofeedback 4 sessions
Burgio 1998	RCT Single site USA	468 screened/197 enrolled	Mean age 68yrs 100% female Ethnicity not reported	Oxy 2.5mg once daily to 5mg three times daily Biofeedback 4 sessions
Burgio 2000 (extension of Burgio 1998)	Modified crossover following the RCT reported in Goode 2002	128 screened/35 enrolled	Mean age 69.3 Female 100% Ethnicity 100% white	Oxy as described in Burgio 1998 added to behavioral therapy patients for 8 weeks. Behavioral therapy as described in Burgio 1998 added to Oxy patients

Oxy = Oxybutynin, Beh = Behavior, Pl = Placebo, ENS = Electrical Nerve Stimulation

Evidence Table 4. Anticholinergic overactive bladder syndrome drugs compared with non-drug therapy

Author, Year	Other population characteristics (diagnosis, etc)	Eligibility criteria	Exclusion criteria
Goode 2002	48% mixed type incontinence Severity of urinary incontinence: 54% severe, 20% mild Previous drugs 28%	Age >=55 yrs, ambulatory, urge incontinence >/= 2x/wk for at least 3 months, urodynamic evidence of bladder dysfunction.	Continual leakage, postvoid residual > 200ml, uterine prolapse past the introitus, narrow-angle glaucoma, unstable angina, decompensated congestive heart failure, history of malignant arrhythmias or impaired mental status.
Burgio 2001	See Goode 2002	See Goode 2002	See Goode 2002
Burgio 1998	Type of Urinary Incontinence: Urge only(%)=49.2 Beh, 49.3 Oxy, 47.7 Pl; Mixed stress and urge(%)=50.8 Beh, 50.7 Oxy, 52.3 Pl; Severity: Mild(<5 accidents per week)=18.5 Beh, 17.9 Oxy, 18.5 Pl; Moderate(5-10 accidents per week)=29.2 Beh, 29.9 Oxy, 27.7 Pl; Severe(>10 accidents per week)=52.3 Beh, 52.2 Oxy, 43.8 Pl Duration of symptoms (years): 9.4 Beh, 9.8 Oxy, 12.7 Pl	Patients aged >= 55 yrs; ambulatory; predominant pattern of urge incontinence of at least a 3 month history; demonstrate at least 2 urge incontinence accidents per week on the baseline bladder diary (number of urge accidents to exceed number of stress accidents); urodynamic evidence of bladder dysfunction (detrusor instability during filling or provocation or maximal cystometric capacity of < or equal to 350 ml.)	Patients with continual leakage; postvoid residual urine volume more than 200 ml; uterine prolapse past the introitus; narrow-angle glaucoma; unstable angina; decompensated congestive heart failure; history of malignant arrhythmias; impaired mental status-Mini Mental Status Evaluation <20)
Burgio 2000 (extension of Burgio 1998)	Ambulatory, community dwelling with urge incontinence	Patients completing the Burgio 1998 RCT in OXY or behavioral therapy treatment arms offered the alternative treatment in combination with the previous for additional 8 weeks. See Burgio 1998 for initial eligibility	See Burgio 1998

Oxy = Oxybutynin, Beh = Behavior, Pl = Placebo, ENS = Electrical Nerve Stimulation

Evidence Table 4. Anticholinergic overactive bladder syndrome drugs compared with non-drug therapy

Author, Year	Number withdrawn/ lost to follow-up/ analyzed	Method of Outcome Assessment and Timing of Assessment	Outcomes
Goode 2002	92 excluded from analysis: 28 did not complete treatment, 64 did not undergo post-treatment cystometry	Bladder diary	Reduction in Voiding frequency/24h: Oxy -2.1 Beh -1.8 Pl -0.3 Reduction in frequency of accidents Oxy 78.3% Beh 82.3% Pl 51.5%
Burgio 2001	42 withdrawn (either did not complete both psychological exams (14), or reasons not reported) 155 analyzed	Hopkins Symptom Checklist at baseline and at 8 weeks. Results in 9 subscales and a Global Severity Index, 50 on any scale is normal, 63+ is "extreme enough to be a case"	Change in Global Severity Index: Oxy 2.1, Beh 3.4, Pl 1.0 (p = 0.26)
Burgio 1998	24 withdrew/0 lost to f/u/190 analyzed	Bladder diaries, patient satisfaction and overall evaluation of perceived improvement questionnaires (2 wks post-treatment),	Change in incontinence episodes: Oxy 10.2/wk Beh 13/wk (p = 0.04 vs. Oxy) Pl 7/wk (p = 0.009 vs. Oxy) In subgroup of women (n=131) with nocturia Mean reduction in nocturia from baseline: Oxy: 0.3 voids/night (p=0.007 vs Pl) Beh: 0.5 voids/night ((p<0.001 vs Pl; p=0.02 vs Oxy) Pl: 0.0 voids/night
Burgio 2000 (extension of Burgio 1998)	1 withdrawal from OXY/0 lost to FU/34 analyzed	See Burgio 1998	Reported percent reduction in incontinence. Behavioral to combined therapy 57.5% to 88.5% Oxy to combined therapy 72.7% to 84.3%

Oxy = Oxybutynin, Beh = Behavior, Pl = Placebo, ENS = Electrical Nerve Stimulation

Evidence Table 4. Anticholinergic overactive bladder syndrome drugs compared with non-drug therapy

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events	Comments
Goode 2002	Not reported	Not reported	Not enough data presented to fully evaluate results. This study includes all the same authors as the Burgio 2000 and Burgio 2001 studies, screened and initially enrolled exactly the same number. The number analyzed differs.
Burgio 2001	See above	See above	This is a subgroup analysis from the Burgio study, of those completing psychological analysis.
Burgio 1998	Unclear how assessed or when. Dry mouth Oxy 97%, Beh 35%, Pl 55% Inability to void Oxy 22%, Beh 6%, Pl 3% Constipation Oxy 39%, Beh 22%, Pl 37% Blurred vision Oxy 15%, Beh 10%, Pl 10% Confusion Oxy 8%, Beh 6%, Pl 11%	Not reported	
Burgio 2000 (extension of Burgio 1998)	Not reported	Not reported	This is a subgroup analysis of patients agreeable to combined therapy post Burgio 1998 trial.

Oxy = Oxybutynin, Beh = Behavior, Pl = Placebo, ENS = Electrical Nerve Stimulation

Evidence Table 4. Anticholinergic overactive bladder syndrome drugs compared with non-drug therapy

Author, Year	Study Design Setting	Number screened/ eligible/enrolled	Age Gender Ethnicity	Interventions (drug, regimen, duration)
Soomro 2001	Randomized Crossover, open label Single site UK	43 enrolled, others not reported	Mean age 50yrs70% female Ethnicity not reported	Oxy 2.5mg twice daily, titrated to 5mg three times daily by day 7. Electrical Nerve Stimulation (ENS): 2 self-adhesive pads applied bilaterally over perianal region. Patients controlled amplitude to produce a tickling sensation, at 20Hz frequency and pulse of 0.2 millisecond on continuous mode. Patients instructed to use up to 6 hrs daily. 6 weeks duration on each arm, with 2 wk washout between arms.
Colombo 1995	RCT Single site USA	81 screened, others not reported	Age: Oxy=48, Beh=49 100 percent female Ethnicity not reported	Oxy 5 mg three times daily or bladder training x 6 weeks

Oxy = Oxybutynin, Beh = Behavior, Pl = Placebo, ENS = Electrical Nerve Stimulation

Evidence Table 4. Anticholinergic overactive bladder syndrome drugs compared with non-drug therapy

Author, Year	Other population characteristics (diagnosis, etc)	Eligibility criteria	Exclusion criteria
Soomro 2001	Mean functional capacity 154	Patients with a history of frequency, urgency and urge incontinence who had not been previously treated at the department, including some who had previously received treatment from a general practitioner at least 6 months prior to study enrollment.	Not Reported
Colombo 1995	Detrusor instability: Oxy=14, Beh=13; Low-compliance bladder: Oxy=9, Beh=8; Sensory bladder: Oxy=15, Beh=16	Patients showing detrusor instability, low-compliance bladder and sensory bladder	Stable bladder at cystometry; neurologic disease; detrusor hyperreflexia; age greater than 65 years; coexisting genuine stress urinary incontinence; genital prolapse; postvoid residual volume greater than 50 ml; previous gynecological or urogynecological operation; prior use of any drug for the treatment of urinary urge incontinence; urethral diverticula; fistulas; urinary tract neoplasia; bacterial or interstitial cystitis; bladder stones; and previous pelvic radiotherapy

Oxy = Oxybutynin, Beh = Behavior, Pl = Placebo, ENS = Electrical Nerve Stimulation

Evidence Table 4. Anticholinergic overactive bladder syndrome drugs compared with non-drug therapy

Author, Year	Number withdrawn/ lost to follow-up/ analyzed	Method of Outcome Assessment and Timing of Assessment	Outcomes
Soomro 2001	Not Reported	Voiding diary, Bristol urinary symptom questionnaire and Quality of Life questionnaire	Reduction in voiding frequency/24h: Oxy -2, ENS: -2 Symptoms by Bristol urinary symptom questionnaire : significant changes in score in both groups on frequency, and dissatisfaction with spending rest of life with current symptoms compared to baseline No difference on leaking or hesitancy compared to baseline Oxy only had significant change in score for incomplete emptying compared to baseline SF-36: No significant differences compared to baseline Patients finding treatment effective: Oxy 10, ENS 4
Colombo 1995	6 withdrawn: Oxy=4 due to anticholinergic adverse events; Beh=2 consent withdrawals	Clinical cure: total disappearance of urge incontinence and did not require protective pads or further therapies	Clinical cure: Detrusor instability group: Oxy=93%, Beh=62% Low-compliance bladder group Oxy=67%, Beh=75% Sensory bladder group: Oxy=60%, Beh=81%

Oxy = Oxybutynin, Beh = Behavior, Pl = Placebo, ENS = Electrical Nerve Stimulation

Evidence Table 4. Anticholinergic overactive bladder syndrome drugs compared with non-drug therapy

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events	Comments
Soomro 2001	Post-treatment side effects questionnaire (at 6 wks) Dry mouth Oxy 87%, ENS 6% Blurred vision Oxy 53%, ENS 6% Dry skin Oxy 30%, ENS 28% Skin irritation Oxy NA, ENS 11% Difficulty using machine ENS 13%	Not reported	
Colombo 1995	Unclear. Oxy: Dry mouth=15; constipation=6; Nausea=5; Dizziness=2; Decrease in visual acuity=1; Tachycardia=1; Beh = none reported	Oxy = 4(3 due to dry mouth; 1 due to glaucoma) Beh = none reported	

Oxy = Oxybutynin, Beh = Behavior, Pl = Placebo, ENS = Electrical Nerve Stimulation

Evidence Table 5. New overactive bladder syndrome drugs compared with placebo

Author Year	Dose	Mean Change in Number of Micturitions/24h		Mean Change in Number of Incontinence Episodes/24h	
		OAB drug (n)	*Placebo* (n)	*OAB drug* (n)	*Placebo* (n)
Rentzhog 1998	TOL 2mg BID	↓20% (not given)	Not reported	↓46% (not given)	Not reported
Jacquetin 2001	TOL 2mg BID	↓1.4 (103)	↓1.2 (51)	↓1.3 (79)	↓0.4 (39)
Malone-Lee 2001	TOL 2mg BID	↓0.7 (73)	0 (42)	↓0.7 (51)	0 (33)
Van Kerrebroeck 1998*	TOL 2mg BID	↓0.1 (17)	↓0.1 (16)	↓2.4 (17)	↓1.9 (16)
Millard 1999	TOL 2mg BID	↓2.3 (129)	↓1.4 (64)	↓1.7 (117)	↓1.3 (55)
Chancellor 2000	TOL 2mg BID	↓1.7 (514)	↓1.2 (507)	↓1.5 (514)	↓1.0 (507)
Zinner 2002	TOL 4mg QD <65y/o	↓2 (292)	↓1.4 (284)	↓1.7 (292)	↓1.1 (284)
	TOL 4mg QD +65y/o	↓1.4 (214)	↓0.9 (223)	↓1.6 (214)	↓0.9 (223)
Chapple 2004	TOL 2 mg BID	↓1.9 (263)	↓1.2 (267)	↓1.1 (263)	↓0.8 (267)
Chapelle 2004	TOL 2 mg BID	↓1.8 (37)	↓1.0 (36)	↓0.4 (37)	↓0.3 (36)
Kelleher 2002	TOL ER 4 mg/day	NR	NR	↓2.2 (507)	↓1.3 (508)
Khullar 2004	TOL ER 4mg/day	↓1.2 (569)	↓0.9 (285)	↓1.5 (569)	↓1.1 (285)
Landis 2004	TOL ER 4 mg/day	↓1.9 (492)	↓0.4 (494)	↓1.3 (492)	↓0.7 (494)
Szonyi, 1995	OXY 2.5mg BID	Daytime frequency lower with Oxy (P = 0.0025)		Not reported	Not reported
Chapple 1990	Flavoxate 200mg TID	Difference in mean change = -0.292 P = 0.95		Not reported	Not reported
Zinner 2004	TROS 20 mg BID	↓2.4 (256)	↓1.3 (256)	↓2.3 (256)	↓1.9 (256)
Alloussi 1999	TROS 20 mg BID	Efficacy assessment done by investigator favored trospium		NR	NR

Author Year	Dose	Mean Change in Number of Micturitions/24h		Mean Change in Number of Incontinence Episodes/24h	
		OAB drug (n)	*Placebo* (n)	*OAB drug* (n)	*Placebo* (n)
Cardozo 2000	TROS 20 mg BID	Efficacy assessment done by investigator favored trospium		NR	NR
Dmochowksi 2002	OXY TD 1.3 mg/day 2.6 mg/day 3.9 mg/day applied twice/week	↓1.8 (130) ↓1.7 (133) ↓2.3 (125) (*P*=0.0457)	↓1.7 (132)	↓2.1 (NS) ↓2.0 (NS) ↓2.7 (*P*=0.0165)	↓2.1
Cardozo 2004	SOL 5 mg 10 mg	↓2.4 (286) ↓2.8 (290)	↓1.6 (281)	↓1.6 (173) ↓1.6 (165)	↓1.3 (153)
Cardozo 2005	DAR 30 mg QD	↓0.8 (35) *P*=NS	↓0.3 (36)	NR	NR
Haab 2004	DAR A: 3.75mg QD B:7.5 mg QD C: 15 mg QD	A: ↓1.7 (49), *P*=NR B: ↓1.6 (219) C: ↓1.7 (106) (*P*<0.001 for both B & C vs placebo)	↓0.8 (152)	A: ↓1.2 (49) B: ↓1.3 (219) C: ↓1.5 (106)	↓1.1 (152)
Muskat 1996	SCP TD Changed every 3 days (4 patches total)	Diurnal frequency: ↓7.5 (10) *P*<0.05	Diurnal frequency: ↓0.7 (10)	NR	NR
Steers 2005	DAR A: 7.5 mg B: 7.5 for 2 wks then 15 mg for 12 wks	A: ↓2.0 (104) B: ↓1.9 (157) (*P*≤ 0.001 for both combined vs. placebo)	↓1.0 (123)	A: ↓1.1 (104) B: ↓1.2 (156)	↓0.3 (123)
Chapple 2007	DAR 7.5 mg/day for 2 wks Optional titration to 15 mg/day for rest of the 12 wk period	Median -3.0(266) (*P*=0.006)	Median -2.2 (133)	Median -2.0 (266) (*P*=0.328)	Median -1.86 (133)
Staskin 2007	TROS 60 mg/day for 12 wks	-2.81 (292) (*P*<0.001)	-1.99 (300)	-2.48 (292) (*P*=0.0022)	-1.93 (300)
Dmochowski 2008	TROS 60 mg/day for 12 weeks	-2.5 (267) (*P*≤0.001)	-1.8 (276)	-2.4 (267) (*P*<0.001)	-1.6 (276)
Zinner 2006	DAR 15 mg/day for 12 wks	Median -2.20 (212) (*P*=0.176)	-1.80 (220)	-1.8 (212) (*P*=0.035)	-1.4 (220)

Author Year	Dose	Mean Change in Number of Micturitions/24h		Mean Change in Number of Incontinence Episodes/24h	
		OAB drug (n)	*Placebo* (n)	*OAB drug* (n)	*Placebo* (n)
Hill 2006	DAR CR A: 7.5mg/day, B: 15/day C: 30mg/day for 12 wks	Median A: -1.7((107) B: -1.9(106) C: -2.2(114) *P* value vs placebo A: *P*=0.066, B: *P*=0.033, C: *P*<0.001	-1.1(108)	Median A: -1.2(107) B: -1.5(106) C: -1.6(114) *P* value vs placebo: A: *P*=0.007, B:*P*<0.001, C: *P*<0.001	Median -0.8(108)
Rudy 2006	TROS 20mg BID for 12 wks	-2.67 (323) (*P*<0.0001)	-1.76 (325)	-1.86(323) (*P*<0.0001)	-1.29 (325)
Rudy, Cline, 2006	TROS 20mg BID for 12 wks	NR	NR	NR	NR
Rackley 2006	TOL ER 4mg/day for 12 wks	NR -15%(429)	NR -9%(421)	NR	NR
Kaplan, 2006	TOL ER 4mg/day for 12 wks	NR -10.8% (371)	NR -7.9% (374)	NR	NR
Kelleher, 2006	SOL A: 5mg/day B: 10mg/day For 12 wks	A: MUI -2.5 (159) A: UUI -2.2 (352) B: MUI -2.6 (452) B: UUI -2.8 (652) *P* value vs placebo all groups: *P*<0.001	MUI -1.4 (430) UUI -1.4 (644)	A: MUI -1.6 (113), *P*<0.05 A: UUI -2.4 (198), *P*<0.001 B: MUI -1.9 (373) , *P*<0.001 B: UUI -1.7 (398) , *P*<0.001 *P* value vs. placebo	MUI -1.3 (365) UUI -0.9 (415)
Nitti, 2006	TOL ER 4mg/day for 12 wks	NR	NR	NR	NR
Roehrborn, 2006	TOL ER 4mg/day for 12 wks	NR -12% (77) *P*=0.22	NR -4% (86)	-11.9 (77) *P*<0.05	-5.9 (86)
Dmochowski, 2007	TOL ER 4mg/day for 12 wks Time of day A:24:00-06:00 B:06:00-12:00 C:12:00-06:00 D:06:00-24:00 E: 24h	A:-0.22 (507), *P*<0.05 B: -0.57 (507), *P*<0.001 C: -0.55 (507), *P*<0.001 D: -.043 (507), *P*<0.002 E: -1.8 (507), *P*<0.001	A: -0.17 (507) B: -0.35 (507) C: -0.39 (507) D: -0.30 (507) E: -1.2 (507)	NR	NR

Author Year	Dose	Mean Change in Number of Micturitions/24h		Mean Change in Number of Incontinence Episodes/24h	
		OAB drug (n)	*Placebo* (n)	*OAB drug* (n)	*Placebo* (n)
Wein, 2007	TOL ER 4mg/day for 12 wks	NR	NR	NR	NR

All weekly rates were divided by 7 and reported as daily rates
Abbreviations: TROS = trospium chloride; OXY = oxybutynin; DAR = darifenacin; TOL = Tolterodine tartrate; SOL = solifenacin; SCP = scopolamine; IR = immediate release; ER = extended release; TD = transdermal;
*****Study of patients with detrusor hyperreflexia

Evidence Table 6. Quality assessment of placebo-controlled trials

Author, Year	Internal validity Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Zinner, 2006	Yes	NR	Yes	Yes	"Double-blind" methods NR	Yes
Staskin, 2007	Yes	Yes	Yes	Yes	Yes	Yes
Hill, 2006	Yes	Yes	Yes	Yes	Yes	Yes
Dmochowski, 2008	Yes	Yes	Yes	Yes	"Double-blind" methods NR	Yes
Chapple, 2007	Yes	Yes	Yes	Yes	Yes	Yes

Evidence Table 6. Quality assessment of placebo-controlled trials

Author, Year	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Attrition: differential/high	Intention-to-treat (ITT) analysis	Quality Rating	Funding
Zinner, 2006	Yes	Attrition yes (15% overall) Crossover NR Protocol violations were reported	No	Yes	Fair	Novartis Pharma AG
Staskin, 2007	Yes	Attrition yes (11.7%) Crossover NR Protocol violations were reported	No	Unclear, NR, but analysis done on all pts, including those who withdrew	Good	Esprit Pharma and Indevus Pharmaceuticals
Hill, 2006	Yes	Attrition yes (11.4% overall) Crossover NR Adherence Yes (>80% in 99% of pts) Contamination NR	No	Unclear, NR, but analysis done on all pts, including those who withdrew	Good	Pfizer, Inc
Dmochowski, 2008	Yes	Attrition for AEs reported, but not for other reasons Crossover NR Adherence Yes (78.3% consumed >75% of study meds) Contamination NR	Unclear	Unclear, NR, but analysis done on all pts, including those who withdrew	Fair	Esprit Pharma and Indevus Pharmaceuticals
Chapple, 2007	Yes	Attrition yes (9.5% overall) Crossover NR Adherence yes (≥89% of pats taking ≥80% of study meds) Protocol violations were reported	No	Yes	Good	Novartis Pharma

Evidence Table 6. Quality assessment of placebo-controlled trials

Rudy, 2006	Not reported	Not reported	Yes	Yes	Yes	Yes
Rackley, 2006	Not reported	Not reported	Yes	Yes	Yes	Yes

Evidence Table 6. Quality assessment of placebo-controlled trials

Rudy, 2006	Yes	Attrition-Yes, Crossover-No, Adherence-NR, Contamination-NR	No/No Non completers: Trospium-7.3% Placebo-4.6%	Yes, LOCF	Fair	Indevus Pharmaceuticals Inc
Rackley, 2006	Yes	Attrition-Yes, Crossover-No, Adherence-NR, Contamination-NR	Yes (14% overall), No	Yes	Fair	

Evidence Table 7. Assessment of abstracts for publication bias

Author Year	Interventions (Drug, dose, sample size)	Micturitions mean change *(time period)*	Urge incontinence episodes mean change *(time period)*
Head-to-head			
Van Kerrebroeck 1997	A: Tolterodine 2 mg BID *(n=120)* B: Oxybutynin 5 mg TID *(n=120)*	A: -2.1 B: -2.7 *(unclear)*	A: -1.7 B: -2.1 *(unclear)*
Lee 2001	A: Tolterodine 2 mg BID (n=112) B: Oxybutynin 5 mg BID (n=116)	A: -2.6 B: -1.8 (24 hours)	A: -2.2 B: -1.4 (24 hours)
Schmidt 1998	A: Oxybutynin-XL 15 mg/day *(n=33)* B: Oxybutynin-IR 15 mg TID *(n=32)* C: Placebo *(n=15)*	Not reported	Mean percent reduction *(weekly)* A: 92% B: 72% C: 45%
Sand 2001	A: Oxybutynin-XL 10 mg/day *(n=nr)* B: Tolterodine 4 mg BID *(n=nr)* *(total n=382)*	Not reported	Not reported
Junemann 2000	A: Trospium Chloride 20 mg BID *(n=57)* B: Tolterodine 2 mg BID *(n=63)* C: Placebo *(n=60)*	A: -3.4 B: -2.6 C: -1.9 *(24 hours)*	Not reported
Zinner 2004	A: Oral darifenacin CR 15 mg QD (*n=58)* B: Oxybutynin 5 mg TID (*n=58)* C: Placebo (*n=58)*	NR	NR
Placebo-controlled			
Garely 2001	A: Tolterodine 4 mg OD *(n=507)* B: Placebo *(n=508)*	Median % decrease A: 17% B: 11%	Median % decrease A: 71% B: 33%
Millard 1997	A: Placebo B: Tolterodine 1 mg BID C: Tolterodine 2 mg BID *(n=unclear)*	A: -1.4 B: -2.3 C: -2.2 *(unclear)*	A: -1.3 B: -1.7 C: -1.8 *(unclear)*
Jonas 1997	A: Tolterodine 1 mg BID *(n=99)* B: Tolterodine 2 mg BID *(n=99)* C: Placebo *(n=44)*	A: -0.6 B: -1.4 C: -1.7 *(24 hours)*	A: -1.5 B: -1.1 C: -1.6 *(24 hours)*

**Data not provided*

Evidence Table 7. Assessment of abstracts for publication bias

Author Year	Interventions (Drug, dose, sample size)	Micturitions mean change *(time period)*	Urge incontinence episodes mean change *(time period)*
Moore 1997	A: Tolterodine 1 mg BID B: Tolterodine 2 mg BID C: Placebo (*Total n=306*)	A: -1.7 B: 1.8 C: not reported *(24 hours)*	Not reported
Whishaw 1997	A: Tolterodine 1 mg BID *(n=unclear)* B: Tolterodine 2 mg BID *(n=unclear)* C: Placebo *(n=unclear)* *(Total n=316)*	A>C* B>C* *(24 hours)*	A=B=C *(24 hours)*
Van Kerrebroeck 2000	A: Tolterodine 4 mg/day *(n=507)* B: Placebo *(n=508)*	Percent change A: -17% B: -11%	Percent change A: -53% B: -30%
Placebo-controlled, cont.			
Hill 2004	A: Darifenacin CR 7.5 mg QD (*n=108)* B: Darifenacin CR 15 mg QD (*n=107)* C: Darifenacin CR 30 mg QD (*n=115)* D: Placebo (*n=109)*	NR	Median % Change A: -9.8 B: -10.9 D: -6.6 (*weekly)*
Rudy 2004	A: Trospium chloride 20 mg BID (*n=329)* B: Placebo (*n=329)*	A: -2.67 B: -1.76	A: -65.9 B: -43.6
Moore 1997	Same as Millard, 1997		
Comparative Observational Studies			
Boccuzzi 2002	Oxybutynin IR Tolterodine IR	12 months	Oxy 83% Tol 76%
Taira 2002	Tol, Oxy, Oxy XL, Hyoscyamine, Flavoxate, imipramine, propantheline		

**Data not provided*

Evidence Table 7. Assessment of abstracts for publication bias

Author Year	Interventions (Drug, dose, sample size)	Micturitions mean change *(time period)*	Urge incontinence episodes mean change *(time period)*
Juzba 2001	Oxybutynin Tolterodine (formulations not stated)	3 months	Cox regression the risk of discontinuation was statistically significantly lower in Tol users, who were 43% less likely to discontinue

**Data not provided*

Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	Setting	Study Design	Eligibility criteria	Exclusion criteria
Tolterodine (Tol)				
Siami 2002	Multicenter USA	Open label, uncontrolled 12 weeks	Men and women age 18+ with diagnosis of overactive bladder with symptoms of urinary frequency (8+ micturitions/24h), urgency (strong and sudden desire to urinate), with or without urge incontinence	Pure or predominantly stress incontinence, indwelling or intermittent catheter, symptomatic or recurrent UTI, hepatic or renal dysfunction, program of electrostimulation, bladder training or pelvic floor exercises within 4 weeks.
Michel 2002	Multicenter Germany	Open label, uncontrolled, cohort 12 weeks	Tol prescription	None specified
Appell 2001	Multicenter (multinational)	Open label 9 month study	Patients completing 12 week RCT enrolled after 1-week washout period.	None specified

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	Interventions	Number screened/ eligible/ enrolled	Age Gender Ethnicity
Tolterodine (Tol)			
Siami 2002	Tol 4mg ER once daily	Number screened not reported. 1147 enrolled 1138 analyzed (9 took no drug) 735 drug naïve 403 previously treated (not with Tol)	Age range 18-91 Mean age drug naive 60yr Mean age prior treatment 62.5yrs Drug naïve;70% female, Prior Treatment; 79% female Drug naïve; 87% white, Prior treatment; 90% white
Michel 2002	Tol - varying doses. Mean dose 2mg twice daily	2250 enrolled	Mean age 61 yrs 77% female
Appell 2001	Tol 2mg twice daily	939 eligible/854 enrolled	Age Range 19-89 Mean 60yrs 76% female

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	How adverse effects assessed	Adverse events reported	Withdrawals due to adverse events
Tolterodine (Tol)			
Siami 2002	Spontaneously reported and elicited during visits (1, 4 and 12 wks). Investigator classified adverse events as mild (does not interfere with patient's usual function), moderate (interferes to some extent), or severe (interferes significantly).	Dry mouth was the most common adverse event reported, at 16%. Of these events 8% were severe, 20% moderate, and 72% were mild. No other adverse events were reported in greater than 6% of patients.	90 (8%)
Michel 2002	Spontaneously reported and elicited during visits (6 and 12 wks). Patients asked to rate tolerability at 12 wks (very good, good, moderate, poor)	127 events were reported by 93 patients (4.1%). Dry mouth was the most common (2%). Tolerability ratings: very good 39% good 56% moderate 4% poor 0.9% Logistic regression showed no association between tolerability rating and age, gender and baseline symptoms, but did show improved tolerability related to higher dose (4mg)	61
Appell 2001	Spontaneously reported adverse events, withdrawals, and dose reductions (by patient as needed). Adverse events classified as mild, moderate, severe. Severe Adverse events were assessed for relationship to Tol. Blood chemistry/hematology. Patients seen at 3 and 9 months.	76% of patients reported adverse events. Dry Mouth 28% (2% of all patients had severe dry mouth) UTI 12% Constipation 7% Headache 7% Abdominal pain 6% 13% reduced dosage 3 serious adverse events were judged possibly or probably related to Tol (constipation, abdominal pain, and tachycardia) 3 cases of urinary retention (0.4%)	73 (9%), of these 12 due to dry mouth (1%)

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	Comments
Tolterodine (Tol)	
Siami 2002	Short-term
Michel 2002	Realistic setting, but unclear if tolerability assessment is made by physician or patient
Appell 2001	

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	Setting	Study Design	Eligibility criteria	Exclusion criteria
Abrams 2001	Multicenter (multinational)	Open label 12 months study	Patients completing 4wk RCT enrolled after 4-week washout period.	None specified
Kreder 2002	Multicenter (multinational)	Open label 12 month study	Patients completing 12 wk RCT enrolled	None specified
Abrams, 2001	Multicenter, Europe	Open label, uncontrolled, 12 months	male and female patients, age >18 (≥65y in one 4-week study), urodynamically proven overactive bladder and symptoms of urinary frequency (average (≥8 micturitions/24h), urgency, an/or urge incontinence (average(≥ 1 incontinence episode/24h).	clinically significant stress incontinence, hepatic or renal disease, recurrent or symptomatic UTI, conditions contraindicating antimuscarinic therapy, clinically significant voiding difficulty with risk of urinary retention, treatment with or initiation during the study of, any antimuscarinic drug or any drug for bladder control problems or bladder training, within 14d prior to the baseline visit.
Michel, 2005	Multicenter, Germany	Open label, uncontrolled, 9 months	none	none

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	Interventions	Number screened/ eligible/ enrolled	Age Gender Ethnicity
Abrams 2001	Tol 2mg twice daily	895 eligible/714 enrolled	Age range 18-92 Mean age 60yrs 69% female
Kreder 2002	Tol ER 4mg once daily (no dose adjustments allowed)	1337 eligible/1077 enrolled	Age range 20-93 Mean age 60 yrs 82% female
Abrams, 2001	Tol 2mg twice daily with optional reduction to 1mg twice daily	screened NR/895 eligible after completion of 4-week RCT studies/714 enrolled	mean age 59.7y, 68.5% women, ethnicity NR
Michel, 2005	Tol 4mg once daily	screened NR/ eligible not applicable/ 3824 enrolled	overall mean age 64.8y. 75.8% female. mean age/gender incontinent patients, 66.3y/ 81.7% female and continent patients, 61.4y/ 62.6% and Ethnicity not reported

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Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	How adverse effects assessed	Adverse events reported	Withdrawals due to adverse events
Abrams 2001	Spontaneously reported adverse events, withdrawals, and dose reductions (by patient as needed). Adverse events classified as mild, moderate, severe. Severe Adverse events were assessed for relationship to Tol. Blood chemistry/hematology. Patients seen at 6 and 12 months.	77% reported an adverse event. Dry mouth 289 (41%) (27% mild, 3% severe) UTI 10% Headache 6% Abdominal pain 6% 5 serious adverse events were considered related to Tol (hernia, dyspepsia, pulmonary edema, and acute urinary retention) 167 (23% reduced dosage).	105 (15%)
Kreder 2002	Spontaneously reported adverse events, withdrawals, and dose reductions (by patient as needed). Adverse events classified as mild, moderate, severe. Severe adverse events were assessed for relationship to Tol. Blood chemistry/hematology. Patients assessed by phone at 1 month, and seen at 3, 6, 9 and 12 months, and again by phone 1 week after end of study.	Dry mouth 139 (12.9%) UTI 44 (4.1%) URI 43 (4%) 4 serious adverse events considered possibly related to Tol ER: urinary retention (2), aggravated MS (1), 'medication error' (1)	107 (10%) Most common reason: dry mouth 19 (18%)
Abrams, 2001	spontaneously reported AE, withdrawals and dosage reductions and at 6 month assessment visit. AE were classified as mild (easily tolerated), moderate (sufficient discomfort for interference with normal daily activities) or severe (incapacitating in terms of work and normal daily activities)	41% dry mouth (27% mild, 10% moderate and 35 severe) Other AE: autonomic nervous system disorders, general body disorders, gastrointestinal disorders and urinary disorders.	105 patients (15%)
Michel, 2005	Physician observed and reported at baseline, 1, 3, 6, and 9 months	overall AE: 13%, dry mouth: 7.8%	2.8% due to lack of tolerability

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	Comments
Abrams 2001	
Kreder 2002	
Abrams, 2001	62% of patients completed 12months' treatment with tol
Michel, 2005	post-marketing surveillance of Tol ER sponsored by Pharmacia (now Pfizer)

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	Setting	Study Design	Eligibility criteria	Exclusion criteria
Takei, 2005	extension of Homma, 2003, a comparative controlled RCT	open label, uncontrolled, 12 months		
Oxybutynin (Oxy)				
Gleason 1999	Multicenter USA	Open label 12 week study	Men and women with idiopathic urge incontinence or mixed incontinence with clinically significant urge component, with at least 6 urge incontinence episodes weekly.	Uncontrolled medical condition, post void residual volume >100ml or significant beruria or pyuria.
Salvatore, 2004	Kings College Hospital London, UK	open label, random allocation to starting dose (not described), open ended continuation, follow-up after 2y	women with videourodynamic diagnosis of DO or low bladder compliance	NR
Oxybutynin (Oxy) vs. Tolterodine (Tol)				
Lawrence 2000	Pharmacy Benefit Management Database USA	Pharmacy Claims Data for April - December 1998	New prescription for Tol or Oxy	Terminated coverage with plan, received more than 30 day supply, incomplete data

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	Interventions	Number screened/ eligible/ enrolled	Age Gender Ethnicity
Takei, 2005	Tol 4mg once daily	188 out of 293 continued open label	mean age 63.6y, 65.4% female, all Japanese
Oxybutynin (Oxy)			
Gleason 1999	Oxy ER 5 to 30mg/day	Number screened not reported. 256 enrolled	38.9% >65 yrs 91% female 92% white
Salvatore, 2004	Oxy IR 2.5mg twice daily or Oxy IR 5mg nightly. These doses were to be self adjusted by the patients to a level where side effects were considered acceptable. The maximum recommended dose was 5mg tid.	screened NR/ eligible NR/ 96 enrolled	mean age 57.5y (range 32-80y), all female, no ethnicity reported
Oxybutynin (Oxy) vs. Tolterodine (Tol)			
Lawrence 2000	Tol or Oxy (IR)	1531 eligible/1020 analyzed	Median age Tol 73 (range 18-93), Oxy 70 (range 18-95) % female: Tol 68%, Oxy 97%

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	How adverse effects assessed	Adverse events reported	Withdrawals due to adverse events
Takei, 2005	safety was assessed at 4, 12, 24, 36 and 52 weeks of the continuation study and at post-treatment follow-up. AE were recorded at each visit. Clinical lab assessment (serum chem, hematology and urinalysis) at 12, 24, and 52 weeks. ECG at baseline, and 12 and 52 weeks or upon withdrawal	total incidence of dry mouth 33.5%, mild in all but one case. Nasopharyngitis (26.6%) considered unrelated to treatment.	19 patients withdrew due to AE
Oxybutynin (Oxy)			
Gleason 1999	Reports of adverse events were solicited at visits at weeks 1, 4, 8 and 12.	Dry mouth 59% (36% mild, 23% moderate to severe) 2 serious adverse events possibly related to Oxy were related to pre-existing gastric reflux disease.	20 (8%) Most commonly nausea, dry mouth and somnolence, urinary retention, and increased post-void residual
Salvatore, 2004	phone or postal questionnaire at 2y after baseline. Questionnaire intended to assess efficacy, acceptability and compliance of two regimens. Not clear if questionnaire was administered prior to treatment.	34.8% complained of side effects. No serious AE reported.	43.2% of women who ceased treatment cited AE as reason for termination.
Oxybutynin (Oxy) vs. Tolterodine (Tol)			
Lawrence 2000	Determined discontinuation of medication by gap in refill data, assessed time to discontinuation.	Continuing therapy for 6 months: Tol 164 (32%), Oxy 111 (22%) (p<0.001) Difference remains significant after controlling for age and co-payment amount. Patients discontinued Oxy significantly earlier (mean 45 days) than Tol (mean 59 days) (p<0.001). Never refilling prescription: Oxy 68% Tol 55%	

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	Comments
Takei, 2005	
Oxybutynin (Oxy)	
Gleason 1999	
Salvatore, 2004	68.75% responded to questionnaire
Oxybutynin (Oxy) vs. Tolterodine (Tol)	
Lawrence 2000	

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	Setting	Study Design	Eligibility criteria	Exclusion criteria
Solifenacin (Sol)				
Haab, 2005	extension of Cardozo, 2004 a placebo controlled trial	open label, uncontrolled, 40 weeks	in addition to criteria for original study: informed consent and completion of treatment in the previous double-blind studies within </= 14d prior to entry into extension study.	clinically significant outflow obstruction, postvoid residual urine≥ 200mL, persistent or recurrent urinary tract infection, bladder stones, chronic interstitial cystitis, previous pelvic radiation or previous or current malignant disease of the pelvic organs and any medical condition contraindicating use of anticholinergic medication. Women of childbearing potential, pregnant or nursing or intended to become pregnant during study or unreliable contraception method.
Darifenacin (Dar)				
Haab, 2006	extension of Steers, 2005 and Haab, 2004, both PCTs	open label, non-comparative, 2 years	in addition to criteria for original study: completion of one of the two feeder trials without no major protocol violation	same as feeder studies

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	Interventions	Number screened/ eligible/ enrolled	Age Gender Ethnicity
Solifenacin (Sol)			
Haab, 2005	Sol 5mg once daily and Sol 10mg once daily with dose adjustments available at weeks 16, 28 and 40.	Screened and eligible NR/ 1633 enrolled in safety analysis	mean age 56.4y with a range of 18-82y, 78% women, 98.1% white, 0.5% black, 0.8% Asian, 0.6% other
Darifenacin (Dar)			
Haab, 2006	Dar 7.5 once daily or Dar 15mg once daily all started with 7.5 mg and were allowed to make dose adjustments after two weeks as needed	719/716/716	mean age 57.3y 85.15 female NR

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	How adverse effects assessed	Adverse events reported	Withdrawals due to adverse events
Solifenacin (Sol)			
Haab, 2005	safety was assessed at 4, 16, 28, 40 and 52 weeks of the extension study. At each visit patients were assessed: vital signs, physical examination, serum chem, hematology and urinalysis, 3-day diary, and QoL questionnaire. ECG and bladder ultrasound were performed week 28 and end of study.	total incidence of dry mouth 21%, with 10% of the lower dose group and 17% of the higher dose group. About 10% reported constipation and 7% reported blurred vision. The majority (> 50%) of the episodes of dry mouth, constipation and blurred vision were mild in severity.	4.7% withdrew due to AE
Darifenacin (Dar)			
Haab, 2006	safety was assessed at 0 and 2weeks and then 3,6,9,12,18,21,24 months adverse events were spontaneously reported by patients or observed by investigators patients also completed a questionnaire on bowel habits at end of feeder study and at 6, 12 and 24 months	treatment related AEs: total=343 (47.9%), serious AEs = 1, dry mouth=166 (23.3%), constipation=142 (19.8%), UTI=8 (1.1%), Dyspepsia=37 (5.2%), headache=14 (2%)	64 (8.9%) withdrew due to AE, 46 (6.4%) withdrew due to treatment-related AE

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	Comments
Solifenacin (Sol)	
Haab, 2005	81% of enrolled patients completed 40 weeks of open label treatment
Darifenacin (Dar)	
Haab, 2006	

Evidence Table 9. Quality assessment of observational study

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?*	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?
Haab, 2006	yes	yes	yes	yes	yes	yes

Evidence Table 9. Quality assessment of observational study

Adequate duration of follow-up?	Adequate sample size?	Overall quality assessment	Comments
yes	yes	good	

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled
Immediate Release vs Immediate Release (IR vs IR)		
Oxybutynin (Oxy) vs. Tolterodine (Tol)		
Leung 2002 Hong Kong	Tol 2mg twice daily Oxy 5mg twice daily	106 enrolled
Lee 2002 South Korea	Tol 2mg twice daily Oxy 5mg twice daily	228 enrolled (Tol 112, Oxy 116)
Malone-Lee 2000 UK and Ireland	Tol 2mg twice daily Oxy 5mg twice daily x 8 weeks Dose reduction allowed in Oxy group	482 screened 379 randomized 378 analyzed (1 received no drugs) Tol 190, Oxy 188

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
Immediate Release vs Immediate Release (IR vs IR)			
Oxybutynin (Oxy) vs. Tolterodine (Tol)			
Leung 2002 Hong Kong	Xerostomia Questionnaire at 4 and 10 weeks, independent reporting of other side effects. Significant deterioration on all measures of dryness except denture fit, for both drugs. NS between groups. Side effects reported: Oxy 49% Tol 60% (NS) Reported to be mostly abdominal aches, general malaise and urinary retention	Unclear. States that most withdrawals not due to side effects, but that patients withdrawing while on Oxy were more likely to have co-existing illnesses (p<0.012).	Fair Compliance measured. Oxy 87.5% (11 to 99.3) Tol 75% (8.9 to 98.8) (NS)
Lee 2002 South Korea	Spontaneously reported adverse events were reported and rated as serious or nonserious and according to intensity, and relationship to study drug. 227 patients assessed Tol: 62 patients reported 101 adverse events Oxy: 94 patients reported 154 adverse events (p = 0.001) Dry mouth: Tol 39 (35%) 72 (63%) (p<0.001) Severe dry mouth: Tol 1 (1%), Oxy 6 (5%) Micturation disorder: Tol 10 (9%), Oxy 16 (14%) Dyspepsia/abdominal pain: Tol 14 (13%), 12 (10%) Headache: Tol 4 (4%), Oxy 6 (5%)	Overall 29 (13%) Tol 11 (6 dry mouth, 55%) Oxy 18 (16 dry mouth, 88%)	Fair
Malone-Lee 2000 UK and Ireland	Spontaneously reported adverse events were reported and rated as serious or nonserious and according to intensity. Special attention to reporting of dry mouth. No description of scale for assessment of intensity or seriousness. At least one adverse event: 69% Tol, 81% Oxy Severe intensity: 13% Tol, 28% Oxy Serious and considered drug-related: 3 patients (1.6%) Tol, 0 Oxy Dry Mouth: overall 37% Tol, 61% Oxy (p<0.0001) Severe: 4% Tol, 15% Oxy (NS)	Overall 50 (13%) 22 (12%) Tol, 28 (15%) Oxy Due to dry mouth: 3% Tol, 7% Oxy	Fair Dose reductions requested by 6% Tol, 25% Oxy (p<0.0001)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled
Abrams 1998 UK, Ireland and Sweden	Tol 2mg twice daily Oxy 5mg three times daily Placebo three times daily Subjects >/= 65 yrs in UK and Ireland could start the dose of Oxy at 2.5mg and increase to 5mg during first 2 weeks Dose reduction allowed	293 enrolled (118 Tol, 118 Oxy, 57 Pl)
Drutz 1999 USA/Canada	Tol 2mg twice daily Oxy 5mg three times daily Placebo three times daily Dose reduction allowed	277 enrolled (Tol 109, Oxy 112, Placebo 56)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
Abrams 1998 UK, Ireland and Sweden	All adverse events were recorded and categorized by intensity (mild, moderate, severe). The likelihood of relationship to study drug was evaluated for serious adverse events and patient withdrawn if deemed medically necessary or patient wished withdrawal. At least one adverse event reported: 89% Tol, 97% Oxy, 81% Pl (Tol vs. Oxy p = 0.023) Dry mouth: 50% Tol, 86% Oxy, 21% Pl (Tol vs. Oxy p<0.001) More patients reported dry mouth to be severe on Oxy than on Tol or Pl (numbers not given) 1 serious adverse event (syncope) was considered related to Tol	Overall: 10% Tol 8%, Oxy 17%, Pl 2% Due to dry mouth: Tol 0.8%, Oxy 13%, Pl 3.5%	Fair Dose reductions requested by 8% Tol, 32% Oxy, 2% Pl (Tol vs. Oxy p<0.001)
Drutz 1999 USA/Canada	Spontaneously reported adverse events were reported and rated as serious or nonserious and according to intensity, at visits at 2, 4, 8 and 12 wks ITT analysis: % reporting adverse events: Tol 78%, Oxy 90, placebo 75 (p = 0.013 Tol vs Oxy) Dry mouth: Tol 30%, Oxy 69%, placebo 15% (p <0.001 Tol vs Oxy) Moderate to severe dry mouth: Tol 9%, Oxy 44%, placebo 7% Other adverse events reported: headache: Tol 15%, Oxy 10% dizziness: Oxy 11% (others not reported) cardiovascular events: Tol 7%, Oxy 8% Dose reduction: Tol 7%, Oxy 23%, placebo 4% (p<0.001 Tol vs Oxy)	Overall 12% Tol 7 (6%), Oxy 23 (21%), placebo 4 (7%) (p = 0.002 Tol vs Oxy)	Poor Only Allowed dose reductions in protocol, but then excluded these from analysis. Incomplete reporting of adverse events. 46 excluded from analysis due to protocol violations, but which groups assigned not reported.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled
Immediate Release vs Immediate Release (IR vs IR)		
Oxybutynin (Oxy) vs Flavoxate (Fla)		
Milani 1993 Italy	Fla 400mg or Oxy 5 mg three times daily, then crossover	50 enrolled
Zeegers 1987 Netherlands, Austria	Randomized to either: Fla 200mg or Emp 200mg or Pl three times daily x 3 weeks each or Oxy 5mg or Emp 200mg or Pl three times daily x 3 weeks each Order of drugs also randomized.	Stated to be consecutive patients 60 enrolled (30 in Fla/Emp/Pl, 30 in Oxy/Emp/Pl)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
Immediate Release vs Immediate Release (IR vs IR)			
Oxybutynin (Oxy) vs Flavoxate (Fla)			
Milani 1993 Italy	Adverse events were elicited at 4 wks, and rated as serious or nonserious and according to intensity. By ITT: Fla 11/50 (22%), Oxy 42/50 (84%), plus 5 patients withdrawn due to adverse events. Dry mouth: Fla 2%, Oxy 78% Abdominal or stomach pain: Fla 24%%, Oxy 36%	5 (10%) not clear when these occurred.	Poor
Zeegers 1987 Netherlands, Austria	Combined in score 15% Pl, 26% Emp, 8% Fla, 17% Oxy	Overall 20% 2 Pl, 8 Emp, 0 Fla, 2 Oxy	Poor

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled
Immediate Release vs Immediate Release (IR vs IR)		
Trospium chloride IR vs Oxybutynin IR		
Halaska 2003	Average 54 weeks of treatment with either Oxy 5 mg twice daily or Trospium 20 mg twice daily. Multiple appointments for evaluation through the course of the trial	Screened NR Eligible 358 Enrolled 357
Maderspacher 1995	Initial one week washout followed by 2 weeks of treatment with either Oxy 5 mg three times daily or Trospium 20 mg twice daily. To maintain double blind conditions the Trospium group received a placebo at midday	Screened NR Eligible NR Enrolled 95 52 Trospium, 43 Oxy.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
Immediate Release vs Immediate Release (IR vs IR)			
Trospium chloride IR vs Oxybutynin IR			
Halaska 2003	All adverse events: Trospium 68%, Oxy 77% All adverse events possibly/probably connected with treatment: Trospium 48%, Oxy 59%, p=0.02. All gastrointestinal adverse events possibly/probably connected with treatment: Trospium 39%, Oxy 51%, p=0.02. Dryness of mouth: Trospium 33%, Oxy 50%, p<0.01. "Time to event" reported as significant in favor of Trospium (p<0.01). Withdrawal due to adverse events classified as having at least a possible association: Trospium 3.7%, Oxy 6.7% Withdrawal due to adverse events classified as having no association: Trospium 0.7%, Oxy 0%. Withdrawal due to other serious adverse events: Trospium 1.5%,Oxy 3.3% Tolerability assessed by subjective appraisal of physicians at 26 & 52 wks:Trospium rated very good by 49% (26 wks) and 63% (52 wks); Oxy rated at 36%(26 wks) and 42%(52 wks). Appraisal by patients reported as "almost identical."	91 withdrew: Trospium 67 (25%), Oxy 24 (26.7%)	Fair. Long FU. Significant number of withdrawals for multiple reasons.
Maderspacher 1995	Analysis of tolerance carried out on all 95 subjects. Twenty "well being" items asked directly by investigator before and at end of trial. Severity grading assessed using 4 point scale. Overall rate of side effects reported as "almost comparable" in both groups. Dry mouth: Trospium 54%, Oxy 56% Severe dry mouth: Trospium 4%, Oxy 23%	10 withdrawals Trospium 3 (6%) Oxy 7 (16%)	Fair. All patients spinal cord injured. Type and level of injury not specified. Concurrent medications not noted.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled
Extended Release vs.Immediate Release (ER vs IR)		
Oxybutynin ER v Oxybutynin IR		
Versi 2000 USA	Oxy ER 5-20mg once daily or Oxy IR 5-20mg/d - schedule not reported	screened 417 eligible/enrolled 226
Birns 2000 UK	Oxy ER 10mg once daily or Oxy 5mg twice daily	162 screened 130 randomized
Anderson 1999 USA	ER Oxy 5-30mg once daily or IR Oxy 5mg once to four times daily. . dose reductions allowed for adverse effects	158 screened 105 enrolled 93 analyzed

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
Extended Release vs.Immediate Release (ER vs IR)			
Oxybutynin ER v Oxybutynin IR			
Versi 2000 USA	Reports of adverse effects recorded at each pt visit Dry mouth: ER 48%, IR 59% Kaplan Meier analysis moderate or severe dry mouth reports indicates a significant difference (p = 0.007) in favor of ER	Overall: 10 (8%) ER: 3 (3%) IR: 7 (6%)	Fair Mean duration of treatment/follow-up not stated. Only dry mouth reported in detail.
Birns 2000 UK	Assessed during visits every two weeks 78 pts reported adverse events (60%) (ER 55%, IR 67%) Dry mouth: ER 23%, IR 17% Dizziness ER 2%, IR 9% Vision abnormality ER 7%, IR 5% Cough ER 3%, IR 5% Headache ER 0, IR 5%	1 (considered unlikely due to study drug)	Fair Mixed types of incontinence Study included a run-in phase to establish tolerability, patients with adverse events excluded during run-in
Anderson 1999 USA	Spontaneously reported and anti-cholinergic effects assessed at each study visit Dry mouth: ER 68%, IR 87% (p = 0.04) Moderate to severe dry mouth: ER 25%, IR 46% (p = 0.03) Somnolence: ER 38%, IR 40% Blurred vision: ER 28%, IR 17% Constipation: ER 30%, IR 31% Dizziness ER 28%, IR 38%	2 (4%) in each group due to anticholinergic adverse events	Fair Previously all pts had responded to IR oxy Very high incidence of adverse events - may reflect the aggressive dose titration Duration of study (mean) not reported, very little data on final dose in either group

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled
Nillsson 1997 Finland	Oxy ER 10mg once daily Oxy 5mg twice daily crossover	17 enrolled
Radomski 2004	Oxy IR twice daily at dose at discretion of investigator for first two weeks (if on Oxy IR prior same dose continued 3 patients, if deemed obese 5 mg twice daily otherwise 2.5 mg twice daily), followed by two week washout, followed by Oxy CR 15 mg once daily for four weeks	# screened not reported. 12 included for safety analysis. 9 included for efficacy analysis (completed 8 week study)
Barkin 2004	Oxy IR 5mg tid, dose titration in 5mg increments in 2 wks followed by stable-dose phase for 4 wks Oxy ER 15mg tid, dose titration in 5mg increments in 2 wks followed by stable-dose phase for 4 wks	125 enrolled (Oxy IR 60, Oxy ER 65)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
Nillsson 1997 Finland	Patients reported on a questionnaire throughout study, classified as mild, moderate, severe 14/16 on ER, 5/17 on IR reported at least one adverse event Dry mouth: ER 69%, IR 82% Headache ER 44%, 41% Dyspepsia ER 31%, IR 12% fatigue ER 13%, 24% Blurred vision 25%, IR 12% % Severe: ER 17%, IR 14% reported that these were NS, but unclear what data being compared.	None reported	Poor Very high numbers of subjects reporting adverse events
Radomski 2004	Adverse events collected during scheduled visits and entered in diary. Dry mouth: ER vs IR (mild, moderate, severe): 25%,25%,8% vs 58%,8%,8%. Constipation: ER 8%, IR 8% Back Pain: ER 8%, IR 8% Pain-unspecified: ER 42%, IR 17% Increased salivation: ER 17%,IR 8% Asthenia: ER 8%, IR 17% Peripheral edema: ER 8%, IR 8%	2 withdrawals in OXY IR phase. 1 withdrawal in Oxy ER phase. Events reported: severe stomach pain, mild peripheral edema, severe vision distortion	Poor All subjects exposed to Oxy IR first, exposed to longer duration of ER. Study open label
Barkin 2004	<u>Oxy ER vs Oxy IR (%)</u> Dry mouth: overall: 68% vs 72%; moderate or severe: 38% vs 45% Pharyngitis (dry throat): 35% vs 40% Dry skin: 17% vs 12% Diarrhea: 14% vs 5% Headache: 12 % vs 22% Uriniary tract infection: 12 % vs 18% Dizziness: 11% vs 18% Dyspepsia: 11% vs 17% Rhinitis: 11% vs 15% Abdominal pain: 9% vs 10% Asthenia: 18% vs 15% Constipation: 8% vs 10% Taste perversion: 8% vs 12% Cough increased: 6% vs 13% Dysphagia: 6% vs 13% Dry eyes: 3% vs 15% Nausea: 5% vs 17%	Oxy IR: 12 (20%) Oxy ER: 11 (17%)	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled
Extended Release vs.Immediate Release (ER vs IR)		
Tolterodine ER vs Tolterodine IR		
Van Kerrebroeck 2001 Multinational	Tol ER 4mg once daily or Tol IR 2mg or Placebo twice daily	1529 enrolled Tol ER: 507 Tol IR: 514 placebo: 508
Swift 2003 Re-analysis of data for women only in Van Kerrebroeck 2001 study (above)	Tol ER 4 mg (n=417) once daily vs. Tol IR 2 mg twice daily (n=408) vs. Pla (n=410) for 12 wks.	1235 enrolled Tol ER: 417 Tol IR: 408 placebo: 410
Extended Release vs.Immediate Release (ER vs IR)		
Oxybutynin ER v Tolterodine IR		
Appell 2001 USA	ER Oxy 10mg once daily Tol 2mg twice daily	378 enrolled (Oxy ER 185, Tol 193) 332 completed (Oxy ER 160, Tol 172)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
Extended Release vs.Immediate Release (ER vs IR)			
Tolterodine ER vs Tolterodine IR			
Van Kerrebroeck 2001 Multinational	Spontaneously reported events were categorized and causation assigned dry mouth further categorized Dry mouth: ER 23%, IR 30%, Placebo 8% Constipation: ER 6%, IR 7%, Placebo 4% Headache: ER 6%, IR 4%, Placebo 5%	Overall 88 (5.7%) ER: 27 (5.3%) IR: 28 (5.5%) placebo 33 (6.5%)	Fair Dry mouth classified as mild/moderate/severe but data only reported for ER
Swift 2003 Re-analysis of data for women only in Van Kerrebroeck 2001 study (above)	Reporting details NR. Tol ER vs. Tol IR vs. Pla: Dry mouth: 105/415 (25.3%) vs. 127/407 (31.2%) vs. 33/410 (8.0%) Dry skin: 2 (0.5%) vs. 5 (1.2%) vs.1 (0.2%) Dizziness: 7 (1.7%) vs. 7 (1.7%) vs. 4 (1.0%) Somnolence: 12 (2.9%) vs. 11 (2.7%) vs. 8 (2.0%) Abnormal vision: 5 (1.2%) vs. 4 (1.0%) vs. 2 (0.5%) Constipation: 27 (6.5%) vs. 27 (6.6%) vs. 14 (3.4%)	Tol ER 22/417 (5%) vs. Tol IR 20/408 (5%) vs. Pla 26/410 (6%)	Fair Dry mouth classified as mild/moderate/severe Reporting details NR Patients excluded from AE assessment (Tol ER=2; Tol IR=1)
Extended Release vs.Immediate Release (ER vs IR)			
Oxybutynin ER v Tolterodine IR			
Appell 2001 USA	Patient reported dry mouth occurred in equal proportion in each group both groups had similar rates of dry mouth and other adverse effects	Overall 7.7% Oxy ER 14 Tol 15	Fair

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled
Extended Release vs.Immediate Release (ER vs IR)		
Tolterodine ER vs. Oxybutynin IR		
Homma 2003	Tol ER 4 mg once daily vs. Oxy IR 3 mg three times daily x 12 wks	Enrolled = 608 Tol ER = 240 Oxy IR = 246 Pla = 122
Extended Release vs.Immediate Release (ER vs IR)		
Solifenacin IR vs. Tolterodine ER		
Chapple 2005 STAR trial	Flexible dosing, Weeks 0-4: Sol 5mg qd Tol ER 4mg qd Stable-dose phase,Weeks 5-12: Sol 5mg qd (Sol 5) Sol 10mg qd (Sol 10) Tol ER 4mg qd (Tol 4)	Full analysis set (FAS): 1177

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
Extended Release vs.Immediate Release (ER vs IR)			
Tolterodine ER vs. Oxybutynin IR			
Homma 2003	Dry mouth: Tol 0.4% vs. Oxy 9.4% All events: Tol 5.0% vs. Oxy 17.1% p<0.001 Serious event, possibly drug related: 1 Oxy cardiac failure. No deaths and no clinically significant changes in lab or ECG values.	Compliance >75% of medication: Tol 98% vs. Oxy 93%	Fair Adverse events undefined; ascertainment techniques NR
Extended Release vs.Immediate Release (ER vs IR)			
Solifenacin IR vs. Tolterodine ER			
Chapple 2005 STAR trial	AE evaluted at each clinic visit in response to questioning by the investigator or volunteered by patient Comparisons: Sol (mild%, moderate%, severe% AEs) vs Tol (mild%, moderate%, severe% AEs) Dry Mouth: (17.5%, 10.8%, 1.7%) vs (14.8%, 7.7%, 1.5%) Constipation: (3.2%, 2.7%, 0.5%) vs (1.3%, 1.0%, 0.2%) Blurred Vision: (0.7, 0%, 0%) vs. (0.7%, 1.0%, 0%)	Withdrawals due to AEs: Sol: 3.5% Tol ER: 3.0%	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled
Extended Release vs.Immediate Release (ER vs IR)		
Darifenacin IR and Darifenacin ER vs. Oxybutynin IR		
Chapple and Abrams 2005	1) Dar IR 2.5mg tid or Oxy IR 2.5mg tid 2) Dar ER 15mg qd or Oxy IR 5mg tid 3) Dar ER 30mg qd or Oxy IR 5mg tid each treatment period was 7 days	65 enrolled
Diokno 2003 OPERA	Oxy ER 10 mg/day vs. Tol ER 4 mg/day x 12 wks	Enrolled 790 Oxy ER= 391 Tol ER = 399

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
Extended Release vs.Immediate Release (ER vs IR)			
Darifenacin IR and Darifenacin ER vs. Oxybutynin IR			
Chapple and Abrams 2005	*Cohort 1% (Dar: # of pts; Oxy: # of pts) vs. Cohort 2% (D: #; O: #) vs. Cohort 3% (D:#; O:#)* All AEs: 43% (D:5, O 8) vs 73% (D:16; O;19) vs 98% (D:22; O:24) Treatment-related AEs: 40% (D:4; O:8) vs 68% (D:14; O:19) vs 98% (D:22; O:24) Discontinued due to AEs: 3.3% (D:0; O:1) vs 2.1% (D:1; O:0) vs 6.4% (D:1; O:2) Discontinued due to treatment-related AEs: 0% vs 2.1% (D:1; O:0) vs 4.3% (D:1; O:1) Dry mouth: 40% (D: 4; O:8) vs 62.5% (D:13; O:17) vs 94%(D:21; O:23) Constipation: 6.7% (D:1; O:1) vs 29.2% (D:8; O:6) vs 25.5% (D:10; O:2) Dyspepsia: 3.3% (D:1; O:0) vs 16.7% (D:3; O:5) vs 8.5% (D:2; O:2) Headache: 3.3% (D:1; O:0) vs 8.3% (D:1; O:3) vs 10.6% (D:2; O:3) Abnormal vision: 6.7% (D:1; O:1) vs 8.3% (D:1; O:3) vs 12.8% (D:4; O:2) Somnolence: 3.3% (D:0; O:1) vs 4.2% (D:1; O:1) vs 4.3% (D:2; O:1) Asthenia: 3.3% (D:0; O:1) vs 0% vs 6.4% (D:3; O:1) Pharyngitis: 0% vs 2.1% (D:O; O:1) vs 4.3% (D:2; O:1) Dysphagia: 0% vs 8.3%(D: 1; O:3) vs 0% Pruritus: 0% vs 2.1% (D:O; O:1) vs 4.3% (D:3; O:0) Dry eyes: 0% vs 0% vs 6.4% (D:1; O:3) Urinary tract disorder: 0% vs 6.3%(D: 2; O:1) vs 0% Confusion: 0% vs 0% vs 4.3% (D:3; O:0) Epistaxis: 0% vs 0% vs 4.3% (D:1; O:2) Dysuria: 0% vs 0% vs 4.3% (D:1; O:2)	Discontinued due to AEs: 3.3% (D:0; O:1) vs 2.1% (D:1; O:0) vs 6.4% (D:1; O:2) Discontinued due to treatment-related AEs: 0% vs 2.1% (D:1; O:0) vs 4.3% (D:1; O:1)	
Diokno 2003 OPERA	Dry mouth: Oxy 116/391 (29.7%) vs. Tol 89/399 (22.3%) (p=0.02) mild: oxy 87/391 (22.3%) vs Tol 69/399 (17.3%) mod-severe: Oxy 29/391 (7.4%) vs Tol 20/399 (5%) Constipation: Oxy 25/391(6.4%) vs. 31/399 (7.8%) (NS)	All events: Oxy 20/391 (5.1%) vs. Tol 19/399 (4.8%) Due to dry mount: Oxy 7, Tol 4	Fair Data collected at each visit or any time reported by participant, rated as mild, moderate, severe by investigator

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled
Transdermal vs. Immediate Release (TD vs. IR)		
Oxybutynin TD vs. Oxybutynin IR		
Davila 2001	Starting dose assigned depending on prior oral oxybutynin dose of </= 10mg, 11-15mg, or >/= 20mg daily: Oxy TD 2.6mg, 3.9mg, or 5.2mg daily (2, 3 or 4 patches per day), patch applied twice weekly Oxy IR 10 mg, 15mg or 22,5mg total daily x 6 weeks Dose titrated up if no side effects after 2 weeks	Enrolled 76 Oxy TD = 38 Oxy IR = 38
Dmochowski 2003	Oxybutynin transdermal (Oxy TD) 3.9 mg/day (applied twice weekly) Tolterodine sustained release (Tol SR) 4 mg/day Placebo 12 wk treatment period	Enrolled 361 Oxy TD: 121 Tol SR: 123 Placebo: 117

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
Transdermal vs. Immediate Release (TD vs. IR)			
Oxybutynin TD vs. Oxybutynin IR			
Davila 2001	Oxy TD vs. Oxy IR Dry mouth: 15 (39%) vs. 31 (82%) (p<0.001) Reduction in severity of dry mouth vs prior treatment: 67% vs. 33% Worse dry mouth: 5% vs. 33% Constipation: 8 (21%) vs. 19 (50%) Somnolence 7 (18%) vs. 14 (37%) Blurred vision: 7 (18%) vs. 9 (24%) Impaired urination: 9 (24%) vs. 9 (24%)	Oxy IR: 1 (dry mouth) Oxy TD: 1 contact dermatitis due to patch	Fair Unvalidated questionnaire to evaluate titration for presence and severity of 10 symptoms assessed at 2, 4 and 6 wks.
Dmochowski 2003	Application site reactions: Oxy 32/121 (25.4%; 5% severe), Tol 7/123 (5.7%), Pla 8/117 (6.9%) Systemic adverse events: Oxy 23/121 (19%), Tol 29/123, Pla 14/117 (12%) Anticholinergic side effects (% only, numbers NR) Dry Mouth Oxy TD 4.1% vs Tol SR 7.3% Constipation Oxy TD 3.3%, Tol SR 5.7%	Oxy TD l= 13/121 (10.7%; 12 due to application site reaction, 1 hot flushes). Tol SR = 2/123 (1.6%; 1 fatigue, 1 dizziness).	Fair Method of assessment not reported

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 11. Clinically significant drug interactions [1]

	Flavoxate Hydrochloride	Oxybutynin Chloride	Tolterodine Tartrate	Darifenacin	Solifenacin Succinate	Trospium Chloride
Drugs affecting hepatic enzymes (CYP 450) Inhibitors of CYP2D6, CYP3A4	Not reported	Not reported	**No significant interaction. No action required.[2]**	**No dose adjustment needed for CYP2D6 and moderate CYP3A4 inhibitor.** Dosage should not exceed 7.5 mg when co-administered with potent CYP3A4 inhibitor.[6]	**Further studies needed.[5]**	Not reported
Fluoxetine	Not reported	Not reported	**No dose adjustment required**. May increase concentration of tolterodine by four fold.[2]	Not reported	Not reported	Not reported
Diuretics	Not reported	Not reported	**No significant interactions.[1]**	Not reported	Not reported	Not reported
Oral Contraceptives	Not reported	Not reported	**No significant interactions. No action required.[2]**	Not reported	Not reported	Not reported
Anticoagulants	Not reported	Not reported	**No significant interactions.[2]**	Not reported	Not reported	Not reported
Alcohol	Not reported	**Monitor**. Increased sedation with CNS depression.[2]	Not reported	Not reported	Not reported	Not reported
Antihistamines	Not reported	**Monitor**. Increased anticholinergic effects.[2]	Not reported	Not reported	Not reported	Not reported
Macrolide antibiotics	Not reported	**Information not available.[2]**	Not reported	Not reported	Not reported	Not reported

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Azole antifungal agents	Not reported	**No significant interaction**. Serum concentrations of oxybutynin increased three fold when coadministered with itraconazole. Half-life was unaffected and the interaction is of only minor significance.[3]	**Dose adjustment required**. May inhibit metabolism of tolterodine. Doses of >1mg twice daily should be avoided.[2]	Not reported	**Monitor.** Co-administration with a single 10 mg solifenacin dose increased solifenacin's concentration by 40%. Half-life increased by 55% and AUC increased by 100%.[5]	Not reported

1 AHFS Drug Information, ASHP, 2002.
2 Drug Information Handbook 7th Ed. Lexi-Comp, 1999-2000.
3 Benedetti et al. Drug Metabolism Reviews, 1999.
4 Epocrates Version 6.02, 2003.
5 Drug Facts and Comparisons, Wolters Kluwer Company. 2004.
6 Drugs@FDA, 2005.