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.
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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### Evidence Table 1. Comparative clinical trials

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<tr>
<th>Author, Year</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
<th>Exclusion criteria</th>
</tr>
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<tbody>
<tr>
<td><strong>Immediate Release vs Immediate Release (IR vs IR)</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Oxybutynin (Oxy) vs. Tolterodine (Tol)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leung 2002</td>
<td>RCT Multicenter Hong Kong</td>
<td>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))</td>
<td>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.</td>
</tr>
<tr>
<td>Lee 2002</td>
<td>RCT Multicenter South Korea</td>
<td>Male or female, 18+ yrs, with overactive bladder defined by symptoms of urinary frequency and urgency with or without incontinence.</td>
<td>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.</td>
</tr>
</tbody>
</table>

* 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
<table>
<thead>
<tr>
<th>Author, Year</th>
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<th>Method of Outcome Assessment and Timing of Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leung 2002</td>
<td>Tol 2mg twice daily x 10 weeks</td>
<td>None reported</td>
<td>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.</td>
</tr>
<tr>
<td>Lee 2002</td>
<td>Tol 2mg twice daily</td>
<td>estrogen allowed.</td>
<td>Micturition diary assessed at 8 wks</td>
</tr>
<tr>
<td></td>
<td>Oxy 5mg twice daily x 8 wks</td>
<td></td>
<td>Patient assessment of treatment benefits as yes/no; with yes further defined as little or much. Compliance assessed by tablet count at 8 wks</td>
</tr>
</tbody>
</table>

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

* 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
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<td><strong>Oxybutynin (Oxy) vs. Tolterodine (Tol)</strong></td>
<td></td>
</tr>
<tr>
<td>Leung 2002</td>
<td>Diaries</td>
</tr>
<tr>
<td></td>
<td>Analysis of variance shows NS between groups on any measure, all groups improved.</td>
</tr>
<tr>
<td></td>
<td>Symptoms</td>
</tr>
<tr>
<td></td>
<td>Change in overall severity (from baseline)</td>
</tr>
<tr>
<td></td>
<td>Oxy: 4 and 10 weeks 0.7</td>
</tr>
<tr>
<td></td>
<td>Tol: 4 and 10 weeks 0.2 (NS by intention to treat, per protocol not reported)</td>
</tr>
<tr>
<td></td>
<td>Perceived change in symptom severity (from baseline)</td>
</tr>
<tr>
<td></td>
<td>Oxy: 4 and 10 weeks 1.0</td>
</tr>
<tr>
<td></td>
<td>Tol: 4 and 10 weeks 2.0</td>
</tr>
<tr>
<td></td>
<td>(NS at 4 weeks, at 10 weeks p = 0.053 by intention to treat, 0.047 by per protocol)</td>
</tr>
<tr>
<td>Lee 2002</td>
<td>ITT analysis:</td>
</tr>
<tr>
<td></td>
<td>Mean change in Micturitions/d:</td>
</tr>
<tr>
<td></td>
<td>Tol -2.6</td>
</tr>
<tr>
<td></td>
<td>Oxy -1.8 (NS)</td>
</tr>
<tr>
<td></td>
<td>Mean change in incontinence/d:</td>
</tr>
<tr>
<td></td>
<td>Tol -2.2</td>
</tr>
<tr>
<td></td>
<td>Oxy -1.4 (NS)</td>
</tr>
<tr>
<td></td>
<td>PP analysis:</td>
</tr>
<tr>
<td></td>
<td>Patient perception of benefit:</td>
</tr>
<tr>
<td></td>
<td>Tol 45% much benefit</td>
</tr>
<tr>
<td></td>
<td>Oxy 46% much benefit (NS)</td>
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*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*
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<th>Adverse effects assessed?</th>
<th>How assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leung 2002</td>
<td>Oxybutynin (Oxy) vs Tolterodine (Tol)</td>
<td>Xerostomia Questionnaire at 4 and 10 weeks, independent reporting of other side effects.</td>
<td>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</td>
</tr>
<tr>
<td>Lee 2002</td>
<td>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&lt;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%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 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
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<th>Withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxybutynin (Oxy) vs. Tolterodine (Tol)</td>
<td>Leung 2002</td>
<td>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&lt;0.012).</td>
<td>Compliance measured. Oxy 87.5% (11 to 99.3) Tol 75% (8.9 to 98.8) (NS)</td>
</tr>
<tr>
<td></td>
<td>Lee 2002</td>
<td>29: Tol 11 (6 dry mouth, 55%) Oxy 18 (16 dry mouth, 88%)</td>
<td></td>
</tr>
</tbody>
</table>

* 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
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<th>Study Design Setting</th>
<th>Eligibility criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrams 1998</td>
<td>RCT Multicenter UK, Ireland and Sweden</td>
<td>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.</td>
<td>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</td>
</tr>
<tr>
<td>Drutz 1999</td>
<td>RCT Multicenter USA/Canada</td>
<td>Age 18+ with evidence of detrusor overactivity on cystometry, along with urinary frequency, and either urge incontinence or urinary urgency.</td>
<td>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 &gt;3L, or risk of urinary retention.</td>
</tr>
</tbody>
</table>

**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

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

**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
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<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Other population characteristics (diagnosis, etc)</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrams 1998</td>
<td>Number screened/eligible not stated 293 enrolled (118 Tol, 118 Oxy, 57 Pl)</td>
<td>Age range 19-80 yrs</td>
<td>Mean age Tol 55, Oxy 58, Pl 58</td>
<td>76% female</td>
<td>Previous drug therapy: Tol 52%, Oxy 60%, Pl 75%</td>
<td>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'.</td>
</tr>
<tr>
<td>Drutz 1999</td>
<td>277 enrolled (Tol 109, Oxy 112, Placebo 56)</td>
<td>mean age: Tol 63 yrs, Oxy 66 yrs, Placebo 62 yrs</td>
<td>% female: Tol 81, Oxy 72, Placebo 80</td>
<td>% Caucasian: Tol 87, Oxy 94, Placebo 93</td>
<td>% hyperreflexia: Tol 7, Oxy 7, Placebo 5</td>
<td>57 withdrew</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% Previous drug therapy: Tol 45, Oxy 45, Placebo 55</td>
<td>% with incontinence: Tol 83, Oxy 92, Placebo 89</td>
<td>% Prior Urinary tract surgery: Tol 27, Oxy 45, Placebo 34</td>
<td>147 analyzed (70 Tol, 41 Oxy, 36 placebo)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>27 excluded due to dose reductions</td>
<td>46 excluded due to protocol violations</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 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
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| 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*
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<tr>
<td>Abrams 1998</td>
<td>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&lt;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</td>
<td></td>
</tr>
<tr>
<td>Drutz 1999</td>
<td>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 &lt;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&lt;0.001 Tol vs Oxy)</td>
<td></td>
</tr>
</tbody>
</table>

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* 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
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</tr>
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<tr>
<td>Abrams 1998</td>
<td>Tol 8%, Oxy 17%, Pl 2% Due to dry mouth: Tol 0.8%, Oxy 13%, Pl 3.5%</td>
<td>Dose reductions requested by 8% Tol, 32% Oxy, 2% Pl (Tol vs. Oxy p&lt;0.001)</td>
</tr>
<tr>
<td>Drutz 1999</td>
<td>Tol 7 (6%), Oxy 23 (21%), placebo 4 (7%) (p = 0.002 Tol vs Oxy)</td>
<td>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.</td>
</tr>
</tbody>
</table>

**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.
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<th>Study Design Setting</th>
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<tr>
<td>Milani 1993</td>
<td>RCT, Crossover Multicenter Italy</td>
<td>Females, 18+, with motor or sensory urgency according to the criteria of the International Continence Society.</td>
<td>Severely ill, overt neurological disease, non-compliant, or taking drugs that could affect urinary symptoms.</td>
</tr>
<tr>
<td>Zeegers 1987</td>
<td>RCT, Cross-over study Multicenter Netherlands, Austria</td>
<td>Weight 56-85kg Symptoms: frequent voiding, urgency or urge incontinence (patients with neurogenic bladder may have been included)</td>
<td>Kidney, liver or cardiovascular pathology, obstruction or infection, ongoing anticholinergic therapy, glaucoma or Parkinson's disease</td>
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<tr>
<td>Milani 1993</td>
<td>Fla 400mg or Oxy 5 mg x 4wks, then crossover after 7 d washout</td>
<td>not given</td>
<td>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).</td>
</tr>
<tr>
<td>Zeegers 1987</td>
<td>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 3 weeks, Emp 200mg three times daily x 3 weeks, Pl three times daily x 3 weeks) with the order of drugs also randomized.</td>
<td>None reported</td>
<td>Patient and physician score at end of each 3 week period; 1 = no effect, 5 = excellent effect.</td>
</tr>
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* 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
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<th>Other population characteristics (diagnosis, etc)</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milani 1993</td>
<td>50 enrolled mean age 51 (range 19 to 78) 100% female</td>
<td>23 (46% sensory urge, 54% motor urge.</td>
<td>9 withdrawn: Fla 3 poor compliance Oxy: 1 poor compliance, 5 side effects 41 analyzed</td>
<td></td>
</tr>
<tr>
<td>Zeegers 1987</td>
<td>Number screened/eligible not stated; stated to be consecutive patients 60 enrolled (30 in Fla/Emp/Pl, 30 in Oxy/Emp/Pl)</td>
<td>Age range 16-78 yrs Reported by center and by completer/noncompleter status rather than by treatment group. 70% female</td>
<td>None reported</td>
<td>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</td>
</tr>
</tbody>
</table>

*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**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| 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 |

* 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
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<tr>
<td>Milani 1993</td>
<td>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%</td>
<td></td>
</tr>
<tr>
<td>Zeegers 1987</td>
<td>Combined in score 15% Pl, 26% Emp, 8% Fla, 17% Oxy</td>
<td></td>
</tr>
</tbody>
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* 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
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<tr>
<th>Author, Year</th>
<th>Withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milani 1993</td>
<td>5 (10%)</td>
<td></td>
</tr>
<tr>
<td>Zeegers 1987</td>
<td>12 withdrawals: 2 Pl, 8 Emp, 0 Fla, 2 Oxy</td>
<td>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</td>
</tr>
</tbody>
</table>

* 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
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<thead>
<tr>
<th>Author, Year</th>
<th>Study Design</th>
<th>Setting</th>
<th>Eligibility criteria</th>
<th>Exclusion criteria</th>
</tr>
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<tbody>
<tr>
<td><strong>Extended Release vs. Immediate Release (ER vs IR)</strong></td>
<td></td>
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<tr>
<td><strong>Oxybutynin ER vs Oxybutynin IR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Versi 2000</td>
<td>RCT</td>
<td>Multicenter USA</td>
<td>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</td>
<td>Clinically significant medical problems, postvoid residual urine volume over 100ml, other conditions in which oxybutynin is contraindicated</td>
</tr>
<tr>
<td>Birns 2000</td>
<td>RCT</td>
<td>Multicenter UK</td>
<td>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</td>
<td>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</td>
</tr>
</tbody>
</table>

*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*
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<tr>
<th>Author, Year</th>
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<th>Method of Outcome Assessment and Timing of Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extended Release vs. Immediate Release (ER vs IR)</td>
<td>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</td>
<td>none reported</td>
<td>7 day urinary diary after maintenance dose determined</td>
</tr>
<tr>
<td>Versi 2000</td>
<td>Oxy ER 10mg once daily or Oxy 5mg twice daily x 6 wks</td>
<td>none reported</td>
<td>Urinary diary (micturition and incontinence episodes) reviewed at visits 2, 3, 4</td>
</tr>
<tr>
<td>Birns 2000</td>
<td>Oxy ER 10mg once daily or Oxy 5mg twice daily x 6 wks</td>
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<tr>
<td></td>
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<td></td>
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<tr>
<td><strong>Extended Release vs. Immediate Release (ER vs IR)</strong></td>
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<tr>
<td><strong>Oxybutynin ER vs Oxybutynin IR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Versi 2000</td>
<td>screened 417 eligible/enrolled 226</td>
<td>Mean age</td>
<td>Urge incontinence episodes/wk:</td>
<td>withdrawn</td>
</tr>
<tr>
<td></td>
<td></td>
<td>59yrs ER; 60yrs IR</td>
<td>ER 18.6, IR 19.8</td>
<td>ER: 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% Female: ER 88%, IR 90%</td>
<td></td>
<td>IR: 9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ethnicity:</td>
<td></td>
<td>Lost to f/u</td>
</tr>
<tr>
<td></td>
<td></td>
<td>White: 86.5 ER; 90.4 IR</td>
<td></td>
<td>ER: 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Black: 5.4ER; 3.5 IR</td>
<td></td>
<td>IR: 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asian: 0.9 ER; 0 IR</td>
<td></td>
<td>analyzed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ER 111</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IR 115</td>
</tr>
</tbody>
</table>

| Birns 2000   | 162 screened 130 randomized | mean age: 56 yrs | 81% with urge or stress/urge incontinence (ER 78%, IR 84%) | Loss to f/u: 2 (1 each arm) |
|              | % female: 68% (ER 71%, IR 66%) | | | Analyzed: 128 by ITT, 125 by PP |

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

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<tr>
<td>Versi 2000</td>
<td>Reports of adverse effects recorded at each pt visit</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dry mouth: ER 48%, IR 59%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kaplan Meier analysis moderate or severe dry mouth reports indicates a significant difference (p = 0.007) in favor of ER</td>
<td></td>
</tr>
<tr>
<td>Birns 2000</td>
<td>Assessed during visits every two weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>78 pts reported adverse events (60%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(ER 55%, IR 67%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dry mouth: ER 23%, IR 17%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dizziness ER 2%, IR 9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vision abnormality ER 7%, IR 5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cough ER 3%, IR 5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Headache ER 0, IR 5%</td>
<td></td>
</tr>
</tbody>
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<td></td>
<td></td>
</tr>
<tr>
<td>Versi 2000</td>
<td>Overall: 10 (8%)&lt;br&gt;ER: 3 (3%)&lt;br&gt;abdominal pain: 1&lt;br&gt;nausea/dysphagia: 1&lt;br&gt;edema/rash: 1&lt;br&gt;IR: 7 (6%)&lt;br&gt;dry mouth: 1&lt;br&gt;blurred vision: 1&lt;br&gt;nausea: 1&lt;br&gt;impaired urination, edema, blood pressure changes, UTI: 1&lt;br&gt;gastric obstruction: 1&lt;br&gt;UTI: 1&lt;br&gt;edema and pain: 1</td>
<td>Mean duration of treatment/follow-up not stated. Only dry mouth reported in detail.</td>
</tr>
<tr>
<td>Birns 2000</td>
<td>1 (considered unlikely due to study drug)</td>
<td>Mixed types of incontinence&lt;br&gt;Study included a run-in phase to establish tolerability, patients with adverse events excluded during run-in</td>
</tr>
</tbody>
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<th>Study Design Setting</th>
<th>Eligibility criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radomski 2004</td>
<td>Single center Open label pilot crossover trial Canada</td>
<td>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.</td>
<td>Use of medications other than study meds, primary diagnosis of stress incontinence, allergy to anticholinergics/antispasmodics, conditions contraindicating anticholinergic therapy, large daily fluid intake (&gt;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</td>
</tr>
<tr>
<td>Anderson 1999</td>
<td>RCT multi-center USA</td>
<td>Men or women, community dwelling, in good health with urge incontinence or mixed urge incontinence with primary urge component (6+ urge incontinence episodes/wk)</td>
<td>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 hyoscymine, oxybutynin, propantheline for incontinence, positive urine drug screen, glaucoma, gastric narrowing or myasthenia gravis</td>
</tr>
<tr>
<td>Nilsson 1997</td>
<td>Crossover study Multicenter Finland</td>
<td>Females with a history of urge incontinence and detrusor instability confirmed by cystometry.</td>
<td>Stress incontinence (as measured by questionnaire), use of loop diuretics, prazosin, anticholinergics, or antidepressants with anticholinergic effects.</td>
</tr>
</tbody>
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<tr>
<td>Radomski 2004</td>
<td>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</td>
<td>Subjects not permitted to use other medications to alleviate incontinence during the 8 week trial</td>
<td>Satisfaction rating at end of week 2 and week 8 using a four point scale.</td>
</tr>
<tr>
<td>Anderson 1999</td>
<td>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</td>
<td>not given</td>
<td>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.</td>
</tr>
<tr>
<td>Nilsson 1997</td>
<td>Oxy ER 10mg once daily</td>
<td>none reported</td>
<td>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</td>
</tr>
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<th>Gender</th>
<th>Ethnicity</th>
<th>Other population characteristics (diagnosis, etc)</th>
<th>Number withdrawn/ lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radomski 2004</td>
<td>#screened not reported. 12 included for safety analysis. 9 included for efficacy analysis (completed 8 week study)</td>
<td>69</td>
<td>female 67%</td>
<td>For efficacy analysis mean age not reported, % females same. Ethnicity not reported</td>
<td>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).</td>
<td>3/0/9</td>
</tr>
<tr>
<td>Anderson 1999</td>
<td>158 screened 105 enrolled 93 analyzed</td>
<td>Mean age: ER 59yrs; IR 60yrs</td>
<td>ER 94%, IR 90%</td>
<td>mean urge incontinence episodes/wk: ER 27.4, IR 23.4 mean voids/wk: ER 48.3, IR 51.5</td>
<td>withdrawn ER 6 lost to F/U not reported analyzed 93 (efficacy analysis)/105 (safety analysis)</td>
<td></td>
</tr>
<tr>
<td>Nilsson 1997</td>
<td>17 enrolled</td>
<td>mean age 46yrs (range 37-65)</td>
<td>100% female</td>
<td>none reported</td>
<td>1 “due to the sponsors’ request” after first study period 16 analyzed in ER group, 17 in IR group</td>
<td></td>
</tr>
</tbody>
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<td>Radomski 2004</td>
<td>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.</td>
</tr>
<tr>
<td>Anderson 1999</td>
<td>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)</td>
</tr>
<tr>
<td>Nilsson 1997</td>
<td>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</td>
</tr>
</tbody>
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<tr>
<td>Radomski 2004</td>
<td>Adverse events collected during scheduled visits and entered in diary. Mild dry mouth most frequent followed by unspecified pain</td>
<td></td>
</tr>
<tr>
<td>Anderson 1999</td>
<td>Spontaneously reported and anti-cholinergic effects assessed at each study visit</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dry mouth: ER 68%, IR 87% (p = 0.04)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate to severe dry mouth: ER 25%, IR 46% (p = 0.03)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Somnolence: ER 38%, IR 40%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blurred vision: ER 28%, IR 17%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Constipation: ER 30%, IR 31%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dizziness ER 28%, IR 38%</td>
<td></td>
</tr>
<tr>
<td>Nilsson 1997</td>
<td>Patients reported on a questionnaire throughout study, classified as mild, moderate, severe</td>
<td></td>
</tr>
<tr>
<td></td>
<td>14/16 on ER, 5/17 on IR reported at least one adverse event</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dry mouth: ER 69%, IR 82%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Headache ER 44%, 41%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dyspepsia ER 31%, IR 12%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fatigue ER 13%, 24%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blurred vision 25%, IR 12%</td>
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<td>% Severe: ER 17%, IR 14%</td>
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<td>reported that these were NS, but unclear what data being compared.</td>
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*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*
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<tbody>
<tr>
<td>Radomski 2004</td>
<td>3 withdrawals due to adverse events--stomach pain (1), mild peripheral edema (1), severe vision distortion</td>
<td>Unusual design--different treatment duration for two drugs and dosing for Oxy may have been low</td>
</tr>
<tr>
<td>Anderson 1999</td>
<td>2 (4%) in each group due to anticholinergic adverse events</td>
<td>Previously all pts had responded to IR oxy&lt;br&gt;Very high incidence of adverse events - may reflect the aggressive dose titration&lt;br&gt;Duration of study (mean) not reported, very little data on final dose in either group</td>
</tr>
<tr>
<td>Nilsson 1997</td>
<td>none reported</td>
<td>Very high numbers of subjects reporting adverse events</td>
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<tr>
<td>Barkin 2004</td>
<td>RCT Multicenter Canada</td>
<td>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</td>
<td>Post-void residual volume &gt;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 &gt;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 (&gt;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</td>
</tr>
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<tr>
<td>Barkin 2004</td>
<td>No-treatment baseline period for 3 wks</td>
<td>Subjects not permitted to use</td>
<td>24h-patient diary assessed during final 2 wks of</td>
</tr>
<tr>
<td></td>
<td>Oxy IR 5mg 3X/day, dose titration in 5mg</td>
<td>other medications to alleviate</td>
<td>treatment, used the Purdue Urgency Questionnaire to</td>
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<tr>
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<td>increments in 2 wks followed by stable-</td>
<td>incontinence during the 9</td>
<td>assess severity of urgency and frequency of urgency</td>
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<tr>
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<td>dose phase for 4 wks</td>
<td>week trial period</td>
<td>[severity scored on scale or 1 (no urgency or ability</td>
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<tr>
<td></td>
<td>Oxy ER 15mg 1X/day, dose titration in</td>
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<td>to delay voiding) to 5 (≥ 6 episodes of urgency or</td>
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<td>5mg increments in 2 wks followed by</td>
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<td>inability to delay voiding/urine leakage with urge])</td>
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<tr>
<td></td>
<td>stable-dose phase for 4 wks</td>
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<td>used Incontinence Impact Questionnaire (evaluates</td>
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<td>effect of incontinence on 8 activities of daily</td>
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<td>living) and the Urogenital Distress Inventory (evaluates</td>
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<td>distress associated with 8 urinary symptoms) to</td>
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<td>assess changes in QoL.</td>
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</table>
| 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 | 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 |

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<tr>
<td>Barkin 2004</td>
<td>Oxy ER vs Oxy IR for all comparisons (endpoint minus baseline):</td>
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<td>Mean reduction in incontinence episodes/wk: 13.9 vs 16.9 (p=NS)</td>
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<tr>
<td></td>
<td>Mean reduction in episodes of voluntary micturition/day: 1.8 vs 2.4 (p=NS)</td>
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<td>Mean increase in vol. of urine voided/micturition: 25mL vs 40mL (p=NS)</td>
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<td>Mean score of urgency decrease: 1.0 vs 1.3 (p=NS)</td>
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<td>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)</td>
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<td>Mean number of pads/day: 0.6 vs 0.5 (p=NS)</td>
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<tr>
<td>Barkin 2004</td>
<td>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)</td>
<td></td>
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</tbody>
</table>

**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%

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<tr>
<td>Barkin 2004</td>
<td>Oxy IR: 12 (20%) Oxy ER: 11 (17%)</td>
<td>sponsored by Purdue Pharma</td>
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<tr>
<td>Tolterodine ER vs Tolterodine IR</td>
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<tr>
<td>Van Kerrebroeck 2001</td>
<td>RCT Multicenter Multinational</td>
<td>Men or women, age 18+ with urinary frequency (8+ micturitions/24h), urge incontinence (5+ /week), or symptoms of overactive bladder for 6+ months</td>
<td>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,</td>
</tr>
<tr>
<td>Swift 2003</td>
<td>RCT Multicenter International</td>
<td>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</td>
<td>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,</td>
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<td>Van Kerrebroeck 2001</td>
<td>Tol ER 4mg once daily or Tol IR 2mg or Placebo twice daily x 12 wks</td>
<td>none reported</td>
<td>micturition diary assessed at baseline and 12 wks 1 week f/u</td>
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<td>Swift 2003</td>
<td>Tol ER 4 mg (n=417) once daily vs. Tol IR 2 mg twice daily (n=408) vs. Pla (n=410) for 12 wks.</td>
<td>Other treatments for OAB not permitted, except estrogen treatment commenced &gt;2 months prior.</td>
<td>micturition diary assessed at baseline and 12 wks 1 week f/u</td>
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<td><strong>Tolterodine ER vs Tolterodine IR</strong></td>
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</table>
| 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 | 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%) |

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</table>
| Van Kerrebroec 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 | 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) |

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<td>Van Kerrebroeck, 2001</td>
<td>Spontaneously reported events were categorized and causation assigned</td>
<td></td>
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<tr>
<td>Swift, 2003</td>
<td>Reporting details NR.</td>
<td></td>
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<tr>
<td>Re-analysis of data for women only in Van Kerrebroeck, 2001 study (above)</td>
<td>Tol ER vs. Tol IR vs. Pla:</td>
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**Evidence Table 1. Comparative clinical trials**

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

* 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

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<tr>
<th>Author, Year</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
<th>Exclusion criteria</th>
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<tr>
<td><strong>Extended Release vs. Immediate Release (ER vs IR)</strong></td>
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<tr>
<td><strong>Oxybutynin ER vs. Tolterodine IR</strong></td>
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</tbody>
</table>
| 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 |

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## Evidence Table 1. Comparative clinical trials

<table>
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<tr>
<th>Author, Year</th>
<th>Interventions (drug, regimen, duration)</th>
<th>Other interventions/medications</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appell 2001</td>
<td>ER Oxy 10mg once daily, Tol 2mg twice daily, 12 week study</td>
<td>Not given</td>
<td>Safety monitoring patient reporting at each visit 2, 4, 8, 12 weeks, number of urge incontinence episodes at 12 weeks vs. baseline, used 7 day urinary diary</td>
</tr>
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* 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
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<thead>
<tr>
<th>Author, Year</th>
<th>Number screened/ eligible/ enrolled</th>
<th>Age Gender Ethnicity</th>
<th>Other population characteristics (diagnosis, etc)</th>
<th>Number withdrawn/ lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extended Release vs. Immediate Release (ER vs IR)</td>
<td>378 randomized (Oxy ER 185, Tol 193) 332 completed (Oxy ER 160, Tol 172)</td>
<td>Mean Age: 59 yrs Female: 83% Ethnicity: White 87% African American 6% Hispanic 4% Asian 2% Other 1%</td>
<td>Drug naive Oxy ER: 109 Tol: 119</td>
<td>Overall: 46  (21 Tol, 25 Oxy ER) Lost to Follow-up Oxy ER: 3 Tol:3</td>
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* 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
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<th>Author, Year</th>
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<td>Extended Release vs. Immediate Release (ER vs IR)</td>
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<tr>
<td>Appell 2001</td>
<td>Mean number of urge incontinence episodes/wk</td>
</tr>
<tr>
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<td>Oxy ER -19.5, Tol -16.3</td>
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<tr>
<td></td>
<td>Mean change in micturition frequency</td>
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<td>Oxy ER -24.7, Tol -20.1</td>
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<th>Author, Year</th>
<th>Adverse effects assessed?</th>
<th>How assessed</th>
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<tr>
<td>Appell 2001</td>
<td>Patient reported</td>
<td>dry mouth occurred in equal proportion in each group</td>
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<td>both groups had similar rates of dry mouth and other adverse effects</td>
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* 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
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<td>Appell 2001</td>
<td>Oxy ER 14, Tol 15</td>
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<td>Sand et al., 2004 OBJECT (subanalysis of women only)</td>
<td>RCT Multicenter USA</td>
<td>see Appell, 2001</td>
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<td>Oxy ER 10mg once daily Tol 2mg twice daily 12 week study</td>
<td>see Appell, 2001</td>
<td>Subjects completed 7-day voiding diaries at baseline and 12-weeks</td>
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<tr>
<td>Sand et al. 2004 OBJECT (subanalysis of women only)</td>
<td>315 women enrolled/276 completed study</td>
<td>mean age: Oxy 58.4y and Tol 58.8y</td>
<td>Naïve to anticholinergics: Oxy 60.5% and Tol 60.7%</td>
<td>see Appell, 2001</td>
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* 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

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<thead>
<tr>
<th>Author, Year</th>
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<tr>
<td>Sand et al. 2004 (subanalysis of women only)</td>
<td>OBJECT</td>
</tr>
<tr>
<td></td>
<td>Decrease in urge incontinence episodes:</td>
</tr>
<tr>
<td></td>
<td>See Appell, 2001</td>
</tr>
<tr>
<td></td>
<td>Mean decrease in micturition frequency episodes</td>
</tr>
<tr>
<td></td>
<td>Oxy ER: -21.9, Tol: -20.4</td>
</tr>
<tr>
<td></td>
<td>Total decrease incontinence episodes</td>
</tr>
<tr>
<td></td>
<td>Oxy ER: -23.7, Tol: -20.4</td>
</tr>
<tr>
<td></td>
<td>NS = No statistical difference</td>
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*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*
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<td>OBJECT (subanalysis of women only)</td>
<td>Oxy ER vs. Tol</td>
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<tr>
<td></td>
<td>Dry mouth: 28.3% vs 33.7%</td>
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<tr>
<td></td>
<td>Constipation: 8.6% vs 6.7%</td>
</tr>
<tr>
<td></td>
<td>Impaired urination/urinary retention: 4.0% vs 1.2%</td>
</tr>
<tr>
<td></td>
<td>Blurred vision: 2.6% vs 0.6%</td>
</tr>
<tr>
<td></td>
<td>Dizziness: 3.9% vs 4.3%</td>
</tr>
<tr>
<td></td>
<td>Somnolence: 3.3% vs 1.8%</td>
</tr>
<tr>
<td></td>
<td>Insomnia: 0.7% vs 1.8%</td>
</tr>
<tr>
<td></td>
<td>Nervousness: 0.0% vs 1.2%</td>
</tr>
<tr>
<td></td>
<td>Headache: 9.2% vs 10.4%</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia: 5.3% vs 6.1%</td>
</tr>
<tr>
<td></td>
<td>Nausea: 3.3% vs 1.8%</td>
</tr>
<tr>
<td></td>
<td>Vomiting: 2.0% vs 1.8%</td>
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<td>withdraws due to AE: Oxy 11 patients and Tol 12 patients</td>
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<td><strong>Tolterodine ER vs. Oxybutynin IR</strong></td>
<td>Men and women, aged ≥20 with symptoms of urinary urgency, frequency (≥8 voids/24h), incontinence (≥5 episodes/wk), or overactive bladder for ≥6months.</td>
<td>Demonstrable stress incontinence; total daily urinary volume &gt;3 L, avg volume &gt;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.</td>
</tr>
<tr>
<td>Homma 2003</td>
<td>RCT Multicenter Japan &amp; Korea</td>
<td></td>
<td></td>
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<tr>
<td>Homma 2004 subanalysis of HRQoL in Japanese OAB patients</td>
<td>RCT Multicenter Japan &amp; Korea (this subanalysis looked at Japanese pts only)</td>
<td>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.</td>
<td>Korean patients were excluded from analysis due to lack of valid King's Health Questionnaire in Korean language</td>
</tr>
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**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
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<tr>
<td>Homma 2003</td>
<td>Tol ER 4 mg once daily vs. Oxy IR 3 mg three times daily x 12 wks</td>
<td>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 &gt;2months), potent CYP3A4 inhibitors, or any investigational drug.</td>
<td>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</td>
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<tr>
<td>Homma 2004</td>
<td>Tol ER 4 mg once daily vs. Oxy IR 3 mg three times daily</td>
<td>See Homma 2003</td>
<td>Micturition diary completed during 7 days of run-in (baseline and the last 7 days of treatment (week 12) King's Health Questionnaire (KHQ) was used to determine health related quality of life (HRQoL) at baseline and week 12</td>
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<tr>
<td>Homma 2003</td>
<td>Screened NR Eligible NR Enrolled = 608</td>
<td>Tol/Oxy grps Age range 26-84, mean age 59.3</td>
<td>Female 70.2%</td>
<td>Ethnicity: Japanese 48.2% Korean 51.8%</td>
<td>Previous OAB drug therapy= 23% &quot;Causes severe problems&quot; or &quot;many severe problems&quot;=52%</td>
<td>3 withdrawn before treatment, not included in ITT Total withdrawn: Tol 25 (10.4%) Oxy 57 (23.2%) Analyzed: 605</td>
</tr>
<tr>
<td>Tol ER = 240 Oxy IR = 246 Pla = 122</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Homma 2004 subanalysis of HRQoL in Japanese OAB patients</td>
<td>293 enrolled: Tol 114, Oxy 122, Placebo 57</td>
<td>Mean age: 63.4 y Range: 25-88y</td>
<td>% female: 66.5%</td>
<td>100% Japanese</td>
<td>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%</td>
<td>see Homma, 2003, not specifically reported in current article</td>
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</table>
| 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**

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<td>How assessed</td>
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<td>Homma 2003</td>
<td>Directly observed and spontaneously reported at visits 3 through 6, rated as mild, moderate or severe.</td>
</tr>
<tr>
<td></td>
<td>(Tol vs. Oxy)</td>
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<td>Dry mouth: 80 (33.5%) vs. 131 (53.7%) p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Severe dry mouth: 0.4% vs 8.2%</td>
</tr>
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<td>Dry eyes: 3 (1.3%) vs. 7 (2.9%)</td>
</tr>
<tr>
<td></td>
<td>Blurred vision: 3 (1.3%) vs. 8 (3.3%)</td>
</tr>
<tr>
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<td>Constipation: 17 (7.1%) vs. 15 (6.1%)</td>
</tr>
<tr>
<td></td>
<td>Somnolence: 1 (0.4%) vs. 4 (1.6%)</td>
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<td>Difficulty in micturition: 3 (1.3%) vs. 21 (8.6%)</td>
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<tr>
<td>Homma 2004 subanalysis of HRQoL in Japanese OAB patients</td>
<td>Tol ER vs Oxy vs Pla</td>
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<td>Dry mouth: 36.9% vs 61.5% vs 5.3% (p=0.002 for Tol vs Oxy)</td>
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<tr>
<td>Homma 2003</td>
<td>Dry mouth: Tol 0.4% vs. Oxy 9.4% All events: Tol 5.0% vs. Oxy 17.1% p&lt;0.001 Serious event, possibly drug related: 1 Oxy cardiac failure. No deaths and no clinically significant changes in lab or ECG values.</td>
<td>Compliance ≥75% of medication: Tol 98% vs. Oxy 93%</td>
</tr>
<tr>
<td>Homma 2004 subanalysis of HRQoL in Japanese OAB patients</td>
<td>Withdrawals due to AEs in Japanese pts: Oxy: 16.4% Tol: 5.3%</td>
<td>See Homma, 2003 for overall withdrawals due to AE.</td>
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**Darifenacin ER vs. Oxybutynin IR**

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<td>Zinner, 2005</td>
<td>RCT, DB Crossover Multicenter USA</td>
<td>Male or female, 18-85 years with urge incontinence (&gt;4 sig incontinent episodes/week), urinary frequency (&gt;8 voids/day)</td>
<td>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</td>
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<tr>
<td>Zinner, 2005</td>
<td>Dar ER 15, 30mg/day Oxy IR 5mg TID</td>
<td>Placebo</td>
<td>Daily paper voiding diaries</td>
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<tr>
<td>Zinner, 2005</td>
<td>NR/NR/76</td>
<td>Mean age: 59.9 yrs Range: 33-84 yrs 93.4% females Ethnicity: NR</td>
<td>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</td>
<td>16/NR/58</td>
</tr>
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| 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) |

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<td>Zinner, 2005</td>
<td>Self report by patient</td>
<td>Incidence of dry mouth</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dar ER 15: 13.1% vs Dar ER 30: 34.4% vs Oxy IR: 36.1% vs Pla: 4.9% (p&lt;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)</td>
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<tr>
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<td>Incidence of constipation</td>
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<td>Dar ER 15: 9.8% vs Dar ER 30: 21.3% vs Oxy IR: 8.2% vs Pla: 3.3% (p&lt;0.05 for Dar 30 ER vs Pla and Dar ER 30 vs Oxy IR)</td>
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<td></td>
<td>Incidence of blurred vision</td>
</tr>
<tr>
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<td>Dar ER 15: 0% vs Dar ER 30: 0% vs Oxy IR: 3.3% vs Pla: 0% (NS)</td>
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<td></td>
<td></td>
<td>Incidence of dizziness</td>
</tr>
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<td>Dar ER 15: 0% vs Dar ER 30: 0% vs Oxy IR: 1.6% vs Pla: 0% (NS)</td>
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<td>Sussman 2002</td>
<td>Two RCTs (one open-label Tol ER 2mg vs. 4mg, the other blinded Oxy ER 5mg or 10mg)</td>
<td>Multicenter USA</td>
<td>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.</td>
<td>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.</td>
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<td>Diokno 2003</td>
<td>RCT</td>
<td>Multicenter USA</td>
<td>Women, aged ≥18, with documented 21-60 urge urinary incontinence episodes per week and avg ≥10 voids per day.</td>
<td>Treatable genitourinary conditions that could cause incontinence, 2 postvoid residual volumes &gt;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.</td>
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<td>Sussman 2002</td>
<td>Tol ER 2mg or 4mg once daily &lt;br&gt; Oxy ER 5mg or 10mg once daily x 8 weeks &lt;br&gt; No dose adjustments allowed</td>
<td>None reported</td>
<td>Patient assessment of symptoms based on 6-point scale (0 = no problems, 6 = severe problems) at baseline and 8 weeks &lt;br&gt; Patient and Physician rated benefit (No, yes - a little, and yes-very much) at 8 weeks</td>
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<tr>
<td>Diokno 2003 OPERA</td>
<td>Oxy ER 10 mg/day vs. Tol ER 4 mg/day x 12 wks</td>
<td>None reported</td>
<td>Diaries at baseline week, and weeks 2, 4, 8, 12. &lt;br&gt; Outcomes: total incontinence episodes, total incontinence episodes, micturition frequency.</td>
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<tr>
<td><strong>Extended Release vs. Extended Release (ER vs ER)</strong></td>
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<tr>
<td><strong>Oxybutynin ER vs. Tolterodine ER</strong></td>
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</tr>
<tr>
<td>Sussman 2002</td>
<td>Number screened/eligible not stated. 1289 enrolled 669 Tol (333 Tol 2mg, 336 Tol 4mg) 620 Oxy (313 Oxy 5mg, 307 Oxy 10mg)</td>
<td>Mean age 62.6 yrs Female 75% Caucasian 84% Black 10% Hispanic 5%</td>
<td>Prevalence of incontinence symptoms: 62% overall (61% Tol, 64% Oxy) Prior Drug Therapy: 19% overall (17% Tol, 21% Oxy) Majority moderate to severe symptoms</td>
<td>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</td>
</tr>
<tr>
<td>Diokno 2003 OPERA</td>
<td>Screened 1485</td>
<td>Mean age =60 100% female</td>
<td>Prior treatment anticholinergic drugs =47%</td>
<td>Total withdrawn: Oxy 52 (13.3%) Tol 42 (10.5%)</td>
</tr>
<tr>
<td></td>
<td>Eligible NR</td>
<td>Ethnicity: White 85%</td>
<td></td>
<td>Lost to followup: Oxy 13 (3.3%) vs. Tol 3 (0.8%)</td>
</tr>
<tr>
<td></td>
<td>Enrolled 790</td>
<td></td>
<td></td>
<td>Sample size at baseline, wk 2, 4, 8, 12: Oxy= 382, 380, 365, 346, 336, 382 Tol = 393, 390, 383, 370, 355, 393</td>
</tr>
<tr>
<td></td>
<td>Oxy ER= 391</td>
<td>Black 8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tol ER = 399</td>
<td>Hispanic 6%</td>
<td></td>
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</tr>
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<td><strong>Sussman, 2002</strong></td>
<td>Patients reporting improvement in symptoms:</td>
</tr>
<tr>
<td></td>
<td>Tol 2mg 60%, Tol 4mg 70%</td>
</tr>
<tr>
<td></td>
<td>Oxy 5mg 59%, Oxy 10mg 60%</td>
</tr>
<tr>
<td></td>
<td>(p&lt;0.01 for all vs Tol 4mg)</td>
</tr>
<tr>
<td></td>
<td>Degree of change in symptoms was greater in Tol 4mg vs Oxy 10mg (p&lt;0.01)</td>
</tr>
<tr>
<td></td>
<td>The peak improvement was 1 point for Tol 4mg and 0 points for Oxy 10mg.</td>
</tr>
<tr>
<td></td>
<td>Subgroup analysis of patients reporting improvement in symptoms who had moderate to severe symptoms at baseline:</td>
</tr>
<tr>
<td></td>
<td>Tol 4mg 77%, Oxy 10mg 65% (p&lt;0.01)</td>
</tr>
<tr>
<td></td>
<td>Subgroup analysis of patients reporting improvement in symptoms who were drug naive at baseline:</td>
</tr>
<tr>
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<td>Tol 2mg 60%, Tol 4mg 69%</td>
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<td>Oxy 5mg 60%, Oxy 10mg 61% (NS)</td>
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<td>Subgroup analysis of patients reporting improvement in symptoms who were drug experienced at baseline:</td>
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<td>Tol 2mg 57%, Tol 4mg 75%</td>
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<tr>
<td></td>
<td>Oxy 5mg 59%, Oxy 10mg 54% (NS)</td>
</tr>
<tr>
<td></td>
<td>No difference between groups on patient or physician assessment of benefit - data not presented</td>
</tr>
<tr>
<td><strong>Diokno, 2003</strong></td>
<td>Mean change in urge incontinence episodes:</td>
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<td></td>
<td>Oxy -26.3 vs. Tol -25.5 (NS)</td>
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<tr>
<td><strong>OPERA</strong></td>
<td>Mean change in total incontinence episodes:</td>
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<td>Oxy -31.1 vs. Tol -28.6 (NS)</td>
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<td></td>
<td>Decrease in mean micturition frequency: Oxy 28.4 vs. Tol 25.2 (p=0.003)</td>
</tr>
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<td></td>
<td>No incontinence in last week:</td>
</tr>
<tr>
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<td>Oxy 23.0% vs. Tol 16.8% (p=0.03)</td>
</tr>
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<td>Sussman 2002</td>
<td>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)</td>
<td></td>
</tr>
<tr>
<td>Diokno 2003 OPERA</td>
<td>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)</td>
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<tr>
<td>Sussman</td>
<td>2002</td>
<td>Only reported for Tol 4mg (19, 6%) and Oxy 10mg 37 (13%).</td>
<td>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.</td>
</tr>
<tr>
<td>Diokno OPERA</td>
<td>2003</td>
<td>All events: Oxy 20/391 (6.1%) vs. Tol 19/399 (4.8%)</td>
<td>Due to dry mount: Oxy 7, Tol 4</td>
</tr>
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<td>Chu et al, 2005</td>
<td>RCT, Multicenter, USA</td>
<td>see Diokno 2003</td>
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<td>Anderson, 2006</td>
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<td>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 &quot;Coding Symbols for Thesaurus of Adverse Reaction Terms&quot; (COSTART V). Focus on AE that COSTART includes under the CNS classification. For additional information see Diokno, 2003</td>
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- **Group 1:** Prior anticholinergic treatment, n=373
  - Oxy ER (180), Tol ER (193)
- **Group 2:** No prior anticholinergic treatment, n=417
  - Oxy ER (211), Tol ER (206)

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<td>Chu et al, 2005 OPERA Extension (subanalysis of CNS AEs)</td>
<td>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%</td>
</tr>
<tr>
<td>Anderson 2006 OPERA post-hoc analysis based on history of prior anticholinergic treatment</td>
<td>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)</td>
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<td>Chu et al, 2005 OPERA Extension (subanalysis of CNS AEs)</td>
<td>Incidence and severity of AEs judged possible or probably related to Oxy ER and Tol ER during OPERA study:</td>
<td>All comparisons are for Oxy ER (mild, moderate, severe) vs Tol ER (mild, moderate, severe)</td>
</tr>
<tr>
<td></td>
<td>Dizziness: (1.8%, 0.8%, 0%) vs (1.5%, 0.5%, 0%)</td>
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<tr>
<td></td>
<td>Insomnia: (0.8%, 0.5%, 0%) vs (0%, 0%, 0%)</td>
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<td></td>
<td>Somnolence: (0.5%, 0.3%, 0%) vs (1.5%, 0.5%, 0%)</td>
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<td></td>
<td>Anxiety: (0.5%, 0.3%, 0%) vs (0%, 0%, 0%)</td>
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<td></td>
<td>Hypertonia: (0%, 0.3%, 0%) vs (0%, 0%, 0%)</td>
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<td></td>
<td>Nervousness: (0%, 0.3%, 0%) vs (0%, 0%, 0%)</td>
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<td></td>
<td>Tremor: (0.3%, 0%, 0%) vs (0.3%, 0%, 0%)</td>
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<td></td>
<td>Confusion: (0.3%, 0%, 0%) vs (0%, 0%, 0%)</td>
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<tr>
<td></td>
<td>Not judged to be related to treatment:</td>
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<tr>
<td></td>
<td>Oxy ER: depression, increased libido, or vertigo.</td>
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<tr>
<td></td>
<td>Tol ER: abnormal dreams, anxiety, depression, facial paralysis, hypertonia, insomnia, paresthesia, or vertigo.</td>
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<tr>
<td>Anderson 2006</td>
<td>Group 1 (n=180) VS. Group 2 (n=193), all nsd except where p value reported</td>
<td></td>
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<td>Data collected at each visit or any time reported by participant, rated as mild, moderate, severe. n (%)</td>
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<tr>
<td></td>
<td>Dry mouth:</td>
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<tr>
<td></td>
<td>any degree: 58 (32.3) vs. 37 (19.2), p=0.004 VS 58 (27.5) vs. 52 (25.2)</td>
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<tr>
<td></td>
<td>mild: Oxy 44(24.4) vs Tol 29 (15.0) VS Oxy 47 (22.3) vs Tol 40 (19.4)</td>
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<tr>
<td></td>
<td>mod-severe: Oxy 18 (10.0) vs Tol 8 (4.1) VS Oxy 13 (6.2) vs Tol 12 (5.8)</td>
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<tr>
<td></td>
<td>Constipation:</td>
<td></td>
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<tr>
<td></td>
<td>Oxy 14 (7.8) vs Tol 10 (5.2) VS Oxy 11 (5.2) vs Tol 21 (10.2)</td>
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<tr>
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<td>Diarrhea:</td>
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<td></td>
<td>Oxy 14 (7.8) vs Tol 11 (5.7) VS Oxy 17 (8.1) vs Tol 14 (6.8)</td>
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<tr>
<td></td>
<td>Headache:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oxy 8 (4.4) vs Tol 10 (5.2) VS Oxy 14 (6.6) vs Tol 14 (6.8)</td>
<td></td>
</tr>
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<td>Withdrawals due to CNS AEs: Oxy: 6 (1.5%) Tol: 2 (0.5%)</td>
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<tr>
<td>Anderson 2006 OPERA post-hoc analysis based on history of prior anticholinergic treatment</td>
<td>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%)</td>
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some analysis of non-ITT population that showed significant differences -- not reported here

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<tr>
<td>Armstrong, 2005 OPERA post-hoc analysis for adverse event, dry mouth</td>
<td>RCT, DB Multicenter</td>
<td>Women &gt;18 years, with urinary urge incontinence (21-60 episodes/week), urinary urgency, and frequency (≥10 voids/day)</td>
<td>Treatable genitourinary conditions that could cause incontinence, 2 postvoid residual volumes &gt;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</td>
</tr>
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<tr>
<th>Trospium chloride vs oxybutynin</th>
<th></th>
</tr>
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<tr>
<td>Halaska 2003 RCT Multi center Europe</td>
<td>Patients with urge syndrome or urge incontinence</td>
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<td>Oxy ER 10mg/day vs. Tol ER 4mg/day x 12 weeks</td>
<td>None</td>
<td>Adverse events data were collected at end of 2, 4, 8, and 12 weeks; investigator assigned severity levels based on observation and patient report</td>
</tr>
</tbody>
</table>

**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. |

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<td>Armstrong, 2005 \ OPERA post-hoc analysis for adverse event, dry mouth</td>
<td>NR/NR/790</td>
<td>Mean age: 60 yrs Range: 18-92 yrs 100% female 84.9% Caucasian</td>
<td>47.2% previously received anticholinergic medication</td>
<td>94</td>
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<tr>
<td></td>
<td></td>
<td></td>
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<td>52 in Oxy ER vs 42 in Tol ER</td>
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**Trospium chloride vs oxybutynin**

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<tr>
<th>Author, Year</th>
<th>Screened NR</th>
<th>Age Gender Ethnicity</th>
<th>Smokers: 13% Previous illnesses: 70% Previous medication: 41% Mean body weight: 71.8 Kg</th>
<th>Number withdrew (Trospium 67, Oxy 24)</th>
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<tbody>
<tr>
<td>Halaska 2003</td>
<td>Eligible 358 Enrolled 357</td>
<td>Mean age 53.7 Female 86% Ethnicity NR</td>
<td></td>
<td>91 withdrew (Trospium 67, Oxy 24)</td>
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| Armstrong, 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.” |

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RCT = Random Controlled Trial, UTI = Urinary Tract Infection,  
NS = No statistical difference
### Evidence Table 1. Comparative clinical trials

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<tr>
<th>Author, Year</th>
<th>Adverse effects assessed?</th>
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</tr>
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<tbody>
<tr>
<td>Armstrong, 2005</td>
<td>Investigator assessed AEs at weeks 2, 4, 8, and 12 or when reported by a patient</td>
<td>Investigator assigned severity of AEs based on following definitions</td>
</tr>
<tr>
<td>OPERA post-hoc analysis for adverse event, dry mouth</td>
<td>Mild: event may be noticeable but does not influence daily activities and usually does not need intervention</td>
<td>Moderate: Event may be sufficiently troublesome to make the person uncomfortable; it may influence performance of daily activities; and it may need intervention</td>
</tr>
<tr>
<td></td>
<td>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</td>
<td></td>
</tr>
</tbody>
</table>

**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. Tros vs. Oxy. Dry Mouth: 33% vs 50% Constipation: 7% vs 4% Visual disturbance: 3% vs 6% | |

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<tr>
<td>Armstrong, 2005 OPERA post-hoc analysis for adverse event, dry mouth</td>
<td>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%)</td>
<td>This study focused only on dry mouth AE, not on effectiveness or efficacy of study medications. Was a subanalysis of bigger OPERA study.</td>
</tr>
</tbody>
</table>

**Trospium chloride vs oxybutynin**

| Halaska 2003 | Trospium 16 (6%) Oxy 9 (10%) |

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<tr>
<td>Madersbacher 1995</td>
<td>RCT Multi-center Germany</td>
<td>Patients with spinal cord injuries and detrusor hyper-reflexia</td>
<td>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.</td>
</tr>
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<tr>
<td>Madersbacher 1995</td>
<td>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</td>
<td>None</td>
<td>Twenty &quot;well being&quot; 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.</td>
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<tr>
<td>Madersbacher 1995</td>
<td>Screened NR, Eligible NR, Enrolled 95</td>
<td>Mean age=32, Female 50%, Ethnicity NR</td>
<td>Type of spinal cord injury not specified. Differences in baseline urodynamic measures for maximum bladder capacity and compliance</td>
<td>10/NR/88</td>
</tr>
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<td>Madersbacher 1995</td>
<td>Not reported. <em>Severe</em> 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.</td>
</tr>
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<td>Madersbacher 1995</td>
<td>Adverse effects assessed via interview focused on &quot;well being&quot; items. Severity grading done--methodology for grading based on a four point scale. Dry mouth: 56% Oxy vs 54% Trospium. &quot;Severe&quot; 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.</td>
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<tr>
<td>Madersbacher 1995</td>
<td>Trospium 3 (6%) Oxy 7 (16%)</td>
<td>No information on nature of spinal cord injury or duration of injury. No information on other medications patients on during trial.</td>
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<td>Davila 2001</td>
<td>RCT Multicenter USA</td>
<td>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 &gt;30%. Diagnosis of detrusor instability based on symptoms and urodynamic study confirming involuntary bladder contractions.</td>
<td>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.</td>
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<tr>
<td><strong>Oxybutynin TD vs. Oxybutynin IR</strong></td>
<td>Starting dose assigned depending on prior oral oxybutynin dose of (\leq 10)mg, 11-15mg, or (&gt;15)mg 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</td>
<td>NR</td>
<td>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.</td>
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<tr>
<td>Davila 2001</td>
<td>Screened NR</td>
<td>Mean age 63.5</td>
<td>Female 92%</td>
<td>White 95%</td>
<td>NR</td>
<td>2/76 (2.6%) withdrawn before 4 wks</td>
</tr>
<tr>
<td></td>
<td>Eligible NR</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Enrolled 76</td>
<td></td>
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<tr>
<td></td>
<td>Oxy TD = 38</td>
<td></td>
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<tr>
<td></td>
<td>Oxy IR = 38</td>
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<tr>
<td>Davila 2001</td>
<td>Oxybutynin TD vs. Oxybutynin IR</td>
<td>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&lt;0.0001)</td>
</tr>
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<td>Davila 2001</td>
<td>Invalidated questionnaire to evaluate titration for presence and severity of 10 symptoms assessed at 2, 4 and 6 wks.</td>
<td>Oxy TD vs. Oxy IR</td>
</tr>
<tr>
<td></td>
<td>Dry mouth: 15 (39%) vs. 31 (82%) (p&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reduction in severity of dry mouth vs prior treatment: 67% vs. 33%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Worse dry mouth: 5% vs. 33%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Constipation: 8 (21%) vs. 19 (50%)</td>
<td></td>
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<tr>
<td></td>
<td>Somnolence 7 (18%) vs. 14 (37%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blurred vision: 7 (18%) vs. 9 (24%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Impaired urination: 9 (24%) vs. 9 (24%)</td>
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<tr>
<td>Davila 2001</td>
<td>Oxybutynin TD vs. Oxybutynin IR</td>
<td>Oxy IR: 1 (dry mouth)</td>
<td>Oxy TD: 1 contact dermatitis due to patch</td>
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<tr>
<td>Dmochowski 2003 RCT Multicenter USA</td>
<td>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.</td>
<td>History of urinary tract surgery in previous 6 months, diagnosis of interstitial cystitis, urethral syndrome, painful bladder syndrome, or overflow urinary incontinence.</td>
<td></td>
</tr>
</tbody>
</table>

| **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 antimuscarinic medication (including narrow-angle glaucoma and urinary or gastric retention), nonpharmaceutical 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. |

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<td><strong>Oxybutynin TD vs. Tolterodine SR</strong></td>
<td>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</td>
<td>Maintain any nonpharmacologic incontinence management program.</td>
<td>Diary of urine volume, urge and incontinence episodes; measured at 0, 2, 6, 12 wks. QOL instrument and VAS &quot;periodically.&quot;</td>
</tr>
<tr>
<td>Dmochowski 2003</td>
<td>12 wk treatment period</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Tolterodine vs. Solifenacin** | 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 |
| Chapple et al. 2004 | | | |

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<td><strong>Oxybutynin TD vs. Tolterodine SR</strong></td>
<td>Screened NR</td>
<td>Mean age 63.5</td>
<td>Female 92.8%</td>
<td>White 94.5%</td>
<td>Prior treatment median duration &gt;1 yr (range 6 wks to 20 years)</td>
<td>41 withdrawn</td>
</tr>
<tr>
<td></td>
<td>Eligible NR</td>
<td></td>
<td>White 94.5%</td>
<td></td>
<td>Oxy 49.6%</td>
<td>1 lost to followup</td>
</tr>
<tr>
<td></td>
<td>Enrolled 361</td>
<td>Mean age 63.5</td>
<td></td>
<td>Black 3.6%</td>
<td>Tol 47.4%</td>
<td>361 analyzed</td>
</tr>
<tr>
<td>Tolterodine vs. Solifenacin</td>
<td>1281 enrolled; 1081 randomized; 1033 evaluated</td>
<td>Mean age: Placebo: 57.8; Tolterodine (2 mg): 56.9; Solifenacin (5 mg): 58.1; Solifenacin (10 mg): 57.2</td>
<td>25% male &gt;98% white</td>
<td>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</td>
<td>Withdrawn: 36/1077 (3.6%); Lost to fu: 11/1077 (1.0%)</td>
<td></td>
</tr>
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<tr>
<td></td>
<td>Mean change in incontinence episodes per day at 12 wks:</td>
</tr>
<tr>
<td></td>
<td>Oxy -2.9, Tol -3.2, Pla -2 (Oxy vs Tol p=0.5878)</td>
</tr>
<tr>
<td></td>
<td>Mean decrease in urinary frequency per day:</td>
</tr>
<tr>
<td></td>
<td>Oxy -1.9, Tol -2.2, Pla -1.4 (Oxy vs Tol p=0.2761)</td>
</tr>
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<td>Frequency reduction greater for patients with 14+ micturitions/day; reduction NS for &lt;10/day.</td>
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<tr>
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<td>Avg urinary volume:</td>
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<tr>
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<td>Oxy +24 mL, Tol +29 mL vs. Pla +5.5 mL (Oxy vs. Tol p=0.7690)</td>
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<td>Global Assessment of Disease State scores:</td>
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<tr>
<td></td>
<td>Oxy vs. Tol p =0.1861</td>
</tr>
<tr>
<td></td>
<td>IIQ (QoL scale): -22 vs -23 (NS)</td>
</tr>
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<td></td>
<td>Urogenital distress Inventory: -25 vs -28 (NS)</td>
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<td><strong>Tolterodine vs. Solifenacin</strong></td>
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</tr>
<tr>
<td>Chapple et al. 2004</td>
<td>Change in mean number of urgency episodes/24 h:</td>
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<tr>
<td></td>
<td><strong>Tolterodine</strong>: -38%, p=0.0511</td>
</tr>
<tr>
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<td><strong>Solifenacin</strong>:</td>
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<tr>
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<td>5mg once daily: -52%, p&lt;0.001</td>
</tr>
<tr>
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<td>10mg once daily: -55%, p&lt;0.001</td>
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<td><strong>Placebo</strong>: -33%, no p-value reported.</td>
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<td></td>
</tr>
<tr>
<td><strong>Oxybutynin TD vs. Tolterodine SR</strong></td>
<td>Method of assessment not reported</td>
<td></td>
</tr>
<tr>
<td>Dmochowski 2003</td>
<td>Application site reactions: Application site reactions:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oxy 32/121 (25.4%; 5% severe), Tol 7/123 (5.7%), Pla 8/117 (6.9%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Systemic adverse events:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oxy 23/121 (19%), Tol 29/123, Pla 14/117 (12%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anticholinergic side effects (% only, numbers NR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dry Mouth</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oxy TD 4.1% vs Tol SR 7.3%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oxy TD 3.3%, Tol SR 5.7%</td>
<td></td>
</tr>
<tr>
<td><strong>Tolterodine vs. Solifenacin</strong></td>
<td>Dry mouth: placebo=13 (4.9%), Sol 5mg=39 (14%), Sol 10mg=57 (21.3%), Tol=49 (18.6%);</td>
<td></td>
</tr>
<tr>
<td>Chapple et al. 2004</td>
<td>Constipation: placebo=5 (1.9%), Sol 5mg=20 (7.2%), Sol 10mg=21 (7.8%), Tol=7 (2.6%);</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blurred vision: Placebo=7 (2.6%), Sol 5mg=10 (3.6%), Sol 10mg=15 (5.6%), Tol=4 (1.5%)</td>
<td></td>
</tr>
</tbody>
</table>

* 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
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<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Transdermal vs. Sustained Release (TD vs. SR)</th>
<th>Oxybutynin TD vs. Tolterodine SR</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dmochowski 2003</td>
<td>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).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Tolterodine vs. Solifenacin</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapple et al. 2004</td>
<td>31/1077 (2.9%) for withdrawals due to all adverse events</td>
<td></td>
</tr>
</tbody>
</table>

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<tbody>
<tr>
<td>Chapple, et al. 2005 STAR (data from uncorrected proof)</td>
<td>RCT, Europe</td>
<td>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</td>
<td>Stress Incontinence (SI) or Mixed Incontinence where SI was predominant and neurogenic DO</td>
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<tr>
<td>Chapple et al 2007 STAR post-hoc</td>
<td>RCT, Europe</td>
<td>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</td>
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**Darifenacin vs. Oxybutinin**

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<tr>
<td>Chapple, et al. 2005 STAR (data from uncorrected proof)</td>
<td><strong>Stable dosing phase: (Weeks 0-4)</strong>&lt;br&gt;Solfenacim 5mg once/d&lt;br&gt;Tolterodine ER 4mg once/d</td>
<td>none reported</td>
<td>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.</td>
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<tr>
<td>Chapple et al. 2007 STAR post-hoc</td>
<td><strong>Stable dosing phase: (Weeks 0-4)</strong>&lt;br&gt;Solfenacim 5mg once/d&lt;br&gt;Tolterodine ER 4mg once/d</td>
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<tr>
<td>Chapple et al. 2005 STAR (data from uncorrected proof)</td>
<td>1355 screened/1200 randomized and enrolled / Full analysis set (FAS): 1177</td>
<td>Mean Age: Sol 5 &amp; 10: 56.5y Tol ER: 56.4y Age range: NR</td>
<td>Sol: 70.8% ≤65y; 29.2% &gt;65y; and 6.7% &gt;75y Tol ER: 70.6% ≤65y; 29.4% &gt;65y; and 6.0% &gt;75y</td>
<td>Withdrawals: Sol: 3.5% Tol ER: 3.0%</td>
</tr>
<tr>
<td>Chapple et al. 2007 STAR post-hoc</td>
<td>1355 screened/1200 randomized and enrolled / Full analysis set (FAS): 1177 post-hoc: Sol 5 NDI: N=297 Tol ER NDI: n=267</td>
<td>Mean Age: Sol 5: 56.5y Tol ER: 56.9y Age range: NR</td>
<td>Sol: 70.0% ≤65y; 30.3% &gt;65y; and 6.7% &gt;75y Tol ER: 70.6% ≤65y; 30.0% &gt;65y; and 7.0% &gt;75y</td>
<td>Withdrawals: Sol: 3.0% Tol ER: 4.2%</td>
</tr>
</tbody>
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<th>Author, Year</th>
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<tr>
<td>Chapple, et al. 2005 STAR (data from uncorrected proof)</td>
<td>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 &amp; 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</td>
</tr>
<tr>
<td>Chapple et al 2007 STAR post-hoc</td>
<td>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</td>
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| 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**

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<tr>
<td>Chapple, et al. 2005 STAR (data from uncorrected proof)</td>
<td>Withdrawals due to AEs: Sol: 3.5% Tol ER: 3.0%</td>
<td>Overall withdrawal rates are unclear. Study funded by Yamanouchi Pharmaceutical Co.</td>
</tr>
<tr>
<td>Chapple et al. 2007 STAR post-hoc</td>
<td>Withdrawals due to AEs: Sol 5 NDI: 1.3% Tol ER: 2.4%</td>
<td>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</td>
</tr>
</tbody>
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**Darifenacin vs. Oxybutinin**

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</tr>
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<tbody>
<tr>
<td>Chapple &amp; Abrams 2005</td>
<td>RCT, Crossover, UK</td>
<td>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)</td>
<td>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 &lt;1 SI episode/week, pregnancy or breast feeding and inadequate contraception, excessive alcohol intake, starting or modifying bladder training program, anticholinergic therapy contraindications.</td>
</tr>
</tbody>
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* 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
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<th>Method of Outcome Assessment and Timing of Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapple &amp; Abrams 2005</td>
<td>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</td>
<td>none reported</td>
<td>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</td>
</tr>
</tbody>
</table>

Each treatment period was for 7 days

---

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

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<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Outcomes</th>
<th>Mean max. decrease in salivary flow from baseline to day 7:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapple &amp; Abrams 2005</td>
<td>urodynamic parameters, salivary flow, heart rate and visual nearpoint</td>
<td>Cohort 1: Dar 2.5 mg tid: -0.90 ml/min; Oxy 2.5 mg tid: -0.88 ml/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cohort 2: Dar 15 mg QD: -0.98 ml/min; Oxy 5 mg tid: -1.55 ml/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cohort 3: Dar 30 mg QD: -1.06 ml/min; Oxy 5 mg tid: -1.30 ml/min</td>
</tr>
</tbody>
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</tr>
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<tr>
<td>Chapple &amp; Abrams 2005</td>
<td>observed or volunteered AE, serious AEs, and discontinuations, clinical lab tests (haematology, biochemistry, urinalysis and physical examinations)</td>
<td>Cohort 1% (Dar: no. of pts; Oxy: no. of pts) vs. Cohort 2% (D: #; O: #) vs. Cohort 3% (D:#; O:#)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pts with all AEs: 43% (D:5, O:8) vs 73% (D:16; O:19) vs 98% (D:22; O:24)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pts with treatment-related AEs: 40% (D:4; O:8) vs 68% (D:14; O:19) vs 98% (D:22; O:24)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Discontinued due to AEs: 3.3% (D:0; O:1) vs 2.1% (D:1; O:0) vs 6.4% (D:1; O:2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Discontinued due to treatment-related AEs: 0% vs 2.1% (D:1; O:0) vs 4.3% (D:1; O:1)</td>
</tr>
<tr>
<td></td>
<td>Dry mouth: 40% (D: 4; O:8) vs 62.5% (D:13; O:17) vs 94%(D:21; O:23)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Constipation: 6.7% (D:1; O:1) vs 29.2% (D:8; O:6) vs 25.5% (D:10; O:2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dyspepsia: 3.3% (D:1; O:0) vs 16.7% (D:3; O:5) vs 8.5% (D:2; O:2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Headache: 3.3% (D:1; O:0) vs 8.3% (D:1; O:3) vs 10.6% (D:2; O:3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abnormal vision: 6.7% (D:1; O:1) vs 8.3% (D:1; O:3) vs 12.8% (D:4; O:2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Somnolence: 3.3% (D:0; O:1) vs 4.2% (D:1; O:1) vs 4.3% (D:2; O:1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Asthenia: 3.3% (D:0; O:1) vs 0% vs 6.4% (D:3; O:1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pharyngitis: 0% vs 2.1% (D:O; O:1) vs 4.3% (D:2; O:1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dysphagia: 0% vs 8.3%(D: 1; O:3) vs 0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pruritus: 0% vs 2.1% (D:O; O:1) vs 4.3% (D:3; O:0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dry eyes: 0% vs 0% vs 6.4% (D:1; O:3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urinary tract disorder: 0% vs 6.3%(D: 2; O:1) vs 0%</td>
<td></td>
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<tr>
<td></td>
<td>Confusion: 0% vs 0% vs 4.3% (D:3; O:0)</td>
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<tr>
<td></td>
<td>Epistaxis: 0% vs 0% vs 4.3% (D:1; O:2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dysuria: 0% vs 0% vs 4.3% (D:1; O:2)</td>
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</tr>
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<tbody>
<tr>
<td>Chapple &amp; Abrams 2005</td>
<td>Discontinued due to AEs: 3.3% (D:0; O:1) vs 2.1% (D:1; O:0) vs 6.4% (D:1; O:2)</td>
<td>Discontinued due to treatment-related AEs: 0% vs 2.1% (D:1; O:0) vs 4.3% (D:1; O:1) sponsored by Pfizer</td>
</tr>
</tbody>
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## Evidence Table 2. Internal validity

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<tr>
<th>Author, Year</th>
<th>Random assignment</th>
<th>Allocation concealed</th>
<th>Groups similar at baseline</th>
<th>Eligibility criteria specified</th>
<th>Outcome assessors blinded</th>
<th>Care provider blinded</th>
</tr>
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<tbody>
<tr>
<td><strong>Immediate Release vs Immediate Release</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leung 2002</td>
<td>Adequate</td>
<td>Not reported</td>
<td>Some differences, Not statistically significant. Menopausal: 45% Oxy, 66% Tol Coexisting illness: 58.5% Oxy, 50.9% Tol Concomitant drugs: 60% Oxy, 72% Tol</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Lee 2002</td>
<td>Adequate</td>
<td>Not reported</td>
<td>Some differences, Previously treated with drug for incontinence: Tol 32%, Oxy 22%; stratification of drugs used Not reported.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Malone-Lee 2000</td>
<td>Adequate</td>
<td>Not reported</td>
<td>Similar</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Drutz 1999</td>
<td>Not reported</td>
<td>Not reported</td>
<td>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,</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Abrams 1998</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Some differences, Not statistically significant. Previously treated with drug for incontinence: 52% Tol, 60% Oxy, 75% PI Some characteristics Not stratified by group, i.e. concomitant disease or drugs, prior urinary tract surgery.</td>
<td>Yes</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Milani 1993</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
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<tbody>
<tr>
<td>Leung 2002</td>
<td>Immediate</td>
<td>No</td>
<td>Stated ITT, but actual numbers analyzed not reported</td>
<td>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.</td>
<td>Withdrawals reported clearly</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Release</td>
<td></td>
<td></td>
<td></td>
<td>Cross over Not reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Compliance: Oxy 88% Tol 75%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>attrition reported clearly, crossovers reported, adherence measured but not reported.</td>
<td></td>
</tr>
<tr>
<td>Lee 2002</td>
<td>Immediate Release</td>
<td>Yes</td>
<td>Yes</td>
<td>Not clear</td>
<td>Yes</td>
<td>18% withdrew from study, 97% of these due to adverse events with higher number in Oxy group.</td>
</tr>
<tr>
<td></td>
<td>Release</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malone-Lee 2000</td>
<td>Immediate Release</td>
<td>Yes</td>
<td>Yes</td>
<td>Not clear</td>
<td>Attrition reported clearly, crossovers Not reported, adherence measured but not reported.</td>
<td>No</td>
</tr>
<tr>
<td>Drutz 1999</td>
<td>Immediate Release</td>
<td>Yes</td>
<td>Only for adverse events</td>
<td>Not clear</td>
<td>Attrition reported clearly, others Not reported</td>
<td>47% of original patients excluded from analysis, 20% withdrew overall, with 12% of original group withdrawing due to adverse events.</td>
</tr>
<tr>
<td>Abrams 1998</td>
<td>Immediate Release</td>
<td>Yes</td>
<td>Yes</td>
<td>Not clear</td>
<td>Withdrawals due to adverse effects reported clearly Others Not reported</td>
<td>No</td>
</tr>
<tr>
<td>Milani 1993</td>
<td>Immediate Release</td>
<td>Yes</td>
<td>No</td>
<td>Not clear</td>
<td>Yes</td>
<td>18% drop out rate, higher in Oxy group due to adverse effects</td>
</tr>
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<tr>
<td>Drutz 1999</td>
<td>Poor</td>
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<tr>
<td>Abrams 1998</td>
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<tr>
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<tbody>
<tr>
<td>Zeegers 1987</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not clear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Zeegers 1987</td>
<td>Yes</td>
<td>No</td>
<td>Not clear</td>
<td>Withdrawals due to adverse effects reported clearly</td>
<td>Yes, high loss to follow-up in Emp group</td>
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<tbody>
<tr>
<td>Halaska 2003</td>
<td>3:1 Trospium: Oxy</td>
<td>Not reported</td>
<td>Similar demographics. Oxy group had somewhat increased frequency of incontinence, micturitions/day and urgency episodes/day</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Madersbacher 1995</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Some differences in gender and baseline urodynamic measures</td>
<td>Yes</td>
<td>Yes</td>
<td>Not reported</td>
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<tr>
<td>Halaska 2003</td>
<td>Yes</td>
<td>Yes</td>
<td>Not clear</td>
<td>Withdrawals due to adverse effects, poor efficacy, poor compliance reported. No crossovers.</td>
<td>Yes, withdrawal rate 25% overall, similar in both arms</td>
</tr>
<tr>
<td>Madersbacher 1995</td>
<td>Yes</td>
<td>No</td>
<td>Not clear</td>
<td>Not clear.</td>
<td>Yes. 11% withdrawal overall Oxy 16% Trospium 6%</td>
</tr>
</tbody>
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<td>Madersbacher 1995</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Kerrebroeck 2001</td>
<td>Adequate</td>
<td>Not reported</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Appell 2001</td>
<td>Adequate</td>
<td>Not reported</td>
<td>Yes, stratified randomization based on the severity of urge incontinence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Birns 2000</td>
<td>Yes, Block randomization 2pts/block Hospitals 5 pts/block OP Clinic</td>
<td>Not reported</td>
<td>Patient demographics Not given other than mean age: 56 yo</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Versi 2000</td>
<td>Not reported</td>
<td>Adequate - central randomization by phone</td>
<td>Stated no significant differences, but not enough data presented to assess</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Nilsson 1997</td>
<td>Non-randomized</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Yes</td>
<td>Not reported (stated ER group took placebo in evening)</td>
<td>Not reported (stated ER group took placebo in evening)</td>
</tr>
<tr>
<td>Anderson 1999</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Some differences, mean number urge incontinence episodes/wk higher in ER group (NS).</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Homma 2003</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>yes</td>
</tr>
<tr>
<td>Swift 2003</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
</tr>
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<th>Differential loss to follow-up or overall high loss to follow-up</th>
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</thead>
<tbody>
<tr>
<td>Van Kerrebroeck 2001</td>
<td>Yes</td>
<td>Yes</td>
<td>Not clear</td>
<td>Yes</td>
<td>95% compliance</td>
<td>12% overall loss to f/u, 6% lost due to adverse events: ER 5%, IR 5%, Placebo 6%</td>
</tr>
<tr>
<td>Appell 2001</td>
<td>Yes</td>
<td>repeated measures analysis done, but only p-values reported</td>
<td>Not clear</td>
<td>Yes</td>
<td>Overall = 12%</td>
<td>14% Oxy ER, 11% Tol</td>
</tr>
<tr>
<td>Birns 2000</td>
<td>Yes</td>
<td>No</td>
<td>Not clear</td>
<td>Yes</td>
<td>1.5% overall</td>
<td></td>
</tr>
<tr>
<td>Versi 2000</td>
<td>Yes</td>
<td>Not clear</td>
<td>Not clear</td>
<td>Yes</td>
<td>7% overall</td>
<td>6% ER, 8% IR</td>
</tr>
<tr>
<td>Nilsson 1997</td>
<td>Not reported</td>
<td>No</td>
<td>Yes</td>
<td>1 patient withdrawn from study by sponsor, adherence Not reported</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Anderson 1999</td>
<td>Yes</td>
<td>No</td>
<td>Not clear</td>
<td>Yes</td>
<td>98% compliance</td>
<td>12% overall withdrawal</td>
</tr>
<tr>
<td>Homma 2003</td>
<td>Yes</td>
<td>Stated ITT. Actual numbers analyzed NR.</td>
<td>Not clear</td>
<td>Attrition yes, crossovers none, adherence yes</td>
<td>Non ADE withdrawals similar between groups, loss to follow up low, but lowest in Oxy grp</td>
<td></td>
</tr>
<tr>
<td>Swift 2003</td>
<td>Yes</td>
<td>Yes, carry forward approach</td>
<td>not clear</td>
<td>Attrition yes; adherence 96% took &gt;75% of prescribed medication</td>
<td>No, 12% overall, distributed fairly evenly.</td>
<td></td>
</tr>
</tbody>
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</tr>
<tr>
<td>Van Kerrebroeck, 2001</td>
<td>Fair</td>
</tr>
<tr>
<td>Appell, 2001</td>
<td>Fair</td>
</tr>
<tr>
<td>Bims, 2000</td>
<td>Fair</td>
</tr>
<tr>
<td>Versi, 2000</td>
<td>Fair</td>
</tr>
<tr>
<td>Nilsson, 1997</td>
<td>Poor</td>
</tr>
<tr>
<td>Anderson, 1999</td>
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<td>Homma, 2003</td>
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<tbody>
<tr>
<td>Radomski 2004</td>
<td>Crossover</td>
<td>Open label</td>
<td>Crossover. IR Oxy always provided first and only 2 weeks. ER provided 4 weeks</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
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<tr>
<td>Radomski 2004</td>
<td>No</td>
<td>No for efficacy, yes for adverse events</td>
<td>Not clear. Three withdrawals included in safety analysis.</td>
<td>Yes</td>
<td>3 of 12 withdrew due to adverse events</td>
</tr>
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<tr>
<td>Barkin, 2004</td>
<td>NR</td>
<td>NR</td>
<td>similar</td>
<td>yes</td>
<td>yes, method NR</td>
<td>yes, method NR</td>
</tr>
<tr>
<td>Chapple et al, 2005</td>
<td>yes</td>
<td>NR</td>
<td>similar</td>
<td>yes</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Chapple &amp; Abrams, 2005</td>
<td>yes</td>
<td>NR</td>
<td>similar</td>
<td>yes</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Chapple, Rechberger et al, 2003</td>
<td>NR</td>
<td>NR</td>
<td>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.</td>
<td>yes</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Zinner, 2005</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (stated but no details reported)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Barkin, 2004</td>
<td>yes, method NR</td>
<td>no</td>
<td>not clear</td>
<td>withdrawals reported clearly, crossover not reported, Compliance not reported in withdrawal reasons: 2 patients in Oxy group, contamination NR</td>
<td>no</td>
</tr>
<tr>
<td>Chapple et al, 2005</td>
<td>yes</td>
<td>yes</td>
<td>not clear</td>
<td>withdrawals reported clearly, crossover not reported, Compliance not reported, contamination NR</td>
<td>NR</td>
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<tr>
<td>Chapple &amp; Abrams, 2005</td>
<td>yes</td>
<td>no</td>
<td>not clear</td>
<td>withdrawals reported clearly, crossover not reported, Compliance described but not reported, contamination NR</td>
<td>no</td>
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<tr>
<td>Chapple, Rechberger et al, 2003</td>
<td>NR</td>
<td>yes</td>
<td>not clear</td>
<td>withdrawals reported clearly, other NR</td>
<td>no</td>
</tr>
<tr>
<td>Zinner, 2005</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>Withdrawals reported, crossover as planned, compliance NR, contamination NR</td>
<td>No</td>
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<td><strong>Extended Release vs Extended Release</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sussman 2002</td>
<td>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.</td>
<td>Not reported</td>
<td>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</td>
<td>Yes</td>
<td>Tol arms stated to be open label. Oxy arms Not clear if blinded.</td>
<td>Tol arms stated to be open label. Oxy arms Not clear if blinded.</td>
</tr>
<tr>
<td>Diokno 2003 OPERA</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Armstrong, 2005</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Transdermal vs. Immediate Release</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Davila 2001</td>
<td>Yes</td>
<td>NR</td>
<td>Yes, except most males (5/6) in Oxy TD group</td>
<td>Yes</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Oxy = Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection
## Evidence Table 2. Internal validity

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Patient unaware of treatment</th>
<th>Intention-to-treat (ITT) analysis</th>
<th>Maintenance of comparable groups</th>
<th>Reporting of attrition, crossovers, adherence, and contamination</th>
<th>Differential loss to follow-up or overall high loss to follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Extended Release vs Extended Release</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sussman 2002</td>
<td>Tol arms stated to be open label. Oxy arms Not clear if blinded</td>
<td>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.</td>
<td>Not clear</td>
<td>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</td>
<td>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%.</td>
</tr>
<tr>
<td>Diokno 2003 OPERA</td>
<td>Yes</td>
<td>Yes (using last observation carried forward)</td>
<td>Unclear</td>
<td>Attrition yes Adherence NR</td>
<td>Slightly more loss in Oxy group, including one death. Total loss 104/790 (13.2%)</td>
</tr>
<tr>
<td>Armstrong, 2005</td>
<td>Yes</td>
<td>NR</td>
<td>Unclear</td>
<td>Attrition yes (12% overall) Crossover NR Adherence NR</td>
<td>No</td>
</tr>
<tr>
<td><strong>Transdermal vs. Immediate Release</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Davila 2001</td>
<td>Yes</td>
<td>No, but only 1 drop out from each group</td>
<td>NR</td>
<td></td>
<td>No</td>
</tr>
</tbody>
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<tbody>
<tr>
<td><strong>Extended Release vs Extended Release</strong></td>
<td></td>
</tr>
<tr>
<td>Sussman 2002</td>
<td>Fair (-)</td>
</tr>
<tr>
<td><strong>Transdermal vs. Immediate Release</strong></td>
<td></td>
</tr>
<tr>
<td>Davila 2001</td>
<td>Fair</td>
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<tr>
<td><strong>Transdermal vs. Extended Release</strong></td>
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<thead>
<tr>
<th>Author, Year</th>
<th>Random assignment</th>
<th>Allocation concealed</th>
<th>Groups similar at baseline</th>
<th>Eligibility criteria specified</th>
<th>Outcome assessors blinded</th>
<th>Care provider blinded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dmochowski 2003</td>
<td>NR</td>
<td>NR</td>
<td>Yes, though more male and black patients in oxy TD group</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
</tr>
</tbody>
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<th>Differential loss to follow-up or overall high loss to follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dmochowski 2003</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Attrition overall 41/361 (11%)</td>
<td>Unclear, not all withdrawals accounted for</td>
</tr>
</tbody>
</table>

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### Evidence Table 2. Internal validity

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<thead>
<tr>
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<tbody>
<tr>
<td>Dmochowski 2003</td>
<td>Fair</td>
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# Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

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

**Oxybutynin**

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

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<tr>
<td><strong>Flavoxate</strong></td>
<td></td>
</tr>
<tr>
<td>Gruneberger 1984</td>
<td>Neurogenic cause: Fla 9 (47%), Cle 14 (70%)</td>
</tr>
<tr>
<td></td>
<td>Mixed incontinence: Fla 3 (16%), Cle 3 (15%)</td>
</tr>
<tr>
<td>Meyhoff 1983</td>
<td>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%)</td>
</tr>
<tr>
<td>Bradley 1970</td>
<td>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</td>
</tr>
</tbody>
</table>

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<tbody>
<tr>
<td>Flavoxate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gruneberger 1984</td>
<td>Not Reported</td>
<td>Not Reported</td>
</tr>
<tr>
<td>Meyhoff 1983</td>
<td>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 &lt;15 ml/s; residual urine volume &lt;50 ml following spontaneous voiding; mid-stream urine culture showing &lt;105 colonies/ml</td>
<td>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</td>
</tr>
</tbody>
</table>

| Oxybutynin   |                      |                   |

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

**Oxybutynin**

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

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Flavoxate</strong></td>
<td></td>
</tr>
</tbody>
</table>
| 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**

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

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Adverse effects assessed?</th>
<th>How assessed</th>
<th>Withdrawals due to adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Flavoxate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gruneberger 1984</td>
<td>Not clear. Fla: 9 reports of gastric side effects, Cle: 4 had trembling and tachycardia, 3 had nervousness</td>
<td>4 withdrew due to gastric complaints, 1 due to severe neurosis, Cle: 1 withdrew due to drug interaction</td>
<td></td>
</tr>
<tr>
<td>Meyhoff 1983</td>
<td>Assessment unclear. Total adverse events reported: Fla 34, Eme 26, Pl 16</td>
<td>Not Reported</td>
<td></td>
</tr>
<tr>
<td>Bradley 1970</td>
<td>Not clear. Fla: Dry mouth 1; Abdominal pain 1; Headache 1</td>
<td>Fla: 2 withdrew; but not clear due to which adverse events</td>
<td></td>
</tr>
<tr>
<td>Herbst 1970</td>
<td>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</td>
<td>Not Reported</td>
<td></td>
</tr>
<tr>
<td><strong>Oxybutynin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
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<tr>
<th>Author, Year</th>
<th>Study Design Setting</th>
<th>Number screened/eligible enrolled</th>
<th>Age Gender Ethnicity</th>
<th>Interventions (drug, regimen, duration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holmes 1989</td>
<td>RCT Crossover Single center London</td>
<td>23 enrolled, others not reported</td>
<td>Age: Oxy 39.6, Pro 44.5 100% female Ethnicity: not reported</td>
<td>Oxy 5 mg or Pro 15 mg three times daily 1 month intervention, 1 week washout, then crossover</td>
</tr>
<tr>
<td>Madersbacher 1999</td>
<td>RCT Multicenter Austria</td>
<td>366 enrolled; others not reported</td>
<td>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</td>
<td>Oxy 2.5 mg or Prov 15 mg three times daily x 4 weeks</td>
</tr>
</tbody>
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<th>Author, Year</th>
<th>Other population characteristics (diagnosis, etc)</th>
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<tr>
<td>Holmes 1989</td>
<td>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</td>
</tr>
<tr>
<td>Madersbacher 1999</td>
<td>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</td>
</tr>
</tbody>
</table>

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<th>Author</th>
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<th>Exclusion criteria</th>
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<tr>
<td>Holmes 1989</td>
<td>Not Reported</td>
<td>Not Reported</td>
</tr>
<tr>
<td>Madersbacher 1999</td>
<td>History of urgency or urge incontinence, a maximum cystometric bladder capacity of &lt; or equal to 300 ml.; age 18 or older; body weight 45 kg. or greater</td>
<td>Detrusor hyperreflexia; postoperative incontinence; infravesical obstruction; a postvoid residual urine of &gt; 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</td>
</tr>
</tbody>
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<tbody>
<tr>
<td>Holmes 1989</td>
<td>Unclear</td>
<td>Daytime frequency: measured in total voids over 3 days; Nocturia: measured by total voids over 3 nights range; Incontinence: rated using linear analogue scale</td>
</tr>
<tr>
<td>Madersbacher 1999</td>
<td>Unclear</td>
<td>Bladder diary</td>
</tr>
</tbody>
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Overactive bladder
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<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| 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 |

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<th>Author, Year</th>
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<th>Withdrawals due to adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holmes 1989</td>
<td>Unclear. Dry mouth: Oxy 29.8, Pro 18.4; Constipation: Oxy 10.1, Pro 9.3; Blurred vision: Oxy 12.1, Pro 16.2</td>
<td>Withdrawals: 3</td>
</tr>
<tr>
<td>Madersbacher 1999</td>
<td>Total incidence: Prov 64%, Oxy 72%, Pl 42%</td>
<td>Withdrawals: Pro 13%, Oxy 11%, Pl 9.7</td>
</tr>
<tr>
<td></td>
<td>Frequency of severe dry mouth: Oxy&gt;Prov (p 0.0093)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Visual disturbance: Prov 27%, Oxy 18%, Pl 14%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nausea: Prov 4.1%, Oxy 9.9%, Pl 8.3%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vomiting: Prov 2.1%, Oxy 1.4%, Pl 2.8%</td>
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</tbody>
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<th>Ethnicity</th>
<th>Interventions (drug, regimen, duration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serels 1998</td>
<td>Unclear Cross-over Single Center USA</td>
<td>34 enrolled; Others not reported</td>
<td>Mean age: 62 yrs Range: 28-91 100% female Ethnicity: NR</td>
<td>Hyoscyamine 0.375 mg bid; Doxazosin 2 mg QHS; Hyo + Dox (combination)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pts got each therapy for a month, unless they were unwilling to cross-over</td>
</tr>
</tbody>
</table>

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<tr>
<td>Hycoscyamine</td>
<td>Serels 1998 NR</td>
</tr>
</tbody>
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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**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Eligibility criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hycoscyamine</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

| Serels 1998  | NR                   | NR                 |

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

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

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| **Hycoscyamine** | 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

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<th>Adverse effects assessed?</th>
<th>How assessed</th>
<th>Withdrawals due to adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hycoscyamine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serels 1998</td>
<td>Percentages are in order: Hyo, Dox, combination</td>
<td>Moderate-to-severe side effects: 19 (61%), 8 (47%), 8 (61%)</td>
<td>Not Reported</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design Setting</th>
<th>Number screened/ eligible/enrolled</th>
<th>Age Gender Ethnicity</th>
<th>Interventions (drug, regimen, duration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goode 2002</td>
<td>RCT Single site USA</td>
<td>486 screened, 197 randomized/105 analyzed</td>
<td>Mean age 67</td>
<td>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</td>
</tr>
<tr>
<td>Burgio 2001</td>
<td>RCT Single site USA</td>
<td>468 screened/ 197enrolled</td>
<td>Age Range: 55 to 91 yrs Mean age 68yrs 97% White 3% African American</td>
<td>Oxy 2.5mg or Pl once daily to 5mg three times daily Biofeedback 4 sessions</td>
</tr>
<tr>
<td>Burgio 1998</td>
<td>RCT Single site USA</td>
<td>468 screened/197 enrolled</td>
<td>Mean age 68yrs 100% female Ethnicity not reported</td>
<td>Oxy 2.5mg once daily to 5mg three times daily Biofeedback 4 sessions</td>
</tr>
<tr>
<td>Burgio 2000</td>
<td>Modified crossover following the RCT reported in Goode 2002</td>
<td>128 screened/35 enrolled</td>
<td>Mean age 69.3 Female 100% Ethnicity 100% white</td>
<td>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</td>
</tr>
</tbody>
</table>

Oxy = Oxybutynin, Beh = Behavior, Pl = Placebo, ENS = Electrical Nerve Stimulation
## Evidence Table 4. Anticholinergic overactive bladder syndrome drugs compared with non-drug therapy

<table>
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<th>Author, Year</th>
<th>Other population characteristics (diagnosis, etc)</th>
<th>Eligibility criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goode 2002</td>
<td>48% mixed type incontinence</td>
<td>Age &gt;=55 yrs, ambulatory, urge incontinence &gt;/= 2x/wk for at least 3 months, urodynamic evidence of bladder dysfunction.</td>
<td>Continual leakage, postvoid residual &gt; 200ml, uterine prolapse past the introitus, narrow-angle glaucoma, unstable angina, decompensated congestive heart failure, history of malignant arrhythmias or impaired mental status.</td>
</tr>
<tr>
<td>Burgio 1998</td>
<td>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(&lt;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(&gt;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</td>
<td>Patients aged &gt;= 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 &lt; or equal to 350 ml.)</td>
<td>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 &lt;20)</td>
</tr>
<tr>
<td>Burgio 2000</td>
<td>Ambulatory, community dwelling with urge incontinence</td>
<td>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</td>
<td>See Burgio 1998</td>
</tr>
</tbody>
</table>

Oxy = Oxybutynin, Beh = Behavior, Pl = Placebo, ENS = Electrical Nerve Stimulation
### Evidence Table 4. Anticholinergic overactive bladder syndrome drugs compared with non-drug therapy

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<tbody>
<tr>
<td>Goode 2002</td>
<td>92 excluded from analysis: 28 did not complete treatment, 64 did not undergo post-treatment cystometry</td>
<td>Bladder diary</td>
<td>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%</td>
</tr>
<tr>
<td>Burgio 2001</td>
<td>42 withdrawn (either did not complete both psychological exams (14), or reasons not reported) 155 analyzed</td>
<td>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 &quot;extreme enough to be a case&quot;</td>
<td>Change in Global Severity Index: Oxy 2.1, Beh 3.4, Pl 1.0 (p = 0.26)</td>
</tr>
<tr>
<td>Burgio 1998</td>
<td>24 withdrew/0 lost to f/u/190 analyzed</td>
<td>Bladder diaries, patient satisfaction and overall evaluation of perceived improvement questionnaires (2 wks post-treatment),</td>
<td>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&lt;0.001 vs Pl; p=0.02 vs Oxy) Pl: 0.0 voids/night</td>
</tr>
<tr>
<td>Burgio 2000</td>
<td>1 withdrawal from OXY/0 lost to FU/34 analyzed (extension of Burgio 1998)</td>
<td>See Burgio 1998</td>
<td>Reported percent reduction in incontinence. Behavioral to combined therapy 57.5% to 88.5% Oxy to combined therapy 72.7% to 84.3%</td>
</tr>
</tbody>
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## Evidence Table 4. Anticholinergic overactive bladder syndrome drugs compared with non-drug therapy

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<tr>
<td>Goode 2002</td>
<td>Not reported</td>
<td>Not reported</td>
<td>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.</td>
</tr>
<tr>
<td>Burgio 2001</td>
<td>See above</td>
<td>See above</td>
<td>This is a subgroup analysis from the Burgio study, of those completing psychological analysis.</td>
</tr>
<tr>
<td>Burgio 1998</td>
<td>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%</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Burgio 2000 (extension of Burgio 1998)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>This is a subgroup analysis of patients agreeable to combined therapy post Burgio 1998 trial.</td>
</tr>
</tbody>
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## Evidence Table 4. Anticholinergic overactive bladder syndrome drugs compared with non-drug therapy

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<tbody>
<tr>
<td>Soomro 2001</td>
<td>Randomized Crossover, open label Single site UK</td>
<td>43 enrolled, others not reported</td>
<td>Mean age 50 yrs 70% female Ethnicity not reported</td>
<td>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.</td>
</tr>
<tr>
<td>Colombo 1995</td>
<td>RCT Single site USA</td>
<td>81 screened, others not reported</td>
<td>Age: Oxy=48, Beh=49 100 percent female Ethnicity not reported</td>
<td>Oxy 5 mg three times daily or bladder training x 6 weeks</td>
</tr>
</tbody>
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### Evidence Table 4. Anticholinergic overactive bladder syndrome drugs compared with non-drug therapy

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</thead>
<tbody>
<tr>
<td>Soomro 2001</td>
<td>Mean functional capacity 154</td>
<td>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.</td>
<td>Not Reported</td>
</tr>
<tr>
<td>Colombo 1995</td>
<td>Detrusor instability: Oxy=14, Beh=13; Low-compliance bladder: Oxy=9, Beh=8; Sensory bladder: Oxy=15, Beh=16</td>
<td>Patients showing detrusor instability, low-compliance bladder and sensory bladder</td>
<td>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</td>
</tr>
</tbody>
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</thead>
<tbody>
<tr>
<td>Soomro 2001</td>
<td>Not Reported</td>
<td>Voiding diary, Bristol urinary symptom questionnaire and Quality of Life questionnaire</td>
<td>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</td>
</tr>
<tr>
<td>Colombo 1995</td>
<td>6 withdrawn: Oxy=4 due to anticholinergic adverse events; Beh=2 consent withdrawals</td>
<td>Clinical cure: total disappearance of urge incontinence and did not require protective pads or further therapies</td>
<td>Clinical cure: Detrusor instability group: Oxy=93%, Beh=62% Low-compliance bladder group Oxy=67%, Beh=75% Sensory bladder group: Oxy=60%, Beh=81%</td>
</tr>
</tbody>
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## Evidence Table 4. Anticholinergic overactive bladder syndrome drugs compared with non-drug therapy

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<th>How assessed</th>
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<th>Comments</th>
</tr>
</thead>
</table>
| 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**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Dose</th>
<th>Mean Change in Number of Micturitions/24h</th>
<th>Mean Change in Number of Incontinence Episodes/24h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>OAB drug</strong> (n)</td>
<td><strong>Placebo</strong> (n)</td>
</tr>
<tr>
<td>Rentzhog</td>
<td>1998</td>
<td>TOL 2mg BID</td>
<td>↓20% (not given)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Jacquetin</td>
<td>2001</td>
<td>TOL 2mg BID</td>
<td>↓1.4 (103)</td>
<td>↓1.2 (51)</td>
</tr>
<tr>
<td>Malone-Lee</td>
<td>2001</td>
<td>TOL 2mg BID</td>
<td>↓0.7 (73)</td>
<td>0 (42)</td>
</tr>
<tr>
<td>Van Kerrebrokeck</td>
<td>1998*</td>
<td>TOL 2mg BID</td>
<td>↓0.1 (17)</td>
<td>↓0.1 (16)</td>
</tr>
<tr>
<td>Millard</td>
<td>1999</td>
<td>TOL 2mg BID</td>
<td>↓2.3 (129)</td>
<td>↓1.4 (64)</td>
</tr>
<tr>
<td>Chancellor</td>
<td>2000</td>
<td>TOL 2mg BID</td>
<td>↓1.7 (514)</td>
<td>↓1.2 (507)</td>
</tr>
<tr>
<td>Zinner</td>
<td>2002</td>
<td>TOL 4mg QD &lt;65y/o</td>
<td>↓2 (292)</td>
<td>↓1.4 (284)</td>
</tr>
<tr>
<td>Zinner</td>
<td>2002</td>
<td>TOL 4mg QD &gt;65y/o</td>
<td>↓1.4 (214)</td>
<td>↓0.9 (223)</td>
</tr>
<tr>
<td>Chapple</td>
<td>2004</td>
<td>TOL 2mg BID</td>
<td>↓1.9 (263)</td>
<td>↓1.2 (267)</td>
</tr>
<tr>
<td>Chapelle</td>
<td>2004</td>
<td>TOL 2mg BID</td>
<td>↓1.8 (37)</td>
<td>↓1.0 (36)</td>
</tr>
<tr>
<td>Kelleher</td>
<td>2002</td>
<td>TOL ER 4mg/day</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Khullar</td>
<td>2004</td>
<td>TOL ER 4mg/day</td>
<td>↓1.2 (569)</td>
<td>↓0.9 (285)</td>
</tr>
<tr>
<td>Landis</td>
<td>2004</td>
<td>TOL ER 4mg/day</td>
<td>↓1.9 (492)</td>
<td>↓0.4 (494)</td>
</tr>
<tr>
<td>Szonyi,</td>
<td>1995</td>
<td>OXY 2.5mg BID</td>
<td>Daytime frequency lower with Oxy (P = 0.0025)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Zinner</td>
<td>2004</td>
<td>TROS 20mg BID</td>
<td>↓2.4 (256)</td>
<td>↓1.3 (256)</td>
</tr>
<tr>
<td>Alloussi</td>
<td>1999</td>
<td>TROS 20mg BID</td>
<td>Efficacy assessment done by investigator favored trospium</td>
<td>NR</td>
</tr>
<tr>
<td>Author Year</td>
<td>Dose</td>
<td>Mean Change in Number of Micturitions/24h</td>
<td>Mean Change in Number of Incontinence Episodes/24h</td>
<td></td>
</tr>
<tr>
<td>-------------</td>
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<td>----------------------------------</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>OAB drug</td>
<td>Placebo</td>
<td>OAB drug</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>(n)</td>
<td>(n)</td>
<td>(n)</td>
<td>(n)</td>
</tr>
<tr>
<td>Cardozo 2000</td>
<td>TROS 20 mg BID</td>
<td>Efficacy assessment done by investigator favored trospium</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Dmochowski 2002</td>
<td>OXY TD 1.3 mg/day</td>
<td>↓1.8 (130)</td>
<td>↓1.7 (132)</td>
<td>↓2.1 (NS)</td>
</tr>
<tr>
<td></td>
<td>2.6 mg/day</td>
<td>↓1.7 (133)</td>
<td>↓2.0 (NS)</td>
<td>(P&lt;0.0165)</td>
</tr>
<tr>
<td></td>
<td>3.9 mg/day applied twice/week</td>
<td>↓2.3 (125)</td>
<td>↓2.7</td>
<td></td>
</tr>
<tr>
<td>Cardozo 2004</td>
<td>SOL 5 mg</td>
<td>↓2.4 (286)</td>
<td>↓1.6</td>
<td>↓1.6 (173)</td>
</tr>
<tr>
<td></td>
<td>10 mg</td>
<td>↓2.8 (290)</td>
<td>(281)</td>
<td>↓1.6 (165)</td>
</tr>
<tr>
<td>Cardozo 2005</td>
<td>DAR 30 mg QD</td>
<td>↓0.8 (35)</td>
<td>P=NS</td>
<td>NR</td>
</tr>
<tr>
<td>Haab 2004</td>
<td>DAR A: 3.75mg QD</td>
<td>↓1.7 (49), P=NR</td>
<td>↓0.8</td>
<td>A: ↓1.2 (49)</td>
</tr>
<tr>
<td></td>
<td>B: 7.5 mg QD</td>
<td>↓1.6 (219)</td>
<td>(152)</td>
<td>B: ↓1.3 (219)</td>
</tr>
<tr>
<td></td>
<td>C: 15 mg QD</td>
<td>↓1.7 (106)</td>
<td>(P&lt;0.001 for both B &amp; C vs placebo)</td>
<td>C: ↓1.5 (106)</td>
</tr>
<tr>
<td>Muskat 1996</td>
<td>SCP TD Changed every 3 days (4 patches total)</td>
<td>Diurnal frequency: ↓7.5 (10)</td>
<td>P&lt;0.05</td>
<td>Diurnal frequency: ↓0.7 (10)</td>
</tr>
<tr>
<td>Steers 2005</td>
<td>DAR A: 7.5 mg</td>
<td>↓2.0 (104)</td>
<td>↓1.0</td>
<td>A: ↓1.1</td>
</tr>
<tr>
<td></td>
<td>B: 7.5 for 2 wks then 15 mg for 12 wks</td>
<td>(P&lt; 0.001 for both combined vs. placebo)</td>
<td>(123)</td>
<td>B: ↓1.2</td>
</tr>
<tr>
<td>Chapple 2007</td>
<td>DAR 7.5 mg/day for 2 wks</td>
<td>Median -3.0 (266)</td>
<td>(P=0.006)</td>
<td>Median -2.2 (133)</td>
</tr>
<tr>
<td></td>
<td>Optional titration to 15 mg/day for rest of the 12 wk period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staskin 2007</td>
<td>TROS 60 mg/day for 12 wks</td>
<td>-2.81 (292)</td>
<td>(P&lt;0.001)</td>
<td>-1.99 (300)</td>
</tr>
<tr>
<td>Dmochowski 2008</td>
<td>TROS 60 mg/day for 12 weeks</td>
<td>-2.5 (267)</td>
<td>(P&lt;0.001)</td>
<td>-1.8 (276)</td>
</tr>
<tr>
<td>Zinner 2006</td>
<td>DAR 15 mg/day for 12 wks</td>
<td>Median -2.20 (212)</td>
<td>(P=0.176)</td>
<td>-1.80 (220)</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Dose</td>
<td>Mean Change in Number of Micturitions/24h</td>
<td>Mean Change in Number of Incontinence Episodes/24h</td>
</tr>
<tr>
<td>---------------</td>
<td>------</td>
<td>-----------------------------</td>
<td>-----------------------------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>OAB drug</strong> (n)</td>
<td><strong>Placebo</strong> (n)</td>
</tr>
<tr>
<td><strong>Hill</strong> 2006</td>
<td>DAR CR</td>
<td>A: 7.5mg/day, B: 15/day, C: 30mg/day for 12 wks</td>
<td>Median A: -1.7(107), B: -1.9(106), C: -2.2(114)</td>
<td>Median A: -1.1(108)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>P value vs placebo</strong> A: P=0.066, B: P=0.033, C: P&lt;0.001</td>
<td><strong>P value vs placebo</strong> A: P=0.066, B: P=0.033, C: P&lt;0.001</td>
</tr>
<tr>
<td><strong>Rudy</strong> 2006</td>
<td>TROS 20mg BID for 12 wks</td>
<td>-2.67 (323) (P&lt;0.0001)</td>
<td>-1.76 (325)</td>
<td>-1.86 (323) (P&lt;0.0001)</td>
</tr>
<tr>
<td><strong>Rudy, Cline, 2006</strong></td>
<td>TROS 20mg BID for 12 wks</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Rackley</strong> 2006</td>
<td>TOL ER 4mg/day for 12 wks</td>
<td>NR -15%(429)</td>
<td>NR -9%(421)</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Kaplan, 2006</strong></td>
<td>TOL ER 4mg/day for 12 wks</td>
<td>NR -10.8% (371)</td>
<td>NR -7.9% (374)</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Kelleher, 2006</strong></td>
<td>SOL</td>
<td>A: 5mg/day, B: 10mg/day For 12 wks</td>
<td>A: MUI -2.5 (159), B: MUI -2.6 (452), B: UUI -2.8 (652)</td>
<td>A: MUI -1.4 (430), UUI -1.4 (644)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>P value vs placebo</strong> A: P&lt;0.001</td>
<td><strong>P value vs placebo</strong> A: P&lt;0.001</td>
</tr>
<tr>
<td><strong>Nitti, 2006</strong></td>
<td>TOL ER 4mg/day for 12 wks</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Roehrborn, 2006</strong></td>
<td>TOL ER 4mg/day for 12 wks</td>
<td>NR -12% (77) P=0.22</td>
<td>NR -4% (86)</td>
<td>-11.9 (77) P&lt;0.05</td>
</tr>
<tr>
<td><strong>Dmochowski, 2007</strong></td>
<td>TOL ER 4mg/day for 12 wks</td>
<td>A: -0.22 (507), P&lt;0.05, B: -0.57 (507), P&lt;0.001, C: -0.55 (507), P&lt;0.001, D: -0.043 (507), P&lt;0.002, E: -1.8 (507), P&lt;0.001</td>
<td>A: -0.17 (507), B: -0.35 (507), C: -0.39 (507), D: -0.30 (507), E: -1.2 (507)</td>
<td>NR</td>
</tr>
<tr>
<td>Author Year</td>
<td>Dose</td>
<td>Mean Change in Number of Micturitions/24h</td>
<td>Mean Change in Number of Incontinence Episodes/24h</td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>------</td>
<td>-----------------------------------------</td>
<td>-----------------------------------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>OAB drug</strong></td>
<td><strong>Placebo</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(n)</td>
<td>(n)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>OAB drug</strong></td>
<td><strong>Placebo</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(n)</td>
<td>(n)</td>
<td></td>
</tr>
<tr>
<td>Wein, 2007</td>
<td>TOL ER 4mg/day for 12 wks</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Randomization adequate?</th>
<th>Allocation concealment adequate?</th>
<th>Groups similar at baseline?</th>
<th>Eligibility criteria specified?</th>
<th>Outcome assessors masked?</th>
<th>Care provider masked?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinner, 2006</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>&quot;Double-blind&quot; methods NR</td>
<td>Yes</td>
</tr>
<tr>
<td>Staskin, 2007</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hill, 2006</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Dmochowski, 2008</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>&quot;Double-blind&quot; methods NR</td>
<td>Yes</td>
</tr>
<tr>
<td>Chapple, 2007</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
### Evidence Table 6. Quality assessment of placebo-controlled trials

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

---

**Overactive bladder**
## Evidence Table 6. Quality assessment of placebo-controlled trials

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Randomization</th>
<th>Blinding</th>
<th>Withdrawals</th>
<th>Analysis</th>
<th>Attrition</th>
<th>Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rudy, 2006</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Rackley, 2006</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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</table>
### Evidence Table 6. Quality assessment of placebo-controlled trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Attrition</th>
<th>Crossover</th>
<th>Adherence</th>
<th>Contamination</th>
<th>Withdrawal</th>
<th>LOCF</th>
<th>Funding Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rudy, 2006</td>
<td>Yes</td>
<td>Yes</td>
<td>No/No</td>
<td>NR</td>
<td>NR</td>
<td>Yes, LOCF</td>
<td>Fair</td>
<td>Indevus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pharmaceuticals Inc</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rackley, 2006</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (14% overall), No</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Fair</td>
<td></td>
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</tbody>
</table>
## Evidence Table 7. Assessment of abstracts for publication bias

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

*Data not provided
**Evidence Table 7. Assessment of abstracts for publication bias**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Interventions (Drug, dose, sample size)</th>
<th>Micturitions mean change (time period)</th>
<th>Urge incontinence episodes mean change (time period)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moore</td>
<td>1997</td>
<td>A: Tolterodine 1 mg BID B: Tolterodine 2 mg BID C: Placebo (Total n=306)</td>
<td>A: -1.7 B: 1.8 C: not reported (24 hours)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Whishaw</td>
<td>1997</td>
<td>A: Tolterodine 1 mg BID (n=unclear) B: Tolterodine 2 mg BID (n=unclear) C: Placebo (n=unclear) (Total n=316)</td>
<td>A&gt;C* B&gt;C* A=B=C (24 hours)</td>
<td></td>
</tr>
<tr>
<td>Van Kerrebroeck</td>
<td>2000</td>
<td>A: Tolterodine 4 mg/day (n=507) B: Placebo (n=508)</td>
<td>Percent change A: -17% B: -11%</td>
<td>Percent change A: -53% B: -30%</td>
</tr>
</tbody>
</table>

**Placebo-controlled, cont.**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Interventions (Drug, dose, sample size)</th>
<th>Micturitions mean change (time period)</th>
<th>Urge incontinence episodes mean change (time period)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hill</td>
<td>2004</td>
<td>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)</td>
<td>NR</td>
<td>Median % Change A: -9.8 B: -10.9 D: -6.6 (weekly)</td>
</tr>
<tr>
<td>Rudy</td>
<td>2004</td>
<td>A: Trospium chloride 20 mg BID (n=329) B: Placebo (n=329)</td>
<td>A: -2.67 B: -1.76</td>
<td>A: -65.9 B: -43.6</td>
</tr>
<tr>
<td>Moore</td>
<td>1997</td>
<td>Same as Millard, 1997</td>
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</tbody>
</table>

**Comparative Observational Studies**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Interventions (Drug, dose, sample size)</th>
<th>Micturitions mean change (time period)</th>
<th>Urge incontinence episodes mean change (time period)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boccuzzi</td>
<td>2002</td>
<td>Oxybutynin IR B: Tolterodine IR</td>
<td>12 months</td>
<td>Oxy 83% Tol 76%</td>
</tr>
<tr>
<td>Taira</td>
<td>2002</td>
<td>Tol, Oxy, Oxy XL, Hyoscyamine, Flavoxate, imipramine, propantheline</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data not provided*
<table>
<thead>
<tr>
<th>Author</th>
<th>Interventions (Drug, dose, sample size)</th>
<th>Micturitions mean change (time period)</th>
<th>Urge incontinence episodes mean change (time period)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juzba</td>
<td>Oxybutynin Tolterodine (formulations not stated)</td>
<td>3 months</td>
<td>Cox regression the risk of discontinuation was statistically significantly lower in Tol users, who were 43% less likely to discontinue</td>
</tr>
</tbody>
</table>

*Data not provided*
## Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Setting</th>
<th>Study Design</th>
<th>Eligibility criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolterodine (Tol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Siami 2002</td>
<td>Multicenter USA</td>
<td>Open label, uncontrolled 12 weeks</td>
<td>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</td>
<td>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.</td>
</tr>
<tr>
<td>Michel 2002</td>
<td>Multicenter Germany</td>
<td>Open label, uncontrolled, cohort 12 weeks</td>
<td>Tol prescription</td>
<td>None specified</td>
</tr>
<tr>
<td>Appell 2001</td>
<td>Multicenter (multinational)</td>
<td>Open label 9 month study</td>
<td>Patients completing 12 week RCT enrolled after 1-week washout period.</td>
<td>None specified</td>
</tr>
</tbody>
</table>

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

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<tr>
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<tbody>
<tr>
<td><strong>Tolterodine (Tol)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Siami 2002</td>
<td>Tol 4mg ER once daily</td>
<td>Number screened not reported. 1147 enrolled 1138 analyzed (9 took no drug) 735 drug naïve 403 previously treated (not with Tol)</td>
<td>Age range 18-91 Mean age drug naïve 60yr Mean age prior treatment 62.5yrs Drug naïve; 70% female, Prior Treatment; 79% female Drug naïve; 87% white, Prior treatment; 90% white</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michel 2002</td>
<td>Tol - varying doses. Mean dose 2mg twice daily</td>
<td>2250 enrolled</td>
<td>Mean age 61 yrs 77% female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appell 2001</td>
<td>Tol 2mg twice daily</td>
<td>939 eligible/854 enrolled</td>
<td>Age Range 19-89 Mean 60yrs 76% female</td>
<td></td>
<td></td>
</tr>
</tbody>
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<tr>
<td><strong>Tolterodine (Tol)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Siami 2002</td>
<td>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).</td>
<td>Dry mouth was the most common adverse event reported, at 16%. Of these events 8% were severe, 20% moderate, and 72% mild. No other adverse events were reported in greater than 6% of patients.</td>
<td>90 (8%)</td>
</tr>
<tr>
<td>Michel 2002</td>
<td>Spontaneously reported and elicited during visits (6 and 12 wks). Patients asked to rate tolerability at 12 wks (very good, good, moderate, poor)</td>
<td>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)</td>
<td></td>
</tr>
<tr>
<td>Appell 2001</td>
<td>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.</td>
<td>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%)</td>
<td>73 (9%), of these 12 due to dry mouth (1%)</td>
</tr>
</tbody>
</table>

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<th>Author, Year</th>
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</thead>
<tbody>
<tr>
<td>Tolterodine (Tol) 2002</td>
<td>Short-term</td>
</tr>
<tr>
<td>Michel 2002</td>
<td>Realistic setting, but unclear if tolerability assessment is made by physician or patient</td>
</tr>
<tr>
<td>Appell 2001</td>
<td></td>
</tr>
</tbody>
</table>

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<th>Study Design</th>
<th>Eligibility criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrams, 2001</td>
<td>Multicenter (multinational)</td>
<td>Open label 12 months study</td>
<td>Patients completing 4wk RCT enrolled after 4-week washout period.</td>
<td>None specified</td>
</tr>
<tr>
<td>Kreder, 2002</td>
<td>Multicenter (multinational)</td>
<td>Open label 12 month study</td>
<td>Patients completing 12 wk RCT enrolled</td>
<td>None specified</td>
</tr>
<tr>
<td>Abrams, 2001</td>
<td>Multicenter, Europe</td>
<td>Open label, uncontrolled, 12 months</td>
<td>male and female patients, age &gt;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).</td>
<td>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.</td>
</tr>
<tr>
<td>Michel, 2005</td>
<td>Multicenter, Germany</td>
<td>Open label, uncontrolled, 9 months</td>
<td>none</td>
<td>none</td>
</tr>
</tbody>
</table>
### Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

<table>
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<tr>
<th>Author, Year</th>
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<th>Number screened/ eligible/ enrolled</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrams, 2001</td>
<td>Tol 2mg twice daily</td>
<td>895 eligible/714 enrolled</td>
<td>Age range 18-92</td>
<td>Mean age 60yrs</td>
<td>69% female</td>
</tr>
<tr>
<td>Kreder, 2002</td>
<td>Tol ER 4mg once daily (no dose adjustments allowed)</td>
<td>1337 eligible/1077 enrolled</td>
<td>Age range 20-93</td>
<td>Mean age 60 yrs</td>
<td>82% female</td>
</tr>
<tr>
<td>Abrams, 2001</td>
<td>Tol 2mg twice daily with optional reduction to 1mg twice daily</td>
<td>screened NR/895 eligible after completion of 4-week RCT studies/714 enrolled</td>
<td>mean age 59.7y, 68.5% women, ethnicity NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michel, 2005</td>
<td>Tol 4mg once daily</td>
<td>screened NR/ eligible not applicable/ 3824 enrolled</td>
<td>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</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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<th>How adverse effects assessed</th>
<th>Adverse events reported</th>
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</tr>
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<tbody>
<tr>
<td>Abrams 2001</td>
<td>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.</td>
<td>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).</td>
<td>105 (15%)</td>
</tr>
<tr>
<td>Kreder 2002</td>
<td>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.</td>
<td>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)</td>
<td>107 (10%)</td>
</tr>
<tr>
<td>Abrams, 2001</td>
<td>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)</td>
<td>41% dry mouth (27% mild, 10% moderate and 35 severe) Other AE: autonomic nervous system disorders, general body disorders, gastrointestinal disorders and urinary disorders.</td>
<td>105 patients (15%)</td>
</tr>
<tr>
<td>Michel, 2005</td>
<td>Physician observed and reported at baseline, 1, 3, 6, and 9 months</td>
<td>overall AE: 13%, dry mouth: 7.8%</td>
<td>2.8% due to lack of tolerability</td>
</tr>
</tbody>
</table>
Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

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<th>Author, Year</th>
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<tbody>
<tr>
<td>Abrams, 2001</td>
<td>62% of patients completed 12 months' treatment with tol</td>
</tr>
<tr>
<td>Kreder, 2002</td>
<td></td>
</tr>
<tr>
<td>Michel, 2005</td>
<td>post-marketing surveillance of Tol ER sponsored by Pharmacia (now Pfizer)</td>
</tr>
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<tr>
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<th>Study Design</th>
<th>Eligibility criteria</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Takei, 2005</td>
<td>extension of Homma, 2003, a comparative controlled RCT</td>
<td>open label, uncontrolled, 12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gleason 1999</td>
<td>Multicenter USA, Open label 12 week study</td>
<td>Men and women with idiopathic urge incontinence or mixed incontinence with clinically significant urge component, with at least 6 urge incontinence episodes weekly.</td>
<td>Uncontrolled medical condition, post void residual volume &gt;100ml or significant bacteruria or pyuria.</td>
<td></td>
</tr>
<tr>
<td>Salvatore, 2004</td>
<td>Kings College Hospital London, UK, open label, random allocation to starting dose (not described), open ended continuation, follow-up after 2y</td>
<td>Women with videourodynamic diagnosis of DO or low bladder compliance</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Lawrence 2000</td>
<td>Pharmacy Benefit Management Database USA, Pharmacy Claims Data for April - December 1998</td>
<td>New prescription for Tol or Oxy</td>
<td>Terminated coverage with plan, received more than 30 day supply, incomplete data</td>
<td></td>
</tr>
</tbody>
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<thead>
<tr>
<th>Author, Year</th>
<th>Interventions</th>
<th>Number screened/eligible/enrolled</th>
<th>Age Gender Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takei, 2005</td>
<td>Tol 4mg once daily</td>
<td>188 out of 293 continued open label</td>
<td>mean age 63.6y, 65.4% female, all Japanese</td>
</tr>
<tr>
<td>Gleason 1999</td>
<td>Oxy ER 5 to 30mg/day</td>
<td>Number screened not reported. 256 enrolled</td>
<td>38.9% &gt;65 yrs, 91% female, 92% white</td>
</tr>
<tr>
<td>Salvatore, 2004</td>
<td>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.</td>
<td>screened NR/eligible NR/96 enrolled</td>
<td>mean age 57.5y (range 32-80y), all female, no ethnicity reported</td>
</tr>
<tr>
<td>Lawrence 2000</td>
<td>Tol or Oxy (IR)</td>
<td>1531 eligible/1020 analyzed</td>
<td>Median age Tol 73 (range 18-93), Oxy 70 (range 18-95), % female: Tol 68%, Oxy 97%</td>
</tr>
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Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection
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<tbody>
<tr>
<td>Takei, 2005</td>
<td>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</td>
<td>total incidence of dry mouth 33.5%, mild in all but one case. Nasopharyngitis (26.6%) considered unrelated to treatment.</td>
<td>19 patients withdrew due to AE</td>
</tr>
<tr>
<td><strong>Oxybutynin (Oxy)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gleason 1999</td>
<td>Reports of adverse events were solicited at visits at weeks 1, 4, 8 and 12.</td>
<td>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.</td>
<td>20 (8%) Most commonly nausea, dry mouth and somnolence, urinary retention, and increased post-void residual</td>
</tr>
<tr>
<td>Salvatore, 2004</td>
<td>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.</td>
<td>34.8% complained of side effects. No serious AE reported.</td>
<td>43.2% of women who ceased treatment cited AE as reason for termination.</td>
</tr>
<tr>
<td><strong>Oxybutynin (Oxy) vs. Tolterodine (Tol)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lawrence 2000</td>
<td>Determined discontinuation of medication by gap in refill data, assessed time to discontinuation.</td>
<td>Continuing therapy for 6 months: Tol 164 (32%), Oxy 111 (22%) (p&lt;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&lt;0.001). Never refilling prescription: Oxy 68% Tol 55%</td>
<td></td>
</tr>
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<td>Oxybutynin (Oxy)</td>
<td></td>
</tr>
<tr>
<td>Gleason, 1999</td>
<td></td>
</tr>
<tr>
<td>Salvatore, 2004</td>
<td>68.75% responded to questionnaire</td>
</tr>
<tr>
<td>Oxybutynin (Oxy) vs. Tolterodine (Tol)</td>
<td></td>
</tr>
<tr>
<td>Lawrence, 2000</td>
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<tr>
<td><strong>Solifenacin (Sol)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haab, 2005</td>
<td>extension of Cardozo, 2004 a placebo controlled trial</td>
<td>open label, uncontrolled, 40 weeks</td>
<td>in addition to criteria for original study: informed consent and completion of treatment in the previous double-blind studies within $\leq$ 14d prior to entry into extension study.</td>
<td>clinically significant outflow obstruction, postvoid residual urine $\geq$ 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.</td>
</tr>
<tr>
<td><strong>Darifenacin (Dar)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haab, 2006</td>
<td>extension of Steers, 2005 and Haab, 2004, both PCTs</td>
<td>open label, non-comparative, 2 years</td>
<td>in addition to criteria for original study: completion of one of the two feeder trials without no major protocol violation</td>
<td>same as feeder studies</td>
</tr>
</tbody>
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<tr>
<td><strong>Solifenacin</strong> (Sol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haab, 2005</td>
<td>Sol 5mg once daily and Sol 10mg once daily with dose adjustments available at weeks 16, 28 and 40.</td>
<td>Screened and eligible NR/ 1633 enrolled in safety analysis</td>
<td>mean age 56.4y with a range of 18-82y, 78% women, 98.1% white, 0.5% black, 0.8% Asian, 0.6% other</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **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 |

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Overactive bladder
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<tbody>
<tr>
<td><strong>Solifenacin</strong> (Sol)</td>
<td>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.</td>
<td>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 (&gt;50%) of the episodes of dry mouth, constipation and blurred vision were mild in severity.</td>
<td>4.7% withdrew due to AE</td>
</tr>
<tr>
<td>Haab, 2005</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Darifenacin</strong> (Dar)</td>
<td>safety was assessed at 0 and 2 weeks 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</td>
<td>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%)</td>
<td>64 (8.9%) withdrew due to AE, 46 (6.4%) withdrew due to treatment-related AE</td>
</tr>
<tr>
<td>Haab, 2006</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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<tr>
<th>Author, Year</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solifenacin (Sol) Haab, 2005</td>
<td>81% of enrolled patients completed 40 weeks of open label treatment</td>
</tr>
<tr>
<td>Darifenacin (Dar) Haab, 2006</td>
<td></td>
</tr>
</tbody>
</table>

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### Evidence Table 9. Quality assessment of observational study

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Non-biased selection?</th>
<th>Low overall loss to follow-up?</th>
<th>Outcomes pre-specified and defined?</th>
<th>Ascertainment techniques adequately described?*</th>
<th>Non-biased and adequate ascertainment methods?</th>
<th>Statistical analysis of potential confounders?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haab, 2006</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
</table>
### Evidence Table 9. Quality assessment of observational study

<table>
<thead>
<tr>
<th>Adequate duration of follow-up?</th>
<th>Adequate sample size?</th>
<th>Overall quality assessment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>yes</td>
<td></td>
<td>good</td>
</tr>
</tbody>
</table>
### Evidence Table 10. Short-term comparative studies: Adverse effects

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

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<th>Immediate Release vs Immediate Release (IR vs IR)</th>
<th>Oxybutynin (Oxy) vs Tolterodine (Tol)</th>
<th>Number of adverse effects</th>
<th>Withdrawals due to adverse events</th>
<th>Quality rating and Comments</th>
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<tr>
<td>Leung</td>
<td>2002</td>
<td>Hong Kong</td>
<td>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</td>
<td>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</td>
<td>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&lt;0.012).</td>
<td>Fair</td>
<td>Compliance measured. Oxy 87.5% (11 to 99.3) Tol 75% (8.9 to 98.8) (NS)</td>
</tr>
<tr>
<td>Lee</td>
<td>2002</td>
<td>South Korea</td>
<td>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&lt;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%)</td>
<td>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&lt;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%)</td>
<td>Overall 29 (13%) Tol 11 (6 dry mouth, 55%) Oxy 18 (16 dry mouth, 88%)</td>
<td>Fair</td>
<td>Overall 29 (13%) Tol 11 (6 dry mouth, 55%) Oxy 18 (16 dry mouth, 88%)</td>
</tr>
<tr>
<td>Malone-Lee</td>
<td>2000</td>
<td>UK and Ireland</td>
<td>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&lt;0.0001) Severe: 4% Tol, 15% Oxy (NS)</td>
<td>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&lt;0.0001) Severe: 4% Tol, 15% Oxy (NS)</td>
<td>Overall 50 (13%) 22 (12%) Tol, 28 (15%) Oxy</td>
<td>Fair</td>
<td>Overall 50 (13%) 22 (12%) Tol, 28 (15%) Oxy</td>
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<tr>
<td>Abrams</td>
<td>1998</td>
<td>UK, Ireland and Sweden</td>
<td>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</td>
<td>293 enrolled (118 Tol, 118 Oxy, 57 Pl)</td>
</tr>
<tr>
<td>Drutz</td>
<td>1999</td>
<td>USA/Canada</td>
<td>Tol 2mg twice daily, Oxy 5mg three times daily, Placebo three times daily, Dose reduction allowed</td>
<td>277 enrolled (Tol 109, Oxy 112, Placebo 56)</td>
</tr>
</tbody>
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<tr>
<td>Abrams</td>
<td>1998 UK, Ireland and Sweden</td>
<td>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&lt;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</td>
<td>Overall: 10% Tol 8%, Oxy 17%, Pl 2% Due to dry mouth: Tol 0.8%, Oxy 13%, Pl 3.5%</td>
<td>Fair Dose reductions requested by 8% Tol, 32% Oxy, 2% Pl (Tol vs. Oxy p&lt;0.001)</td>
</tr>
<tr>
<td>Drutz</td>
<td>1999 USA/Canada</td>
<td>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 &lt;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&lt;0.001 Tol vs Oxy)</td>
<td>Overall 12% Tol 7 (6%), Oxy 23 (21%), placebo 4 (7%) (p = 0.002 Tol vs Oxy)</td>
<td>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.</td>
</tr>
</tbody>
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<tr>
<td>Milani</td>
<td>1993</td>
<td>Italy</td>
<td>Oxy 5mg vs Fla 400mg or Oxy 5 mg three times daily, then crossover</td>
<td>50 enrolled</td>
</tr>
</tbody>
</table>

| 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 | Stated to be consecutive patients (60 in Fla/Emp/Pl, 30 in Oxy/Emp/Pl) |

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<td>Immediate Release vs Immediate Release (IR vs IR)</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td><strong>Oxybutynin (Oxy) vs Flavoxate (Fla)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milani</td>
<td>1993</td>
<td>Italy</td>
<td>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%</td>
<td>5 (10%) not clear when these occurred.</td>
<td>Poor</td>
</tr>
<tr>
<td>Zeegers</td>
<td>1987</td>
<td>Netherlands, Austria</td>
<td>Combined in score 15% Pl, 26% Emp, 8% Fla, 17% Oxy</td>
<td>Overall 20% 2 Pl, 8 Emp, 0 Fla, 2 Oxy</td>
<td>Poor</td>
</tr>
</tbody>
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<tbody>
<tr>
<td>Halaska</td>
<td>2003</td>
<td>Immediate Release vs Immediate Release (IR vs IR) Trospium chloride IR vs Oxybutynin IR</td>
<td>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</td>
<td>Screened NR Eligible 358 Enrolled 357</td>
</tr>
<tr>
<td>Maderspacher</td>
<td>1995</td>
<td>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</td>
<td>Screened NR Eligible NR Enrolled 95</td>
<td>52 Trospium, 43 Oxy.</td>
</tr>
</tbody>
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<th>Quality rating and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halaska</td>
<td>2003</td>
<td>Trospium chloride IR vs Oxybutynin IR</td>
<td>All adverse events: Trospium 68%, Oxy 77%&lt;br&gt; All adverse events possibly/probably connected with treatment: Trospium 48%, Oxy 59%, p=0.02.&lt;br&gt; All gastrointestinal adverse events possibly/probably connected with treatment: Trospium 39%, Oxy 51%, p=0.02.&lt;br&gt; Dryness of mouth: Trospium 33%, Oxy 50%, p&lt;0.01.&lt;br&gt; &quot;Time to event&quot; reported as significant in favor of Trospium (p&lt;0.01).</td>
<td>91 withdrew: Trospium 67 (25%), Oxy 24 (26.7%)</td>
<td>Fair. Long FU. Significant number of withdrawals for multiple reasons.</td>
</tr>
<tr>
<td>Maderspacher</td>
<td>1995</td>
<td>Analysis of tolerance carried out on all 95 subjects.</td>
<td>Twenty &quot;well being&quot; items asked directly by investigator before and at end of trial.&lt;br&gt; Severity grading assessed using 4 point scale.&lt;br&gt; Overall rate of side effects reported as &quot;almost comparable&quot; in both groups.&lt;br&gt; Dry mouth: Trospium 54%, Oxy 56%&lt;br&gt; Severe dry mouth: Trospium 4%, Oxy 23%</td>
<td>10 withdrawals&lt;br&gt; Trospium 3 (6%)&lt;br&gt; Oxy 7 (16%)</td>
<td>Fair. All patients spinal cord injured.&lt;br&gt; Type and level of injury not specified.&lt;br&gt; Concurrent medications not noted.</td>
</tr>
</tbody>
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<tr>
<td>Versi</td>
<td>2000</td>
<td>USA</td>
<td>Oxy ER 5-20mg once daily or Oxy IR 5-20mg/d - schedule not reported</td>
<td>screened 417</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>eligible/enrolled 226</td>
</tr>
<tr>
<td>Birns</td>
<td>2000</td>
<td>UK</td>
<td>Oxy ER 10mg once daily or Oxy 5mg twice daily</td>
<td>162 screened</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>130 randomized</td>
</tr>
<tr>
<td>Anderson</td>
<td>1999</td>
<td>USA</td>
<td>ER Oxy 5-30mg once daily or IR Oxy 5mg once to four times daily. .dose reductions allowed for adverse effects</td>
<td>158 screened</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>105 enrolled</td>
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<tr>
<td>Versi</td>
<td>2000</td>
<td>USA</td>
<td>Number of adverse effects overall: 10, 8% with 3 (3%) in ER and 7 (6%) in IR. Reports of adverse effects recorded at each pt visit. Kaplan Meier analysis moderate or severe dry mouth reports indicates a significant difference (p = 0.007) in favor of ER.</td>
<td>Overall: 10 (8%)</td>
<td>Fair Mean duration of treatment/follow-up not stated. Only dry mouth reported in detail.</td>
</tr>
<tr>
<td>Birns</td>
<td>2000</td>
<td>UK</td>
<td>Number of adverse effects overall: 78, 60% with 55% in ER and 67% in IR. 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%.</td>
<td>1 (considered unlikely due to study drug)</td>
<td>Fair Mixed types of incontinence. Study included a run-in phase to establish tolerability, patients with adverse events excluded during run-in.</td>
</tr>
<tr>
<td>Anderson</td>
<td>1999</td>
<td>USA</td>
<td>Number of adverse effects overall: 2 (4%) in each group due to anticholinergic adverse events. Spontaneously reported and anti-cholinergic effects assessed at each study visit. 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%.</td>
<td>2 (4%) in each group due to anticholinergic adverse events</td>
<td>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.</td>
</tr>
</tbody>
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<tr>
<td>Nillsson</td>
<td>1997</td>
<td>Finland</td>
<td>Oxy ER 10mg once daily, Oxy 5mg twice daily crossover</td>
<td>17 enrolled</td>
</tr>
<tr>
<td>Radomski</td>
<td>2004</td>
<td></td>
<td>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</td>
<td># screened not reported. 12 included for safety analysis. 9 included for efficacy analysis (completed 8 week study)</td>
</tr>
<tr>
<td>Barkin</td>
<td>2004</td>
<td></td>
<td>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</td>
<td>125 enrolled (Oxy IR 60, Oxy ER 65)</td>
</tr>
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<tr>
<td>Nillsson</td>
<td>1997</td>
<td>Finland</td>
<td>Patients reported on a questionnaire throughout study, classified as mild, moderate, severe. Withdrawals due to adverse events: 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.</td>
<td>None reported</td>
<td>Poor</td>
</tr>
<tr>
<td>Radomski</td>
<td>2004</td>
<td></td>
<td>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%.</td>
<td>2 withdrawals in OXY IR phase. 1 withdrawal in Oxy ER phase. Events reported: severe stomach pain, mild peripheral edema, severe vision distortion</td>
<td>Poor</td>
</tr>
<tr>
<td>Barkin</td>
<td>2004</td>
<td></td>
<td>Oxy ER vs Oxy IR (%)</td>
<td>Oxy IR: 12 (20%)</td>
<td>Oxy ER: 11 (17%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>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%</td>
<td>Oxy IR: 12 (20%)</td>
<td>Oxy ER: 11 (17%)</td>
</tr>
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<td>Van Kerrebroeck</td>
<td>2001</td>
<td>Multinational</td>
<td>Tol ER 4 mg once daily or Tol IR 2 mg or Placebo twice daily</td>
<td>1529 enrolled</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tol ER: 507</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tol IR: 514</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo: 508</td>
</tr>
<tr>
<td>Swift</td>
<td>2003</td>
<td>Re-analysis of data for women only in Van Kerrebroeck 2001 study (above)</td>
<td>Tol ER 4 mg (n=417) once daily vs. Tol IR 2 mg twice daily (n=408) vs. Pla (n=410) for 12 wks.</td>
<td>1235 enrolled</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tol ER: 417</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tol IR: 408</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo: 410</td>
</tr>
</tbody>
</table>

### Extended Release vs. Immediate Release (ER vs IR)

#### Tolterodine ER vs Tolterodine IR

- **Van Kerrebroeck 2001**
  - Multinational
  - Tol ER 4 mg once daily or Tol IR 2 mg 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 10 mg once daily
  - Tol 2 mg twice daily
  - 378 enrolled (Oxy ER 185, Tol 193)
  - 332 completed (Oxy ER 160, Tol 172)

---

*Pad test = patient fills bladder to 300 ml, 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

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

*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**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Setting</th>
<th>Interventions (drug, regimen, duration)</th>
<th>Number Enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homma</td>
<td>2003</td>
<td>Tol ER 4 mg once daily vs. Oxy IR 3 mg three times daily x 12 wks</td>
<td>Enrolled = 608 Tol ER = 240 Oxy IR = 246 Pla = 122</td>
<td></td>
</tr>
</tbody>
</table>

**Extended Release vs. Immediate Release (ER vs IR)**

**Tolterodine ER vs. Oxybutynin IR**

**Extended Release vs. Immediate Release (ER vs IR)**

**Solifenacin IR vs. Tolterodine ER**

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

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</tr>
</thead>
<tbody>
<tr>
<td>Homma</td>
<td>2003</td>
<td>Extended Release vs. Immediate Release (ER vs IR)</td>
<td>Tolterodine ER vs. Oxybutynin IR</td>
<td>Compliance &gt;75% of medication: Tol 98% vs. Oxy 93% Fair</td>
<td>Adverse events undefined; ascertainment techniques NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dry mouth: Tol 0.4% vs. Oxy 9.4%</td>
<td>All events: Tol 5.0% vs. Oxy 17.1% p&lt;0.001 Serious event, possibly drug related: 1 Oxy cardiac failure. No deaths and no clinically significant changes in lab or ECG values.</td>
<td></td>
</tr>
</tbody>
</table>

**Extended Release vs. Immediate Release (ER vs IR)**

<table>
<thead>
<tr>
<th>Author</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Chapple</td>
<td>2005</td>
<td>STAR trial</td>
<td>Solifenacin IR vs. Tolterodine ER</td>
<td>AE evaluated at each clinic visit in response to questioning by the investigator or volunteered by patient</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>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%)</td>
<td>Withdrawals due to AEs: Sol: 3.5% Tol ER: 3.0%</td>
<td></td>
</tr>
</tbody>
</table>

* 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
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<tr>
<td></td>
<td></td>
<td></td>
<td>Extended Release vs. Immediate Release (ER vs IR)</td>
<td></td>
</tr>
<tr>
<td>Chapple and Abrams</td>
<td>2005</td>
<td></td>
<td>Darifenacin IR and Darifenacin ER vs. Oxybutynin IR</td>
<td>65 enrolled</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1) Dar IR 2.5mg tid or Oxy IR 2.5mg tid</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2) Dar ER 15mg qd or Oxy IR 5mg tid</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3) Dar ER 30mg qd or Oxy IR 5mg tid</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>each treatment period was 7 days</td>
<td></td>
</tr>
<tr>
<td>Diokno</td>
<td>2003</td>
<td>OPERA</td>
<td>Oxy ER 10 mg/day vs. Tol ER 4 mg/day x 12 wks</td>
<td>Enrolled 790</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oxy ER= 391</td>
<td>Tol ER = 399</td>
</tr>
</tbody>
</table>

* 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

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

* 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
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<tr>
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<th>Year</th>
<th>Setting</th>
<th>Interventions (drug, regimen, duration)</th>
<th>Number Enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davila</td>
<td>2001</td>
<td>Transdermal vs. Immediate Release (TD vs. IR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oxybutynin TD vs. Oxybutynin IR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Davila</td>
<td>2001</td>
<td>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</td>
<td>Enrolled 76 Oxy TD = 38 Oxy IR = 38</td>
<td></td>
</tr>
<tr>
<td>Dmochowski</td>
<td>2003</td>
<td>Oxybutynin transdermal (Oxy TD) 3.9 mg/day (applied twice weekly) Tolterodine sustained release (Tol SR) 4 mg/day Placebo</td>
<td>Enrolled 361 Oxy TD: 121 Tol SR: 123 Placebo: 117</td>
<td></td>
</tr>
</tbody>
</table>

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

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### Evidence Table 11. Clinically significant drug interactions

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Flavoxate Hydrochloride</th>
<th>Oxybutynin Chloride</th>
<th>Tolterodine Tartrate</th>
<th>Darifenacin</th>
<th>Solifenacin Succinate</th>
<th>Trospium Chloride</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drugs affecting hepatic enzymes (CYP 450)</strong></td>
<td>Not reported</td>
<td>Not reported</td>
<td>No significant interaction. No action required.</td>
<td>No dose adjustment needed for CYP2D6 and moderate CYP3A4 inhibitor. Dosage should not exceed 7.5 mg when co-administered with potent CYP3A4 inhibitor.</td>
<td>Further studies needed.</td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Fluoxetine</strong></td>
<td>Not reported</td>
<td>Not reported</td>
<td>No dose adjustment required. May increase concentration of tolterodine by four fold.</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
<td>Not reported</td>
<td>Not reported</td>
<td>No significant interactions.</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Oral Contraceptives</strong></td>
<td>Not reported</td>
<td>Not reported</td>
<td>No significant interactions.</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Anticoagulants</strong></td>
<td>Not reported</td>
<td>Not reported</td>
<td>No significant interactions.</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Alcohol</strong></td>
<td>Not reported</td>
<td><strong>Monitor</strong></td>
<td>Increased sedation with CNS depression.</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Antihistamines</strong></td>
<td>Not reported</td>
<td><strong>Monitor</strong></td>
<td>Increased anticholinergic effects.</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Macrolide antibiotics</strong></td>
<td>Not reported</td>
<td>Information not available.</td>
<td></td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
### Evidence Table 11. Clinically significant drug interactions

<table>
<thead>
<tr>
<th>Azole antifungal agents</th>
<th>Flavoxate Hydrochloride</th>
<th>Oxybutynin Chloride</th>
<th>Tolterodine Tartrate</th>
<th>Darifenacin</th>
<th>Solifenacin Succinate</th>
<th>Trospium Chloride</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not reported</td>
<td><strong>No significant interaction.</strong> Serum concentrations of oxybutynin increased three fold when coadministered with itraconazole. Half-life was unaffected and the interaction is of only minor significance.(^3)</td>
<td><strong>Dose adjustment required.</strong> May inhibit metabolism of tolterodine. Doses of &gt;1 mg twice daily should be avoided.(^2)</td>
<td>Not reported</td>
<td><strong>Monitor.</strong> 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)</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

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1 AHFS Drug Information, ASHP, 2002.
3 Benedetti et al. Drug Metabolism Reviews, 1999.
6 Drugs@FDA, 2005.