

## Genitourinary Smooth Muscle Relaxants STEPS/Side-by-Side Comparison

DRUG	<i>oxybutynin chloride</i> (Ditropan®, Ditropan XL®; Oxytrol® patch)	<i>tolterodine tartrate</i> (Detrol®, Detrol LA®)	<i>solifenacin succinate</i> (Vesicare®)	<i>darifenacin</i> (Enablex®)	<i>tropium chloride</i> (Sanctura®)
<b>SAFETY</b>	=	=	=	=	=
<b>Contraindications</b>	In patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions; myasthenia gravis. Hypersensitivity.				
<b>Warnings/ Precautions</b>	Use with caution in patients with bladder obstruction, gastrointestinal obstruction, or narrow-angle glaucoma. May cause significant anticholinergic effects. Patients should be informed that heat prostration (fever and heat stroke due to decreased sweating) can occur when anticholinergics are administered in the presence of high environmental temperature. Patients should be advised that anticholinergic agents may produce drowsiness, or blurred vision. May aggravate symptoms of hyperthyroidism, coronary heart disease, congestive heart failure, arrhythmias, hiatal hernia, tachycardia, hypertension, myasthenia gravis, and prostatic hypertrophy.				
	<p><b>Pregnancy Category B</b> Excretion in breast milk unknown/use caution.</p> <p>IR may be used in pediatrics 5 years old and older; ER may be used in pediatrics 6 years old and older who can swallow a whole tablet; topical formulation has not been studied in pediatric patients.</p> <p>Use with caution in the frail elderly, in patients with hepatic or renal impairment, and in patients with myasthenia gravis.</p> <p>Transdermal patch may contain conducting metal (eg. Al); remove patch prior to MRI</p>	<p><b>Pregnancy Category C</b> Excretion in breast milk unknown/use caution. Safety and efficacy not established in pediatric patients.</p> <p><b>Reduce dose in patients with significantly reduced renal or hepatic function.</b></p> <p>May prolong QT interval.</p>	<p><b>Pregnancy Category C</b> Excretion in breast milk unknown/use caution. Safety and efficacy not established in pediatric patients</p> <p><b>Use with caution in patients with reduced renal function; do not exceed 5 mg/day in patients with CrCl less than 30 mL/min.</b></p> <p><b>Use with caution in patients with reduced hepatic function; do not exceed 5 mg/day in patients with moderate dysfunction (Child-Pugh B). Not recommended for use in patients with severe hepatic impairment.</b></p> <p>Caution in patients with known QT prolongation.</p>	<p><b>Pregnancy Category C</b> Excretion in breast milk unknown/use caution. Safety and efficacy not established in pediatric patients</p> <p><b>No adjustment needed in renal patients.</b></p> <p><b>Reduce dose in patients with moderate hepatic impairment; not recommended for use in patients with severe hepatic impairment.</b></p>	<p><b>Pregnancy category C</b> Excretion in breast milk unknown/use caution. Safety and efficacy not established in pediatric patients</p> <p><b>Reduce dose in patients with CrCl less than 30 mL/min. (20mg once daily)</b></p> <p><b>Use with caution in patients with moderate to severe hepatic impairment.</b></p>
<b>Drug Interactions</b>	<p>Use with other anticholinergic medications (tricyclic antidepressants, antihistamine, and phenothiazines) may increase frequency of anticholinergic effects such as dry mouth, constipation, somnolence, and blurred vision. Absorption of some drugs may be reduced due to decreased gastrointestinal motility. Alcohol may enhance drowsiness.</p> <p>CYP3A4 inhibitors: azole antifungals, clarithromycin, diclofenac, doxycycline, erythromycin, imatinib, isoniazid, nefazodone, nicardipine, propofol, protease inhibitors, quinidine, telithromycin, and verapamil.</p> <p>CYP3A4 inducers: aminoglutethimide, carbamazepine, nafcillin, nevirapine, phenobarbital, phenytoin and rifamycins.</p> <p>CYP2D6 inhibitors: chlorpromazine, delavirdine, fluoxetine, miconazole, paroxetine, pergolide, quinidine, ritonavir, and ropinrole.</p> <p>CYP2D6 substrates: amphetamines, selected beta-blockers, dextromethorphan, fluoxetine, lidocaine, mirtazapine, nefazodone, paroxetine, risperidone, ritonavir, thioridazine, tricyclic antidepressants, and venlafaxine.</p> <p>CYP2D6 prodrug substrates: codeine, hydrocodone, oxycodone, and tramadol.</p>				
	Levels may be increased when administered with potent CYP3A4 inhibitors (weak); inhibits CYP2C8 (weak), 2D6 (weak).	CYP3A4 inhibitors may increase the levels of tolterodine. CYP3A4 inducers may decrease levels of tolterodine. CYP2D6 inhibitors may increase levels of tolterodine. Use caution when administering concurrently with other drugs known to cause QT prolongation. May prolong INR when used with warfarin.	CYP3A4 inhibitors may increase the levels of solifenacin. Do not exceed 5 mg/day when administered with ketoconazole or other potent CYP3A4 inhibitors. CYP3A4 inducers may decrease the levels of solifenacin. Use caution when administering concurrently with other drugs known to cause QT prolongation.	Do not exceed 7.5 mg/day when using concomitantly with potent CYP3A4 inhibitors. CYP3A4 inducers may decrease the levels of darifenacin, Darifenacin may increase the levels of CYP2D6 substrates. Darifenacin may decrease the levels of CYP2D6 prodrug substrates. Use with caution in combination with drugs extensively metabolized by CYP2D6 that have a narrow therapeutic window (e.g. flecainide, thioridazine, etc.).	Coadministration with drugs that are eliminated by active renal tubular secretion may increase the serum concentration of either drug due to competition for this elimination pathway. Careful monitoring is recommended in patients receiving such drugs (e.g., digoxin, pancuronium, morphine, vancomycin, metformin, etc.).
<b>Sound-alike</b> <b>Look-alike</b> ~ (confused with)	Oxybutynin ~ Oxycontin® Ditropan® ~ Detrol®, diazepam, Diprivan®, dithranol	Detrol® ~ Ditropan® Detrol® ~ Desuroil®	VESicare® ~ Visicol®		

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TOLERABILITY	IR – , ER = , Top =	IR – , ER =	=	=	=
	Extended release formulations improve tolerability without impairing effectiveness. Dry mouth is the most common adverse event and occurs less with tolterodine vs. oxybutynin. Other adverse effects include constipation, diarrhea, headache, urinary tract infection.  Moderate to Severe Dry mouth: Tolterodine 67% less likely to cause vs. oxybutynin <sup>5</sup> Oxybutynin ER 29% vs. tolterodine ER 20% <sup>2</sup>		Uroselective drugs (solifenacin and darifenacin) may offer enhanced tolerability. Trospium may be less likely to cross the blood-brain barrier (water soluble and quaternary ammonium group). M3 selective blockade by darifenacin may also have a theoretical advantage in more selective effect on bladder.		
Adverse Events	Patch: Itching at the application site is a problem for the transdermal dosage form. (15%)  Oxybutynin patch vs. tolterodine LA Dry mouth (all levels) 4.1% oxybutynin patch vs. 7.3% for tolterodine LA vs. placebo 1.7% <sup>3</sup> Constipation 3.3% oxybutynin patch vs. 5.7% for tolterodine LA <sup>3</sup>		Dry mouth (all levels) <sup>1</sup> 14% solifenacin 5mg 21.3 % solifenacin 10mg 18.6 % tolterodine 2mg BID	Dry mouth (all levels) <sup>6</sup> 13.1% darifenacin 15mg/day 34.1 % darifenacin 30mg/day (above marketed dose) 36.1 % Oxybutynin IR 5mg TID 4.9% Placebo	Dry mouth <sup>4</sup> : 30% vs. oxybutynin IR 50% Constipation <sup>4</sup> : 7% vs. oxybutynin IR 4% Data DOES NOT SUPPORT the fact that trospium would offer fewer CNS effects because it is water soluble and therefore not cross the blood-brain barrier.
EFFICACY	= / = / =	=	=	=	=
FDA-Approved Indications	<ul style="list-style-type: none"> <li>IR and syrup: For the relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (ie. urgency, frequency, urinary leakage, urge in continence, dysuria).</li> <li>ER: Treatment of OAB with symptoms of urge UI, urgency and frequency.</li> </ul> <p>Oxybutynin is also indicated for treatment of pediatric patients aged 6 years and older with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida).</p>	Treatment of OAB with symptoms of urge UI, urgency, and frequency	Treatment of OAB with symptoms of urge UI, urgency, and frequency.		
Comments		Limited efficacy data for 2mg XL	Head to head studies comparing these agents with oxybutynin and tolterodine suggest similar effectiveness across the class.		

Flavoxate not included due to the lack of quality studies for efficacy and limited usage.

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<b>Pharmacology</b>	Muscarinic receptors, especially of the M <sub>3</sub> subtype, play an important role in several cholinergically mediated functions, including contractions of the urinary and gastrointestinal smooth muscle, saliva production, and iris sphincter function. These agents are competitive muscarinic receptor antagonists. Enblex has greatest affinity for M <sub>3</sub> receptors (in vitro) and claims to be selective to the bladder, however, this or its clinical advantage has not been validated. Enblex (darifenacin) and Vesicare (solifenacin) are uroselective.				
<b>Pharmacokinetics</b>	Bioavailability: oral absorption rapid and well absorbed; transdermal high. t <sub>1/2</sub> : IR: 2–3 hrs; ER: 12-13hrs; Topical: 7–8 hrs Time to Peak: IR: <1hr; ER: 11.8-12.7hrs; Topical: 10-48 hrs  Metabolism: hepatic (via CYP3A4) Excretion: feces Lipophilic	Bioavailability: 75% t <sub>1/2</sub> : IR: 2-4 hrs ER: 7-10 hrs Time to Peak: IR: 1–2 hrs; ER: 2-6hrs. Metabolism: hepatic (to active metabolite via CYP2D6 or CYP3A4) Excretion: urine (77%), feces (17%) Lipophilic	Bioavailability: 90% t <sub>1/2</sub> : 40-65 hrs Time to Peak: 3-6 hrs Metabolism: hepatic (via CYP3A4) Excretion: urine (70%), feces (22%) Lipophilic	Bioavailability: 15–20% t <sub>1/2</sub> : 7.4-20 hrs Time to Peak: 5.2 – 7.6 hrs Metabolism: hepatic via CYP3A4 Excretion: urine (60%), feces (40%) Lipophilic	Bioavailability: <10% t <sub>1/2</sub> : 5-20 hrs Time to Peak: 5-6 hrs Metabolism: Renally ester hydrolysis, conjugation Excretion: feces (85%), urine (~6%) Hydrophilic  Administration with a fatty meal reduces absorption 70-80%.
<b>Selected Clinical Studies</b>	<ol style="list-style-type: none"> <li>Chapple CR, Rechberger T, Al-Shukri S, et al. <i>BJU Int.</i> 2004;93:303-10. International, multicenter, randomized, double-blind, placebo-controlled trial to assess and compare safety and tolerability of <b>solifenacin versus tolterodine</b> in patients with OAB (n=1081). Patients received <b>solifenacin 5 or 10 mg once daily, tolterodine 2 mg twice daily, or placebo for 12 weeks. Compared to placebo</b>, solifenacin significantly reduced mean number of urgency episodes/day, episodes of UI, and mean number of voids/day. Each parameter was reduced with tolterodine, but only mean number of voids/day was significantly reduced versus placebo. Rates of major side effects for solifenacin 5 and 10 mg, and tolterodine were as follows, respectively: dry mouth (14, 21.3, 18.6%), constipation (7.2, 7.8, 2.6%), and blurred vision (3.6, 5.6, 1.5%).</li> <li>Diokno AC, Appell RA, Sand PK, et al. <i>Mayo Clin Proc.</i> 2003;78:687-95. Multicenter, randomized, double-blind, study to compare <b>ER formulations of oxybutynin 10 mg/day and tolterodine 4 mg/day in women</b> with OAB (n=790). Reductions in weekly urge UI episodes were similar between agents. Patients receiving oxybutynin experienced significantly reduced micturition frequency (p=0.003) and were more likely to experience complete resolution of symptoms (p=0.03). More patients receiving oxybutynin experienced dry mouth (29.7 vs. 22.3%, p=0.02).</li> <li>Dmochowski RR, Sand PK, Zinner NR, et al. <i>Urology.</i> 2003;62:237-42. Randomized, double-blind, double-dummy study over 12 weeks to compare twice-weekly topical <b>oxybutynin 3.9 mg/day and ER tolterodine 4 mg/day versus placebo</b> in patients with urge and mixed UI (n=361). Topical oxybutynin and ER tolterodine both significantly reduced number of daily UI episodes compared to placebo (-3, -3 vs. -2, respectively; p&lt;0.05). The most common adverse effect with topical oxybutynin was application-site pruritus (14 vs. 4% placebo); dry mouth occurred in 4.1%. Dry mouth was the most common adverse effect with ER tolterodine (7.3 vs. 1.7% placebo).</li> <li>Halaska M, Ralph G, Wiedemann A, et al. <i>World J Urol.</i> 2003;20:392-9. Multicenter, randomized, double-blind study over 52 weeks to determine tolerability and efficacy of <b>tropium 20 mg twice daily compared to oxybutynin 5 mg twice daily</b> in patients with urge syndrome (n=358). There were reductions in micturition frequency, UI frequency, and urgencies in both groups. Adverse events, mostly dry mouth, occurred in 64.8% of the tropium group and 76.7% of the oxybutynin group. Risk for dry mouth was lower with tropium (0.021 vs. 0.045).</li> <li>Harvey MA, Baker K, Wells GA. <i>Am J Obstet Gynecol.</i> 2001;185:56-61. Meta-analysis of four randomized trials <b>comparing tolterodine with oxybutynin</b> in adults with urge UI. Both drugs similarly reduced number of micturitions/day; oxybutynin significantly reduced number of incontinent episodes/day compared to tolterodine. Fewer patients receiving tolterodine experienced dry mouth (relative risk 0.54) or withdrew due to side effects (relative risk 0.63).</li> <li>Zinner N, Tuttle J, Marks L. <i>World J Urol.</i> 2005;23:248-52. Randomized, double-blind, placebo-controlled, four-way crossover study comparing darifenacin and oxybutynin in patients with OAB (n=76). Patients received <b>darifenacin 15 and 30 mg once daily, oxybutynin 5 mg three times/day, and placebo</b>, each in random sequence at 10-day intervals. Incontinence episodes and the number/severity of urgency episodes were significantly reduced with both darifenacin and oxybutynin versus placebo (p&lt;0.05 for all). Dry mouth was less common with darifenacin 15 mg compared to oxybutynin (13 vs. 36%, p&lt;0.05); rates of constipation were comparable (10 and 8%, respectively).</li> <li>Epstein, B.J., Gums, J.G., Molina, E. Newer Agents for the Management of Overactive Bladder. <i>American Family Physician.</i> 2006;74(12):2061-2068.</li> <li>Weiss, B.D. Selecting Medications for the Treatment of Urinary Incontinence. <i>American Family Physician.</i> 2005;71(2):315-322.</li> <li>DeMaagd G., Geibig, J.D. An Overview of Overactive Bladder and Its Pharmacological Management with a Focus on Anticholinergic Drugs. <i>P&amp;T.</i> 2006;31(8): 462-471.</li> </ol>				

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### Summary of Studies with Older Agents [oxybutynin (Ditropan®, Ditropan XL®), tolterodine Detrol®, Detrol LA®]

Outcomes reviewed in studies were mean change per 24 hours (or week) of number of incontinence episodes, number of micturitions per 24 hours, number of pads used per 24 hours. These agents have been the mainstay of overactive bladder (OAB) treatment.

#### **IR vs. IR**

- Oxybutynin IR vs. Tolterodine IR (4 studies)

##### Efficacy:

Change in *number of micturitions per day* was not significantly different

Oxy marginally better in *decrease in incontinent episodes per day* although statistically significant. Both groups had a decrease but oxy had a mean of nearly one-half fewer episodes of incontinence per day.

Oxy showed a statistically significant difference in *mean voided volume per micturition* (? Clinically significant – 8 ml)

##### Tolerability: Oxybutynin IR higher than tolterodine IR

Tolterodine patients were 67% less likely to have moderate to severe dry mouth. Risk of withdrawing because of side effects was decreased by 37% with tolterodine. (short-term trials)

#### **IR vs. ER**

- Oxy IR vs. Oxy ER (4 studies)/Tol IR vs. Tol ER (1 study)

No difference in efficacy

Tolerability better with ER formulations of both drugs

- Tol IR vs Oxy ER (1 study)

Oxy superior

- Oxy IR vs Tol ER (1 study)

Tol superior

#### **ER vs. ER**

Mixed results or equal

OPERA TRIAL (Oxybutynin 10mg and tolterodine 4mg, enrolled only women)

##### Efficacy:

Weekly UUI episodes were similar

Oxybutynin more effective than tolterodine in reducing micturition frequency

23% of oxybutynin reported no episodes of incontinence compared with 16.8 % in tolterodine

##### Tolerability: (OPERA p. 694)

Both groups had similar discontinuation of treatment due to adverse events, but dry mouth was more common with oxybutynin (29.7% vs. 22.3%). Most were defined as mild without influencing daily activities and usually would not need intervention. The frequency of other events such as blurred vision and urinary retention was less than 5% in each group and similar in magnitude for both groups. Regarding CNS effects such as dizziness, somnolence, insomnia, and depression, they were reported at rates between 1% and 4% for both drugs. Other CNS effects were reported by less than 1% of participants. This and the OBJECT study verify that there is no clinically significant difference in tolerability profiles of tolterodine and oxybutynin.

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<b>PRICE</b>	IR + / ER = + / Top = -	IR = - / ER = -	= -	= -	= -
<b>Drug Store.com</b> (accessed 2-27-07)	5mg \$0.21 each <b>Monthly \$12.60 to 25.20</b> (5mg/5ml syrup \$0.42 per 5mg)  5mg XL \$2.90 each 10mg XL \$2.92 each 15 mg XL \$2.99 each <b>Monthly \$ 87.00-\$89.70</b> Oxytrol 3.9 mg/24 hr patch \$13.31 each Monthly \$93.17-133.10	1 mg \$2.03 each 2 mg \$3.97 each <b>Monthly \$121.80-238.20</b>  LA 2 mg \$3.27 each Monthly \$98.10 LA 4 mg \$3.61 each <b>Monthly \$108.30/month</b>	5mg \$3.81 each 10mg \$3.81 each <b>Monthly \$114.30</b>	7.5 mg tab \$3..53 each <b>Monthly \$105.90</b>  15 mg tab \$3.73 each <b>Monthly \$111.90</b>	20 mg tabs \$2.03 each Daily Cost \$4.06 <b>Monthly \$121.80</b>
<b>Market approval</b>			Approved 11-19-04	Approved 12-22-04	Approved 5-28-04
<b>Patent expiration</b>	Generic available	Patent challenge on Detrol LA			
<b>Manufacturer</b>	Oxytrol - Watson	Pfizer	GSK	Novartis	Indevus
<b>SIMPLICITY</b>	IR- / ER = / Top -	IR - / ER =	=	=	-
<b>Usual Dose</b>	<b>IR:</b> Adults: 5 mg PO two to three times/day, not to exceed four times/day. <b>Pediatrics:</b> 5 mg PO two times/day, not to exceed three times/day. <b>ER:</b> Adults: 5-10 mg PO once daily at the same time each day, up to a maximum of 30 mg once daily. <b>Pediatrics:</b> 5 mg PO once daily, up to a maximum of 20 mg once daily. <i>Do not chew or crush.</i> <b>Topical:</b> One system (3.9 mg/day) applied twice weekly (every 3 or 4 days).	<b>IR:</b> 2 mg PO twice daily. <i>Do not exceed 1 mg twice daily in patients with severe renal or hepatic impairment, or those concomitantly receiving potent CYP3A4 inhibitors</i> <b>ER:</b> 4 mg PO once daily. <i>Do not chew or crush. Do not exceed 2 mg daily in patients with severe renal or hepatic impairment, or those concomitantly receiving potent CYP3A4 inhibitors</i>	5-10mg once daily  <i>Administer with liquid. Do not chew or crush.</i>  <i>Do not exceed 5mg/day in patients with renal or hepatic impairment.</i>	Starting: 7.5 mg once daily  May be increased to 15 mg once daily after 2 weeks.  <i>Administer with liquid. Do not chew or crush.</i>  <i>Take without regard for meals.</i>	20 mg PO twice daily on an empty stomach.  <i>Administer 20 mg once daily at bedtime to patients with CrCl less than 30 mL/min and in patients 75 years old and older.</i>  <i>Take at least one hour before meals or on an empty stomach.</i>
<b>Available Strengths/Dosage Forms</b>	IR tablets: 5 mg Syrup: 5 mg/5 mL ER tablets: 5 mg, 10 mg, 15 mg Transdermal system (Oxytrol): 36 mg (3.9 mg/day).	IR tablets: 1 mg, 2 mg ER capsules: 2 mg, 4 mg  <i>Can sprinkle Detrol LA on food.</i>	Tablet: 5mg, 10mg	ER Tablets: 7.5 mg, 15 mg.	Tablets: 20 mg.

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BSBCM	Generic Tier One Ditropan XL, Oxytrol – non formulary	Detrol, Detrol LA Tier two	Non Formulary	Non Formulary	Non Formulary
UPHP	Oxybutynin IR preferred Ditropan ER PA Oxytrol not covered	Tolterodine PA Detrol LA Step	PA	PA	PA

OAB=overactive bladder; UI=urinary incontinence; IR=immediate release; ER=extended-release; CYP=cytochrome P450 enzyme system; CrCl=creatinine clearance; INR=international normalized ratio; AC=anticholinergic

**Recommendation:**

Nonpharmacologic therapy should be the mainstay of OAB treatment. The above agents are available to offer to patients that remain symptomatic despite nonpharmacologic therapy. Compared to placebo **all of the agents offer similar efficacy or benefit**. Selection of an agent should be based on cost and tolerability. The majority of patients should be able to be treated with generic oxybutynin; if long-term tolerability is a problem then a longer-acting older agent (oxybutynin XL or tolterodine LA) is an option. The various agents have differences in their muscarinic activity, dosing formulations, pharmacokinetic profiles and tolerability, however, validation of significance of these differences are lacking. There is no convincing evidence that newer agents offer any advantage in efficacy or tolerability over long-acting tolteridone or oxybutynin. A Cochrane Database systematic review reports that 60% of patients receiving an anticholinergic drug and 45% receiving placebo to treat urge UI perceive a change in symptomology (2002). Therefore, only 15% of patients may experience a true effect. DRUG THERAPY RESULTED IN APPROXIMATELY ONE LESS EPISODE OF LEAKAGE AND ONE LESS VOID PER 24 hours compared with placebo. This is a marginal placebo-adjusted effectiveness and risk of adverse events should be considered. Adverse effects of IR oxybutynin and IR tolterodine may be overcome by use of ER counterparts. The newer agents darifenacin, solifenacin, or trospium should be viewed as an option for treatment failures due to cost and no efficacy advantage. Presently the most cost-effective choices are oxybutynin followed by oxybutynin ER. Given specific clinical parameters the following chart can assist in selection of an agent.

Factor/Condition	Consider	Comments
Efficacy	Oxybutynin	Head to head studies with tolterodine and oxybutynin have suggested improved efficacy with oxybutynin
Tolerability	ER products over IR products	Extended release products improve tolerability.
CNS adverse effects	There is no proof of benefit of a hydrophilic agent (trospium) or an agent with receptor selectivity (darifenacin) if cognitive effects are a concern.	
Pregnancy	Oxybutynin	Oxybutynin is pregnancy risk category B, whereas all other agents are category C.
Severe hepatic impairment	Trospium	Consider trospium. Trospium is eliminated renally whereas all other agents undergo extensive hepatic metabolism.
Severe renal impairment	Oxybutynin, tolterodine, darifenacin, solifenacin	Avoid trospium because it is eliminated renally.
Drug-drug interactions	Trospium	Consider trospium. Agents other than trospium are metabolized by CYP 3A4 or 2D6, which are responsible for elimination of hepatically metabolized drugs.
Cost	Oxubutynin IR	Extended release agents and newer agents are significantly more expensive.

Adapted From: Epstein, B.J., Gums, J.G., Molina, E. Newer Agents for the Management of Overactive Bladder. *American Family Physician*. 2006;74(12):2061-2068.