

# Oxybutynin: an overview of the available formulations

Rebecca J McCrery  
Rodney A Appell

Scott Department of Urology, Baylor  
College of Medicine, Houston, TX,  
USA

**Abstract:** Overactive bladder (OAB) is a common problem presented to by physicians. Standard treatment with antimuscarinic medication is directed at suppressing involuntary detrusor contractions by blocking the binding of acetylcholine to muscarinic receptors in the bladder. Oxybutynin chloride is the first of several antimuscarinic medications to be marketed for OAB. Although efficacious for treating OAB symptoms, the side effects and suboptimal dosing regimen decrease its utility. To improve patient compliance and tolerability, alternative delivery systems for oxybutynin have subsequently been developed and include a once-daily formulation and a transdermal system. The currently available formulations of oxybutynin are the subject of this review.

**Keywords:** overactive bladder, antimuscarinic, urinary incontinence, detrusor overactivity

## Introduction

Overactive bladder (OAB) is defined by the International Continence Society as a syndrome associated with symptoms of urgency, with or without urge incontinence, usually with frequency and nocturia, in the absence of infection or other obvious pathology (Abrams et al 2002). The prevalence of continent and incontinent OAB in the US is estimated to be 16.6%, affecting approximately 33 million men and women (Stewart et al 2003). The high prevalence of urinary incontinence and OAB translates to an estimated annual economic cost in US of \$19.5 billion for urinary incontinence and \$12.6 billion for OAB (Hu et al 2004). In addition, indirect costs are incurred as up to 65% of patients with OAB may have a reduced ability to perform daily tasks (Rovner 2004). Although OAB has a significant negative impact on health-related quality of life, mental health, and quality of sleep, the majority of OAB patients do not seek treatment for their condition (Stewart et al 2002; Van der Vaart et al 2002).

Antimuscarinic agents, with the advent of immediate-release oxybutynin (OXY-IR), have been the mainstay of treatment for OAB for the past 30 years. Although many patients respond favorably to antimuscarinic agents, only a small percentage of patients achieve total dryness (Appell et al 2001). Additionally, because muscarinic receptors are found elsewhere in the body, nontissue-specific antimuscarinic agents result in significant systemic side effects (Lai et al 2002; Dmochowski and Appell 2003). The combination of intolerable side effects, expense, and an often incomplete improvement, result in a mediocre-at-best rate of patient compliance with antimuscarinic medications. In one representative study involving patients taking OXY-IR, adherence dropped from 91% at 3 months to 18% at 1 year (Echols et al 2000). These shortcomings have prompted the development of several new delivery systems of oxybutynin: an extended-release formulation (OXY-ER), and a transdermal system (OXY-TDS), as well as several other different antimuscarinic agents.

---

Correspondence: Rodney A Appell  
6560 Fannin Street, Suite 2100, Houston,  
TX 77030, US  
Tel +1 713-798-4001  
Fax +1 713 798 5553  
Email rappell@bcm.tmc.edu

## Oxybutynin immediate-release

Oxybutynin chloride is a well established antimuscarinic drug that has long been recognized for its efficacy in the treatment of OAB symptoms. It remains the gold standard with which newer agents are compared once efficacy over placebo has been established. Oxybutynin is a tertiary amine that has anticholinergic, spasmolytic, and local anesthetic properties (Yarker et al 1995). It acts as a competitive antagonist of acetylcholine at postganglionic muscarinic receptors on the detrusor muscle of the bladder, resulting in relaxation of the smooth muscle (OMNP 2003). Oxybutynin has higher affinity for  $M_1$  and  $M_3$  receptor subtypes than for other muscarinic subtypes. Also, it has a 10-fold greater selectivity for  $M_3$  over  $M_2$  receptors (Noronha-Blob and Kachur 1991; Nilvebrant et al 1997). Oxybutynin is a chiral compound, and its anticholinergic effects are primarily attributed to the (R) enantiomer (Noronha-Blob and Kachur 1991). As a spasmolytic, it has a nonstereoselective relaxant effect on the smooth muscle of the bladder, although in vitro studies suggest the spasmolytic effects are about 500 times weaker than the antimuscarinic effects (Kachur et al 1988). The contribution of the local anesthetic effects following oral administration has yet to be determined.

Oxybutynin in the immediate-release form (OXY-IR) is rapidly absorbed from the gut, with the mean  $t_{max}$  in the range of 0.5–1 hour. OXY-IR then undergoes extensive upper gastrointestinal and first-pass hepatic metabolism via the CYP3A4 enzyme, which is part of the cytochrome P-450 system, into multiple metabolites. Many of the other available antimuscarinic medications are also metabolized by the cytochrome P450 enzyme system, most commonly involving enzymes CYP2D6 and CYP3A4 (Guay 2003). With any of these medications there is a risk for drug–drug interactions, resulting in either reduced (enzyme induction) or increased (enzyme inhibition, substrate competition) plasma concentration of either the antimuscarinic and/or interacting drug. Coadministration of oxybutynin with a potent CYP3A4 inhibitor such as itraconazole results in increased mean oxybutynin plasma concentrations (Lukkari et al 1997). No interaction appears to exist when oxybutynin and oral contraceptives are coadministered (Guay 2003). Less than 0.1% of the administered OXY-IR is excreted unchanged in the urine (OMNP 2003). Studies evaluating the pharmacokinetics of intravesical OXY-IR have determined that significant systemic absorption occurs following this route of administration; however, the drug/metabolite ratio is increased after intravesical instillation

and its elimination is relatively protracted (Lehtoranta et al 2002).

The primary metabolite of oxybutynin, N-desethyl-oxybutynin (DEO), has pharmacologic properties similar to those of the parent compound. In vitro studies involving both DEO and OXY-IR have demonstrated equivalent activity in antagonizing detrusor contractions, suggesting that a proportion of the therapeutic efficacy is likely attributable to DEO. Higher affinity for the metabolite relative to the parent compound has been noted in the parotid gland, and DEO has therefore been implicated as the major cause of the troublesome side effect of dry mouth (Waldeck et al 1997).

The most frequently reported adverse effects related to oxybutynin and all other antimuscarinic agents are due to the anticholinergic actions of the drugs. These include dry mouth, constipation, diarrhea, impaired urination, somnolence, blurry vision, dizziness, nervousness, and nausea. The frequency and severity of the side effects are dose dependent (Comer and Goa 2000). Both oxybutynin and DEO are highly lipophilic compounds: a property that allows them to be well absorbed, but also allows them to cross the blood–brain barrier and potentially cause central nervous system (CNS) effects. The high lipophilicity, neutrality, and small molecular size of oxybutynin may allow it to more readily cross the blood–brain barrier and skin (discussed below) relative to other antimuscarinic agents (Scheife and Takeda 2005). Contraindications to oxybutynin include urinary retention, severely decreased gastric motility conditions, and untreated narrow-angle glaucoma (OMNP 2003).

## Oxybutynin extended-release

Designed to allow for once daily dosing and decrease adverse side effects, OXY-ER was approved by the US Food and Drug Administration (FDA) in 1999. OXY-ER uses an osmotic system (OROS<sup>®</sup>) to deliver oxybutynin chloride to the gastrointestinal (GI) tract over a 24-hour period (ALZA 2004). This eliminates the serum concentration fluctuations that contribute to the intolerable side effects associated with OXY-IR (Preik et al 2004). OROS consists of a semi-permeable membrane-enclosed bilayer core containing oxybutynin chloride in one layer and osmotic agents in the other layer. Once in the GI tract, water enters the capsule and the oxybutynin forms a suspension. The expanding osmotic layer then pushes the oxybutynin suspension out of the capsule through a tiny laser-drilled hole in the capsule

membrane (Comer and Goa 2000; ALZA 2004). Oxybutynin is then released continuously throughout the entire GI tract, but primarily in the colon. OXY-ER reaches the colon approximately 3–5 hours after oral administration (Sathyan et al 2001). Because the CYP3A4 enzyme is located in higher concentrations in the upper small intestine relative to the lower GI tract, the amount of first-pass metabolism and resulting DEO is reduced. This is reflected by a higher mean bioavailability (153%) for oxybutynin and a lower bioavailability (69%) for DEO following OXY-ER administration compared with OXY-IR (Gupta and Sathyan 1999). Fluctuations in oxybutynin plasma concentration are also minimized by the OROS system. Following oral administration of OXY-ER, the plasma concentration gradually increases for 4–6 hours, and then stabilizes for the duration of the 24-hour dosage interval.  $T_{\max}$  is about 11–13 hours following a single dose (Siddiqui et al 2004).

## Oxybutynin transdermal

An oxybutynin transdermal delivery system (OXY-TDS) was approved by the FDA in 2003. OXY-TDS offers a twice-weekly dosing regimen and the potential for improved patient compliance and tolerability. The lipophilic quality of oxybutynin allows for it to be adequately absorbed transdermally. OXY-TDS utilizes a transdermal matrix system that is composed of three layers. The first layer is a thin flexible polyester–ethylene-vinyl acetate film that forms a protective barrier. The second layer is an acrylic adhesive that contains oxybutynin and triacetin, a skin permeation enhancer that temporarily changes the characteristics of the stratum corneum to allow diffusion of the oxybutynin from the transdermal system through the skin. The third layer consists of siliconized polyester strips that are peeled off and discarded prior to use by the patient (WP 2003).

The transdermal delivery system bypasses the first-pass metabolism that occurs in the GI tract and the liver. Relatively small amounts of the CYP3A4 are found in the skin, therefore limiting the presystemic metabolism, and reducing the plasma concentration of DEO. There is an absence of high peak concentrations and low metabolite levels with OXY-TDS. Minimal fluctuations in plasma concentration of oxybutynin are observed throughout the 96-hour wear period of the transdermal system. A steady state concentration was achieved during the second application (Zobrist et al 2003). Bioequivalent oxybutynin absorptions resulted from buttock and hip applications. Stereoselective metabolism was evident following OXY-TDS administration

with slightly lower plasma concentrations of the R-enantiomers of oxybutynin and DEO (Zobrist et al 2001).

Currently, the only size patch commercially available is the 3.9 mg/day patch. There is a size restriction based upon the fact that 1 mg of oxybutynin to be delivered daily for up to four days requires 1 cm<sup>2</sup> of patch. The patch may be cut and remain intact. This has allowed dose escalation studies to be performed using doses of 5.2 mg/day and 7.8 mg/day. There have been no reports on the correlation between efficacy or adverse events upon increasing the dose of OXY-TDS. Furthermore, there has not been a rigorously established conversion factor between oral and transdermal dosing of oxybutynin.

## Comparative studies

Clinical practice and the literature support the efficacy of oxybutynin for the treatment of OAB. Numerous studies exist in the literature comparing OXY-IR to placebo, tolterodine, propantheline, propiverine, trospium, darifenacin, the extended-release formulation of tolterodine (TOL-LA), OXY-ER, and OXY-TDS (Riva and Casolati 1984; Tapp et al 1990; Thuroff et al 1991; Madersbacher et al 1995, 1999; Abrams et al 1998; Drutz et al 1999; Appell et al 2001; Halaska et al 2003; Homma et al 2003; Chapple and Abrams 2005). Compared with placebo, OXY-IR reduces urinary frequency by about 50% and urge incontinence episodes by up to 70%, but the prevalence of dry mouth varies between 12%–70%, depending on dosage (Douchamps et al 1988). Although most patients respond favorably to antimuscarinic medications such as OXY-IR, smaller percentages achieve total dryness. In general, the new formulations of oxybutynin and other antimuscarinic agents offer patients efficacy roughly equivalent to that of OXY-IR, and the advantages of the newer formulations lie in improved dosing schedules and side effect profile (Lawrence et al 2000; Appell et al 2001; Diokno et al 2003).

Several randomized, double-blind trials comparing OXY-ER and OXY-IR have demonstrated that they are similarly effective in relieving symptoms of OAB (Anderson et al 1999; Versi et al 2000; Barkin et al 2004). Urge urinary incontinence episodes, micturition frequency, and total continence rates were similarly improved; however, OXY-ER resulted in better tolerability (Anderson et al 1999). Another randomized, double-blind, crossover study comparing OXY-ER (10 mg once daily) and OXY-IR (5 mg twice daily) established that OXY-ER was associated with 57% less side effects relative to OXY-IR (Birns et al 2000).

OXY-ER was compared with tolterodine in a randomized, double-blind study referred to as the OBJECT (Overactive bladder: judging effective control and treatment) trial. In terms of the number of episodes of urge incontinence, total incontinence, and micturition frequency, OXY-ER was found to be more effective than immediate-release tolterodine (TOL-IR). Rates of dry mouth and other adverse events were similar (Appell et al 2001). Subsequently, with the development of TOL-LA, the OPERA (Overactive bladder: performance of extended release agents) trial was designed as a head-to-head comparative study between OXY-ER and TOL-LA. This study randomized 790 women with 21–60 urge urinary incontinence episodes per week and 10 or more voids per 24 hrs to receive either OXY-ER 10mg/day or TOL-LA 4mg/day for 12 weeks. The primary end point was urge urinary incontinence episodes. Both antimuscarinic agents showed similar reductions in weekly urge urinary incontinence and total incontinence episodes. OXY-ER participants had a greater decrease in micturition frequency and a higher proportion of participants who reported total dryness in the last week of the study when compared with the TOL-LA group (23.0% vs 16.8%, respectively,  $p=0.03$ ). Dry mouth was the most common adverse effect in both groups; it was more common with OXY-ER group relative to the TOL-LA group (29.7% vs 22.3%, respectively,  $p=0.02$ ). This problem was generally mild and was the reason for discontinuation of the medication for only a few patients (OXY-ER=7; TOL-LA=4). Other adverse events were rare in both groups, with no serious adverse events being attributed to either drug in the study (Diokno et al 2003). A one-year open-label trial of OXY-ER found that 60% of patients remained on OXY-ER (dose of 15 mg or less) at 12 months. This is much higher than the continuation rate reported in the literature for OXY-IR, which is only 18%–22% of patients continuing the medication at 6 months (Kelleher et al 1997; Appell et al 2000; Lawrence et al 2000).

The efficacy and safety of OXY-TDS in patients with urge urinary incontinence has been demonstrated in several studies. In a phase three study involving 520 patients, utilizing doses ranging from 1.3 mg/day to 3.9 mg/day, OXY-TDS at 3.9 mg/day significantly reduced the number of weekly incontinence episodes, reduced average daily urinary frequency, increased average voided volume, and improved quality of life relative to placebo. OXY-TDS was well tolerated, with the most common adverse effect being application site pruritus (10.8%–16.8%). The incidence of dry mouth with OXY-TDS was similar to placebo (OXY-

TDS=7%; placebo=8.3%,  $p=0.98$ ) (Dmochowski et al 2002).

OXY-TDS has also been compared with OXY-IR in a randomized double-blind dose titration study. Both OXY-TDS and OXY-IR demonstrated a similar decrease in daily incontinent episodes (OXY-TDS=66%; OXY-OR=72%,  $p=0.39$ ); however, significantly fewer patients complained of dry mouth in the OXY-TDS group (OXY-TDS=38%, OXY-IR=94%,  $p<0.001$ ). Similar improvement in urodynamic parameters was also demonstrated between the two groups. Ninety percent of patients in the OXY-TDS group had no or mild skin erythema (Davila et al 2001).

In a third study, OXY-TDS was compared with both placebo and TOL-ER. TOL-ER was associated with a significantly higher rate of antimuscarinic adverse events relative to both OXY-TDS and placebo. The primary adverse event for OXY-TDS was application site reaction pruritis (14%) and erythema in (8.3%). These application site reactions were severe enough to result in nearly 10% of patients withdrawing from the study (Dmochowski et al 2003).

The side effect of xerostomia has been further evaluated in studies that have evaluated saliva output as a surrogate measure for dry mouth. In a crossover study comparing placebo, OXY-ER (10 mg), TOL-IR (2 mg), and OXY-IR (5 mg), salivary output was measured at baseline and at numerous points following dosing. All three active treatments resulted in decreased salivary output, however OXY-ER and TOL-IR had significantly greater output relative to OXY-IR (Chancellor et al 2001). More recently, OXY-TDS (3.9 mg/day) and OXY-ER (10 mg/day) were compared, correlating salivary output and plasma concentrations of oxybutynin and DEO with symptomatic dry mouth. Relative to OXY-ER, blood samples indicated that OXY-TDS resulted in greater systemic availability and minimal metabolism to DEO. Mean plasma concentrations of oxybutynin were less variable in the OXY-TDS group. The decreased plasma concentration of DEO corresponded with greater salivary output and less complaints of dry mouth in the OXY-TDS group compared with OXY-ER (Appell et al 2003).

While most studies have focused on the symptom of dry mouth as the main tolerability end point, it is also important to consider other potential adverse effects. CNS safety is important to consider when treating patients for OAB, especially in the elderly. Both OXY-IR and DEO are both highly lipophilic compounds which aid in absorption from the GI tract, skin, or bladder, but also potentially allow for



penetration into the CNS. In a randomized controlled dose-titration trial involving OXY-IR and OXY-ER, there were no significant differences in incidences of somnolence, dizziness, or nervousness (Anderson et al 1999). In the OBJECT trial which compared OXY-ER and TOL-IR, there were similar rates on CNS adverse events between the groups (Appell et al 2001). More recently, in a subanalysis of the OPERA study, OXY-ER and TOL-ER were compared and found to have a similarly low incidence of CNS adverse effects (OXY-ER=9% vs TOL-LA=8%,  $p=0.8$ ), most of which were mild or moderate in severity. No serious adverse events were reported in either group. The incidence of adverse CNS events was highest in the first 14 days of treatment, demonstrating a trend toward increased tolerance with time for both drugs (Chu et al 2005). Another study comparing quantitative electroencephalography (qEEG) effects of OXY-IR (20 mg), TOL-IR (2 mg), and trospium chloride (45 mg), found that only OXY-IR produced significant power reductions in the middle-frequency bands ( $p<0.01$ ) (Todorova et al 2001). Although CNS concentrations of the drugs and metabolites were not measured, this may indicate that oxybutynin and/or DEO more readily penetrate the blood-brain barrier due to their high lipophilicity, neutrality, and small molecular size relative to other antimuscarinic agents (Scheife and Takeda 2005).

Ocular side effects were targeted in another randomized trial between OXY-IR (5 mg thrice daily) and TOL-ER (2 mg twice daily). Following 4 weeks of treatment, OXY-IR significantly decreased the accommodation amplitude, whereas this effect was not noted following TOL-ER. Both drugs caused a shorter tear film break-up time that could potentially cause problems for patients with dry eyes (Altan-Yaycioglu et al 2005).

## Conclusion

Compared with OXY-IR, the more recently developed delivery systems of oxybutynin, OXY-ER and OXY-TDS, offer improved tolerability and dosing options for patients. While these agents are often touted for causing less dry mouth, these newer medications are currently more expensive for patients, while being no more efficacious in treating OAB symptoms. These issues are often reflected in lower than expected patient compliance rates. Clearly there is still a need for the development of other pharmacological agents that prove to be more effective in helping patients achieve total dryness and/or alleviation of OAB symptoms,

while having a favorable side effect profile and acceptable dosing regimen.

## References

- Abrams P, Freeman R, Anderstrom C, et al. 1998. Tolterodine, a new antimuscarinic agent: as effective but better tolerated than oxybutynin in patients with an overactive bladder. *Br J Urol*, 81:801–10.
- Abrams P, Cardozo L, Fall M, et al. 2002. The standardisation of terminology of lower urinary tract function: report from the standardization sub-committee of the International Continence Society. *Neurourol Urodyn*, 21:167–78.
- Altan-Yaycioglu R, Yaycioglu O, Aydin Akova Y, et al. 2005. Ocular side-effects of tolterodine and oxybutynin, a single-blind prospective randomized trial. *Br J Clin Pharmacol*, 59:588–92.
- [ALZA] Alza Corporation. Product monograph: Ditropan XL® (oxybutynin extended-release tablets) [online]. Accessed 26 Aug 2005. URL: <http://www.ditropanxl.com>.
- Anderson RU, Mobley BB, Saltzstein D, et al. 1999. Once daily controlled versus immediate release oxybutynin chloride for urge urinary incontinence. *J Urol*, 161:1809–12.
- Appell RA, Chancellor MB, Zobrist RH, et al. 2003. Pharmacokinetics, metabolism, and saliva output during transdermal and extended-release oral oxybutynin administration in healthy subjects. *Mayo Clin Proc*, 78:696–702.
- Appell RA, Diokno A, Antoci J, et al. 2000. One-year, prospective, open-label trial of controlled-release oxybutynin for overactive bladder in a community-based population [abstract]. *Neurourol Urodyn*, 19:526.
- Appell RA, Sand P, Dmochowski R, et al. 2001. Prospective randomized controlled trial of extended-release oxybutynin chloride and tolterodine tartrate in the treatment of overactive bladder: results of the OBJECT trial. *Mayo Clin Proc*, 76:358–63.
- Barkin J, Corcos J, Radomski S, et al. 2004. A randomized, double-blind, parallel-group comparison of controlled- and immediate-release oxybutynin chloride in urge urinary incontinence. *Clin Ther*, 26:1026–36.
- Birns J, Lukkari E, Malone-Lee JG, et al. 2000. A randomized controlled trial comparing the efficacy of controlled-release oxybutynin tablets (10 mg once daily) with conventional oxybutynin tablets (5 mg twice daily) in patients whose symptoms were stabilized on 5 mg twice daily of oxybutynin. *BJU Int*, 85:793–8.
- Chancellor MB, Appell RA, Sathyan G, et al. 2001. A comparison of the effects on saliva output of oxybutynin chloride and tolterodine tartrate. *Clin Ther*, 23:753–60.
- Chapple CR, Abrams P. 2005. Comparison of darifenacin and oxybutynin in patients with overactive bladder: assessment of ambulatory urodynamics and impact on salivary flow. *Br J Urol*, 48:102–9.
- Chu FM, Dmochowski RR, Lama DJ, et al. 2005. Extended-release formulations of oxybutynin and tolterodine exhibit similar central nervous system tolerability profiles: a subanalysis of data from the OPERA trial. *Am J Obstet Gynecol*, 192:1849–54.
- Comer AM, Goa KL. 2000. Extended-release oxybutynin. *Drugs Aging*, 16:149–55.
- Davila GW, Daugherty CA, Sanders SW, et al. 2001. A short-term multicenter, randomized double-blind dose titration study of the efficacy and anticholinergic side effects of transdermal compared to immediate release oral oxybutynin treatment of patients with urge urinary incontinence. *J Urol*, 166:140–5.
- Diokno AC, Appell RA, Sand PK, et al. 2003. Prospective, randomized double-blind study of the efficacy and tolerability of the extended-release formulations of oxybutynin and tolterodine for overactive bladder: results of the OPERA trial. *Mayo Clin Proc*, 78:687–95.
- Dmochowski R, Appell RA. 2003. Advancements in minimally invasive treatments for female stress urinary incontinence. *Curr Urol Rep*, 4:350–5.

- Dmochowski RR, Davila GW, Zinner, et al. 2002. Efficacy and safety of transdermal oxybutynin in patients with urge and mixed urinary incontinence. *J Urol*, 168:580–6.
- Dmochowski RR, Sand PK, Zinner NR, et al. 2003. Comparative efficacy and safety of transdermal oxybutynin and oral tolterodine versus placebo in previously treated patients with urge and mixed urinary incontinence. *Urology*, 62:237–42.
- Douchamps J, Derenne F, Stockis A, et al. 1988. The pharmacokinetics of oxybutynin in man. *Eur J Clin Pharmacol*, 35:515–20.
- Drutz HP, Appell RA, Gleason D, et al. 1999. Clinical efficacy and safety of tolterodine compared to oxybutynin and placebo in patients with overactive bladder. *Int Urogynecol J Pelvic Floor Dysfunct*, 10: 283–9.
- Echols K, Verma U, Policaro F, et al. 2000. Idiopathic bladder hyperactivity and ditropan: an efficacy and compliance issue [abstract]. *Obstet Gynecol*, 95:S24.
- Guay DRP. 2003. Clinical pharmacokinetics of drugs used to treat urge incontinence. *Clin Pharmacokinet*, 42:1243–85.
- Gupta SK, Sathyan G. 1999. Pharmacokinetics of an oral once-a-day controlled-release oxybutynin formulation compared with immediate-release oxybutynin. *J Clin Pharmacol*, 39:289–96.
- Halaska M, Ralph G, Wiedemann A, et al. 2003. Controlled, double-blind, multicentre clinical trial to investigate long-term tolerability and efficacy of trospium chloride in patients with detrusor instability. *World J Urol*, 20:392–9.
- Homma Y, Paick JS, Lee JG, et al. 2003. Clinical efficacy and tolerability of extended-release tolterodine and immediate-release oxybutynin in Japanese and Korean patients with an overactive bladder: a randomized, placebo-controlled trial. *BJU Int*, 92:741–7.
- Hu T, Wagner TH, Bentkover JD, et al. 2004. Costs of urinary incontinence and overactive bladder in the United States: a comparative study. *Urology*, 63:461–5.
- Kachur JF, Peterson JS, Carter JP, et al. 1988. R and S enantiomers of oxybutynin: pharmacological effects in guinea pig bladder and intestine. *J Pharmacol Exp Ther*, 247:867–72.
- Kelleher CJ, Cardozo LD, Khullar V, et al. 1997. A new questionnaire to assess the quality of life of urinary incontinent women. *Br J Obstet Gynaecol*, 104:1374–9.
- Lai HH, Boone TB, Appell RA. 2002. Pharmacologic treatment for detrusor overactivity. *Curr Urol Rep*, 3:365–72.
- Lawrence M, Guay, Benson SR, et al. 2000. Immediate-release oxybutynin versus tolterodine in detrusor overactivity: a population analysis. *Pharmacotherapy*, 20:470–5.
- Lehtoranta K, Tainio H, Lukkari-Lax E, et al. 2002. Pharmacokinetics, efficacy, and safety of intravesical formulation of oxybutynin in patients with detrusor overactivity. *Scand J Urol Nephrol*, 36:18–24.
- Lukkari E, Juhakoski A, Aranko K, et al. 1997. Itraconazole moderately increases serum concentrations of oxybutynin but does not affect those of the active metabolite. *Eur J Clin Pharmacol*, 52:403–6.
- Madersbacher H, Stohrer M, Richter R, et al. 1995. Trospium chloride versus oxybutynin: a randomized, double-blind, multicentre trial in the treatment of detrusor hyperreflexia. *Br J Urol*, 75:452–6.
- Madersbacher H, Halaska M, Voigt R, et al. 1999. A placebo-controlled, multicentre study comparing the tolerability and efficacy of propiverine and oxybutynin in patients with urgency and urge incontinence. *BJU Int*, 84:646–51.
- Nilvebrant L, Andersson KE, Gillberg PG, et al. 1997. Tolterodine – a new bladder-selective antimuscarinic agent. *Eur J Pharmacol*, 327:195–207.
- Noronha-Blob L, Kachur JF. 1991. Enantiomers of oxybutynin: in vitro pharmacological characterization at M1, M2, and M3 muscarinic receptors and in vivo effects on urinary bladder contraction, mydriasis and salivary secretion in guinea pigs. *J Pharmacol Exp Ther*, 256: 562–7.
- [OMNP] Ortho-McNeil Pharmaceutical, Inc. Product monograph: Ditropan® (oxybutynin chloride). [online]. Accessed 26 Aug 2005. URL: <http://www.orthomcneil.com>.
- Preik M, Abrecht D, O'Connell M, et al. 2004. Effect of controlled-release delivery on the pharmacokinetics of oxybutynin at different dosages: severity-dependent treatment of the overactive bladder. *BJU Int*, 94:821–7.
- Riva D, Casolati E. 1984. Oxybutynin chloride in the treatment of female idiopathic bladder instability. Results from double blind treatment. *Clin Exp Obstet Gynecol*, 11:27–42.
- Rovner ES. 2004. Trospium chloride in the management of overactive bladder. *Drugs*, 64:2433–46.
- Sathyan G, Chancellor MB, Gupta SK. 2001. Effect of OROS® controlled-release delivery on the pharmacokinetics and pharmacodynamics of oxybutynin chloride. *Br J Clin Pharmacol*, 52:409–17.
- Scheife R, Takeda M. 2005. Central nervous system safety of anticholinergic drugs for the treatment of overactive bladder in the elderly. *Clin Ther*, 27:144–53.
- Siddiqui MAA, Perry CM, Scott LJ. 2004. Oxybutynin extended-release, a review of its use in the management of overactive bladder. *Drugs*, 64:885–912.
- Stewart K, McGhan WF, Offerdahl T, et al. 2002. Overactive bladder patients and the role of the pharmacist. *J Am Pharm Assoc*, 42: 469–76.
- Stewart WF, Van Rooyen JB, Cundiff GW, et al. 2003. Prevalence and burden of overactive bladder in the United States. *World J Urol*, 20:327–36.
- Tapp AJ, Cardozo LD, Versi E, et al. 1990. The treatment of detrusor instability in post-menopausal women with oxybutynin chloride: a double blind placebo controlled study. *Br J Obstet Gynaecol*, 97: 521–6.
- Thuroff JW, Bunke B, Ebner A, et al. 1991. Randomized, double-blind, multicenter trial on treatment of frequency, urgency and incontinence related to detrusor hyperactivity: oxybutynin versus propantheline versus placebo. *J Urol*, 145:813–16.
- Todorova A, Vonderheid-Guth B, Dimpfel W. 2001. Effects of tolterodine, trospium chloride, and oxybutynin on the central nervous system. *J Clin Pharmacol*, 41:636–44.
- van der Vaart CH, De Leeuw JRJ, Roovers JPWR, et al. 2002. The effect of urinary incontinence and overactive bladder symptoms on quality of life in young women. *BJU Int*, 90:544–9.
- Versi E, Appell RA, Mobley D, et al. 2000. Dry mouth with conventional and controlled-release oxybutynin in urinary incontinence. *Obstet Gynecol*, 95:718–21.
- Waldeck K, Larsson B, Andersson KE. 1997. Comparison of oxybutynin and its active metabolite, N-desethyl-oxybutynin, in the human detrusor and parotid gland. *J Urol*, 157:1093–7.
- [WP] Watson Pharma, Inc. Product monograph: Oxytrol™ (oxybutynin transdermal system) [online]. Accessed 26 Aug 2005. URL: <http://www.oxytrol.com>.
- Yarker YE, Goa KL, Fitton A. 1995. Oxybutynin. A review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic use in detrusor instability. *Drugs Aging*, 6:243–62.
- Zobrist RH, Schmid B, Feick A, et al. 2001. Pharmacokinetics of the R- and S-enantiomers of oxybutynin and N-desethyloxybutynin following oral and transdermal administration of the racemate in healthy volunteers. *Pharm Res*, 18:1029–34.
- Zobrist RH, Quan D, Thomas HM, et al. 2003. Pharmacokinetics and metabolism of transdermal oxybutynin: In vitro and in vivo performance of a novel delivery system. *Pharm Res*, 20:103–9.