Will the Evolution of Overactive Bladder Delivery Systems Increase Patient Compliance?

Nirit Rosenblum, MD

New York University Langone Medical Center, New York, NY

The negative impact of overactive bladder (OAB) on daily quality of life drives the large market of pharmacotherapy targeted at symptoms of urinary frequency and urgency, with or without urinary urge incontinence. Currently, the primary pharmacologic treatment modality is aimed at modulation of the efferent muscarinic receptors (M2 and M3) predominant in detrusor smooth muscle and responsible for involuntary or unwanted bladder contractions. However, due to drug effects in the muscarinic receptors of the salivary glands and intestinal smooth muscle, as well as extensive first-pass metabolism in the liver and intestinal tract yielding parent drug metabolites, adverse side effects are common and can be quite bothersome. These issues, encountered with many of the oral antimuscarinic formulations, limit their tolerability and affect long-term patient compliance and satisfaction. Thus, the benefit of pharmacotherapy for OAB must be a balance between efficacy and tolerability, also known as therapeutic index. This article reviews the current pharmacologic delivery systems available for the treatment of OAB, patient compliance, and reasons for discontinuation of medication.

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Overactive bladder syndrome (OAB) is a condition affecting millions of adults in the aging US population, with prevalence rates estimated at 17% in both men and women.[1] Quality of life and symptom bother have become important parameters in the treatment of many disease states, with efficacy of treatment measured by perceived improvements in these variables. OAB is largely characterized by its negative impact on daily quality of life. Specifically, the subjective impact of urinary frequency and urgency (with or without urge

incontinence) on psychosocial and physical factors has become an important aspect of caring for this group of patients. The severity and degree of bother associated with OAB symptoms can directly influence a person's mobility, degree of social isolation, and impairment in work-related productivity, and may also cause clinical depression, disruptions in sleep, and impairment in domestic and sexual life.[2] In addition, the patient may develop extreme coping strategies including severe, self-imposed fluid restrictions, avoidance of social events and travel, and dependence on costly protective undergarments. Although all of these factors drive patients to seek evaluation and treatment, persistence and compliance with medical OAB therapy remain astoundingly low both in the clinical setting and in large-scale clinical trials. High rates of discontinuation are multifactorial: adverse side effects, lack of perceived efficacy, polypharmacy, medication cost, poor counseling regarding compliance and successful treatment, and dosing frequency. Because adverse side effects are experienced by a significant portion of patients treated with oral antimuscarinic therapy, thereby limiting their long-term utilization, the development of new drug delivery systems for OAB pharmacotherapy has been critical. The focus has been on less frequent dosing intervals with longer acting formulations, reduction in side-effect profile by altering pharmacokinetics of both parent compound and active metabolites, and alternative methods of drug delivery that avoid first-pass liver metabolism.

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Immediate Release (IR) Drug Formulations

Developed approximately 30 years ago, oxybutynin IR (Ditropan®; Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ) was the first of the class of antimuscarinic therapies in use for the treatment of OAB.[3] Oxybutynin IR is a tertiary amine with anticholinergic properties that promote smooth muscle relaxation as well as local anesthetic properties. The drug undergoes extensive first-pass liver metabolism that limits its bioavailability to approximately 6%. The most common dosing regimen prescribed is 5 mg orally 3 times daily. Its half-life ranges between 2 and 5 hours and the primary metabolite is known as *N*-desethyloxybutynin (*N*-DEO), equivalent in activity to the parent drug.[2]

Because its antimuscarinic effects are nonspecific, *N*-DEO does have significant activity in the salivary gland, leading to the most common adverse side effect, dry mouth, in 72% to 94% of patients.[3] The *N*-DEO metabolite is largely responsible for the effect of dry mouth due to its high affinity for the M3 muscarinic receptors located in the salivary gland. Additional bothersome side effects associated with oxybutynin IR include constipation, dry eyes, headaches, blurred vision, dizziness, and cognitive dysfunction. Although its efficacy in clinical trials is similar to tolterodine, there is a high discontinuation rate (approximately 25%) associated with oxybutynin IR likely attributable to adverse effects and the inconvenience of multiple daily doses.[2,3]

Tolterodine IR (Detrol®; Cerner Multum, Inc., Denver, CO) is a target-specific antimuscarinic drug with stronger selectivity for the bladder than for the salivary gland. Tolterodine IR is dosed as 2 mg twice daily. Metabolism of the drug occurs through the cytochrome P450 2D6 enzyme and results in a pharmacologically active metabolite known as 5-hydroxy-methyltolterodine (5-HMT) that retains antimuscarinic activity similar to the parent compound. In a pooled analysis of clinical phase II trials, the number of micturitions was significantly decreased from baseline compared with placebo as was the number of incontinence episodes per 24 hours. Dry mouth was reported by 40% of the 2-mg tolterodine group compared with 16% of the placebo group and 78% of the oxybutynin group.[2] In comparative clinical trials, tolterodine IR was associated with a reduced rate of discontinuation (approximately 6%-8%) in a clinical trial comparing tolterodine IR and oxybutynin IR.[3]

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The clinical utility of both oxybutynin and tolterodine in their IR formulations is quite limited now that most OAB pharmacotherapy is available in extended-release formulation. The multiple daily dosing regimens of IR formulations, especially when taken in the setting of polypharmacy,

negatively impact on long-term patient adherence. In addition, the IR formulations are associated with increased rates of adverse events, limiting further compliance in most OAB patient populations.

Trospium chloride (Sanctura®; Cerner Multum, Inc.), another oral antimuscarinic agent for OAB, gained US Food and Drug Administration (FDA) approval in 2004 as a twice-daily formulation. Trospium is a quaternary ammonium compound that is a positively charged hydrophilic molecule, which limits its ability to cross the blood-brain barrier, thereby reducing the incidence of central nervous system adverse events. Furthermore, it is not metabolized by the cytochrome p450 isoenzyme system, which limits its potential for metabolic drug-drug interactions. The parent compound is largely eliminated unchanged in the urine and this may allow local effects on the urothelium.[4] In phase III clinical trials, trospium IR exhibited a favorable side-effect profile with a reported incidence of dry mouth and constipation of 20.1% and 9.6%, respectively.[2]

Extended Release (ER) Drug Formulations

Oxybutynin ER (Ditropan XL®; Ortho-McNeil Pharmaceutical, Inc.) was developed in an effort to overcome the poor tolerability and multiple daily dosing regimen issues associated with the IR formulation. The once-daily ER formulation gained FDA approval in 1999 and uses a patented push-pull osmotic-release oral system (OROS) to deliver oxybutynin at a fixed rate over 24 hours. The ER formulation is available in 3 doses (5, 10, and 15 mg tablets) and total daily dosing ranges from 5 mg to 30 mg. This resulted in a significantly improved pharmacokinetic profile, eliminating the plasma peaks and troughs and achieving a steady-state serum concentration, thereby leading to improved patient tolerability. Plasma levels of oxybutynin rise over a 4- to 6-hour period and achieve steady-state concentration after 3 days of ingestion.[5] OROS has a rapid small gut transit time of 3 to 5 hours, with the majority of the drug compound being absorbed in the large intestine, where there is a lower concentration of cytochrome p450 enzymes compared with the small intestine. This results in absorption of more parent compound and comparatively less metabolite (*N*-DEO), which has been associated with lower rates of dry mouth and improved tolerability.[2] Unfortunately, despite improvements in tolerability, oxybutynin ER did not appear to improve persistence with therapy in a large open-label trial where 1067 patients were treated with 10 mg of oxybutynin ER. The discontinuation rate attributable to adverse events was 24%, similar to that reported with oxybutynin IR. Only 46% of the 1067 patients persisted with treatment over the 12-month study period.[6]

Tolterodine ER (Detrol® LA; Pfizer Inc, New York, NY) was developed as a once-daily capsule formulation to offer a more convenient dosing regimen and improve the tolerability profile. It is available in 2 mg and 4 mg once-daily ER capsules. The peak serum concentrations following tolterodine ER administration were specifically aimed to be lower than the twice-daily IR regimen, in an effort to reduce the incidence of dry mouth. The once-daily ER formulation is an encapsulated microsphere platform that prolongs release of tolterodine over the entire physiologic pH range of the gastrointestinal tract. As the outer layer of microspheres dissolves, the drug is slowly released. As a result, the ER formulation has a half-life of 6 to 8 hours compared with 3 hours with the IR compound. In addition, the peak serum concentration of the active moiety following administration of tolterodine ER is around 75% of that observed with the IR tablet with fewer peaks and fluctuations. These pharmacokinetic advantages of the ER formulation are apparent clinically with lower rates of dry mouth (approximately 23%) observed with the 4 mg once-daily dosage.[7]

Tolterodine ER was evaluated in a 12-month open-label, extension study that included 1077 patients initially enrolled in the 12-week randomized, controlled trial. A total of 759 patients (71%) completed the 1-year trial, a substantially improved medication compliance rate when compared with oxybutynin ER at 1 year. The discontinuation rate due to adverse events of 9.9% with tolterodine ER is much lower than the 24% discontinuation rate with oxybutynin ER.[8] One must keep in mind that long-term patient adherence to medication is not as simple as adverse events. Clinical effectiveness, tolerability, and cost all play important roles in determining patient adherence with prescribed OAB pharmacotherapy. In addition, drug trials data do not translate into real-life compliance with medications prescribed in the clinical setting.

D'Souza and colleagues[9] analyzed a large population of managed care patients between 1999 and 2003, specifically focusing on persistence with OAB therapy, switch rates between drugs (ER and IR formulations of tolterodine and oxybutynin), and adherence rates. Persistence was measured as the proportion of patients continuing therapy for 12 months without discontinuation or switching to other OAB drugs. In this study population, the most commonly prescribed index drug was tolterodine ER (40.6%), followed by tolterodine IR (27.4%), oxybutynin ER (22.3%), and

oxybutynin IR (9.7%). Overall, only 13.2% of patients persisted for 12 months of therapy with the index drug. There were no differences seen in persistence with therapy between oxybutynin ER and tolterodine ER. The highest proportion of non-refills was seen for the oxybutynin IR (59.3%) group. Adjusted persistence rates at the end of follow-up were 11.0% for tolterodine ER, 13.2% for oxybutynin ER, 9.0% for tolterodine IR, and 9.0% for oxybutynin IR. Of the total cohort analyzed, only 13.3% switched from index medication to other OAB drugs. Both oxybutynin ER and oxybutynin IR users were twice as likely to switch compared with tolterodine ER users. This particular type of pharmacy claims study is more representative of patient compliance issues in the general population and illustrates the overall low long-term adherence rates seen with medical OAB therapy. Unfortunately, the study is unable to provide patient-reported data as to reasons for nonpersistence with therapy, including adverse events, perceived clinical effectiveness, cost, lack of understanding of long-term goals of OAB pharmacotherapy, et cetera.

Trospium chloride ER (Sanctura XR™; Indevus Pharmaceuticals, Inc., Irvine, CA) is a once-daily 60 mg formulation that gained FDA approval in August 2007. This ER formulation was developed to improve patient convenience and compliance, analogous to the development of other antimuscarinic ER formulations. This particular compound is made up of a timed-release and a pH-dependent coating disintegration system. The drug is layered on a sugar sphere and coated with sustained release polymers. This new once-daily formulation reduces the maximum plasma concentration (C_{max}), thereby reducing the common adverse events of dry mouth and constipation seen with the IR formulation (20.1% vs 10.7% dry mouth and 9.6% vs 8.5% constipation with IR and ER formulations, respectively).[2] In phase III clinical trials, trospium ER was effective in reducing OAB symptoms with statistically significant reductions in urinary frequency and urge incontinence episodes.[10]

Darifenacin hydrobromide (Enablex®; Novartis Pharmaceuticals Corporation, Annandale, NJ) is an M3 receptor–selective antimuscarinic OAB agent that is available in once-daily doses of 7.5 and 15 mg. Because of its high affinity for the M3 receptor subtype, darifenacin has the advantage of improved safety and tolerability for potential CNS and cardiac effects.[11] In a large multicenter, double-blind, placebo-controlled study of 561 patients treated with darifenacin versus placebo, statistically significant improvements in micturition frequency, bladder capacity, frequency of urgency, severity of urgency, and number of incontinence episodes were seen at both the 7.5- and 15-mg doses. The most common adverse events reported were constipation (14.4% and 13.9% with 7.5 and 15 mg darifenacin, respectively, vs 6.7% with placebo) and dry mouth (18.8% and 31.3% with 7.5 and 15 mg darifenacin, respectively, vs 8.5% with placebo).[11] In this 12-week trial, a total of 10 patients discontinued from the study due to adverse events, the majority of which were reported as either dry mouth or constipation. This trial represents a short-term use of medication and further long-term trials are needed to assess patient compliance with darifenacin.

Solifenacin succinate (VESIcare®; Astellas Pharma US, Inc., Deerfield, IL) is a competitive M3 antagonist available in 5- and 10-mg doses. Similar to other antimuscarinics, solifenacin is metabolized hepatically by the cytochrome p450 system while approximately 50% of the dose is eliminated renally as a parent compound. The elimination half-life of solifenacin ranges between 36 to 64 hours, with a time to maximum concentration of 3 to 8 hours. Steady-state serum concentration is achieved after 10 days of consecutive dosing.[12,13] In phase III clinical trials, solifenacin exhibited superiority over placebo in improving primary OAB symptoms. Specifically, solifenacin treatment was associated with statistically significant reductions in incontinence episodes, micturition frequency, and urgency episodes as well as significant increases in volume voided per micturition. The most common adverse side effects were dry mouth (10.9% vs 3.5% with placebo), constipation (5.4% vs 1.9% with placebo), and blurred vision (3.8% vs 2.5% with placebo). The incidence of dry mouth and constipation reported was higher in the 10-mg treatment group. In 2 of 3 phase III studies, 3.2% and 2.3% of patients receiving solifenacin 5 mg discontinued treatment due to adverse events.[13] Further long-term studies are needed to determine adherence rates with solifenacin treatment and specific reasons for nonpersistence or discontinuation of therapy.

Fesoterodine (Toviaz™; Pfizer Inc) is the newest of the orally administered, ER OAB pharmacologic armamentarium. This drug was developed to eliminate substantial interindividual variability in the cytochrome p450 2D6 enzyme system seen in the metabolism of tolterodine, leading to markedly different proportions of plasma tolterodine to 5-hydroxymethyltolterodine (5-HMT, the active metabolite). Fesoterodine is rapidly converted by nonspecific esterases to its active metabolite, 5-HMT. These esterases do not exhibit genotypic variations and are not involved in drug-drug interactions. In addition, all antimuscarinic activity is

due to 5-HMT after fesoterodine administration.[14]

Fesoterodine is available in 4 mg and 8 mg daily doses. Similar to oxybutynin, tolterodine, darifenacin, and solifenacin, the availability of 2 doses of fesoterodine allows an opportunity to find an optimal balance between efficacy and tolerability in individual patients. This particular drug may provide a unique opportunity to test its efficacy in patients unsatisfied with tolterodine therapy. In fact, a large, multinational trial of flexible-dose fesoterodine included patients who previously reported dissatisfaction with tolterodine therapy. Patients received 4 mg of fesoterodine daily for 4 weeks and were then assessed to discuss the option of continuing on the 4-mg dose or escalating to the 8-mg dose. Significant improvements from baseline to week 12 of therapy were observed in micturitions, urgency urinary incontinence episodes, and micturition-related urgency episodes. Dry mouth (23%) and constipation (5%) were the most frequently reported adverse events. The rate of withdrawal due to treatment-emergent adverse events was 7%. Overall, approximately 50% of patients in this study opted for dose escalation at week 4 to fesoterodine 8 mg, following a discussion of efficacy and tolerability.[14] Long-term trials of fesoterodine treatment for OAB are needed to assess patient compliance with therapy.

Transdermal Drug Delivery Systems (TDS)

Transdermal drug delivery has the potential to yield more stable plasma drug levels and to bypass the organs involved in first-pass metabolism.[15] The development of transdermal medications offers an advantage in drug delivery for the treatment of numerous medical conditions, including estrogen and androgen deficiency, contraception, analgesia, smoking cessation, and OAB. This mode offers improved pharmacokinetics, convenient dosing schedules, and a substantially lower incidence of adverse events.[5] This last advantage is particularly appealing for OAB treatment, as adverse events associated with antimuscarinics are problematic and associated with significant rates of nonpersistence or withdrawal. Thus, transdermal drug delivery for OAB may provide an ideal opportunity to improve patient compliance with medical therapy if tolerability remains a major inhibiting factor.

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Transdermal drug delivery systems must penetrate the avascular epidermis and reach the rich capillary system in the underlying dermis to allow systemic absorption. Drug absorption is affected by biologic and physiochemical skin properties, the nature of the medication, and the design of the drug delivery system.[5] The major rate-limiting barrier to the absorption of most drugs is the lipid- and keratin-rich stratum corneum of the epidermis. Skin permeability may be increased by physical, chemical, or disease-related mechanisms and is influenced by dermal blood flow. Furthermore, the presence of cutaneous drug-metabolizing enzymes may affect drug absorption. For example, cutaneous cytochrome p450 enzymes can oxidize drugs. Overall, bioavailability is greater after transdermal delivery of agents that are subject to significant first-pass intestinal and hepatic metabolism when delivered orally.[15] Lipophilic drugs like oxybutynin are better suited for transdermal delivery because of their increased solubility and diffuseability.[5] Properties affecting absorption include the vehicle's nature and the presence of sorption promoters (accelerants or penetration enhancers). Finally, penetration is strongly influenced by the concentration gradient between the delivery device and the tissues. Most transdermal devices contain 20-fold more drug than will be absorbed during the application period.[15]

Oxybutynin transdermal delivery system (OXY-TDS, Oxytrol®; Watson Pharma Inc., Morristown, NJ) offers OAB patients a transdermal route of delivery with significant pharmacokinetic and pharmacodynamic advantages. The OXY-TDS is a matrix-type system made up of 3 layers; the middle layer contains oxybutynin and triacetin, a skin permeation enhancer. The interaction of triacetin and lipids in the skin controls the rate of oxybutynin diffusion through the stratum corneum. The 39-cm^2 patch contains 36 mg of oxybutynin and delivers approximately 3.9 mg daily. Steady-state plasma concentrations are maintained for approximately 96 hours, allowing for twice-weekly application. Advantages include improved patient adherence, enhanced pharmacokinetics, and a lower incidence of adverse events. By avoiding first-pass intestinal and hepatic metabolism, transdermal administration significantly alters the AUC (area under the curve) ratio of parent compound to its metabolites in the serum. Oxybutynin TDS dramatically reduces the amount of *N*-DEO metabolite absorbed into the systemic circulation, translating into improved tolerability, with dry mouth and constipation rates similar to placebo. Transdermal delivery of oxybutynin is associated with local

adverse skin reactions, most commonly erythema, dryness, and itchiness.[2]

Clinical trials have supported the efficacy of OXY-TDS in the treatment of OAB. In a randomized, placebo-controlled phase III trial, OXY-TDS significantly reduced the number of weekly incontinence episodes, 24-hour frequency of urination, and increased the mean voided volume.[6] Furthermore, OXY-TDS was compared with tolterodine ER in a placebo-controlled trial and exhibited equal effectiveness in reducing incontinence episodes and urinary frequency compared with tolterodine.[17]

Oxybutynin chloride topical gel (Gelnique™; Watson Pharma Inc.) recently gained FDA approval for the treatment of OAB. This formulation is a once-daily gel that is applied to the abdomen, thigh, shoulder, or upper arm. The gel formulation dries quickly, is colorless, and leaves no residue. It utilizes ethanol as a skin permeation enhancer as well as a glycerin emollient to soften skin and minimize application site dryness. The daily dose is made up of 1.14-mL volume.[5] Steady-state plasma concentrations of oxybutynin and *N*-DEO are achieved within 1 week of Gelnique application and are similar to oxybutynin transdermal delivery system plasma concentrations. Its pharmacokinetic profile is not adversely affected by sunscreen application or showering. The gel formulation further improves the metabolite-to-parent plasma concentration ratio (*N*-DEO/oxybutynin) seen with the transdermal patch formulation.

The efficacy and safety of oxybutynin gel was evaluated in a phase III, randomized, placebo-controlled, double-blind study at multiple sites in the United States. Treatment with the gel resulted in a statistically significant reduction in daily urge incontinence episodes and daily frequency as well as significant increases in voided volume compared with placebo. Dry mouth was reported in 6.9% of patients treated with Gelnique compared with 2.8% in the placebo group. Application site reactions were reported by 5.4% in the Gelnique group compared with 1.0% in the placebo group. Overall, less than 1% of patients discontinued therapy with Gelnique.[18]

The evolution of transdermal OAB therapy offers patients improved tolerability with a lower incidence of bothersome side effects and more convenient dosing. Many patients may find the option of a transdermal treatment appealing because it lacks the addition of yet another pill to their polypharmacy. Furthermore, the avoidance of first-pass metabolism and more stable plasma drug levels afford additional advantages to any transdermal formulation. Future long-term studies are needed to assess the clinical impact of the transdermal routes of OAB therapy in terms of patient compliance. The theoretical advantages offered by transdermal application should ideally impact on persistence with medical therapy.

Conclusions

The treatment of OAB syndrome has evolved over the past decade with the addition of numerous ER formulations and recent advances in transdermal application of drug delivery. In an effort to improve tolerability and maintain clinical effectiveness, pharmaceutical companies have improved upon existing OAB drug delivery with the hopes of improving long-term patient compliance with therapy. Adherence to medical therapy is a complex process affected by social, economic, condition-related, therapy-related, and patient-related factors. Nonadherence to prescribed treatment regimens in chronic conditions compromises quality of care and increases health care costs dramatically. Particular focus should be given to ineffective patient counseling by health care providers when treating OAB, thereby leading to unmet patient expectations in the initial days and weeks of therapy. Realistic goals must be set and made clear to the patient at the initiation of therapy and during subsequent adjustments in dosing or

Main Points

- The negative impact of overactive bladder on daily quality of life drives the large market of pharmacotherapy. The focus has been on less frequent dosing intervals with longer acting formulations, reduction in side-effect profile by altering pharmacokinetics of both parent compound and active metabolites, and alternative methods of drug delivery that avoid first-pass liver metabolism.
- Extended-release formulations of oxybutynin, tolterodine, trospium chloride, and other agents reduced adverse events, especially the rate of dry mouth, compared with immediate-release formulations.
- Transdermal drug delivery systems offer improved pharmacokinetics, convenient dosing schedules, and substantially lower incidence of adverse events. Modes of delivery include skin patch and topical gel.
- Many patients may find the option of transdermal treatment appealing because it lacks the addition of another pill to their polypharmacy.

switching of OAB medications. Compliance with therapy can be substantially improved with education of patients, particularly in understanding that OAB is a chronic condition.

Future long-term clinical studies are necessary to evaluate whether these drug delivery strategies ultimately influence the clinical effectiveness of OAB therapy. As urologists, we have many more options in treating our OAB patients with the ability to tailor individual therapy based on efficacy, tolerability, and patient goals. Flexible dosing strategies have proven to be beneficial in large-scale trials and should be considered when offering patients long-term therapeutic options. ■

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