Overactive Bladder: Improving the Efficacy of Anticholinergics by Dose Escalation

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Overactive bladder (OAB) affects millions of people in the United States and significantly impacts their quality of life. New antimuscarinic anticholinergic medications have improved the treatment of OAB, offering patients efficacy equal to that of immediate-release oxybutynin with fewer side effects and an improved dosing schedule. The commonly reported range of reduction of urge incontinence episodes is between 46% and 92%. Although patients are improving, continence rates are lower and many responders continue to leak significantly. The literature supports that the efficacy of anticholinergics is enhanced by dose escalation, but using higher dosages has not become routine in clinical practice. Although dose escalation can be implemented with all of the anticholinergics, it is done most easily and approved by the US Food and Drug Administration with extended-release oxybutynin. This paper critically evaluates the pros and cons of dose escalation in the hope to improve efficacy in patients with OAB.

Introduction

Overactive bladder (OAB), a medical condition with symptoms of urinary frequency, urgency, and urge incontinence, affects more than 17 million people in the United States [1]. It is well recognized that OAB has detrimental affects on quality of life and is costly to the American health care system [2] and to the individual patient. As a result of new and improved pharmacotherapies and increased community and physician awareness and education, millions more are receiving affective therapy.

Clinical practice and the literature support the efficacy of anticholinergic medications in the treatment of OAB. The reported reduction in urge incontinence episodes with the newer anticholinergics, tolterodine immediate-release (TOL-IR), tolterodine extended-release (TOL-ER), oxybutynin extended-release (OXY-ER), and oxybutynin transdermal delivery system (OXY-TDS), ranges between 46% and 92% [3–6,7••,8••]. Although most patients respond favorably to medication, smaller percentages achieve total dryness.

Clinical studies and standard practice methods suggest that a significant number of patients who are successfully managed by anticholinergic therapy could achieve further therapeutic benefit by a number of simple techniques, including dose escalation. For years, it has been recognized that the efficacy of anticholinergics is enhanced by the addition of behavioral therapy [9,10]. Similarly, the literature supports that many patients respond more favorably to higher dosages of medication, but dose escalation has not become routine in clinical practice. The improved therapeutic impact from dose escalation is especially important to realize with the newer anticholinergics, all of which have improved side-effect profiles.

This article reviews the pharmacologic treatments of OAB and critically evaluates the pros, cons, and barriers associated with dose escalation. The goal of this paper is to educate the reader regarding the potential benefits of higher dosages of anticholinergics in hope that this may translate into improved therapeutic outcomes in many of their patients.

Efficacy Data

Multiple new and effective antimuscarinic anticholinergic medications have emerged for the treatment of OAB and urge incontinence. These include TOL-IR, TOL-ER, OXY-ER, and OXY-TDS. In general, these new formulations offer patients efficacy equivalent to that of immediate-release oxybutynin (OXY-IR) with a much improved dosing schedule and side-effect profile.

The efficacy and tolerability of immediate-release tolterodine, the first drug developed specifically for the treatment of OAB, has been demonstrated in a number of placebo-controlled, randomized clinical trials. A total of 1120 patients were treated in four multicenter studies and subsequently evaluated in a pooled analysis [3]. Of the 1120 patients randomized, 121, 474, 349, and 176 patients were treated with 1 mg of TOL-IR twice daily, 2 mg of TOL-

IR twice daily, 5 mg of OXY-IR three times daily, and placebo, respectively. In three of the studies, tolterodine achieved a mean reduction in daily urge incontinence episodes of 50%, 56%, and 55%, respectfully, which was not statistically superior to placebo. When the data were pooled, tolterodine statistically reduced urge incontinence compared with placebo and it was better tolerated than oxybutynin. In another study, Chancellor *et al.* [4] evaluated 1022 patients with urge incontinence randomized to treatment with 2 mg of TOL-IR twice daily or placebo. Tolterodine reduced urge incontinence from baseline by 46% versus a 30% reduction with placebo ($P = 0.0005$). Dry mouth was the most commonly reported adverse event and occurred in 30% and 8% of the tolterodine and placebo patients, respectively.

An extended-release once-daily oral formulation of oxybutynin (OXY-ER) gained approval by the US Food and Drug Administration (FDA) and was introduced into the market in 1999. OXY-ER uses a patented, push-pull, osmotic delivery system to deliver oxybutynin at a fixed rate over 24 hours. In a prospective, randomized, double-blind, parallel-group study [5] (referred to as the OBJECT study), the efficacy and tolerability of 10 mg of OXY-ER was compared with 2 mg of TOL-IR administered twice daily. Of the 378 patients randomized, 276 women and 56 men completed the study. The reduction in weekly urge incontinence episodes in patients treated with OXY-ER and TOL-IR was 76% and 68%, respectively ($P = 0.03$). Similarly, oxybutynin was statistically more effective than tolterodine in reducing total incontinence: 75% with OXY-ER versus 66% with TOL-IR ($P = 0.02$). Both medications were equally well tolerated.

Tolterodine extended-release, a newer once-daily formulation of tolterodine, was designed to provide greater patient convenience and improved compliance compared with the twice-daily formulation. The efficacy and tolerability of 4 mg of TOL-ER administered daily was compared with 2 mg of TOL-IR twice daily in a large double-blind, multicenter, placebo-controlled study [6]; 1529 patients were randomized to treatment with TOL-ER ($n = 507$), TOL-IR ($n = 514$), or placebo ($n = 508$). The mean reduction in weekly urge incontinence episodes with TOL-ER and TOL-IR was 53% and 46%, respectively ($P > 0.05$). The median reduction in urge incontinence episodes from baseline was 71% for TOL-ER, 60% for TOL-IR, and 33% for placebo, with the OXY-ER being 18% more effective than the immediate-release formulation ($P < 0.05$). The rate of dry mouth was 23% for TOL-ER, 30% for TOL-IR, and 8% for placebo.

In a randomized, double-blind study (OPERA) [7••], the efficacy and tolerability of the extended-release formulations of oxybutynin and tolterodine were compared. Four mg of TOL-ER or 10 mg of OXY-ER were administered to 790 women with 21 to 60 urge incontinence episodes per week. The mean reduction in weekly urge and total incontinence episodes with the two drugs was statistically similar, ranging from 67% to 72%. The proportion of patients who reported total continence was 23% for those taking OXY-ER versus 16.8% with TOL-ER and this difference was statistically significant ($P = 0.03$). The reported dry mouth rate was statistically lower in patients treated with tolterodine (29.7% vs 22.3%) primarily because of a lower incidence of mild dry mouth. The incidence of moderate and severe dry mouth and the patient drop-out rate because of anticholinergic side effects were similar with both medications.

Oxybutynin transdermal delivery system was approved by the FDA for the treatment of OAB. The OXY-TDS offers several advantages over oral dosing, including twice-weekly dosing and the potential for improved patient compliance and tolerability. The transdermal delivery system avoids the extensive pre-systemic metabolism that occurs with oral administration, greatly reducing the formation of the metabolite *N*-desethyloxybutynin. It generally is thought that *N*-desethyloxybutynin is primarily responsible for the dry mouth associated with anticholinergics. In a multicenter, randomized, placebo-controlled, dose-titration study [8••] involving 520 patients, 3.9 mg of OXY-TDS significantly reduced the median number of weekly incontinence episodes by 19 (61%) versus a 14.5 (50%) reduction with placebo ($P = 0.0165$). Sixteen (13%) of the 123 patients treated with 3.9 mg achieved complete urinary continence. The incidence of dry mouth and constipation with 3.9 mg of OXY-TDS was 9.6% and 0.8%, which was equivalent to placebo.

How Good Are We Doing with Anticholinergics?

The data clearly support that the newer oral and transdermal anticholinergic formulations are effective for the treatment of OAB and achieve significant reductions in urge incontinence, but only a percentage of patients reach total dryness. Because of this, many patients are dissatisfied with treatment and the discontinuation rates in clinical practice are seemingly high. Analysis of nationwide prescription data tracking a cohort of 26,200 patients revealed that less than 15% of patients treated with immediate-and extended-release tolterodine and oxybutynin refilled their prescription at 1 year (data on file at Watson Pharma, Inc., Corona, CA). Although the reason for this is unclear from the analysis, it likely is caused by a number of factors including lack of efficacy, poor tolerability, poor patient selection, and cost. In a separate analysis, many patients expressed dissatisfaction with medical therapy. Although physicians voiced that side effects likely were the primary reason for their dissatisfaction, 29% of patients cited lack of efficacy (data on file at Ortho-McNeil Pharmaceuticals, Inc., Raritan, NJ).

Unlike the expectations we have regarding anti-incontinence surgery, OAB always has been viewed as a condition that can be helped by medication, but often is not com-

pletely controlled or cured. Most urologists recognize that anticholinergics are not the panacea and do not address all of the pathophysiologic processes involved in patients with OAB. For this reason, there has been a natural tendency by physicians to accept the patient's initial favorable response to therapy, but not to try to be more aggressive, pushing the patient closer to achieving dryness. Any degree of leakage can adversely affect quality of life and most patients would rather be as dry as possible, as long as side effects and cost were kept under control. By making more patients drier, perhaps more of them would be satisfied with treatment and continue with their therapy.

A Second Look at the Efficacy Data

When efficacy data are evaluated more closely, it is obvious that many patients who respond favorably to anticholinergics continue to report a significant number of leaking episodes. In the OBJECT study [5], the mean number of weekly urge and total incontinence episodes at baseline in both treatment groups ranged between 24.1 and 28.6 events. The mean number of urge incontinence episodes at the end of the study for patients treated with OXY-ER and TOL-IR was 6.1 and 7.8, respectively. Similarly, patients treated with OXY-ER and TOL-IR still reported 7.1 and 9.3 weekly total incontinence episodes after 3 months of therapy.

In the OPERA study [7••], patients with more severe urge or total incontinence were evaluated. The average number of weekly urge incontinence episodes decreased from 37.1 at baseline to 10.8 for the oxybutynin group and from 36.7 to 11.2 for patients treated with tolterodine. The decrease from baseline in the mean number of total incontinence episodes was statistically similar with oxybutynin (from 43.4 to 12.3) and tolterodine (from 42.4 to 13.8). For the sake of discussion, if one evenly distributes the number of residual incontinence episodes over each day of the week, patients in these two studies continue to leak an average of one-and-a-half to two times daily after 3 months of therapy. Data regarding the severity of each leaking episode are not available. Furthermore, if one excludes the patients (23% of oxybutynin and 16.8% of tolterodine) who achieved total dryness from the 3-month calculations, the mean number of weekly (and daily) leaking episodes for the patients who are still incontinent at the end of the study would increase substantially.

Greater reductions in urge and total incontinence have been reported in patients treated in dose-escalation studies with extended-release oxybutynin. In two randomized studies, the efficacy and tolerability of OXY-ER were compared with immediate-release oxybutynin (OXY-IR). In the first study [11•], 105 patients with urge or mixed incontinence (with predominantly an urge component) were randomized to receive 5 to 30 mg of OXY-ER once daily or 5 mg of OXY-IR one to four times daily. Dose titration started at 5 mg and the dose was increased every 4 to 7 days until one of three endpoints was achieved: the patient reported no urge incontinence during the final 2 days of the dosing period, the maximum tolerable dose (defined as 5 mg lower than that which resulted in significant side effects) was reached, or the maximum allowable dose (30 mg for OXY-ER and 20 mg for OXY-IR) was administered. The mean number of weekly urge incontinence episodes decreased from 27.4 to 4.8 and from 23.4 to 3.1 in patients treated with OXY-ER and OXY-IR, respectively. Total incontinence episodes decreased from baseline of 29.6 to 6 with OXY-ER and from 26.3 to 3.8 with OXY-IR. The mean percent reduction in weekly urge and total incontinence episodes with OXY-ER was 84% and 82%, respectively, which was statistically similar to the immediate-release formulation. Complete urinary continence was achieved in 41% of the OXY-ER patients and 40% of those treated with OXY-IR. Dry mouth was reported more often with immediate-release oxybutynin (87% vs 68%, $P = 0.03$).

In a second dose-titration study [12], 226 patients were randomized to receive OXY-ER or OXY-IR. All of the patients were started on 5 mg daily and the dose was increased weekly by 5 mg to a maximum of 20 mg daily or when patients reached the most favorable balance between efficacy and side effects. The mean reduction in weekly urge incontinence with OXY-ER and OXY-IR was 83% (18.6 to 2.9 episodes) and 76% (19.8 to 4.4 episodes), respectively. The mean reduction in total incontinence episodes with OXY-ER was 81% versus 75% with OXY-IR.

In both dose-escalation studies, OXY-ER achieved a > 80% reduction in urge and total incontinence episodes and a significant percentage of patients became dry. When averaged over a week, the mean number of daily incontinence episodes was reduced to approximately five to less than one accident daily. These results are superior to those achieved by the same or by other anticholinergics in other series and may be caused by a number of factors.

Some would argue that this improved efficacy was partially caused by patient selection. In both studies, all of the enrolled patients were known responders to oxybutynin or to another anticholinergic medication. Although patient selection may be a factor, similar efficacy results have been achieved with OXY-ER in a treatment-naïve population. Gleason *et al.* [13] evaluated 256 patients with urge or mixed incontinence treated with increasing dosages of OXY-ER from 5 mg once daily up to 30 mg. Seventy-two percent of the patients were naïve to anticholinergics. Patients increased the dosage weekly by 5 mg until continence was achieved for 2 days or until a satisfactory balance between continence and adverse effects was attained. The reduction in mean weekly urge and total incontinence was 83% and 81%, respectively. A subgroup analysis of the patients who received previous anticholinergic therapy did not demonstrate any differences in efficacy.

The consistent superior efficacy demonstrated in these studies with OXY-ER was primarily caused by dose escalation. Patients were asked to increase the dosage until they

Table 1. Maintenance dose chosen with dose escalation

	Anderson study	Gleason study
Dose, *mg/d*	**Percent (*n*)**	**Percent (*n*)**
5	21.7 (10)	21.0 (46)
10	13.0 (6)	30.1 (66)
15	26.1 (12)	19.6 (43)
20	8.7 (4)	12.3 (27)
> 20	30.4 (14)	16.9 (37)

Data from Anderson *et al.* [11•] and Gleason *et al.* [12].

achieved the best balance between efficacy and side effects. In the series by Gleason *et al.* [13], although clinical efficacy was seen across all of the dosages, 48.8% of the patients chose a maintenance dose higher than 10 mg (Table 1). Of the 219 patients included in the efficacy analysis, 122 (55.7%) were free of urge incontinence episodes at the end of the study. Of these 122 patients, 33 (27.0%), 39 (32.0%), 22 (18.3%), and 29 (23.8%) were on a maintenance dose of 5 mg, 10 mg, 15 mg, and > 15 mg daily, respectively. Therefore, more than 40% of patients who reported no urge incontinence episodes at the end of the study were taking more than 10 mg daily. In a study by Anderson *et al.* [11•], 46 patients treated with OXY-ER were evaluated. At the end of the study, nearly 65% of the patients titrated their OXY-ER to a maintenance dose higher than 10 mg (Table 1). Eighteen patients (41%) achieved total urinary continence. Eleven of the 18 continent patients (61.1%) were taking more than 10 mg of OXY-ER.

Dose escalation of OXY-ER similarly has been shown to be effective in patients with neurogenic bladder dysfunction. In a study by O'Leary *et al.* [14], 20 patients with multiple sclerosis were initiated on 10 mg of OXY-ER and were instructed to increase their dose bi-weekly or weekly until satisfaction was achieved or up to a maximum dose of 30 mg daily. Thirteen of 20 patients (85%) chose a final dose higher than 10 mg. Thirteen patients (65%) were taking a daily dose of at least 20 mg at the end of study. Four patients (20%) preferred to continue taking 30 mg daily. The mean number of weekly urge incontinence episodes significantly decreased from 1.2 at baseline to 0.3 episodes at the end of the study (P = 0.0046). There was no reported significant increase in side effects with increasing dosing. In a second study [15], O'Leary *et al.* repeated their dose escalation study in 10 patients with spinal cord injury. All of the patients chose a final effective dose higher than 10 mg, with four patients taking 30 mg daily. The mean number of weekly urge incontinence episodes significantly decreased from 13 at baseline to 6 after 3 months of therapy.

The efficacy of other anticholinergics also has been shown to be somewhat dose-dependent. A randomized, double-blind, placebo-controlled, multicenter study [16] of 90 patients with OAB and detrusor hyper-reflexia treated with immediate-release tolterodine demonstrated a dose-dependent effect on bladder function. Patients were randomized to receive 0.5, 1, 2, or 4 mg of TOL-IR twice daily or placebo. Linear regression analysis showed that the effect of tolterodine on volume at first contraction and on maximum cystometric capacity was significantly dose-related (P = 0.011 and P = 0.009, respectively). Similarly, there was a trend toward an improvement in the micturition diary variables and subjective assessment of symptoms with increasing doses of tolterodine. In a study by Larsson *et al.* [17], 319 patients with urge incontinence were randomized to receive placebo or 0.5, 1, 2, or 4 mg of tolterodine twice daily. After 2 weeks of treatment, there was a dose-related improvement in micturition diary variables, which reached statistical significance for frequency and average volume voided, but was not statistically significant for the number of urge incontinence episodes. The mean increase in postvoid residual urine volume in patients taking 4 mg of TOL-IR twice daily was 163 mL and four of the five patients who developed urinary retention during the study were treated with this higher dosage. Although 4 mg is the recommended daily dose for immediate- and extended-release tolterodine, many physicians anecdotally report success stories with 8 mg daily in select patients. The author recommends monitoring postvoid residual urine volume in patients effectively managed with higher dosages of tolterodine.

Improved efficacy associated with dose-escalation also has been demonstrated with OXY-TDS. In a multicenter, double-blind study [8••], 520 patients treated with OXY-TDS were randomized to 1.3, 2.6, or 3.9 mg daily. OXY-TDS 3.9 mg significantly reduced the median number of weekly incontinence episodes by 19 (61%) versus a 14.5 (50%) reduction with placebo. The reductions achieved with 1.3 and 2.6 mg of OXY-TDS were not statistically different from placebo. Because of its excellent side-effect profile, OXY-TDS may prove to be the ideal delivery system for the administration of higher dosages. A multicenter, double-blind, placebo-controlled, dose-titration study of OXY-TDS is underway evaluating its efficacy at higher dosages.

Barriers to Dose Escalation

When patients are given the option to increase the dose of their medication to achieve the best balance between efficacy and side effects, they often choose higher dosages than 5 and 10 mg of OXY-ER. In contrast, most prescriptions in the United States are for 5 or 10 mg. According to nationwide prescription data (data on file, Ortho-McNeil Pharmaceuticals, Inc., Raritan, NJ), the percentage of 5-mg, 10-mg, and 15-mg prescriptions written by health care providers are 41%, 48%, and 11%, respectively. It is estimated that only a small percentage of these patients are doubling or tripling their 10-mg tablet and taking higher dosages. The efficacy of OXY-ER, which was demonstrated in the

previous dose-escalation studies, would have been significantly impaired if patients were limited to the two lowest dosages. In the series by Gleason *et al.* [13], only 58.9% of the 122 patients who reported no urge incontinence were taking 5 or 10 mg. In the study by Anderson *et al.* [11•], of the 18 patients who were dry, only seven (38.9%) achieved dryness on 5 or 10 mg.

There appears to be a discrepancy between the doses of OXY-ER most commonly prescribed by health care providers and those, which in many patients, provide better efficacy. This discrepancy can be explained by a number of factors. Many physicians are well aware of the dose-related side effects associated with immediate-release oxybutynin and are concerned about the same phenomenon with the newer anticholinergics. In the dose-escalation study by Anderson *et al.* [11•], 87% of patients treated with OXY-IR reported dry mouth (moderate or severe dry mouth in 46% of cases) because they increased the dosages up to 20 mg. Although it is well recognized that anticholinergic side effects are dose-related with all of the anticholinergics, the detrimental effects of dose escalation appears to be much lower with the newer formulations. In the case of OXY-ER, this is caused by its patented, push-pull, osmotic delivery system, which delivers oxybutynin at a controlled rate allowing for once-daily dosing and an improved side-effect profile. Most of the compound is absorbed in the large intestine, minimizing cytochrome P450 metabolism, which primarily occurs in the liver and gut wall. This, in turn, lowers the formation of the metabolite *N*-desethyloxybutynin, which is primarily responsible for dry mouth.

Of the 46 patients in the study by Anderson *et al.* [11•] who were treated with OXY-ER, 25% reported moderate or severe dry mouth, which was statistically less than OXY-IR. The incidence of moderate or severe dry mouth in those treated with 15 and 20 mg of OXY-ER was 18% and 22%, respectively. In a study by Versi *et al.* [12], the cumulative proportion of patients taking 15 mg of OXY-ER reporting moderate or severe dry mouth was 19.4%. Although these percentages are not insignificant, the data conversely demonstrate that approximately 80% of patients treated with higher dosages of OXY-ER experienced no or only mild dry mouth. In the author's opinion, this acceptable tolerability results from the reduction in the metabolite *N*-desethyloxybutynin and from patient selection. If a patient can tolerate 10 mg of OXY-ER, the physician likely is selecting a patient who can tolerate higher dosages. In contrast, every physician has experienced those patients who cannot tolerate oxybutynin or other anticholinergics even at lower dosages. Why some patients are more sensitive to anticholinergics is unclear.

In addition to concerns regarding tolerability, there are a number of other factors that likely play a role in influencing prescribing habits. Physicians obviously prescribe the dosage of medication approved by the FDA and the dosage that is reported most commonly in the literature. In addition to this, marketing and education largely sponsored by the pharmaceutical industry also plays an influential role. In the case of OXY-ER, 5 to 30 mg is approved by the FDA, but most of the education and marketing efforts have been directed toward 5 and 10 mg of OXY-ER. The competitive OAB marketplace also has been deemed by many as a tolerability market versus one that attempts to maximize the efficacy in individual patients. This focus on tolerability and safety has obvious important merits and is further targeted with the recognition that 52% of the total prescriptions written are by primary care physicians. With the well-recognized time restraints facing most physicians, there also has been a tendency to promote a single-dose pill or patch. Although all of these factors are legitimate, a single dose of any of the anticholinergics will not maximize its efficacy in many patients.

Many well-intended physicians claim that they do not push therapy further if the patients are content with their response to treatment. Although at first glance this "if the patient is happy, I'm happy" approach appears to make perfect sense, the author does not endorse it totally. Most patients who claim they are pleased with their degree of improvement would rather be even drier or reach total dryness if presented with an opportunity to do so.

Cost obviously is an important factor when considering dose escalation. The monthly cost of 15 mg of OXY-ER is approximately 10% greater than that of the 5- and 10-mg pill and thus should not be considered as a major barrier. Higher dosages of OXY-ER (> 20 mg), OXY-TDS, and tolterodine are achieved only by doubling the medication, which obviously is more expensive. Many patients are willing to accept the higher costs if they are significantly better or reach total dryness. When analyzing the expense of medication for the treatment of OAB, it is especially important to consider the direct and indirect costs associated with incontinence [2] and the negative impact the condition has on quality of life [18,19].

Dose Flexibility

Although much has been said about dose escalation, the literature also supports that 5 mg of OXY-ER also is effective in many patients [11•,12,13]. Why some patients respond positively to low dosages of OXY-ER or to lower dosages of other anticholinergics is unknown. Treatment options for those who are sensitive to anticholinergics include 5 mg of OXY-ER and 2 mg of immediate- and extended-release tolterodine daily. Because of the excellent side-effect profile associated with OXY-TDS, it is less likely that lower dosages with this formulation will be necessary. Although some have advocated cutting the patch in half, there are no data regarding its efficacy and its adherence qualities. The integrity of the matrix transdermal delivery system is not disrupted by cutting. OXY-ER offers physicians the greatest flexibility in dosing, allowing them to tailor their treatment to each individual patient.

Conclusions

More emphasis should be placed on maximizing efficacy in patients with OAB. It is clear from the literature and from personal experience that many patients can enjoy even greater improvements in symptoms and quality of life with dose escalation. This is especially the case with OXY-ER, which offers physicians the greatest flexibility in dosing. It is important for us to set our goals high and to take a few moments to quantitate our patient's response to therapy to provide them with the best care possible.

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