# Concomitant Medications and Possible Side Effects of Antimuscarinic Agents

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*Antimuscarinic agents are the treatment of choice for overactive bladder syndrome; clinical experience and the literature support their efficacy, tolerability, and safety. The most common side effects experienced include dry mouth and constipation. Many commonly prescribed drugs have anticholinergic effects that could increase the anticholinergic "load" or "burden" in patients with overactive bladder, potentially increasing the frequency and severity of side effects. In addition, the adverse events associated with antimuscarinics may be more pronounced in the elderly, especially those taking multiple medications. Knowledge regarding the potential side effects associated with antimuscarinics is important so that patients can be advised and effectively treated.*
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Antimuscarinic agents are the treatment of choice for overactive bladder (OAB). Their efficacy, tolerability, and safety have been well established in the literature and in clinical practice. As physicians gain experience and expertise in treating OAB, they have become more aware and knowledgeable regarding the potential side effects associated with this drug class. Though dry mouth and constipation are the most frequently experienced side effects, there are less commonly reported adverse events of which physicians should be cognizant.

Not surprising, the potential for increasing side effects may be greater in select patient populations, especially the elderly and in those already taking multiple

medications. Many commonly prescribed drugs have anticholinergic effects that could increase the anticholinergic "load" or "burden" in OAB patients managed with antimuscarinic agents, thus potentially increasing the frequency and severity of side effects.

Concern regarding potential side effects associated with antimuscarinics is a barrier for some physicians aggressively managing OAB, especially in older patients. A more comprehensive understanding of the overall tolerability of this drug class and the various treatment options available may help ease physician concern and translate into improved therapeutic outcomes. This article evaluates the tolerability of antimuscarinic agents, with emphasis placed on the incidence of dry mouth and constipation, and addresses the issue of increased anticholinergic burden in OAB patients.

## Tolerability Data

### *Phase III Studies*

The side-effect profile of antimuscarinic agents has been established in their respective registration trials. The data support that the most common adverse events associated with oral antimuscarinics are dry mouth and constipation; the incidence of central nervous system (CNS) side effects is low and similar to that with placebo. Local adverse skin reactions are the most commonly reported side effect with the oxybutynin transdermal delivery system (OXY-TDS). The incidence of adverse events reported in the registration trials closely mirrors what I have observed in clinical practice.

In a large 12-week, double-blind, phase III trial of more than 1500 patients, the efficacy and tolerability of both extended-release (TOL-ER) and immediate-release tolterodine (TOL-IR) compared with placebo were evaluated.[1] The incidence of dry mouth was 23% in the TOL-ER group, 30% in the group treated with TOL-IR, and 8% with placebo. In the majority of patients experiencing dry mouth, the degree was mild to moderate, with only 1.8% of patients treated with TOL-ER reporting severe dry mouth. Other adverse events included constipation (6% with TOL-ER vs 4% with placebo), headache (6% with TOL-ER vs 4% with placebo), and abdominal pain (4% with TOL-ER vs 2% with placebo). The incidence of CNS adverse events was low in the TOL-ER group and comparable to that seen with placebo; somnolence and dizziness occurred in 3.0% and 2.0% of patients, respectively (vs placebo, 2.0% and 1.0%).

The efficacy and tolerability of solifenacin 5 and 10 mg were evaluated in 4 pivotal trials.[2-4] Two of the 4 studies evaluated solifenacin 5 mg and 10 mg, 2 studied solifenacin 10 mg; 1 also included TOL-IR 2 mg twice daily as an active treatment arm, but no statistical comparisons were performed between the active treatment arms. The most common adverse events associated with solifenacin 5 mg were dry mouth (10.9%, vs placebo 4.2%), constipation (5.4%, vs placebo 2.9%), blurred vision (3.8%, vs placebo 1.8%), and dyspepsia (1.4%, vs placebo 1.0%). The incidence of anticholinergic side effects increased with 10 mg (dry mouth 27.6%, constipation 13.4%, blurred vision 4.8%, and dyspepsia 3.9%). The incidence of treatment-emergent CNS-related events was low with both 5 and 10 mg of solifenacin and similar to that seen with placebo.

Three phase III, randomized, fixed-dose, placebo-controlled, double-blind 12-week trials evaluated the efficacy, tolerability, and safety of once-daily controlled-release darifenacin in the treatment of OAB.[5] Dry mouth and constipation were the 2 most commonly reported adverse events (Table 1). The discontinuation rates due to dry mouth and constipation

**Table 1**
**Pooled Adverse Events Reported in Fixed-Dose Phase III Trials With Darifenacin**

| | Darifenacin | | |
|---|---|---|---|
| Adverse Event* | 7.5 mg (n = 337) | 15 mg (n = 334) | Placebo (n = 388) |
| Dry mouth | 20.2 | 35.5 | 8.2 |
| Constipation | 14.8 | 21.3 | 6.2 |
| Dyspepsia | 2.7 | 8.4 | 2.6 |
| Abdominal pain | 2.4 | 3.9 | 0.5 |
| Nausea | 2.7 | 1.5 | 1.5 |
| Diarrhea | 2.1 | 0.9 | 1.8 |
| Urinary tract infection | 4.7 | 4.5 | 2.6 |
| Dizziness | 0.9 | 2.1 | 1.3 |
| Asthenia | 1.5 | 2.7 | 1.3 |
| Dry eyes | 1.5 | 2.1 | 0.5 |

Values are percentages.
* ≥ 2% for any group.
Data from Novartis Pharmaceutical Corporation (data on file); pooled studies 1001, 1002, 1041.

were less than or equal to 1.2% and similar to those with placebo. Though the incidence of constipation seems higher than that reported by other agents in independent studies, the rate of laxative usage was low, and discontinuation from study due to constipation was 0.6% (7.5 mg) and 1.2% (15 mg), versus 0.3% with placebo.

The literature supports the efficacy and safety of OXY-TDS in treating patients with OAB.[6] Transdermal delivery of oxybutynin has important metabolic and clinical implications, especially with regard to tolerability and safety. Transdermal administration essentially bypasses the presystemic hepatic and intestinal metabolism of oxybutynin, dramatically reducing the amount of N-desethyloxybutynin (N-DEO) absorbed into the systemic circulation. Lower N-DEO levels translate into improved tolerability, with dry mouth and constipation rates similar to those seen with placebo.[7] The most common treatment-related systemic adverse events experienced during the integrated phase III studies of transdermal oxybutynin include dry mouth (7.0%, vs placebo 5.3%), constipation (2.1%, vs placebo 2.0%), nausea (2.1%, vs placebo 3.3%), abnormal vision (1.2%, vs placebo 1.2%), and dysuria (1.2%, vs placebo 0.4%).[6] Somnolence and dizziness both occurred in 0.8% of patients, rates similar to those with placebo. Local adverse skin reactions are the most common side effects associated with OXY-TDS. Patients may experience skin erythema, dryness, or itchiness, but it is usually mild or moderate in severity and well tolerated.[6] Severe skin reactions such as skin blistering occur in a minority of cases.

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Two phase III, multicenter, parallel, randomized, double-blind, placebo-controlled studies evaluated the efficacy and safety of trospium chloride extended release 60 mg in treating patients with overactive bladder.[8,9] In a pooled analysis, the adverse events that occurred in at least 1.0% or more of patients, and with a higher incidence in the trospium group, were dry mouth (10.7%, vs placebo 3.7%), constipation (8.5%, vs placebo 1.5%), dyspepsia (1.2%, vs placebo 0.7%), abdominal pain (1.4%, vs placebo 0.3%), and urinary tract infection (1.2%, vs placebo 0.9%) (data on file, Indevus Pharmaceutical, Lexington, MA). The dry mouth rate experienced with trospium chloride extended release compares favorably to the 20.1% incidence reported with the twice-daily formulation. The incidence of headache and dizziness was 2.4% and 1.0%, respectively, and similar to that seen with placebo.

*Dose-Escalation Studies*

Clinical practice and the literature clearly support improved efficacy of antimuscarinic agents with dose escalation.[10] Though the incidence of adverse events increases with higher dosages, their overall tolerability is acceptable.

The solifenacin versus tolterodine multinational trial (STAR study) was a head-to-head comparative trial between solifenacin 5 or 10 mg and TOL-ER 4 mg, both taken once daily for 12 weeks.[11] After 1 month there was an option to increase the initial lowest starting dose of each medication to solifenacin 10 mg or to tolterodine 4 mg plus placebo. Approximately 50% of patients in both arms requested a dose increase. The most common treatment-emergent adverse events reported were dry mouth and constipation. The rate of dry mouth with 5 and 10 mg of solifenacin was 27.6% and 33.7%, respectively, and for constipation was 4.0% and 8.1%, respectively. The discontinuation rate due to adverse events for solifenacin 5 and 10 mg was 3.5%.

In a phase III, double-blind, randomized, placebo-controlled, parallel-group study, the efficacy and tolerability of an escalating darifenacin dosing regimen were evaluated.[12] Patients were randomized (2:1) to treatment with once-daily controlled-release darifenacin (7.5 mg or matching placebo for 12 weeks). At 2 weeks, on the basis of efficacy and tolerability, patients could voluntarily dose-adjust upward to 15 mg (or placebo pseudo-equivalent). The dry mouth and constipation rates in patients who dose-adjusted upward were 7.5% and 6.3%, respectively, with 7.5 mg and 17.5% and 20.0%, respectively, with 15.0 mg. The discontinuation rate due to adverse events was 6.7% with darifenacin and 3.1% with placebo.

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The higher but acceptable rate of adverse events associated with increasing dosages of antimuscarinics is related to a number of factors. First, antimuscarinic agents are a reasonably well-tolerated drug class, and in most cases the side effects are not severe. Second, dose escalation is generally done in patients already taking and tolerating the lower initial starting dose, and those who can likely

tolerate higher dosages are selected. Increasing side effects associated with dose escalation is an uncommon cause for discontinuation of therapy in clinical practice; more commonly the higher dosages are stopped owing to lack of efficacy. Importantly, OXY-TDS may be an ideal agent for dose escalation owing to the low incidence of anticholinergic adverse events associated with it.

*Head-to-Head Studies*

Comparing the rate of adverse events associated with different antimuscarinic agents according to independent trials is not a fair comparison for a number of reasons. Patient populations differ, as do the methods of eliciting, defining, and documenting the incidence and severity of each side effect. Unfortunately, there are only a limited number of head-to-head comparative trials in the literature.

In the STAR study,[11] the rates of dry mouth and constipation with tolterodine 4 mg were 24.1% and 2.5%, respectively, compared with rates of 30.0% and 6.4% with solifenacin 5 and 10 mg. In Overactive Bladder Performance of Extended-Release Agents (OPERA),[13] a head-to-head trial comparing the efficacy and tolerability of extended-release oxybutynin 10 mg and TOL-ER 4 mg, the incidence of dry mouth was lower with tolterodine (22.3% vs oxybutynin 29.7%), whereas constipation was more common with tolterodine. Not surprisingly, in a head-to-head, placebo-controlled trial comparing OXY-TDS with TOL-ER, the incidence of dry mouth and constipation associated with OXY-TDS was lower than that with tolterodine and equal to that with placebo.[14]

*Open-Label Studies*

Antimuscarinic agents consistently demonstrate acceptable and, in most cases, improved tolerability in open-label trials. Their lower rate of adverse events may be due to improved tolerance over time but is more likely a result of patient selection. Patients who experience side effects with antimuscarinics during 3-month, placebo-controlled trials are less likely to enter the open-label phase of the study; thus, participants are selected who can tolerate the medicine.

After completion of the pivotal, 12-week, double-blind studies, patients treated with solifenacin entered the 40-week open-label extension study and were given solifenacin 5 mg daily for 4 weeks. At weeks 16, 28, and 40 the dose could be changed (from 5 mg to 10 mg or from 10 mg to 5 mg), remain the same, or be discontinued. The rates of dry mouth and constipation with solifenacin 5 mg were 10.2% and 4.9%, respectively, compared with 17.4% and 7.9% with 10 mg.[15]

Upon completion of the 12-week, multicenter, double-blind, placebo-controlled phase III trials evaluating trospium chloride extended release, patients could participate in an open-label OAB trial and receive 60 mg trospium chloride daily for up to 9 months. In patients who were taking trospium in the placebo-controlled phase, the rates of dry mouth and constipation in the open-label study were 3.3% and 4.8%, respectively. In those patients initially taking placebo and who switched to trospium in the open-label phase, the rates were 9.3% and 7.7%, respectively (data on file, Indevus Pharmaceuticals).

*Data from Elderly Patients*

Most studies of anticholinergic agents have performed subanalyses of their efficacy and safety data in elderly patients. Though many clinicians might suspect that the incidence of adverse events is higher among older patients, the literature does not support this. Physicians should be cognizant of the elderly data because the population is so adversely affected by the condition.

The efficacy and tolerability of TOL-ER was compared in older (≥ 65 years) versus younger (< 65 years) patients in a double-blind, placebo-controlled clinical trial.[16] A total of 1015 patients (43.1% aged ≥ 65 years) were evaluated; mean age in the older and younger cohorts was 74 and 51 years, respectively. Dry mouth was the most common adverse event experienced with TOL-ER (< 65 years, 22.7%; ≥ 65 years, 24.3%). The incidence of CNS side effects, including dizziness, somnolence, and abnormal vision, was low for elderly and younger patients and was comparable to that with placebo.

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The efficacy, tolerability, and safety of darifenacin were evaluated in a subgroup analysis of elderly patients from 3 phase III, randomized, double-blind clinical trials.[17] Three hundred seventeen patients aged 65 years or older with overactive bladder received darifenacin 7.5 mg daily, 15 mg, or matching placebo. The most common treatment-related adverse events were dry mouth (7.5 mg, 20.6%; 15 mg, 30.9%; placebo, 4.5%) and constipation (7.5 mg, 18.6%; 15 mg, 23.6%; placebo, 6.4%). The incidence of CNS side effects was low and equal to that with placebo. The rate of adverse events experienced in the elderly population compared favorably with the entire patient population.

A pooled analysis of elderly patients (≥ 65 years) from 4 12-week, double-blind, phase III, randomized,

placebo-controlled trials and from a 40-week, open-label, flexible-dose extension trial was performed to evaluate the efficacy and tolerability of solifenacin 5 and 10 mg in the elderly.[18] The mean age of the subjects in the double-blind and open-label studies was 71.9 and 71.2 years, respectively. Dry mouth was reported in 13.5%, 29.7%, and 4.5% of patients treated with solifenacin 5 mg, 10 mg, and placebo, respectively; rates of dry mouth associated with solifenacin were comparable to those for the entire patient population.

Critics of the data from elderly patients contest that the study definition of elderly as age 65 years or older does not represent the "older" population in clinical practice. With the exception of the Multicenter Assessment of Transdermal Therapy in Overactive Bladder With Oxybutynin (MATRIX) study,[19] there are minimal data supporting the tolerability of antimuscarinics in even older patients, especially those with multiple medical comorbidities and taking several medications.

In the MATRIX study,[19] an open-label, prospective, randomized, multicenter study, the effects of OXY-TDS 3.9 mg/day on health-related quality of life and safety were evaluated. Of the 2877 patients studied, 699 (24%) were aged 75 years or older, and 131 were aged 85 years and older (median age, 88 years). A significant percentage of those aged 85 or more years suffered from a number of medical comorbidities, including cardiovascular (70%), musculoskeletal (59%), gastrointestinal (42%), and neurological/psychiatric diseases (21%); and 48% were taking 6 or more medications. The most commonly reported treatment-related adverse events in those aged 85 or more years were application-site erythema, pruritus, and irritation, occurring respectively in 5.3%, 4.6%, and 3.1% of patients—rates comparable to those for the entire population and significantly lower than previously reported in earlier phase III studies, presumably owing to improved skin care and education.[20] Importantly, the prevalence of treatment-related adverse events was lower among patients aged 85 or more years (22.1%) than among the overall study population (30.0%). Of the 2878 participants who received at least 1 dose of medication, CNS side effects were minimal: dizziness (0.7%), somnolence (0.3%), and confusion (0.1%).

## Anticholinergic Burden

There is increasing awareness and concern regarding the accumulation of anticholinergic "burden" or "load" associated with antimuscarinic agents as a result of taking multiple medications, leading to increased adverse events, especially in the elderly.[21] A number of pharmacologic classes contain drugs with anticholinergic effects, including antihistamines, anti-ulcer drugs, bronchodilators, cardiovascular drugs (angiotensin-converting enzyme inhibitors, anticoagulants, calcium channel blockers), muscle relaxants, and CNS medications (antidepressants, antipsychotics, benzodiazepines, and narcotic analgesics).[21] Adverse effects as a result of increased anticholinergic burden may include an increased incidence of dry mouth, constipation, blurred vision, and cognitive impairment, including sedation, confusion, and memory impairment. The morbidity associated with these adverse effects may be compounded by the possible downstream consequences of them, especially in the elderly. Dry mouth may result in poor oral intake and nutrition, dental problems, and impaired communication. Similarly, constipation may cause abdominal pain, poor nutritional status, and fecal impaction. Blurred vision may result in increased falls and fractures, and cognitive impairment could significantly affect patient performance and quality of life. Importantly, in the MATRIX trial there was no increase in anticholinergic side effects or downstream consequences noted in patients taking OXY-TDS, which reminds us again of its excellent tolerability.

## Practical Points to Minimize Adverse Events

When treating patients with OAB, care givers should be cognizant of a number of factors that can help prevent or minimize adverse events. Awareness and expectations are important; I typically tell patients that there is an approximately 5% chance that they may experience bothersome side effects, most commonly dry mouth or constipation. Patients' individual response to each agent is heterogeneous, and they may need to try 3 or 4 different agents until they find their best-tolerated drug. In addition, patients should be given the opportunity to choose the OXY-TDS because it is not associated with anticholinergic side effects.

When dry mouth and constipation occur, some simple instructions can help minimize their severity (Table 2). In addition, we provide our patients with constipation a dietary fiber information sheet. Similarly, a number of techniques have proven successful in minimizing the incidence and severity of skin adverse events associated with OXY-TDS. These include frequent patch site rotation, application to healthy and dry skin locations, and the liberal use of skin moisturizer to help maintain healthy skin.

## Conclusion

The tolerability of antimuscarinic agents is clearly documented in the literature, and the data closely reflect what is experienced in clinical practice.

### Table 2
### Recommendations to Help Minimize Bothersome Side Effects Secondary to Antimuscarinic Agents

**Dry mouth**

1. Sugar-free or regular candy/lozenges
2. Sugar-free or regular gum
3. Artificial saliva or mouthwash
4. Modest increase in fluid intake. Patients with overactive bladder should drink approximately 6 8-oz glasses of fluid daily. Attempts to control dry mouth by excessive fluid intake may worsen urinary frequency and incontinence

**Constipation**

1. Increase fluid intake to 6 8-oz glasses of fluid daily
2. Increase fluids that stimulate bowel movements, including prune/apple juice
3. Increase fiber in diet (eg, bran, bananas, oatmeal)
4. Metamucil® (Procter & Gamble, Cincinnati, OH), 1 teaspoon in the morning and evening before breakfast and dinner
5. Colace® (Roberts Pharmaceutical, Eatontown, NJ), 1 tablet 1 to 3 times daily

There is no question that dry mouth and constipation are the 2 most common side effects, which often can be eliminated or reduced by switching agents or by using simple techniques to help control the symptoms. Physicians need to be cognizant of the potential problems associated with increasing anticholinergic burden, especially in elderly patients taking multiple medications. ■

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## Main Points

- Data from phase III studies show that the most common adverse events associated with oral antimuscarinics (tolterodine, solifenacin, darifenacin, and trospium chloride) are dry mouth and constipation; the incidence of central nervous system side effects is low and similar to that with placebo. Local adverse skin reactions are the most common side effects reported with the oxybutynin transdermal delivery system.
- Clinical practice and the literature clearly support improved efficacy of antimuscarinic agents with dose escalation. Though the incidence of adverse events increases with higher dosages, their overall tolerability is acceptable.
- Antimuscarinic agents consistently demonstrate acceptable and, in most cases, improved tolerability in open-label trials. Their lower rate of adverse events may be due to improved tolerance over time but is more likely a result of patient selection.
- Most studies of anticholinergic agents have performed subanalyses of their efficacy and safety data in elderly patients. Critics of the data from elderly patients contest that the study definitions of elderly (≥ 65 years) does not represent the "older" population in clinical practice.
- Many commonly prescribed drugs have anticholinergic effects that could increase the anticholinergic "load" or "burden" in patients with overactive bladder managed with antimuscarinic agents, potentially increasing the frequency and severity of side effects, especially in the elderly.
- When dry mouth and constipation occur, some simple instructions can help minimize their severity.

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