ABSTRACT

Overactive bladder therapy options include behavioral therapy, pharmacotherapy, and surgical interventions including Botox, neuromodulation, and bladder augmentation, however, these are only appropriate for patients who have failed nonsurgical treatments. Behavioral management is safe and free of adverse effects but has limited efficacy that is highly dependent on patient compliance and cooperation. Drug therapy, primarily in the form of antimuscarinics, is effective but has bothersome side effects that can interfere with compliance and persistence. Combining the 2 modalities offers the potential to improve efficacy over what can be achieved with either modality alone. Currently, only 3 antimuscarinics are available in the United States. They have similar efficacy and side-effect profiles. New antimuscarinics in clinical development offer the promise of improved efficacy with a more favorable side-effect profile. (Adv Stud Med. 2004;4(10C):S856-S859)

Clinicians have 2 nonsurgical approaches to management of overactive bladder (OAB) and urgency, behavior modification techniques and pharmacologic therapy. Because both approaches offer potential advantages, the strategy of combined pharmacologic and behavioral therapy has evolved.

Behavioral modification techniques include timed voiding, bladder retraining drills, dietary modification, and pelvic floor exercises. They have the advantage of safety and absence of adverse effects. However, some patients are incapable of engaging these techniques due to impaired cognition or mobility. In those patients able to utilize behavior modification therapies, response tends to be delayed for 2 to 4 months, and only about 30% of patients report significant improvement. In contrast, pharmacologic therapy is fast acting and effective in a majority of patients, although bothersome side effects occur in many patients and can limit the effectiveness of therapy.1-4 Combined treatment with medication and behavioral techniques often results in a therapeutic reinforcement effect. Pharmacologically induced reductions in urgency can help improve a patient’s response to behavioral modification by providing a modicum of control as the patient strengthens the levator muscles and improves bladder capacity and interval intervals with bladder retraining drills. These additive beneficial effects are well illustrated in recent studies. The proportion of patients satisfied with therapy improved significantly when pharmacologic or behavioral treatment was added to initial monotherapy. Significant improvement was seen with combined therapy regardless of whether patients began treatment with pharmacologic or behavioral therapy.2,5

ANTIMUSCARINICS: MAINSTAY OF PHARMACOTHERAPY

Antimuscarinics, or anticholinergics, have emerged as the mainstay of pharmacologic treatment for OAB. The agents work by blocking activation of acetylcholine receptors on bladder smooth muscle cell membranes. While effective in suppressing involuntary bladder contractions and reducing pathologic urinary urgency, anticholinergics do not inhibit voluntary detrusor contractions that occur during normal micturi-
tion. The most widely used antimuscarinics are oxybutynin and tolterodine, both of which are available in immediate-release (IR) and extended-release (ER) formulations. Recently, a third antimuscarinic, trospium, has become available in the United States for treatment of OAB.6,7

Little comparative data is available in which the different antimuscarinic agents are directly compared with each other. One relevant “head to head” trial, the Overactive Bladder: Performance of Extended-Release Agents (OPERA) trial, compared the ER formulations of oxybutynin and tolterodine in approximately 800 women with OAB and urgency.8 Patients were randomized to oxybutynin ER 10 mg once daily or tolterodine IR 4 mg/day for 12 weeks. The results demonstrated no overall difference in weekly urge incontinence episodes between treatment groups. However, patients randomized to oxybutynin had a statistically significant reduction in micturition frequency compared with tolterodine (P = .003), and significantly more oxybutynin patients became totally dry according to 7 day diary (23% vs 16%, P = .03). Paradoxically, there were no statistically or clinically significant differences in urge urinary incontinence or incontinence episode frequency on analysis of last observation carried forward in the OPERA trial. The incidence of adverse events was similar between groups, but oxybutynin was associated with a statistically higher incidence of dry mouth (29.7% vs 22.3%, P = .02).

Oxybutynin has also become available in a formulation delivered by transdermal patch. The formulation represents an attempt to maintain efficacy of the medication while reducing the incidence of side effects and improving tolerability.

Though just recently approved in the United States, trospium has been used in Europe for almost 20 years. Unlike the long-acting formulations of oxybutynin and tolterodine, trospium is a twice-daily dosing formulation. The agent has demonstrated efficacy similar to that of other antimuscarinics. In a randomized placebo-controlled clinical trial, trospium reduced urgency episodes by 20% per 24-hour period, compared with 9% with placebo (P = .0001).9 Trospium is a quaternary amine secreted in large part intact to the bladder. Its quaternary structure is associated with low lipophilicity, the clinical ramifications of which include the likelihood that it may not cross the blood-brain barrier, and that bioavailability is greatly reduced by a high-fat meal. The incidence of dry mouth with trospium is reportedly similar to that of other antimuscarinic agents. Other adverse events associated with the drug are constipation, headache, abdominal pain, and diarrhea. Discontinuation because of adverse events occurred in 8.8% of trospium-treated patients as compared with 5.7% of placebo patients in recent US clinical trials.9,10

To summarize characteristics of existing pharmacologic therapy for OAB, the current available therapies for OAB have similar efficacy in controlling incontinence episodes and micturition. Tolterodine and oxybutynin achieve total dryness in 17% to 23% of patients. Trospium’s bioavailability is adversely affected by dietary fat intake. Patient compliance with all the agents is limited by tolerability. Dry mouth has been reported by 22% to 60% of patients treated with ER formulations of oxybutynin and tolterodine and with 22% of patients treated with twice-daily trospium. Some patients also are bothered by constipation during antimuscarinic therapy.

**NEW ANTIMUSCARINICS IN DEVELOPMENT**

Solifenacin and darifenacin are 2 new antimuscarinics still in clinical development. Solifenacin has demonstrated ability to improve urgency, frequency, incontinence, volume voided, and nocturia. The agent is selective for muscarinic receptors in the bladder over salivary tissue, and salivary flow has been similar to placebo during treatment, creating a potential for a lower incidence of treatment-limiting dry mouth. Darifenacin is being investigated as therapy for OAB and for irritable bowel syndrome. The agent has demonstrated ability to improve urgency, frequency, incontinence, volume voided, and nocturia. Darifenacin is highly selective for M3 receptors. The drug does not affect heart rate or heart rate variability and does not affect cognitive function at standard doses.7,11-13

In a placebo-controlled clinical trial, darifenacin 7.5 mg once daily or 15 mg once daily significantly reduced the median number of urgency episodes per 24-hour period by 2.0 episodes. The reductions translated into a difference of almost 29% from baseline for both doses. Women taking the 7.5- and 15-mg doses experienced a statistically significant reduction in weekly incontinence episodes. At 3.75 mg, a dose that will not be available with US Food and Drug Administration approval, neither urgency nor incontinence episodes were reduced to a statistically significant degree.12

Adverse events with darifenacin were consistent with what would be expected of an anticholinergic
agent. The incidence of dry mouth appeared somewhat lower with the 3.75- (13.2%) and 7.5-mg doses (18.8%) of darifenacin compared with what has been reported with other antimuscarinics, although direct comparisons are lacking. A dose-related increase in dry mouth was seen in the trial, as patients treated with 15 mg darifenacin had a 31.3% incidence of the side effect. Constipation occurred in about 14% of patients treated with the 2 higher doses. Dyspepsia occurred in 1.7% and 7.8% of patients treated with the 7.5-mg and 15-mg doses, respectively, but gastritis occurred in less than 1% of patients treated at those doses. Headache occurred in 0.9% and 3.5% of patients treated with 7.5 mg or 15 mg of darifenacin, respectively. The majority of these side effects were rated by participants as mild, and correlated with side-effect withdrawal rates that were not statistically or clinically significantly different than placebo over the course of the 12-week study, occurring in 2.6% of the 15-mg group and 1.3% of the 7.5-mg group, as compared to a 1.2% withdrawal rate in the placebo group.12

An evaluation of the impact of darifenacin on the quality of life of OAB patients using the King’s Health Questionnaire demonstrated significant improvement in several parameters versus placebo.14 Both the 7.5-mg and 15-mg doses resulted in significant improvement in incontinence impact, emotions, social limitation, role limitation, physical limitation, and severity measures compared with placebo. Personal relationships, sleep and energy, and general health also were improved more with darifenacin than placebo, but the differences did not reach statistical significance. Impact on cognitive function is a new area of clinical focus. Prior studies show a clear cognitive function impact from non-OAB anticholinergic medications and metabolites such as scopolamine in both young and mature adults.15-18 There is a dearth of data regarding overactive bladder anticholinergic medications and cognitive function. In a preliminary clinical trial, darifenacin shows no impact on cognitive function as compared to placebo in a group of subjects aged 65 and older.19 A growing body of cognitive function data is anticipated in medications used to treat OAB.

In clinical trial, solifenacin, also available in 2 different doses (5 mg and 10 mg), demonstrated significant improvement in 24-hour urgency episodes. The 5-mg dose achieved a 52% average reduction ($P < .001$), from 5.77 at baseline to 2.92, and the 10-mg dose a 55% average reduction ($P < .001$), from 5.82 at baseline to 2.75.20 In another clinical trial that included both placebo controls and IR tolterodine (2 mg twice daily) treatment groups, solifenacin 5 mg and 10 mg resulted in more than a 60% reduction in urge incontinence episodes per 24 hours, both of which were statistically significant compared with placebo. In contrast, tolterodine’s effect was not significantly different from that of placebo.11

Adverse events with solifenacin have been similar to those observed with other antimuscarinic agents. The incidence of dry mouth has appeared to be somewhat lower than what has been reported with oxybutynin, tolterodine, and trospium, although no direct comparisons have been made. The incidence of dry mouth has been especially low with the 5-mg dose of solifenacin, occurring in single-digit incidences in some trials. Withdrawal due to adverse events has been similar to placebo.

Data from one recent study showed increased improvement when patients were switched from tolterodine to solifenacin.17 After 12 weeks of treatment with IR tolterodine 2 mg twice daily, patients were switched to solifenacin and then continued on therapy for a total of 52 weeks. Following the switch to solifenacin, patients achieved further improvement over the tolterodine treatment phase with respect to voided volume, frequency, urgency, and urge incontinence. Solifenacin also has demonstrated good tolerability with long-term therapy.

In these 52-week extension trials, more than 90% of patients chose to continue extended therapy after completion of 12-week trials and more than 80% remained on therapy during extensions of up to 40

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**Darifenacin and Solifenacin: Summary**

- Have significantly better efficacy for all OAB symptoms, compared with placebo:
  - Darifenacin 7.5 mg/day and 15 mg/day
  - Solifenacin 5 mg/day and 10 mg/day
- Broad efficacy profile: Urgency episodes, incontinence episodes, micturition frequency, volume voided per micturition, and nocturia
  - $>50\%$ of incontinent patients became “dry” on solifenacin
- Dry mouth incidence at effective dosages:
  - Darifenacin: 18.8% to 31.3%
  - Solifenacin: 7.4% to 23.1%

OAB = overactive bladder.

Data from Chapple et al11; Haab et al12; Cardozo.13
weeks. During treatment for up to a year, more than 90% of patients reported satisfaction with the therapy. When patients chose to increase their solifenacin dose, symptoms improved to a greater extent with no evidence of a decrease in tolerability.21

In summary, both solifenacin and darifenacin significantly improve OAB symptoms compared with placebo, and solifenacin demonstrated superiority in reduction of urge incontinence episodes as compared with tolterodine. The improvement has been demonstrated for darifenacin 7.5 mg and 15 mg and for solifenacin 5 mg and 10 mg (see Sidebar).11,12,22

**SUMMARY**

Behavior modification and pharmacotherapy both have a role in the management of OAB. Combination therapy may potentiate the effects of individual interventions and result in greater efficacy. Antimuscarinic agents remain the mainstay of pharmacologic therapy for OAB, and all available antimuscarinic agents have been shown to be clinically effective. However, currently available agents cause side effects that limit efficacy in some cases. Newer agents in development offer comparable efficacy and the potential for fewer treatment-limiting side effects.

**REFERENCES**