Preview of New Drugs for Overactive Bladder and Incontinence: Darifenacin, Solifenacin, Trospium, and Duloxetine

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This year, the US Food and Drug Administration will approve four new drugs indicated for the treatment of lower urinary tract dysfunction. Darifenacin, solifenacin, and trospium are antimuscarinic agents aimed at relieving the symptoms of overactive bladder and urge incontinence in men and women. Duloxetine will be the first drug approved for the treatment of female stress urinary incontinence. This article presents current data on the efficacy and tolerability of these new agents and invites the reader to decide whether they offer any potential advantages over existing therapies.

Introduction

This year will bring the approval of four new drugs designed for the treatment of urinary incontinence by the US Food and Drug Administration (FDA). Three of these drugs, darifenacin, solifenacin, and trospium, will be marketed for the treatment of the overactive bladder (OAB) and urge incontinence. The fourth, duloxetine, will be the first FDA-approved drug indicated for the treatment of female stress urinary incontinence (SUI). Such an onslaught of new agents developed for the treatment of vesico-urethral dysfunction is unprecedented. There are several compelling reasons why the pharmaceutic industry is investing so much money, time, and effort into producing, testing, and marketing these drugs at the present date. First, currently available agents, although effective, are by no means a panacea and their clinical benefits are beset by limited bladder selectivity and resultant peripheral side effects, hampering tolerability. Second, the known overall prevalence of OAB and incontinence is enormous, with OAB affecting upward of 17 million people in the United States and many millions more in Europe, and with SUI affecting up to 35% of the adult female population [1,2]. Third, this is a huge business, with $1 billion being spent on drugs for OAB alone in 2002. Because many people do not seek therapy secondary to ignorance of effective treatments or fear of invasive surgery, these numbers can only be expected to increase over time with the promotion of newly available oral agents. Direct-to-consumer marketing already has proven effective in bringing patients to the physician's office and requesting specific medication. The question remains whether these new drugs will improve on the currently available armamentarium of agents. It is hoped that the data presented in this discourse will allow the readers to draw their own conclusions in this regard.

Overactive Bladder: The Ideal Agent

Overactive bladder as defined by the International Continence Society is a symptom complex of urinary urgency with or without urge incontinence, usually with frequency and nocturia for which a pathologic or metabolic cause has not been identified [3]. Although increased bladder sensation and other factors may contribute to this syndrome, the most common cause of OAB is detrusor overactivity (involuntary detrusor contractions during bladder filling) [3]. Because detrusor contraction is mediated by the binding of acetylcholine to muscarinic receptors at the neuromuscular junction, antimuscarinic agents have become the mainstay of therapy for OAB. Although there are five known muscarinic receptor subtypes, the M3 receptor appears to be of singular importance in mediating detrusor contraction in humans [4]. The M2 receptor also may be critical in mediating detrusor contraction under certain pathologic conditions. Notwithstanding the fact that the ideal agent for treating OAB would treat increased bladder sensation and overactive detrusor function, this article discusses what the ideal antimuscarinic agent should look like because these agents are, and will be for the foreseeable future, the foundation of available therapy.

The primary aim of antimuscarinic therapy for the treatment of OAB is to relieve symptoms by the suppression of involuntary bladder contractions. The ideal agent would achieve this without inhibiting volitional bladder-emptying function. In addition, this agent would be 100%

bladder selective and ignorant of the muscarinic receptors of other organ systems. High bladder selectivity would preclude the common side effects of dry mouth, constipation, and headache associated with currently available agents. This agent should be easy to administer and be lacking in significant drug-drug interactions. Whether this agent should be highly selective for the bladder M3 receptor or whether it interacts with M2 receptors and possibly M1 receptors (present in bladder prejunctional cholinergic nerve terminals) remains to be definitively established.

New Drugs for Overactive Bladder

Darifenacin hydrobromide

Darifenacin's novelty among the antimuscarinics is its selectivity for the M3 muscarinic receptor [5,6]. It is the first M3 selective agent ever to reach clinical trials and will be the first approved for the treatment of OAB. At initial glance, it seems obvious that a selective M3 antagonist may be advantageous in treating OAB, maximizing therapeutic efficacy while minimizing the potential adverse effects of nonselective blockade. As previously mentioned, the M3 receptor has been shown to be of individual prime importance in mediating detrusor contractility in OAB [7,8]. However, the key factor for success of such an agent is whether it will retain bladder selectivity, because M3 receptors are densely present in the salivary glands and intestinal tract [9,10]. Although laboratory evidence has suggested that darifenacin is more highly selective for the bladder over the salivary gland, the clinical significance of this in terms of limiting xerostomia has not been proven [11,12]. Another question is whether selective M3 blockade will prove advantageous in terms of overall drug efficacy. Although controversial, there is evidence to suggest that the M2 receptor, more populous in the detrusor muscle than M3, may play a major role in mediating detrusor contraction during pathologic states, such as diabetes and neurologic injury [13–17]. A highly selective agent such as darifenacin theoretically could be less effective under certain conditions [18].

Darifenacin is to be marketed in once-daily doses of 7.5 or 15 mg formulated in a controlled-release system. It is extensively metabolized in the liver by the cytochrome P450 system. The hydroxylated metabolite has a negligible effect on salivary flow relative to the parent compound [19]. Steady state is achieved in plasma by 6 days with once-daily dosing. Pharmacokinetics are not affected by the coadministration of food so it may be administered without regard to meals.

Clinical Data

Initial clinical studies on darifenacin were carried out by Rosario *et al.* [20,21] on a small group of patients with symptoms of OAB and detrusor overactivity. In these short-term, placebo-controlled studies, the authors were able to demonstrate that darifenacin, in daily doses of 5 and 10 mg is effective in reducing OAB symptoms. Observed symptomatic improvement correlated with a reduction in detrusor overactivity on ambulatory urodynamic testing. In a small, randomized, double-blind crossover study, Mundy *et al.* [22] went on to demonstrate that darifenacin had equivalent efficacy to immediate-release oxybutynin in reducing detrusor overactivity with less effect on salivary flow.

Chapple *et al.* [23•] recently reported the results of pooled data from three large, multicenter, double-blind, placebo-controlled studies assessing efficacy, safety, and tolerability of darifenacin. All of the enrolled patients (n = 1049) suffered from OAB for a minimum of 6 months. After a 2-week washout phase followed by a 2-week placebo run-in, patients were randomized to receive once-daily darifenacin 7.5 mg, 15 mg, or placebo for 12 weeks. Results were expressed as median and percent change from baseline to week 12. The primary efficacy variable was incontinence episodes/week and darifenacin at the 7.5- and 15-mg doses showed statistically significant decreases in this variable relative to placebo (percent median reduction, 68.4%, 76.8%, 53.8%, and 58.3% for the 7.5-, 15-mg doses of darifenacin and the two placebo arms, respectively). When the authors looked at the number of patients achieving a 50% or greater reduction in incontinence episodes per week, both doses of the drug demonstrated statistically significant efficacy (66% and 70% of patients receiving the 7.5- and 15-mg dose, respectively [$P <$ 0.001]). Either dose of darifenacin resulted in significant improvement in all of the measured secondary outcome parameters including frequency, voided volume, urgency, urge severity, and the weekly number of severe incontinence episodes requiring a pad or clothing change. Darifenacin appeared to be more effective at 15 rather than 7.5 mg, but resulted in more side effects. Dry mouth occurred in 20% and 35% of the patients taking 7.5 and 15 mg, respectively, versus 8% for placebo. Rates of constipation were significant and occurred in 15% and 21% of patients taking the 7.5- and 15-mg doses, respectively, versus 6% for placebo. Despite this, most patients completed the study. Central nervous system (CNS) and cardiovascular adverse events were similar to placebo.

Khullar [24] reported on the efficacy of darifenacin in reducing nocturia, a component of OAB that often is difficult to treat. In this multicenter, double-blind, placebo-controlled study, 439 patients were randomized to darifenacin 7.5 mg, 15 mg, or placebo for a period of 12 weeks. Data from 317 patients were included in the final analysis, which demonstrated a significant reduction in the median number of nocturnal awakenings in patients on either dose of darifenacin relative to placebo (median percent change from baseline was -22.1%, -22.7%, and -3.6% for darifenacin 7.5 mg, 15 mg, and placebo, respectively). However, if one looks at the maximal median decrease in nocturnal awakenings per week, this was only two at best; therefore, the overall clinical value of this finding is debat-

able. This study also confirmed the efficacy of darifenacin in reducing weekly incontinence episodes (68.7% reduction at 7.5 mg and 76.5% reduction at 15 mg) compared with placebo (46% reduction).

In another recently published 12-week, multicenter, double-blind, placebo-controlled study of 561 patients, darifenacin was shown to have a rapid onset of clinical efficacy, apparent by 2 weeks after administration [25]. At 12 weeks, there was a statistically significant reduction in weekly incontinence episodes by 67.7% and 72.8% of patients on darifenacin 7.5 mg and 15 mg, respectively, compared with 55.9% of patients taking placebo. Both darifenacin doses resulted in significant improvements in the secondary parameters of frequency, voided volume, frequency and severity of urgency, and number of severe incontinence episodes relative to placebo. In contrast to the reported results of Khullar [24], there was no significant improvement in nocturia observed in patients taking darifenacin.

Solifenacin succinate

Solifenacin is a new, non-selective muscarinic antagonist, demonstrated to bind to M1, M2, and M3 receptor subtypes [26]. Similar to tolterodine and darifenacin, solifenacin has been shown to have higher in vitro affinity for the bladder than the salivary gland [27]. Animal studies have suggested that it has the highest degree of bladder selectivity in vitro and in vivo compared with tolterodine, oxybutynin, and darifenacin [28,29]. Pharmacokinetic studies have revealed it to have a long half-life (50 hours). Phase-1 trials demonstrated solifenacin to be safe and well tolerated at daily doses of 5 to 10 mg [30]. Phase-2 trials of patients with OAB demonstrated maximal drug efficacy at doses of 10 mg in reducing urinary frequency and urge incontinence. Higher doses failed to improve efficacy, but significantly limited tolerability [31].

In a 4-week multicenter, placebo-controlled trial of 225 patients, the 5- and 10-mg doses produced statistically significant ($P < 0.05$) improvements in urinary frequency (18% and 21% reduction, respectively) and mean voided volume (28% and 35% increase, respectively). There also was a trend toward reduction of daily urge incontinence episodes in patients receiving solifenacin, but this did not reach statistical significance. The medication demonstrated a rapid onset of clinical action with patients gaining the most benefit by 2 weeks. Dry mouth was the most commonly reported adverse event (14% for either dose) followed by constipation.

Chapple [32•] reported the results of a phase-3a randomized, double-blind, placebo- and tolterodine-controlled trial of 1033 patients with OAB. This study was unique in that it was the first phase-3 study to evaluate urgency as a primary efficacy variable in patients with OAB. Patients were randomized to receive 12 weeks of solifenacin at 5 or 10 mg, immediate-release tolterodine, or placebo. Outcomes were assessed by measuring the change from baseline in mean number of urgency episodes, urge incontinence and total incontinence episodes, voids per 24 hours, and voided volume. Patients who received 5 or 10 mg of solifenacin experienced equivalent statistically significant reductions in daily urgency episodes relative to placebo (5 mg, -2.85[-52%]; 10mg, -3.07 [-55%]). They also saw significant reductions in daily urge incontinence episodes (5 mg, -1.41[-65%]; 10 mg, -1.36 [-63%]) and total incontinence episodes. Solifenacin at 10 mg resulted in the greatest significant reduction in mean daily voids (-2.61 [-20%]) followed by the 5-mg dose (-2.19 [17%]) and tolterodine (-1.88 [-15%]). Mean volume voided also significantly increased with either dose of solifenacin relative to placebo (5 mg, +32.9 mL [+25%]; 10 mg, +39.2 mL [+29%]). Solifenacin was well tolerated in this study with equivalent drug discontinuation rates to placebo. The major adverse event with the use of solifenacin was dry mouth, which occurred in 14% of the patients taking 5 mg and 21.3% of patients taking 10 mg. This was comparable with the 18.6% incidence in patients taking immediate-release tolterodine. The authors reported that most of the patients (80%) taking the 5-mg dose who experienced dry mouth described it as mild. Constipation occurred in 7.2% and 7.8% of patients treated with solifenacin 5 and 10 mg, respectively, compared with only 2.6% of patients on immediate-release tolterodine. Blurred vision occurred in 3.6% and 5.6% of patients on 5 and 10 mg of solifenacin, respectively, compared with 2.6% of patients receiving placebo.

Gittelman *et al.* [33] reported on the results of two phase-3, randomized, double-blind, placebo-controlled studies of solifenacin 10 mg daily in 1208 patients with OAB. The results paralleled the previously mentioned data and demonstrated the 10-mg dose to be statistically significantly superior to placebo in improving urinary frequency, urgency, and urge incontinence while increasing voided volume. In this study, solifenacin was twice as effective as placebo in reducing daily micturitions (-2.7 vs -1.4; $P < 0.001$) while increasing mean voided volume by 46.8 mL (relative to 7.7 mL for placebo; $P < 0.001$).

Kaufman *et al.* [34] evaluated the data from this same cohort of patients to determine the ability of solifenacin to result in total continence. Of the initial cohort, 475 of the patients assigned to placebo and 455 assigned to active drug had incontinence at baseline. Fifty-three percent of the patients taking 10 mg of solifenacin became continent by the end of the study versus 31% of patients receiving placebo ($P < 0.001$). Eighty-two percent of the patients on active drug experienced at least a 50% reduction in incontinence episodes relative to 57% of those receiving placebo ($P < 0.001$).

Trospium chloride

Trospium chloride (TCl) was approved by the FDA for the treatment of OAB in June 2004. It is unique among the new antimuscarinic agents in several ways. It has been

available in Europe for more than 20 years and during this time, it has been demonstrated to be safe and effective for the treatment of OAB and detrusor overactivity. More than 10,000 patients have participated in postmarketing surveillance studies, demonstrating improvement in micturition patterns, urinary incontinence, and quality of life [35]. Trospium has the least selectivity and the highest overall affinity to all of the muscarinic receptor subtypes relative to other agents used for OAB. Its chemical structure as a positively charged quaternary amine is distinct from the available and upcoming agents, which are negatively charged tertiary amines. The positive charge and hydrophilic chemistry of trospium prevent it from crossing the blood-brain barrier and slow its absorption from the gastrointestinal tract. Trospium is dosed at 20 mg twice daily. Maximal plasma levels occur 5 hours after oral administration. The half-life of TCl is longer than the currently available agents at 12 to 18 hours (compared with 13.2 hours for extended-release oxybutynin and 8.4 hours for tolterodine) [36•,37]. The drug is minimally metabolized by the cytochrome P450 system and more than 80% of the active compound is excreted unchanged in the urine as TCl [1,35]. Trospium has been shown to be rapidly effective, reducing urinary frequency and urge incontinence within 3 to 7 days after administration [38].

European Data

Since its introduction in the 1980s, a number of clinical trials and postmarketing surveillance studies have examined the role of TCl in the treatment of detrusor overactivity. In one European placebo-controlled, randomized, double-blind trial, 208 patients (between the ages of 18 and 70 years) with detrusor overactivity were randomized to receive placebo or TCl (20 mg twice daily) for 3 weeks. Trospium resulted in significant improvements in maximum cystometric bladder capacity (+22 mL vs +10 mL for placebo) and volume at first unstable contraction (+45 mL vs +2 mL for placebo). Patients' assessment of efficacy showed greater clinical improvement in the TCl group than the placebo group. Similar rates of adverse events were seen in both groups (68% for TCl and 62% for placebo), with dry mouth being the most frequently reported event (41% for TCl and 17% for placebo). No CNS side effects occurred in patients in the TCl group [39]. These findings were consistent with an earlier randomized, placebo-controlled, double-blind urodynamic study on the efficacy of TCl (20 mg twice daily for 3 weeks) in the treatment of detrusor overactivity. Patients receiving TCl demonstrated an increase in maximum bladder capacity by 79 mL (no difference for placebo). Volume of the first unstable contraction increased by nearly 100 mL for the TCl group versus 40 mL for the placebo group. Again, similar rates of adverse events and discontinuation were observed in both groups [40].

Trospium chloride also has been tested in the treatment of neurogenic detrusor overactivity. In a multicenter, placebo-controlled trial of 61 patients with spinal cord injuries and detrusor overactivity, patients who received 20 mg of TCl twice daily for 3 weeks saw significant improvements in mean maximum cystometric capacity (+138 mL), maximum detrusor pressure (-38 cm H_20), and compliance (+12 mL/cm H_20) relative to placebo [41]. Madersbacher *et al.* [42] compared the effects of TCl versus immediate-release oxybutynin in 95 patients with spinal cord injuries and neurogenic detrusor overactivity. After 2 weeks of therapy (TCl 20 mg twice daily or oxybutynin 5 mg three times daily), although both drugs resulted in statistically significant improvement in maximum bladder capacity, maximum voiding detrusor pressure, and compliance, the TCl group reported fewer adverse events, especially severe dry mouth (4% vs 23%) compared with the immediate-release oxybutynin group [42].

Long-term efficacy and tolerability of TCl has been demonstrated in several studies. Halaska *et al.* [43] reported the results of a trial of 358 patients with OAB randomized to 20 mg of TCl twice daily versus immediate-release oxybutynin 5 mg twice daily over 52 weeks. The two drugs, proven to be equally effective, showing no statistically significant differences in the resulting increases in maximum cystometric bladder capacity (+115 mL in TCl and +119 mL in IR oxybutynin), volume at first uninhibited contraction (+46 mL in TCL and +37 in immediate-release oxybutynin), or volume at first sensation to void (+79 mL in TCl and +70 mL in immediate-release oxybutynin). Both groups also experienced similar reductions in micturition frequency, frequency of incontinence episodes, and episodes of urgency. However, drug-related adverse event rates were higher in the immediate-release oxybutynin group (59% vs 48%), with dry mouth predominating (50% vs 33%). The authors found that immediate-release oxybutynin increased the risk of dry mouth by a factor of 2.3 relative to TCl. In this study, constipation was more common in the TCl group relative to the immediate-release oxybutynin group (7% vs 4%). After 1 year of treatment, TCl was considered to have very good tolerability by 63% of patients (compared with 42% of patients taking immediate-release oxybutynin). These results are comparable with a similar study by Hofner *et al.* [44] who also demonstrated a lower percentage of adverse events at 1 year in patients taking TCl versus immediate-release oxybutynin (47.9% vs 58.9%).

United States Data

Zinner *et al.* [45] recently reported the results of a US phase-3 FDA trial of TCl for the treatment of OAB. This multicenter, randomized, double-blind, placebo-controlled trial enrolled a total of 521 patients. Patients who received TCl (20 mg twice daily) saw clinical benefit as early as 1 week after initiation of treatment. Statistically

significant improvements in urinary frequency, patient perception of urge severity, and urge incontinence episodes were seen in the TCl group relative to placebo, which continued through the duration of the study (12 weeks). By the end of the study, patients receiving TCl saw a 60% improvement in daily incontinence episodes relative to a 44% improvement with placebo. Seventy-one percent of the patients taking TCl had at least a 50% reduction in daily incontinence episodes compared with 54% of patients taking placebo, with twice as many becoming completely dry relative to placebo (21% vs 11%). TCl demonstrated statistically significant superiority to placebo in improving average volume voided, the frequency and severity of urgency, and the frequency of diurnal and nocturnal voids. Although total Incontinence Impact Questionnaire scores were significantly improved in the female patients only, a subgroup analysis revealed that there was no significant difference in drug effectiveness with respect to gender.

In terms of adverse events, TCl demonstrated a 22% incidence of dry mouth (vs 6.5% with placebo) and a 10% incidence of constipation (vs 4% with placebo). These tended to occur early and resolved with continued treatment. CNS-related side effects were equivalent to placebo. The overall drug discontinuation rate was equivalent to placebo (16.4%).

Objective urodynamic data and subjective quality-of-life reports have confirmed the efficacy of TCl in treating OAB. In addition, comparative studies have shown TCl to be equally efficacious in the treatment of OAB as other antimuscarinic agents. TCl appears to have some minor advantages with regard to its rapid onset of action (1 week; which may allow nonresponders to move onto other treatment modalities more rapidly) and low incidence of CNS adverse events relative to other agents. CNS effects are thought to be averted by TCl through its quaternary amine structure, which prevents it from crossing the blood-brain barrier. This may make TCl better tolerated by elderly patients who are more susceptible to CNS side effects. Todorova *et al.* [46] compared the effects of tolterodine, TCl, and oxybutynin versus placebo on electroencephalogram parameters and found TCl to have an effect comparable with placebo (Detrol [Pfizer, New York, NY], a tertiary amine, had equivalently minor CNS effects). TCl's quaternary structure also avoids metabolism by the cytochrome P-450 system, limiting drug-drug interactions. TCl does not appear to provide any particular advantage over available agents in terms of gastrointestinal side effects including xerostomia [46]. A potential disadvantage of TCL is its twice-daily dosing schedule. Patient compliance with drug treatment often correlates with ease of use and once-daily agents will have a selective advantage in certain patients to whom this appeals.

Duloxetine

Upon its final FDA approval, duloxetine is set to become the first drug indicated for the treatment of female SUI in the United States. Short of sporadically effective behavioral therapy, patients with pelvic floor muscle training and biofeedback have had to rely on effective surgical therapy for SUI cure. This has hampered some patients from seeking therapy because of fear of undergoing invasive surgery or ineligibility as a result of medical comorbidities. Although oral agents such as tricyclic antidepressants, estrogens, and adrenergic agonists have been used off-label for the treatment of SUI, such agents have had limited efficacy and substantial side effects, precluding their widespread use and acceptance. If effective, duloxetine potentially could revolutionize the way women are treated for SUI, much like the way Viagra (Pfizer, New York, NY) revolutionized the treatment of male erectile dysfunction.

Duloxetine functions as a balanced dual reuptake inhibitor of the neurotransmitters serotonin (5-HT) and norepinephrine. Both of these neurotransmitters have been shown to be involved in the neural control of vesicourethral function in animal models [47,48]. Onuf's nucleus, located in the lateral border of the ventral horn of the sacral spinal cord, is centrally involved in the somatic regulation of muscular tone at the striated urethral sphincter (rhabdosphincter) through the pudendal nerve. It is densely innervated with noradrenergic and serotonergic nerve terminals [49]. α-1 adrenoceptors and 5-HT receptors in these terminals play a role in activating the urine storage reflex by facilitating rhabdosphincter contraction, thereby increasing urethral closure pressure. Duloxetine, by preventing reuptake of 5-HT and norepinephrine, results in increased pudendal nerve stimulation and increased tone at the striated rhabdosphincter [50]. In effect, this should help increase urethral resistance to leakage during periods of urine storage, reducing SUI.

Phase-I studies have demonstrated that duloxetine is safe and tolerable in healthy subjects [51,52]. Norton *et al.* [53•] conducted the first placebo-controlled, randomized efficacy trial in the United States involving 553 women (between the ages of 18 and 65 years) with SUI. To be included, patients needed to have had SUI for at least 3 months (≥ four weekly stress incontinent episodes), normal bladder capacity (tolerating 400-mL saline infusion), objective evidence of SUI on a cough stress test and stress pad test, and no previous anti-incontinence surgery. Of the 553 women enrolled, 86 underwent urodynamic testing and of these, 92% were found to have urodynamic evidence of SUI, which indicated accurate patient enrollment. Because this phase-2 study was interested in determining the optimal dosage of duloxetine, subjects were randomized to 12 weeks of treatment with placebo or duloxetine at twice-daily divided doses of 20, 40, or 80 mg. Treatment efficacy was assessed by measurement of patient-recorded incontinence episode frequency (IEF), Patient Global Impression of Improvement scale (PGI-I), and Incontinence Quality-of-Life (I-QOL) questionnaires. The authors found that duloxetine resulted in significant dose-dependent decreases in IEF with corresponding improvements

observed in PGI-I and I-QOL scores. The median decrease of IEF with placebo was 41% compared with 54%, 59%, and 64% for duloxetine 20, 40, and 80 mg, respectively, daily. Dose-dependent adverse events and discontinuation rates also were observed. Nausea was the most common adverse event, occurring in 13% of the patients taking duloxetine at 80 mg daily. However, it led to drug discontinuation in only one third of the patients who suffered from it. Overall discontinuation rates caused by adverse events were 5% for the placebo group and 9% to 15% for the duloxetine groups corresponding to dose.

Confirmatory results were seen in a phase-3, double-blind, randomized, placebo-controlled study of 683 North American women (between the ages of 22 and 84 years) with SUI [54]. This study had similar inclusion criteria to that of the study by Norton *et al*. [53•], except that patients were required to have seven or more SUI episodes weekly, could be older than 65 years of age, and may have undergone prior anti-incontinence surgery. Women were randomized to receive placebo or duloxetine 40 mg twice daily (80 mg/d) for 12 weeks. At the completion of the study, patients on duloxetine had a median absolute decrease in IEF of seven episodes per week, compared with a decrease of three episodes per week for patients taking placebo ($P < 0.001$). Fifty-one percent of the patients taking duloxetine experienced at least a 50% decrease in IEF compared with 34% of those on placebo. Duloxetine also was associated with significant improvements in I-QOL scores (+11 vs +6.8 with placebo), PGI-I scores, and prolongation of the voiding interval compared with placebo (+20 vs +2 minutes). Patients with more severe incontinence (≥ 14 incontinent episodes/week) were equally responsive to treatment. Significant treatment effect was seen by 4 weeks after randomization (the first assessment visit). Nausea again was the most common side effect, occurring in 22.7% of patients receiving duloxetine (compared with 2.1% of those receiving placebo) and accounted for 6.4% of drug discontinuation. Overall drug discontinuation rate was significantly higher for the duloxetine group than the placebo group (24.1% vs 4.1%). Only 69% of the patients who received duloxetine completed the trial compared with 87% of patients on placebo, likely because of adverse events. Only 10.5% of the patients receiving duloxetine reported complete cure (no incontinence episodes).

Two other concurrent phase-3 trials outside of the United States have revealed similar results to the US trial. In a study of 494 European and Canadian women, 52% of women taking 40 mg of duloxetine twice daily demonstrated at least a 50% reduction in IEF compared with 34% of those taking placebo. Discontinuation rates again were higher in the duloxetine group (22% vs 5%), with nausea being the major reason for discontinuation [55]. In a phase-3, randomized study of 458 women on four continents, duloxetine resulted in significant decreases in IEF (59% of those in the duloxetine group had at least a 50% decrease), improvements in quality-of-life scores, and a 17% discontinuation rate, with nausea again being the most common cause (3.1%) [56].

A more recent study compared the effects of duloxetine alone, pelvic floor exercise, or combined therapy in 201 women (between the ages of 18 and 75 years) with symptoms of SUI. After 12 weeks, duloxetine appeared superior to pelvic floor exercise alone in reducing IEF (57 vs 35 median percent decrease). Although combined therapy appeared to be no more effective than duloxetine alone in reducing IEF, patients who received combined therapy used fewer pads and were more satisfied, demonstrating a greater improvement in I-QOL scores [57].

Review of the above data suggests that duloxetine results in improvement of objective symptoms and quality of life in approximately 50% of the SUI patients who take it. Lacking from any of the aforementioned clinical trials was categorization of the type of SUI (intrinsic sphincter deficiency, urethral hypermobility, mixed) in the patients who were observed. It has been suggested that duloxetine efficacy may depend on adequate intact peripheral nervous innervation to a functional rhabdosphincter. Both of these components are known to be predisposed to damage, with prolonged vaginal labor and age-dependent atrophy. Additional clinical studies with more rigorous inclusion criteria, such as video urodynamic testing and previous birth history, perhaps can explain the 50% success rate and further pin-point the optimal target patient population.

Duloxetine-associated nausea commonly was observed and responsible for most of the discontinuation from these short-term clinical studies. If nausea is to occur, it occurs in 91% of patients by 4 weeks and in most patients within the first 2 days [54]. Although nausea is mostly transient (resolves by 1 month in 81% of patients) and tolerable (mild to moderate in 87% of patients), long-term safety data are not available. Other side effects included dry mouth (12%), fatigue (15%), insomnia (14%), constipation (10%), and somnolence (9%). Duloxetine appears to have negligible effects on the cardiovascular system. A 1-year safety study of duloxetine (40 mg twice daily) did not demonstrate any changes in blood pressure, heart rate, or electrocardiogram intervals [58].

As a dual reuptake inhibitor of 5-HT and norepinephrine, duloxetine is efficacious for the treatment of major depressive disorder [59]. FDA approval is pending for this indication and will be marketed by Eli Lilly (Indianapolis, IN) under the name Cymbalta at doses of 60 to 120 mg daily. The psychologic effect of duloxetine in non-depressed SUI patients is poorly understood. Recently, the suicide death of a 19-year-old woman led to the termination of a four-continent safety trial of duloxetine. She was identified as a healthy subject without depression at the pretrial screening. At the time of her death, the patient was taking placebo rather than duloxetine during a washout period. Although there is no reported antidepressant effect of duloxetine at the recommended dosage for SUI, this suicide should raise awareness about the dual indications for this

Table 1. Properties of available and upcoming antimuscarinic agents

	Oxybutynin	Tolterodine	Darifenacin	Solifenacin	Trospium
Muscarinic receptor selective? [36•]	M3 > M2	M3 > M2	M3 >> M2	M3 > M2	M3 = M2
Structure	Tertiary amine	Tertiary amine	Tertiary amine	Tertiary amine	Quaternary amine
Dosing interval (hours)	8(IR), 24(ER), 72–96(TDS)	12(IR), 24(LA)	24	24	12
Hapatic metabolism?	Yes	Yes	Yes	Yes	Minimal
Active metabolite	Yes	Yes	No	Unknown	No

Table 2. Efficacy of available and upcoming antimuscarinic agents

	ER Oxybutynin	Tolterodine LA	Darifenacin (15 mg qd)	Solifenacin (10 mg qd)	Trospium (20 mg bid)
% Mean reduction in frequency	-30% [61]	-22% to -25% [61,63]	-17% [32•]	-20% [23•]	-18% [45]
% Mean reduction in IEF/week	-75%, 82% [61,62]	-46% to -65% [61,63]	-77% [32•]	-63% [23•]	-60% (IEF/24 h) [45]
% Mean increases in voided volume, mL	31% [62]	24% [63]	18% [32•]	29% [23•]	21% [45]
% Mean reduction in nocturia/week	N/A	N/A	-23% [24]	N/A	-22% [45]
Dry	23% to 41% [62,60]	17% [60]	N/A	53% [34]	21% [45]

bid—twice daily; IEF—incontinence episode frequency; N/A—not available; qd—every day.

Table 3. Side effects associated with available and upcoming antimuscarinic agents

	Oxybutynin [61,62,64]	Tolterodine [63]	Darifenacin (15 mg) [32•]	Solifenacin (10 mg) [23•]	Trospium (20 mg bid) [45]
Dry mouth	87% (IR), 28% (10 mg ER), 10% (TDS)	30% (IR), 23% (LA)	35%	21%	22%
Constipation	31% (IR), 7% (10 mg ER), 1% (TDS)	7% (IR), 6% (LA)	21%	8%	10%
Headache	4% (ER), 2% (TDS)	4% (IR), 6% (LA)	Placebo	6%	7%
Blurred vision	2% (10 mg ER), 0% (TDS)	1% (IR), 1% (LA)	Placebo	6%	Placebo
Somnolence	40% (IR), 4% (ER), 2% (TDS)	Yes	Placebo	N/A	Placebo

bid—twice daily; ER—extended release; IR—immediate release; N/A—not available; LA—long-acting; TDS—transdermal system.

drug. Patients who are deemed good candidates for a trial of duloxetine for treatment of SUI should be screened carefully for the coexistence of depression. There is some debate as to whether the abrupt cessation of similar medications such as selective serotonin reuptake inhibitors may lead to withdrawal symptoms including anxiety and mood changes. Patients with SUI identified with depression should be counseled appropriately when started on this agent.

Conclusions

For the foreseeable future, antimuscarinics will remain the standard in pharmacotherapy for OAB. To maximize clinical effectiveness, new agents should provide excellent symptomatic relief of frequency, urgency, urge incontinence, and nocturia while minimizing adverse events that limit tolerability. The addition of darifenacin, solifenacin, and trospium to the current armamentarium of drugs will greatly enhance the choices available to patients and their physicians. A comparison of the properties, efficacy, and side-effect profiles of these new agents compared with currently existing agents can be found in Tables 1 through 3. It appears that all three of the new agents demonstrate equivalent efficacy in reducing the symptoms of OAB as extended-release oxybutynin and long-acting tolterodine. In general, side-effect profiles also are similar to existing agents. Darifenacin appears to have an increased risk of constipation. Trospium chloride, with its quaternary structure, may have a potential advantage in terms of the minimization of CNS effects and reduction of drug-drug interactions. However, its twice-daily dosing schedule may counteract these potential advantages by limiting patient compliance. Unfortunately, none of the new agents have been able to eliminate the troublesome side effect of

xerostomia, often a hindrance to patient compliance. Pursuit of the ideal antimuscarinic agent hopefully will continue. In the meantime, head-to-head comparison studies of these new and currently available agents will help determine which comes closest to the ideal.

Approval by the FDA will make duloxetine the first pharmaceutic agent indicated for the treatment of female SUI. Short-term, phase-3 studies have demonstrated clinical efficacy over placebo; however, success with this agent falls short of currently available surgical therapy. It is likely that direct-to-consumer marketing will drive patients to their physicians asking for "the incontinence pill." Whether duloxetine will prove to have sufficient long-term clinical efficacy to warrant its prolonged use will be determined by follow-up, placebo-controlled clinical trials.

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