Persistence with antimuscarinic therapy in patients with overactive bladder

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SUMMARY
Overactive bladder (OAB) is a chronic condition, which impacts patients’ health and quality of life. The primary symptoms of OAB are distressing and may interfere with work, psychosocial and sexual functioning. OAB also is associated with increased risk of urinary tract infections, fractures from falls, skin infections and depression. Patient’s concerns about the effects of incontinence on lifestyle highlight the need to restore continence. The mainstay of treatment is antimuscarinic drug therapy, which may often produce only modest reductions in OAB symptoms and may be accompanied by bothersome adverse effects, leading to poor adherence to prescribed medications. Successful treatment of OAB depends on persistence with the prescribed medication, and efficacy and tolerability are key influencers of persistence. New antimuscarinic agents are now available for treating OAB that significantly improve symptoms of incontinence, urgency and frequency with few adverse effects. An improved efficacy and tolerability profile should result in greater patient satisfaction and persistence with therapy during long-term therapy.

Keywords: Solifenacin; overactive bladder; persistence; tolterodine; oxybutynin; darifenacin

INTRODUCTION
The International Continence Society defines overactive bladder (OAB) as urgency, with or without urge incontinence, which is often accompanied by increased micturition frequency (≥8 voids per day) and nocturia. OAB is a chronic disease that is very common in the general population, but is currently under-diagnosed. Almost one-sixth of the general population have symptoms associated with OAB, and these are not confined to the elderly; a significant proportion of symptomatic patients are between the ages of 40 and 64 (1,2). Patients with OAB report seeing their physicians more often than do people without OAB (3). OAB patients have more urinary tract infections and are at greater risk of falls and fractures (3). Moreover, the symptom of urge incontinence also can predispose OAB patients to skin infections and may contribute to depression (4,5) and has a significantly negative impact on patients’ quality of life (6). Effective antimuscarinic drug therapy improves symptoms and may decrease the risks of these complications of OAB, but the benefits continue only as long as a patient persists with treatment. The purpose of this review was to examine determinants of persistence with and adherence to antimuscarinic drug therapy for OAB.

TREATMENT CONSIDERATIONS
Fear of incontinence, particularly a public episode, is a major concern of OAB patients. A major goal of treatment therefore should be restoration of continence (7). The physiological basis of OAB is generally attributed to dysfunctional activity of the detrusor muscle, and the key symptom is urinary urgency (Figure 1) (8,9). The International Continence Society has defined OAB as urgency, with or without urge incontinence, usually accompanied by frequency (10). Antimuscarinic medications are the mainstay of OAB management, and drug therapy is associated with greater symptomatic improvement than non-pharmacologic treatment alone (11). However, most antimuscarinic drugs produce anticholinergic adverse effects such as dry mouth, blurred vision, and constipation. These adverse effects are often troublesome and poorly tolerated and are one reason for treatment discontinuation in a substantial proportion of patients (12,13). Inadequate efficacy and intolerable adverse effects are the leading cause of discontinuing drug treatment for OAB (14). Because OAB potentially requires long-term treatment, it is desirable to maintain efficacy and minimise the unwanted effects of therapy.

Clinical effectiveness, defined as a combination of efficacy, tolerability and persistence, is a more meaningful criterion for drug evaluation than selective outcome measures (15). As such, clinical effectiveness may provide an indicator of a patient’s likelihood of remaining on therapy. But persistence with therapy also is important for patients to achieve optimal benefit in controlling the symptoms of OAB and improving quality of life (16). Persistence with OAB therapy also has the
potential to impact on the risks of developing OAB-associated comorbidities, such as fractures related to falls. The latter are distressing to patients and costly to treat, and therefore, it is not surprising that successful therapy of OAB has been shown to be cost-effective (17). Furthermore, the possibility exists that prompt initiation of optimal OAB treatment may delay or avoid progression of the disease process (18).

**IMPACT OF OAB DRUGS ON PERSISTENCE WITH TREATMENT**

**Oxybutynin Chloride**

Oxybutynin chloride (oxybutynin) has been in use for 30 years for the treatment of OAB symptoms. Oxybutynin is effective in alleviating urgency, frequency and urge incontinence (19). Although oxybutynin has direct spasmolytic effects on the detrusor muscle, its antimuscarinic effects are non-specific, preferentially affecting salivary gland tissue over bladder tissue (20). This preference for the salivary gland accounts for the principal side effect of oxybutynin, dry mouth, which occurs in up to 72–94% of patients receiving the immediate-release (IR) formulation (21–23). Adverse effects of oxybutynin IR result in a discontinuation rate of up to 25% (24); this rate has reached 27% in postmenopausal women on the highest recommended dose (25).

Development of an extended-release (ER) formulation of oxybutynin resulted in efficacy comparable with the IR version, while decreasing both the incidence and the severity of the characteristic anticholinergic adverse effects (26,27). In a 12-week, randomised, controlled trial, 23% of patients on oxybutynin ER achieved continence (28). However, despite an improvement in the tolerability profile, oxybutynin ER does not appear to improve persistence with therapy. In a long-term, open-label study, 1067 community-dwelling patients were treated with oxybutynin ER 10 mg, and the discontinuation rate attributable to adverse effects was 24% (29), which is similar to that reported with oxybutynin IR. A further 10.1% of patients stopped treatment due to lack of efficacy. Overall, only 46.2% of 1067 patients persisted with treatment for the 12-month study duration (Figure 2).

A transdermal oxybutynin formulation was developed in an effort to further improve the tolerability profile of oxybutynin. In 12-week, randomised, placebo-controlled trials, transdermal oxybutynin was significantly more effective than placebo and comparable with tolterodine ER for improving symptoms of incontinence (30,31). The incidence of dry mouth was 7.3% with tolterodine, and 4.1 and 1.4% with oxybutynin and placebo (31). However, no studies have been reported in which the long-term tolerability or persistence with transdermal oxybutynin was evaluated.

**Tolterodine Tartrate**

Tolterodine tartrate (tolterodine) was the first antimuscarinic drug to be developed specifically for the treatment of OAB. In contrast to oxybutynin, tolterodine is a target-specific, rather than a receptor subtype-specific, antimuscarinic drug (20,32). Thus, tolterodine has stronger selectivity for the bladder than for the salivary glands. This is consistent with a reduced incidence and severity of dry mouth for tolterodine IR compared with oxybutynin IR, although both agents provide similar improvement in OAB symptoms (32). The superior tolerability of tolterodine is associated with lower rates of treatment discontinuation (6–8%) compared with rates of 21–27% for oxybutynin when evaluated in head-to-head trials (33,34). Both efficacy and persistence with treatment are maintained with tolterodine IR during long-term therapy; 62–70% of patients completed the study, and 6% or fewer patients discontinued treatment due to lack of efficacy, and 9–15% discontinued due to adverse effects (35,36).

In a 12-week, randomised controlled trial of 1529 patients with OAB, tolterodine ER reduced the median number of incontinence episodes by 71 vs. 60% for tolterodine IR and 33% for placebo (37). The incidence of dry mouth was 30% with tolterodine IR vs. 23% with tolterodine ER and 8% with placebo (p < 0.02, ER vs. IR) (37). In this short-term study, withdrawal rates due to adverse effects were 5–6% with placebo and tolterodine ER and IR groups. A 12-month open-label, extension study evaluated 1077 patients from the 12-week study who continued on with tolterodine ER and showed no loss of efficacy and no increase in the incidence of adverse effects (38). However, the 71% completion rate (759 of 1077 patients) for tolterodine ER in the 12-month study was significantly better than for oxybutynin ER in a similar study (29). Further, the discontinuation rate due to adverse effects was much lower with tolterodine ER (9.9%) than the 24% discontinuation rate reported with oxybutynin ER in another long-term study, while the discontinuation rate...
due to lack of efficacy was 10% with both drugs (Figure 2). A 12-week study directly comparing tolterodine ER and oxybutynin ER was conducted in 790 women with OAB found a similar reduction in incontinence with both drugs, although micturition frequency and continence rates were significantly improved with oxybutynin ER (28). At endpoint, 23% of oxybutynin ER and 17% of tolterodine ER patients were continent. However, dry mouth was reported with 30% on oxybutynin ER and 22% on tolterodine ER.

It is well accepted that observations made under controlled conditions such as during clinical trials are not necessarily reflective of day-to-day clinical practice. In a recent analysis of withdrawal rates based on prescription data, in almost 20,000 patients receiving treatment for OAB with oxybutynin or tolterodine IR or ER, fewer than 20% of patients were still taking their medication after 1 year (Figure 3) (39).

**Trospium Chloride**

Trospium chloride (trospium) has been in use in Europe for the treatment of OAB for more than 20 years, but has only recently become available in the United States. No direct comparisons have as yet been done between trospium and the ER formulations of oxybutynin or tolterodine. Trospium was similar to oxybutynin IR and tolterodine IR for reducing urinary frequency, but was more effective than tolterodine IR for reducing the frequency of episodes of incontinence and better tolerated than oxybutynin IR (40,41). During a 12-week evaluation, continence was achieved in 21% of patients on trospium and 11% on placebo; completion rates were similar for trospium and placebo (83.6%); and discontinuation rates due to adverse effects were 8.8% with trospium and 5.7% with placebo (42). A randomised, blinded 52-week trial was conducted to evaluate the tolerability and efficacy of trospium 20 mg twice daily vs. oxybutynin IR 5 mg twice daily in 357 patients with detrusor overactivity (41). Both drugs produced reductions in the frequency of micturitions, incontinence and urgency. Dry mouth occurred in 33% of the trospium group and 50% of the oxybutynin IR group. The completion rate during long-term treatment with trospium was 75% and for oxybutynin IR 73% at 1 year; only 3% on trospium and 2.2% on oxybutynin IR discontinued therapy due to inadequate efficacy, while 3.7% on trospium and 6.7% on oxybutynin IR withdrew due to confirmed, treatment-related adverse effects (Figure 2) (41).

**Propiverine Hydrochloride**

Propiverine hydrochloride (propiverine) has combined anticholinergic and calcium-antagonistic actions. It has been used for the treatment of OAB symptoms, mainly in Japan and other countries. A limited number of published clinical studies indicate that propiverine is effective for reducing symptoms of incontinence (43–45). A placebo-controlled comparison of propiverine 15 mg three times daily and oxybutynin 5 mg twice daily in 366 patients with incontinence showed similar efficacy for the two drugs. The most common adverse event was dry mouth, occurring in 53% of patients on propiverine, 67% on oxybutynin and 28% on placebo (45). No long-term studies evaluating tolerability or persistence with propiverine have been published.
Darifenacin Hydrobromide

Darifenacin hydrobromide is an M3-receptor-selective antimuscarinic agent recently approved for the treatment of OAB. Darifenacin at doses of 7.5 and 15 mg/day demonstrates superiority to placebo for treating the major symptoms of OAB, including incontinence, frequency and urgency (46–48). A comparative trial of darifenacin 15 mg/day vs. oxybutynin IR 5 mg three times a day found comparable efficacy, but a higher rate of dry mouth and blurred vision with oxybutynin (47). Mild-to-moderate dry mouth occurred in 19–31% of patients on darifenacin vs. 9% with placebo, and constipation occurred in 14% with darifenacin vs. 7% with placebo (46). Currently, there are no published data evaluating long-term treatment with darifenacin.

Solifenacin Succinate

Solifenacin succinate (solifenacin) is an antimuscarinic drug, which was recently approved in the United States and Europe for the treatment of OAB. Solifenacin has been evaluated in four randomised, double-blind, placebo-controlled trials of more than 3000 patients with OAB (49,50). Results from these trials demonstrate that solifenacin significantly reduces all symptoms of OAB including urinary urgency, frequency and urge incontinence (9,51–53). Solifenacin is the first antimuscarinic drug to show a clinically significant reduction in the number of urgency episodes across multiple trials.

In a pooled analysis of the four phase III trials, 51–52% of patients who were incontinent at baseline achieved continence after 12 weeks’ treatment with solifenacin 5 or 10 mg, which was significantly greater compared with the 34% in the placebo group who achieved continence (7,49). Solifenacin at once-daily doses of 5 and 10 mg reduced the mean number of daily episodes of urgency by over 50% (9,51,54). The discontinuation rate due to adverse effects was 4.4 and 6.8% with solifenacin 5 and 10 mg, respectively, vs. 2.2% with placebo (49). Treatment was generally well tolerated, and the most common adverse event, dry mouth of mild severity, occurred in approximately 11% of patients on solifenacin 5 mg, 28% on solifenacin 10 mg and 4% on placebo. A recently completed 12-week study compared solifenacin 5 or 10 mg and tolterodine ER 4 mg in 1200 patients with OAB (55). Significantly, more patients on solifenacin (58.7%) than on tolterodine ER (48.9%) were dry at 12 weeks, and both treatments were comparable for tolerability.

A 40-week, open-label, flexible-dose, extension trial enrolled patients from two of the 12-week double-blind studies to evaluate the safety, tolerability and efficacy of long-term treatment with solifenacin (52). Of 1802 patients who had completed the two 12-week studies, 91% chose to participate in the open-label extension study, where a flexible dose regimen of solifenacin 5 or 10 mg was continued for up to 40 weeks (52). The completion rate with solifenacin for those who entered the extension study was 81%, which was higher than corresponding rates previously recorded for other antimuscarinic agents (29,38,41). The withdrawal rate with solifenacin due to poor tolerability was 4.7% (Figure 4), which suggests improved persistence with therapy (52). Dry mouth occurred in 10 and 17% of patients on solifenacin 5 or 10 mg. Long-term treatment with solifenacin was associated with further small incremental improvements in resolution of incontinence and urgency and normalisation of frequency (Figure 5) (52). Improvements in quality of life resulting from the favourable therapeutic profile of solifenacin that were first seen during the double-blind studies were further enhanced during ongoing treatment (16,51,52,56).

CONCLUSIONS

To optimally alleviate symptoms, improve the poor quality of life and improve undesirable consequences associated with OAB, long-term persistence with drug therapy is vital. However, antimuscarinic therapy often produces unacceptable adverse effects and limited or modest symptom relief. On
the basis of a review of published studies with antimuscarinic drugs used to treat OAB, a major determinant of persistence with therapy is the clinical effectiveness or combined efficacy and tolerability of treatment. Inadequate clinical effectiveness likely may account for at least some of the high rates of discontinuation observed in everyday clinical practice. Long-term studies with antimuscarinic drugs demonstrate that improvements in efficacy and tolerability are associated with higher patient satisfaction and better persistence with therapy. The long-term benefits of persistent OAB therapy should include sustained symptom improvement over time, acceptable safety and tolerability, better quality of life, less morbidity and fewer physician visits, all of which will help to reduce costs among this patient group (57). Newer antimuscarinic agents demonstrate efficacy and tolerability profiles, which suggest that they might provide better persistence with long-term therapy. Although it is difficult to compare different drugs across studies that use different study designs, a thorough evaluation of long-term efficacy and persistence studies in OAB should be considered when selecting antimuscarinic drugs.

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