Treatment of overactive bladder in the aging population: focus on darifenacin

Swati Jha
Matthew Parsons

Department of Urogynaecology, Birmingham Women's Hospital, Birmingham. UK

Abstract: Anticholinergics are commonly used in primary and secondary care settings for the treatment of overactive bladder syndrome. The number of anticholinergic drugs available on the market is increasing and various studies, both observational and randomized controlled trials, have evaluated effectiveness of the different preparations available. When anticholinergic therapy is prescribed, there is still uncertainty about which anticholinergic drugs are most effective, at which dose, and by which route of administration. There is also uncertainty about the role of anticholinergic drugs in different patient groups, particularly in the elderly. The rationale for using anticholinergic drugs in the treatment of overactive bladder syndrome is to block the parasympathetic acetylcholine pathway and thus abolish or reduce the intensity of detrusor muscle contraction. There are currently five recognized subtypes of muscarinic receptor; the M_1, M_2, and M_3 subtypes are of interest in bladder activity. Muscarinic receptors are found in other parts of the body, eg, in the gut, salivary glands, tear ducts. Side effects associated with non-selective antimuscarinics can be particularly distressing in the elderly. The development of bladder selective M_3 specific antagonists has the advantage of providing increased efficacy with minimal side effects. Darifenacin is one such preparation. The aim of this review is to assess the pharmacology, interactions and the safety and tolerability of darifenacin in the treatment of overactive bladder in the elderly population with particular reference to clinical trial data available.

Keywords: darifenacin, antimuscarinics, overactive bladder, detrusor overactivity, urinary incontinence

Introduction

Overactive bladder (OAB) is a common condition characterized by urinary urgency, with or without urge incontinence usually with frequency and nocturia (Abrams et al 2002). Epidemiological studies from the US have reported the prevalence of OAB to be 16.9% (Stewart et al 2003); it can affect men and women alike, but the prevalence increases with age. OAB can have a detrimental effect on physical functioning and psychological well-being, as well as significantly reducing quality of life (Abrams et al 2000). In patients under 25 the prevalence is 4.8% and in those over the age of 65 years 30.9% (Milsom et al 2001; Stewart et al 2003). In the elderly the commonest manifestation is urinary incontinence (Castleden et al 1981).

Antimuscarinic drug therapy, in conjunction with behavioral therapy such as bladder retraining, remains the first line of management in patients with irritative bladder symptoms or OAB. Several antimuscarinic agents are currently available for the treatment of OAB in adults. The antimuscarinics all appear to exert their clinical effect through inhibition of the bladder muscarinic receptors, but they vary in their functional profile and can be associated with troublesome side effects such as dry mouth, constipation, somnolence, and blurred vision. In a questionnaire follow-up study of women with detrusor overactivity, just 5.5% were cured of their urinary

Correspondence: Swati Jha
Department of Urogynaecology, Birmingham Women's Hospital, Metchley Park Rd, Edgbaston, Birmingham, UK B15 2TG
Tel +44 121 243 9095
Fax +44 121 627 2667
Email swatijha83@hotmail.com

symptoms and only 18.2% of women continued drug therapy for more than 6 months (Kelleher et al 1997). The development of relatively bladder selective antimuscarinic drugs such as tolterodine has helped to reduce adverse effects, but the development of darifenacin and the recent marketing of solifenacin represent the first highly selective bladder specific anti-muscarinic (M_3 specific antimuscarinics) agents for the management of OAB.

While efficacy of antimuscarinics has been demonstrated in adult populations (including patients >65 years of age), few studies have been reported specifically in a geriatric population, and antimuscarinics are often underutilized in the elderly despite the marked increase in the prevalence of OAB in this age group. One explanation for this apparent under-use of an effective treatment option may be concerns about the frequency of anticholinergic adverse events, such as dry mouth; the likelihood of detrimental central nervous system (CNS) effects, including cognitive impairment and sleep disturbances; and the potential for harmful interactions with existing pharmacotherapy.

Muscarinic receptors and effects of aging

Molecular cloning studies have revealed the existence of five genes for muscarinic receptors in rats and humans. This corresponds to five subtypes of muscarinic receptors, M_1–M_5 (Caulfield and Birdsall 1998). The distribution of the different subtypes in the human body varies and so does their functional importance. Table 1 shows the distribution of different muscarinic receptors in the body.

Detrusor muscle from various species including man contains M_2 and M_3 receptors. Although the M_2 receptors predominate (approximately M_2:M_3:2:1), in humans it is the M_3 receptors that are thought to cause a direct muscle contraction via phosphoinositide hydrolysis (Harriss et al 1995), whereas M_1 receptors have never been demonstrated (Yamaguchi et al 1996). It is thought that the M_3 receptor is responsible for the normal micturition contraction (Caulfield and Birdsall 1996). The M_2 receptors may become more important in mediating detrusor contractions in certain disease states such as neurogenic bladder dysfunction (Braverman et al 1998).

Animal studies show there is no change in the relative abundance of M_2 and M_3 receptors with advancing age; this is accompanied by only minor if any alterations in receptor responsiveness (Schneider et al 2005).

Table 1 Distribution of muscarinic receptors

Subtypes	Distribution
M_1	Brain (cortex, hippocampus), sympathetic ganglia, glands
M_2	Heart, smooth muscle, hindbrain
M_3	Smooth muscle, glands, brain
M_4	Brain (forebrain, striatum)
M_5	Brain (substantia nigra), eye

Pharmacology: darifenacin

Darifenacin is a highly specific M_3 receptor antagonist which is used in the US and Europe, and is yet to be launched in the UK. It has been shown to have a higher degree of selectivity for the M_3 receptors (Tables 2 and 3) than the commonly used antimuscarinics currently available and has activity both in vitro (Wallis 2006) and in vivo (Quinn 2006). It may be expected that drugs selective for the M_3 receptors in the bladder have greater clinical efficacy in detrusor overactivity. It has also been shown to have a reduced adverse side effect profile (Anderson 2006).

Darifenacin was acquired by Novartis in May 2003 and is expected to be marketed as Enablex in the UK in the near future.

Effects in vivo

In bladder and salivation models of conscious rats, darifenacin has been compared with oxybutynin (Williamson et al 2006). The micturition interval and volume as well as the peak micturition pressure were assessed before

Table 2 Affinity (pKi) of antimuscarinic compounds for the human recombinant receptor subtypes M_1– M_5 (Anderson 2006) (Mean)

	M_1	M_2	M_3	M_4	M_5
Darifenacin	8.2	7.4	9.1	7.3	8.0
Oxybutynin	8.7	7.8	8.9	8.0	7.4
Tolteridine	8.8	8.0	8.5	7.7	8.0
Propiverine	6.6	5.4	6.4	6.0	6.5
Trospium	9.1	9.2	9.3	9.0	8.6

Table 3 Comparison of M_3:M_1 selectivity of the antimuscarinic compounds (Napier and Gupta 2002)

	M_3 versus M_1	*P*
Darifenacin	9.3	<0.001
Tolteridine	0.6[a]	<0.05
Oxybutynin	1.5[b]	<0.05
Propiverine	0.6[a]	<0.05
Trospium	1.5	NS

Notes: [a]Significant selectivity for M_1, but unlikely to be biologically significant; [b]Significant, but unlikely to be biologically relevant.

and an hour after injection with the test compound (darifenacin 0.1–0.3 mg/kg; oxybutynin 0.1–3.0 mg/kg). Dose-related decreases were seen in all micturition parameters, which were significantly greater than those seen with oxybutynin ($p<0.05$), although the effect was equipotent on salivation.

Effects on CNS

The side effects of antimuscarinics on the CNS have been well documented. Adverse effects such as somnolence and cognitive impairment are a result of M_1 blockade in the brain. The role of M_1 receptors in cognitive function is well accepted, and is the basis of the therapeutic principle in the treatment of Alzheimer's disease (Anderson 2006). The elderly therefore are particularly at risk of cognitive side effects with non-specific antimuscarinics hence the reluctance to use them in the elderly population.

To assess the effects of darifenacin controlled-release and oxybutynin extended-release (ER) on cognitive function (particularly memory) 150 patients ≥60 years old, were randomized to darifenacin, oxybutynin ER or placebo in a multicenter, double-blind, double-dummy, parallel-group, 3-week study (Kay et al 2006). Doses were administered according to US labels: oxybutynin ER 10 mg once daily (od), increasing to 15 mg od in weeks 1 and 2, then 15 mg od in week 3. The primary end point was accuracy on the Name-Face Association Test (delayed recall) at week 3. While darifenacin had no significant effects on memory versus placebo, oxybutynin ER caused significant memory deterioration (magnitude of effect comparable with brain aging of 10 years).

Similar studies in younger populations testing the effects of darifenacin on cognitive function at doses of 7.5 mg or 15 mg, did not produce any detectable effects relative to placebo (Nichols et al 2006). The sparing of cognitive function in relation to the use of darifenacin (and trospium) is an attractive result of the M_1-sparing effect of darifenacin and is therefore potentially very useful in the elderly.

Effects on the cardiovascular system and the electrocardiogram

A study in the chioralose–urethane anesthetized beagle dog assessed the potency of darifenacin, tolterodine, oxybutynin, and propiverine on pelvic nerve-stimulated bladder contractions, trigeminal nerve stimulated salivation, and heart rate (Gupta et al 2006). Darifenacin did not increase the heart rate at doses required to maximally inhibit bladder contractility (100 μg/kg), whereas tolterodine increased heart rate at doses within the range needed to inhibit contractility. In the study by Nichols and colleagues (2006), darifenacin (7.5 mg and 15 mg) had no significant effect on heart rate or heart rate variability, whereas dicyclomine (dicycloverine) significantly reduced heart rate (–4.79 bpm, $p=0.003$) and increased variability (12%, $p=0.005$) compared with placebo. No changes in either the vital signs or electrocardiogram (ECG) were found to be due to darifenacin. Prolongation of QT interval on an ECG is a valuable predictor of a drug's ability to cause potentially fatal ventricular tachyarrhythmia. Serra and colleagues (2005) found there was no significant increase in QT interval with darifenacin treatment compared with placebo.

Pharmacokinetics

The pharmacokinetics of darifenacin have been determined in human volunteers after oral administration of the drug and studied in animal models after oral and intravenous administration (Beaumont et al 1998). Pooled data have been used to model population pharmacokinetics (Kerbusch et al 2003). Plasma concentrations were calculated using (Anderson 2006) C-labelled darifenacin 5 mg dose, after 5 days of achieving a steady-state plasma concentration.

Darifenacin is well absorbed in humans. Unchanged darifenacin is present in very small amounts in the feces, showing that it is almost completely absorbed from the gastro-intestinal tract (Beaumont et al 1998). Compared with immediate release preparations, higher bioavailability has been noted with extended release preparations (Kerbusch et al 2003). This may be due to differing activity of the metabolizing mechanisms in the lower intestinal tract (Paine et al 1997). Food has no effect on absorption (Nichols 2006).

Darifenacin is highly protein-bound in the plasma (>96% in all species tested; 98% in man) (Beaumont et al 1998). Volumes of distribution are higher than body water in the animal models after intravenous administration (12 L/kg, 7 L/kg, and 6.8 L/kg in mouse, rat, and dog, respectively).

Darifenacin has an efficient hepatic metabolism (Beaumont et al 1998) and this is demonstrated by plasma clearance values that are high relative to hepatic blood flow. This leads to a short half-life in man. Darifenacin has three principal mechanisms of metabolism: monohydroxylation in either the dihydrobenzfuran or diphenylacetamide moieties; opening of the dihydrobenzfuran ring; or N-dealkylation at the pyrrolidine nitrogen. The main metabolite, UK-148993 (Beaumont et al 1998), is formed primarily through hydroxylation of darifenacin by cytochrome P4503A4 (CYP3A4) and cytochrome P4502D6

(CYP2D6) and is 50-fold less potent than the parent drug (Kerbusch et al 2004). There is a great deal of polymorphism in CYP2D6, and individuals with poor CYP2D6 metabolism may have higher plasma levels of the drug, with 20% reduction in clearance of the drug, and 52% increase in bioavailability (Kerbusch et al 2003) when compared with homozygote extensive metabolizers. Japanese subjects have a 56% lower availability of darifenacin than Caucasians (Kerbusch et al 2003). No other racial differences in bioavailability were seen, indicating that the difference is due to increased first pass metabolism in the liver (by CYP3A4 and CYP2D6). Distribution of alleles pertaining to CYP2D6 is known to differ between Japanese and Caucasian races (Xie et al 2001), but when the CYP2D6 activity was controlled for separately, and knowing that no ethnic differences seem to exist in CYP3A4 activity (Xie et al 2001), it appears that other as yet unidentified factors are involved. Women have a 31% lower rate of clearance of darifenacin than men (Kerbusch et al 2003), which is felt to be due to a lower activity of CYP2D6 in women (Tanaka 1999) and which would seem therefore to draw parallels with the CYP2D6 poor-metabolizers previously alluded to (despite a higher activity of CYP3A4 in women [Tanaka 1999]). Biotransformation by the cytochrome P450 (CYP450) system is an important step in the activation or elimination of a large number of drugs, including oxybutynin, tolterodine, darifenacin, and solifenacin, raising the possibility of clinically relevant and potentially serious drug interactions. In elderly patients, such interactions are of particular relevance given the potential for declining activity of certain members of the CYP450 family combined with decreased hepatic blood flow, which can reduce first-pass metabolism and thus the bioavailability of drugs metabolized via this route.

After administration of 14C-labelled darifenacin, most of the radioactive dose was recovered within 48 h, balanced between urine and feces in humans (Beaumont et al 1998). Approximately 44% of a dose was recovered from the feces and 58% from the urine, in both cases predominantly as metabolites.

Drug interactions

Data assessing drug and food interactions of darifenacin are relatively scarce. Kerbusch and colleagues (2003) have looked at the effect of ketoconazole (an azole used in the treatment of fungal conditions) and erythromycin (a macrolide antibiotic) on the metabolism of darifenacin. Both of these agents are CYP3A4 inhibitors, although ketoconazole is 50 times more potent than erythromycin. Use of ketoconazole reduced clearance of darifenacin by 68% (Kerbusch et al 2003) and increased the bioavailability of the drug to 100%. Erythromycin had no effect on clearance but increased bioavailability to 97%. Ketoconazole and erythromycin also affected levels of the active darifenacin metabolite, although this was thought to be due to a reduction in metabolism from the parent drug, rather than an increase in clearance of the metabolite.

Caution is therefore warranted in the use of darifenacin in patients taking CYP3A4 inhibitors. Potent inhibitors should be avoided in view of their combined effect on clearance and metabolism. Higher doses of darifenacin are generally well tolerated, and so modest increases in drug concentration with less potent inhibitors are not clinically relevant.

Efficacy studies

Darifenacin has been the subject of several well conducted and extensive trials with rigorous entry criteria. Analysis of pooled data from three such studies enrolled 1059 patients (85% of whom were female; age range 19–88 years) with at least 6-month history of overactive bladder symptoms (urgency, frequency, and urge incontinence) (Chapple et al 2005). All had a 2-week washout and a 2-week placebo run-in, prior to commencing active participation. Participants were randomized to receive either darifenacin-controlled release 7.5 mg or matched placebo (n=335/271, respectively) or darifenacin controlled release 15 mg or matched placebo (n=330/384, respectively). Outcome data were collected by use of an electronic diary (hand-held computerized diaries have been developed to overcome the lack of patient compliance that has been noted in many studies [Rabin et al 1993]; patients felt that their symptoms were more properly reflected by the computerized version, felt more motivated to provide data, and found it easier to remember to enter data).

Both doses of darifenacin were significantly superior to placebo in alleviating the symptoms associated with OAB (Table 4), however, a marked placebo response was noted. Darifenacin (15 mg controlled release) has also been compared with oxybutynin (5 mg TDS) and matched placebo (Zinner et al 2005). Seventy-six patients (93% female) had detrusor overactivity (urodynamically verified OAB) with ≥4 urinary incontinence (UI) episodes per week and a frequency of >8 micturitions per day; all underwent a 2-

Table 4 Outcomes comparing darifenacin or matched placebo after 12 weeks of treatment (Chapple et al 2005)

	Darifenacin(%) (7.5 mg QD)	Placebo (%)	Darifenacin(%) (15 mg QD)	Placebo (%)
Incontinence episodes /week	–8.8(–68.4)*	–7(–53.8)	–10.6(–76.8)**	7.5 (–58.3)
Incontinence episodes resulting in pad change	–4(–77.1)	–2(–47.7)	–4.8(–78.6)**	–2.7(–55.1)
Frequency of urgency/day	–2(–29)**	–1(–14.3)	–2.3(–29)**	–1.2(–16.7)
Micturition Frequency/day	–1.6(–16.6)**	–0.9(–9.1)	–1.9(–17.4)**	–1(–9.9)
Bladder capacity (mean vol void:ml)	15.4(9.6)*	7.6(4.9)	26.9(17.5)**	5.9(3.9)
Severity of urgency	–7.8(–14.2)**	–4.2(–7.8)	–9.3(–16.1)**	–4.5(–8)

Notes: Results expressed as median (%) change from baseline, at week 12; *p<0.01; **p<0.001 (Wilcoxon rank-sum test).

week run-in period prior to 2 weeks of treatment in each arm, in a randomized sequence. Outcomes were assessed using a paper diary (Table 5). The results revealed comparable efficacy with oxybutynin, in terms of significant improvement of the major symptoms of OAB, when compared with placebo.

Rapid onset of action of darifenacin is a useful attribute and has been assessed in a well conducted study (Haab et al 2004). In this study, 561 patients (age range 19–88 years; 85% female) were enrolled with OAB symptoms of more than 6-month duration. After a 2-week washout and a 2-week placebo run-in, the participants were randomized in a 1:4:2:3 ratio to 3.75 mg darifenacin, 7.5 mg darifenacin, 15 mg darifenacin, or placebo. Significant and rapid onset of action was noted by 2 weeks, although evolving benefit was seen up to 12 weeks in this study. Benefits to patients taking darifenacin have been shown, not only in terms of symptom improvement but also by demonstrable improvements in quality of life, as assessed by the King's Health Questionnaire (Chapple 2006). The low incidence of cognitive side effects has been discussed as a benefit in the elderly. Efficacy in an elderly population has been studied by Foote and colleagues (2005), by analysis of pooled data. This included 317 patients aged 65 years or more, in one of three multicenter, randomized, double-blind, placebo controlled studies. All had OAB symptoms of more than 6-month duration. All had a 2-week washout (only if needed) and a 2-week drug-free/placebo run-in, prior to receiving once daily orally administered controlled-release darifenacin 7.5 mg (n=97) and matching placebo (n=72), or controlled-release darifenacin 15 mg (n=109) and matching placebo (n=108). At 12 weeks, both doses of darifenacin were significantly superior to placebo ($p<0.05$) in improving all OAB parameters studied, confirming efficacy in an elderly population (Table 6).

Safety and tolerability

The proposed doses of darifenacin are 7.5 mg or 15 mg and in studies reporting safety and tolerability these doses been well tolerated (Kirwin 2006). Side effects are generally dose-related and of mild-to-moderate severity when they occur.

Chapple and colleagues (2005) report the commonest side effects to be dry mouth (7.5 mg 20%; 15 mg 35%; placebo 8%) and constipation (7.5 mg 15%; 15 mg 21%; placebo 6%), although these resulted in low rates of discontinuation (7.5 mg 0.6%; 15 mg 2.1%; placebo 0.3%). On the other hand, CNS and cardiovascular safety were comparable with placebo. Different studies report similar findings with regard to side effects profile. Zinner and colleagues (2005) in their comparison of darifenacin (15 mg QD), oxybutynin (5 mg TDS) and placebo also confirmed dry mouth and constipation as the commonest side effects of darifenacin. Dry mouth was 36.1% in the oxybutynin arm compared with 13.1% of darifenacin patients ($p<0.05$) and 4% in the placebo group ($p<0.05$). Rates of constipation were comparable in darifenacin (10%) and oxybutynin (8%)

Table 5 Comparison of 2 weeks treatment outcomes of darifenacin, oxybutynin, or placebo (Zinner et al 2005)

	Darifenacin (n=58) 15 mg QD	Oxybutynin (n=58) 5 mg TDS	Placebo (n=58)
Micturition/day	9.33	9.24	9.62
Incontinence episodes/week	10.93*	9.45*	14.64
Urgency episodes/day	7.95*	8.12*	8.71
Severity of urgency episode**	1.93*	1.89*	2.03

Notes: Evaluable patients (n=58). Values shown are means adjusted for sequence and period from the crossover analysis of variance; *p<0.05 vs placebo, accounting from multiplicity by least significant difference method; **1=mild, 2=moderate, 3=severe.

Abbreviations: QD, once daily; TDS, three times daily

Table 6 Outcome following 12 weeks of treatment in elderly patients (Foote et al 2005)

Efficacy parameters	Darifenicin (7.5 mg QD)	Placebo	Darifenacin (15 mg QD)	Placebo
Micturitions /day	−1.8(−18.2)	−0.6(−6.5)	−1.8(−16.9)	−1.0(−9.1)
Incontinence episodes/week	−11.2(−66.7)	−4.8(−34.8)	−10.8(−75.9)	−6.8(−44.8)
Number of urgency episodes/day	−2.1(−25.7)	−0.6(−6.6)	−2.4(−25.7)	−0.8(−10.4)
Bladder capacity (mean vol voided mls)	14(10.4)	2(1.3)	27(18.0)	2(1.3)

Notes: Results expressed as median (%) change from baseline to week 12; $p<0.05$ in improving all four efficacy parameters (Wilcoxon rank-sum test, stratified by study).
Abbreviations: QD, once daily.

and significantly higher than placebo (3%, $p<0.05$). Most of the side effects were mild to moderate in both groups; no patients in the darifenacin group discontinued treatment. There were no clinically relevant, treatment-emergent changes in blood pressure, pulse rate, or ECG. Dizziness and blurred vision were reported in patients taking oxybutynin.

In a comparison with tolterodine immediate-release (Foote 2006), dry mouth was the commonest side effect (darifenacin 7.5 mg 20.2%; darifenacin 15 mg 35%; tolterodine 26.9%; placebo 8%) in all groups. Constipation (darifenacin 7.5 mg 14.8%; darifenacin 15 mg 21%; tolterodine 10.3%; placebo 5.4%) and dyspepsia (darifenacin 7.5 mg 1.8%; darifenacin 15 mg 7.5%; tolterodine 7.6%; placebo 1.5%) were also reported. Dizziness and somnolence were reported, but the numbers were very small and no significant differences were detected in the different groups. All reported side effects are transient and tolerable. Even though constipation is one of the commonest side effects, the use of laxatives and stool softeners is low and comparable with their use in the placebo groups. Treatment-related adverse events infrequently lead to withdrawal (Steers et al 2005). Studies to date have excluded patients with hepatic disease (Haab et al 2004) in keeping with the nature of the metabolism of darifenacin. However, pharmacokinetic analyses have shown a 4.7-fold increase in drug concentrations with moderate hepatic impairment (Croom and Keating 2004). If being used, dose adjustment of darifenacin would be necessary in this group of patients. No clinically significant change in dose concentrations arose as a result of mild hepatic impairment, or renal impairment of varying degrees (Croom and Keating 2004), and so no dose adjustment is necessary.

Patient perspectives

Urinary incontinence is an important contributor to the complications and economic cost of OAB for both community-dwelling and institutionalized elderly individuals. Many patients with OAB do not seek treatment because of embarrassment, fear of surgery, or the misperceptions that the problem is untreatable, or is a normal and inevitable consequence of aging. Nonpharmacological therapies improve bladder control by modifying lifestyle and behavior to prevent urine loss. This requires patient and caregiver motivation and can be time consuming. However optimal results may be obtained by combining these strategies with pharmacotherapy or by means of pharmacotherapy alone. Important considerations for elderly patients include tolerability, absence of drug interactions, and the availability of a range of dosages to tailor treatment to individual patients. As demonstrated in this review of literature, darifenacin favorably fulfills these criteria. These results are supported by significant improvements in quality of life, which have paralleled the overactive bladder symptom reductions (Haab 2005; Chapple 2006). Both fixed and flexible darifenacin dosing regimens produce these beneficial effects, which extend to the more vulnerable population of older patients.

There may also be a place for incorporating patient-initiated dose adjustment into the protocol (Staskin and MacDiarmid 2006a, 2006b). The primary care physician can then effectively manage adverse events associated with OAB without compromising efficacy. Given some control in the process, patients are willing to tolerate certain side effects in exchange for symptom relief.

Conclusion

Evidence would suggest that darifenacin is an antimuscarinic drug particularly useful in the elderly population and therefore a useful addition to the current range of medications available on the market. Being an M_3-specific antagonist, it is part of an important advance in the development of drugs for the treatment of OAB. Data from clinical trials have shown that darifenacin is efficacious and well tolerated in addition to providing improvements in lower urinary tract symptoms with minimal CNS side effects.

It also results in significant improvements in quality of life scores. The dosage of drug also represents a compromise between efficacy and tolerability, and thus, it is important, particularly in the clinical setting, to have a range of doses that may then be tailored to patients' individual needs. Darifenacin has been compared with immediate-release tolterodine, and further studies are warranted to compare the drug with the newer QD preparations of both oxybutynin and tolterodine to examine whether the theoretical advantages of an M_3-specific antagonist translate into clinical practice. Compliance with medical therapy remains a significant problem in the treatment of the overactive bladder. When selecting an antimuscarinic agent for the management of an elderly patient presenting with OAB, in addition to considering evidence of clinical efficacy and tolerability, issues of safety specific to an older population should be borne in mind. In particular, the likelihood of detrimental CNS effects should be considered, including cognitive impairment and sleep disturbances, secondary to anticholinergic load. Oxybutynin and tolterodine have both been associated with cognitive adverse events and effects on sleep architecture and quality. In contrast, darifenacin does not appear to be associated with cognitive adverse events and does not negatively affect sleep architecture or quality though it is just as if not more efficacious (Kay et al 2006). Darifenacin in the treatment of the OAB represents a pharmacological advance as one of a new type and class of drug.

This new addition to the armamentarium available for the management of OAB is welcome to both clinician and patient alike, and the evidence so far would suggest that darifenacin should have a major effect in this difficult-to-manage condition.

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