

# Darifenacin: a selective M<sub>3</sub> muscarinic receptor antagonist for the treatment of overactive bladder

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Overactive bladder is a common and distressing disorder that imposes significant financial and quality-of-life costs. The current therapeutic paradigm aims to decrease detrusor overactivity via blockade of bladder M<sub>3</sub> muscarinic receptors, the primary cholinergic receptors responsible for detrusor contraction. However, systemic antimuscarinic adverse effects, such as dry mouth and constipation, limit the tolerability of antimuscarinic treatment. Therefore, a uroselective M<sub>3</sub> receptor antagonist would be considered optimal therapy for overactive bladder. Darifenacin (Enblex<sup>®</sup>) is the most recent antimuscarinic drug approved for the treatment of overactive bladder. It demonstrates M<sub>3</sub> receptor selectivity, but is not M<sub>3</sub> specific. Despite animal data suggesting uroselectivity, it is not sufficiently uroselective in therapeutic use. While effective in reducing symptoms related to overactive bladder, dry mouth and constipation remain common. There are no comparative trials comparing darifenacin with existing agents, therefore it is not known if darifenacin represents an improvement over existing agents.

Overactive bladder (OAB) is characterized by the lower urinary tract symptoms of urgency, urge incontinence, urinary frequency and nocturia. It is a common and distressing problem, estimated to afflict 15–17% of adult men and women in the USA [1,2]. OAB is associated with an impaired quality of life, depression and poor sleep [1]. The economic burden is difficult to quantitate, but is estimated at US\$9.1 billion (year 2000 values) annually [2]. The etiology of the disorder is unknown and most cases are regarded as idiopathic.

The therapeutic model used in the treatment of OAB is primarily concerned with suppressing undesired activity of the detrusor muscle. The detrusor muscle contracts in response to the release of acetylcholine, via activation of muscarinic cholinergic receptors. Five subtypes of the muscarinic receptor have been identified: M<sub>1</sub>, M<sub>2</sub>, M<sub>3</sub>, M<sub>4</sub> and M<sub>5</sub>. The detrusor expresses receptor subtypes M<sub>2</sub> and M<sub>3</sub> in a 2:1 ratio [3]. Activation of the M<sub>3</sub> receptors by acetylcholine released by efferent terminals results in phosphoinositide hydrolysis, leading to muscle contraction [4,5]. The M<sub>2</sub> receptors are not associated with phosphoinositide accumulation in the detrusor [4] and, therefore, the M<sub>3</sub> receptors are thought to be primarily responsible for detrusor contraction [3].

All antimuscarinic drugs currently available for the treatment of OAB block the bladder M<sub>3</sub> receptors, and by this means are thought to decrease motor overactivity. Since muscarinic

receptors are not unique to the bladder, adverse effects would be expected from blockade of muscarinic receptors in other organ systems. The systemic adverse effects of antimuscarinic agents are attributed to the lack of organ specificity to the M<sub>3</sub> muscarinic receptors in the bladder (uroselectivity) and to the indiscriminate blockade of other muscarinic receptor subtypes (M<sub>1</sub>, M<sub>2</sub>, M<sub>4</sub> and M<sub>5</sub>). M<sub>1</sub> receptors are abundant in the cerebral cortex, hippocampus and neostriatum [6] and may be important for cognitive functions, such as memory, learning and attention [7–9]. CNS M<sub>1</sub> blockade impairs cognition [3]. M<sub>1</sub> and M<sub>3</sub> receptors are both involved in salivary secretion [10] and indiscriminate blockade of M<sub>1</sub> and M<sub>3</sub> salivary receptors causes significant dry mouth. Inhibition of M<sub>3</sub> muscarinic receptors in the gastrointestinal tract and the eye also causes constipation and blurred vision, respectively. Finally, M<sub>2</sub> receptors play a role in modulating heart rate and cardiac output [11]. Interference with cardiac M<sub>2</sub> receptor function may be associated with EKG changes, such as bradycardia and arrhythmias [3].

These significant adverse effects limit the ability to dose-titrate antimuscarinic drugs to an optimal therapeutic dose. Thus, an agent that selectively targets the bladder M<sub>3</sub> receptors and so minimizes adverse effects might be expected to offer the best overall therapeutic effect [12]. Animal studies have demonstrated a greater specificity of darifenacin to the M<sub>3</sub> receptor compared with other muscarinic

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subtypes, as well as M<sub>3</sub> uroselectivity, suggesting its potential as an improvement over existing antimuscarinic agents.

### Darifenacin

Darifenacin hydrobromide is the most recent addition to the antimuscarinic formulary intended for use in the treatment of OAB. Antimuscarinics currently approved for use in the USA for OAB include oxybutynin chloride (Ditropan<sup>®</sup> and generic), tolterodine tartrate (Detrol<sup>®</sup>), trospium chloride (Sanctura<sup>®</sup>), solefenacin succinate (Vesicare<sup>™</sup>) and darifenacin (Enablex<sup>®</sup>). Oxybutynin is available in immediate-release oral, extended-release oral and transdermal formulations. Tolterodine is available in immediate-release and extended-release oral formulations. Trospium chloride is currently only available as an immediate-release agent, but solefenacin and darifenacin are both available as extended-release oral forms.

Darifenacin is the first M<sub>3</sub>-selective receptor antagonist [13]. It was approved by the US FDA for the treatment of overactive bladder in December 2004, and was brought to market in February 2005. It is marketed in the USA as Enablex (Novartis Pharmaceuticals, Proctor and Gamble Pharmaceuticals). It is available in extended-release oral tablets containing either 7.5 or 15 mg of darifenacin hydrobromide as the active agent.

### Chemistry

Chemically, darifenacin is (S)-2-[1-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl]-2,2-diphenylacetamide and has a molecular weight of 507.5. The structural formula is shown in Figure 1. It is a white crystalline powder. It is only moderately stereoselective, the R enantiomer being slightly less potent in guinea pig ileum preparations [14].

### Pharmacology

Darifenacin is a M<sub>3</sub>-selective receptor antagonist. *In vitro* studies using Chinese hamster ovary (CHO) cells demonstrate a sixfold greater affinity

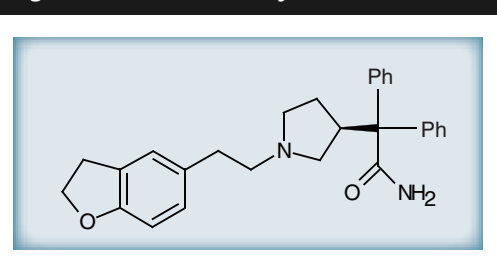
to M<sub>3</sub> receptors than to M<sub>1</sub> receptors (K<sub>d</sub> = 1.6 vs 0.33) and minimal binding to M<sub>2</sub>, M<sub>4</sub> and M<sub>5</sub> receptors [13]. Darifenacin demonstrates enhanced binding at the M<sub>3</sub> receptor compared with other muscarinic subtypes by a ratio of 9, 59, 60 and 12, when compared with M<sub>1</sub>, M<sub>2</sub>, M<sub>4</sub> and M<sub>5</sub> subtypes, respectively [15]. Darifenacin binds competitively to the M<sub>3</sub> muscarinic receptors and has a dissociation constant for the M<sub>3</sub> receptors greater than tolterodine and oxybutynin [16,17]. In human bladder strips, darifenacin inhibited carbachol-induced contractions, but did not inhibit KCl- or CaCl<sub>2</sub>-induced contractions [16]. Thus, its anticontractile action is consistent with M<sub>3</sub> blockade rather than action as a calcium channel antagonist [18].

In animal *in vitro* and *in vivo* studies, darifenacin demonstrates greater effect on bladder M<sub>3</sub> receptors than in other tissues, such as the salivary gland. Darifenacin was found to be more effective on smooth muscle preparations from guinea pig ileum and bladder than on the salivary glands. It is as potent as atropine at inhibiting carbachol-induced contractions in smooth muscle but has a sixth of the potency of atropine in the salivary glands [14]. In beagle dogs, darifenacin inhibited induced jejunal motility similar to atropine, with significantly less effect than atropine at inhibiting salivation [19]. In a mouse model, darifenacin induced tremor (an M<sub>1</sub> receptor-mediated effect) and inhibited salivation less than atropine, and was equipotent to atropine at inhibiting smooth muscle contraction [18]. It was compared with other anticholinergic drugs in anesthetized dog experiments evaluating the effect on pelvic nerve-stimulated bladder contractions, trigeminal nerve stimulated salivation and heart rate changes. These data demonstrate that the selectivity of darifenacin for bladder over salivary glands is a factor of ten, roughly twice that of oxybutynin, tolterodine and propiverine, as shown in Table 1 [20]. No human *in vitro* studies have specifically investigated the relative bladder M<sub>3</sub> specificity demonstrated by animal studies.

### Pharmacokinetics

Darifenacin is well absorbed from the gut [21], primarily from the colon in the prolonged-release form available for clinical use [22]. A study of pooled data from 337 patients in Phase I and II trials described the pharmacokinetics of several different formulations of the drug [23]. The drug was given orally (1–45 mg) in immediate- and extended-release forms, as well as intravenously

Figure 1. Darifenacin hydrobromide.



**Table 1. ID<sub>50</sub> values of various antimuscarinic drugs in various tissues.**

Antimuscarinic drug	Bladder (ID <sub>50</sub> value)	Salivary (ID <sub>50</sub> value)	Heart rate (ID <sub>50</sub> value)
Darifenacin	6.7	67	>100
Oxybutynin	30	123	>300
Tolterodine	37	185	265
Propiverine	1139	4755	>10000

From [14]. ID<sub>50</sub>: 50% inhibitory value.

(0.6–6 mg). The half-life of absorption increased as the release duration was extended. The drug is completely absorbed, with the immediate-release form being primarily in the upper gastrointestinal (GI) tract, whereas the extended-release formulation reaches the lower gut and, thus, is exposed to less metabolic activity in the first pass. Relative bioavailability of the prolonged-release form is approximately twice that of the immediate-release form [22]. Absolute bioavailability of the prolonged-release form of the drug is estimated to be 15.4% for the 7.5 mg dose and 18.6% for the 15 mg tablets in cytochrome P450 (CYP)2D6 extensive metabolizers.

The volume of distribution of darifenacin has been calculated to be 165–276 l in healthy volunteers [22]. In humans, the drug is 98% protein bound and its primary metabolite is 87% bound. The metabolite has 11% of the activity of the drug. Correcting for the *in vivo* protein binding, the metabolite is 50-fold less potent than the parent drug [21]. It is a lipophilic molecule, thus some degree of CNS penetration might be expected; however, there are no data regarding specific distribution of the drug in human tissues [22].

The drug undergoes hepatic metabolism via three main pathways: monohydroxylation, oxidative dihydrobenzofuran ring opening and *N*-dealkylation. There are no marked species differences in metabolism [21]. Darifenacin is a CYP pathway substrate that is metabolized via CYP2D6 and CYP3A4 pathways [22]. The CYP3A4 inhibitors ketoconazole and erythromycin increase the bioavailability to 100% and decrease the exposure to metabolites [21]. Clearance of the drug was found to be 40.2 l/h and ketoconazole decreased clearance by 67.5%. The clearance is 31% lower in females and 10% lower at night [23]. The drug is excreted as its metabolites, approximately 60% via urine and 40% via feces. Food does not affect the pharmacokinetics of darifenacin. Hepatic impairment increases plasma concentrations, as do the drugs ketoconazole, erythromycin and

fluconazole. Plasma concentrations of imipramine may be elevated by the concurrent use of darifenacin [22].

### Clinical efficacy

Clinical efficacy of antimuscarinic drugs in treating OAB has been hampered by frequent adverse effects, such as dry mouth, constipation, blurred vision, drowsiness and cognitive changes in elderly patients [26]. These dose-related adverse effects limit the maximum therapeutic dose that can be tolerated and are often bothersome enough to cause patient nonadherence, suboptimal dosing and drug discontinuation. For instance, only 18–22% of patients prescribed with immediate-release oxybutynin remained on the medication after 6 months owing to intolerable adverse effects [27,28]. Since OAB is a chronic debilitating condition requiring long-term treatment to alleviate the symptoms, it is important that the anticholinergic medication are not only effective but also well tolerated.

While darifenacin preferentially blockades M<sub>3</sub> receptors versus other muscarinic subtypes, it is not completely bladder M<sub>3</sub> specific. The *in vitro* animal data demonstrating relative uroselectivity has not been confirmed by *in vivo* human studies, as suggested by the results obtained by Rosario [24]. Although the drug may not be uroselective, it has less indiscriminate blockade of other muscarinic receptor subtypes. The theoretical advantages are that there may be less cognitive changes (less CNS M<sub>1</sub> blockade), fewer cardiovascular effects (less M<sub>2</sub> blockade) and less dry mouth (less salivary gland M<sub>1</sub> blockade [10]).

Rosario and colleagues randomized 18 patients to receive either darifenacin or placebo [24]. Urodynamic and salivary flow testing was used to study the 10 and 2.5 mg doses. Salivary flow was reduced by the 10 mg dose, whereas 2.5 mg had no effect on salivary flow. The volume threshold for detrusor activity was increased by the 10-mg dose, with no change in the amplitude of overactivity contractions. The 2.5-mg dose did not alter urodynamic parameters [24]. In a Phase II study of

darifenacin, patients with detrusor activity were monitored by continuous ambulatory urodynamics. Multiple doses were well tolerated and reduced the total number, maximum amplitude and duration of detrusor overactivity-associated contractions [25].

Darifenacin (7.5 or 15 mg/day) is more effective than placebo in alleviating OAB symptoms. Results from several large Phase III, randomized, multicenter, double-blind, placebo-controlled, parallel-group trials are summarized in Table 2 [29–33]. Patient age in these trials covered a wide range (20–93 years), but the mean ages were typically in the high 50s. Approximately a third of patients are aged over 65 years. Most patients were white (>90%) and females (>80%), who complained of typical OAB symptoms. Both naive patients who had never received prior antimuscarinic drugs and those who had were included in these studies. The improvements in weekly incontinence episode and weekly urgency episode were consistent among the studies. However, the improvements were only moderate. At the maximum recommended dosage (15 mg/day), only 62–70% of patients experienced a greater

than 50% reduction in weekly incontinent episode [32,33]. An even smaller percentage (34%) of patients reported greater than 50% reduction in weekly urgency episode [33]. No improvement in nocturia was noted. One placebo-controlled study demonstrated an improvement in warning time of 4.3 min compared with placebo with darifenacin 30 mg (two- to four-times the recommended dosage) [34]. Another placebo-controlled study failed to demonstrate any improvement in warning time with darifenacin 15 mg [30], although these studies were performed to evaluate warning time as a possible OAB outcome parameter, and were not intended as efficacy trials for darifenacin.

The clinical response was dose responsive in placebo-controlled studies. A small (~10%) improvement in the median number of weekly incontinent episodes was noted when the dosage was increased from 7.5 to 15 mg/day [29,31,33]. Further improvement (~20%) in the mean number of incontinent episodes was noted when the dosage was increased from 15 to 30 mg/day [35]. The onset of efficacy was rapid. Two-thirds of the therapeutic benefits were already experienced by the second week of treatment [29,32]. Efficacy

**Table 2. Clinical efficacy of darifenacin versus placebo or oxybutynin.**

Study	Efficacy reported at (weeks)	Reduction in median number of weekly incontinent episodes (%)				Reduction in median number of weekly urge episodes (%)				Ref.		
		Darifenacin (mg)			Placebo	Oxybutynin 5 mg t.i.d.	Darifenacin (mg)				Placebo	Oxybutynin 5 mg t.i.d.
		7.5	15	30			7.5	15	30			
Haab <i>et al.</i> (2004)	2 12	43 69	53 72	34 51		29	29	13		[29]		
Zinner <i>et al.</i> (2006)	12		67	47			22*	18*		[30]		
Steers <i>et al.</i> (2005)	2 12	43 63 <sup>‡</sup>		29 48		14 28 <sup>‡</sup>		4 11		[32]		
Chapple <i>et al.</i> (2005)	12	68	77	55–58		29	29	14–17		[33]		
Hill <i>et al.</i> (2006)	12	69	77	77	46	29	27	33	16	[31]		
Zinner <i>et al.</i> <sup>§</sup> (2005)	2		46	57	28	54	15	18	6	13	[35]	
Habb <i>et al.</i> <sup>¶</sup> (2006)	2 years	84 <sup>¶</sup>				56 <sup>¶</sup>					[36]	

\*The 15 mg darifenacin result was not statistically significant from that of placebo.

<sup>‡</sup>By 12 weeks, patients were taking either 7.5 or 15 mg/day of darifenacin in this dose-titration study.

<sup>§</sup>Mean (not median) results.

<sup>¶</sup>Extension study of [29,32], patients were taking either 7.5 or 15 mg/day.

t.i.d.: Three-times daily.

continued to improve at 12 weeks when the studies concluded. Habb and colleagues recently published the results of a multicenter, noncomparative, open-label extension study in which patients chose to take either 7.5 or 15 mg/day after they had finished the 12-week feeder studies [29,32,36]. At a median follow-up of 2 years (the longest yet published for a trial of a controlled-release antimuscarinic), the efficacy of darifenacin was maintained in the 66% of patients who completed the extension study (a 84% decline in the number of incontinent episodes per week, compared with feeder study baseline;  $p < 0.001$ ) (Table 2). Good clinical response has been reported in men and women over a wide range of ages, although patients with OAB secondary to interstitial cystitis, anterior vaginal prolapse (cystocele), bladder outlet obstruction, prostatic enlargement or mixed incontinence with significant stress component have not been studied specifically since these are common exclusion criteria in OAB trials [29–33].

There are no well-designed, randomized, comparative studies comparing darifenacin with currently marketed antimuscarinic drugs. The only published report that compared darifenacin (15 or 30 mg/day) to immediate-release oxybutynin (5 mg three-times daily) was a four-way crossover study (a suboptimal experimental design) that was too short in duration (2 weeks for each drug) and enrolled too few patients (76 total in all arms) to really address the difference in efficacy [35]. Plus, it is not fair to compare darifenacin with oxybutynin 5 mg three-times daily since the former is an extended-release formulation while the latter is not. Nevertheless, in that particular study [35], darifenacin 15–30 mg had similar efficacy as oxybutynin 5 mg three-times daily (46–57% vs 54% reduction in weekly incontinent episodes,  $p > 0.05$ ; 15–18% reduction in weekly urgency episodes,  $p > 0.05$ ). There are currently no randomized studies that compare darifenacin with any of the currently routinely used antimuscarinics (extended-release oxybutynin, tolterodine, trospium chloride or solefenacin). Without well-designed head-to-head studies, one simply do not know whether darifenacin is more effective than other antimuscarinic drugs. In the absence of head-to-head studies, adjusting drug response rates for the placebo response (so-called ‘delta-efficacy’ or ‘effect-size’) may be one method of comparing the efficacy data from placebo-controlled darifenacin studies [29–33] with those from placebo-controlled oxybutynin or

tolterodine studies [37–39]. The placebo effect of darifenacin trials (~50%) was significantly higher than that of other antimuscarinic trials (~30%), therefore the delta-efficacy (defined as drug effect minus placebo effect) of darifenacin may actually be smaller. Whether the disparity of delta-efficacy represents a true difference in drug efficacy or reflects different experimental designs remains to be determined.

### Adverse effects & tolerability

Despite a good level of efficacy in OAB patients, dry mouth and constipation continued to plague a significant number of patients taking darifenacin. In Phase III, randomized, multicenter, double-blind, parallel-group, placebo-controlled trials lasting 1–12 weeks, the incidences of dry mouth and constipation for darifenacin were higher than that of placebo ( $p > 0.05$ ) (Table 3) [29–33,40–42]. These adverse effects were mild to moderate, as they were rarely severe enough to cause discontinuation of the medication or dosage reduction (0–2.3% for dry mouth, 0–2.3% for constipation) [30–33]. The incidence of dry mouth of darifenacin was dose dependent [41]. Despite a high incidence of constipation, the percentage of darifenacin patients using laxatives or stool softeners was similar to placebo (30% in the darifenacin 15 mg group, 25% in the placebo group) [33], suggesting that the drug-induced constipation (or even its definition in the studies) may not be severe.

A 2-year, open-label extension study demonstrated that darifenacin (7.5 or 15 mg/day) was well tolerated in the long term [36]. At median follow-up of 2 years, 66% of patients completed the extension study, while 9% discontinued due to adverse effects (most of the withdrawals were during the first 3 months of the extension). A total of 23% of patients reported dry mouth, although only 1.3% were severe enough to cause discontinuation. Constipation was reported by 20% of patients, yet only 2.4% withdrew due to constipation. Use of fiber supplements, stool softeners or laxatives was initiated by only 5.6% of patients during the study. Analysis of bowel-habit questionnaires revealed that the reporting of constipation was related to minor changes in bowel habit rather than true constipation.

Three studies have compared the adverse effect profiles of darifenacin with either immediate-release [35,41] or extended-release oxybutynin [42]. Zinner and colleagues randomized 76 patients to receive 2 weeks of darifenacin 15 mg, darifenacin 30 mg, oxybutynin 5 mg three-times daily or

**Table 3. Incidence of adverse effects of darifenacin versus placebo or oxybutynin.**

Study	Side effects at (weeks)	Dry mouth (%)				Constipation (%)				Ref.		
		Darifenacin (mg)			Placebo	Oxy	Darifenacin (mg)				Placebo	Oxy
		7.5	15	30			7.5	15	30			
Haab <i>et al.</i> (2004)	12	19	31		9	14	14		7	[29]		
Zinner <i>et al.</i> (2006)	12		29		6		18		5	[30]		
Steers <i>et al.</i> (2005)	12	19*				21*				[32]		
Chapple <i>et al.</i> (2005)	12	20	35		8	15	21		6	[33]		
Hill <i>et al.</i> (2006)	12	23	40	60	6	16	25	28	5	[31]		
Kay <i>et al.</i> (2005)	7 days	30	48		13					[40]		
Kay <i>et al.</i> (2006)	3		27		12		20		2	4 (20 mg ER od) <sup>‡</sup>	[42]	
Lipton <i>et al.</i> (2005)	2	7	9		3	8	12		9	13 (5 mg IR t.i.d.) <sup>§</sup>	[41]	
Zinner <i>et al.</i> (2005)	2		13	30	5		10	21	3	8 (?? mg IR t.i.d.) <sup>§</sup>	[35]	
Habb <i>et al.</i> <sup>¶</sup> (2006)	2 years	23				20					[36]	

\*By 12 weeks, patients were taking either 7.5 mg or 15 mg daily of darifenacin in this dose-titration study.

<sup>‡</sup>Oxybutynin 20 mg extended-release (ER) daily (od).

<sup>§</sup>Oxybutynin 5 mg immediate-release (IR) thrice daily (t.i.d.).

<sup>¶</sup>Open extension study of [29,32], patients were taking either 7.5 or 15 mg daily.

ER: Extended release; IR: Immediate release; od: Once daily; Oxy: Oxybutynin; t.i.d.: Three-times daily.

placebo in a four-way crossover study [35]. The group showed that the incidence of dry mouth for darifenacin 15 mg (13.1%) was statistically equivalent to that of placebo (4.9%;  $p > 0.05$ ), but much less than that of either darifenacin 30 mg (34.4%;  $p < 0.05$ ) or immediate-release oxybutynin (36.1%;  $p < 0.05$ ). The dry mouth adverse effect of darifenacin 30 mg was as poor as that of oxybutynin 5 mg three-times daily ( $p > 0.05$ ). The incidence of constipation of low-dose, darifenacin 15 mg (13.1%) was statistically similar to that of oxybutynin 5 mg three-times daily (8.2%;  $p > 0.05$ ) and placebo (3.3%;  $p > 0.05$ ). The incidence of high dose, darifenacin 30 mg (21.3%) was significantly worse than that of 5 mg three-times daily oxybutynin or placebo ( $p < 0.05$ ). Lipton and colleagues demonstrated no differences in the incidence of dry mouth between the darifenacin groups and the immediate-release oxybutynin group in a three-period crossover study (4.2% with darifenacin 3.75 mg, 6.8% with darifenacin 7.5 mg, 9.2% with darifenacin 15 mg, 12.7%

with oxybutynin 5 mg three-times daily;  $p > 0.05$ ) [41]. Also, no differences in constipation rates were noted ( $p > 0.05$ ). In the third study (randomized, double-blind, non-crossover), Kay and colleagues demonstrated that the incidence of dry mouth was lower in the darifenacin 15 mg group than in the extended-release oxybutynin group after 3 weeks of treatment (27% with darifenacin 15 mg, 40% with oxybutynin 20 mg and 12% with placebo) [42]. The constipation rate of darifenacin in that trial (20%) was actually higher than that of oxybutynin (4%) and placebo (2%).

None of the studies in the aforementioned published literature answered the question as to whether darifenacin causes less dry mouth or constipation than other antimuscarinic drugs. All of these studies [35,41,42] were suboptimal since:

- The study durations were too short (2–3 weeks);
- They were complex crossover studies rather than head-to-head, randomized, blinded clinical trials;

- The sampling sizes were too small to achieve statistical power;
- The studies were not designed to compare adverse effects as primary end points.

No other trials have compared darifenacin with tolterodine, trospium chloride or solefenacin. Head-to-head, randomized, blinded, comparative studies of longer duration (>12 weeks) must be performed to determine if darifenacin offers a better tolerability profile than other antimuscarinic agents. Given the lack of demonstrated human uroselectivity of darifenacin, one would not expect darifenacin to have less dry mouth or constipation than other antimuscarinics.

One potential advantage of M<sub>3</sub> receptor selectivity of darifenacin over other antimuscarinics is less cognitive changes owing to less CNS M<sub>1</sub> blockade. Theoretically, CNS adverse effect may be an issue in the elderly since:

- They often have other comorbidities that might predispose them to neurocognitive problems;
- They may take multiple medications that exacerbate the adverse effects on cognition;
- Most antimuscarinic drugs, including darifenacin, undergo hepatic-cytochrome metabolism and are subject to altered metabolism due to polypharmacy.

Darifenacin did not cause cognitive adverse effects in young [40] or elderly patients [41,42] when used at 15 [29] or 30 mg (twice the recommended dose) [31,35]. The lack of CNS adverse effects may be attributed to:

- No crossing of the blood–brain barrier (in animal studies) due to darifenacin's moderate lipophilicity, large molecular size, polarity and active efflux out of the CNS through the P-glycoprotein pumps [22,43];
- Its M<sub>3</sub> receptor selectivity with less interference of CNS M<sub>1</sub> activity that mediates cognitive functions, such as memory, learning and attention [7–9].

One double-blind, randomized trial compared the cognitive changes in 150 healthy male and female elderly volunteers (aged >60 years) after 3-week treatments of darifenacin (7.5–15 mg), versus extended-release oxybutynin (10–15 mg), versus placebo [42]. Results of the Name-Face Association Test showed no significant difference between darifenacin and placebo on delayed recall

(mean difference: -0.06,  $p > 0.05$ ). By contrast, oxybutynin resulted in memory impairment, with significantly lower Name-Face Association Test scores than placebo and darifenacin (mean differences: -1.30 and -1.24,  $p > 0.05$ ). Additional tests of delayed recall indicated significant memory impairment with oxybutynin versus placebo, whereas darifenacin was similar to placebo. While statistical difference has been reached, it is unclear whether it translates to clinical significance. CNS adverse effects have not been a significant clinical issue when other antimuscarinic drugs were used. Even if darifenacin offers marginal improvement over other antimuscarinics, if at all, it is unclear if the difference is clinically significant.

Cardiac adverse effects were very rare with darifenacin (up to 1.5%) [32] with the incidence being similar to that of placebo [33,44]. No significant changes in heart rate, heart rate variability, electrocardiogram (ECG) and vital signs were noted in several studies [40,41]. In Haab's study, one patient out of 344 who took darifenacin 7.5 mg reported second-degree atrioventricular heart block [29]. In this patient, the heart block was a pre-existing condition and it was unclear whether it was associated with darifenacin usage. No adverse cardiac events were noted when twice the recommended daily dose (30 mg) was used [31].

Despite the importance of M<sub>3</sub> receptors in visual accommodation, darifenacin is not associated with visual near-point change [40] or blurred vision [29,35].

## Conclusions & outlook

Darifenacin is the latest addition to the antimuscarinic armamentarium for the treatment of overactive bladder. It is the first M<sub>3</sub>-selective receptor antagonist, although it is not completely M<sub>3</sub> specific. Animal data suggest it may be more uroselective than other anticholinergics. Despite these theoretical advantages, it has not demonstrated a conclusive therapeutic efficacy or tolerability profile above and beyond existing antimuscarinic agents, due in part to its lack of demonstrated uroselectivity in humans. Systemic anticholinergic adverse effects (dry mouth and constipation) are common and limit its potential. At recommended doses, it has minimal impact on cognition, vision and cardiovascular function. In the current therapeutic model, a uroselective M<sub>3</sub>-specific receptor antagonist would be the optimal anticholinergic drug to treat OAB. Such a drug does not yet exist in the marketplace.

The failure of current antimuscarinic drugs to predictably improve symptoms of OAB with minimum adverse effects mandates an exploration of other treatment paradigms. Direct impairment of detrusor contractility with botulinum toxin A, in cases of refractory detrusor overactivity, has been reported to be effective and safe [45]. The effectiveness of botulinum toxin may also depend upon sensory changes via decreases in purinergic and vanilloid receptor concentrations [46]. The incidence of overactive bladder increases with age and may be a result of changes in urothelial receptor function. Reports on the effects of age have demonstrated a decrease in M<sub>3</sub> receptors, but the effect on the relative concentration of M<sub>3</sub> and M<sub>2</sub> receptors is not agreed upon [47,48]. Purinergic

pathways become more prominent with aging and, therefore, might contribute to OAB, particularly as they regulate sensation of fullness and efferent transmitter release and, thus, may be suitable therapeutic targets [49]. Serotonergic pathways via 5-HT receptors modulate the sympathetic reflex storage function of the bladder as well as inhibit the parasympathetic voiding functions [50]. Opioid receptors, dopaminergic pathways and noradrenergic α-receptors may also be targets for treatment [3]. Gabapentin has been reported to relieve symptoms in some patients otherwise refractory to antimuscarinic therapy [51]. The use of local anesthetics or intravesical vanilloid, such as capsaicin or resiniferatoxin, to dampen afferent activity has been a subject of research [52].

### Highlights

- Darifenacin is a M<sub>3</sub>-selective receptor antagonist for the treatment of overactive bladder.
- Despite encouraging animal data, it does not appear to be uroselective, and may cause systemic side effects (dry mouth and constipation).
- It has been demonstrated to be safe and effective at recommended doses (7.5 and 15 mg daily).
- No head-to-head, comparative studies have compared the clinical efficacy and tolerability profile of darifenacin with other currently marketed antimuscarinics.
- Darifenacin has not demonstrated a conclusive therapeutic efficacy or tolerability profile above and beyond existing antimuscarinic agents.
- The use of antimuscarinic agents, while the current standard for the treatment of overactive bladder, may not represent the ideal approach to this distressing problem.

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