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Solifenacin significantly improves all symptoms of overactive bladder syndrome

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SUMMARY

Overactive bladder syndrome (OAB) is a chronic condition characterised by urgency, with or without associated urge incontinence. Solifenacin succinate is a once daily, bladder selective antimuscarinic available in two doses (5 and 10 mg). The recommended dose is 5 mg once daily and can be increased to 10 mg once daily if 5 mg is well tolerated. This article presents pooled efficacy and safety data from four large, placebo-controlled, multinational phase III trials of solifenacin succinate with a total enrolment of over 2800 patients. Data from these trials show that solifenacin 5 and 10 mg once daily is significantly more effective than placebo at reducing urgency, incontinence, micturition frequency and nocturia and at increasing volume voided per micturition. Adverse events were mainly mild-to-moderate in all treatment groups. The results of these phase III trials support the use of solifenacin in the treatment of OAB.

Keywords: Solifenacin; overactive bladder; antimuscarinic

INTRODUCTION

Overactive bladder syndrome (OAB) is defined by the International Continence Society (ICS) as urgency, with or without urge incontinence, usually with frequency and nocturia (1). As such, it is a symptomatic diagnosis acknowledging the presence of storage symptoms, based on a patient's history alone, which is suggestive of urodynamically demonstrable detrusor overactivity, in the absence of proven infection or obvious pathology (1). In defining OAB and considering the individual components comprising this symptom complex, the ICS has highlighted the significant role of urgency (1). Urgency is important as it is thought to play a pivotal role in driving the other symptoms of OAB (urinary incontinence, frequency and nocturia) (2). As illustrated in Figure 1, urgency is thought to cause these other OAB symptoms by reducing the time that voiding can be deferred, thereby increasing micturition frequency and reducing the volume voided per micturition. Urgency is also thought to contribute to incontinence and nocturia, but the relationship is less direct (2).

Bladder storage symptoms have a severe impact on all areas of quality of life (QoL) including social, psychological and work function (3,4). Therapy for chronic, non-life threatening conditions, such as OAB, should focus on patient benefit and in doing so must take account of patient perceived outcomes, rather than simple symptom resolution alone. Efficacy of OAB therapy needs to be balanced against tolerability, as a low incidence of adverse events (AEs) improves compliance with treatment. This balance between efficacy and tolerability should provide palpable benefits from a patient's perspective, and promote persistence with a therapy, which is of course an important issue in chronic conditions, such as OAB, that require continued therapy. Unfortunately, many antimuscarinics, especially older agents, have modest clinical efficacy and are associated with unfavourable side effects, leading to poor persistence with therapy (5). Many clinical trials of antimuscarinics have not published efficacy endpoints for all the symptoms contained within the ICS definition for OAB and, further, often overlook patient benefits such as treatment satisfaction and QoL.

Antimuscarinic agents are the mainstay of OAB pharmacotherapy, and exert their effects by competitively blocking acetylcholine binding at the muscarinic receptors within the various histological compartments of the bladder. As well as being released from efferent cholinergic nerves innervating

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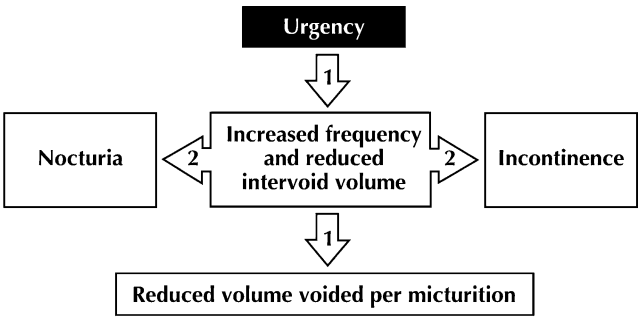

Figure 1 The role of urgency in initiating overactive bladder syndrome symptoms (reproduced from Chapple et al. 2005 – permission requested (2))

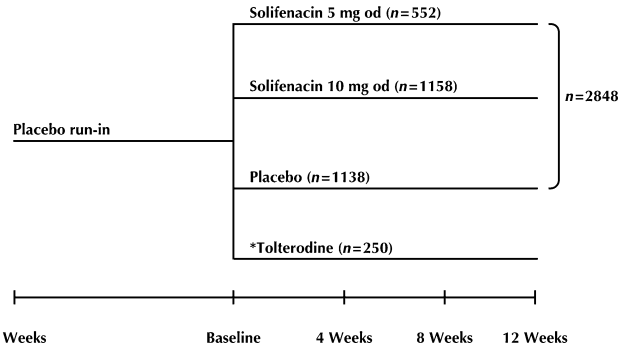

Figure 2 Study design. n = number of patients evaluated for efficacy; od = once daily. The tolterodine treatment arm was included in only one of the four phase III studies

the detrusor, recent experimental work has suggested that acetylcholine can be released by stretch of the urothelium from non-neuronal sources, in addition to being related to leakage from neurones (6). There is also increasing evidence that acetylcholine may act on receptors in the suburothelial plexus, thereby influencing the afferent system and detrusor contraction.

Solifenacin succinate is a once-daily, oral antimusarinic agent, which shows *in vitro* selectivity for bladder tissue over salivary preparations (7,8). Solifenacin has also displayed efficacy in the treatment of OAB, as demonstrated in four large double-blind, placebo-controlled, 12-week, phase III studies assessing over 3000 patients (9–12). As protocols were similar, we are able to present the pooled data from these four studies, allowing an objective evaluation of the efficacy and tolerability of once-daily solifenacin 5 and 10 mg in reducing all symptoms of OAB in one of the largest pooled analyses of an antimuscarinic agent to date.

MATERIALS AND METHODS

Study design and protocol

Four multinational, double-blind, randomised, phase III studies were conducted with similar protocols (9–12). A tolterodine 2 mg twice daily active treatment arm was included in one of the four studies, but was not powered for comparison. The methods, design and results of this single study have been previously published (10); the tolterodine data are excluded from the pooled analysis in this current report (Figure 2).

Patients completed a 3-day micturition diary before the first visit and before all subsequent monthly visits. All patients underwent a baseline assessment including medication history, physical examination, vital signs, laboratory tests and electrocardiogram. After completing a 2-week placebo run-in or screening/washout period, patients began their treatment regimen on the first day of the study. In two of the studies, patients were randomised to once-daily treatment with solifenacin 10 mg or placebo. In the other two studies, patients were randomised to once-daily treatment with 5 mg solifenacin, 10 mg solifenacin or placebo.

These studies were performed in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines, and the principles of the Declaration of Helsinki. The study protocol was approved by the responsible ethical committee at each study site. All patients were informed of the nature and purpose of the study, and written informed consent was obtained before screening.

Patients

Outpatient men and women, at least 18 years of age, with symptoms of OAB were eligible for enrolment. During a baseline 3-day micturition diary period, patients were required to report a mean of $\geq$8 micturitions per 24 h, and either a mean of $\geq$1 incontinence episode per 24 h or a mean of $\geq$1 urgency episode per 24 h.

Efficacy analysis

Data on urgency, incontinence, micturition frequency, nocturia episodes and volume voided were collected using a 3-day micturition diary, and reported at baseline and before visits at weeks 4, 8 and 12. For each episode, date and time, whether or not the patient voided, the presence of urgency and incontinence, volume voided (for at least 2 of the 3 days), and whether or not the episode disturbed the patient's sleep (episodes of nocturia) were recorded; the time of rising from and going to bed were also recorded. Efficacy analyses included mean and median changes from baseline to endpoint in the number of each of the following per 24 h: episodes of urgency, incontinence, nocturia and micturitions. The volume voided per micturition was also

recorded. Patients without at least one on-treatment efficacy assessment were excluded from the analyses. In line with ICS guidelines for the presentation of data, symptom 'resolution'/'normalisation' rates were also examined, as well as an assessment of the 50% improvement in the symptoms of urgency, incontinence, number of micturitions and nocturia (13). Symptom 'resolution' was defined as the complete absence of symptoms at the study endpoint that were present at baseline. Symptom 'normalisation' applied only to micturition frequency, and was defined as a reduction to below eight micturitions per 24 h.

Two of the four trials described in this analysis measured QoL changes using the King's Health Questionnaire (KHQ) (14). Solifenacin significantly improved KHQ scores from baseline in nine of 10 domains compared with placebo, demonstrating statistically significant improvements in patient QoL (15,16). The clinical relevance of improvements in the KHQ scores was determined using a scale based on a global rating of patient-perceived treatment benefit, and perceived disease impact (25): a minimally important difference (MID) was defined as a $>5\%$ point change from baseline, which focussed on the differences between the solifenacin- and placebo-treatment groups for each individual KHQ domain.

Safety assessments

Treatment emergent adverse events (TEAEs) were evaluated for the safety population. A TEAE was defined as an AE that occurred after the first dose of study medication that was not evident before treatment, or worsening of an AE that was present before start of treatment. Treatment-emergent adverse events were classified into mild/moderate and severe groups, as determined by the investigator. Serious AEs were reported based on the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) criteria. Discontinuation rates due to AEs were also evaluated.

Statistical methods

Mean changes from baseline to endpoint in all symptoms were compared by analysis of covariance (ANCOVA) for each OAB outcome, with treatment and centre as terms and baseline as a covariate. Treatment group comparisons of 'responder' or 'normalisation' rates were based on Fisher's exact test. Actual mean change from baseline to endpoint was normally distributed; therefore, p-values were based on the ANCOVA model. The percent change from baseline to endpoint was not normally distributed; therefore, p-values for the percent change were based on Van Elteren's test stratified by pooled centre. Endpoint was defined as the last available on-treatment assessment. The p-values for the pairwise testing of solifenacin vs. placebo differences in MID for KHQ changes were based on a logistic regression model with treatment and study as terms, and baseline as a covariate.

RESULTS

Patients

Baseline characteristics and OAB symptoms for the pooled study population are summarised in Table 1. From a total of 3032 patients randomised to 5 mg solifenacin, 10 mg solifenacin or placebo, data from 2848 patients were available for the analysis of efficacy and was defined as the full analysis set (Figure 2). Of the patients included in the present analysis, 99% of patients reported an urgency episode, 66% reported an incontinence episode and 89% reported a

Table 1 Baseline demographics and efficacy characteristics for the full analysis set

	Placebo	*Solifenacin 5 mg od*	*Solifenacin 10 mg od*
Number of subjects (*n*)	1138	552	1158
Age (years)			
Mean	58.0	56.7	57.9
<65 years, *n* (%)	742 (65)	370 (67)	756 (65)
≥ 65 years, *n* (%)	396 (35)	182 (33)	402 (35)
Gender			
Male (%)	219 (19)	121 (22)	242 (21)
Female (%)	919 (81)	431 (78)	916 (79)
Baseline OAB symptom levels, mean (SE)			
Urgency episodes per 24 h ($n = 2823$)	6.3 (0.12)	5.9 (0.20)	6.2 (0.12)
Incontinence episodes per 24 h ($n = 1873$)	2.9 (0.10)	2.6 (0.14)	2.9 (0.10)
Micturitions per 24 h ($n = 2848$)	11.9 (0.11)	12.1 (0.16)	11.9 (0.10)
Volume voided per micturition (ml) ($n = 2843$)	165.5 (2.24)	149.0 (2.30)	163.4 (2.08)
Nocturia episodes per 24 h ($n = 2534$)	1.8 (0.04)	2.0 (0.05)	1.8 (0.04)

od, once daily; OAB, overactive bladder syndrome; SE, standard error of mean.

nocturia episode at baseline, as assessed by a 3-day diary. As part of the inclusion criteria, all patients had a micturition frequency of ≥8 micturitions per day.

Improvements in overactive bladder symptoms

Changes from baseline to endpoint in urgency, incontinence, micturition frequency, volume voided and nocturia are summarised in Table 2. Compared with placebo, solifenacin treatment at either the 5 or 10 mg dose resulted in a significant improvement in all of the symptoms measured. This was statistically significant for both 5 and 10 mg solifenacin doses, when comparing mean actual reductions for all of the OAB symptoms and for the mean actual increase in volume voided per micturition (Table 2). When assessing urgency (mean absolute values and median percentage values), treatment with solifenacin 5 and 10 mg resulted in a −2.9 (−66.1%) and −3.4 (−70.0%) baseline to endpoint reduction in urgency episodes, respectively, compared with a −2.0 (−40.0%) episode reduction in patients receiving placebo ($p < 0.001$ for both solifenacin doses vs. placebo). The reduction in incontinence for 5 and 10 mg solifenacin was −1.5 (−100%) and −1.8 (−100%) baseline to endpoint reduction in episodes compared with a −1.1 (−63.6%) episode reduction for patients receiving placebo ($p < 0.001$ for both doses vs. placebo). The frequency of micturition was significantly reduced in patients receiving both solifenacin 5 mg (−2.3; −19.4%) and 10 mg (−2.7; −22.5%), compared with placebo (−1.4; −12.0%; $p < 0.001$ for both doses); this was reflected in the number of nocturia episodes, which were also reduced significantly in solifenacin 5 mg recipients (−0.6; −35.5%) and 10 mg recipients (−0.6; −36.4%), compared with patients receiving placebo (−0.4; −25.0%; $p < 0.05$ and <0.001 for solifenacin 5 and 10 mg, respectively). In addition, the volume voided per micturition increased significantly after solifenacin treatment, both with 5 mg (32.3 ml; 19.0%) and 10 mg (42.5 ml; 25.7%), compared with treatment with placebo (8.5 ml; 3.1%; $p < 0.001$ for both doses) (Figure 3). The greater efficacy seen with solifenacin at both doses, compared with placebo was not affected by either age or gender (Table 2).

'Resolution'/'normalisation' rates and ≥50% improvements from baseline

In patients treated with solifenacin 5 and 10 mg who had urgency at baseline, 29% and 25%, respectively, had no urgency episodes at endpoint when compared with placebo (15%). This difference was statistically significant for both doses of solifenacin ($p < 0.001$) (Table 3). Furthermore, of those patients who had incontinence at baseline, 51% and 52% of patients receiving 5 and 10 mg solifenacin, respectively, reported no incontinence episodes at the study endpoint, compared with only 34% of patients receiving placebo ($p < 0.001$; Table 3). Patients treated with either solifenacin dose also experienced normalisation of micturition frequency, which was statistically significantly greater than placebo ($p < 0.001$ for both solifenacin dose groups; Table 3). Similar results were seen with respect to resolution

Table 2 Mean actual change in overactive bladder syndrome symptoms from baseline to endpoint

	Mean baseline to endpoint change per 24 h									
	Number of urgency episodes		*Number of incontinence episodes*		*Micturition frequency*		*Volume voided per micturition*		*Number of nocturia episodes*	
	n	*Change*	*n*	*Change*	*n*	*Change*	*n*	*Change*	*n*	*Change*
Placebo (total)	1124	−2.0	781	−1.1	1138	−1.4	1135	8.5	1005	−0.4
Placebo (<65 years)	733	−2.2	494	−1.2	742	−1.6	739	8.2	640	−0.5
Placebo (≥65 years)	391	−1.6	287	−1.0	396	−1.1	396	9.1	365	−0.3
Placebo (males only)	217	−1.9	94	−0.7	219	−1.2	219	−0.9	194	−0.4
Placebo (females only)	907	−2.0	687	−1.2	919	−1.5	916	10.8	811	−0.4
Solifenacin 5 mg (total)	548	−2.9†	314	−1.5†	552	−2.3†	552	32.3†	494	−0.6*
Solifenacin 5 mg (<65 years)	366	−2.8†	208	−1.6†	370	−2.5†	370	33.4†	326	−0.6
Solifenacin 5 mg (≥65 years)	182	−3.2†	106	−1.5*	182	−2.0†	182	30.2†	168	−0.6
Solifenacin 5 mg (males only)	121	−2.7*	43	−1.7	121	−1.9*	121	25.7†	109	−0.5
Solifenacin 5 mg (females only)	427	−3.0†	271	−1.5†	431	−2.4†	431	34.2†	385	−0.6*
Solifenacin 10 mg (total)	1151	−3.4†	778	−1.8†	1158	−2.7†	1156	42.5†	1035	−0.6†
Solifenacin 10 mg (<65 years)	753	−3.5†	482	−1.7†	756	−2.8†	755	40.5†	666	−0.6*
Solifenacin 10 mg (≥65 years)	398	−3.2†	296	−1.9†	402	−2.5†	401	46.2†	369	−0.5*
Solifenacin 10 mg (males only)	242	−3.2†	111	−1.6*	242	−2.5†	242	32.7†	212	−0.4
Solifenacin 10 mg (females only)	909	−3.4†	667	−1.8†	916	−2.8†	914	45.1†	823	−0.6†

*$p < 0.05$ vs. placebo; †$p < 0.001$ vs. placebo.

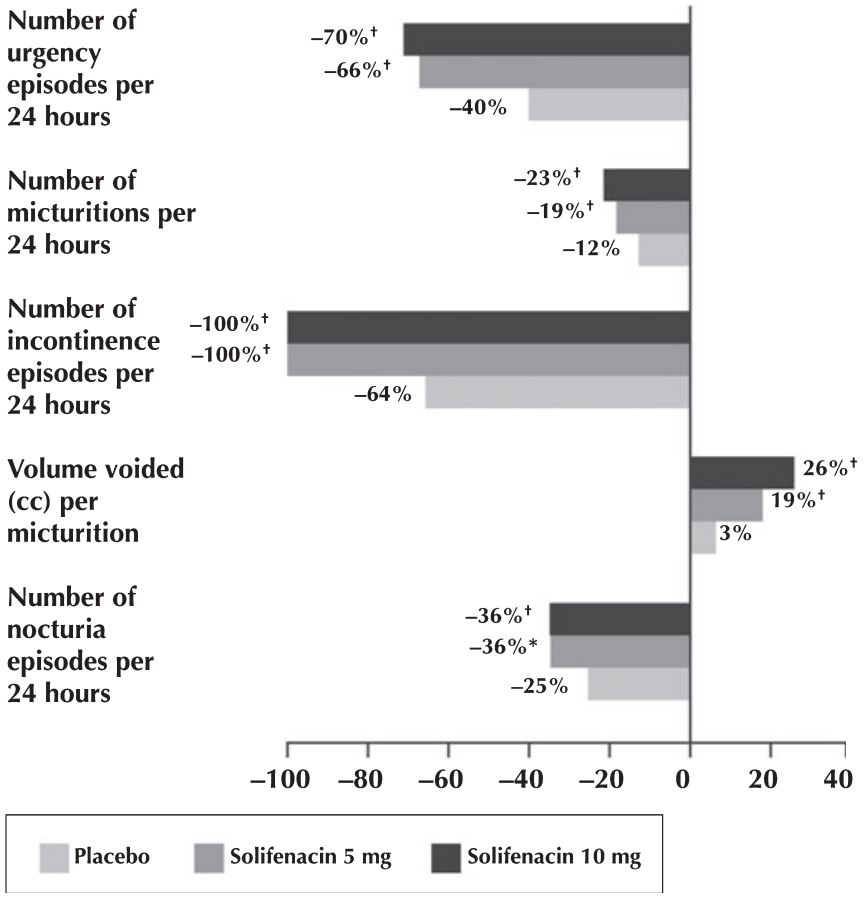

Figure 3 Median per cent changes in overactive bladder syndrome symptoms from baseline to endpoint. *p < 0.05 vs. placebo; †p < 0.001 vs. placebo. p-values for the per cent change from baseline are based on the Van Elteren's test. od = once daily

Table 3 'Resolution'*/'normalisation' rates for symptoms of overactive bladder syndrome

	Patients achieving resolution of urgency		*Patients achieving continence*		*Patients achieving normalisation of micturition frequency*		*Patients achieving resolution of nocturia*	
	%	*n (N)*	*%*	*n (N)*	*%*	*n (N)*	*%*	*n (N)*
Placebo	15.5	174 (1124)	34.1	266 (781)	22.4	255 (1138)	14.5	146 (1005)
Solifenacin 5 mg	28.6‡	157 (548)	50.6‡	159 (314)	33.0‡	182 (552)	16.2	80 (494)
Solifenacin 10 mg	25.5‡	293 (1151)	51.8‡	403 (778)	37.3‡	432 (1158)	19.0†	197 (1036)

*Resolution is defined as an absence of the symptom at endpoint; †p < 0.01 vs. placebo; ‡p < 0.001 vs. placebo; *n*, number of patients achieving 'resolution'/'normalisation'; *N*, number of patients with specified overactive bladder syndrome symptom at baseline assessment.

of nocturia, with 10 mg solifenacin producing statistically significant resolution of symptoms compared with placebo. In line with ICS guidelines for the presentation of data (1), the ≥50% improvement rates (i.e. the per cent of patients who achieved ≥50% improvement in symptoms that were present at baseline) are provided in Table 4. The per cent of solifenacin-treated patients achieving a ≥50% reduction in symptoms was significantly greater than placebo for urgency, incontinence, frequency and nocturia.

Achievement of a minimally important difference in quality of life from baseline

In the two studies which examined QoL data, solifenacin significantly improved KHQ scores from baseline in nine of 10 domains compared with placebo, demonstrating statistically significant improvements in patient QoL (15,16). When the MID was examined for each of the individual KHQ domains, it was shown that a significantly greater percentage of patients receiving solifenacin achieved an MID in certain individual domains than those receiving placebo [solifenacin 5 mg: general health perception, incontinence impact, role limitations, social limitations, emotions, sleep/energy, severity measures and symptom severity; p < 0.05 vs. placebo; solifenacin 10 mg: general health perception, incontinence impact, role limitations, physical limitations, social limitations, emotions, sleep/energy, severity measures and symptom severity; p < 0.05 vs. placebo (Figure 4)].

Table 4 Patients achieving a ≥50% reduction in overactive bladder syndrome symptoms

	Urgency episodes		*Incontinence episodes*		*Micturitions*		*Nocturia episodes*	
	%	*n (N)*	*%*	*n (N)*	*%*	*n (N)*	*%*	*n (N)*
Placebo	43.8	492 (1124)	57.6	450 (781)	43.5	495 (1138)	36.2	364 (1005)
Solifenacin 5 mg	61.9†	339 (548)	70.7†	222 (314)	60.5†	334 (552)	43.3%*	214 (494)
Solifenacin 10 mg	66.2†	762 (1151)	78.5†	611 (778)	63.6†	736 (1158)	43.6†	452 (1036)

*p < 0.01 vs. placebo; †p < 0.001 vs. placebo. *n*, number of patients achieving 'resolution'/'normalisation'; *N*, number of patients with specified overactive bladder syndrome symptom at baseline assessment. p-values for between-treatment comparisons of 'responder' and 'normalisation' rates were based on Fisher's exact test.

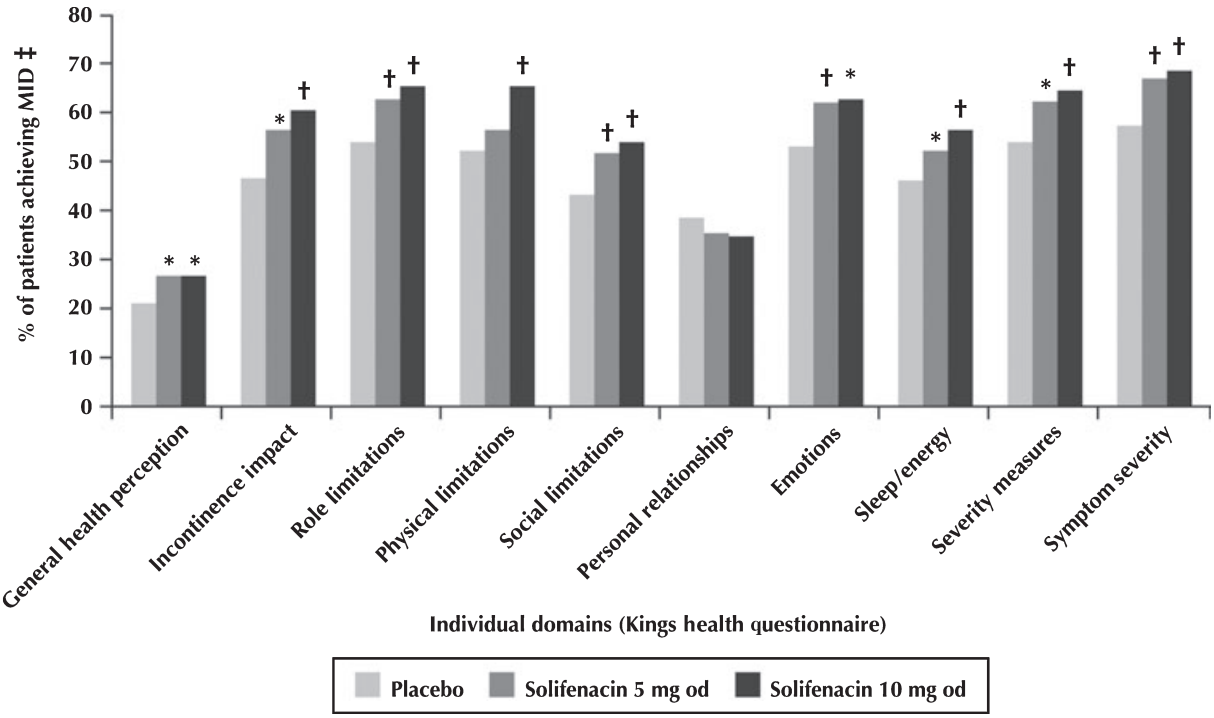

Figure 4 Percentage of subjects achieving a clinically meaningful minimally important difference (MID) (≥5 points)‡ in King's Health Questionnaire individual domain scores (mean change from baseline to end of study). *p < 0.05; †p ≤ 0.001 vs. placebo using a logistic regression model. od = once daily; ‡MIDs based on Reese et al. (25)

Safety

Treatment was well tolerated with both doses of solifenacin, with the majority of AEs being mild-to-moderate in nature. The most common TEAEs were dry mouth, constipation, and blurred vision, all of which are recognised side effects of antimuscarinic therapy (Table 5). Although the incidence of dry mouth was higher in the 10 mg solifenacin treated group compared with patients receiving 5 mg solifenacin, the number of patients discontinuing treatment due to AEs was low and comparable with placebo at both solifenacin doses (4.4% placebo, 2.8% solifenacin 5 mg, 6.8% solifenacin 10 mg). Completion rates in the studies were also high (86.4% placebo, 91.0% solifenacin 5 mg, 86.7% solifenacin 10 mg).

DISCUSSION

Overactive bladder syndrome is a chronic condition encompassing the bothersome storage symptoms of urgency, with or without urge incontinence, usually with frequency and nocturia. Therefore, effective treatment of OAB must result in a reduction meaningful to the patient in all of these symptoms. This review of the data clearly shows that treatment with once-daily solifenacin 5 and 10 mg is associated with significant improvements in all of the symptoms of OAB. Indeed, >25% of solifenacin-treated patients experienced resolution of urgency, >50% of solifenacin-treated patients achieved continence, and at least one-third of solifenacin-treated patients experienced 'normalisation' of micturition frequency to eight or fewer voids per day by study

Table 5 Rates of dry mouth, constipation and blurred vision, and discontinuation rates due to adverse events

Treatment emergent adverse events	*Placebo*		*Solifenacin 5 mg*		*Solifenacin 10 mg*	
	n	%	*n*	%	*n*	%
Dry mouth						
Mild/moderate	50	4.1	62	10.7	323	26.2
Severe	1	0.1	1	0.2	19	1.5
Constipation						
Mild/moderate	35	2.9	30	5.2	151	12.2
Severe	0	0	1	0.2	15	1.2
Blurred vision						
Mild/moderate	22	1.8	21	3.6	56	4.5
Severe	0	0	1	0.2	4	0.3
Discontinuation due to all adverse events*	53	4.4	16	2.8	84	6.8

*Adverse events were given as the primary reason for discontinuation.

endpoint. Treatment with both doses of solifenacin was also well tolerated by patients, with a few discontinuations due to AEs. If one acknowledges the importance of urgency as a pivotal symptom in this symptom complex; then clearly the high resolution and improvement rates may well be due to solifenacin's impact on the key symptom of urgency (2).

Clearly, pharmacotherapy for OAB should not only improve symptoms, but also be tolerable, both of which will contribute to treatment persistence. One very effective measure of this 'clinical effectiveness' is assessment of QoL. Two of the four trials described in this analysis measured QoL changes (10,12), using the KHQ (14). Solifenacin significantly improved KHQ scores from baseline in nine of 10 domains compared with placebo, demonstrating statistically significant improvements in patient QoL (15,16). The clinical relevance of these improvements to patients was determined using a scale based on a global rating of patient-perceived treatment benefit, and perceived disease impact (15,16). When using the following definition of clinical meaning: MID $\leq$ 5 percentage point change from baseline; it was shown that patients who were treated with both 5 and 10 mg solifenacin demonstrated a statistically significant and clinically meaningful MID improvement from baseline in almost all KHQ domains, compared with patients receiving placebo. These improvements in QOL are likely to have contributed to the high persistence rates with solifenacin described in the present analysis (approximately 90% for patients receiving solifenacin). Similarly, high persistence rates have also been observed with longer-term treatment with solifenacin. In a 40-week, open-label extension of two of the studies included in this analysis, 81% of patients remained on solifenacin treatment for the full treatment period (17). Furthermore, patient satisfaction with treatment efficacy and tolerability was high (74% and 85%, respectively) when assessed at the end of the extension study (17).

The differences in the methodology used to record efficacy data (e.g. different study populations, different inclusion and exclusion criteria, different ways to measure and define urgency, and varying diary durations) and the selective presentation of data for symptom reduction, make it difficult and indeed academically questionable whether one can compare the results presented here with those of other published clinical trials. However, globally allowing for these misgivings, solifenacin appears to compare favourably to other antimuscarinics with respect to treating urgency and all of the other symptoms of OAB (18–21). This drug is the first antimuscarinic for which there are published reports of improvements in all the key symptoms of OAB – frequency, urgency, incontinence and nocturia. Other publications of pivotal trial data for other antimuscarinic agents have reported data for some, but not all, of these symptoms (18–21).

When considering the current published literature, there are few data available that report the 'normalisation' rates for OAB symptoms (18–21). Most reports only provide this information for incontinence rates and do not present similar results for the proportion of patients who achieve cessation of urgency and nocturia, or normalisation of micturition frequency ($<$8 micturitions per 24 h). Symptomatic outcome measures such as this should be considered to be an essential facet of the assessment of treatment efficacy and should, therefore, be of keen interest to both clinicians and other healthcare providers in determining the clinical effectiveness and utility of different antimuscarinics.

In conclusion, solifenacin's efficacy has clearly been demonstrated in published studies for all symptoms of the OAB complex, with a high degree of tolerability and patient benefit. Whilst it is interesting to speculate that the symptom improvements may be driven by the favourable impact that solifenacin has on urgency, clearly, further studies using more accurate measures of patient perceived outcome are necessary to compare this agent to other antimuscarinics. Recently published results from the STAR study have provided a head-to-head comparison between solifenacin and tolterodine ER (22,23). This study suggested that flexible dosing with both 5 and 10 mg solifenacin is more effective in reducing OAB symptoms such as urgency, incontinence, urge incontinence and improving volume voided, as well as improving patient perception of bladder condition, when compared with the highest (and recommended) dose of tolterodine ER (4 mg). The flexibility associated with solifenacin dosing may further increase its efficacy, as well as allowing treatment regimens to be designed for the needs of the individual patient, thus improving patient compliance and satisfaction (24). Although the occurrence of common antimuscarinic AEs was greater with solifenacin-treated patients than with tolterodine-treated patients, the rate of patient discontinuation was low with solifenacin use, and comparable with tolterodine (23), due to the high rate of

patient satisfaction. Patient satisfaction is also high with the long-term use of solifenacin (17). Further head-to-head comparison studies with other antimuscarinic OAB therapies are needed before definitive conclusions can be drawn.

AUTHOR DISCLOSURE

Christopher Chapple, BSc, MD, FRCS (Urol), is an investigator/consultant for Pfizer, Astellas, Schwarz Pharma, Novartis and UCB Pharma. Linda Cardozo, MD, FRCOG, receives money for consultancy and/or advisory work, or research or lecturing from the following companies: Astellas, Lilly/Boehringer Ingelheim, UCB Pharma, Pfizer, Gynecare, Plethora and Cook. William D. Steers, MD, is an investigator/consultant for Sanofi, Pfizer, Lilly and Astellas. Fred E. Govier, MD, has nothing to disclose.

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REFERENCES

1 Abrams P, Cardozo L, Fall M et al. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. *Urology* 2003; **61**: 37–49.
2 Chapple CR, Artibani W, Cardozo LD et al. The role of urinary urgency and its measurement in the overactive bladder symptom syndrome: current concepts and future prospects. *BJU Int* 2005; **95**: 335–40.
3 Kobelt G. Economic considerations and outcome measurement in urge incontinence. *Urology* 1997; **50** (6A Suppl.): 100–7; discussion 108–10.
4 Liberman JN, Hunt TL, Stewart WF et al. Health-related quality of life among adults with symptoms of overactive bladder: results from a U.S. community-based survey. *Urology* 2001; **57**: 1044–50.
5 Wein AJ. Diagnosis and treatment of the overactive bladder. *Urology* 2003; **62** (5 Suppl. 2): 20–7.
6 Andersson KE. Antimuscarinics for treatment of overactive bladder. *Lancet Neurol* 2004; **3**: 46–53.
7 Kobayashi S, Ikeda K, Miyata K. Comparison of in vitro selectivity profiles of solifenacin succinate (YM905) and current antimuscarinic drugs in bladder and salivary glands: a Ca^{2+} mobilization study in monkey cells. *Life Sci* 2004; **74**: 843–53.
8 Ikeda K, Kobayashi S, Suzuki M et al. M(3) receptor antagonism by the novel antimuscarinic agent solifenacin in the urinary bladder and salivary gland. *Naunyn Schmiedebergs Arch Pharmacol* 2002; **366**: 97–103.
9 Cardozo L. Randomized, double-blind placebo-controlled trial of once-daily antimuscarinic agent solifenacin succinate in patients with overactive bladder. *J Urol* 2004; **172**: 1919–1924.
10 Chapple CR, Rechberger T, Al-Shukri S et al. Randomized, double-blind placebo- and tolterodine-controlled trial of the once-daily antimuscarinic agent solifenacin in patients with symptomatic overactive bladder. *BJU Int* 2004; **93**: 303–10.
11 Gittelman MC, Kaufman J. Solifenacin succinate 10 mg once daily significantly improves symptoms of overactive bladder. Presented at the 17th International Federation of Gynecology and Obstetrics World Congress, Abstract 111. November 2–7, 2003; Santiago, Chile.
12 Gittelman M. The efficacy and safety of solifenacin in adults with overactive bladder: a multicenter, placebo-controlled study. *Int J Gynaecol Obstetr* 2003; **83** (Suppl. 3): 94 (abstract TP76).
13 Mattiasson A, Djurhuus JC, Fonda D et al. Standardization of outcome studies in patients with lower urinary tract dysfunction: a report on general principles from the Standardisation Committee of the International Continence Society. *Neurourol Urodyn* 1998; **17**: 249–53.
14 Kelleher CJ, Cardozo L, Chapple CR et al. Improved quality of life in patients with overactive bladder symptoms treated with solifenacin. *BJU Int* 2005; **95**: 81–5.
15 Kelleher CJ, Pleil AM, Reese PR et al. How much is enough and who says so? *BJOG*, 2004; **111**: 605–12.
16 Payne C, Kelleher CJ. Redefining response in overactive bladder syndrome – impact on quality of life. Presented at the 36th International Continence Society Congress, August 31–September 2 2005, Abstract 310. November 2–7, 2003; Montreal, Canada.
17 Haab F, Cardozo L, Chapple C et al. Long-term open-label solifenacin treatment associated with persistence with therapy in patients with overactive bladder syndrome. *Eur Urol* 2005; **47**: 376–84.
18 Haab FL, Dwyer P. Darifenacin, an M3 selective receptor antagonist, is an effective and well-tolerated once-daily treatment for overactive bladder. *Eur Urol* 2004; **45**: 420–9; discussion 429.
19 Van Kerrebroeck P, Kreder K, Jonas U et al. Tolterodine once-daily: superior efficacy and tolerability in the treatment of the overactive bladder. *Urology* 2001; **57**: 414–21.
20 Diokno AC, Appell RA, Sand PK et al. Prospective, randomized, double-blind study of the efficacy and tolerability of the extended-release formulations of oxybutynin and tolterodine for overactive bladder: results of the OPERA trial. *Mayo Clin Proc* 2003; **78**: 687–95.
21 Zinner N, Gittelman M, Harris R et al. Trospium chloride improves overactive bladder symptoms: a multicenter phase III trial. *J Urol* 2004; **171** (6 Pt 1): 2311–5.
22 Chapple C, Ballanger P, Hatzichristou D et al. Improvements in bladder condition in OAB perceived and experienced by patients in a solifenacin vs. tolterodine multinational trial (STAR study). *Neurol Urodyn* 2005; **24**: 401–598 (abstract 111).
23 Chapple CR, Martinez-Garcia R, Selvaggi L et al. A comparison of the efficacy and tolerability of solifenacin succinate and extended release tolterodine at treating overactive bladder syndrome: results of the STAR trial. *Eur Urol* 2005; **48**: 464–70.
24 Reese PR, Pleil AM, Okano GJ et al. The Star study: analysis of symptom severity and treatment response in overactive bladder. *Proc Eur Assoc Urol* 2005 (abstract 380).
25 Reese PR, Pleil AM, Okano GJ et al. Multinational study of reliability and validity of the King's Health Questionnaire in patients with overactive bladder. *Qual Life Res* 2003; **12**: 427–442.

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