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ORIGINAL ARTICLE

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Solifenacin: as effective in mixed urinary incontinence as in urge urinary incontinence

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Abstract Patients with mixed urinary incontinence (MUI) are frequently treated with antimuscarinic therapy, despite little data being previously published for this patient group. We present a subgroup analysis of patients with overactive bladder syndrome, assessing the efficacy of once-daily solifenacin succinate in patients with MUI (n=1041) or urge urinary incontinence (UUI; n=1648) only. A greater proportion of patients receiving solifenacin achieved resolution of incontinence in both the MUI and UUI groups (MUI: 5 mg=43%, 10 mg=49%; UUI: 5 mg=55%, 10 mg=54%) compared with patients receiving placebo (MUI 33%, UUI 35%). Baseline to endpoint improvements in all other symptoms were statistically significant vs placebo for both solifenacin doses in both cohorts. The incidence of adverse events was comparable between the MUI and UUI cohorts. This analysis shows that once-daily solifenacin was as effective and well tolerated in patients with MUI as in patients with UUI.

Keywords OAB · MUI · UUI · Antimuscarinic

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Introduction

Overactive bladder syndrome (OAB) is a highly prevalent condition that adversely affects the quality of life (QoL) of many individuals [1]. The OAB syndrome is subjectively defined by the presence of urgency, with or without urge incontinence, and often accompanied by increased micturition frequency (≥8 voids per day) and nocturia [2]. Those OAB sufferers with urinary incontinence (UI) have been shown to have worse QoL than their continent OAB-suffering counterparts [1]. The presence of UI has been found to be the major determining factor for sufferers to seek medical assistance [1] and for clinicians to provide treatment [3]. Although incontinence is only present in approximately one-third of OAB patients [4], the significant impact of this symptom on QoL makes the OAB wet patients an important group for which an effective treatment should be sought.

The diagnosis of the type of UI present in a patient is usually made by subjectively reported symptoms and a physical examination. UI is generally classified into two forms: (1) urge urinary incontinence (UUI), which is the complaint of involuntary leakage accompanied by, or immediately preceded by, urgency, or (2) stress urinary incontinence (SUI), defined as the complaint of involuntary leakage on effort or exertion, or on sneezing or coughing [2]. Unfortunately, patients often present with mixed urinary incontinence (MUI), when SUI occurs concurrently with UUI.

As most patients are offered treatment based on symptoms, it is often difficult to clearly evaluate their true underlying condition. Conducting a more comprehensive evaluation using conventional urodynamics would provide a clearer diagnosis, but this is usually not practical in the primary care setting due to the specialized and invasive nature of the assessments. Evidence from epidemiological surveys, primarily using patient symptoms, suggests that the prevalence of the incontinence types is highly dependent on gender, with nearly half of women with UI having SUI compared with only 8% of men (Fig. 1) [5]. UUI is the predominant type of incontinence in men

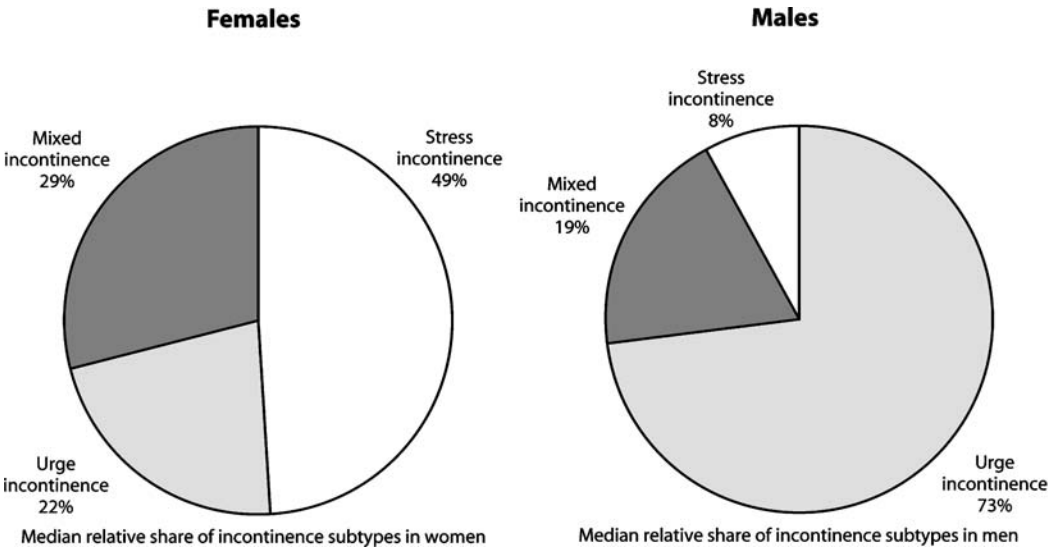

Fig. 1 Median relative share of incontinence subtypes in men and women [5]

(73%), but accounts for only 22% of incontinence in women. In comparison, the proportion of individuals with MUI is more constant across the sexes, accounting for 29% of women and 19% of men [5]. Even though women with SUI are more likely to be incontinent and develop coping strategies compared with women with MUI or UUI, they are less likely to suffer from less QoL impairment because of their urinary symptoms [6]. The prevalence of MUI is thought to generally increase with age in women [7].

As determined by urodynamic assessment, the cause of UUI is primarily attributed to involuntary and inappropriate contractions of the detrusor muscle during bladder filling or on provocation, known as detrusor overactivity (DO) [8]. Detrusor muscle contractions are mediated predominantly through muscarinic receptors on the bladder smooth muscle and, as such, are effectively controlled by antimuscarinics [9]. Antimuscarinics are the mainstay of treatment for UUI, and these agents have previously been shown to effectively reduce UUI episodes associated with DO [10].

Stress urinary incontinence is not a component of OAB and possesses a distinct etiology from UUI, which does not involve DO and therefore should not be impacted by antimuscarinics. Despite this, antimuscarinics are often used for patients with MUI. MUI patients all have some form of OAB symptoms (urgency with frequency and/or nocturia), irrespective of their SUI or UUI, and their treatment with antimuscarinics is justified, as these agents will help reduce the severity of the urgency and UUI components. Furthermore, it is reasonable to focus treatment on those symptoms that are most bothersome to the patients, and most MUI patients find the urge component of their condition more unpredictable and bothersome than the stress component [11]. However, few studies have evaluated the relative efficacy of antimuscarinic agents for the treatment of SUI and UUI in the same patient (mixed symptoms; MUI).

Solifenacin succinate is a once-daily oral antimuscarinic agent commercially available in Europe and the United States for the treatment of OAB at 5 mg (recommended dose) and 10 mg (if required) dosage strengths. In four individuals, double-blind, placebo-controlled 12-week studies, solifenacin therapy has demonstrated statistically significant reductions in all key symptoms of OAB, including incontinence, urgency, and frequency [12–15], as well as significantly increasing the volume voided per micturition. Additionally, rates of dry mouth with the 5 mg dose were among the lowest published for oral antimuscarinic treatment.

In this report, a subgroup analysis of data pooled from these four 12-week phase III studies was evaluated to assess the efficacy and acceptability of 5 and 10 mg solifenacin, once daily, in cohorts of OAB patients with either pure UUI or MUI symptoms.

Materials and methods

Study design and protocol

The four studies were conducted globally and had similar protocols, thus enabling pooling of efficacy and safety data (Fig. 2) [12]. All patients underwent a comprehensive baseline physical examination during screening and investigators classified patients as having either MUI or UUI based on their history and the results of a cough test. Patients began their treatment regimen on the first day of the study. In two of the studies, patients were randomized to 12 weeks of once-daily treatment with 10 mg solifenacin or placebo. In the other two studies, patients were randomized to 5 mg solifenacin once daily, 10 mg solifenacin once daily, placebo once daily, or 2 mg tolterodine twice daily, for 12 weeks (tolterodine was included as an active treatment arm in one study only). Study designs and endpoints have previously been published [12–15]. The cohort of patients treated with tolterodine in the single study was not powered for comparison with solifenacin and, therefore, was not included in this pooled analysis.

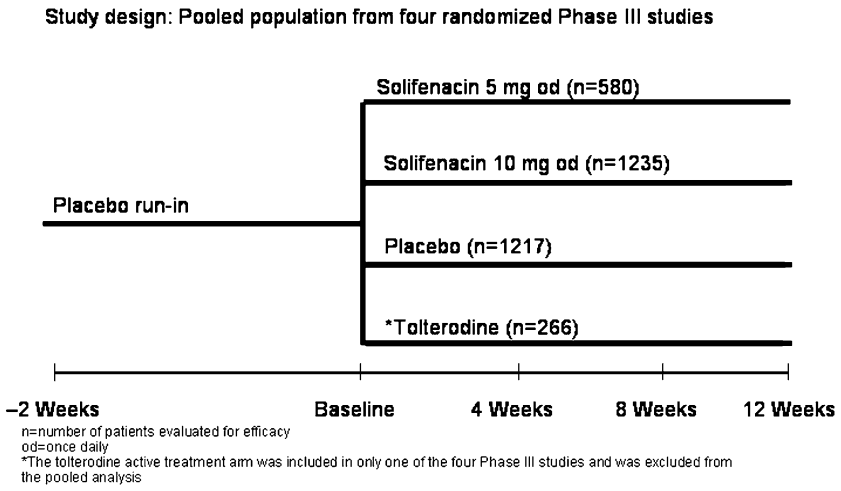

Fig. 2 Study design and patient numbers

All OAB symptoms data were collected from 3-day micturition diaries completed by the patients prior to baseline and prior to each subsequent scheduled visit at weeks 4, 8, and 12. For each episode of urinary symptoms, the patient recorded the date and time of each episode, whether or not they voided, the presence of urgency, the presence of incontinence, the volume voided (for 2 of the 3 days), and whether or not the episode disturbed the patient's sleep; the time of rising from and retiring to bed were also recorded.

These studies were performed in accordance with the International Conference on Harmonisation of 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 prior to screening.

Patients

Outpatient men and women, at least 18 years of age, were included in the studies, and their baseline demographics and characteristics are summarized in Table 1. To be eligible for study participation, patients were required to have a mean of ≥8 micturitions per 24 h in addition to a mean of ≥1 incontinence episode per 24 h or a mean of ≥1 urgency episode per 24 h during the baseline 3-day micturition diary period. Individuals who had SUI as the most bothersome component of their MUI condition were excluded from the studies. This was determined by the investigator based on voiding diary data, medical history, and a physical examination. For female patients, this had to be confirmed by a cough provocation test which included an ultrasound to check that a minimum of 100 mL of urine was present in the bladder, followed by the patient coughing vigorously in the standing position. An immediate loss of urine was considered as confirmation of SUI. A total of 3,032 patients were randomized to treatment or placebo across the four phase III studies evaluating the short-term efficacy, safety, and tolerability of solifenacin. Of these, 2,848 were evaluable for efficacy, and 2,689 had incontinence at baseline, representing the full analysis set used for this report. Sixty-one percent (n=1648) of this group had UUI only, and 39% (n=1041) had urge predominant MUI (placebo n=644, 5 mg solifenacin n=352, 10 mg solifenacin n=652 for UUI cohort; placebo n=430, 5 mg solifenacin n=159, 10 mg solifenacin n=452 for MUI cohort).

Efficacy assessment and statistical methods

The baseline to endpoint changes in 24-h frequency of incontinence episodes, urgency episodes, and micturitions, as well as the volume voided per micturition, were analyzed for all patients. Patients without at least one on-treatment efficacy assessment were excluded from the analysis.

Patients were classified as having MUI or UUI at study-entry, using patient history. This diagnosis was based on an indefinite time period (i.e., there is no time frame during

Table 1 Patient demographics at baseline for the mixed urinary incontinence and urge urinary incontinence patient cohorts

		Placebo		Solifenacin (5 mg)		Solifenacin (10 mg)	
		MUI	UUI	MUI	UUI	MUI	UUI
Age	Mean, years	58.8	58.1	59.1	55.9	58.6	57.8
	<65, % (n)	67% (288)	63% (408)	62% (99)	68% (238)	65% (295)	64% (420)
	≥65, % (n)	33% (142)	37% (236)	38% (60)	32% (114)	35% (157)	36% (232)
Gender	Male, % (n)	5% (22)	27% (176)	8% (13)	26% (91)	6% (28)	29% (186)
	Female, % (n)	95% (408)	73% (468)	92% (146)	74% (261)	94% (424)	71% (466)

MUI mixed urinary incontinence, *UUI* urge urinary incontinence

which the patient had to experience these symptoms). The urgency, incontinence, and micturition data, however, come from the baseline 3-day patient diary. As such, not all patients presented with all symptoms within this defined baseline time period, thereby resulting in variation in symptom denominators.

Treatment group comparisons of mean actual change from baseline were based on analysis of covariance (ANCOVA) with the baseline mean value of symptoms per 24 h as a covariate and terms for treatment group and pooled center as fixed effects. Data for the percent change from baseline were not normally distributed. Therefore, treatment group comparisons of the percent change from baseline were based on Van Elteren's test stratified by pooled center. These analyses were conducted separately for the MUI and UUI patient cohorts.

Safety

Treatment-emergent adverse events (TEAEs) were evaluated in the MUI and UUI cohorts combined and separately. A TEAE was defined as an adverse event (AE) occurring after the first dose of study medication, or an exacerbation of an AE that was present before the first dose of the study medication. Discontinuation rates due to AEs were also investigated and are reported here.

Results

Baseline to endpoint improvements in key OAB symptoms

At baseline, patients in the UUI and MUI cohorts were comparable with respect to clinical characteristics (Table 1). The mean actual and median percent baseline to endpoint changes in micturition frequency, volume voided, and the number of episodes of incontinence and urgency are summarized in Table 2 and Fig. 3. Greater baseline to endpoint reductions in incontinence, micturition frequency and urgency were observed in both solifenacin treatment groups compared with placebo in both the MUI and UUI cohorts. Mean actual reductions in all key symptoms were statistically significant vs placebo for patients in both the 5 and 10 mg solifenacin dose groups, in both the MUI and UUI cohorts (Table 2). Similar results were found in both the MUI and UUI cohorts when median percent reductions were analyzed, with statistically significant differences with both 5 and 10 mg solifenacin compared to placebo for all key symptoms measured, the exception being urgency episodes for patients receiving the 5 mg dose in the MUI cohort (Fig. 3). The baseline to endpoint increase in volume voided was statistically significant vs placebo with both solifenacin doses, for both the MUI and UUI patient cohorts.

Resolution and normalization rates

Resolution and normalization rates were collected using a 3-day patient diary. Resolution was considered as patients reporting no incidence at endpoint of symptoms that were present at baseline. Normalization of micturition frequency was considered as those patients achieving <8 micturitions per 24 h. A greater proportion of patients in both MUI and UUI cohorts achieved continence with solifenacin compared with placebo at study endpoint (Table 3). This between-treatment difference was statistically significant for 10 mg solifenacin in both MUI and UUI cohorts ($P<0.001$) and for 5 mg solifenacin in patients with UUI ($P<0.001$). Additionally, in both the MUI and UUI patient cohorts, a

Table 2 Mean baseline to endpoint actual changes in key overactive bladder (OAB) symptoms

OAB symptom	Placebo			Solifenacin (5 mg)			Solifenacin (10 mg)		
	n	Baseline (SD)	Mean actual change	*n*	Baseline (SD)	Mean actual change	*n*	Baseline (SD)	Mean actual change
Incontinence episodes per 24 h									
MUI	365	3.0 (0.15)	−1.3	113	3.1 (0.27)	−1.6*	373	3.2 (0.16)	−1.9**
UUI	415	2.9 (0.15)	−0.9	198	2.4 (0.16)	−1.5**	398	2.6 (0.13)	−1.7**
Urgency episodes per 24 h									
MUI	423	6.2 (0.18)	−2.1	155	6.1 (0.38)	−3.4**	445	6.3 (0.20)	−3.4**
UUI	637	6.4 (0.17)	−1.8	352	5.8 (0.26)	−2.7**	652	5.9 (0.16)	−3.3**
Micturition frequency per 24 h									
MUI	430	11.5 (0.14)	−1.4	159	12.2 (0.28)	−2.5**	452	11.7 (0.15)	−2.6**
UUI	644	12.1 (0.15)	−1.4	352	12.0 (0.22)	−2.2**	652	12.0 (0.14)	−2.8**
Volume voided per micturition (mL)									
MUI	428	176.1 (4.23)	11.0	159	149.6 (4.39)	31.3**	450	170.0 (3.55)	46.2**
UUI	643	160.6 (2.63)	6.7	352	149.0 (2.91)	32.6**	652	160.2 (2.63)	40.5**

P values comparing mean actual change are based on an ANCOVA model with treatment and center as terms and baseline measures as covariate

SD standard deviation

*$P<0.05$ vs placebo

**$P<0.001$ vs placebo

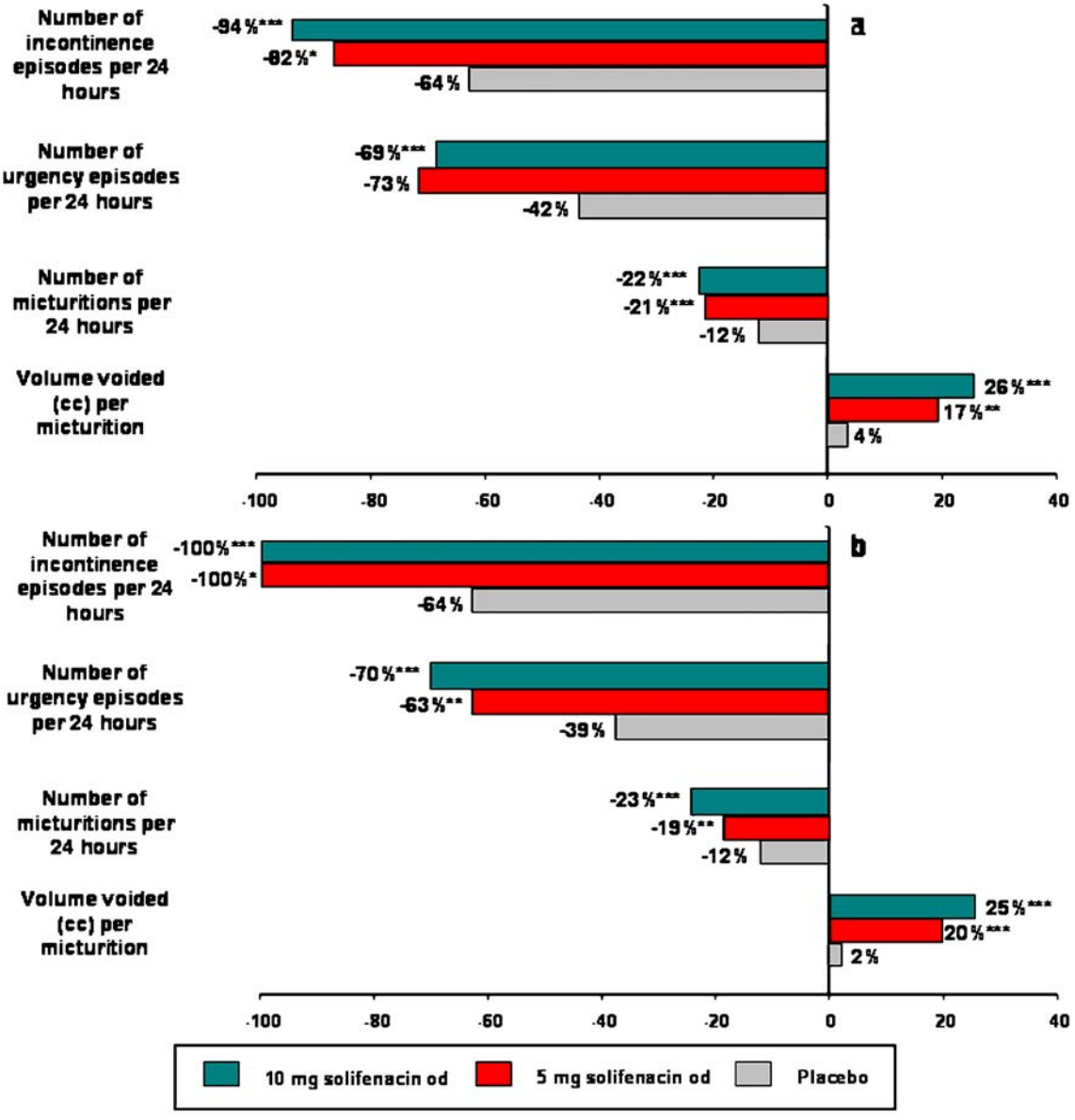

Fig. 3 Median baseline to endpoint percent changes in patients with (**a**) mixed urinary incontinence (MUI) and (**b**) urge urinary incontinence (UUI). **P*<0.05 vs placebo, ***P*<0.01 vs placebo, ****P*<0.001 vs placebo. *P* values for the median percent change from baseline to endpoint are based on van Elteren's test, stratified by pooled center

statistically significant proportion of patients receiving either dose of solifenacin experienced resolution of urgency at the study endpoint compared with placebo (*P*<0.001 for both treatment groups). A significantly greater proportion of patients with UUI also experienced normalization of micturition frequency (<8 micturitions per day) with both 5 and 10 mg solifenacin compared with placebo-matched controls (*P*<0.001, both groups). In patients with MUI, 5 and 10 mg solifenacin treatment resulted in a greater proportion of patients with normal micturition frequency compared with patients receiving placebo; this was statistically significant for 10 mg solifenacin (*P*<0.001).

Safety

In the total population of patients in the four pooled phase III studies (*n*=3298), the most common TEAEs in the solifenacin treated patients were dry mouth, constipation, and blurred vision–all well-recognized side effects of antimuscarinic therapy. Dry mouth was reported by 4, 11, and 28% of patients receiving placebo, 5 and 10 mg solifenacin, respectively. Constipation occurred in 3, 5, and 13% of patients on placebo, 5 and 10 mg solifenacin, respectively. Blurred vision was reported by ≤5% of study subjects in any patient group (placebo, 2%; 5 mg soli-

Table 3 Resolution and normalization rates for key symptoms of overactive bladder syndrome in urge and mixed urinary incontinence cohorts

	Patients achieving continence, % (*n*/*N*)		Patients achieving resolution of urgency, % (*n*/*N*)		Patients achieving normalization of micturition frequency, % (*n*/*N*)	
	MUI	UUI	MUI	UUI	MUI	UUI
Placebo	33% (122/365)	35% (143/415)	14% (61/423)	16% (100/637)	24% (101/430)	22% (141/644)
Solifenacin (5 mg)	43% (49/113)	55%* (109/198)	27%* (42/155)	29%* (103/352)	31% (49/159)	33%* (117/352)
Solifenacin (10 mg)	49%* (184/373)	54%* (214/398)	24%* (105/445)	27%* (178/652)	39%* (174/452)	38%* (245/652)

n=number of patients achieving resolution of symptom experienced during baseline evaluation, *N*=number of patients with symptom during baseline 3-day diary
*$P<0.001$ vs placebo

fenacin, 4%; 10 mg solifenacin, 5%). The majority of AEs were mild in nature and although the incidence of dry mouth was higher in the 10 mg solifenacin-treated group compared with that in patients receiving 5 mg solifenacin, the number of patients discontinuing treatment due to AEs was low (placebo, 4.4%; 5 mg solifenacin, 2.8%; 10 mg solifenacin, 6.8%) and comparable to placebo at both solifenacin doses.

Treatment was well tolerated in patients with either MUI or UUI, with AEs being similar between the two cohorts with both doses. Study discontinuations due to side effects were low and comparable across both patient cohorts. In patients with MUI, 4 and 8% of patients receiving 5 and 10 mg solifenacin, respectively, discontinued treatment due to AEs, compared with 6% of patients receiving placebo. For patients with UUI, 2 and 6% of patients discontinued prematurely due to AEs on 5 and 10 mg solifenacin, respectively, compared with 3% of patients receiving placebo.

Discussion

It has been previously demonstrated that the effects of MUI on health-related QoL (HRQoL) are similar to UUI and greater than SUI, suggesting that the urge, relative to the stress, component has a more significant impact on patients' HRQoL [16]. Additionally, compared with individuals with SUI, patients with MUI report more incontinence episodes and significantly worse HRQoL [16]. Primarily due to these factors, antimuscarinic therapy is commonly used in OAB patients experiencing urge predominant MUI. However, this is one of only two published studies formally evaluating the efficacy of modern antimuscarinics in individuals with MUI [11].

The justification for use of antimuscarinics in these patients is clear. The majority of primary care physicians (PCPs) will see many patients with mixed forms of urinary incontinence who find the urge components of their condition the most bothersome and detrimental to their daily QoL. The ability of antimuscarinics to reduce these symptoms is well established, and the tolerability of more modern antimuscarinics, such as solifenacin, is well known. Therefore, using solifenacin to treat the OAB patients with MUI is justified, as it makes their symptoms better and improves their QoL. This is also beneficial to the PCPs as they can significantly help their patients deal with the most bothersome aspects of their OAB and MUI without the need for complex and invasive urodynamic assessments. The current report has investigated the efficacy of solifenacin in OAB, assessing the compound's ability to allow patients to achieve continence and also its effects on other key OAB symptoms that can negatively impact on a patient's HRQoL [11]. The differences from placebo were statistically significant in favor of both doses of solifenacin for each of these study endpoints.

In patients with MUI, solifenacin treatment resulted in a median reduction in incontinence episodes of 82 and 94% with 5 and 10 mg solifenacin, respectively, compared with a 64% reduction for patients receiving placebo. Micturition frequency reduced by 21 and 22% (5 and 10 mg solifenacin, respectively) compared with a 12% reduction in the placebo group. Volume voided increased by 17 and 26% (5 and 10 mg solifenacin, respectively) compared with only a 4% increase in the patients receiving placebo. When the proportion of patients who achieved continence was assessed, 43 and 49% of patients having received 5 and 10 mg solifenacin once daily, respectively, reported no incontinence at endpoint compared with 33% in the placebo group. The increase in volume voided in the MUI group does not appear to have worsened these patients' SUI component, as concurrent reductions in incontinence episodes were also realized. This may suggest that the patients' coping strategies were originally a significant problem for them, and that they may have been increasing micturition frequency to reduce volume, with the aim of reducing their SUI episodes.

With the new definition of OAB provided by the International Continence Society, urgency has become the defining and driving symptom of the OAB syndrome. Therefore, treating urgency is of significant importance not only in patients with UUI but also those with MUI. In OAB patients with MUI, solifenacin treatment resulted in a reduction in urgency episodes of around 70% (73 and 69% on 5 and 10 mg solifenacin, respectively) compared with a 42% reduction in patients receiving placebo.

A recent publication has evaluated the efficacy of 2 or 4 mg tolterodine in reducing OAB symptoms in patients with MUI and UUI [11]. In this published study, tolterodine treatment of patients with MUI resulted in a 67% reduction in incontinence episodes, a 15% reduction in micturition

frequency, and a 16% increase in volume voided [11]. When assessing the proportion of patients achieving continence, 39% of MUI patients achieved continence after 16 weeks of tolterodine treatment. Changes in placebo-treated patients, or effects of treatment on urgency, were not reported in this publication [11].

The pooling of data from the four solifenacin studies in the analysis reported herein allows increased power to detect differences between treatment groups, making treatment effects clearer than in a single study with fewer patients. However, it is worth noting that the tolterodine study only evaluated the per-protocol population and would not have included patients who terminated early or who deviated from the protocol. This may have afforded some bias in favor of treatment, by selecting data for only those patients who completed the full 16 weeks of treatment. The solifenacin studies reported here evaluated the intent-to-treat populations, thus removing the possibility of this treatment bias.

In summary, this analysis demonstrates that solifenacin may be an appropriate choice of antimuscarinic agent for the first-line treatment of patients with urge predominant MUI and those with UUI. Solifenacin has been shown to effectively improve the whole range of key OAB symptoms in both of these patient types.

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