Solifenacin Is Effective and Well Tolerated in Patients With Neurogenic Detrusor Overactivity: Results From the Double-Blind, Randomized, Active- and Placebo-Controlled SONIC Urodynamic Study

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Aims: To investigate the effect on urodynamics of 4 weeks treatment with solifenacin succinate in patients with neurogenic detrusor overactivity (NDO) due to multiple sclerosis (MS) or spinal cord injury (SCI). **Methods:** SONIC was a prospective, multicenter, double-blind, phase 3b/4 study investigating the efficacy and safety of solifenacin 10 mg in patients with NDO due to MS or SCI. Patients (n = 189) were randomized to placebo or active treatment (solifenacin 5 mg, 10 mg or oxybutynin hydrochloride 15 mg) for 4 weeks, after a 2-week, single-blind, placebo run-in period. The primary endpoint was change in maximum cystometric capacity (MCC) from baseline to end of treatment. The primary analysis compared solifenacin 10 mg versus placebo; all other comparisons were considered secondary. Secondary endpoints included changes in urodynamic parameters, patient-reported outcomes, and safety assessments. **Results:** In the primary analysis, solifenacin 10 mg significantly improved mean change from baseline MCC versus placebo ($P < 0.001$) and was associated with improvements in bladder volume at first contraction and at first leak as well as detrusor pressure at first leak. Similar results were obtained for oxybutynin versus placebo. Patient perception of bladder condition significantly improved with solifenacin 10 mg versus placebo ($P = 0.041$). There was a clear improvement in quality of life (QoL) in the solifenacin arms versus placebo. The overall incidence of adverse events was low. **Conclusions:** In patients with NDO due to MS and SCI, 4 weeks of treatment with solifenacin 10 mg improved urodynamic variables and QoL versus placebo and was well tolerated. *Neurourol. Urodynam.* © 2015 Wiley Periodicals, Inc.

Key words: cystometry; incontinence quality-of-life (I-QoL); multiple sclerosis (MS); neurogenic detrusor overactivity (NDO); solifenacin; SONIC; spinal cord injury (SCI); urodynamic

INTRODUCTION

Neurogenic detrusor overactivity (NDO) is a urodynamic observation characterized by involuntary contraction of the detrusor muscle of the bladder during the filling phase, which may be spontaneous or provoked, where there is evidence of a neurological disorder.[1] This condition commonly occurs in patients with numerous and various neurological diseases, such as multiple sclerosis (MS) or spinal cord injury (SCI), owing to disturbances of the neurological control mechanisms. Symptoms, including overactive bladder (OAB) syndrome with increased urinary frequency, urgency, urge incontinence, and incontinence without urgency[2] may significantly impair patient quality of life (QoL).[3] Unmanaged symptoms can lead to upper urinary tract damage (e.g., bladder deformities, reflux, and upper urinary tract alterations).[4]

NDO treatment routinely includes pharmacological therapy with antimuscarinics for OAB, combined with clean intermittent self-catheterization, based on objective criteria.[5–8] However, few studies have evaluated the effectiveness of such agents in these patients.[6] Antimuscarinic treatments are associated with improved urodynamic variables and patient-reported outcomes compared with placebo, but also a high incidence of adverse events (AEs), particularly dry mouth and constipation.[2] Moreover, higher doses of antimuscarinics may be needed in NDO patients (in order to decrease the risk of

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upper urinary tract alteration) than in patients with non-neurogenic DO,[9] further increasing AE incidence and the risk of treatment discontinuation.[10] Thus, there is a need to evaluate the benefit of these therapies in NDO more thoroughly, taking into account their side effects and impact on QoL.

Treatment with the oral antimuscarinic agent solifenacin succinate significantly improves the major symptoms of OAB syndrome, including urgency and urge incontinence.[11–13] Improved symptoms from baseline were also seen in a small, prospective, open-label study with this agent in patients with MS.[14] The SONIC (SOlifenacin in NeurogenIC detrusor overactivity) study investigated the efficacy and safety of solifenacin as a treatment for patients with NDO due to MS or SCI. This report focuses on the efficacy (in terms of urodynamics), tolerability, and patient-reported outcomes associated with solifenacin treatment compared with placebo, and in relation to the effect of oxybutynin as an active control.

MATERIALS AND METHODS

SONIC was a prospective, randomized, phase 3b/4 parallel-group trial conducted at 32 sites in 11 countries (Australia and across Europe) from March 2008 to January 2011 (Clinicaltrials.gov identifier: NCT00629642). The study consisted of a 2-week single-blind placebo run-in period followed by a 4-week randomized, double-blind, placebo-, and active-controlled treatment period. A 4-week study length was considered the minimum needed to observe an effect of the study medication on urodynamics. This minimum period and the parallel design were selected to reduce the length of time for subjects randomized to the placebo arm. Variables such as renal function, reflux, and detrusor–sphincter–dyssynergia were not examined. The study was conducted in accordance with Good Clinical Practice Guidelines, International Conference on Harmonisation guidelines, and the Declaration of Helsinki. The protocol was reviewed by the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) at each study site. All patients provided written informed consent before screening.

Patients

The study enrolled patients aged 18–65 years with NDO due to MS (Expanded Disability Status Scale $\leq$8) or SCI (partial or complete lesions), with stable disease symptoms for $\geq$6 months. Patients were excluded if they had a maximum bladder capacity $\geq$400 ml, or if they were receiving antidepressants, muscle relaxants, or treatments for OAB. Other exclusion criteria included Sjögren's syndrome or similar symptoms; symptomatic urinary tract infection; chronic inflammation of the urinary tract; bladder stones; previous pelvic radiation therapy; previous or concurrent malignant disease of the pelvic organs; stress incontinence or mixed incontinence; and history of bladder sphincterotomy. The majority of patients (77.2%) used concomitant medication throughout the study, the most common being immunostimulants (26.5%), ophthalmological agents (25.4%), and analgesics (22.2%). Although generally not permitted at baseline, addition of muscle relaxants (used by 24.9% of subjects) was allowed during the study in order to decrease general spasticity. As the first phase 3 trial of onabotulinumtoxinA in NDO was not performed until 2011,[15] and the current study completed in January 2011, previous use of onabotulinumtoxinA was not an exclusion criterion.

Patients meeting inclusion criteria at the end of the placebo run-in period were randomized 1:1:1:1 using a central computerized randomization scheme, prepared by IFE Europe GmbH, Essen, Germany, to receive once-daily solifenacin 5 mg (1 $\times$ 5 mg tablet) or 10 mg (2 $\times$ 5 mg tablets), oxybutynin hydrochloride 15 mg (5 mg capsules, three times daily) or placebo for 4 weeks. Each patient took an identical regimen of two tablets and three capsules in the same time pattern each day to ensure blinding. Doses were based on licensed doses frequently prescribed in clinical practice.

Endpoints

The primary endpoint was the change from baseline to end of treatment in maximum cystometric capacity (MCC; ml), performed according to a standard protocol and calculated as the sum of the drained volume at the end of the cystometry and leakage.

Secondary endpoints included changes from baseline to end of treatment in urodynamic variables as measured by cystometry (bladder volume at first involuntary contraction, detrusor pressure at first leak, bladder volume at first leak, and maximal detrusor pressure); micturition diary variables (micturition, catheterization, and incontinence); and patient-reported outcome variables (patient perception of bladder condition [PPBC], incontinence Quality of Life (I-QoL), visual analogue scale to rate treatment satisfaction [VAS-TS] and Euroqol 5-dimension questionnaire [EQ-5D]).

Safety assessments included the incidence and severity of AEs over the study period, and changes in VAS from baseline to end of treatment for dry mouth, constipation, blurred vision, fatigue, memory, and attention.

Study Assessments and Analysis

Study assessments were conducted at randomization (baseline) and the end of study visit (Week 4) or at end of treatment. Urodynamic tests were performed using cystometry with a standard protocol between study sites. Filling rate was $\leq$50 ml/min. Pressure was measured either by external water transducers connected to the patient with fluid-filled manometer lines and catheters, or by microtip catheters. Bladder catheters were as thin as possible, preferably a 6F or 8F double lumen. Zero setting (atmospheric pressure), calibration, and establishment of reference level pressure were performed before each set of measurements. Quality was checked by asking the patient to cough at regular intervals, and ensuring that P_{ves} and P_{abd} traces rose equally. Micturition diaries were completed by the patient for 3 days prior to each visit. At both visits, patients completed the PPBC 6-point scale,[16] the I-QoL questionnaire,[17] and VAS-TS. The EQ-5D was also completed by patients at baseline and end of study; EQ-5D results are not reported here. AEs were monitored throughout the treatment period.

Statistical Methodology

The sample size was based on the primary comparison of solifenacin 10 mg versus placebo. With 43 evaluable subjects in both the placebo and the solifenacin 10 mg group, a difference of 80 ml (thought likely to reflect clinically relevant improvement) in mean change from baseline in bladder volume at MCC between the two treatment groups could be detected with a power of 80%, using a *t*-test with a two-sided significance level of 5% and a standard deviation of 130 ml. Based on the literature review of studies in neurogenic bladder, a 5% screening drop-out rate and a 15% post-randomization drop-out rate were assumed. Therefore, it was planned to enroll 215 subjects into the placebo run-in phase, so that 204 could be

randomized, meaning approximately 172 would be evaluable in the efficacy analysis.

The primary analysis was changed from baseline in MCC for 10 mg solifenacin versus placebo. All other treatment comparisons (including MS and SCI subgroup analyses) were exploratory and, therefore, no adjustment for multiplicity was performed. Efficacy variables were analyzed using an analysis of covariance (ANCOVA) model (SAS Proc Mixed), with treatment group and geographical region (Western Europe and Australia, and Eastern Europe) as fixed factors and the baseline as a covariate. All analyses of both primary and secondary endpoints used two-sided contrasts at a significance level of 5%. Contrasts of active treatment versus placebo are presented with a 95% confidence intervals for the primary endpoint.

Efficacy analyses are provided for the full analysis set (FAS), defined as patients who took at least one dose of study medication and had an efficacy assessment, including a valid MCC measurement, at baseline and at end of treatment. Baseline demographics and safety assessments were based on the safety population, defined as all randomized subjects who took at least one dose of study medication.

RESULTS

Patient Baseline Characteristics

Of 248 patients screened, 194 were randomized at the end of the single-blind placebo-run in period. Of these, five discontinued prior to administration of the first dose (two due to withdrawal of consent, two due to lack of efficacy, and one lost to follow-up), thus 189 received at least one dose of medication (safety population) and 176 were included in the FAS (Fig. 1). One patient aged 66 years with SCI was mistakenly enrolled and treated with oxybutynin; this patient was included in the FAS and safety analyses. Baseline characteristics were similar between groups (Table I). Overall, mean age was 43.7 years (range 19–66), and 50.3% were male. There were more patients with MS than with SCI (55.0% and 45.0%, respectively); patients with SCI were predominantly male (77.6%), whereas those with MS were predominantly female (72.1%). Six patients discontinued during the double-blind treatment period: two in the placebo group due to AEs and four in the oxybutynin group, (two due to AEs, one due to withdrawal of consent, and one "other" reason).

Urodynamic Variables

Mean increase from baseline to end of treatment in MCC was 134.2 ml with solifenacin 10 mg versus 5.4 ml with placebo ($P < 0.001$; Table II). MCC was also significantly improved with solifenacin 5 mg and oxybutynin versus placebo, with increases of 77.8 and 165.4 ml, respectively ($P = 0.007$ and $P < 0.001$ vs. placebo; Table II).

In the MS subgroup, mean MCC was significantly increased following treatment with solifenacin (5 mg: 64.5 ml, $P = 0.030$; 10 mg: 132.9 ml, $P < 0.001$) and oxybutynin (114.5 ml, $P = 0.001$) compared with placebo (Table III). Similarly, mean MCC was significantly increased in the SCI subgroup following treatment with solifenacin (5 mg: 97.1 ml, $P = 0.038$; 10 mg: 135.8 ml, $P = 0.001$) and oxybutynin (231.4 ml, $P < 0.001$) (Table III).

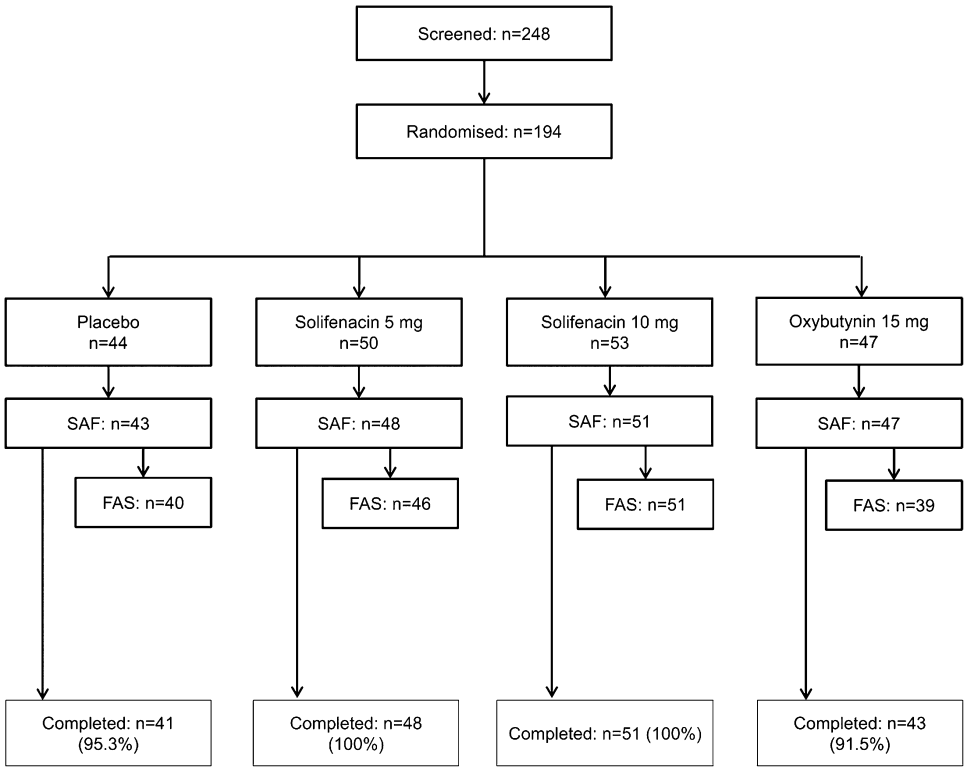

Fig. 1. Patient flow. A total of 13 patients were included in the SAF but excluded from the FAS due to missing or invalid urodynamic assessments (seven due to no cystometry at the end of treatment visit, four due to maximum bladder capacity >400 ml at baseline, one due to urinary tract infection during the placebo run-in period, and one due to history of bladder sphincterotomy). FAS, full analysis set; SAF, safety analysis set.

TABLE I. Patient Demographics and Baseline Characteristics (Safety Analysis Set)

	Placebo (n = 43)	Solifenacin 5 mg (n = 48)	Solifenacin 10 mg (n = 51)	Oxybutynin 15 mg (n = 47)	Total (n = 189)
Indication, n (%)					
Multiple sclerosis	19 (44.2)	28 (58.3)	28 (54.9)	29 (61.7)	104 (55.0)
Spinal cord injury	24 (55.8)	20 (41.7)	23 (45.1)	18 (38.3)	85 (45.0)
Sex, n (%)					
Male	23 (53.5)	27 (56.3)	26 (51.0)	19 (40.4)	95 (50.3)
Female	20 (46.5)	21 (43.8)	25 (49.0)	28 (59.6)	94 (49.7)
Age, years					
Mean (SD)	40.0 (10.6)	44.6 (12.5)	45.7 (12.0)	43.9 (11.9)	43.7 (11.9)
Median (range)	41.0 (20–61)	45.5 (19–65)	46.0 (22–65)	44.0 (22–66)	43.0 (19–66)
Ethnicity, n (%)					
White	41 (95.3)	46 (95.8)	49 (96.1)	42 (89.4)	178 (94.2)
Black	1 (2.3)	2 (4.2)	1 (2.0)	1 (2.1)	5 (2.6)
Asian	0	0	0	2 (4.3)	2 (1.1)
Other	1 (2.3)	0	1 (2.0)	2 (4.3)	4 (2.1)

However, the study was not powered to detect statistically significant effects between active treatments in subgroups (Table III).

Improvements in secondary urodynamic variables were greater with solifenacin and oxybutynin compared with placebo. Summaries of bladder volume at first involuntary contraction and at first leak, as well as detrusor pressure at first leak, are presented in Table II for all patients with such events during the urodynamic measurement reported at baseline or end of treatment visit. The number of patients with this measurement at the end of treatment visit was reduced compared with baseline in all active treatment arms; individual patient data suggested that maximum bladder capacity was significantly improved compared with baseline in patients with no leakage or involuntary contraction during end of treatment urodynamic measurement. Therefore, the actual solifenacin and oxybutynin treatment effects may be even larger than shown by the mean change from baseline values. Four weeks of treatment with either dose of solifenacin or oxybutynin was associated with significant improvements versus placebo in bladder volume at first involuntary contraction, bladder volume at first leak, mean detrusor pressure at first leak, and maximum detrusor pressure (Table II).

Although not sufficiently powered to detect statistically significant differences between the two solifenacin doses, these data suggest a dose–response effect with solifenacin for MCC, bladder volume at first involuntary contraction and bladder volume at first leak. Such a dose trend was not seen for detrusor pressure at first leak or for maximum detrusor pressure. Differences between the solifenacin 10 mg and oxybutynin 15 mg group were not statistically significant for any urodynamic variable in the total study population; however, responses in MCC and bladder volume at first involuntary contraction were significantly greater with oxybutynin than with solifenacin 5 mg ($P = 0.002$ and 0.022, respectively).

Micturition Diary Variables

Overall, mean number of micturitions per 24 h or catheterisation episodes per 24 h, in patients with at least one episode at baseline, were not statistically different from baseline to end of treatment (Table II). However, compared with placebo (−0.30), decreases in the mean number of incontinence episodes per 24 hr were significant after solifenacin 5 mg (–1.33, $P = 0.015$) and oxybutynin 15 mg (–2.71; $P < 0.001$), although not with solifenacin 10 mg treatment (–0.57; $P = 0.612$).

Patient-Reported Outcomes

Compared with placebo, all active treatment groups showed reductions in PPBC from baseline to end of treatment, but these were statistically significant only for solifenacin 10 mg versus placebo (–0.6 vs. –0.1; $P = 0.041$; Table II).

Of the I-QoL subscales, changes in "avoidance and limiting behavior" reached statistical significance for both solifenacin doses versus placebo (5 mg, $P = 0.014$;10 mg, $P = 0.030$; Table II), whereas oxybutynin had no significant effect on any I-QoL subscore compared with placebo. Mean VAS-TS scores increased in all three active treatment groups versus placebo: by 10.3 with solifenacin 5 mg ($P = 0.013$); by 14.3 with solifenacin 10 mg ($P = 0.011$); and by 11.7 with oxybutynin 15 mg ($P = 0.009$) (Table II).

Safety

Treatment-emergent AE (TEAE) incidence was low and was reported in 25.4% of patients; most events were considered mild in severity (Table IV). The most common TEAEs were dry mouth and urinary tract infections. TEAEs led to treatment discontinuation in two patients in the placebo group and one in the oxybutynin group. Serious TEAEs were reported in two patients: one in the placebo group and one in the solifenacin 10 mg group; neither was considered treatment-related. Patients receiving oxybutynin were more likely to be bothered by dry mouth than those receiving placebo, according to the change in VAS dry mouth score from baseline to end of treatment (38.7 vs. 4.4; $P < 0.001$). Changes from baseline in VAS dry mouth in the solifenacin groups were not significantly different to placebo (4.2 for 5 mg and 10.4 for 10 mg vs. 4.4; ANCOVA; all $P > 0.20$). For all other VAS scores, there was no significant difference for any treatment compared with placebo.

DISCUSSION

Antimuscarinics are frequently used for the first-line treatment of NDO in patients with MS or SCI; however, this practice is not based on good quality evidence in these populations. SONIC evaluated the efficacy and safety of fixed doses of solifenacin as a treatment for NDO. This is currently

TABLE II. Change in Mean (Standard Deviation) Urodynamic and Micturition Diary Variables, and Patient-Reported Outcomes From Baseline to End of Treatment (FAS)

	Placebo		Solifenacin 5 mg		Solifenacin 10 mg		Oxybutynin 15 mg	
Urodynamic and micturition diary variables from baseline to end of treatment (FAS)								
Maximum cystometric capacity, ml								
Baseline	n = 40	226.9 (108.1)	n = 46	222.9 (115.4)	n = 51	225.1 (107.5)	n = 39	214.7 (102.7)
End of treatment	n = 40	232.4 (101.9)	n = 46	300.7 (149.7)	n = 51	359.3 (152.3)	n = 39	380.1 (169.3)
Change[a]		5.4 (120.3)		77.8 (115.4)**,††		134.2 (124.7)***		165.4 (145.6)***
LSmean change versus placebo (95%CI)				72.1 (19.6, 124.6)		128.9 (77.7, 180.2)		158.4 (103.6, 213.1)
Bladder volume at first involuntary contraction, ml								
Baseline	n = 39	137.8 (85.5)	n = 46	138.8 (84.8)	n = 51	142.3 (87.4)	n = 39	124.8 (88.3)
End of treatment	n = 38	130.6 (62.8)	n = 42	192.7 (112.3)	n = 45	215.8 (142.1)	n = 36	234.8 (105.6)
Change[a]		−10.1 (83.1)		60.0 (109.2)**,†		79.2 (122.3)***		113.4 (101.4)***
Bladder volume at first leak, ml								
Baseline	n = 26	155.0 (94.7)	n = 28	157.0 (102.6)	n = 25	137.4 (91.9)	n = 23	165.7 (105.5)
End of treatment	n = 25	141.2 (62.5)	n = 21	202.2 (142.0)	n = 21	230.3 (141.4)	n = 12	215.3 (138.8)
Change[a]		−13.2 (110.2)		59.8 (101.6)		83.3 (134.7)*		142.5 (130.8)**
Detrusor pressure at first leak, cmH_2O								
Baseline	n = 26	57.3 (27.3)	n = 26	68.0 (38.3)	n = 24	63.0 (35.8)	n = 22	67.3 (42.7)
End of treatment	n = 24	73.2 (39.5)	n = 18	55.5 (28.7)	n = 19	44.4 (16.2)	n = 10	50.9 (33.0)
Change[a]		7.7 (20.3)		−14.8 (24.4)*		−11.7 (20.8)*		−27.6 (43.7)**
Maximum detrusor pressure, cmH_2O								
Baseline	n = 40	74.0 (40.2)	n = 46	74.0 (42.7)	n = 51	60.6 (32.8)	n = 39	68.9 (36.7)
End of treatment	n = 40	81.5 (60.8)	n = 46	57.4 (37.9)	n = 50	49.8 (40.5)	n = 39	44.6 (26.4)
Change[a]		7.5 (51.0)		−16.6 (32.9)**		−10.5 (37.2)**		−24.3 (27.6)***
Number of natural micturitions/24 hr[b]								
Baseline	n = 26	9.22 (5.90)	n = 38	8.84 (4.27)	n = 38	10.07 (3.40)	n = 28	10.04 (3.84)
End of treatment	n = 26	8.57 (5.86)	n = 38	7.10 (3.78)	n = 38	9.09 (4.01)	n = 28	8.29 (4.17)
Change[a]		−0.67 (2.60)		−1.76(3.12)		−0.97 (3.31)		−1.74 (2.90)
Number of catheterizations/24 hr[b]								
Baseline	n = 24	5.45 (3.26)	n = 22	5.37 (2.92)	n = 18	5.68 (3.64)	n = 19	5.06 (2.99)
End of treatment	n = 23	5.03 (3.24)	n = 21	5.04 (2.16)	n = 18	4.93 (2.80)	n = 19	4.73 (2.20)
Change[a]		−0.21 (0.84)		−0.33(1.45)		−0.76 (2.01)		−0.31 (1.95)
Number of incontinence episodes/24 hr[b]								
Baseline	n = 30	2.62 (2.80)	n = 31	2.12 (1.88)	n = 38	2.47 (3.09)	n = 22	4.22 (4.42)
End of treatment	n = 29	2.22 (2.83)	n = 31	0.80 (1.24)	n = 38	1.88 (3.51)	n = 22	1.52 (2.97)
Change[a]		−0.30 (1.20)		−1.33 (1.50)*		−0.57 (2.29)††		−2.71 (2.84)***
Patient-reported outcomes from baseline to end of treatment (FAS)								
n	40		46		51		39	
PPBC score								
Baseline	4.2 (1.19)		4.2 (0.98)		4.5 (1.05)		4.2 (1.16)	
End of treatment	4.2 (1.17)		3.8 (1.22)		3.9 (1.28)		3.7 (1.31)	
Change[a]	−0.1 (0.92)		−0.4 (1.04)		−0.6 (1.04)*		−0.5 (1.02)	
I-QoL questionnaire								
Total score								
Baseline	44.63 (21.83)		51.04 (20.76)		44.73 (23.30)		52.33 (22.35)	
End of treatment	48.49 (22.26)		59.17 (23.24)		54.21 (25.16)		57.96 (24.13)	
Change[a]	3.86 (13.26)		8.13 (15.05)		9.48 (17.69)		5.63 (17.34)	
Avoidance and limiting behavior score								
Baseline	45.60 (20.69)		50.88 (18.68)		46.18 (21.72)		51.54 (20.80)	
End of treatment	47.47 (22.90)		60.01 (21.74)		55.12 (23.49)		58.30 (21.55)	
Change[a]	1.87 (12.35)		9.14 (15.97)*		8.96 (18.60)*		6.76 (17.22)	
Psychosocial impact score								
Baseline	49.37 (25.20)		56.77 (25.13)		49.29 (26.48)		57.55 (24.80)	
End of treatment	53.15 (23.75)		65.33 (25.38)		58.60 (26.71)		60.79 (27.24)	
Change[a]	3.77 (13.79)		8.54 (16.31)		9.30 (17.04)		3.24 (18.91)	
Social embarrassment score								
Baseline	38.96 (24.83)		45.46 (24.25)		38.73 (25.14)		47.95 (26.85)	
End of treatment	44.88 (24.87)		52.17 (26.41)		48.92 (28.06)		54.83 (27.06)	
Change[a]	5.92 (19.50)		6.71 (17.60)		10.20 (20.86)		6.88 (20.59)	
VAS-TS								
Baseline	39.8 (34.13)		52.8 (38.06)		47.0 (38.62)		53.1 (35.97)	
End of treatment	42.6 (33.09)		63.1 (33.81)		61.3 (33.67)		64.7 (31.43)	
Change[a]	1.3 (35.55)		10.3 (47.23)*		14.3 (34.43)*		11.7 (44.86)**	

P-values for contrasts are calculated with an analysis of covariance model. Differences in the number of subjects at baseline and post-baseline can be due to missing values. LSmean, least squares mean value from ANCOVA model.

*$P < 0.05$ versus placebo.

**$P < 0.01$ versus placebo.

***$P < 0.001$ versus placebo.

†$P < 0.05$ versus oxybutynin 15 mg.

††$P < 0.01$ versus oxybutynin 15 mg.

[a]From baseline to end of treatment.

[b]Patients with at least one episode at baseline.

TABLE III. Change in Maximum Cystometric Capacity (ml): Subgroup Analysis of Subjects With Multiple Sclerosis and With Spinal Cord Injury

	Placebo (n = 40)	Solifenacin 5 mg (n = 46)	Solifenacin 10 mg (n = 51)	Oxybutynin 15 mg (n = 39)
		Multiple sclerosis		
n[a]	17	28	28	22
Baseline	230.2 (124.10)	217.1 (117.01)	211.5 (91.93)	207.7 (88.21)
End-of-study visit	222.2 (103.41)	282.5 (138.27)	344.4 (139.41)	322.1 (138.78)
Change from baseline	−8.0 (106.20)	65.4 (120.74)	132.9 (131.48)	114.5 (126.63)
P (vs. placebo)	–	0.030	<0.001	0.001
P (vs. oxybutynin)	0.001	0.170	0.521	–
		Spinal cord injury		
n[a]	23	18	23	17
Baseline	224.5 (97.46)	232.0 (115.64)	241.7 (124.05)	223.8 (121.10)
End-of-study visit	239.8 (102.49)	329.1 (166.04)	377.4 (168.13)	455.1 (179.40)
Change from baseline	15.3 (131.10)	97.1 (106.97)	135.8 (118.80)	231.4 (145.37)
P (vs. placebo)	–	0.038	0.001	<0.001
P (vs. oxybutynin)	<0.001	0.003	0.026	–

Values are means (standard deviation). All *P*-values based on an analysis of covariance model with fixed effects for treatment group and geographic region and baseline maximum cystometric capacity as covariate.
[a]Number of subjects with baseline and end-of-study cystometry data.

TABLE IV. Summary of Treatment-Emergent Adverse Events and Patient-Reported Outcomes for Change From Baseline to End of Treatment (Safety Analysis Set)

	Placebo (n = 43)	Solifenacin 5 mg (n = 48)	Solifenacin 10 mg (n = 51)	Oxybutynin 15 mg (n = 47)	Total (n = 189)
Any TEAE	10 (23.3)	6 (12.5)	16 (31.4)	16 (34.0)	48 (25.4)
Mild	9 (20.9)	6 (12.5)	14 (27.5)	13 (27.7)	42 (22.2)
Moderate	1 (2.3)	0	4 (7.8)	4 (8.5)	9 (4.8)
Severe	1 (2.3)	0	1 (2.0)	2 (4.3)	4 (2.1)
Serious TEAE	1 (2.3)[a]	0	1 (2.0)[b]	0	2 (1.1)
Deaths	0	0	0	0	0
TEAE leading to discontinuation	2 (4.7)	0	0	1 (2.1)	3 (1.6)
Treatment-related TEAE	4 (9.3)	2 (4.2)	10 (19.6)	10 (21.3)	26 (13.8)
TEAEs in ≥2 patients					
Gastrointestinal disorders	2 (4.7)	2 (4.2)	7 (13.7)	10 (21.3)	21 (11.1)
Dry mouth	1 (2.3)	2 (4.2)	4 (7.8)	8 (17.0)	15 (7.9)
Constipation	0	2 (4.2)	3 (5.9)	2 (4.3)	7 (3.7)
Diarrhoea	1 (2.3)	0	1 (2.0)	0	2 (1.1)
Infections and infestations	3 (7.0)	3 (6.3)	6 (11.8)	4 (8.5)	16 (8.5)
Urinary tract infection	2 (4.7)	3 (6.3)	4 (7.8)	4 (8.5)	13 (6.9)
Influenza	0	0	2 (3.9)	0	2 (1.1)
Eye disorders	1 (2.3)	1 (2.1)	7 (13.7)	4 (8.5)	13 (6.9)
Vision blurred	0	1 (2.1)	4 (7.8)	3 (6.4)	8 (4.2)
Dry eye	0	0	1 (2.0)	1 (2.1)	2 (1.1)
Nervous system disorders	2 (4.7)	1 (2.1)	3 (5.9)	1 (2.1)	7 (3.7)
Multiple sclerosis[b]	1 (2.3)	1 (2.1)	0	1 (2.1)	3 (1.6)
General disorders and administration site conditions	1 (2.3)	0	0	1 (2.1)	2 (1.1)
Injury, poisoning, and procedural complications	1 (2.3)	0	1 (2.0)	0	2 (1.1)
Musculoskeletal and connective tissue disorders	1 (2.3)	0	0	1 (2.1)	2 (1.1)
Renal and urinary disorders	0	1 (2.1)	1 (2.0)	0	2 (1.1)
Urethral haemorrhage	0	1 (2.1)	1 (2.0)	0	2 (1.1)
Respiratory, thoracic, and mediastinal disorders	0	0	0	2 (4.3)	2 (1.1)
Skin and subcutaneous tissue disorders	2 (4.7)	0	0	0	2 (1.1)
Rash	2 (4.7)	0	0	0	2 (1.1)
Change from baseline in patient-reported outcomes (VAS score)					
Dry mouth: mean (SD)	4.4 (22.5)	4.2 (23.5)	10.4 (29.3)	38.7 (39.6)*	
Constipation: mean (SD)	2.1 (27.0)	2.9 (28.1)	0.4 (26.8)	9.4 (27.4)	
Blurred vision: mean (SD)	6.4 (27.8)	7.8 (21.7)	5.5 (27.0)	7.7 (26.3)	
Fatigue: mean (SD)	5.7 (31.4)	−2.3 (27.2)	−0.5 (21.1)	3.4 (28.8)	
Memory and attention: mean (SD)	0.5 (22.0)	0.7 (24.1)	−0.8 (21.8)	6.5 (19.5)	

Data are presented as n (%) unless otherwise noted.
TEAE, treatment-emergent adverse event (an adverse event that started after the first administration and within 7 days of the last dose of the test or comparative drug).
*$P < 0.001$ versus placebo, other treatment comparisons versus placebo in VAS scores not significant ($P > 0.05$.).
[a]A wrist fracture and impaired healing; the patient discontinued the study.
[b]Demyelination; the patient continued the study and adverse event resolved.

the largest study to evaluate use of an antimuscarinic in these two key NDO patient populations—MS and SCI—and the first to evaluate its effects on patient QoL using validated tools.

Solifenacin significantly improved urodynamic variables and patient-reported outcomes in these patients compared with placebo. After 4 weeks, solifenacin 10 mg produced significant changes from baseline in MCC, bladder volume, and detrusor pressure compared with placebo, as did oxybutynin. Improved urodynamic variables compared with placebo were also observed for solifenacin 5 mg, but the change from baseline in MCC was only 58% of that observed for solifenacin 10 mg (77.8 vs. 134.2 ml). However, only 29% of patients receiving either placebo or active treatment achieved a reduction in maximum detrusor pressure to <40 cm H_2O, considered the clinically relevant cut-off for "normal" function.

These improvements were reflected in patient-scored treatment satisfaction (VAS-TS) for all three active treatment groups, with significant improvements recorded by patients after 4 weeks of treatment compared with placebo. Significantly improved PPBC was observed with the 10 mg solifenacin dose versus placebo but not with the 5 mg dose or oxybutynin 15 mg. Overall, either dose of solifenacin, as well as oxybutynin, was effective for NDO in these patients, although there was evidence of a potential dose effect with solifenacin.

Although few studies have evaluated the efficacy of antimuscarinics in NDO, despite these agents being the first-line treatment option, results from this study agree with the limited data previously reported. Of note, a retrospective observational study of 35 SCI patients receiving solifenacin for treatment of NDO concluded that solifenacin treatment significantly improved bladder capacity, detrusor compliance, reflex volume, and maximum detrusor pressure, although this open-label study lacked a control group and should be cautiously interpreted.[18] A recent systematic review and meta-analysis of studies between 1966 to May 2011, identified 16 randomized clinical trials with a total of 960 patients investigating antimuscarinic agents in NDO.[2] In these studies, maximum detrusor pressure was reduced by ~30% with antimuscarinic treatment. Similarly, in a literature review, antimuscarinic treatment resulted in decreases in maximum detrusor pressure of 30–40% from baseline, which were paralleled by similar increases in maximum cystometric bladder capacity.[19] However, these studies were generally conducted in small numbers of patients and over short time frames, making the overall quality of evidence unsatisfactory. Furthermore, clinical effects were more pronounced in patients with a lower cystometric bladder capacity at baseline.

Well-documented AEs associated with antimuscarinics may lead to therapy discontinuation.[9,20] In the current study, solifenacin was well tolerated and the overall incidence of AEs was low, although 4 weeks may be too short a period for full evaluation of AEs and withdrawals. Consistent with previous studies,[11,13,20] both solifenacin and oxybutynin were associated with dry mouth, constipation, and blurred vision. The observed incidence of dry mouth was numerically higher with oxybutynin (17.0%) compared with solifenacin 5 mg (4.2%) and 10 mg (7.8%), and patients in the oxybutynin group reported a statistically significant increase in VAS dry mouth score compared with placebo.

The study had a number of important limitations that should be considered when interpreting the data. MCC is a standard endpoint used in studies on NDO. In MS and SCI, bladder sensations can be absent or severely disturbed, leading to unreliable subjective reporting (5;7). MCC can guide the catheterization schedule of patients and is also the most robust urodynamic parameter in these populations. As sample sizes were based on the primary comparison of solifenacin 10 mg versus placebo for MCC, comparisons between other treatment arms and comparisons in some secondary efficacy variables were underpowered. In addition, the small sample sizes of the MS and SCI subgroups do not allow for statistical comparisons between them.

Furthermore, the short duration of this study does not provide information on the long-term efficacy or tolerability of solifenacin in these patients, some of whom may require lifelong treatment for DO.

CONCLUSIONS

The SONIC study demonstrates that solifenacin 10 mg significantly improves urodynamic variables and patient-reported outcomes versus placebo in patients with NDO due to MS or SCI. There were no clear differences between solifenacin 10 mg and oxybutynin 15 mg regarding urodynamic variables, but solifenacin appeared to show an advantage in patient-reported outcomes, although the study was not powered to show a difference between active treatment groups. Both solifenacin doses were well tolerated in MS or SCI patients. These results support the use of short-term treatment with antimuscarinics; however, longer duration trials are required to determine long-term efficacy and tolerability in these patient groups.

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