Parkinsonism and Related Disorders 21 (2015) 514–520

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Randomized, controlled pilot trial of solifenacin succinate for overactive bladder in Parkinson's disease

Theresa A. Zesiewicz [a, *], Marian Evatt [b], Camille P. Vaughan [c], Israt Jahan [a], Carlos Singer [d], Raul Ordorica [e], Jason L. Salemi [f], Jessica D. Shaw [a], Kelly L. Sullivan [g], Non-Motor Working Group of the Parkinson Study Group (PSG)

[a] Department of Neurology, University of South Florida, Tampa, FL, USA
[b] Department of Neurology, Atlanta VA Medical Center and Emory University, Atlanta, GA, USA
[c] Department of Medicine, Atlanta VA Medical Center and Emory University, Atlanta, GA, USA
[d] Department of Neurology, University of Miami, Miami, FL, USA
[e] Department of Urology, University of South Florida, Tampa, FL, USA
[f] Department of Family and Community Medicine, Baylor College of Medicine, Houston, TX, USA
[g] Department of Epidemiology, Jiann-Ping Hsu College of Public Health, Georgia Southern University, Statesboro, GA, USA

ARTICLE INFO

Article history:
Received 27 October 2014
Received in revised form
13 February 2015
Accepted 25 February 2015

Keywords:
Parkinson's disease
Overactive bladder
Urinary incontinence
Solifenacin succinate
Non-motor symptoms

ABSTRACT

Objective: To evaluate the efficacy of solifenacin succinate in Parkinson's disease (PD) patients suffering from overactive bladder (OAB).
Background: Urinary dysfunction is a commonly encountered non-motor feature in PD that significantly impacts patient quality of life.
Design/methods: This was a double-blind, randomized, placebo-controlled, 3-site study with an open label extension phase to determine the efficacy of solifenacin succinate in idiopathic PD patients with OAB. Patients were randomized to receive solifenacin succinate 5–10 mg daily or placebo for 12 weeks followed by an 8-week open label extension. The primary outcome measure was the change in the mean number of micturitions per 24 h period. Secondary outcome measures included the change in the mean number of urinary incontinence episodes and the mean number of nocturia episodes.
Results: Twenty-three patients were randomized in the study. There was no significant improvement in the primary outcome measure in the double-blind phase, but there was an improvement in the number of micturitions per 24 h period in the solifenacin succinate group compared to placebo at a mean dose of 6 mg/day ($p = 0.01$). In the open label phase, the mean number of urinary incontinence episodes per 24 h period decreased ($p = 0.03$), as did the number of nocturia episodes per 24 h period ($p = 0.01$). Adverse events included constipation and xerostomia, which resolved after treatment was discontinued.
Conclusions: In this pilot trial, solifenacin succinate treatment led to an improvement in urinary incontinence, despite persistence in other OAB symptoms.

1. Introduction

Parkinson's disease (PD) is a degenerative disorder caused by a progressive loss of dopaminergic neurons in the substantia nigra, and is characterized by both motor and non-motor symptoms, including urinary dysfunction. Urinary incontinence, frequency, and overactive bladder (OAB) symptoms contribute to decreased quality of life for patients with PD [1,2]. Urinary dysfunction occurs more commonly in patients with PD than healthy control populations and affects approximately 30–40% of PD patients based on validated questionnaires [3–5]. Despite the high prevalence of urinary symptoms in the PD population, there are no published double-blind, randomized, placebo controlled clinical trials that have evaluated treatments for OAB in this population. The identification of effective treatments for OAB is an unmet need in PD patients.

While the etiology of urinary dysfunction in PD is complex, the deposition of alpha-synuclein in brain structures may contribute to

* Corresponding author. University of South Florida, Department of Neurology, 12901 Bruce B. Downs Blvd, MDC Box 55, Tampa, Florida 33612, USA. Tel.: +1 813 974 5909.
E-mail address: tzesiewi@health.usf.edu (T.A. Zesiewicz).

http://dx.doi.org/10.1016/j.parkreldis.2015.02.025
1353-8020/

impaired cortical integration of sensory input from the bladder. The loss of appropriate basal ganglia output reduces inhibition of the micturition reflex, causing detrusor muscle hyperactivity [6]. Acetylcholine binding of the M3and M2 muscarinic receptor subtypes found in the bladder also leads to detrusor contraction [7].

Solifenacin succinate, a drug approved by the United States (US) Food and Drug Administration (FDA) to treat OAB symptoms, acts by competitively inhibiting the action of acetylcholine. Because solifenacin succinate has been studied previously in older adult populations as a muscarinic receptor antagonist with greater selectivity for bladder muscarinic receptors [8], we hypothesized it would be well tolerated in PD patients with OAB symptoms.

2. Methods

This was a double-blind, randomized, placebo-controlled study that evaluated the efficacy of solifenacin succinate in idiopathic PD patients with OAB, defined as at least 8 voids per 24 h period and at least daily urinary urgency. The study was conducted at 3 centers in the US, each of which obtained institutional research board approval, and was registered on clinicaltrials.gov as NCT01018264. Eligibility criteria required participants to be aged 40–80 years, have a stable dose of anti-parkinsonian medication 4 weeks prior to study entry, score 1.0 to 3.0 on the Modified Hoehn and Yahr scale, have evidence of prostate specific antigen less than or equal to 4 (males only) within the last 12 months, and have a bladder scan at screening documenting post void residual of 200 ml or less. Inclusion criteria included patients with PD as determined by the UK Parkinson's Disease Society Brain Bank Criteria for the diagnosis of Parkinson's Disease [9]. Participants were not eligible if any of the following were present: history of prostate cancer or transurethral resection of the prostate (TURP) (males only), severe renal disease, blood urea nitrogen (BUN) 50% greater than normal (normal BUN levels should be within a range of 5–20 mg/dL with creatinine between 0.7 and 1.4 mg/dL), major hepatic impairment (cirrhosis, viral hepatitis, nonalcoholic steatohepatitis, Wilson's disease, or hemochromotosis), history of bladder outflow obstruction or gastrointestinal obstructive disorders, history of narrow angle glaucoma, history of pelvic radiation, active urinary tract infection, or history of chronic severe constipation. Additional exclusion criteria included: current treatment with ketaconazole, CYP3A4 inhibitors, certain contraindicated antiarrhythmics (flecainide, digoxin), antipsychotics, tricyclic anti-depressants, psychotropics, anticholinergics/antispasmodics, arylalkylamines, anti-androgens, antihypertensives. Participants who were currently taking selective serotonin-norepinephrine reuptake inhibitors, estrogens or acetylcholinesterase inhibitors were required to have a stable dose for 90 days prior to enrollment. All participants were on optimal treatment for their PD symptoms and PD medications were at stable doses prior to enrollment.

Using a computer generated randomization schedule, participants were randomized to receive solifenacin succinate or placebo for 12 weeks followed by an 8-week open-label extension (Fig. 1) in a 1:1 ratio without blocking or stratification. An unblinded team member who was not involved in patient enrollment or assessments labeled medication kits with study ID numbers according to the randomization schedule. Kits were dispensed to participants in sequential order and were identical in appearance other than ID number. Sealed emergency unblinding envelopes were available at each site in case required by adverse events, but all blinded team members and participants remained blinded until the open label phase. Participants were enrolled from March 2010–March 2013.

The primary outcome in the double-blind phase was the change in mean number of micturitions per 24 h period as recorded on a 3-day bladder diary. Secondary outcome measures included the change in the mean number of urinary incontinence episodes, the mean number of nocturia episodes, urinary urgency as measured by the Patient Perception of Intensity of Urgency Scale (PPIUS) [10], the mean change in Patient Perception of Bladder Condition (PBC/PPBC) [11], PD quality of life (PDQOL) [12], incontinence quality of life (IQOL) [13], and clinical global impression (CGI). In order to calculate nocturia episodes, participants recorded in a bladder diary the time they went to bed for the night, the time they awoke for the day, and the times during each void. Nocturia episodes were defined as voids occurring after bedtime and before awake time. The Unified Parkinson's Disease Rating Scale (UPDRS) [14] was also performed at each visit.

Baseline data were compared using t-tests for continuous measures and Fisher exact or Freeman–Halton tests for categorical measures. Changes in primary and secondary outcome measures from baseline to endpoint were calculated and compared between treatment groups. For participants who withdrew prior to the double-blind endpoint, but completed a follow-up visit, endpoint values were determined using the last observation carried forward (LOCF) method. For continuous outcomes (mean number of micturitions, urinary incontinence episodes, and nocturia episodes, PDQOL, IQOL, and UPDRS), analysis of covariance (ANCOVA) was used to compare changes from baseline to endpoint during the double-blind phase, adjusting for the baseline value. Similarly for ordinal outcomes (PBC/PPBC, PPIUS, Hoehn & Yahr stage, and CGI measures), ordinal logistic regression was used with the ordinal change as the dependent variable, treatment group as the primary independent variable, and adjusting for the baseline value.

During the open-label phase of the study, changes from pre-treatment to post-treatment were assessed using the Wilcoxon signed-rank test (continuous outcomes) or the sign test (ordinal outcomes) for paired data. During both the double-blind and open-label analyses, effect sizes were calculated using the standardized mean difference (Cohen's *d*-statistic). In the open-label phase (a one group pre-post design) the effect size was calculated as the mean difference between pre- and post-treatment divided by the sample standard deviation of the difference [15]. The double-blind phase mirrored an independent two-group pre-post design; therefore, the effect size was first calculated for each treatment group. The overall effect size was computed as the difference in-group effect sizes between the solifenacin succinate and placebo groups [16]. All analyses were performed using SAS 9.3 (SAS Institute, Inc. Cary, N.C.). A SAS macro created by the University of South Florida was used to implement design-specific calculation of effect size [17].

The study was approved by Independent Ethics Committee/Institutional Review Boards and performed in accordance with the International Conference for Good Clinical Practice, the national regulations and ethical principles of the Declaration of Helsinki. All patients provided written informed consent.

3. Results

The final randomized sample consisted of 23 patients (10 solifenacin, 13 placebo) whose baseline characteristics are shown in Table 1. There were no statistically significant differences between the two groups on any baseline characteristic. Two participants failed to return bladder diaries at both follow up visits during the open-label phase. Although they were therefore excluded from the analysis of open-label diary data, they were still included in analyses of other outcomes during the open-label phase. While UI was not a criteria for inclusion, 65% (15/23) of participants reported an average of at least 1 daily episode of UI at baseline.

In the double-blind phase, the primary outcome measure (mean number of micturitions per 24 h period) did not significantly improve with the use of solifenacin succinate. However, the average number of urinary incontinence episodes per 24 h period decreased significantly in the solifenacin group (1.48 ± 2.56 to 0.30 ± 0.31) compared to placebo (1.78 ± 1.27 to 1.61 ± 1.40, $p = 0.01$). Most participants (6/9, 67%) in the active treatment group received 5 mg of solifenacin succinate throughout the double-blind portion of the study. Other measures of urinary function, including number of micturitions per 24 h period and number of nocturia episodes per 24 h period, also decreased in both groups; however, the differences in the baseline-to-endpoint changes between the groups were not statistically-significant (Table 2).

Participants who received solifenacin succinate demonstrated more of a trend toward improvement on the PPBC, a measure of perceived bother from urinary symptoms, as well as for motor function as assessed by the UPDRS. There were no significant changes in the PPIUS or measures of quality of life (PD QOL, IQOL).

In the open label phase of the study significant improvements were observed from baseline to endpoint in the mean daily number of urinary incontinence episodes (baseline $= 1.33 \pm 1.54$ to 0.52 ± 1.01; $p = 0.03$), the number of nocturia episodes (from 2.67 ± 1.08 to 1.64 ± 1.09; $p = 0.01$), the patient's perception of their bladder condition ($p = 0.01$), and the motor component of the UPDRS ($p = 0.04$) (Table 3). By the end of the open-label phase, 56% (9/16) of participants took 10 mg solifenacin succinate daily. There was no significant change in the PD-QOL or I-QOL during the open-label portion.

Solifenacin succinate was generally well tolerated. Treatment associated adverse events during the double-blind period included constipation ($n = 1/9$ participants on active treatment, 0/12 on placebo), xerostomia ($n = 2/9$ participants on active treatment, 0/12 on placebo), and urinary retention ($n = 1/9$ participants on active treatment, 0/12 on placebo), which all resolved upon treatment discontinuation.

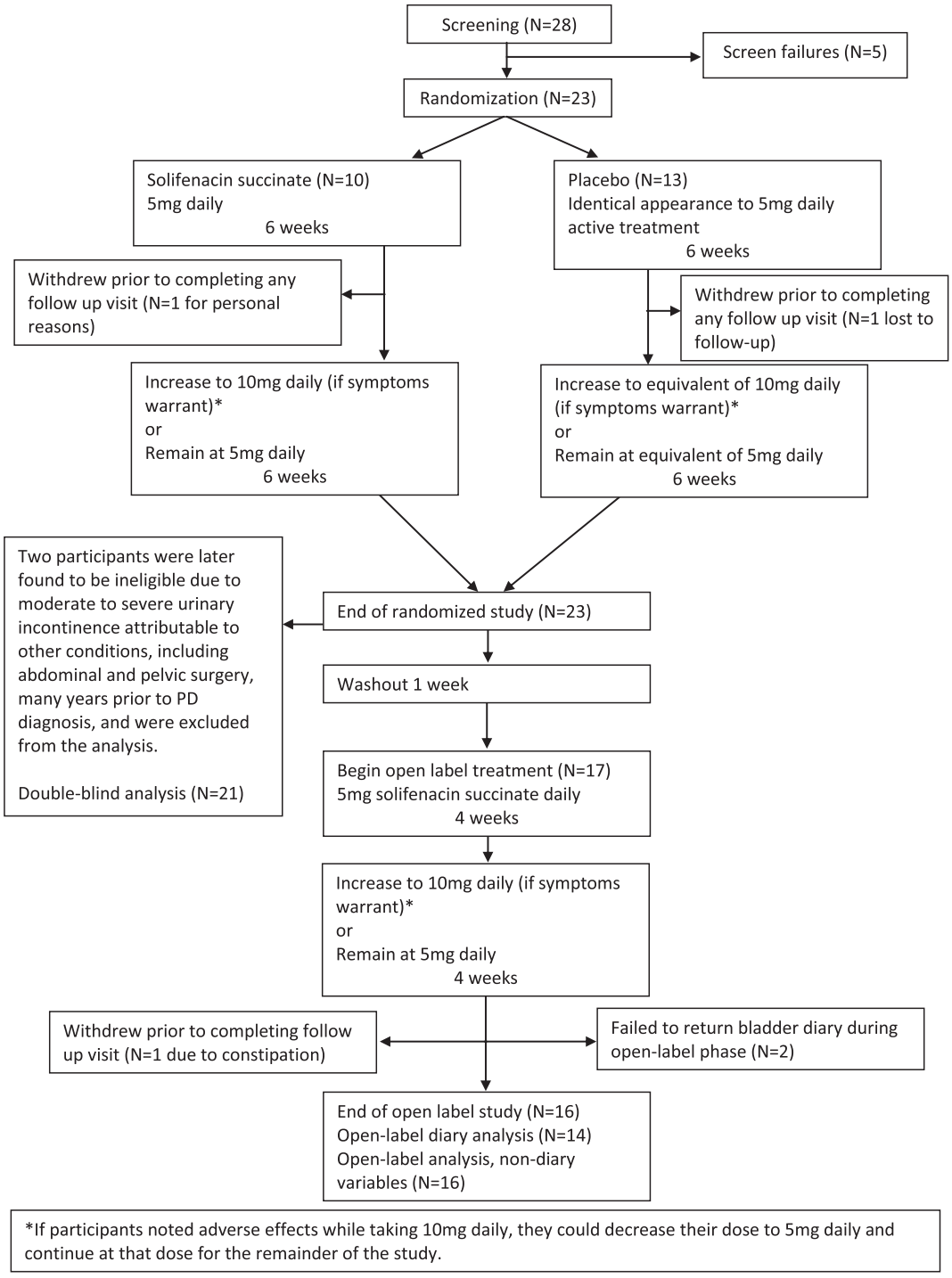

Fig. 1. Study flow.

4. Discussion

PD patients commonly suffer from urinary symptoms. In addition to the classic motor symptoms that have been well described in PD, it is estimated that 30%–50% of PD patients suffer from urinary symptoms including more than 25% who have UI [6,18]. Randomized controlled trials of therapeutic intervention for OAB symptoms in adults with PD are lacking, and current treatment guidelines are based on clinical practice experience and expert opinion [19]. Antimuscarinic drugs, commonly used to treat similar symptoms in OAB, both reduce bladder contractility and impact bladder afferent nerve activity [7].

In this study, patients taking solifenacin experienced significant improvements in several measures of urinary dysfunction, both in the controlled and open-label aspects of the study, although the primary outcome measure was not met. In the double-blind phase, patients taking solifenacin were noted to have a significant reduction in the number of incontinence episodes in a 24 h period, while during the open-label phase, patients taking solifenacin had significant improvements in the number of incontinence episodes

Table 1
Baseline characteristics for all randomized participants (N = 23).

Variable	Solifenacin (N = 10)	Placebo (N = 13)	p-Value[a]
Demographics			
Age (years), Mean ± SD	67.6 ± 6.6	66.5 ± 9.3	0.74
Sex, N (%)			1.00
Female	3 (30.0)	5 (38.5)	
Male	7 (70.0)	8 (61.5)	
Race/Ethnicity, N (%)			1.00
White	8 (80.0)	10 (76.9)	
Black or African American	1 (10.0)	1 (7.7)	
Hispanic/Latino	1 (10.0)	1 (7.7)	
Native Hawaiian or other Pacific Islander	0 (0.0)	1 (7.7)	
PD characteristics			
UPDRS ADL subsection (possible range 0–52), Mean ± SD	9.50 ± 5.40	11.23 ± 4.76	0.42
UPDRS motor subsection (possible range 0–56), mean ± SD	12.60 ± 4.38	14.69 ± 5.19	0.32
UPDRS total score (possible range 0–124), mean ± SD	24.00 ± 9.67	25.08 ± 11.93	0.82
PDQOL total (possible range 37–185), Mean ± SD	124.10 ± 19.96	115.31 ± 10.68	0.23
Hoehn & Yahr stage, N (%)			0.87
Stage 1: unilateral symptoms only	1 (10.0)	0 (0.0)	
Stage 1.5: unilateral and axial involvement	1 (10.0)	1 (7.7)	
Stage 2: bilateral symptoms. No impairment of balance	1 (10.0)	2 (15.4)	
Stage 2.5: mild bilateral disease with recovery on pull test	6 (60.0)	7 (53.8)	
Stage 3: balance impairment. Mild to moderate disease. Physically independent	1 (10.0)	3 (23.1)	
Urinary characteristics			
IQOL total (possible range 22–110), Mean ± SD	78.00 ± 20.03	75.92 ± 18.87	0.80
Bladder diary:# micturitions, Mean ± SD	9.03 ± 2.21	9.23 ± 3.31	0.87
Bladder diary:# leaks, mean ± SD	1.33 ± 2.45	1.72 ± 1.23	0.66
Bladder diary:# nocturia episodes, mean ± SD	2.23 ± 1.69	1.90 ± 1.09	0.57
PBC/PPBC, N (%)			0.83
Causes me (some) moderate problems	5 (50.0)	5 (38.5)	
Causes me severe problems	4 (40.0)	7 (53.8)	
Causes me many severe problems	1 (10.0)	1 (7.7)	
PPIUS, N (%)			0.53
Mild urgency: I could postpone voiding as long as necessary without fear of wetting myself	3 (30.0)	1 (7.7)	
Moderate urgency: I could postpone voiding for a short while without fear of wetting myself	4 (40.0)	5 (38.5)	
Moderate-severe	0 (0.0)	1 (7.7)	
Severe urgency: I could not postpone voiding but had to rush to the toilet in order not to wet myself	3 (30.0)	6 (46.2)	

UPDRS = Unified Parkinson's disease rating scale; ADL = activities of daily life; PDQOL = Parkinson's disease quality of life; IQOL = incontinence quality of life; PBC/PPBC = patient perception of bladder condition; PPIUS = patient perception of intensity of urgency scale.
[a] For continuous variables (all those with mean ± SD), the p-value is generated from an independent samples t-test. For categorical variables, the p-value is generated from either a Fisher's exact test or Freeman–Halton test.

and nocturia in a 24 h period, as well as reduced urinary urgency compared to baseline. With an average decrease of 1.18 UI episodes per day among patients taking solifenacin succinate during the double-blind phase, a 79.7% reduction from baseline, the improvement in this study was impressive and greater than other studies involving solifenacin succinate for OAB, which have typically shown a mean reduction of 0.77–0.81 UI episodes per day depending on the dose of solifenacin succinate used in the trial [20].

As a pilot study, these results may contribute to the design of larger trials of treatments for urinary dysfunction in PD. Previous studies of solifenacin succinate in adults without PD have demonstrated larger effect sizes for several urinary symptoms (voiding frequency, nocturia, urinary urgency) than detected in this small pilot study with PD patients [20]. However, the effect size for urinary incontinence in the current study is similar to results from a meta-analysis of solifenacin succinate in non-PD populations with overactive bladder [20]. While it is not possible to determine the specific pathophysiologic mechanisms underlying the observed results, there are several potential pathways to consider. Solifenacin succinate acts primarily to reduce bladder contractility, which may allow more time to reach the bathroom when urgency episodes occur. Additionally, bladder diaries, which are commonly used in studies of urinary symptoms, allow for self-monitoring and could impact voiding behavior by increasing self-awareness of voiding frequency and urgency episodes for both drug and placebo groups. The lack of effect for voiding frequency and urinary urgency may point to underlying mechanisms related to central sensory integration that are not as responsive to medication-based approaches. Future, larger studies could further define baseline patient characteristics, such as cognitive function or the presence of urinary incontinence in the setting of urinary urgency, as predictors of response to a particular treatment strategy.

Anticholinergic medications typically used to treat urinary symptoms can add to the anticholinergic burden of anti-parkinsonian therapy, and possibly to cognitive impairment [21] and autonomic burdens (e.g., constipation, orthostasis) found in PD. Prior evaluation of solifenacin succinate in patients susceptible to mild cognitive impairment have demonstrated its relative safety [22], but further study in patients with PD is warranted.

Although the exact pathophysiology of urinary incontinence in PD is unknown, one theory is that the loss of appropriate basal ganglia output reduces cortical inhibition of the micturition reflex, which in turn results in detrusor hyperreflexia with concomitant symptoms (the need to urinate, followed by contraction of the bladder and potential involuntary loss of urine). Cortical alpha-synuclein pathology and impaired basal ganglia function are theorized to impact sensory integration of bladder afferent signaling and contribute to detrusor hyperactivity in PD. Prior

Table 2
Double-blind results for randomized participants for whom follow-up data were available.[a]

Variable	Solifenacin (N = 9) baseline	Solifenacin (N = 9) endpoint	Placebo (N = 12) baseline	Placebo (N = 12) endpoint	Effect size	p-Value
Primary measure	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	[b]	[c]
Number of micturitions per 24 h period	8.78 ± 2.18	8.00 ± 3.36	9.19 ± 3.46	8.94 ± 3.06	0.20	0.53
Secondary measures						
Number of urinary incontinence episodes per 24 h period	1.48 ± 2.56	0.30 ± 0.31	1.78 ± 1.27	1.61 ± 1.40	0.53	0.01
Number of nocturia episodes per 24 h period	2.48 ± 1.59	2.04 ± 1.96	1.92 ± 1.14	1.78 ± 0.88	0.11	0.94
UPDRS Total	25.00 ± 9.70	21.67 ± 9.59	25.67 ± 12.26	25.75 ± 8.76	0.35	0.22
UPDRS ADL	9.89 ± 5.58	8.11 ± 5.37	11.75 ± 4.58	11.75 ± 3.98	0.32	0.09
UPDRS motor	13.22 ± 4.15	12.11 ± 5.21	14.92 ± 5.35	13.08 ± 6.46	−0.07	0.79
PDQOL	125.00 ± 20.95	116.00 ± 26.42	114.50 ± 10.73	112.92 ± 17.19	0.27	0.47
IQOL	76.78 ± 20.85	84.89 ± 25.97	74.58 ± 19.05	77.00 ± 20.96	−0.22	0.33
Categorical measures	**N (%)**	**N (%)**	**N (%)**	**N (%)**		[d]
PBC/PPBC					0.45	0.31
Causes me some very minor problems	0 (0.0)	1 (11.1)	0 (0.0)	1 (8.3)		
Causes me some minor problems	0 (0.0)	2 (22.2)	0 (0.0)	3 (25.0)		
Causes me (some) moderate problems	4 (44.4)	5 (55.6)	4 (33.3)	1 (8.3)		
Causes me severe problems	4 (44.4)	0 (0.0)	7 (58.3)	6 (50.0)		
Causes me many severe problems	1 (11.1)	1 (11.1)	1 (8.3)	1 (8.3)		
PPIUS					0.23	0.19
No urgency	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)		
Mild urgency	2 (22.2)	4 (44.4)	1 (8.3)	2 (16.7)		
Moderate urgency	4 (44.4)	2 (22.2)	4 (33.3)	7 (58.3)		
Moderate-severe	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)		
Severe urgency	3 (33.3)	2 (22.2)	6 (50.0)	2 (16.7)		
Urge incontinence	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)		
Hoehn & Yahr stage					−0.11	0.79
Stage 1: unilateral symptoms only	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)		
Stage 1.5: unilateral and axial involvement	1 (11.1)	1 (11.1)	1 (8.3)	1 (8.3)		
Stage 2: bilateral symptoms. No impairment of balance	1 (11.1)	2 (22.2)	2 (16.7)	1 (8.3)		
Stage 2.5: mild bilateral disease with recovery on pull test	5 (55.6)	5 (55.6)	6 (50.0)	7 (58.3)		
Stage 3: balance impairment. Mild to moderate disease. Physically independent	1 (11.1)	1 (11.1)	3 (25.0)	3 (25.0)		
CGI Measures	**N (%)**	**N (%)**	**N (%)**	**N (%)**		[e]
CGI-improvement					−3.49	0.66
Not assessed		0 (0.0)		0 (0.0)		
Very much improved		0 (0.0)		1 (8.3)		
Much improved		3 (33.3)		3 (25.0)		
A little improved		4 (44.4)		3 (25.0)		
No change		2 (22.2)		4 (33.3)		
Much worse		0 (0.0)		1 (8.3)		
CGI-therapeutic					0.15	0.47
Not assessed		0 (0.0)		0 (0.0)		
Marked - vast improvement. complete or nearly complete remission of all symptoms		1 (11.1)		1 (8.3)		
Moderate – decided improvement. partial remission of symptoms		3 (33.3)		3 (25.0)		
Minimal – slight improvement which does not alter the status of care of patient		3 (33.3)		3 (25.0)		
Unchanged or worse		2 (22.2)		5 (41.7)		

UPDRS = Unified Parkinson's Disease Rating Scale; ADL = Activities of Daily Life; PDQOL = Parkinson's Disease Quality of Life; IQOL = Incontinence Quality of Life; PBC/PPBC = Patient Perception of Bladder Condition; PPIUS = Patient Perception of Intensity of Urgency Scale.

[a] Two of the 23 randomized participants (1 solifenacin, 1 placebo) were excluded due to lack of follow-up data.

[b] Effect size is measured by Cohen's *d* statistic for an independent groups pre-post design. Positive values indicate that the Solifenacin group had a greater mean reduction from baseline-to-endpoint relative to the placebo group.

[c] P-value generated using analysis of covariance with the treatment group as the primary independent variable, adjusting for the baseline measure.

[d] P-value generated using ordinal logistic regression with the treatment group as the primary independent variable, adjusting for the baseline measure.

[e] P-value generated using Wilcoxon-Mann Whitney test to assess whether endpoints were different between placebo and treatment groups.

studies have also demonstrated increased rates of detrusor hyperreflexia and voiding dysfunction in patients with PD [23]. In this study, PD motor symptom severity was correlated with the number of nocturia episodes per 24 h period (Pearson correlation $r = 0.53$, $p = 0.01$) but not with total number of micturitions per 24 h period ($r = -0.02$, $p = 0.93$) or number of leaks per 24 h period ($r = 0.17$, $p = 0.47$). Further study is needed to determine the mechanism of effect for reducing urinary incontinence episodes among PD patients.

Because this trial was designed as a pilot study, it was underpowered to detect the primary outcome measure. To detect a difference of 1.3 between the solifenacin and placebo groups in the

Table 3
Open-label results for participants reaching the end of the open-label phase (N = 16).

Variable	Open Label solifenacin baseline	Open Label solifenacin endpoint	Effect size	p-Value
Bladder diary measures (n = 14)	Mean ± SD	Mean ± SD	[a]	[b]
Number of micturitions per 24 h period	8.88 ± 3.37	7.76 ± 2.17	0.43	0.13
Number of urinary incontinence episodes per 24 h period	1.33 ± 1.54	0.52 ± 1.01	0.66	0.03
Number of nocturia episodes per 24 h period	2.67 ± 1.08	1.64 ± 1.09	0.82	0.01
Other measures (n = 16)				
UPDRS total	25.50 ± 9.76	21.78 ± 6.49	0.54	0.05
UPDRS ADL	10.25 ± 3.66	9.13 ± 3.58	0.39	0.14
UPDRS motor	14.38 ± 6.72	11.63 ± 4.73	0.56	0.04
PD-QoL	111.75 ± 26.19	120.63 ± 21.56	0.47	0.08
I-QoL	82.75 ± 18.35	88.81 ± 17.55	−0.36	0.18
Categorical measures (n = 16)	**N (%)**	**N (%)**		[c]
PBC/PPBC			0.68	0.01
Causes me some very minor problems	0 (0.0)	3 (18.8)		
Causes me some minor problems	3 (18.8)	4 (25.0)		
Causes me (some) moderate problems	4 (25.0)	6 (37.5)		
Causes me severe problems	7 (43.8)	3 (18.8)		
Causes me many severe problems	2 (12.5)	0 (0.0)		
PPIUS			0.78	0.02
Mild urgency	2 (12.5)	7 (43.8)		
Moderate urgency	6 (37.5)	6 (37.5)		
Severe urgency	8 (50.0)	3 (18.8)		
Hoehn & Yahr stage			0.08	0.45
Stage 1: unilateral symptoms only	2 (12.5)	1 (6.3)		
Stage 1.5: unilateral and axial involvement	1 (6.3)	0 (0.0)		
Stage 2: bilateral symptoms. No impairment of balance	1 (6.3)	4 (25.0)		
Stage 2.5: mild bilateral disease with recovery on pull test	8 (50.0)	7 (43.8)		
Stage 3: balance impairment. Mild to moderate disease. Physically independent	4 (25.0)	4 (25.0)		
CGI measures (n = 16)	**N (%)**	**N (%)**		[d]
CGI-improvement			N/A	<0.01
Very much improved		4 (25.0)		
Much improved		5 (31.3)		
A little improved		5 (31.3)		
No change		1 (6.3)		
Minimally worse		0 (0.0)		
Much worse		1 (6.3)		
CGI-therapeutic			N/A	<0.01
Marked - vast improvement. complete or nearly complete remission of all symptoms		3 (18.8)		
Moderate – decided improvement. Partial remission of symptoms		7 (43.8)		
Minimal – slight improvement which does not alter the status of care of patient		5 (31.3)		
Unchanged or worse		1 (6.3)		

UPDRS = Unified Parkinson's Disease Rating Scale; ADL = Activities of Daily Life; PDQOL = Parkinson's Disease Quality of Life; IQOL = Incontinence Quality of Life; PBC/PPBC = Patient Perception of Bladder Condition; PPIUS = Patient Perception of Intensity of Urgency Scale.

[a] Effect size is measured by Cohen's *d* statistic for an one group pre-post design. Positive values indicate a mean reduction from baseline-to-endpoint. Effect sizes were not calculated for the CGI measures.

[b] P-value generated using a Wilcoxon signed-rank test.

[c] P-value generated using a sign test.

[d] P-value generated using a one-sample median test (is median different from “no change”).

mean change in daily micturitions from baseline to endpoint, with 80% power, a 5% type I error rate, and assuming a standard deviation of 3.0 for both groups, the study would have required 85 participants randomized to each treatment group [18]. This could be performed in the future.

Anticholinergic medications typically used to treat urinary symptoms can add to the anticholinergic burden of anti-parkinsonian therapy, and thus to the cognitive (e.g. mild cognitive impairment or dementia) [16] and autonomic burdens (e.g., constipation, orthostasis) of the illness. Prior evaluation of solifenacin in patients susceptible to cognitive impairment have demonstrated its relative safety [17], but further study in patients with PD is warranted.

In this study, the use of solifenacin succinate led to a significant improvement in urinary incontinence in PD patients, a benefit that continued in the open label portion of the study along with reduction in nocturia, although other symptoms of OAB persisted. While results from this small study are encouraging, further studies are needed to evaluate the treatment of urinary dysfunction in PD. Such studies might primarily focus on the number of UI episodes that seemed to

be most affected in this trial. Additionally, this study provides guidance for estimating expected differences between groups and data for sample size calculations for larger, powered trials.

Financial disclosures

The authors have no conflicts of interest or financial disclosures relevant to this paper.

Funding sources

Solifenacin succinate and matching placebo was supplied by Astellas Pharmaceuticals who had no role in patient randomization, evaluation, or statistical analysis.

Acknowledgment

This study was sponsored by Astellas Pharma US, Inc. Patients were not compensated for study participation.

References

[1] Pohar SL, Allyson Jones C. The burden of Parkinson disease (PD) and concomitant comorbidities. Arch Gerontol Geriatr 2009;49:317–21.
[2] Gallagher DA, Lees AJ, Schrag A. What are the most important nonmotor symptoms in patients with Parkinson's disease and are we missing them? Mov Disord 2010;25:2493–500.
[3] Araki I, Kuno S. Assessment of voiding dysfunction in Parkinson's disease by the international prostate symptom score. J Neurol Neurosurg Psychiatry 2000;68:429–33.
[4] Campos-Sousa RN, Quagliato E, da Silva BB, de Carvalho Jr RM, Ribeiro SC, de Carvalho DF. Urinary symptoms in Parkinson's disease: prevalence and associated factors. Arq Neuropsiquiatr 2003 Jun;61:359–63.
[5] Lemack GE, Dewey RB. Questionnaire-based assessment of bladder dysfunction in patients with mild to moderate Parkinson's disease. Urology 2000;56:250–4.
[6] Winge K, Fowler CJ. Bladder dysfunction in Parkinsonism: mechanisms, prevalence, symptoms, and management. Mov Disord 2006;21:737–45.
[7] Andersson KE. Antimuscarinic mechanisms and the overactive detrusor: an update. Eur Urol 2011;59:377–86.
[8] Wagg A, Gibson W, Ostaszkiewicz J, Johnson 3rd T, Markland A, Palmer MH, et al. Urinary incontinence in frail elderly persons: report from the 5th international consultation on incontinence. Neurourol Urodyn 2014. http://dx.doi.org/10.1002/nau.22602.
[9] Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease. A clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181–4.
[10] Cartwright R, Panayi D, Cardozo L, Khullar V. Reliability and normal ranges for the patient's perception of intensity of urgency scale in asymptomatic women. BJU Int 2010;105:832–6.
[11] Coyne KS, Matza LS, Kopp Z, Abrams P. The validation of the patient perception of bladder condition (PPBC): a single-item global measure for patients with overactive bladder. Eur Urol 2006 Jun;49:1079–86.
[12] de Boer AG, Wijker W, Speelman JD, de Haes JC. Quality of life in patients with Parkinson's disease: development of a questionnaire. J Neurol Neurosurg Psychiatry 1996;61:70–4.
[13] Patrick DL, Martin ML, Bushnell DM, Yalcin I, Wagner TH, Buesching DP. Quality of life of women with urinary incontinence: further development of the incontinence quality of life instrument (I-QOL). Urology 1999;53:71–6.
[14] Fahn S, Elton RL. UPDRS program members. Unified Parkinsons disease rating scale. In: Fahn S, Marsden CD, Goldstein M, Calne DB, editors. Recent developments in Parkinsons disease, vol. 2. Florham Park, NJ: Macmillan Healthcare Information; 1987. p. 153–63.
[15] Morris SB, DeShon RP. Combining effect size estimates in meta-analysis with repeated measures and independent-groups designs. Psychol Methods 2002;7:105–25.
[16] Becker BJ. Synthesizing standardized mean change measures. Br J Math Stat Psychol 1988;41:257–78.
[17] Kadel RP, Kip KE. A SAS macro to compute effect size (Cohen's d) and its confidence interval from raw survey data. In: Proceedings of the Annual Southeast SAS Users Group Conference; 2012. paper SD-06.
[18] K1 Winge, Skau AM, Stimpel H, Nielsen KK, Werdelin L. Prevalence of bladder dysfunction in Parkinson disease. Neurourol Urodyn 2006;25:116–22.
[19] Zesiewicz TA, Sullivan KL, Arnulf I, Chaudhuri KR, Morgan JC, Gronseth GS, et al. Standards Subcommittee of the American Academy of Neurology. Practice parameter: treatment of nonmotor symptoms of Parkinson disease: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2010;74:924–31.
[20] Chapple CR, Khullar V, Gabriel Z, Muston D, Bitoun CE, Weinstein D. The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis. Eur Urol 2008;54:543–62.
[21] Jost WH. Urological problems in Parkinson's disease: clinical aspects. J Neural Transm 2013;120(4):587–91.
[22] Wagg A, Dale M, Tretter R, Stow B, Compion G. Randomised, multicentre, placebo-controlled, double-blind crossover study investigating the effect of solifenacin and oxybutynin in elderly people with mild cognitive impairment: the SENIOR study. Eur Urol 2013;64:74–81.
[23] Araki I, Kitahara M, Oida T, Kuno S. Voiding dysfunction and Parkinson's disease: urodynamic abnormalities and urinary symptoms. J Urol 2000;164:1640–3.