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A RANDOMIZED CONTROLLED TRIAL OF DULOXETINE ALONE, PELVIC FLOOR MUSCLE TRAINING ALONE, COMBINED TREATMENT AND NO ACTIVE TREATMENT IN WOMEN WITH STRESS URINARY INCONTINENCE

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ABSTRACT

Purpose: We primarily compared the effectiveness of combined pelvic floor muscle training (PFMT) and duloxetine with imitation PFMT and placebo for 12 weeks in women with stress urinary incontinence (SUI). In addition, we compared the effectiveness of combined treatment with single treatments, single treatments with each other and single treatments with no treatment.

Materials and Methods: This blinded, doubly controlled, randomized trial enrolled 201 women 18 to 75 years old with SUI at 17 incontinence centers in the Netherlands, United Kingdom and United States. Women averaged 2 or more incontinence episodes daily and were randomized to 1 of 4 combinations of 80 mg duloxetine daily, placebo, PFMT and imitation PFMT, including combined treatment (in 52), no active treatment (in 47), PFMT only (in 50) and duloxetine only (in 52). The primary efficacy measure was incontinence episode frequency. Other efficacy variables included the number of continence pads used and the Incontinence Quality of Life questionnaire score.

Results: The intent to treat population incontinence episode frequency analysis demonstrated the superiority of duloxetine with or without PFMT compared with no treatment or with PFMT alone. However, pad and Incontinence Quality of Life analyses suggested greater improvement with combined treatment than single treatment. A completer population analysis demonstrated the efficacy of duloxetine with or without PFMT and suggested combined treatment was more effective than either treatment alone.

Conclusions: The data support significant efficacy of combined PFMT and duloxetine in the treatment of women with SUI. We hypothesize that complementary modes of action of duloxetine and PFMT may result in an additive effect of combined treatment.

KEY WORDS: urinary incontinence, stress; pelvic floor, exercise therapy, duloxetine, drug therapy

Stress urinary incontinence (SUI) is the most common type of urinary incontinence in women.[1] The recommended first line treatment for women with SUI is pelvic floor muscle training (PFMT).[2] Although duloxetine has recently been approved in Europe, there is no pharmacological treatment currently approved in the United States for SUI.

PFMT is accepted as effective for SUI. The second International Consultation on Incontinence concluded "there is level 1B evidence to suggest that for women with stress . . . incontinence, PFMT is better than no treatment."[3] A subsequent Cochrane review also concluded that PFMT is effective for women with SUI and is superior to no treatment, but noted that limitations in study designs made it difficult to compare PFMT to other treatments.[4]

PFMT is believed to limit vaginal movement with a physical stress, enhancing compression of the urethra against the anterior vaginal wall.[5] The 2 elements of PFMT are strength and skill training. Strength training is believed to result in muscle hypertrophy by repeated exercise over weeks to months, improving urethral compression during activity.[6] Skill training involves learning to contract the muscles with events that cause leakage. It differs from strength training because it shows effects almost immediately.[7] Women taught skill training can significantly reduce leakage within 1 week of learning the technique, although most do not eliminate leakage.[7] In summary, strength training decreases the frequency of incontinence episodes with time. Skill training immediately reduces the amount of leakage.

In 5 randomized, placebo controlled trials there was significant improvement in SUI with the serotonin-norepinephrine reuptake inhibitor, duloxetine.[8–12] Duloxetine's presumed mechanism of action is stimulation of pudendal nerve output to the striated urethral sphincter as a result of increased levels of serotonin and norepinephrine in the pudendal nucleus in the sacral spinal cord.[13]

While duloxetine is believed to enhance rhapbdosphincter function via the pudendal nerve, the pelvic floor muscles are not

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supplied by this nerve but by other sacral somatic efferents.[14] Furthermore, there is evidence that a pelvic floor muscle contraction activates the muscles of the pelvic floor but not the rhabdosphincter.[15] These observations suggest that PFMT and duloxetine could have additive effects on the stress continence mechanism.

To assess the effects of PFMT and duloxetine, we conducted this randomized, doubly controlled trial comparing combinations of 4 interventions, namely PFMT, imitation PFMT, 80 mg duloxetine daily and placebo. The primary objective was to compare the effectiveness of combined PFMT plus duloxetine with imitation PFMT plus placebo for 12 weeks in women with moderate to severe SUI. Secondary objectives were to compare the effectiveness of combined treatment with each single treatment, single treatments with each other and single treatments with no active treatment.

METHODS

Women 18 to 75 years old with SUI were eligible for this blinded, controlled, randomized, multicenter trial. Subjects were enrolled at 16 tertiary continence centers in the Netherlands, United Kingdom and United States. The ethics review committee for each site approved the study and written informed consent was obtained from every participant.

Subjects were required to have urodynamic stress incontinence and no detrusor overactivity on studies within 6 months before entry (36 subjects) or a positive cough stress test and normal micturition frequency (less than 8 voids daily) at entry (165 subjects). All subjects had predominant symptoms of SUI with an average of at least 2 stress incontinent episodes daily.

Additional major exclusions included advanced pelvic organ prolapse, active or recurrent urinary tract infections, continence surgery within 1 year, current device or pharmaceutical incontinence treatment, prior hip fracture or replacement and any prior formal PFMT with a continence nurse or physical therapist.

Figure 1 summarizes the study design. Subjects were randomized to 1 of 4 treatments, namely 40 mg duloxetine twice daily plus imitation PFMT (duloxetine only), duloxetine plus PFMT (combined treatment), placebo plus PFMT (PFMT only) or placebo plus imitation PFMT (no active treatment) for 12 weeks. Treatments were assigned using a centralized computer voice response system and were balanced at each site. Duloxetine and placebo were administered in double-blind fashion, and only the subject was blinded to the PFMT regimen.

Qualified instructors gave subjects assigned to PFMT verbal instructions and manual feedback. During a digital pelvic examination, the subject was asked to contract the muscles she would use to prevent urine or flatus loss and hold for 6 to 8 seconds. The examiner confirmed the pelvic floor muscles were contracted without dominant contractions of the abdominal, gluteal or hip adductor muscles. Once proper contractions were confirmed, subjects received written instructions to perform 3 sets of 10 long (6 to 8 seconds) and 2 sets of 10 rapid (1 to 2 seconds) contractions 4 days weekly, for a total of 200 contractions weekly. At every visit subjects were given a training log in which to record the number of contractions performed. Finally subjects were given instructions to contract the pelvic muscles with physical events that usually caused them to experience accidental leakage (skill training).

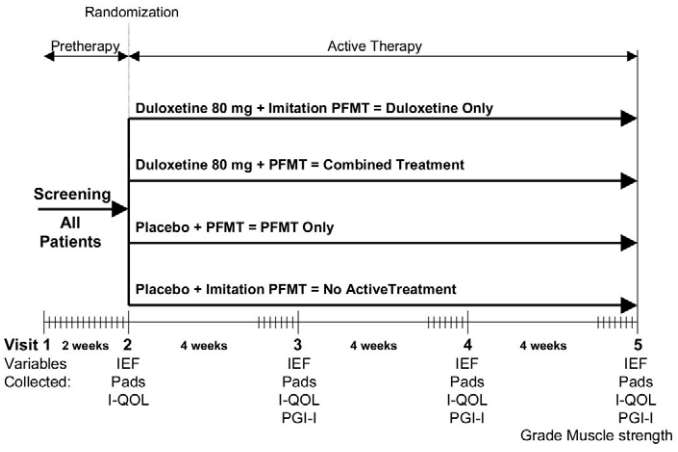

FIG. 1. Study design and timing of collection of baseline and outcome variables.

The imitation PFMT regimen was based on one described by Ramsay and Thou.[16] The subject was instructed to cross her legs at the ankles with her knees and hips flexed while sitting or supine and abduct the hips, holding the contraction for 6 to 8 seconds while the therapist palpated the hip abductors and abdominal muscles and confirmed the abductors were contracted without dominant contractions of abdominal muscles. Once proper contractions were confirmed subjects received written instructions and a training log. Again 3 sets of 10 long and 2 sets of 10 rapid contractions 4 days weekly were recommended but no recommendation for skill training was given.

PFMT groups received 30 minutes of instruction and feedback initially and 15 minutes of re-instruction and manual feedback at 4 and 8 weeks. Pelvic floor muscle strength was graded using a 9-point strength/duration/displacement scale at baseline (PFMT group only) and after 12 weeks of treatment (both groups). Hip abductor muscle strength was graded at baseline for imitation PFMT groups but pelvic floor muscle strength was not graded to avoid coaching on the performance of PFMT.

The primary efficacy measurement, incontinence episode frequency (IEF), was computed from subject completed paper diaries at each visit. Other efficacy variables included the number of continence pads used, the validated Incontinence Quality of Life (I-QOL) questionnaire[17] score (Appendix 2), and the rating from the validated Patient Global Impression of Improvement scale[18] (PGI-I, Appendix 3). For some prespecified analyses a responder was defined as a woman who had a 50% or greater decrease in IEF with treatment. Safety was assessed by the evaluation of treatment emergent adverse event (AE), discontinuations due to adverse events, vital signs and clinical laboratory values.

Prespecified and post hoc analyses were performed. The primary prespecified analysis compared weekly IEF before and after randomization, pooling all diaries between visits 1 and 2 for the baseline and all diaries between visits 2 through 5 for the end point. This pooled analysis assesses the overall success of treatments throughout the 12-week trial. A post hoc IEF analysis was performed using last visit diary data only for those subjects who completed visit 5. This completer analysis gives an estimate of the treatment effects at the end of the trial. The prespecified analysis was an intent to treat (ITT) analysis, including data from all assessable subjects who were randomized to a treatment, even if the subject did not receive the treatment, received the incorrect treatment or did not follow the protocol. Prematurely discontinuing subjects had the last outcome measure carried forward (LOCF) only in this analysis.

Pairwise comparisons of treatments for the percent change in IEF and continence pad use were performed using the Wilcoxon-Mann-Whitney test. This test was used instead of an ANOVA model because the hypothesis of normality was rejected. The nonparametric 95% confidence intervals for treatment differences were obtained using the Hodges-Lehman estimation and for individual treatment effects using order statistics. Pairwise treatment comparisons and the 95% confidence intervals for I-QOL were determined using an ANCOVA model that included the change in score as the dependent variable and treatment, baseline score, and study

site as independent variables. PGI-I data were analyzed using the Cochran-Mantel-Haenszel test and IEF responder data were analyzed using the Fisher exact test. The sample size was determined to provide at least an 87% power to detect a treatment difference of 20% in the decrease in IEF between combined treatment and no active treatment groups with a Type I error of 0.05. Analyses were performed using SAS 8.1 (SAS Institute, Cary, North Carolina). A 2-sided p value of 0.05 was considered significant.

RESULTS

A total of 201 women 29 to 75 years old were studied between January 2002 and July 2003. Figure 2 summarizes the flow of subjects through the study. Overall 180 (90%) women completed post-randomization diaries and were included in the ITT IEF analysis, which included 90 women receiving placebo (94%) and 90 receiving duloxetine (87%).

Table 1 presents baseline demographic and clinical characteristics. There were no significant differences among the treatment groups. Compliance rates for placebo or duloxetine and for PFMT or imitation PFMT were high, and did not differ significantly among treatment groups (table 2). Significant improvements were demonstrated in pelvic floor muscle grade from baseline to end point in the active PFMT treatment groups with a 1.34 increase (SD 1.28, paired t test $p < 0.001$) for combined treatment and 1.41 (SD 1.93, $p < 0.001$) for PFMT only. End point mean muscle grades for the imitation PFMT groups (4.7 and 5.3 points) were similar to the baseline grades for the PFMT groups.

Using the ITT population analysis combined treatment was superior to no treatment for all outcome variables (table 3). Duloxetine alone and PFMT alone results are presented in table 4. Duloxetine alone had a significantly greater impact in decreasing incontinence episodes than PFMT alone but there were no significant differences between the single treatments with respect to impact on quality of life or pad use. Combined treatment (table 3) was not significantly different from duloxetine alone (table 4), although the difference in the change in I-QOL scores approached significance ($p = 0.059$). Combined treatment (table 3) was significantly better than PFMT alone (table 4) for decrease in IEF ($p < 0.001$), and for the proportion of subjects who were responders ($p < 0.001$). It approached significance for the reduction in pad use ($p = 0.07$) and improvement in I-QOL score ($p = 0.063$). Comparing single treatments to no treatment, duloxetine alone was significantly more effective than no treatment for the reduction in IEF ($p < 0.001$), for the proportion of subjects who were responders ($p = 0.002$) and for the decrease in pad use ($p = 0.001$). PFMT alone was significantly more effective than no treatment for the decrease in pad use ($p = 0.028$).

Table 5 presents results by treatment group for completers.

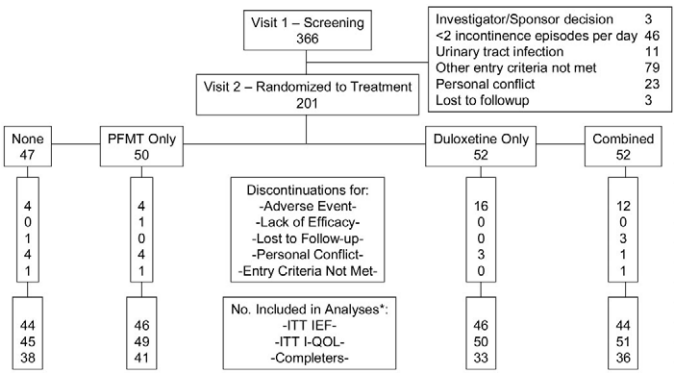

FIG. 2. Consort diagram for subject disposition through randomized controlled trial.

While reduced group sizes limit the power of these analyses, the combined treatment group again had significantly better responses than the no treatment group for all 5 variables, than PFMT alone for 3, and than duloxetine alone for 1. None of the differences between single treatments were significant. The only significant differences between single treatment groups and the no treatment group favored duloxetine only for reduction in pad use and PFMT only for PGI-I ratings.

Treatment emergent adverse events were experienced by significantly more subjects in the 2 duloxetine treated groups than those in the 2 placebo treated groups and significantly more duloxetine than placebo treated subjects discontinued due to adverse events (table 6). Nausea was the most common side effect with duloxetine and the most common event associated with discontinuation. Most (33 of 40 or 83%) subjects who experienced nausea with duloxetine completed the study. One subject in the duloxetine group experienced a serious adverse event, rectal bleeding secondary to an anal fissure requiring hospitalization not attributed to the study drug. Laboratory and vital sign data indicated no clinically relevant safety issues for duloxetine compared with placebo.

DISCUSSION

Overall data from this study support the significant efficacy of combined duloxetine and PFMT in the treatment of women with SUI. The efficacy of duloxetine alone was similar to that described in previously reported trials.[8–12] In some analyses duloxetine was superior to PFMT. However, in many instances both single treatments had similar effects and there was evidence for additional efficacy when they were combined. The 76% median reduction in IEF with combined treatment in the completer population compares with reductions of 50% to 60% in the completer populations of previously reported duloxetine trials.[9–12] The high percentage of subjects perceiving improvement likely reflects the benefit of the treatments and of the intense interaction between patients, and knowledgeable and supportive continence care providers during the trial.

It is important to understand the clinical implications of the 2 analyses presented in this report. The pooled diary analysis assesses the benefits throughout the 12-week trial, reflecting the more rapid efficacy of duloxetine (within 3 days to 2 weeks[12]) and PFMT skill training[7] compared with the more gradual efficacy of strength training. In this analysis of IEF, duloxetine with or without PFMT was superior to no treatment and to PFMT alone. In contrast, analysis of continence pad and quality of life data suggested greater improvement with combined treatment than with either single treatment possibly due to complementary clinical effects of duloxetine (reduction in number of incontinence episodes) and PFMT skill training (reduction in leakage amount with each episode). The completer last diary analysis reflects the benefits at the end of 12 weeks of treatment and should optimally reflect the effects of PFMT strength training. Here the suggestion of an additive effect of duloxetine and PFMT may be explained by the complementary modes of action (enhanced rhabdosphincter activity and enhanced pelvic floor activity, respectively).

A unique strength of our study is our use of a randomized, blinded, inactive control for PFMT. The only such previous trial[16] cited in the 2003 Cochrane review[3] was published only in abstract form. While that small study showed no treatment differences between PFMT and placebo PFMT, training compliance was low (about 15%) with both regimens. In contrast, training compliance was good in our study and we documented significant improvements in pelvic floor muscle strength. While it is possible that subjects assigned to the imitation PFMT regimen also exercised their pelvic floor, the fact that their ending pelvic floor muscle strength grade was

TABLE 1. *Baseline demographic and clinical characteristics by treatment group*

Treatment Group (No. subjects)	None (47)	PFMT Only (50)	Duloxetine Only (52)	Combined (52)
Mean pt age (range)	51 (29–68)	54 (36–75)	53 (34–70)	54 (31–75)
Mean body mass index (kg/m^2)	28.2	30.6	30.2	28.9
No. white race	46	47	49	49
No. prior continence surgery	6	8	4	4
Median IEF/wk (range)	18.9 (10.3, 299.4)	22.0 (13.0, 140.9)	18.3 (6.4, 78.5)	19.4 (10.0, 70.5)
Median pads/wk (range)	9.8 (0, 43.1)	8.6 (0, 45.9)	8.1 (0, 44.0)	9.7 (0, 53.5)
Mean I-QOL score (SD)	64.9 (17.1)	61.4 (22.2)	59.8 (20.6)	61.6 (22.3)
Mean PFM grade (SD)	Not done*	5.2 (1.7)	Not done*	5.2 (1.7)

* Not done at baseline to avoid teaching PFMT to the imitation PFMT group.

TABLE 2. *Compliance rates for medication doses and PFMT contractions by visit and treatment group*

No. Wk Visit	No Active Treatment	PFMT Only	Duloxetine Only	Combined
Medication compliance rate (% of prescribed doses taken)				
4	88	88	82	87
8	92	92	88	89
12	92	93	93	93
PFMT compliance rate (% of prescribed contractions performed)				
4	82	91	83	87
8	90	84	77	88
12	89	88	76	86

similar to the baseline grade seen in the PFMT group is indirect evidence against this possibility.

While most comparisons of PFMT and imitation PFMT did not demonstrate significant differences, it is important to recognize 3 limitations of the study. First, the study was powered specifically to compare combined treatment with no treatment, and many of the secondary analyses, particularly those using the completer population, lacked power to make definitive conclusions. However, in many instances PFMT demonstrated numeric superiority compared to imitation PFMT that were clinically important although statistically insignificant.

The second limitation is that our PFMT regimen was of shorter duration than regimens recommended by some authorities.[3] However, substantial decreases in SUI incontinence episodes have been demonstrated with PFMT in controlled studies within 8 weeks.[19]

The final limitation is that our PFMT program was less intense than others. For example, subjects in the trial by Goode et al[19] had an initial 20-minute biofeedback session during which 3 anorectal balloons were used to provide feedback to the patient and nurse practitioner. This biofeedback was repeated at 4 weeks if a subject had not achieved at least a 50% reduction in incontinence. Their subjects had a 77.5% median reduction in IEF after 8 weeks. Bø et al used vaginal and perineal palpation, and the observation of appropriate movement of a vaginal balloon catheter to train subjects followed by weekly 45-minute group sessions with an instructor for 6 months.[20] They compared this intensive exercise group to a home exercise group, receiving the same initial instruction but completing 6 months of training at home without further instruction. They showed 60% of the intensive exercise group was continent or almost continent after 6 months compared with 17% of the home exercise group ($p < 0.01$).

Our findings do not support a conclusion that all PFMT is ineffective. However, they do suggest that the specific regimen we used was not optimally effective compared with a blinded control treatment. Individual continence care providers should compare their PFMT regimens to the one we have used to determine if our findings might be applicable to their practices. Furthermore, our study supports the feasibility of performing placebo controlled PFMT clinical trials in an attempt to identify optimally effective PFMT regimens.

The median percent reductions in IEF in the study by Goode et al were greater (63% for a self-help book control group, 78% for a PFMT group and 84% for a PFMT plus electrical stimulation group) than in the active treatment groups in the current study after 8 weeks (44% for PFMT only, 65% for duloxetine only and 64% for combined treatment).[19] In addition to the differences between the PFMT regimens, baseline severity in the Goode et al study (15.2 mean IEF weekly) was less than that in our study (26.3 mean IEF weekly). A secondary analysis of data from the Goode et al trial demonstrated that successful treatment of SUI with PFMT was associated with fewer initial incontinence episodes.[21] In contrast, secondary analysis of data from placebo controlled duloxetine trials demonstrated that less severe baseline incontinence was associated with enhanced placebo response but did not affect the response to duloxetine.[22] It is possible the more severe SUI at baseline in our population

TABLE 3. *Combined PFMT plus duloxetine group and no active treatment group comparisons for intent to treat population*

Treatment Group	No. Pts	% Outcome	95% CI	p Value
Median decrease in IEF (pooled diary):				
Combined	44	57.4	15.7, 42.4	
None	44	28.9		<0.001
IEF responder rate (pooled diary):*				
Combined	44	61.4	17.1, 55.6	
None	44	25.0		<0.001
Median decrease in pad use (pooled diary):				
Combined	44	45.7	14.8, 50.4	
None	44	10.5		0.001
Mean increase in I-QOL score (LOCF):				
Combined	51	13.1	1.7, 12.7	
None	45	4.8		0.011
Improved using PGI-I (LOCF):†				
Combined	51	70.6	9.3, 47.5	
None	45	42.2		0.005

* Subjects with a decrease in IEF of 50% or greater.
† Subjects indicating they were "very much better," "much better" or "a little better" on PGI-I.

TABLE 4. *PFMT only group and duloxetine only group comparisons for intent to treat population*

Treatment Group	No. Pts	% Outcome	95% CI	p Value
Median decrease in IEF (pooled diary):				
Duloxetine only	46	56.5		
PFMT only	46	34.7	6.8, 31.5	
				0.004
IEF responder rate (pooled diary):*				
*Duloxetine only	46	56.5		
PFMT only	46	26.1	11.3, 49.6	
				0.003
Median decrease in pad use (pooled diary):				
Duloxetine only	46	35.3		
PFMT only	46	24.8	−5.4, 29.8	
				0.144
Mean increase in I-QOL score (LOCF):				
Duloxetine only	50	8.3		
PFMT only	49	7.8	−5.5, 5.4	
				0.979
Percent improved using PGI-I (LOCF):†				
Duloxetine only	50	54.0		
PFMT only	49	65.3	−30.5, 7.9	
				0.252

* Subjects with decrease in IEF of 50% or greater.
† Subjects indicating they were "very much better," "much better" or "a little better" on PGI-I.

TABLE 5. *Treatment group comparisons for the completer population*

Treatment Group	No. Pts	% Outcome	95% CI
Median decrease in IEF (visit 5 diary):			
Combined*,†	36	75.8	54.3, 85.2
None	38	42.7	30.3, 56.3
PFMT only	41	46.8	36.4, 60.8
Duloxetine only	33	61.1	30.9, 68.4
IEF responder rate (visit 5 diary):‡			
Combined§,‖	36	72.2	57.6, 86.9
None	38	42.1	26.4, 57.8
PFMT only	41	48.8	33.4, 64.1
Duloxetine only	33	60.6	43.9, 77.1
Median decrease in pad use (visit 5 diary):			
Combined§	36	54.5	32.1, 65.7
None	38	13.0	0.0, 30.6
PFMT only	41	29.6	13.3, 39.5
Duloxetine only¶	33	36.4	5.9, 52.2
Mean increase in I-QOL score (visit 5 questionnaire):			
Combined§,¶	36	15.9	11.1, 20.8
None	39	5.2	0.5, 9.9
PFMT only	41	9.1	4.5, 13.6
Duloxetine only	33	10.8	5.7, 15.8
Improved using PGI-I:**			
Combined*,††	36	83.3	71.2, 95.5
None	39	46.2	30.5, 61.8
PFMT only¶	41	70.7	56.8, 84.6
Duloxetine only	33	57.6	40.7, 74.4

* $p < 0.001$ vs no treatment.
† $p = 0.01$ vs PFMT only.
‡ Subjects with decrease in IEF of 50% or greater.
§ $p < 0.01$ vs no treatment.
‖ $p < 0.05$ vs PFMT only.
¶ $p < 0.05$ vs no treatment.
** Subjects indicating they were "very much better," "much better" or "a little better" on PGI-I.
†† $p < 0.05$ vs duloxetine alone.

explains some of the decreased treatment response to PFMT compared with that observed by Goode et al.

CONCLUSIONS

Our data support the efficacy of duloxetine combined with PFMT for the treatment of women with SUI. They also provide support for the theory that combining PFMT and duloxetine may be complimentary and afford greater improvement than either treatment alone. Finally, the findings suggest that PFMT regimens need to be more intensive than the one we used to realize optimal benefits.

APPENDIX 1: DULOXETINE/PFMT STUDY GROUP PRINCIPAL INVESTIGATORS

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TABLE 6. *All treatment emergent adverse events that were significantly more common with duloxetine than with placebo and discontinuation rates*

	No. AE (%)			No. Discontinuation AE (%)*		
	Duloxetine (104 pts)	Placebo (97 pts)	p Value*	Duloxetine (104 pts)	Placebo (97 pts)	p Value (Fisher exact test)
Pts with any AE	85 (81.7)	58 (59.8)	0.001	28 (26.9)	8 (8.2)	0.001
Nausea	40 (38.5)	5 (5.2)	<0.001	7 (6.7)	0	0.014
Dizziness	19 (18.3)	5 (5.2)	0.004	2 (1.9)	0	0.498
Dry mouth	19 (18.3)	3 (3.1)	0.001	0	0	
Constipation	15 (14.4)	3 (3.1)	0.006	0	1 (1.0)	
Insomnia	12 (11.5)	1 (1.0)	0.003	5 (4.8)	0	0.060
Somnolence	11 (10.6)	1 (1.0)	0.005	2 (1.9)	0	0.498
Asthenia	6 (5.8)	0	0.029	1 (1.0)	0	

* No other AE was associated with discontinuation of more than 1 patient in either treatment group.

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APPENDIX 2: INCONTINENCE QUALITY OF LIFE QUESTIONS, RESPONSE OPTIONS AND SCORING

Questions:

1. I worry about not being able to get to the toilet on time.
2. I worry about coughing or sneezing because of my incontinence.
3. I have to be careful standing up after I've been sitting down because of my incontinence.
4. I worry about where toilets are in new places.
5. I feel depressed because of my incontinence.
6. Because of my incontinence, I do not feel free to leave my home for long periods of time.
7. I feel frustrated because my incontinence prevents me from doing what I want.
8. I worry about others smelling urine on me.
9. Incontinence is always on my mind.
10. It's important for me to make frequent trips to the toilet.
11. Because of my incontinence, it's important to plan every detail in advance.
12. I worry about my incontinence getting worse as I grow older.
13. I have a hard time getting a good night of sleep because of my incontinence.
14. I worry about being embarrassed or humiliated because of my incontinence.
15. My incontinence makes me feel like I'm not a healthy person.
16. My incontinence makes me feel helpless.
17. I get less enjoyment out of life because of my incontinence.
18. I worry about wetting myself.
19. I feel like I have no control over my bladder.
20. I have to watch what or how much I drink because of my incontinence.
21. My incontinence limits my choice of clothing.
22. I worry about having sex because of my incontinence.

Responses:

1__extremely; 2__quite a bit; 3__moderately; 4__a little; 5__not at all.

Scoring.

Score = 100 × ([raw score - lowest possible score] ÷ [highest possible score - lowest possible score]).

0 = lowest quality of life; 100 = highest quality of life.

APPENDIX 3: PATIENT GLOBAL IMPRESSION OF IMPROVEMENT (PGI-I) RATING

Check the one number that best describes how your urinary tract condition is now, compared with how it was before you began taking medication in this study.

1. Very much better
2. Much better
3. A little better
4. No change
5. A little worse
6. Much worse
7. Very much worse

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