Duloxetine versus Placebo for the Treatment of Korean Women with Stress Predominant Urinary Incontinence

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Purpose: To compare duloxetine with placebo for the treatment of Korean women with stress urinary incontinence (SUI).
Materials and Methods: This was a phase 3, double-blind, stratified, randomized, parallel, placebo-controlled, multi-center study investigating efficacy and safety of a of duloxetine compared with placebo in the treatment of SUI. After a 2-week no-drug screening period, women ages 29-69 were randomly assigned to placebo (n=60) or duloxetine (n=61) as 40mg twice daily for 8 weeks followed by a 2 week no-drug period. Women were seen at 4-week intervals. The primary efficacy variable was percent change in incontinence episodes frequency (IEF)/week. Secondary variables included percent change in, changes in Incontinence Quality of Life (I-QoL) total and 3 sub-scale scores, and Patient Global Impression of Improvement (PGI-I) ratings. Safety was evaluated by treatment emergent adverse events (TEAE), discontinuations due to adverse events, vital signs measurements, and clinical laboratory tests.
Results: There were statistically significant improvements with duloxetine compared with placebo in IEF (duloxetine baseline 16.4IEF/wk, endpoint 7.7IEF/wk, median percent reduction=50.0% vs placebo baseline 13.3IEF/wk, endpoint 8.8IEF/wk, median percent reduction=37.1%, p=0.033), and avoidance and limiting behavior subscale (p=0.006) in I-QoL. TEAEs were reported significantly more often in the duloxetine group compared with the placebo group (82.0% vs 31.7%; $p<0.001$); common AEs ($\geq 5\%$ in duloxetine-treated subjects and $p<0.05$) were nausea, dizziness, anorexia, fatigue, lethargy, abdominal discomfort, and constipation. Discontinuation rates because of AEs were 34.4% for duloxetine and 8.3% for placebo.
Conclusions: These data provide evidence for the safety and efficacy of duloxetine for the treatment for Korean women with SUI. **(Korean J Urol 2006;47:527-535)**

Key Words: Urinary incontinence, stress; Duloxetine

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PURPOSE

Stress urinary incontinence (SUI) is the complaint of involuntary leakage of urine on effort or exertion, or on sneezing or coughing in women.[1] Approximately three quarters of women with incontinence present with the symptom of SUI in either pure or mixed forms.[1] SUI prevalence rates may be different between ethnic groups.[1,2] There are a limited number of epidemiologic studies evaluating urinary incontinence in Asian

women. Available studies list prevalence rates for urinary incontinence in Asian women ranging from 4.8-53.7%.[3-6] In a study of 1,303 Korean women, 41.2% reported urinary incontinence, comprising 37.8% with SUI, 18.0% with urge urinary incontinence, 14.9% with mixed urinary incontinence and .4% with an unclassified form.[2] Differences in urinary incontinence definitions, types or severity of urinary incontinence, studied populations, as well as study design, and means of data assessment and collection are responsible for the wide prevalence estimates.

SUI results when the urethra is unable to maintain a positive closure gradient compared with the bladder when physical activities cause an increase in abdominal pressure. Factors associated with the inability to maintain urethral closure include: (1) an anatomic failure to maintain support of the proximal urethra and bladder neck, (2) neuromuscular damage to the pelvic floor and urethra, and (3) weakness of the intrinsic urethral closure mechanism.[1] Traditional SUI treatments have been directed at correcting or compensating what was considered mainly an anatomical defect with behavioral interventions, pelvic floor muscle training (PFMT), or surgery rather than pharmacological intervention.[1]

Despite the high degree of bother associated with SUI and concomitant impact on quality of life, only approximately 25-33% of American and European women with UI seek help.[7-10] The number of treatment seekers in North America increases with severity of SUI (54% in women with severe UI),[10] but behavioral interventions are seen as coping mechanisms rather than as treatments, compliance with PFMT programs is low, and limited availability of surgery and associated surgical complications decrease the viability of surgery as an option. Different pharmacological agents have previously been used off-label, but an evidence-based pharmacological treatment has not been available until recently.[1]

Numerous animal studies have implicated serotonin (5-HT) and norepinephrine (NE) in the central control of lower urinary tract function. In non-rodent species, serotonergic agonists suppress parasympathetic activity and enhance sympathetic and somatic activity in the lower urinary tract[11] promoting urine storage by relaxing the bladder and increasing outlet resistance. Noradrenergic agonists and antagonists variably affect sympathetic and somatic activity in the lower urinary tract, depending on the adrenergic receptor subtype.[11] Duloxetine hydrochloride, a dual serotonin and norepinephrine reuptake inhibitor (SNRI) with little or no affinity for cholinergic receptors has demonstrated to increase bladder capacity and striated urethral sphincter activity presumably through central actions in the spinal cord in cats.[11] The ability of duloxetine to centrally stimulate pudendal motor neurons and increase striated urethral sphincter tone and contractility is thought to be the basis for its efficacy in women with SUI.

In August 2004, duloxetine became the first medication approved for the treatment of women with moderate to severe SUI throughout the European Union, a number of countries in North and South America, and Israel. Regulatory approval was primarily based on the demonstration of the safety and efficacy of duloxetine in 4 randomized placebo-controlled core registration trials enrolling 1,913 women from Africa, Australia, Europe, and North and South America.[12-15] This study was conducted to comply with local Korean regulatory requirements as a supplement to these existing core trials. The primary objective was to compare the efficacy and safety of duloxetine 80mg/day (administered as 40mg twice daily) with that of placebo in the treatment of Korean women with a predominant symptoms of SUI.

MATERIALS AND METHODS

Non-pregnant women 20 years of age and older with predominant symptoms of SUI at least 3 months in duration were enrolled in this double-blind, placebo-controlled, randomized, parallel, clinical trial conducted at 7 study centers in Korea. The study design was reviewed by a local ethics committee and written informed consent was obtained from all participants. Concomitant medications including urinary continence promoting drugs, antidepressants, drugs for obesity (including over-the-counter appetite suppressants and diet pills), and illicit drugs were not allowed in the study. Enrolled women reported the predominant symptoms of SUI during the last 3 months with at least $\geq$1 incontinent episode/day. Additional history requirements included daytime voiding frequency $\leq$8 voids daily, nocturnal frequency $\leq$2 voids daily and no predominant urge incontinence symptoms. All women had a retrograde bladder filling performed. With the patient supine the bladder was filled with saline at 100ml/min via a catheter with no pressure measurements. Patients who were unable to tolerate this simple filling cystometry procedure to 400ml were excluded, as were those who experienced a first sensation of bladder filling at $<$100

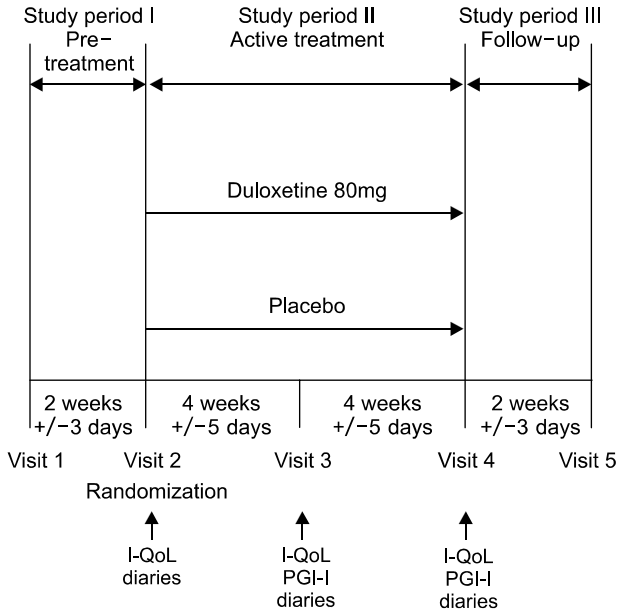

Fig. 1. Study design and the timing of acquiring the urinary diaries and reports on the quality of life measurements. I-QoL: Incontinence Quality of Life questionnaire, PGI-I: Patient Global Inpression of Improvement.

ml, or who had no sensation at any time during the filling. A positive cough stress test with visualization of urine leakage concurrent with a cough was required after filling the bladder.[12-15]

Fig. 1 provides an overview of the study design and timing of acquisition of diaries and other variables. After a 2-week, no drug, lead-in period, women were randomly assigned under double-blind conditions to 8 weeks of 80mg/day (40mg twice daily) of duloxetine or placebo administered as 2 identical (20mg) capsules twice daily. Women were evaluated at 4-week intervals. The treatment phase of the core registration trials was 12-weeks; however, the majority of the these adverse events emerged within the first 4 weeks and the number of duloxetine responders ($\geq$50% reduction in median percent incontinence episode frequency [IEF]) did not change significantly after 4 weeks post-randomization. Randomization was controlled by a computerized interactive voice response system at a central location for all study sites. Stratified randomization using baseline IEF of $<$14 or $\geq$14 episodes/week obtained from patient diaries was used to prevent potential imbalance in incontinence severity.

Weekly paper diaries were also used to collect the number of voids, the time of voids, the time study medication was taken, and the number of continence pads used. Diaries were collected to determine baseline incontinence severity the last week before visit 2 during the no drug lead-in period (Fig. 1).

The primary efficacy variable in this study was percent chae in IEF/week from baseline to endpoint, which was calculated from subject completed, real-time, paper diaries. Approximately 50% reduction in IEF has been generally accepted as a clinically relevant threshold for response in SUI outcomes research for interventions such as bladder training and PFMT,[16] devices,[17] surgery,[18,19] and a pharmacological agent.[12-15] That convention was followed in this paper and an IEF responder was defined as a woman who had at least a 50% decrease in IEF with treatment.

Secondary efficacy variables included: 1) Incontinence Quality of Life (I-QoL) questionnaire total and subscale scores,[20] 2) Patient Global Impression of Improvement (PGI-I) rating,[21] 3) time between voids/day, and 4) continence pad use/week.

The I-QoL questionnaire is a globally-validated, disease-specific instrument endorsed by the International Consultation on Incontinence, which was administered at each visit and evaluates the effects of urinary incontinence in 3 domains: avoidance and limiting behavior, social embarrassment, and psychosocial impact. An I-QoL score of 100 represents the best possible quality of life and 0 represents the worst possible quality of life. To ensure appropriate translation the questionnaire was linguistically validated.[22]

The PGI-I rating is a globally-validated 1-question questionnaire and was obtained at each post-randomization visit. The PGI-I measures subject self-perceived improvement in the condition since starting treatment with a single question.[21] To ensure appropriate translation the questionnaire was translated from English to Korean and than back to English.

Compliance with the required study drug regiment was examined at each visit following initiation of treatment. Unused study drug was returned to Eli Lilly and Company, and compliance was assessed by counting returned study drug. Investigators encouraged compliance with study medication but subjects were not discontinued from the study for poor compliance only.

Safety was assessed by evaluation of treatment-emergent adverse events (TEAEs), discontinuations due to adverse events, serious adverse events, discontinuation emergent adverse events, vital signs measurements, and clinical laboratory tests. Adverse events were elicited by nonprobing inquiry at each visit and

were recorded regardless of perceived causality. An event was considered treatment emergent if it occurred for the first time or worsened during the double-blind treatment period.

A serious adverse event was defined according to the International Consultation on Harmonization guidelines and included any adverse events associated with death, initial or prolonged inpatient hospitalization, a life-threatening experience (ie, immediate risk of dying), persistent or significant disability/incapacity, congenital anomaly/birth defect, or is significant for any other reason.

The statistical analysis plan was specified a priori and was performed in accordance with intent-to-treat (ITT) principles. Subjects with baseline and at least 1 post-baseline measurement were included in the analysis. The percent change in IEF was compared between treatment groups using the van Elteren's test, a type of stratified Wilcoxon test, with baseline incontinence severity as the stratification variable. This primary analysis compared IEF before and after randomization, pooling all diaries between visits 1 and 2 for the baseline and all diaries between visits 2 and 4 for the end point. The changes in I-QoL scores were analyzed using an ANCOVA model that included terms for baseline scores, treatment, site, and baseline incontinence severity. The endpoint PGI-I was analyzed using the Cochran-Mantel-Haenszel test with the baseline incontinence severity as the strata. The missing values in the above analyses were imputed via LOCF.

Enrollment in the study was set to end when approximately 120 women (60 per treatment group) had been assigned to a treatment group. The sample size was determined to provide 97.3% power for detecting a treatment difference of 23% in the median percent change in IEF from baseline to endpoint.

Analyses were performed using SAS 8.1 (SAS Institute, Cary, USA). A two-sided alpha level of 0.05 was considered statistically significant for treatment effects.

RESULTS

A total of 121 women 29-69 years of age were randomly assigned to receive duloxetine 80mg/day (n=61) or placebo (n=60) between December 2003 and October 2004. Approximately 81% of women completed at least 1 post-randomization diary (73.8% duloxetine, 88.3% placebo), while 93.3% completed at least 1 I-QoL questionnaire (91.8% duloxetine, 95% placebo). In total, 68.6% of women completed the 8-week study (60.7% duloxetine, 76.7% placebo).

Table 1. Baseline* clinical characteristics for all the randomized women

	Duloxetine	Placebo
Randomized N†	61	60
Age, years	50.67 (±9.01)	48.52 (±8.05)
BMI, kg/m^{2}‡	23.77 (±2.46)	23.42 (±3.17)
IEF/week (SD)	15.74 (±11.35)	13.27 (±7.04)
[range]	[3.0-59.0]	[6.42-41.42]
Mean time between voids, min	215.86 (±60.72)	241.90 (±56.40)
Total I-QoL score	49.37 (±21.57)	51.38 (±20.66)
Previou scontinence surgery	3	2

*: Baseline is the last visit score on or prior to randomization, †: Every randomized subject did not provide information for each variable; percentages are calculated using the number of responding women as the denominator, ‡: 0.01. Data are means (SD) unless otherwise indicated, BMI: body mass index, PFMT: pelvic floor muscle training, IEF: incontinence episode frequency, I-QoL: Incontinence Quality of Life questionnaire.

Table 1 shows the baseline clinical characteristics of the women randomized to each treatment group. The only statistically significant baseline difference between treatment groups was for time between voids, with the duloxetine treatment group having less time between voids than the placebo treatment group.

On average, patients in the placebo group took 74% of their treatment doses compared with 60% of doses in the duloxetine group (p=0.016). This difference in compliance was due to limited duloxetine consumption by subjects who discontinued from the trial early and was not significant after the first post-randomization visit.

The decrease in IEF, as demonstrated by median percent change, was significantly greater in the duloxetine group than in the placebo group (Table 2). The improvements with duloxetine were observed at the first post-randomization visit (4 weeks) and were maintained throughout the study. Overall, 51% of duloxetine-treated subjects and 35.8% of placebo-treated subjects were IEF responders (p=0.128).

The duloxetine treatment group demonstrated numerically, although not statistically significant, improvement in the I-QoL total score and in 2 of the 3 I-QoL subscale scores when compared with the placebo treatment group (Table 3A, 3B). The

Table 2. Frequency of incontinence episodes

Treatment group (N)*	Time point	n†	Absolute mean IEF/week	Median percent change from baseline	95% CI for median percent change in IEF	p
Placebo (60)	Baseline	53	11.00			
	Endpoint		6.72			
	Change		−3.83	−37.14	−45.45, −27.27	
Duloxetine (61)	Baseline	45	12.92			
	Endpoint		6.13			
	Change		−6.54	−50.00	−60.20, −40.91	0.033

*N: number randomized, † n: number with diary data available for specified analysis, CI: confidence interval, IEF: incontinence episode frequency

Table 3A. Incontinence Quality of Life questionnaire: subscale scores

Treatment group (N)*	Time point	n†	I-QoL total score			
			Mean I-QoL	Mean change in I-QoL from baseline‡	95% CI for treatment difference in I-QoL§	p
Placebo (60)	Baseline	57	51.52			
	Endpoint		60.23	8.71		
Duloxetine (61)	Baseline	56	48.64			
	Endpoint		63.41	14.77	−0.37,11.16	0.066

*N: number randomized, † n: number with diary data available for specified analysis, ‡ : Baseline is the last nonmissing visit score on or before randomization, §: 95% CI for treatment difference. CI: confidence interval, I-QoL: Incontinence Quality of Life questionnaire

mean change in the I-QoL subscale "Avoidance and Limiting Behavior" score showed a statistically significant difference in favor of duloxetine when compared to placebo (15.57 vs 6.25; p=0.006).

The analysis of the PGI-I data revealed results similar to those observed with the I-QoL analysis. Only a few more women in the duloxetine group than in the placebo group considered their urinary tract condition to be 'very much better, much better, or a little better' (35 vs 33, respectively).

The change in mean time between voids/day was significantly greater for duloxetine-treated women when compared with change in placebo-treated women (34.33 vs −3.61 minutes, respectively; $p<0.001$). Women in the duloxetine group used significantly less continence pads compared with those in the placebo group (−3.82 vs −1.65, respectively; p=0.040).

TEAEs were experienced by significantly more women in the duloxetine group compared with the placebo group (82.0% vs 31.7%; $p<0.001$). Table 4 lists all of the adverse events that occurred in at least 5% of women on duloxetine, or that were statistically significantly more common with duloxetine. Nausea was the most common adverse event in the study. Most nausea was reported early in the study, 65% was mild to moderate in severity at onset, and in no instance did it increase in severity. The majority (18 of 23; 78.3%) of women that developed nausea remained on the study. Of these, 11.1% reported resolution of nausea within 1-3 days, 38.9% within 1 week, 66.7% within 2 weeks and 88.9% within 1 month.

For women who remained in the study despite experiencing these TEAEs, the majority had resolution of the event within 30 days (abdominal discomfort 4 of 6, 67%; anorexia 16 of 17, 94%; constipation 3 of 6, 50%; dizziness 18 of 19, 95%; fatigue 7 of 9, 78%; lethargy 4 of 4, 100%; nausea 16 of 18, 89%).

The discontinuation rate due to adverse events was significantly greater for the duloxetine group compared with the placebo group (34.4% vs 8.3%; $p<0.001$). The most common adverse events leading to discontinuation ($\geq$5% in the duloxe-

Table 3B. Incontinence Quality of Life questionnaire: subscale scores

Treatment group (N)*	Time point	n†	I-QoL avoidance and limiting behavior subscale score				I-QoL psychological impact subscale score				I-QoL social embarrassment subscale score			
			Mean I-QoL	Mean change in I-QoL from baseline‡	95% CI for treatment difference in I-QoL§	p	Mean I-QoL	Mean change in I-QoL from baseline‡	95% CI for treatment difference in I-QoL§	p	Mean I-QoL	Mean change in I-QoL from baseline‡	95% CI for treatment difference in I-QoL§	p
Placebo (60)	Baseline	57	54.17				55.70				39.74			
	Endpoint		60.42	6.25			64.47	8.77			52.28	12.54		
					2.34				−2.14				−3.94	
					13.88				10.49				9.80	
Duloxetine (61)	Baseline	56	50.78				52.33				38.57			
	Endpoint		66.35	15.57		0.006	65.97	13.64		0.193	54.11	15.54		0.399

*N: number randomized, † n: number with diary data available for specified analysis, ‡: Baseline is the last nonmissing visit score on or before randomization, §: 95% CI for treatment difference. CI: confidence interval, I-QoL: Incontinence Quality of Life questionnaire

Table 4. Treatment-emergency adverse events occurred in ≥5% of the women randomized to the duloxetine group or they occurred significantly more often with duloxetine than with placebo

	Duloxetine (n=61)	Placebo (n=60)	p
Total number of women with ≥1 TEAE	50 (82)	19 (31.7)	<0.001
Nausea	23 (37.7)	4 (6.7)	<0.001
Dizziness	20 (32.8)	2 (3.3)	<0.001
Anorexia	17 (27.9)	2 (3.3)	<0.001
Fatigue	14 (23.0)	1 (1.7)	<0.001
Lethargy	9 (14.8)	0 (0.0)	0.003
Abdominal discomfort	8 (13.1)	1 (1.7)	0.032
Somnolence	7 (11.5)	1 (1.7)	0.061
Constipation	6 (9.8)	0 (0.0)	0.027
Headache	6 (9.8)	5 (8.3)	0.999
Dry mouth	5 (8.2)	2 (3.3)	0.439

Values are expressed as n (%).

Table 5. Discontinuations due to adverse events occurred in ≥1% of women randomized to the duloxetine group

	Duloxetine (n=61)	Placebo (n=60)	p
For any adverse event	21 (34.4)	5 (8.3)	0.001
Fatigue	5 (8.2)	0 (0.0)	0.057
Lethargy	5 (8.2)	0 (0.0)	0.057
Nausea	5 (8.2)	1 (1.7)	0.207
Abdominal discomfort	2 (3.3)	0 (0.0)	0.496
Disturbance in attention	1 (1.6)	0 (0.0)	>0.999
Dizziness	1 (1.6)	1 (1.6)	>0.999
Dyspepsia	1 (1.6)	0 (1.6)	>0.999

Values are expressed as n (%).

tine treatment group) were fatigue, lethargy, and nausea. Table 5 lists all adverse events that resulted in a 1% or higher discontinuation rate for duloxetine.

There was a statistically significant increase in mean heart rate during treatment with duloxetine compared with placebo; however, the >3 beats per minute increase with duloxetine was within the normal range. There were no statistically significant differences in the mean change for systolic or diastolic blood pressure between duloxetine and placebo groups. Clinical laboratory assessments, vital signs, and physical findings were stable relative to baseline and no clinically relevant differences were

detected between treatment groups. There were 3 discontinuation emergent adverse events reported during the last 2-week no-drug observation period, 2 associated with placebo treatment (1 woman had abdominal pain and 1 woman needed surgery) and 1 with duloxetine treatment (woman experienced dizziness, headache and nausea). There were no serious adverse events including deaths in this study.

DISCUSSION

In this study of Korean women with predominant SUI, duloxetine 80mg/day (40mg twice daily) as measured by the primary efficacy analysis (median percent change in IEF/week) and several of the secondary analyses (I-QoL "Avoidance and Limiting Behavior" subscale, mean time between voids/day, and percent change in continence pad use/week) was noted to be significantly more effective than placebo. The significant reductions in SUI episodes and numerical improvements in I-QoL and PGI-I scores with duloxetine compared with placebo in this non-core registration trial are consistent with responses in core registration trials conducted in Europe, North America, South America, Australia and Africa.[12-15]

Most Korean women treated with duloxetine did not eliminate their SUI; however, duloxetine-associated treatment effect was apparent within the first 4 weeks of treatment and was maintained throughout the duration of the 8-week study. In a recent study in patients with severe incontinence awaiting surgery, 86% of women that responded to duloxetine responded within 1 week and 100% of women that responded, responded within 2 weeks.[23]

Urinary incontinence is a psychologically distressing, socially secluding, and potentially disabling condition. In Western countries the impact of urinary incontinence on quality of life has been compared to the impact of diabetes on quality of life.[24,25] Baseline measurements of total I-QoL scores in the Korean women in this study demonstrated that these women viewed their quality of life as more impaired even though they reported fewer IEF/week (approximately 12 vs 17 IEF/week, respectively) than 1,913 women in an integrated analysis of 4 other studies (duloxetine=63.81; placebo=64.06).[12-15] However, during the study the improvement of quality of life was substantial even in subjects treated with placebo. This phenomenon is often seen in treatment naive women and it is related to the active participation in the trial and exposure to the research setting: the Hawthorne effect. We did not monitor the experience with PFMT, but only 5 of the 121 women had had previous continence surgery.

Duloxetine-associated improvements were numerically present but not statistically significant for quality of life as measured by total I-QoL score, 2 of the I-QoL subscale scores, and PGI-I. However, this study was not powered to detect changes in I-QoL. In 3 of 4 core registration trials powered to detect changes in I-QoL, duloxetine treatment resulted in significant improvements in I-QoL total and subscale scores.[12,15]

As in the other studies, incontinence improved despite significant increases in voiding intervals with duloxetine, indicating the improvement did not result from more frequent emptying of the bladder.

Overall, fewer Korean women reported at least 1 TEAE than in previous studies; however, Korean women reporting a TEAE were more likely to discontinue,[12-15] suggesting that the Korean women perceived the adverse events as more severe. Unlike previous studies, this study did not have a 2-week placebo lead-in phase. Lack of the placebo lead-in phase may increase the number of TEAEs reported. Mean body mass index (BMI) of the Korean women was lower than the mean BMI of women in other studies which could suggest that the increased number of TEAEs and discontinuations may also be related to the lower BMI.

Nausea was the most frequent adverse event associated with duloxetine treatment. Nausea tended to have a fast onset after initiation of duloxetine treatment. It was mild to moderate in most cases, did not worsen after its onset, and resolved within 1 week to 1 month of therapy in most cases. A recent clinical trial demonstrated duloxetine dose escalation from 20mg twice daily to 40mg twice daily over 2 weeks may be an effective tactic to diminish but not eliminate the risk of nausea.[26] Consequently, combining proactive counselling about the natural history of nausea when taking duloxetine (mild to moderate, non-progressive, and transient) with dose escalation may decrease incidents of nausea and discontinuation prior to achieving duloxetine-associated benefits.

Other common TEAEs included dizziness, anorexia, fatigue, lethargy, abdominal discomfort, somnolence, constipation, headache, and dry mouth. These data are largely consistent with published data from Africa, Australia, Europe, and North and South America.[12-15] TEAEs including anorexia and abdominal discomfort are observed at much lower percentage rates in other

studies. It is possible that the increased rate is reflective of the small number of women in the study. The improvement associated with duloxetine treatment must be weighed against a considerable discontinuation rate due to early adverse events.

This study was conducted in response to a request from the local Korean regulatory authorities. It is the first comprehensive study of the safety and efficacy of duloxetine in Korean women. The safety measures and the primary efficacy variable demonstrated that duloxetine was safe and efficacious for the treatment of SUI in Korean women; however, lack of statistical significance but numerical improvements in the secondary efficacy variables may have been a result of small sample sizes and a notable placebo effect[27] in these women.

CONCLUSIONS

These data support the conclusion that duloxetine has demonstrated similar statistically significant and clinically relevant efficacy in Korean women with SUI as has been demonstrated in women in Africa, Australia, Europe, and North and South America. Adverse events were common but not serious. Duloxetine administered at 40mg twice daily up to 8 weeks for the treatment of Korean women with SUI is safe and efficacious. Finally, the data also support the conclusion that the findings from studies in other populations can be reasonably extrapolated to the Korean population.

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