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The effect of duloxetine on stress urinary incontinence

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Abstract

Background and Aims: This study aims to evaluate the effect of duloxetine on stress urinary incontinence (SUI) episode frequency (IEF) per week IEF.

Methods: In this clinical trial, 100 women aged 20–80 years with urinary incontinence were assessed based on the standard questionnaire of urinary tract disorders. All the patients received a placebo for 2 weeks. Patients were then randomly divided into two groups of 50 patients each, receiving duloxetine (40 mg twice a day for 12 weeks) and placebo. The two groups were compared in terms of IEF and the mean score of quality of life and side effects.

Results: The two groups of duloxetine and placebo recipients were matched at the beginning of the study in terms of age, BMI, IEF, parity, and type of delivery. IEF significantly decreased in the duloxetine recipient group compared to the placebo group. The mean score of quality of life in the duloxetine recipient group increased significantly. The rate of study abandonment in the duloxetine recipient group was significantly higher than in the placebo group. Vertigo was the most common complication that caused patients to discontinue the use of the drug.

Conclusion: Duloxetine is therapeutically effective for SUI in women. Patients should be provided information regarding potential side effects and their management.

KEYWORDS

bladder, duloxetine, norepinephrine, placebo, stress urinary incontinence, women

1 | INTRODUCTION

Stress urinary incontinence (SUI) is defined by the International Continence Society (ICS) as "the complaint of any involuntary loss of urine on effort or physical exertion (e.g., sporting activities) or on sneezing or coughing."[1] SUI is the most common form of urinary incontinence in women, characterized by involuntary urinary excrement following pressure on the bladder due to sneezing, coughing, or laughing.[1,23] SUI is also called anatomical incontinence, mainly due to excessive mobility of the urethral bladder segment, which occurs due to poor pelvic floor muscle.[4] SUI occurs when pelvic and urinary support structures are drawn or damaged or ineffective, which is common in women of all ages, but often in women after middle age, with a history of multiple parity and vaginal delivery.[5] Billions of dollars are spent each year to improve conditions and quality of life associated with SUI.[6]

In the past, improving SUI was limited to behavioral interventions, pelvic floor muscle strengthening, absorption, and surgical procedures.[7] Several pharmacological therapies are used for the management of SUI, such as estrogen replacement therapy, α-adrenergic receptor agonists,

β-adrenergic receptor antagonists (e.g., propranolol), and tricyclic antidepressants. However, none of these drugs are approved for the treatment of SUI and are associated with side effects, that limit the usage.[8] In August 2004, for the first time in Europe, regions of North America, and the Middle East, duloxetine was used to treat women with moderate and severe SUI.[9] Duloxetine is a dual serotonin reuptake inhibitor and norepinephrine (SNRI).[10] It is the first and only drug proposed by ICS to treat SUI and is used as an alternative to surgery in specific cases.[11] According to the recent guidelines by The European Association of Urology, duloxetine is recommended in selected SUI patients in whom surgery is not indicated, and it should be withdrawn using dose titration due to adverse effects and complications.[12] Maund et al.[13] reported that the harmful effects of duloxetine outweigh its beneficial effects. Several patients discontinue duloxetine owing to the adverse outcome of the drug.

Surgical procedures used to treat SUI are associated with several complications such as urinary incontinence,[14] bladder defect, frequent urinary tract infection,[15] pain, and sexual problems.[16] Given the multi-faceted challenges associated with surgical procedures and the absence of research on the effects of duloxetine in the context of SUI treatment in Iranian women, this study endeavors to evaluate the efficacy of duloxetine in the management of SUI in women. The investigation extends its focus to encompass the impact on quality of life and the potential for associated side effects, shedding light on the role of nonsurgical interventions in addressing this prevalent condition. Importantly, recent findings[17] underscore the fact that more than 60% of SUI patients do not require surgical interventions, highlighting the pressing need to explore nonsurgical treatment alternatives. This statistic emphasizes the relevance and importance of evaluating the effectiveness of nonsurgical options such as Kegel exercises and extracorporeal magnetic innervation in managing SUI. By doing so, this study aligns with the broader context of SUI management strategies, catering to the diverse needs of SUI patients, and addresses the evolving landscape of treatment options for this condition.

2 | MATERIALS AND METHODS

The study is an interventional study double-blinded clinical trial. The study population included all the women with urinary incontinence (based on biographies and Eurodynamic studies) referred to Asalian Hospital and the private clinic. The patient presented with incontinent episodes of ≥4 in a week due to stress, such as cough, sneezing, or physical activity leading to wetting of pads or clothing. Additionally, urine frequency of ≤7 times per day and ≤once during the night and patients without a history of prolapse during the surgery were included in the study. SUI was evaluated using a cough stress test and a 1 h stress pad test, where leakage of 2.0 g was considered for inclusion, as indicated in the previous studies.

Random sampling was performed, and patients were randomly divided into two groups (intervention and placebo). The patients were not aware of their groups and the type of intervention (blinded). One hundred women between 20 and 80 years of age, who are nonpregnant, and have urinary incontinence by the Standard Sexual Dysrhythmia Inventory,[5] were followed up based on a physician's written explanation. The written consent form was obtained for the participation in the study. Initially, all the patients received a placebo for 2 weeks and filled out a daily diary during pretreatment (one diary), treatment (three diaries), and posttreatment (one diary) phases. They were randomly divided into two groups of drug and placebo after 2 weeks. Meanwhile, age, parity, type of delivery, and incontinence were matched in a week. Subsequently, a placebo group and a duloxetine group received 80 mg (40 mg twice a day) for 12 weeks, as indicated in previous clinical studies,[18,19] and during the treatment, SUI questionnaires were used to determine the number of incontinence episode frequency (IEF) per week, and the daily side effects were collected on monthly visits. All the participants were asked not to consume any other medicine during the study period. Data regarding the standard of quality of life at the beginning and end of the study was also obtained using the standard quality-of-life during urinary incontinence questionnaire.[3]

To blind the study, the drug and placebo were labeled 1 and 2 and distributed by the clerk of the women's clinic, who was not aware of the drug and placebo tablets. To cope with withdrawal, the sample size was 10% higher, so the sample size was 90 patients.

Patients with reduced incidence of urinary incontinence or having a higher quality-of-life score in the next phase of treatment, based on the quality-of-life questionnaire, were considered as successful cases. This study was approved by the Research Ethics Board of Lorestan University of Medical Sciences. (LUMS-REC.146WJ).

2.1 | Data analysis

Data analysis was performed using SPSS statistical software. For qualitative variables, frequency and frequency percent, and for quantitative variables, the mean and standard deviations were calculated. An independent *t*-test was used to test the hypothesis, and in the case of non-normalization, the same nonparametric method and χ^2 were used.

3 | RESULTS

There was no significant difference between the two groups regarding age, BMI, parity, and type of delivery. The results show that there is a significant difference in the number of urinary incontinences in the group receiving duloxetine at the end of the study compared to the beginning of the study (15.38 vs. 4.12, $p < 0.001$). There was no significant difference in the frequency of urinary incontinence in the placebo group at the end of the study compared to the beginning of the study (15.22 vs. 12.24, $p = 0.753$) (Table 1). At the beginning of the study, the frequency of urinary incontinence per week was not significantly different among the two groups ($p = 0.943$). The mean IEF/week in the duloxetine recipient group was 38.539 ± 15.2, and in the placebo group was 38.539 ± 15.2. Following 12 weeks of intervention, the frequency of urinary

incontinence per week was significantly different among the two groups ($p < 0.001$). The mean IEF/week in the duloxetine group was 12.803 ± 4.1, and in the placebo group was 24.890 ± 12.1 (Table 2).

The mean quality of life score was significantly greater in the duloxetine group at the end of the study compared to the start of the study (76.29 vs. 62.55, $p < 0.001$) (Table 3). However, in the placebo group, no such difference was reported (67.55 vs. 61.24, $p = 0.339$. The mean quality of life score was not significantly different among the two groups at the start of the study ($p = 0.504$), which was 62.55 ± 8.001 in the duloxetine group and 61.24 ± 6.818 in placebo. Following 12 weeks of intervention, the mean quality of life score in the duloxetine group was 76.29 ± 2.699, and in placebo was 67.55 ± 3.434 (Table 4), and this difference was statistically significant ($p = 0.040$).

The frequency of side effects was significantly greater among the duloxetine group $n = 48$ (96.0%) compared to the placebo group, $n = 27$ (54.0%), $p = 0.003$. The frequency and percentage of women who left the study due to any side effect in the duloxetine group were 16 (32.0%) and in the placebo group 4 (8%), which was significantly higher in the duloxetine group, $p = 0.003$ (Table 5).

4 | DISCUSSION

In the present study, an interventional double-blinded clinical trial performed on 100 women with urinary incontinence, patients were divided into two groups of 50 patients receiving duloxetine and placebo and were compared for the number of incontinences per week, the mean score of life quality before and after treatment, as well as the rate of side effects. The two groups were matched for confounding variables and there was no significant difference between the two groups in terms of age, BMI, IEF, number of deliveries, and type of delivery. The incidence of weekly incontinence in the duloxetine recipient group was significantly reduced in comparison with the placebo group. The mean score of quality of life in the duloxetine recipient group was significantly higher than the placebo group. The rate of withdrawal of patients due to side effects was significantly higher in the duloxetine group than in the placebo group, and the most common complication of this problem was vertigo.[11] The incidence of urinary incontinence in Tabriz and Tehran, Iran, is reported to be higher than in other studies.[20] Owing to cultural barriers and their impact on social and intimate life, women are likely to feel embarrassed and stressed about discussing these issues with healthcare providers.[21]

A recent study[22] investigating a digital therapeutic device for urinary incontinence further accentuates the necessity for incorporating objective parameters into the evaluation of SUI therapies. This study advocates for innovative approaches in treating SUI, recognizing the profound impact of this condition on overall quality of life, sexual function, and mental health. However, this study raised methodological concerns regarding its initial screening criteria, which lacked precision and failed to include objective measures, such as physical examinations or validated tools for assessing pelvic floor muscle strength.[23]

TABLE 1 Comparison of the number of urinary incontinences per week at the beginning and the end of the study among the two groups.

Group		Average	Standard deviation	Abundance	*p* Value
Duloxetine	IEF At the beginning of the study	15.38	2.539	50	<0.001
	IEF At the end of the study	4.12	1.803	34	
Placebo	IEF At the beginning of the study	15.22	2.534	50	0.753
	IEF At the end of the study	12.24	1.890	46	

Abbreviation: IEF, incontinence episode frequency.

TABLE 2 Number of incontinences per week by treatment group, comparison between the intervention and placebo group.

Group		Average	Standard deviation	Abundance	*p* Value
Number of incontinences per week at the beginning of the study	Duloxetine	15.38	2.539	50	0.943
	Placebo	15.22	2.534	50	
	Total	15.30	2.525	100	
Number of incontinences per week at the end of the study	Duloxetine	4.12	1.803	34	<0.001
	Placebo	12.24	1.890	46	
	Total	8.18	2.124	80	

TABLE 3 Comparison of mean score of quality of life at the beginning and the end of the study by treatment group among the two group.

Group		Average	Standard deviation	Abundance	*p* Value
Duloxetine	Quality of life score at the beginning of the study	62.55	8.001	50	<0.001
	Quality of life score at the end of the study	76.29	6.818	34	
Placebo	Quality of life score at the beginning of the study	61.24	2.699	50	0.339
	Quality of life score at the end of the study	67.55	3.434	46	

TABLE 4 Data related to the standard quality of life questionnaire on incontinence of urine stress according to different groups, comparison between the two groups.

Group		Average	Standard deviation	Abundance	*p* Value
Quality of life scores in incontinence of urine stress at the beginning of the study	Duloxetine	62.55	8.001	50	0.504
	Placebo	61.24	6.818	50	
	Total	61.85	7.374	100	
Quality of life score in the incontinence of urine stress at the end of the study	Duloxetine	76.29	2.699	34	0.040
	Placebo	67.55	3.434	46	
	Total	71.92	3.219	80	

TABLE 5 The total number of women with one or more side effects by treatment group.

			Group		
			Duloxetine	Placebo	Total
The number of women with one or more side effects	Positive	Abundance	48	27	75
		Percentage	96.0%	54.0%	75.0%
	Negative	Abundance	2	23	25
		Percentage	4.0%	46.0%	25.0%
	Total	Abundance	50	50	100
		Percentage	48%	27%	75%

Early studies have reported a placebo response of up to 40%, indicating the nonpharmacological effects of "being in a trial" on the patients such as follow-up visits and contact with incontinence advisor.[24,25] Dmochowski et al. evaluate the efficacy of duloxetine for the treatment of urinary incontinence. In this study, the incidence of weekly incontinence was significantly lower in[20] the duloxetine recipient group than in the placebo group, which was consistent with the present study. Also, the mean quality of life score in the duloxetine recipient group was significantly higher than that of the placebo group, which was by the present study.[26] In this study, the rate of withdrawal was significantly higher in patients receiving duloxetine than in the placebo group.[27] Nausea was the most common complication that led to the discontinuation.[10] Millard et al. conducted a study to evaluate the efficacy of duloxetine in the treatment of urinary stress incontinence and reported that duloxetine significantly reduces the incidence of weekly incontinence with improvement in quality of life. Nausea was the most common side effect that led to the study being discontinued, but in the present study, the most common complication that left the study was dizziness.[28] Similar findings were reported by Van Carrock et al. and Maripan et al.[29] The results of this study were also consistent with studies in the United States, Canada, and Australia.

Our study does not include data regarding the disease-related and population-related risk factors (education, employment) of SUI in the population, pelvic floor measurements, and the intensity of physical activity. Therefore, further studies are required to include these parameters and evaluate long-term therapeutic effects.

5 | CONCLUSION

In conclusion, our study reported the therapeutic effects of duloxetine among Iranian women presented with SUI in comparison to placebo. The usage of duloxetine was also associated with better quality of life, following 12 weeks of the treatment. However, vertigo was one of the significant side effects that led to the withdrawal of the drug.

AUTHOR CONTRIBUTIONS

Nahid Lorzadeh: Funding acquisition; investigation; methodology; project administration; validation; visualization; writing—original draft; writing—review and editing. **Moghadaseh Jahanshahi**: Funding acquisition; investigation; methodology; project administration; validation; visualization; writing—original draft; writing—review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All relevant data and materials are provided in the manuscript.

TRANSPARENCY STATEMENT

The lead author, Moghadaseh Jahanshahi, affirms that this manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned (and if relevant, registered) have been explained.

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