REVIEW
Functional

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Duloxetine in the Treatment of Women with Urinary Incontinence: A Systematic Review and Meta-analysis of Efficacy Data from Randomized Controlled Clinical Trials

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Abstract

Duloxetine is the only available agent for the medical treatment of stress urinary incontinence (SUI). In this systematic review, we analyzed the efficacy and safety of duloxetine treatment in women with SUI and stress-predominant mixed urinary incontinence (SPMUI). We searched the literature using OVID MEDLINE, Embase and ULAKBIM (Turkish database) databases for placebo-controlled studies on the use of duloxetine in women with SUI or SPMUI. Data on change in incontinence episode frequency (IEF), decrease in the number of continence pads used, increase in voiding interval (minute) and discontinuation rates due to adverse effects and lack of efficacy (%) were extracted. A total of 12 randomized controlled trials were included. Duloxetine treatment results in an 18% decrease in IEF and 16% decrease in the number of incontinence pads used compared to pre-treatment status. It also increases the time interval between the voids by 18 min. Duloxetine treatment was associated with higher treatment discontinuation rates compared with placebo. The reason for discontinuation was related to the side effects of the treatment rather than lack of efficacy. Duloxetine can be an effective treatment option in women with UI based on high-level evidence supporting its efficacy. Further studies with larger patient populations and longer durations of follow-up are required to assess its safety profile.

Keywords: Urinary incontinence, stress, urinary incontinence, mixed, duloxetine hydrochloride, systematic review

Introduction

Stress urinary incontinence (SUI) is the involuntary leakage of urine on effort or exertion, or on sneezing or coughing (1). The prevalence of SUI increases with age, affecting 1 in 5 women in the population (2,3), necessitating a surgical intervention in most of these patients. Recently, the surgical treatment of SUI in women has come under serious public scrutiny after the recent issues related to the use of vaginal mesh products (4,5). The mid-urethral sling surgeries using a vaginally inserted polypropylene mesh, has been the first line surgical treatment for women with SUI in the last 10-20 years with success rates up to 93% in 5 years of follow-up (4). Despite high success rates, life changing complications have been reported in some patients (6). Currently the vaginal mesh issue is pronounced as the second biggest health scandal after the thalidomide disaster and many countries are now suspending the use of vaginal mesh products for the treatment of women with SUI. This creates an unmet clinical need in this area and urologists are now revisiting other available treatment options for the treatment of SUI such as duloxetine and laser therapies (7).

Duloxetine is the only available agent that can be used in medical therapy of SUI. It is a potent inhibitor of serotonin (5-

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hydroxytriptamine = 5-HT) and norepinephrine (NE) reuptake at the neuromuscular junction. Increased concentrations of serotonin and NE are thought to increase the stimulation of the pudendal nerve efferent neurons leading to an increased resting tone and contraction strength of the external urethral sphincter (8). Currently, the use of duloxetine for this indication is approved by the European Medicines Agency but not the US Food and Drug Administration.

Data from clinical trials support the use of duloxetine in the treatment of SUI in women (9). A meta-analysis of randomized controlled clinical trials showed the effectiveness of duloxetine in reducing the frequency of incontinence episodes and improving quality of life. Additionally, some clinical trials demonstrated a decrease in the number of incontinence pads used in women with SUI and stress-predominant mixed urinary incontinence (SPMUI) (10). However, this comes at the cost of side effects on various organ systems including the central nervous system and gastrointestinal tract, most frequent ones being nausea, constipation, dizziness, fatigue, headache and insomnia (11).

The main concern for a practicing urologist when prescribing duloxetine is probably more related to its side effects rather than its efficacy. Particularly, side effects related to mental health and suicidality would be the most concerning for the treating physicians, due to the relatively controversial reports on the association between suicidal behavior and antidepressant medications (12). This issue pertains mainly to a specific group of patients with mental disorders and more to children and adolescents with mental health problems, however it has also been suggested that some anti-depressant medications can double the risk of events that may lead to suicide and violence in healthy individuals (13). In the context of urinary incontinence, a recent meta-analysis of clinical study reports (data submitted to regulatory bodies) did not find any reported cases of suicidality, violence, or akathisia with duloxetine use (14). Current urology guidelines support the use of duloxetine in adult women with SUI for whom surgical treatment is not indicated. Duloxetine has also been demonstrated to be effective in treating symptoms of MUI (15) and is recommended when a patient is unresponsive to conservative treatment options (16). Therefore, duloxetine is accepted as an effective treatment option for SUI but the adverse effects are still debatable.

The role of duloxetine in the treatment of women with SUI was been reviewed in a recent meta-analysis (9) which confirmed the efficacy and the higher discontinuation rates with duloxetine treatment. However, the reasons for discontinuation (lack of efficacy vs side effects) were not assessed in this meta-analysis. More importantly, the risk of bias in the clinical trials included in the systematic review was not reported in detail. Additionally, the efficacy parameters in this systematic review were expressed as categorical rather than continuous variables, which is not very useful when making a judgment on risk- benefit ratio. Altogether, this meta-analysis is limited in supporting the daily clinical decisions of urologists.

In this study, we wanted to systematically review all the evidence from randomized controlled trials assessing the efficacy of duloxetine in the treatment of women with SUI and SPMUI, to obtain quantitative figures of efficacy that can help practicing urologists when counseling women with SUI or MUI for duloxetine treatment. We also performed an assessment of discontinuation rates and the risk of bias that may influence the outcomes of the clinical trials reporting on the role of duloxetine in the treatment of women with SUI and SPMUI.

Methods

Literature Search

We conducted a systematic search of the literature using OVID MEDLINE, Embase and ULAKBIM (Turkish database) databases. The PRISMA guidelines were followed during the systematic review (Figure 1). The inclusion criteria were as follows: 1) the study was an randomized controlled trials (RCT); 2) the patient was diagnosed with SUI or SPMUI; 3) the treatment intervention was duloxetine vs. placebo; 4) objective and/or subject outcome measures were clearly defined. Studies were excluded if the following: 1) they were not RCTs; 2) patients were diagnosed

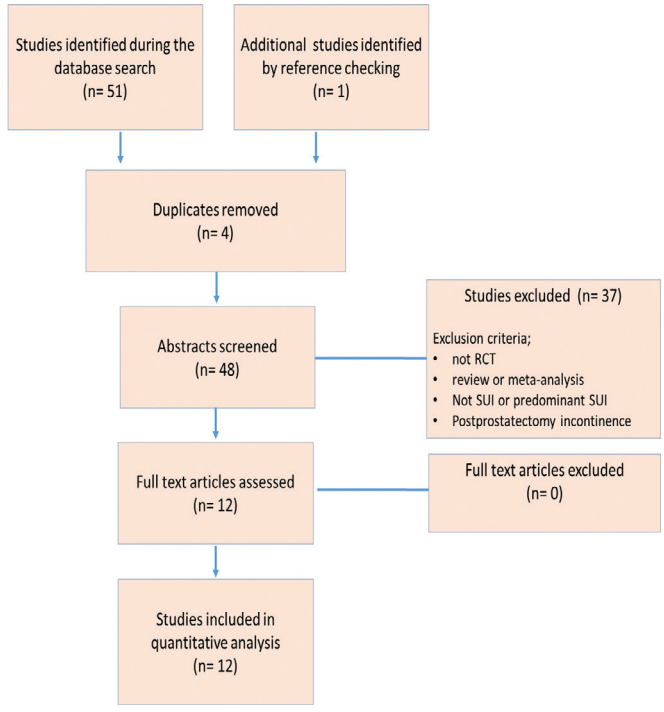

Figure 1. The preferred reporting items for systematic reviews and meta-analysis (PRISMA) flow diagram to demonstrate the search conducted

RCT: Randomized controlled trials

with urge or urge dominant urinary incontinence. The study protocol was registered beforehand and published online in PROSPERO (registration number: CRD42019149197).

Data Extraction

Two investigators evaluated all the potentially eligible studies independently and performed the data extraction separately. Any disagreements that could not be reconciled by discussion were considered by a third person.

The following data were extracted from each study independently by two authors; 1) study characteristics, 2) median change in IEF, 3) mean decrease in number of continence pads used, 4) mean increase in voiding interval (minutes), 5) discontinuation rates due to adverse effects and lack of efficacy (%).

During the meta-analysis, imputation of missing data was performed when necessary. The estimated mean and standard deviation (SD) values were calculated from the reported median value using the sample's reported median, range and number of measurements according to the method devised by Hozo et al. (17). For missing SD values, a study-level imputation of the missing data was performed assuming that the missing SD is similar to the SD of the same study baseline values (18). Missing data imputation was only performed where baseline values were presented. Review Manager 5.3 was used to conduct the meta-analysis.

Assessment of Risk of Bias

The risk of bias was assessed using the Cochrane risk of bias (RoB) assessment tool for randomized trials (19). Two researchers scored each study independently following the checklist provided. A total of five domains, each of which contains several items were assessed. An overall RoB judgment was reached following the Cochrane guidelines (20). An RCT was deemed at a high risk of bias in one particular domain when it had a high risk of bias in at least one item of that domain.

Results

Study Characteristics

A total of 12 randomized controlled trials were included in the systematic review (Table 1). In most the studies duloxetine treatment regimen of 40 mg BID was used. The duration of the studies was 8 weeks in most of them (n=6), followed by 12 weeks (n=4), 36 weeks (n=1) and 6 weeks (n=1).

Table 1. A summary of studies included in the systematic review

Trials	Total (n)	Duloxetine (n)	Placebo (n)	Treatment Regimen	Duration (w)	Outcome Measures
Norton 2002 (24)	278	140	138	40 mg BID	12	IEF, I-QoL, PGI-I, MTBV, SPT, CST, TEAE
Dmochowski 2003 (28)	683	344	339	40 mg BID	12	IEF, I-QoL, PGI-I, MTBV, continence pad use/week, TEAEs
Milliard 2004 (29)	458	227	231	40 mg BID	8	IEF, I-QoL, PGI-I, TEAEs
Van Kerrebroeck 2004 (11)	494	247	247	40 mg BID	8	IEF, I-QoL, PGI-I, TEAEs
Cardozo 2004 (27)	109	55	54	40 mg BID and 60 mg BID	8	IEF, I-QoL, PGI-I, TEAEs
Kinchen 2005 (30)	451	224	227	40 mg BID	36	I-QoL, PGI-I, TEAEs
Ghoniem 2005 (31)	97	52	47	40 mg BID	12	IEF, I-QoL, PGI-I, continence pad use
Mah 2006 (32)	121	61	60	40 mg BID	8	IEF, I-QoL, PGI-I, MTBV, continence pad use/week, TEAEs
Castro-Diaz 2007 (33)	256	136	120	40 mg BID	8	IEF, ICIQ-SF, I-QoL, PGI-I, TEAEs
Lin 2008 (34)	121	60	61	40 mg BID	8	IEF, I-QoL, PGI-I, MTBV, continence pad use/week, TEAEs
Schagen van Leeuwen 2008 (35)	265	134	131	20 mg BID and 40 mg BID	12	IEF, I-QoL, PGI-I, MTBV, continence pad use/week, BDIII, 3MS, TEAEs
Cardozo 2010 (10)	2758	1378	1380	40 mg BID	6	IEF, PGI-I, KHQ, SPT, TEAEs

IEF: Incontinence episode frequency, BID: Twice a day, I-QoL: Incontinence quality of life questionnaire, PGI-I: Patients' Global Impression of improvement, treatment emergent adverse effects, MTBV: Mean time between voids, CST: Cough stress test, KHQ: King's health questionnaire, SPT: Stress pad test, 3MS: Modified mini-mental state exam

Efficacy Outcomes

Decrease in the Frequency of Incontinence Episodes

Nine RCTs with 2.251 and 2.476 patients in duloxetine and placebo groups, respectively, were included in the meta-analysis. Duloxetine resulted in an 18.81 [95% confidence interval (CI) of 12.45-25.18, p<0.000] percentage decrease in incontinence episode frequency (IEF) (Figure 2).

The Decrease in the Number of Pads Used

Three RCTs reported a percentage decrease in the number of pads used per week. Duloxetine treatment resulted in a 15.6 (95% CI of 12.45- 25.18, p<0.000) percent decrease in the number of pads used per week compared to placebo (Figure 3).

Increase in Voiding Intervals

Five studies reported a mean increase in time between voids (based on voiding diary) after treatment. Duloxetine treatment resulted in 18.02 minutes (95% CI of 13.64- 22.4, p<0.000) increase in time between voids compared to placebo (Figure 4).

Adverse Effects

Treatment emergent adverse effects (TEAE) with the use of duloxetine have been reported in all studies. The most common side effect in the duloxetine group was nausea in 10 studies, in 1 study was dry mouth and in 1 study was constipation and dry mouth. The most common side effects were significantly higher in the duloxetine group than placebo in all studies. The most common side effects in the placebo group were headache in 5 studies, nausea in 4 studies, dizziness in 2 studies, fatigue in 2 studies.

Compliance with Duloxetine Treatment

An analysis of 2.845 and 2.931 patients randomized to duloxetine or placebo groups, respectively, treatment discontinuation due to adverse effects was significantly more common compared to placebo. The odds ratio (OR) was 5.52 (95% CI of 4.20-7.26, p<0.0001) (Figure 5).

There was no difference between the rates of discontinuation due to lack of efficacy between the treatment arms. The OR for treatment discontinuation due to lack of efficacy was 0.7 (95% CI of 0.33-1.45, p=0.33) (Figure 6).

Risk of Bias

All studies in the review had a low risk of biased allocation to interventions with a clear description of the randomization process and with adequate concealment of allocations before

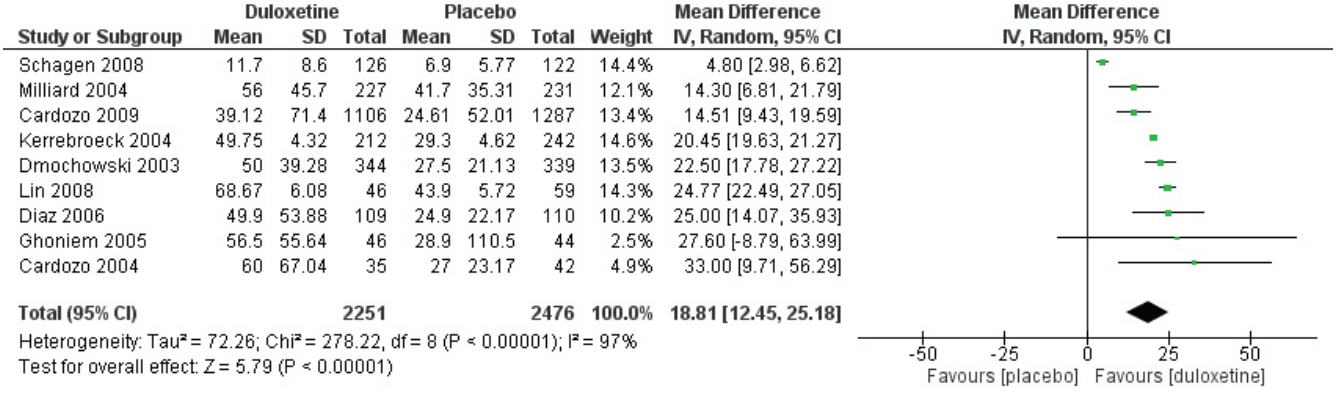

Figure 2. The percentage decrease in incontinence episode frequency (IEF) after treatment with duloxetine compared with placebo

SD: Standard deviation, CI: Confidence interval

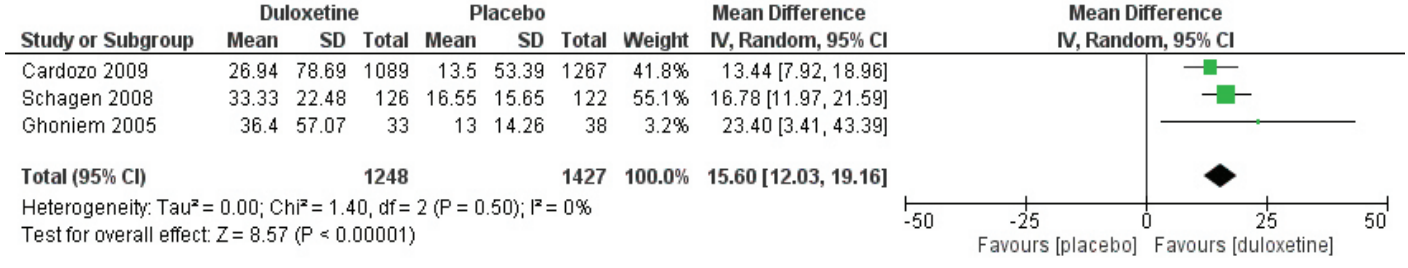

Figure 3. The percentage decrease in the number of incontinence pads after treatment with duloxetine compared with placebo

SD: Standard deviation, CI: Confidence interval

assignment. In all studies the medical staff and patients were blinded and outcomes were assessed with blinding thereby leading to a low risk of detection and performance biases (Figure 7).

However, most clinical trials included in this review had a high risk of bias in the outcome assessment domain. This was due to the disproportionately higher ratio of missing outcome data in the duloxetine group compared to the placebo group (28.4±6.4

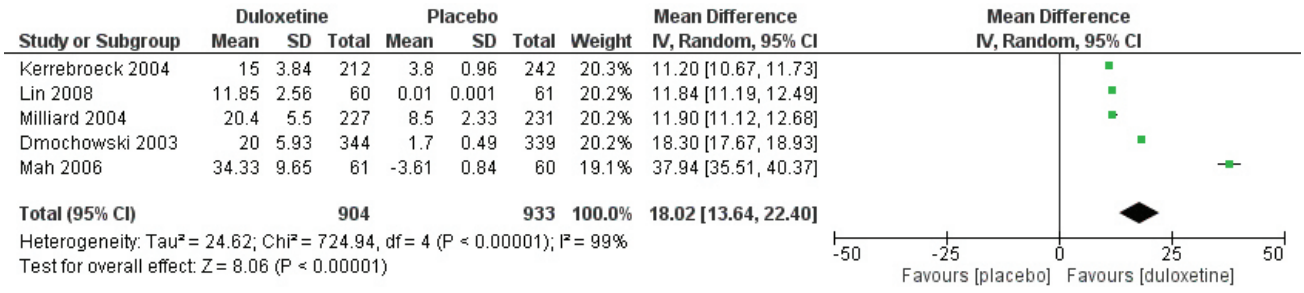

Figure 4. The mean increase in voiding intervals after treatment with duloxetine compared with placebo

SD: Standard deviation, CI: Confidence interval

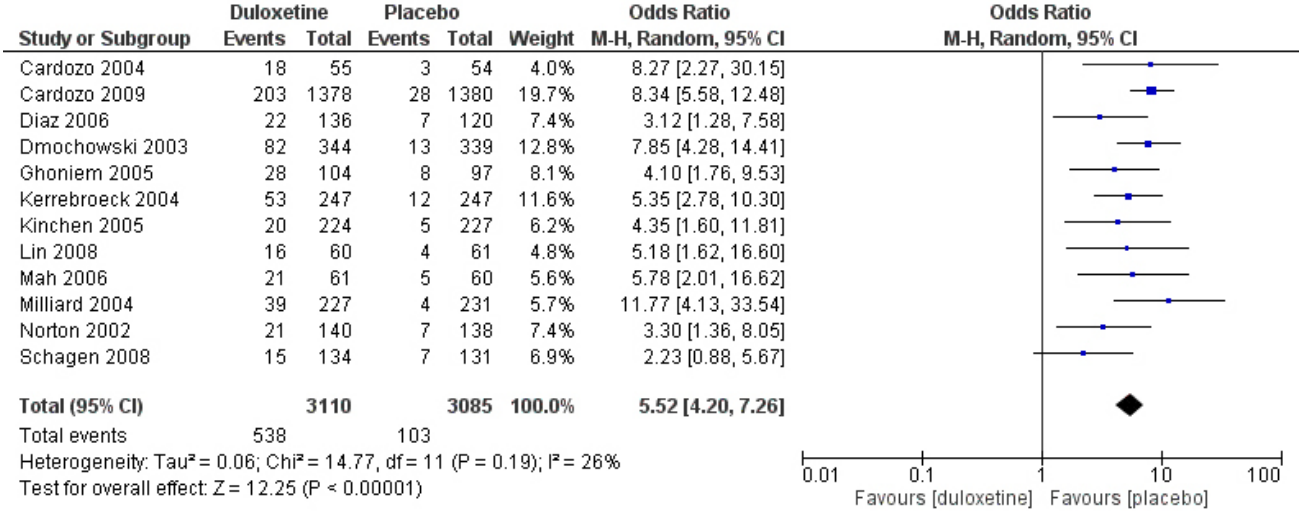

Figure 5. Number of patients discontinuing treatment due to adverse effects in the duloxetine group compared to placebo

CI: Confidence interval

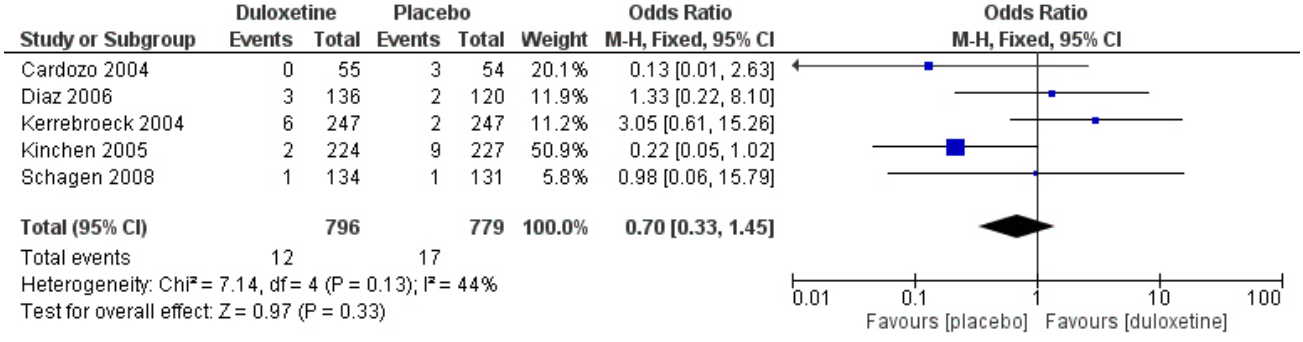

Figure 6. Number of patients discontinuing treatment due to lack of efficacy in the duloxetine group compared with placebo

CI: Confidence interval

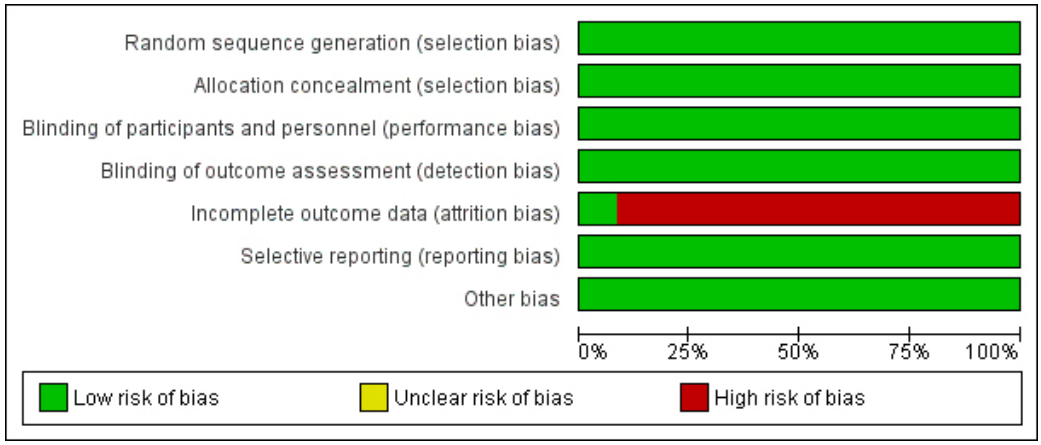

Figure 7. Summary of assessment of risk of bias among the randomized controlled trials included in the systematic review

versus 14.9±5.6, respectively). The most common reason for treatment discontinuation was related to treatment side effects rather than lack of efficacy or other reasons.

Discussion

This study provides the practicing urologists with useful quantitative figures on the clinical efficacy of duloxetine in women with SUI and SPMUI. Our meta-analysis shows that duloxetine treatment results in an 18% decrease in IEF and 16% decrease in the number of pads used compared to pre-treatment status. Also, the time interval between voids was increased by 18 minutes with duloxetine treatment compared to placebo. Such quantitative representation of the available clinical evidence can provide the clinicians with practical figures to guide their consultations with patients. This can be particularly useful when the decision on the risk- benefit ratio with duloxetine treatment is not straightforward.

The given data for the clinical efficacy of duloxetine are not biased, with a clear definition of appropriately used methods to prevent selection, detection, reporting and performance bias. With regard to the attrition bias arising from the missing data, all RCTs included have correctly used an intention to treat principle making the efficacy outcome data reliable. However, the evaluation of the safety of duloxetine will be biased by the missing outcome data. Generally, the extent of bias will increase as the amount of missing outcome data increase (21). If the percentage of missing outcome data is <5% it is generally deemed at a low risk of bias, whereas if it is more than 20% it is more likely to risk the biased outcomes (22). It is not only the proportion of the missing outcome data but whether or not the missingness of the outcome data relates to its true value (20). Within the context of this systematic review because the discontinuation rates were significantly higher in the duloxetine group compared to placebo and because the most common reason for discontinuation was reported as the side effects, it would be reasonable to think that the missingness of the outcome data is related to the true value of the outcome variable when assessing drug safety. Therefore, we made a judgment that most of the trials included in this review have a high risk of bias for the outcome variable safety/side effects.

Duloxetine is traditionally known to be effective for the treatment of SUI. Many RCTs evaluating duloxetine treatment in women with UI have included women with SUI and SPMUI, excluding women with predominant urgency. There is some evidence from animal studies that suggest duloxetine may decrease bladder over activity. However, this has not been thoroughly investigated. Clinically, one study showed that women with SPMUI, urgency predominant MUI and balanced MUI benefit from duloxetine treatment (15). Therefore, duloxetine can also be used for the treatment of MUI. The recent guidance recommends using duloxetine in the treatment of women with SUI when surgery is not indicated (level of recommendation strong). In women with MUI, duloxetine is recommended only for those who are unresponsive to other conservative treatments and who are not seeking a cure for their condition (23).

TEAE are frequently encountered with duloxetine treatment (24). Most TEAEs occur in the first 4 weeks of treatment and nausea is the most common TEAE in the duloxetine group (25,26). If patients can complete the first month of treatment, the side effects are less frequent in the later weeks (27). The current systematic review confirms that patients discontinue duloxetine treatment due of side effects rather than lack of efficacy.

This study provides the urologists with some useful figures on the magnitude of treatment efficacy obtained by systemic analysis of available clinical data from RCTs. However, there are some limitations. Firstly, we used statistical estimates to

impute missing data when necessary. This has been done by established methods, but the estimates may differ from the actual measurements. Secondly, we may have overlooked RCTs published in other languages or databases as we have only conducted the search in two different languages (English and Turkish) in the most frequently used databases. Thirdly, patient-reported outcomes were excluded from the meta-analysis.

In conclusion, duloxetine can is an effective treatment option in women with SUI and SPMUI. The efficacy of duloxetine is supported by a high level of clinical evidence from randomized controlled trials. Patients appear to discontinue treatment due to side effects rather than lack of efficacy. Further studies using more complicated analytical methods are needed to establish whether the benefits of treatment outweigh the risks or not.

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Authorship Contributions

Concept: N.M., Ö.G., C.Ö., O.D., T.T., Design: N.M., O.D., T.T., Data Collection or Processing: N.M., M.U., T.T., Analysis or Interpretation: N.M., M.U., T.T., Literature Search: N.M., M.U., T.T., Writing: N.M., M.U., Ö.G., C.Ö., O.D., T.T.

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References

1. Haylen BT, de Ridder D, Freeman RM, Swift SE, Berghmans B, Lee J, Monga A, Petri E, Rizk DE, Sand PK, Schaer GN. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Int Urogynecol J 2010;21:5-26.
2. Zhang L, Zhu L, Xu T, Lang J, Li Z, Gong J, Liu Q, Liu X. A Population-based Survey of the Prevalence, Potential Risk Factors, and Symptom-specific Bother of Lower Urinary Tract Symptoms in Adult Chinese Women. Eur Urol 2015;68:97-112.
3. Coyne KS, Sexton CC, Thompson CL, Milsom I, Irwin D, Kopp ZS, Chapple CR, Kaplan S, Tubaro A, Aiyer LP, Wein AJ. The prevalence of lower urinary tract symptoms (LUTS) in the USA, the UK and Sweden: results from the Epidemiology of LUTS (EpiLUTS) study. BJU Int 2009;104:352-360.
4. Mangir N, Aldemir Dikici B, Chapple CR, MacNeil S. Landmarks in vaginal mesh development: polypropylene mesh for treatment of SUI and POP. Nat Rev Urol 2019;16:675-689.
5. Mangir N, Roman S, Chapple CR, MacNeil S. Complications related to use of mesh implants in surgical treatment of stress urinary incontinence and pelvic organ prolapse: infection or inflammation? World J Urol 2020;38:73-80.
6. Roman S, Mangir N, MacNeil S. Designing new synthetic materials for use in the pelvic floor: what is the problem with the existing polypropylene materials? Curr Opin Urol 2019;29:407-413.
7. Preti M, Vieira-Baptista P, Digesu GA, Bretschneider CE, Damaser M, Demirkesen O, Heller DS, Mangir N, Marchitelli C, Mourad S, Moyal-Barracco M, Perematteu S, Tailor V, Tarcan T, De EJB, Stockdale CK. The Clinical Role of LASER for Vulvar and Vaginal Treatments in Gynecology and Female Urology: An ICS/ISSVD Best Practice Consensus Document. J Low Genit Tract Dis 2019;23:151-160.
8. Jost W, Marsalek P. Duloxetine: mechanism of action at the lower urinary tract and Onuf's nucleus. Clin Auton Res 2004;14:220-227.
9. Li J, Yang L, Pu C, Tang Y, Yun H, Han P. The role of duloxetine in stress urinary incontinence: a systematic review and meta-analysis. Int Urol Nephrol 2013;45:679-686.
10. Cardozo L, Lange R, Voss S, Beardsworth A, Manning M, Viktrup L, Zhao YD. Short- and long-term efficacy and safety of duloxetine in women with predominant stress urinary incontinence. Curr Med Res Opin 2010;26:253-261.
11. van Kerrebroeck P, Abrams P, Lange R, Slack M, Wyndaele JJ, Yalcin I, Bump RC; Duloxetine Urinary Incontinence Study Group. Duloxetine versus placebo in the treatment of European and Canadian women with stress urinary incontinence. BJOG 2004;111:249-257.
12. Spielmans GI, Spence-Sing T, Parry P. Duty to Warn: Antidepressant Black Box Suicidality Warning Is Empirically Justified. Front Psychiatry 2020;11:18.
13. Bielefeldt AØ, Danborg PB, Gøtzsche PC. Precursors to suicidality and violence on antidepressants: systematic review of trials in adult healthy volunteers. J R Soc Med 2016;109:381-392.
14. Maund E, Guski LS, Gøtzsche PC. Considering benefits and harms of duloxetine for treatment of stress urinary incontinence: a meta-analysis of clinical study reports. CMAJ 2017;189:E194-E203.
15. Bent AE, Gousse AE, Hendrix SL, Klutke CG, Monga AK, Yuen CK, Muram D, Yalcin I, Bump RC. Duloxetine compared with placebo for the treatment of women with mixed urinary incontinence. Neurourol Urodyn 2008;27:212-221.
16. Nambiar AK, Bosch R, Cruz F, Lemack GE, Thiruchelvam N, Tubaro A, Bedretdinova DA, Ambühl D, Farag F, Lombardo R, Schneider MP, Burkhard FC. EAU Guidelines on Assessment and Nonsurgical Management of Urinary Incontinence. Eur Urol 2018;73:596-609.
17. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5:13.
18. Wiebe N, Vandermeer B, Platt RW, Klassen TP, Moher D, Barrowman NJ. A systematic review identifies a lack of standardization in methods for handling missing variance data. J Clin Epidemiol 2006;59:342-353.
19. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
20. Higgins JPT, S. J. P. M. E. R. S. J. Chapter 8: Assessing risk of bias in a randomized trial | Cochrane Training. https://training.cochrane.org/handbook/current/chapter-08.
21. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c869.
22. Schulz KF, Grimes DA. Sample size slippages in randomised trials: exclusions and the lost and wayward. Lancet 2002;359:781-785.
23. Burkhard FC, Bosch JLH, Cruz F, Lemack G, Nambiar A, Thiruchelvam N, Tubaro A. Guidelines Associates: Ambühl D, Bedretdinova D, Farag F, Lombardo R, Schneider M. Urinary Incontinence in Adults EAU Guidelines on, 2018.
24. Norton PA, Zinner NR, Yalcin I, Bump RC; Duloxetine Urinary Incontinence Study Group. Duloxetine versus placebo in the treatment of stress urinary incontinence. Am J Obstet Gynecol 2002;187:40-48.

25. Vella M, Duckett J, Basu M. Duloxetine 1 year on: the long-term outcome of a cohort of women prescribed duloxetine. Int Urogynecol J Pelvic Floor Dysfunct 2008;19:961-964.

26. Bump RC, Voss S, Beardsworth A, Manning M, Zhao YD, Chen W. Long-term efficacy of duloxetine in women with stress urinary incontinence. BJU Int 2008;102:214-218.

27. Cardozo L, Drutz HP, Baygani SK, Bump RC. Pharmacological treatment of women awaiting surgery for stress urinary incontinence. Obstet Gynecol 2004;104:511-519.

28. Dmochowski RR, Miklos JR, Norton PA, Zinner NR, Yalcin I, Bump RC; Duloxetine Urinary Incontinence Study Group. Duloxetine versus placebo for the treatment of North American women with stress urinary incontinence. J Urol 2003;170:1259-1263.

29. Millard RJ, Moore K, Rencken R, Yalcin I, Bump RC; Duloxetine UI Study Group. Duloxetine vs placebo in the treatment of stress urinary incontinence: a four-continent randomized clinical trial. BJU Int 2004;93:311-318.

30. Kinchen KS, Obenchain R, Swindle R. Impact of duloxetine on quality of life for women with symptoms of urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2005;16:337-344.

31. Ghoniem GM, Van Leeuwen JS, Elser DM, Freeman RM, Zhao YD, Yalcin I, Bump RC; Duloxetine/Pelvic Floor Muscle Training Clinical Trial Group. A randomized controlled trial of duloxetine alone, pelvic floor muscle training alone, combined treatment and no active treatment in women with stress urinary incontinence. J Urol 2005;173:1647-1653.

32. Mah SY, Lee KS, Choo MS, Seo JT, Lee JZ, Park WH, Kim JC, Lee SY, Zhao YD, Beyrer J, Wulster-Radcliffe M, Levine L, Viktrup L. Duloxetine versus Placebo for the Treatment of Korean Women with Stress Predominant Urinary Incontinence. Korean J Urol 2006;47:527.

33. Castro-Diaz D, Palma PC, Bouchard C, Haab F, Hampel C, Carone R, Zepeda Contreras S, Rodriguez Ginorio H, Voss S, Yalcin I, Bump RC; Duloxetine Dose Escalation Study Group. Effect of dose escalation on the tolerability and efficacy of duloxetine in the treatment of women with stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2007;18:919-929.

34. Lin AT, Sun MJ, Tai HL, Chuang YC, Huang ST, Wang N, Zhao YD, Beyrer J, Wulster-Radcliffe M, Levine L, Chang C, Viktrup L. Duloxetine versus placebo for the treatment of women with stress predominant urinary incontinence in Taiwan: a double-blind, randomized, placebo-controlled trial. BMC Urol 2008;8:2.

35. Schagen van Leeuwen JH, Lange RR, Jonasson AF, Chen WJ, Viktrup L. Efficacy and safety of duloxetine in elderly women with stress urinary incontinence or stress-predominant mixed urinary incontinence. Maturitas 2008;60:138-147.