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# The role of duloxetine in stress urinary incontinence: a systematic review and meta-analysis

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**Abstract**
*Objectives* This systematic review determined whether the duloxetine can get more benefits versus placebo in managing women with stress urinary incontinence (SUI) all over the world.
*Methods* We performed a systematic review and meta-analysis of randomized controlled trials (RCTs) comparing duloxetine with placebo in these patients. The eligible RCTs were identified from the following electronic databases: Cochrane CENTRAL, Medline and EMBASE. We treated the incontinence episode frequency (IEF) as the main outcome, and the secondary outcomes were cured, average voiding interval, incontinence quality of life (I-QOL), treatment-emergent adverse events (TEAEs) and discontinuation.
*Results* The review contained ten trials including 5,738 women who were randomized to take duloxetine or placebo. All arms in individual trials were comparable for various baseline characteristics. Individual studies showed a significantly greater decrease in IEF than placebo group. The total IEF responders (defined as a woman who had at least a 50 % decrease in IEF with treatment) within the duloxetine-treated women were more than the placebo-treated women (52.5 vs. 33.7 %; RR = 1.56; 95 %CI, 1.46–1.66; $p < 0.00001$). TEAEs were commonly experienced by both two groups (62.7 vs. 45.3 %) though they were not critical.
*Authors' conclusions* Our meta-analysis showed that significant efficacy can be found in women treated with a certain dose of duloxetine. The adverse events like nausea, constipation, dry mouth, fatigue etc. are common.

**Keywords** Stress urinary incontinence · Duloxetine · Medical management · Systematic review · Meta-analysis

**Abbreviations**

| | |
|---|---|
| SUI | Stress urinary incontinence |
| UI | Urinary incontinence |
| PFMT | Pelvic floor muscle training |
| SNRI | Serotonin and noradrenaline reuptake inhibitor |
| IEF | Incontinence episode frequency |
| I-QOL | Incontinence quality of life |
| TEAEs | Treatment-emergent adverse events |

## Introduction

Stress urinary incontinence (SUI) is defined by the international continence society and the international

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urogynecological association as the complaint of involuntary loss of urine on effort or physical exertion (e.g. sporting activities), or on sneezing or coughing [1]. SUI was a common disorder that affects a large number of women and their quality of life [2], and it was the most type of urinary incontinence (UI), experienced by 50 % of incontinent women, whereas 11 % reported urgency incontinence alone and 36 % reported mixed symptoms [3].

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 [4]. At present, pelvic floor muscle training (PFMT), behavioural intervention and continence surgery are the most accepted treatment for SUI.

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 [6]. And 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 [5]. This systematic review focuses on the efficacy and safety of duloxetine in the therapy of SUI.

## Methods

We searched the following database: Cochrane Central Register of Controlled Trials (CENTRAL), Medline (via OVID) and EMBASE. There was no restriction on the language of the publication. The following search terms were used to identify any relevant studies: "stress urinary incontinence or SUI" and "duloxetine or serotonin or thiophene or noradreneline or serotonin uptake inhibitor or dopamine uptake inhibitor" and "randomized controlled trial".

Two investigators evaluate all the potentially eligible studies independently without prior consideration of the result and assess the methodological quality separately. The following criteria were used for study selection: (1) the study was a randomized controlled trial (RCT); (2) the patient was diagnosed as stress urinary incontinence; (3) the treatment intervention was duloxetine versus placebo; (4) objective and/or subject outcome measures were clearly defined. Studies were excluded if: (1) the studies were not RCTs; (2) patients were diagnosed as urge urinary incontinence; (3) previous anti-incontinence surgery or the presence of neurologic bladder of psychiatric disease; and (4) the studies included other interventions except for duloxetine alone.

The primary outcome measure was incontinence episode frequency (IEF) and the secondary outcomes included cured, average voiding interval, incontinence quality of life (I-QOL), adverse events and discontinuation rates.

Data extraction was undertaken independently by two reviewers and then cross checked. Any disagreements that could not be reconciled by discussion were considered by a third person. Included trial data were processed as described in the Cochrane Reviewers' handbook [13]. Statistical analyses were conducted by Review Manager 5.1. $\chi^2$ tests and $I^2$ tests were used to assess heterogeneity in study results. If $\chi^2$ heterogeneity was reported as $p > 0.10$ and $I^2 \leq 50$ %, heterogeneity was low. A fixed effect was used for calculations in the absence of evidence of heterogeneity; otherwise, a random effects model was applied. We reported risk ratio (RR) for dichotomous data and weighted mean differences (WMD) for continuous data, accompanied by 95 % confidence intervals (CI). A p value $<0.05$ was considered statistically significant.

## Results

Our search identified 283 reports, of which 261 were excluded on the basis of title or abstract due to irrelevant to the topic, diagnosing as urge urinary incontinence and multiple interventions, and 12 were excluded from the remaining 22 literatures after we finished the reading of full text. Therefore, data from a total of 10 studies were included in this systematic review. Table 1 shows the characteristics of the included studies. Overall, 5,738 women were randomized to receive duloxetine ($n = 2{,}870$) or placebo ($n = 2{,}868$).

IEF was calculated from subject-completed real-time paper diaries. Based on the reason that approximately 50 % reduction in IEF has been generally accepted as a clinically relevant threshold for response in SUI outcomes research for interventions including bladder training and pelvic floor muscle training [21], devices [22], surgery [23–25] and a pharmacological agent [8, 9, 11, 12], IEF responder was defined as a

**Table 1** Characteristics of included studies

| Trials | Designs | Level of evidence | Participants | | | Dosages and duration | Screening lead-in (weeks) | Outcome measures |
|---|---|---|---|---|---|---|---|---|
| | | | Total | Duloxetine group | Placebo group | | | |
| Lin [7] | RCT(placebo-controlled) double-blind multi-centre | A | 121 | 60 | 61 | 40 mg bid for 8 weeks | 2 | IEF, I-QoL, PGI-I, MTBV, continence pad use/week, TEAEs |
| Mah [5] | RCT (placebo-controlled) double-blind multi-centre | A | 121 | 61 | 60 | 40 mg bid for 8 weeks | 2 | IEF, I-QoL, PGI-I, MTBV, continence pad use/week, TEAEs, |
| Millard [8] | RCT (placebo-controlled) double-blind multi-centre | A | 458 | 227 | 231 | 40 mg bid for 12 weeks | 2 | IEF, I-QoL, PGI-I, TEAEs |
| Van Kerrebroeck [9] | RCT (placebo-controlled) double-blind multi-centre | A | 494 | 247 | 247 | 40 mg bid for 12 weeks | 2 | IEF, I-QoL, PGI-I, TEAEs |
| Cardozo 2004 [10] | RCT (placebo-controlled) double-blind multi-centre | A | 109 | 55 | 54 | 40 mg bid for 4 weeks, then escalating to 60 mg bid for 4 weeks | 2 | IEF, I-QoL, PGI-I, TEAEs |
| Dmochowski [11] | RCT(placebo-controlled) double-blind multi-centre | A | 683 | 344 | 339 | 40 mg bid for 12 weeks | 2 | IEF, I-QOL, PGI-I, BDI-II, TEAEs |
| Norton [12] | RCT (placebo-controlled) double-blind | A | 278 | 140 | 138 | 40 mg bid for 2 weeks | 2 | IEF, I-QOL, PGI-I, TEAEs, SPT, CST, MTBV |
| Kinchen [15] | RCT (placebo-controlled) double-blind multi-centre | A | 451 | 224 | 227 | 40 mg bid for 36 weeks | NA | I-QOL, PGI-I, TEAEs |
| Schagen van Leeu wen [16] | RCT (placebo-controlled) double-blind multi-centre | A | 265 | 134 | 131 | 20 mg bid for 2 weeks, then escalating to 40 mg bid 10 weeks | 3 | IEF, I-QOL, PGI-I, MTBV, continence pad use/week, BDI-II, 3MS, TEAEs |
| Cardozo 2010 [17] | RCT (placebo-controlled) double-blind multi-centre | A | 2,758 | 1,378 | 1,380 | 40 mg bid for 6 weeks | 2 | IEF, PGI-I, KHQ, Stress pad test, TEAEs |

*RCT* randomized controlled trial, *IEF* Incontinence Episode Frequency *I-QOL* incontinence quality of life, *PGI-I* patient's global impression of improvement, *TEAEs* treatment-emergent adverse events, *NA* not available, *MTBV* mean time between voids, *BDI*-II beck depression inventory II, *SPT* stress pad test, *CST* cough stress test, 3*MS* modified mini-mental state exam, *KHQ* king's health questionnaire

woman who had at least a 50 % decrease in IEF with treatment. Seven studies [5, 7–9, 11, 16, 17] including 4,900 subjects were analysed for the outcome of IEF responders. The numbers of the IEF responders in the duloxetine group were higher compared with placebo group with data (Fig. 1: 52.5 vs. 33.7 %, overall RR = 1.56; 95 %CI, 1.46–1.66; $p < 0.00001$). Patients with no incontinence episodes at the last diary were regarded as cured. The numbers of cured patients in the group allocated duloxetine were a little higher than in the group with placebo in three trials [8, 11, 12] with the data (Fig. 2: 10.8 vs 7.8 %, overall RR = 1.39; 95 %CI, 1.00–1.93; $p = 0.05$).

In addition to decreasing their IEF, seven studies [5, 7–9, 11, 12, 16] addressed patients' average voiding interval in both two groups. Mah et al. [5] noted that the change in mean time between voids/day was significantly greater for duloxetine-treated women when compared with change in placebo-treated women (34.44 vs 3.61 min, respectively; $p < 0.001$). Lin et al. [7] reported that duloxetine group numerically increased average voiding interval compared with placebo group (11.85 vs 0.01 min, $p = 0.13$). The increase of average voiding interval (duloxetine group vs placebo group) from Millard et al. [8], van Kerrebroeck et al. [9], Dmochowski et al. [11], Norton et al. [12] and Schagen van Leeuwen et al. [16] were 20.4 : 8.5 min $p < 0.001$, 15.0 : 3.8 min $p < 0.001$, 20.0 : 1.7 min $p < 0.001$, 24.0 : 7.0 min $p < 0.001$ and 24.2 : 8.1 min $p < 0.001$, respectively.

Incontinence Quality of Life (I-QOL) questionnaire total score evaluated the effects of urinary incontinence in the three domains of avoidance and limiting behaviour, social embarrassment and psychosocial impact, and it was endorsed by the International Consultation on Incontinence. Three studies [8, 10, 11] showed that duloxetine-treated subjects had significantly greater overall improvement in I-QOL (Fig. 3: MD = 4.50; 95 %CI, 2.83–6.18; $p < 0.00001$).

All of the included trials [5, 7–12, 15–17] mentioned the treatment-emergent adverse events. About 62.7 % subjects allocated duloxetine reported the side effects. However, nearly half (45.3 %) of those allocated to placebo also reported adverse effects. Among all studies, the most common adverse event was nausea and other side effects like constipation, dry mouth, fatigue, dizziness and insomnia can also be found in both two groups. Figure 4 showed that the overall RR was 1.37 (95 %CI, 1.26–1.49; $p < 0.00001$). Across the nine trials, 17.3 % patients treated with duloxetine withdrew compared with 3.0 % in the placebo group (Fig. 5: overall RR = 5.75; 95 %CI, 4.58–7.21; $p < 0.00001$).

## Discussion

The WHO-sponsored International Consultation on Incontinence 2002 (ICI 2002) did not recommend pharmacological agents for the treatment of SUI [14]. At present, the most accepted forms of the treatment for stress urinary incontinence are continence surgery, pelvic floor muscle training and different kinds of behavioural interventions. Although the effects of surgical treatments, particularly tension-free mid-urethral sling procedures and bladder suspensions, are good [18], the complications associated with the sling material are great concerns [19]. Until 2004, duloxetine, a serotonin and noradrenaline reuptake inhibitor (SNRI), became the approved medication for SUI and its presumed mechanism of action in the cat

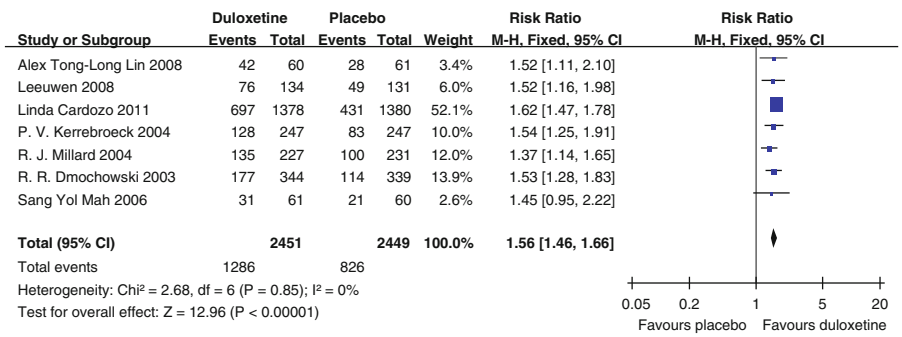



**Fig. 1** Numbers of the IEF responders: duloxetine vs placebo

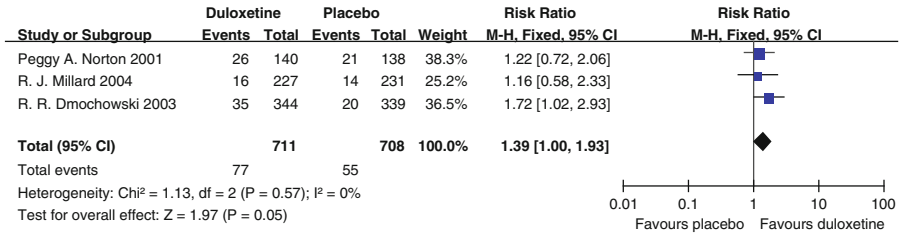
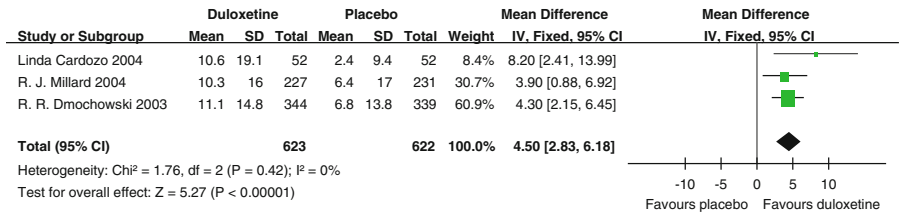



**Fig. 2** Numbers cured during treatment: duloxetine vs placebo

**Fig. 3** Assessment of I-QOL change: duloxetine vs placebo



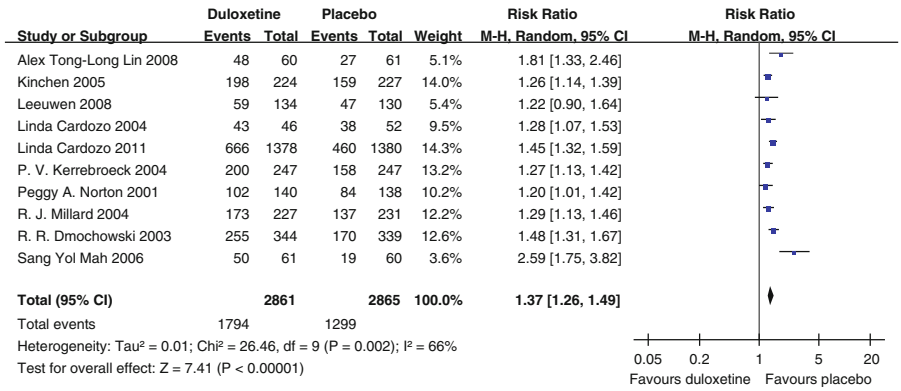




**Fig. 4** Adverse events: duloxetine vs placebo

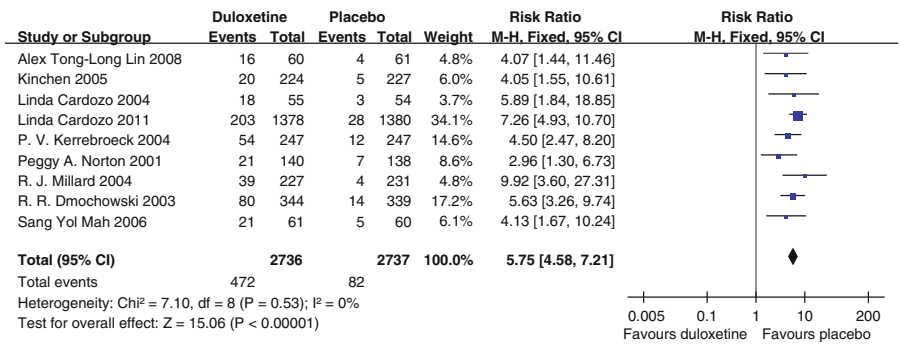



**Fig. 5** Discontinuation rates: duloxetine vs placebo

model is stimulation of pudendal nerve motor nerve output resulting from increased levels of serotonin and noradrenaline in the pudendal motor nucleus (Onuf's nucleus) in the sacral spinal cord [6, 20]. Our review of published data from the ten randomized trials indicated that duloxetine with 80 mg per day had better results than placebo although the cure rate in placebo group were almost the same as duloxetine group

(7.8 vs 10.8 %). The decrease in IEF was significantly greater in the duloxetine and sustained throughout the course of the treatment. Almost all these trials reported an improvement in incontinence episode frequency of about 50 % and I-QOL score also favoured duloxetine. Incontinence improved despite significant increases in voiding intervals with duloxetine indicating the improvement did not result from frequent emptying of the bladder.

Most (62.7 %) of the participants treated with duloxetine reported an adverse effect. However, nearly half (45.3 %) of the patients in placebo group reported side effects, and the high incidence of side effect in control group may be explained by the subjective symptoms like nausea, constipation, fatigue, insomnia and dizziness or caused by the SUI itself. Overall, 17.3 % stopped treatment in the duloxetine group, and the main cause for discontinuation is nausea. Although the nausea trended to start soon after the initiation of the treatment, it did not worsen after its onset and could be resolved within 1 week to 1 month of therapy. Most of the adverse events were of mild or moderate grade, and the overall safety profile of these agents was generally deemed to be well accepted. However, no accurate data could be found to rule out rare longer-term serious complications.

The trials included in this review were all described as double-blind, randomized placebo-controlled trials and the description of randomization and the concealment of allocation into groups were found to be adequate. Sample number calculation, withdrawals, dropouts and adverse events were described clearly in all the 10 included papers. Selection bias is unlikely given the double-blind randomized study design in all trials.

Almost all the authors of trials except for Cardozo et al. [10] recruited women with moderate-to-severe symptoms (based on PGI-S), and in this study, the subject should be a woman with severe stress urinary incontinence. In seven studies [5, 7–9, 11, 15, 17], stratified randomization used baseline IEF of $<14$ or $\geq$ 14 episodes/week obtained from patient diaries to prevent potential imbalance in incontinence severity, and two studies used different baseline IEF to prevent (baseline IEF $<4$ or $\geq 4$ episodes per day in Cardozo's study [10] and baseline IEF $>0$ and $<10$ episode per week, $\geq 10$ and $<20$ episode per week, $\geq 20$ episode per week in Norton's study [12]).

It was not made clear, in several trials, whether the recruits had been treated in other therapeutic methods before the beginning of the trials and this is a limitation in their methods. All trials compared duloxetine alone with placebo, and the dosage always was 80 mg per day except the Carzozo's study [10], the Norton's study [12] and Schagen van Leeuwen's study [16]. However, the number of patients with different dosages was excluded in this review. Thus, collecting the data with different doses (especially high doses) of the agent to determine that which is the best for patients should now be a priority. In Cardozo's study [17], the study design contained the uncontrolled open-label phrase, and because there was no control group, the data from this phrase were not extracted. However, this was the only study in this review for reporting the long-term efficacy and safety. Limited evidence from the trial [17] suggested that the improvements appeared to persist over a long period in a considerable number of women, without major safety concerns.

From our analyses of the data, the symptoms of women with moderate-to-severe SUI can be largely improved after treating with duloxetine. However, the cure rate in duloxetine-treated group is slightly higher than placebo-treated group. Thus, the duloxetine should be recommended as the initial treatment for SUI patients. Lifestyle interventions, pelvic floor muscle training and duloxetine are the initial therapeutic regimens, and surgery will be considered if the initial therapy fails. Almost all trials reveal that duloxetine administered at 40 mg twice per day for up to 8 weeks is safe and efficacious. However, no evidence is available on the maintenance regimens for duloxetine. The duration of the five trials [8, 9, 11, 12, 16] was 12 weeks, three trials [5, 7, 10] lasted for 8 weeks and in Kinchen's study [15] and Cardozo's study [17] it was 36 weeks and 6 weeks separately. There was no clear data to determine what the duration of treatment should be and whether the efficacy of duloxetine was sustainable during the long-term therapy except Cardozo's study [17]. So, more data of long-term treatment should be collected in the future to identify the sustained efficacy.

SNRIs have recognized interactions with other medicines such as non-steroidal anti-inflammatory drugs, barbiturates and antidepressants. But in all the trial reports, no any specific interactions were mentioned. Duloxetine is a drug used for treating

depression; thus, the improvement in the measurement of I-QOL may be the result of central nervous system effect.

Compared with previous reviews, this meta-analysis (1) contained the RCTs of the last 5 years, (2) excluded the studies with lower dose of agent which is rarely used in the most parts of the world, (3) clearly compared duloxetine with placebo without other interventions and(4) had no ethnic restrictions in study especially including the Asian.

## Conclusions

Based on the data available, duloxetine is better than the placebo in terms of the incontinence episode frequency and I-QOL. There are also side effects (most often nausea) in women treated with duloxetine. However, these adverse events are of mild or moderate grade. No RCT-based evidence shows whether the duloxetine is more cost-effective compared with the most accepted approaches currently such as PFMT and surgery.

This review analyses the therapeutic effect of duloxetine with a certain dosage in the treatment of SUI compared with placebo. Whether there is sustained efficacy in long-term therapy, whether it does work in male SUI and whether higher dosages can get more benefits should be the priority during experiment in the near future.

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## References

1. Haylen BT, de Ridder D, Freeman RM et al (2010) An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Int Urogynecol J 21:5–26
2. Buckley BS, Lapitan MC, Epidemiology Committee of the Fourth International Consultation on Incontinence, Paris (2008) Prevalence of urinary incontinence in men, women, and children: current evidence-findings of the fourth international consultation on incontinence. Urology 2010(76):265–270
3. Imamura M, Abrams P, Bain C, et al. (2010) Systematic review and economic modeling of the effectiveness and cost-effectiveness of non-surgical treatments for women with stress urinary incontinence. Health Technol Assess 14:No.40
4. Abrams P, Cardozo L, Khoury S, Wein A (2005) International consultation on incontinence, 3rd edn. Health Publication Ltd, Plymouth
5. Mah SY, Lee KS, Choo MS et al (2006) Duloxetine versus placebo for the treatment of Korean women with stress predominant urinary incontinence. Korean J Urol 47(5):527–535
6. Thor KB, Katofiasc MA (1995) Effects of duloxetine, a combined serotonin and norepinephrine reuptake inhibitor, on central neural control of lower urinary tract function in the chloraloseanesthetized female cat. J Pharmacol Exp Ther 274:1014–1024
7. Lin AT, Sun MJ, Tai HL, et al. (2008) Duloxetine versus placebo for the treatment of women with stress predominant urinary incontinence in Taiwan: a double-blind, randomized, placebo-controlled trial. BMC Urology 8:2 (25 January 2008)
8. Millard RJ, Moore K, Rencken R et al (2004) Duloxetine vs placebo in the treatment of stress urinary incontinence: a four-continent randomized clinical trial. BJU Int 93(3): 311–318
9. van Kerrebroeck P, Abrams P, Lange R et al (2004) Duloxetine versus placebo in the treatment of European and Canadian women with stress urinary incontinence. BJOG 111:249–257
10. Cardozo L, Drutz HP, Baygani SK et al (2004) Pharmacological treatment of women awaiting surgery for stress urinary incontinence. Obstet Gynecol 104(3):511–519
11. Dmochowski RR, Miklos JR, Nortan PA et al (2003) Duloxetine versus placebo for the treatment of North American women with stress urinary incontinence. J Urol 170:1259–1263
12. Norton PA, Zinner NR, Yalcin I et al (2002) Duloxetine versus placebo in the treatment of stress urinary incontinence. Am J Obstet Gynecol 187:40–48
13. Higgins J, Green S (2005) editors. Cochrane handbook for systematic reviews of interventions 4.2.5 [updated May 2005]. In the Cochrane Library, Issue 3, Chichester, United Kingdom: John Wiley and Sons
14. Mariappan P, Alhasso AA, Grant A et al (2009) Serotonin and noradrenaline reuptake inhibitors (SNRI) for stress urinary incontinence in adults (Review). Cochrane Lib 1:1–56
15. Kinchen KS, Obenchain R, Swindle R (2005) Impact of duloxetine on quality of life for women with symptoms of urinary incontinence. Int Urogynecol J 16:337–344
16. Schagen van Leeuwen JH, Lange RR, Jonasson AF, Chen WJ et al (2008) Efficacy and safety of duloxetine in elderly women with stress urinary incontinence or stress-predominant mixed urinary incontinence. Maturitas 60:138–147
17. Cardozo L, Lange R, Voss S, Beardsworth A et al (2010) Short- and long-term efficacy and safety of duloxetine in women with predominant stress urinary incontinence. Curr Med Res Opin 26(2):253–261
18. Pradhan A, Jain P, Latthe PM (2012) Effectiveness of midurethral slings in recurrent stress urinary incontinence:

a systematic review and meta-analysis. Int Urogynecol J 23:831–841
19. Ho CP, Bhatia NN (2012) Development of stem cell therapy for stress urinary incontinence. Curr Opin Obstet Gynecol 24(5):311–317
20. Katofiasc MA, Nissen J, Audia JE et al (2002) Comparison of the effects of serotonin selective, norepinephrine selective, and dual serotonin and norepinephrine reuptake inhibitors on lower urinary tract function in cats. Life Sci 71:1227–1236
21. Wyman JF, Fantl JA, McClish DK et al (1998) Comparative efficacy of behavioral interventions in the management of female urinary incontinence. Continence Program for Women Research Group. Am J Obstet Gynecol 179(4): 999–1007
22. Kondo A, Yokoyama E, Koshiba K et al (1997) Bladder neck support prosthesis: a nonoperative treatment for stress or mixed urinary incontinence. J Uro 157(3):824–827
23. Bodell DM, Leach GE (2002) Needle suspension procedures for female incontinence. Urol Clin North Am 29(3): 575–584
24. Rodriguez LV, Raz S (2003) Prospective analysis of patients treated with a distal urethral polypropylene sling for symptoms of stress urinary incontinence: surgical outcome and satisfaction determined by patient driven questionnaire. J Urol 170(3):857–863
25. Itano N, Berman C, Rodriguez LV et al (2003) Polypropylene sling for the treatment of stress urinary incontinence: intermediate-term results. J Urol 169S:270