Initial management of stress urinary incontinence: pelvic floor muscle training and duloxetine

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Stress urinary incontinence (SUI) is common among women of all ages and can have a negative impact on quality of life (QoL). Often, women refrain from seeking treatment due to the fear that surgery might be the only option, or that no other treatments exist. SUI symptoms can often be treated with simple measures such as pelvic floor muscle training (PFMT), weight loss, devices, etc. However, PFMT has low compliance rates, and few continue long term. More recently, another treatment option has been introduced, i.e. the relatively balanced serotonin and noradrenaline reuptake inhibitor (SNRI) duloxetine. PFMT and/or SNRI are recommended as a first-line therapy for the initial management of SUI in women in the guidelines of the third International Consultation on Incontinence. SNRI have received a grade A recommendation. As PFMT and duloxetine target different areas (i.e. pelvic floor muscle and distal urethral sphincter/rhabdosphincter, respectively), combined therapy might provide additional benefit. A recent study comparing the effect of combined treatment with no active treatment found that combination therapy was significantly better for all outcomes, including frequency of SUI episodes, pad use, improvements in QoL and global impression of improvement scores. The data suggest that combination therapy might provide another treatment option for SUI symptoms in women.

Keywords Combination therapy, duloxetine, pelvic floor muscle training, stress urinary incontinence, therapy.

Introduction

The International Consultation on Incontinence (ICI) has recently revised their recommendations for the initial management of urinary incontinence in women1 (Figure 1). Treatment of symptomatic stress urinary incontinence (SUI) should include assessment of oestrogen status, lifestyle interventions (such as weight loss, stopping smoking and limiting caffeine intake) and supervised pelvic floor muscle training (PFMT).

The ICI reiterated the views of the Cochrane Collaboration2 that PFMT is better than ‘no treatment’ (i.e. ‘sham’ or placebo) and that supervised treatment was more effective than ‘standard treatment’ (i.e. verbal or written instruction only) and concluded that PFMT should be offered as a first-line therapy for SUI (grade A recommendation).3 In addition, it was recommended that primigravid women should be offered intensive (i.e. supervised) PFMT to prevent postnatal urinary incontinence (grade B evidence). This was based on studies showing that antenatal PFMT can result in a reduced incidence of postpartum SUI.4,5

While the recommendation is that PFMT should be first-line therapy for SUI, it is debatable if this happens in practice. Evidence suggests that surgery for women with SUI is more commonly performed in the UK than in other European countries.6 This is despite evidence suggesting that PFMT is often the preferred option expressed by many women.7,8 In one study, approximately 60% stated that they would be prepared to perform PFMT for 6 months but fewer would wish to do this for life and only a small percentage would want drugs for life or a major operation.8

Pelvic floor muscle training

The results of PFMT are unclear. While short-term success rates of 50–75% have been quoted,2,9 the long-term outcomes are unknown. In addition, different regimens for PFMT have been used, so comparing the outcomes across studies is difficult.

Like all forms of muscle training, the two most important factors for success are compliance and motivation. The Cochrane review of PFMT2 suggests that only 15–20% of...
women comply with a regimen. Not surprisingly, the outcomes are better ‘in those who do than in those who do not’.2

It would seem that while most women express a preference for PFMT7,8, few comply. Glazener et al.10 have shown that 6 years after an intensive postnatal PFMT programme, only 50% were performing any PFMT compared with 80% at baseline (i.e. at 3 months postnatally). Bø et al.,11 in a 15-year follow up of a small number of women who underwent an intensive training programme versus a home exercise programme, reported that only six women overall (25%) were performing PFMT for more than three times a week as recommended. The reasons stated for poor compliance include lack of knowledge and that ‘women are rarely taught how to do them’.12 However, despite having the knowledge, it is claimed that few practice PFMT outside pregnancy and only 45% of the women are aware that the exercises should be continued indefinitely.12 Consequently, many women are not confident that they are performing PFMT exercises correctly, which has been cited as an important barrier to compliance.12

Other factors that might affect compliance, in addition to the patient’s perception of her ability to contract the pelvic floor, include the severity of the incontinence and lifestyle factors such as time, work and family commitments.13

PFMT regimens
As there are many different methods used for PFMT and problems with compliance, the Second ICI recommended a standardised regimen, which includes three sets of 8–12 slow-velocity, maximal-voluntary pelvic floor muscle contractions sustained for 6–8 seconds each.14 These should be performed three to four times a week and continued for at least 15–20 weeks.14 It has been shown that strength and/or timing of the contraction can be improved within 4–8 weeks,15 but clinical improvement might take as long as 5 months.16

PFMT requires strength as well as skill training. Strength training, which requires repeated exercise over weeks to months, is believed to result in muscle hypertrophy, thereby improving urethral compression during activity and...
decreasing the frequency of incontinence episodes. The effect of strength training on SUI takes time.3

Skill training (sometimes referred to as ‘the Knack’) involves learning to contract the muscles during events that might cause urine leakage (e.g. coughing), thereby reducing the amount of leakage.17 Contrary to strength training, the effects of skill training are almost immediate.17

Duloxetine

The efficacy of the relatively balanced serotonin and noradrenaline reuptake inhibitor (SNRI) duloxetine in SUI in women has been confirmed in several double-blind, placebo-controlled randomised clinical trials.18–22 Further details on the mechanism of action and the efficacy of duloxetine are found in the papers by Drutz23 and Schuessler24 in this supplement. It is thought that the drug reduces incontinence episode frequency (IEF) by strengthening rhabdosphincter contraction through the pudendal nerve. While the initial results with duloxetine are encouraging, women require counselling about potential adverse effects, e.g. nausea. These tend to occur early in treatment but are usually transient and self-limiting within 2–4 weeks.25

The combined efficacy of duloxetine and PFMT: a randomised controlled study

Duloxetine is believed to enhance rhabdosphincter contraction through the pudendal nerve, while the pelvic floor muscles are innervated by other sacral somatic efferents.26,27 Contraction of these muscles might not directly affect the rhabdosphincter, and duloxetine is unlikely to improve pelvic floor strength. A combination of PFMT and duloxetine might therefore strengthen pelvic floor support of the rhabdosphincter and also improve sphincter function.

In a recently published trial of women with at least two daily episodes of SUI, 47 were randomised to ‘no treatment’ (i.e. placebo plus ‘imitation’ PFMT [iPFMT]), 50 to ‘PFMT’ alone (i.e. placebo drug and PFMT), 52 to ‘duloxetine’ (i.e. duloxetine 40 mg twice a day plus imitation PFMT) and 52 to ‘combination therapy’ (i.e. duloxetine 40 mg bd plus PFMT).26 The primary outcome was the percentage change in IEF. Secondary outcomes included quality of life (QoL) score, continence pad use (percentage change) and the patient global impression of improvement.26

Methods

The protocol for this study had been approved prior to the introduction of the Second ICI recommended PFMT regimen14 and included strength and skill training as well as ‘imitation/sham’ training supervised by a physiotherapist or by a continence advisor. Ten long and ten quick contractions were performed three times a day (total of 50 contractions) four times a week, i.e. a total of 200 contractions per week (Table 1).

The imitation/sham exercises (iPFMT) were based on the study by Ramsay and Thou,28 and included 30 minutes of initial instruction on training the hip abductors. Again, these were performed under the supervision of a trained continence advisor or by a physiotherapist. Fifteen minutes of repeat instruction took place at 4 and 8 weeks, and a compliance diary was completed.

The PFMT involved skill training (the Knack)17 where women were instructed to contract the pelvic floor prior to coughing or any activity that might result in SUI. Strength training involved repetitive exercising to increase the mechanical support of the urethra and bladder neck during stressful activity. Again, there was 30 minutes of initial instruction by a physiotherapist or by a continence advisor, and the correct type of contraction was confirmed by pelvic examination. Fifteen minutes of repeat instruction was given at 4 and 8 weeks. Strength training and skill training were performed as per the above regimen (Table 1), and a compliance diary was completed.

The study was powered to compare combination therapy with no treatment (i.e. placebo drug and iPFMT) only; not combination versus single therapies alone. Approximately 200 women were required to show a 20% difference in reduction of incontinence episodes between the combined group and the no-treatment group.

Results

Table 2 shows the baseline severity of SUI expressed as the median IEF per week, median pad use and median scores on the Incontinence Quality of Life (I-QOL) questionnaire.26 There was over 80% compliance with drug therapy based on the number of unused tablets.26

Compliance with PFMT and iPFMT was also high, with 82–91% of the assigned contractions being completed at 4 weeks, and 76–88% at 12 weeks.26

![Table 1. Training schedule for PFMT and iPFMT](https://example.com/table1.png)
Intent-to-treat analysis
On the intention-to-treat (ITT) analysis, there was a significant reduction in the IEF in the combination group (57%) compared with 29% in the no treatment group \((P < 0.001)\) (Figure 2). In the secondary outcomes, there was no difference between combination and duloxetine alone, but there was a significant improvement with both combination and duloxetine over PFMT and no treatment groups (Figures 3, 4).

It has been shown that a 50% reduction in incontinence episodes is associated with improved QoL scores.\(^{30}\) In the study of Ghoniem \textit{et al.}, of the combined group, 61% achieved a 50% reduction in incontinence episodes compared with 56.5% in the duloxetine group \((P < 0.001, \text{Wilcoxon–Mann–Whitney test})\). In addition, 26.1% achieved a 50% reduction in incontinence episodes with PFMT versus 25% with no treatment \((P < 0.003, \text{Wilcoxon–Mann–Whitney test})\).\(^{26}\)

QoL improvement and Patient Global Impression of Improvement (PGI-I) scores are presented in Figures 3 and 4, respectively. Again, a significant reduction in combination over no treatment was seen for the increase in I-QOL scores \((P < 0.011, \text{analysis of covariance test})\) as well as PGI-I scores \((P < 0.005, \text{Cochran–Mantel–Hansel test})\). Likewise, there was a significant reduction in pad usage (46% with combination versus 11% on no treatment; \(P < 0.001, \text{Wilcoxon–Mann–Whitney test})\).\(^{26}\)

It was noted with interest that the PFMT group, despite having a lower reduction in incontinence episodes than the combination and duloxetine groups (Figure 2), felt that their condition had improved on the PGI-I (compared with no treatment) (Figure 4).

Completer/per protocol analysis
A completer/per protocol analysis was performed to see what effect the combination therapy had in women who complied with the training and drug therapy. A 76% reduction in IEF was noted in the combination group compared with 43% in the no-treatment group \((P = 0.01)\). Similar improvements to the ITT analysis were seen with I-QOL and PGI-I scores (Figures 5, 6).

In the secondary analyses, combination therapy was better than duloxetine only with regard to PGI-I (83.3 versus 57.6%; \(P < 0.05)\) (Figure 6). There were no significant differences between single treatments. Duloxetine was superior to no treatment only for reduction in pad use (36.4 versus 13.0%; \(P < 0.05)\). PFMT was significantly different from the no-treatment group for improvement using PGI-I scores (70.7 versus 46.2%; \(P < 0.05)\) (Figure 6).

Discussion
The study suggests that a combination of duloxetine and PFMT is better than no treatment in reducing incontinence episodes, reducing pad usage and improving QoL and PGI-I scores.\(^{26}\) This might be due to the rapid onset of action of duloxetine\(^{21}\) and skill training.\(^{17}\)
The trial was powered to compare combined treatment with no active treatment only, but some of the secondary ITT analyses did approach statistical significance, e.g. combination therapy versus duloxetine alone for I-QOL and PGI-I. There were significant differences between combination therapy and duloxetine for PGI-I in the completer population. However, these analyses lack power to make definitive conclusions and are liable to bias.

The reduction in SUI episodes with PFMT alone was disappointing. This might be because the duration and intensity of the regimen was not as recommended by the ICI,14 i.e. 15–20 weeks of training; the above study was for 12 weeks only.
As mentioned, the protocol had been finalised before the ICI recommendation was made. Also, there was no use of biofeedback techniques as adjuncts for those with a weak pelvic floor contraction at baseline, unlike clinical practice.

Despite the poor reduction in incontinence episodes, PGI-I scores in the PFMT group were significantly greater than those in the no treatment group (Figure 3). A possible explanation might be reduced volume leakage (as opposed to reduced episodes/IEF), but there are no data to confirm this hypothesis.

The study lasted for 12 weeks only, and longer term data are required to see if the positive effects are maintained. A follow-up study is ongoing, with all women being on combination therapy, i.e. PFMT and duloxetine 40 mg twice a day. The results will be awaited with interest.

**Mode of action and a suggested treatment regimen**

The mode of action of combined treatment is probably by duloxetine strengthening the rhabdosphincter and PFMT improving sphincter support. Previous studies have shown that duloxetine might produce an improvement within 2–4 weeks,

while improvement with PFMT takes time, e.g. 15–20 weeks.

Further studies are required to see if duloxetine can be used in combination with PFMT in courses rather than taking the drug long-term. For example, it takes time for muscle training (PFMT) to show an effect on SUI, and some women might not have the morale and motivation to comply with the regimen due to persistent leakage. Adding duloxetine that appears to have a rapid onset of action might help incontinence episodes, thus enabling the woman to comply with the PFMT. If, after 15–20 weeks of combined treatment, there is a clinical improvement, then it should be possible to stop duloxetine and continue with PFMT alone. The drug therapy can be reintroduced if relapse occurs. Further studies are required to test this regimen.

**Conclusions**

PFMT and duloxetine are both recommended as a first-line treatment option for SUI. The efficacy of PFMT requires motivation and compliance, but there is poor long-term compliance and possibly a lack of training in the correct technique. Duloxetine has been shown to reduce incontinence episodes and improve QoL scores. Evidence suggests that the combination of PFMT and duloxetine might provide an additional benefit. The results of the study comparing combined duloxetine plus PFMT with no active treatment seem to support this hypothesis, but further research with long-term follow up is warranted. If compliance with PFMT can be improved by the addition of duloxetine, then this combination might improve the outcome of conservative measures for SUI.

**Conflict of interest**

R.M.F. has been a member of an Advisory Board for Eli Lilly/Boehringer Ingelheim for the drug duloxetine, has participated in research projects and spoken at pharmaceutically sponsored international meetings and has received funding for this work which has helped to fund non-commercial research in his unit.

**References**


