

Pelvic Floor Muscle Training With Or Without Tibial Nerve Stimulation and Lifestyle Changes Have Comparable Effects on The Overactive Bladder. A Randomized Clinical Trial

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Purpose: To compare effects of transcutaneous posterior tibial nerve stimulation (TPTNS) and pelvic floor muscle training (PFMT) in women with overactive bladder syndrome (OAB).

Material and Methods: We randomized 67 women ≥ 18 years with OAB to three parallel groups: group I ($n = 22$) received life-style recommendations (LSR) only; group II ($n = 24$) had LSR + PFMT and group III ($n = 21$) had LSR + PFMT + TPTNS. Urgency, evaluated by a 3-day voiding diary before treatment and six weeks later, was the main outcome measure. The King's College Health Questionnaire was also administered.

Results: Urgency was significantly reduced in all three groups from 5.1 ± 3.7 to 3.8 ± 3.2 episodes/day, $P = .016$ in group I, from 5.2 ± 3.6 to 3.2 ± 2.9 , $P = .006$ in group II and from 6.8 ± 3.1 to 4.4 ± 3.5 in group III, $P = .013$. There were no intergroup differences. The questionnaire results improved significantly only in group III as regards general health perception, role limitation, physical and social limitations without intergroup differences. Women improved their micturition frequency in two groups from 8.9 ± 3.2 to 7.5 ± 2.3 episodes/per day, $P = .025$ in group II, and from 8.8 ± 2.3 to 7.4 ± 2.0 , $P = .001$ in group III, but only in group II was a significant reduction of urinary incontinence seen from 3.8 ± 4.6 to 2.9 ± 4.8 episodes/day, $P = .045$.

Conclusion: All three treatments lead to effective short-term reduction of urgency in women with OAB, but long-term efficacy evaluation is required.

Keywords: multimodal treatment; overactive bladder; pelvic floor muscle training; posterior tibial nerve; transcutaneous electrical nerve stimulation.

INTRODUCTION

According to the International Continence Society (ICS) and International Urogynecological Association (IUGA), overactive bladder syndrome (OAB) is defined as urinary urgency, usually accompanied by frequency and nocturia, with or without urgency incontinence, in the absence of urinary tract infection or other obvious pathology⁽¹⁾. This is a chronic condition affecting millions of women worldwide and morbidity increases with age⁽²⁾. Though not life-threatening, it has a great impact on quality of life (QoL)^(3,4). While OAB pathogenesis is still not well understood, the main purpose of treatment is to reduce OAB symptoms and thus improve patient's QoL. In older age groups co-morbidities and medications affect both pharmaceutical and invasive treatment options. Therefore, there is a demand to develop more tolerable and effective treatments to manage overactive bladder states.

All guidelines recommend pelvic floor muscle training (PFMT) as a first-line treatment for patients with OAB or urge urinary incontinence⁽⁵⁻⁷⁾, but the evidence for effectiveness is limited. The rationale is that increased PFM strength would allow better urge control by interfering with urethral–detrusor reflexes, thus producing inhibition of pathological detrusor contractions. Another well tolerated, non-invasive new treatment option is transcutaneous posterior tibial nerve stimu-

lation (TPTNS)⁽⁸⁻¹⁴⁾. As the S2-S4 nerve roots (mainly S3) provide motor supply to the bladder and the posterior tibial nerve contains S3 fibres, the hypothesis is that retrograde impulses during TPTNS reach the sacral micturition centre and thus cause detrusor relaxation by inhibiting parasympathetic motor neurons. Evidence for the effectiveness of TPTNS has grown and may be similar or even better than antimuscarinics such oxybutynin^(8,9). As PFMT (reducing urge incontinence) and TPTNS (reducing urgency) act in different ways, their combination could lead to summation effects. Schreiner at al.⁽¹⁰⁾ evaluated PFMT and TPTNS in combination and their results supported this. Our objective was to evaluate PFMT and TPTNS combination efficacy for women with OAB and to compare it with the effects of PFMT alone.

MATERIAL AND METHODS

Study design

A randomized multi-arm parallel-group clinical trial with balanced randomization (1:1:1 for three groups) was conducted from April 2015 to June 2017 at the Department of Rehabilitation of Lithuanian University of Health Sciences in Kaunas, Lithuania. The study was approved by the Kaunas Regional Biomedical Research Ethics Committee (No BE-2-8) and all participants signed an informed consent. All new outpatients who

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Table 1. Pre-treatment demographic and clinical evaluation data among groups.

Variables	Control (N = 22)	PFMT (N = 20)	PFMT+TPTNS (N = 19)	P-value
Age, years	59.36.1 ± 10.47	63.95 ± 10.75	63.95 ± 9.87	.262 ^a
BMI, kg/m ²	30.54 ± 5.42	30.12 ± 5.66	28.43 ± 6.06	.470 ^a
Duration of the OAB symptoms, years	6.05 ± 5.41	4.95 ± 5.70	10.93 ± 13.75	.093 ^a
Presence of menopause	18 (82)	17 (85)	16 (84)	1.00 ^b
Menopause duration, years	10.58 ± 6.74	13.06 ± 8.99	12.44 ± 7.89	.614 ^a
Presence of abdomen or pelvis operations	16 (73)	14 (72)	17 (90)	.293 ^b
Dominant mode of delivery (vaginal or Caesarean section)	vaginal	vaginal	vaginal	.715 ^b
Presence of perineal lesion (rupture, episiotomy) during labour	19 (95)	16 (89)	16 (89)	.377 ^b
Newborn weight, kg	3.83 ± 0.42	3.41 ± 0.52	3.61 ± 0.35	.019 ^{*a}
PFM Power	1.95 ± 1.20	2.25 ± 0.72	1.89 ± 0.88	.462 ^a
PFM Endurance, s	7.43 ± 3.16	8.45 ± 2.50	6.79 ± 3.17	.217 ^a
PFM Repetition	8.57 ± 2.06	9.65 ± 0.88	9.58 ± 0.90	.030 ^{*a}
PFM Fast repetition	18.19 ± 12.03	16.85 ± 5.47	17.58 ± 7.18	.887 ^a

Abbreviations: PFMT, Pelvic Floor Muscle Training; BMI, Body Mass Index; OAB, Overactive Bladder; PFM, pelvic floor muscle; TPTNS, Transcutaneous Posterior Tibial Nerve Stimulation; Values are given as mean ± SD or number (percentage); a - P value based on ANOVA; b - P value based on Fisher's Exact Test; * - statistically significant difference among groups.

came during that time to the Rehabilitation Department were assessed for eligibility. The study group allocation was by a sequentially running computer-generated⁽¹⁶⁾ block randomization list (prepared by the statistician from Lithuanian University of Health Sciences) as blocks of three unique numbers/block, ranging from 1 to 3 unsorted. Women were evaluated for eligibility and assigned to the groups by the same person. On the basis of the reduction rate of urgency incontinence after the PFMT by 27% and after the PFMT+TPTNS by 76%(10) we conducted a test with a significance level of 0.05 and power of 0.80 and anticipated that groups of equal size were required. We concluded that at least 19 women were needed in each group.

Inclusion and exclusion criteria

Inclusion criteria were as follows: non-pregnant women ≥ 18 years with clinical complaints of OAB (urgency, urinary frequency, nocturia, and/or urgency incontinence) or mixed urinary incontinence with predominant urgency urinary incontinence type. Exclusion criteria were: positive urine analysis and culture, residual urine ≥ 100ml, measured before for all women by bladder scanning, pelvic organ prolapse higher than grade II by the POP-Q quantification system, inability to perform the Kegel exercises, presence of TPTNS contraindications (active implants (including cardiac pacemakers), malignancy, tissue bleeding or skin damage in the stimulation site).

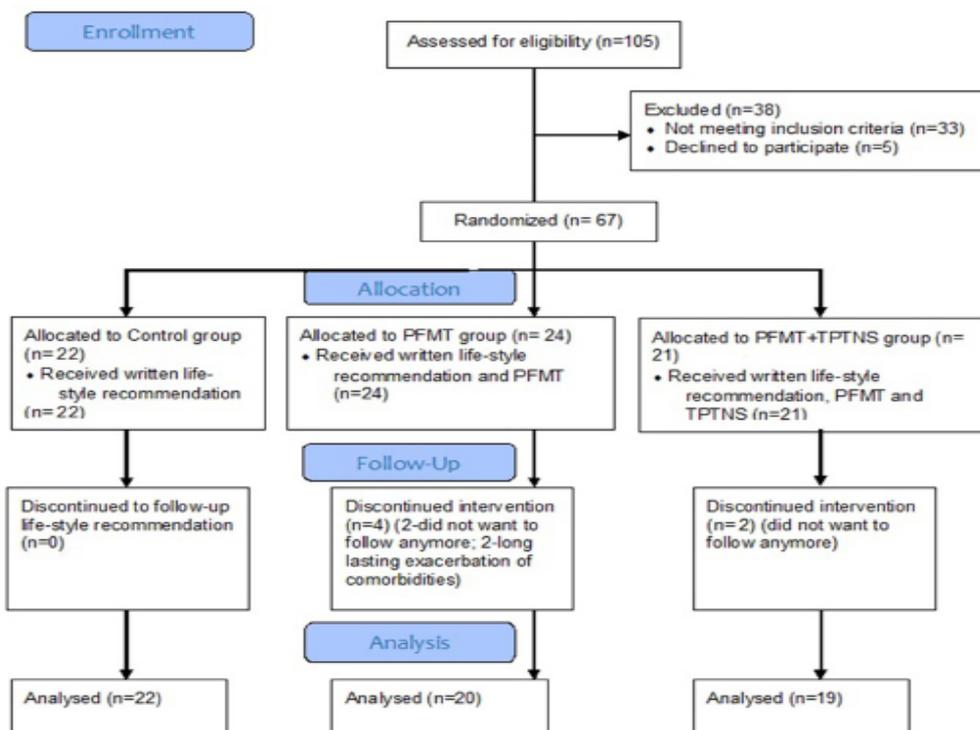
**Figure 1.** Patient flow chart of the clinical study.

Table 2. KHQ results within and among groups.

Domain (%):	Control (N=22)	PFMT (N = 20)	PFMT+TPTNS (N=19)	P ^a -value	d
General health perceptions					
Before	51.14 ± 14.39	50.00 ± 11.47	51.32 ± 19.50	.958	
After	53.41 ± 17.75	43.75 ± 13.75	46.05 ± 17.21	.143	.054
P ^a -value	.427	.056	.042*		
d	.099	.361	.203		
Incontinence impact					
Before	65.59 ± 30.82	68.33 ± 25.38	73.77 ± 23.75	.623	
After	69.77 ± 25.04	66.67 ± 26.56	63.18 ± 24.66	.711	.036
P ^a -value	.394	.716	.082		
d	.105	.045	.317		
Role limitations					
Before	54.52 ± 34.55	54.10 ± 24.75	63.16 ± 23.99	.536	
After	58.32 ± 22.91	45.82 ± 28.04	42.07 ± 23.85	.098	.082
Pa-value	.504	.231	.001*		
d	.092	.235	.626		
Physical limitations					
Before	61.35 ± 31.44	52.48 ± 35.55	64.95 ± 27.71	.453	
After	67.42 ± 24.38	47.43 ± 30.18	53.53 ± 29.23	.066	.065
P ^a -value	.293	.522	.019*		
d	.153	.111	.284		
Social limitations					
Before	35.55 ± 30.25	25.28 ± 23.37	36.81 ± 24.84	.327	
After	36.31 ± 28.71	20.29 ± 25.28	25.67 ± 26.61	.154	.049
P ^a -value	.893	.298	.016*		
d	.018	.145	.306		
Personal relationships					
Before	22.70 ± 35.17	43.37 ± 41.03	16.67 ± 29.64	.193	
After	26.70 ± 33.49	39.58 ± 45.37	22.92 ± 34.43	.859	.054
P ^a -value	.359	.593	.598		
d	.084	.062	.138		
Emotions					
Before	58.06 ± 31.11	52.78 ± 32.27	62.01 ± 30.67	.655	
After	56.52 ± 34.34	45.02 ± 27.40	49.09 ± 35.42	.513	.024
P ^a -value	.779	.172	.058		
d	.033	.183	.276		
Sleep/energy					
Before	49.26 ± 34.24	44.98 ± 28.06	55.28 ± 25.52.559		
After	50.03 ± 26.22	40.78 ± 22.56	49.09 ± 29.69	.471	.024
P ^a -value	.874	.361	.087		
d	.018	.117	.158		
Severity measures					
Before	50.95 ± 22.20	56.32 ± 16.63	56.14 ± 24.45	.652	
After	51.61 ± 27.13	49.67 ± 20.95	49.09 ± 29.48	.948	.030
P ^a -value	.842	.062	.120		
d	.019	.249	.184		

Abbreviations: KHQ, King's Health Questionnaire; PFMT, Pelvic Floor Muscle Training; TPTNS, Transcutaneous Posterior Tibial Nerve Stimulation

Values are given as mean ± SD; *P* value based on ANOVA; P^a - within groups; P^b - between groups; * - statistically significant difference.

Evaluations

In an initial interview age, duration of OAB symptoms, menopause status, parity with birthweight(s), mode of delivery, perineal birth trauma or episiotomy, abdominal or pelvic operations were recorded. The King's Health Questionnaire (KHQ), validated for the Lithuanian language, was used to evaluate QoL. It consists of nine domains: general health perceptions, incontinence impact, role limitations, physical limitations, social limitations, personal relationships, emotions, sleep/energy, severity measures. Each domain is evaluated from 0 to 100% (0% – the best QoL, 100% – the worst QoL). Clinical examination included body mass index (BMI) and functional assessment of the pelvic floor muscles (PFM) by the PERFECT scheme⁽¹⁵⁾. The latter was performed with the women in the supine position with her knees flexed and apart. PFM functions were evaluated by one-finger intravaginal palpation. The PFM contraction power (P) was graded according to the modified Oxford grading system (from 0 meaning no contraction to 5 meaning strong contraction). The PFM contractions endurance (E) (in seconds), repetition (R) and fast repetition (F) were evaluated as numerical variables. The three-day voiding diary provided the number of daytime urinary frequency, urgency, nocturia, and uri-

nary incontinence measured as the numerical variables (calculated as means of three days).

Interventions

The treatment was as follows:

Control group I:

Participants were provided with written common lifestyle changing recommendations (LSR) regarding weight loss, fluid intake, decreasing caffeine and alcohol intake as well as smoking cessation, limiting spicy food, sour, gassy products, artificial sweeteners, increasing fiber-rich food, physical activity and Kegel exercises (common, not individualized written instructions were provided to the women). Patients were encouraged to follow these recommendations for six weeks.

Group II: PFMT

Participants were provided with the same recommendations as in the control group. According to the PERFECT scheme evaluation records, they were instructed via digital palpation to perform an individualized PFMT program at home. For example, if the PERFECT scheme was 2/5/6/11 (P/E/R/F), the participant was instructed to hold submaximal to maximal PFM contractions for 6 seconds and repeat this seven times with a 4 second rest period after each contraction, and after

Table 3. Voiding diary results within and among groups.

Voiding diary variables:	Control (N=22)	PFMT (N=20)	PFMT+TPTNS (N=19)	P ^a -value	d
Fluid intake/day (ml)					
Before	1574.55 ± 643.85	1704.44 ± 579.86	1540.86 ± 461.03	.637	
After	1347.91 ± 468.98	1485.37 ± 452.47	1431.24 ± 465.11	.626	.015
P ^a -value	.017	.054	.301		
d	.285	.299	.169		
Urination amount/day (ml)					
Before	1988.82 ± 1041.85	1887.03 ± 577.01	1728.51 ± 427.95	.540	
After	1845.62 ± 1107.11	1597.98 ± 645.32	1553.57 ± 547.73	.471	.016
P ^a -value	.501	.036*	.137		
d	.094	.334	.255		
Urinary frequency/day					
Before	9.83 ± 6.92	8.86 ± 3.24	8.81 ± 2.31	.733	
After	8.58 ± 4.58	7.52 ± 2.30	7.36 ± 2.04	.427	.017
P ^a -value	.109	.025*	.001*		
d	.151	.338	.471		
Incontinence episodes/day					
Before	2.06 ± 2.46	3.84 ± 4.62	1.78 ± 2.16	.055	
After	2.27 ± 3.07	2.89 ± 4.83	1.58 ± 2.14	.516	.061
P ^a -value	.616	.045*	.608		
d	.053	.142	.066		
Urgency epizodes/day					
Before	5.14 ± 3.73	5.24 ± 3.64	6.76 ± 3.12	.278	
After	3.79 ± 3.22	3.17 ± 2.87	4.43 ± 3.49	.485	.033
P ^a -value	.016	.006*	.013*		
d	.274	.447	.523		
Nocturia epizodes/day					
Before	2.17 ± 1.96	1.55 ± 1.80	1.93 ± 1.00	.480	
After	1.82 ± 1.35	1.60 ± 1.54	1.56 ± 1.04	.787	.019
P ^a -value	.226	.819	.170		
d	.147	.021	.270		

Abbreviations: PFMT, Pelvic Floor Muscle Training; TPTNS, Transcutaneous Posterior Tibial Nerve Stimulation

Values are given as mean ± SD; *P* value based on ANOVA; *P^a* - within groups, *P^b* - between groups. * - statistically significant difference.

few minutes to perform 12 fast contractions. All women were instructed to practice this regimen five times daily (in the lying, standing, and sitting position alternately with the legs apart). The women were also instructed to contract their PFM during an urge to void. After three weeks participants re-evaluation by the PERFECT scheme was done and a new exercise program established with reference to this new records. Compliance over the six weeks time was monitored.

Group III: PFMT + TPTNS

These women were provided with the same recommendations as patients in the control group and in the PFMT group. In addition, they had 18 TPTNS procedures at the Department of Rehabilitation, i.e. 30 min, three times/week over six weeks. TPTNS was performed by a rehabilitation nurse who used a programmed device for urge incontinence ("BTL-5000", program No E-5781, www.btl.net.com), programmed for 10 Hz frequency, 300 µs pulse width with a work/rest regimen to cover work – 10 s, rest – 15 s, ramp up – 3 s, ramp down – 2 s. Intensity was adjusted to the highest level (10 – 50 mA), but lower than possibly causing pain or discomfort to the patient. Two surface electrodes (5 x 5 cm) were placed along the posterior tibial nerve path on each leg: one surface electrode was placed behind the medial malleolus (negative) and another was placed 10 cm above the first one (positive).

Outcome assessment

All patients completed the KHQ and the 3-day voiding diary before treatment and after six weeks by themselves. Primary outcomes of efficacy were urgency episodes/day (from the voiding diary) as the most bothersome and most significant symptom of OAB. Secondary outcomes: QoL changes measured by KHQ questionnaire, other voiding diary variables (daytime urinary frequency, nocturia and urinary incontinence episodes/day), pain in lumbosacral, pelvic or perineal

regions during PFMT and skin irritation, allergic reactions, pain under the electrodes or intolerance of electrical currents during TPTNS.

Statistical analysis

Statistical analysis was performed using the SPSS software package. The reliability of the KHQ was investigated by Cronbach's coefficient alpha (α) using data provided by the total baseline sample and after treatment. Descriptive analysis was carried out using frequencies, means, and standard deviations. For comparison between groups, we used chi-Squared or Fisher's exact test if an expected chi-value was < 5 for categorical variables. Student's *t*-test used for independent samples to verify differences between means. To compare the means before and after intervention in each group, we used the Student's *t*-test for paired samples. The ANOVA was used for repeated measures and Tukey's test for multiple comparisons. *P* < .05 was considered significant.

RESULTS

A total of 67 women were randomized and 61 completed the study. Six patients failed to comply with the study protocol and were excluded from trial: four from the PFMT group (two refused because of time needed for treatment, two had long-lasting exacerbation of co-morbidities) and two women from the PFMT + TPTNS group refused participation because of time needed for treatment. Withdrawal rate – 9%. A study overview for the per-protocol analysis is shown in **Figure 1**.

Prior the treatment, there were no significant differences between groups for most characteristics and clinical evaluation variables, except birthweight of the women's children (I vs II group, 3.83 ± 0.42 kg vs 3.41 ± 0.52 kg, respectively, *P* = .014) and PFM Repetition from the PERFECT scheme (*P* = .030) (**Table 1**). There were no significant differences among groups in all KHQ

domains (**Table 2**) or 3-day voiding diary variables (**Table 3**). Both PFMT and PFMT+TPTNS groups accomplished their individualized PFMT home program in 82% and 83% respectively, $P = .875$.

KHQ questionnaire

KHQ internal consistency was high with the Cronbach α -values ranging from 0.861 of baseline data to 0.886 after six weeks treatment. The questionnaire results improved significantly only within group III as regards general health perception, role limitation, physical and social limitations without intergroup differences (**Table 2**).

Voiding diary

Women in all three groups had significantly reduced urgency after treatment without a difference among them (**Table 3**). Urinary frequency had decreased significantly after treatment within groups II and III, but only group II showed significantly reduced urinary incontinence episodes/day within group (**Table 3**). Women significantly reduced fluid intake after treatment within control group: 14% = 227ml/day, $P = .017$. There were no significant differences in all voiding diary variables after treatments as compared between the three study groups.

No side effects were noticed with the PFMT or TPTNS therapies.

DISCUSSION

Women in all groups improved significantly according to the voiding diary assessment. However, only in the control (LSR) group did women significantly decrease the fluid intake by the end of the treatment period. Hashim et al. evaluated fluid management for patients with OAB and reported that a 25% reduction in fluid intake was associated with improved daily urgency, frequency and nocturia episodes⁽¹⁷⁾. The control women reduced just one OAB symptom, urgency, by 25% / day. The LSR+PFMT and LSR+PFMT+TPTNS groups decreased the fluid intake by 13% (219 ml/day) and 7% (110 ml/day), respectively, compared to 14% (227 ml/day) among the controls, but still reduced their urgency episodes by 40% and 34%, respectively. While urgency can be reduced by life-style regulation, greater reductions are achieved by combining this with PFMT. The difference between the groups were, however, small and not of clinical significance. Urgency reduction by combination of PFMT and TPTNS for women with OAB has, however, not been evaluated before.

An important aspect in OAB management is the patient's appreciation of their quality of life. There are several validated and reliable questionnaires to measure urinary symptom impact on QoL. According to the European Association of Urology guidelines on urinary incontinence⁽⁶⁾ KHQ is valid, reliable and responsive as a means to measure change over time. Only the women treated by the combination of LSR, PFMT and TPTNS most effectively improved their QoL, i.e. in four of nine KHQ domains. In contrast, within groups I and II, LSR alone or when added to PFMT had no significant impact on KHQ domains after six weeks of treatment. Schreiner's at al.⁽¹⁰⁾ study revealed significantly greater improvement in the similar multimodal (PFMT + TPTNS) group than in the PFMT group in several KHQ fields, including impact of urinary incontinence, limitations of daily activities, physical limitations, emotions,

sleep/provision, and measures of severity. The multimodal group was in their study significantly superior to the PFMT group in reducing urgency incontinence episodes and nocturia and reduction was significantly greater than the PFMT group, but changes of urgency were not measured. We could not reveal differences in voiding diary variables. Both our and Schreiner's studies had relatively small study groups of older women by mean age with the long lasting OAB symptoms, but Schreiner's study had no control group, treatment duration was twice as long, TPTNS was used in continuous electrical current mode once a week and PFMT regimen was less intensive and not individualized. Supposedly, Schreiner at al. study showed greater improvements than ours due to longer treatment duration or continuous electrical current mode of TPTNS procedure. There is no study that compares interrupted stimulation with continuous mode during TPTNS procedure.

In another study⁽¹⁸⁾ three different treatments for women with OAB with a similar PFMT arm were compared (n = 34). Women were instructed to perform an individualized PFMT according to the PERFECT scheme, but at least three times daily and for six weeks longer than in our study. All KHQ domains were improved, but voiding diaries were incomplete contrasting with our study where they were fully completed. Scaldazza et al. investigated similar multimodal (PFMT and non-invasive electrical stimulation) treatment, showing significantly improved women's QoL according to the OAB-q SF questionnaire, but not a significant reduction of OAB symptoms according to 3-day micturition diary, using intravaginal electrical stimulation with different parameters instead of posterior tibial nerve stimulation⁽¹⁹⁾. Though intravaginal stimulation has been considered effective for reduction of OAB symptoms and improvement of quality of life^(18,20-22), TPTNS may be more acceptable than intravaginal treatment in some cultures, such as ours, and it is also a cheaper approach. TPTNS has not been compared with intravaginal stimulation for OAB treatment.

A novel treatment approach used in our study was the bilateral TPTNS. The decision to stimulate both legs at the same time was made because it is unclear which leg should be stimulated for better results. TPTNS has an inhibitory effect on involuntary detrusor contractions through inhibition of somatic sacral and lumbar nerve fiber depolarization without affecting the micturition reflex⁽¹³⁾. Possibly, stimulation of both tibial nerves could lead to better inhibitory effects as highlighted recently⁽²³⁾. Adding bilateral TPTNS to PFMT we most effectively improved participants' quality of life, but results were not superior to the PFMT or LSR alone. PFMT can also modulate overactive bladder syndrome. Increased urethral pressure can inhibit the sacral preganglionic innervation to the bladder through the guarding reflex⁽²⁴⁾. Moreover, PFM contraction can stimulate the sympathetic nerve fibers of the internal urethral sphincter thereby causing a decrease in detrusor muscle pressure⁽²⁵⁾. It has been shown that PFMT improves urinary incontinence more often than no treatment⁽²⁶⁾ and greater efficacy could be achieved by increasing intensity⁽⁶⁾, but there is limited evidence about efficacy to patients with OAB⁽²⁷⁾.

A limitation of our study was the short treatment duration with interrupted electrical current mode during the TPTNS procedure as well as unknown long-term

effects of all three treatments. The study groups were also relatively small, but this also applies to the other studies referred to above^(10,14,18-19). Despite random allocation we were not able to conceal group assignment during the evaluation procedures. However, the women answered all questionnaires by themselves and the evaluator could not influence this.

CONCLUSIONS

TPTNS and PFMT require an investment of time and effort by the patient and clinician to achieve maximum benefits, but the results show that the benefits are marginal in the short term and they do not add much to simpler advice forms while conferring similar improvements to OAB symptom, urgency. More sustained study for longer periods still appear indicated in order to fully assess two treatment modes which have the benefit of lacking invasiveness and may be of help to some of the patients who suffer from an overactive bladder.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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