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Effects of nonsurgical, minimally or noninvasive therapies for urinary incontinence due to neurogenic bladder: a systematic review and meta-analysis

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Abstract

Objective: To determine the effects of nonsurgical, minimally or noninvasive therapies on urge urinary incontinence (UUI) symptoms and quality of life (QoL) in individuals with neurogenic bladder (NGB).

Data Sources: Cochrane library, EMBASE, MEDLINE, PEDro, Scopus, and Web of Science databases were searched from inception to September 2021.

Review Methods: Randomized controlled trials that compared therapies such as intravaginal electrical stimulation (IVES), transcutaneous electrical nerve stimulation (TENS), neuromuscular electrical stimulation (NMES), transcutaneous tibial nerve stimulation (TTNS), pelvic floor muscle training (PFMT), and behavioural therapy (BT) to control were included. Study screening, data extraction, and study quality assessments were performed by two independent authors.

Results: Fourteen trials with 804 participants were included in the study after screening of 4281 potentially relevant articles. Meta-analyses revealed a significant effect of electrical stimulation on UUI due to multiple sclerosis (standardized mean difference (SMD): −0.614; 95% confidence interval (CI): −1.023, −0.206; $p = 0.003$) and stroke (SMD: −2.639; 95% CI: −3.804, −1.474; $p = 0.000$). The pooled analyses of TTNS (weighted mean difference (WMD): −12.406; 95% CI: −16.015, −8.797; $p = 0.000$) and BT (WMD: −9.117; 95% CI: −14.746, −3.487; $p = 0.002$) revealed significant effects of these interventions on QoL in people with Parkinson's disease. However, meta-analyses revealed nonsignificant effects for PFMT (WMD: −0.751; 95% CI: −2.426, 0.924; $p = 0.380$) and BT (WMD: −0.597; 95% CI: −1.278, 0.083; $p = 0.085$) on UUI due to Parkinson's disease.

Conclusions: Our meta-analyses found electrical stimulation to be beneficial for improving the symptoms of UUI among people with multiple sclerosis and those with stroke. Our review also revealed that TTNS and BT might improve QoL for people with NGB due to Parkinson's disease, although the effects of PFMT and BT on UUI warrant further investigation.

Keywords: neurogenic bladder, systematic review and meta-analysis, therapies, urinary incontinence

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Introduction

Lower urinary tract dysfunction caused by nervous system lesions or trauma is termed neurogenic bladder (NGB)[1] and can be life-threatening if not managed adequately.[2] The epidemiology of NGB varies, including multiple sclerosis (40–90%), Parkinson's disease (37–72%), spinal cord injury (70–84%), stroke (57–83%) and spina

bifida (40–60.9%).[3,4] NGB represents a substantial issue in clinical practice in the United States, with a prevalence that increased from 26.1% in 2016 to 31.1% in 2018.[5] Neurogenic lower urinary tract dysfunction distorts detrusor pressure and bladder emptying regulation, leading to urge urinary incontinence (UUI).[1,6] UUI symptoms in people with NGB include increased urinary frequency, urgency and leakage, which is immediately preceded by a sudden urge to void.[7] The stress and discomfort associated with UUI due to NGB can have major negative impacts on quality of life (QoL), resulting in social isolation, depression and embarrassment.[8] Patients with UUI tend to experience low self-esteem, report effects on their social, sexual and work activities.[9] In addition, UUI causes psychological stress and can restrict participation in social activities.[10]

Pharmacological management options for NGB include oral agents such as anticholinergic drugs (antimuscarinics), beta-adrenergic and selective serotonin re-uptake inhibitor; intravesicular injection; transdermal agents.[11] However, the persistence rate for response to medication after 1 year is only 12–39%,[12] and people with NGB often discontinue medications due to adverse effects or a lack of improvement in symptoms.[12,13] Surgical interventions for NGB can be performed in patients who are unresponsive to conservative or less invasive treatments; however, the surgical management of NGB is expensive and associated with post-operative complications[14] and some requiring tension-free vaginal tape and translabial ultrasound assessing technical errors after mid-urethral transobturator tape.[15]

Nonsurgical, minimally or noninvasive therapies for NGB include transcranial magnetic stimulation,[16] transcranial direct current stimulation,[17] transcutaneous electrical nerve stimulation (TENS),[17] neuromuscular electrical stimulation (NMES),[18] biofeedback,[19] transcutaneous tibial nerve stimulation (TTNS),[20] intravaginal electrical stimulation (IVES),[21] pelvic floor muscle training (PFMT),[19] cognitive behavioural training and vaginal cones.[22] The efficacies of some of these interventions have been evaluated in previous systematic reviews.[2,23–27] However, previous reviews did not include meta-analyses,[23–26] evaluate the efficacy of only a single intervention,[23,25,26] result in inconclusive outcomes due to the limited number of included studies[26] or were not conducted within the last 5 years.[23,25] The current review is the first to include all nonsurgical, minimally or noninvasive therapies for the management of UUI due to NGB,[2,23–27] with the aim of evaluating treatment effects for symptom management and QoL.

Methods

Search strategy and study screening

The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines were incorporated during the development and reporting of this review.[28] The review was registered with the International Prospective Register of Systematic Reviews (PROSPERO; ID: CRD42021236522) prior to the commencement of database searches. Six electronic databases, including the Cochrane library, EMBASE, MEDLINE, Physiotherapy Evidence Database (PEDro), Scopus, and Web of Science, were searched from database inception to 30 September 2021. Search terms for the review were formulated into three themes, including NGB, treatments and study design. The defined search terms within each of the individual themes were combined using the Boolean operator 'OR', and the three themes were combined using the Boolean operator 'AND'. A detailed description of the search terms developed for databases is presented in the supplementary file. The selection of studies for this review was based on the PICOS (Patient problem, Intervention, Comparison, Outcome measure, and Study design) framework.[29] The articles identified through electronic database searches were exported to the EndNote X9 citation manager (Clarivate Analytics, Philadelphia, Pennsylvania, USA) for screening. Ethical approval is not required for this review because data from previously published studies in which informed consent was obtained were retrieved and analysed.[30]

Study selection

Studies were included in this systematic review if they (1) were randomized controlled trials (RCTs), pilot RCTs, randomized cluster trials, randomized crossover trials, or unpublished theses; (2) included adults (of both sexes) with UUI due to NGB, due to spinal cord injury, stroke, Parkinson's disease, or multiple sclerosis; (3) compared therapies, such as IVES, TENS, NMES, TTNS, PFMT, behavioural therapy

(BT), against controls consisting of no treatment, sham, or PFMT and (4) trials that utilized the Overactive Bladder Questionnaire-V8 (OAB-V8), the Overactive Bladder Symptom Score Questionnaire, or a voiding diary to evaluate the symptoms of UUI, or trials that utilized the Qualiveen questionnaire, Incontinence Impact Questionnaire-7 (IIQ-7), or International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) to measure QoL. Studies were excluded if they (1) were published as non-English studies, (2) were quasi-experimental trials/cross-over studies/wait-list studies, (3) involved medical or surgical interventions or (4) were conference proceedings.

Data extraction

Electronic searches, title, and abstract screening were performed by one review author (M.U.A.). The full-text screening was performed by two independent review authors (M.U.A. and U.M.B.). Discrepancies were resolved by discussion between the two review authors until consensus was reached. For unresolved discrepancies, a third review author (P.K.) was consulted. Manual searching of the reference lists for included studies and relevant systematic reviews were also conducted to identify any additional potentially relevant articles. Data extraction for each included study was performed by two independent review authors (M.U.A. and U.M.B.). The following data were extracted from each included study: first author, year of publication, country of study, participant characteristics (mean age and standard deviation (SD)), the sample size of each group, intervention, control, outcome measure(s), and pre- and post-treatment results.

Quality assessment

For each included study, the methodological quality and quality of evidence were evaluated using the PEDro scale[31,32] and the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool,[33] respectively. The PEDro scale has been reported as a reliable and valid tool for evaluating methodological quality.[31] The PEDro scale is an 11-item checklist: item 1 assesses external validity, items 2–9 assess internal validity, and items 10 and 11 assess interpretability.[34] Each item on the PEDro scale is scored as 'yes' or 'no', resulting in a maximum score of 10, with higher scores indicating higher study quality. Studies scoring $\geqslant 7$ are considered high quality, scores of 5 and 6 are considered moderate quality, and scores of 0–4 are low-quality.[31] One review author (M.U.A.) evaluated the methodological quality of the included studies, and the scores were compared against existing scores reported on the PEDro website.[35] Disagreements in scores between the author and the PEDro website score were resolved by discussion with a second review author (U.M.B.).

The quality of evidence was evaluated using GRADEpro software.[36] According to the GRADE system, the quality of a body of evidence can be categorized as 'very low', 'low', 'moderate', or 'high'.[37] The overall quality of evidence for an outcome measure was based on the lowest quality score for the assessed outcome.[37] The following factors were considered when rating the quality of evidence:

Study limitations. Evidence was rated according to the presence of methodological flaws, such as the absence of concealed allocation, inadequate follow-ups, and the inadequate reporting of outcome measures.[38] Given the nature of the intervention, studies were not downgraded for the lack of participant blinding; however, studies were downgraded by one level for the lack of either therapist or assessor blinding and by two levels for the lack of both therapist and assessor blinding.[38]

Indirectness of evidence. Studies were rated down if a substantial difference was identified between the intervention and control populations across the studies and when surrogate outcome measures were used which may reduce the quality of evidence.[39]

Imprecision. Studies were downgraded in quality of evidence for imprecision if the confidence interval around the estimate of treatment effect is not sufficiently narrow in the presence of small total sample size.[40]

Inconsistency of results across studies. Studies were downgraded for minimal or no overlap or evidence of statistical heterogeneity, as indicated by a large Chi-square value.[41]

Publication bias. If studies were industry-sponsored, likely to be industry-sponsored, or conflict of interest was reported, the quality of evidence was

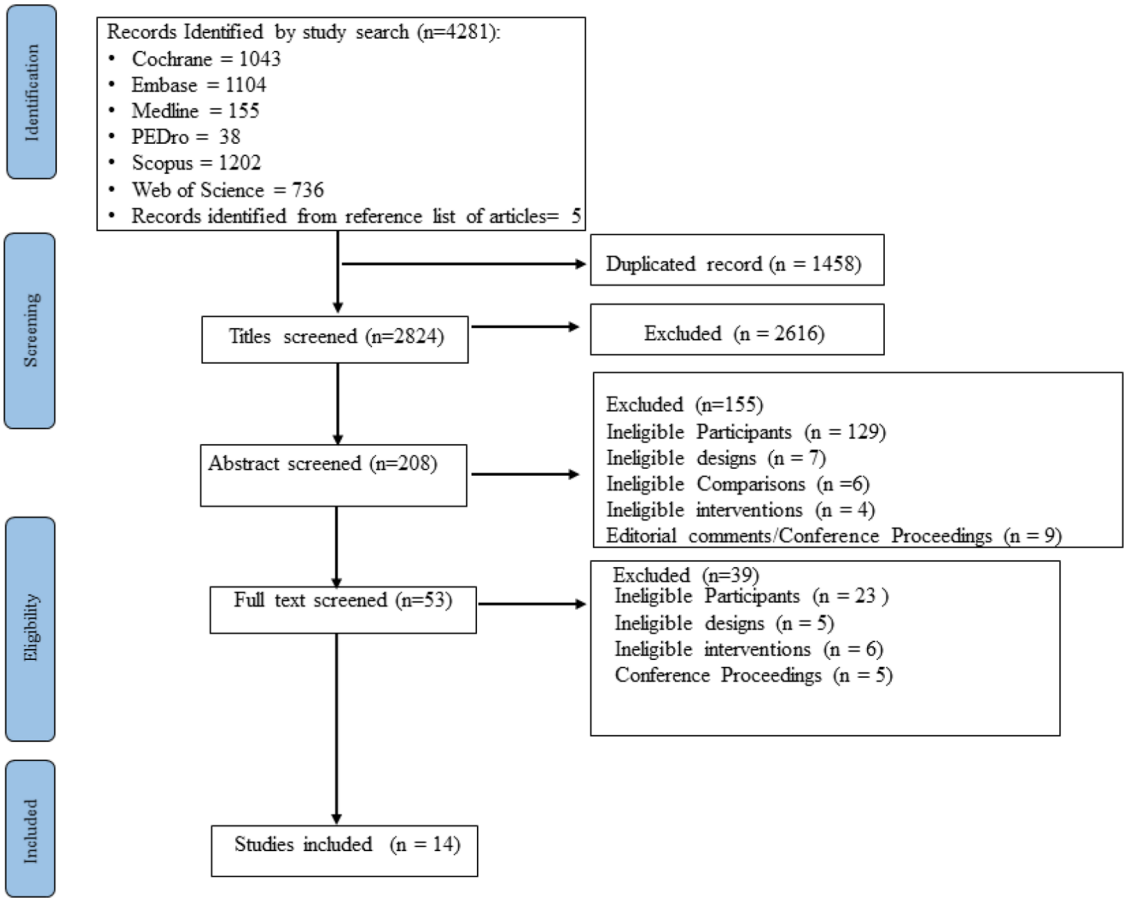

Figure 1. Flowchart of screened studies.

downgraded.[42] A funnel plot was planned if more than 10 studies were included in a meta-analysis.

Data analysis

The meta-analysis of the included studies was conducted using the Comprehensive Meta-Analysis software (version 3). Trials that used similar interventions and outcome measures were pooled together. Weighted mean differences (WMDs) and standardized mean differences (SMDs) and 95% confidence intervals (CIs) were used to assess the intervention effects of continuous outcomes. Where studies used different outcome measures to assess the same outcome, SMD was computed using Hedges' *g*. Statistical heterogeneity was evaluated using the chi-square test ($I^2 > 50\%$ was considered substantial heterogeneity). When minimal heterogeneity was identified ($I^2 < 50\%$), a fixed-effects model was used, whereas a random-effects model was used when maximum heterogeneity was identified ($I^2 > 50\%$).[43,44] Asymmetry could not be evaluated by funnel plot analyses because fewer than 10 studies were included in the pooled meta-analyses.[29]

Results

Study selection

Figure 1 presents a flowchart of the screening process used to select studies, with the reasons for exclusion at each stage. The electronic database searches resulted in 4281 potentially relevant articles. Following import into the citation manager, 1458 duplicate records were identified and removed. The review of the study titles and abstracts resulted in the exclusion of 2616 and 155 articles, respectively. The full-text screening of the remaining 53 studies led to the exclusion of 39 articles, and 9 studies were determined to meet

the inclusion criteria of the study. A manual search of the reference lists for the included studies (forward search) and relevant systematic reviews revealed an additional 5 studies, resulting in 14 total studies included in the review. Interventions identified in the included studies include IVES,[45,46] TENS,[47,48] NMES,[18,49] TTNS,[20,50] PFMT,[51–53] and BT.[54,55] Studies evaluating the effects of other therapies, such as repetitive transcranial magnetic stimulation[16]and functional magnetic stimulation,[56–60] were also identified during the database searches; however, these interventions[16,56,61,62] could not be included in the review because they were evaluated in quasi-experimental trials lacking a control group.

Study characteristics

The characteristics of the included studies are presented in Table 1. The 14 included studies included a total of 804 participants. The sample sizes in the included studies ranged from 13 to 82. The ages of the participants ranged from 18 to 90 years. The included studies were published between 2004 and 2021, including 11 of 14 studies that were published within the last 7 years (2014–2021). Five studies were conducted in Brazil,[20,45,46,50,63] three in Denmark,[51–53] three in China,[18,47,48] two in the United Kingdom,[49,54] and one study from the United States.[55] Twelve studies evaluated UUI,[18,45–49,51–55,63] and four studies evaluated QoL.[20,50,54,55]

Methodological quality

The PEDro scores for the included studies are shown in Table 2. The mean PEDro score of the included studies was 6 out of 10, with a range of 4–9. Of the 14 included studies, 8 studies were of high methodological quality, 5 were of moderate methodological quality, and one study was of low methodological quality. Among the 14 included studies, 7 studies did not report allocation concealment, 10 lacked intention-to-treat analysis, 10 lacked assessor blinding, and 3 studies lost >15% of participants to follow-up. All 14 studies lacked therapist blinding.

Quality of evidence

Table 3 presents a summary of the findings generated by the GRADE profiler software. The GRADE quality of evidence for the 14 trials included in the five meta-analyses ranged from 'low' to 'moderate'. The overall GRADE quality of evidence for the included trials ranged from low to moderate for UUI and moderate for QoL.

Effects of interventions on UUI

Electrical stimulation versus *PFMT on UUI due to multiple sclerosis.* Four studies[45,46,49,63] compared the effects of electrical stimulation (IVES and NMES) with those of PFMT on UUI among people with multiple sclerosis. The number of treatment sessions in the four included trials ranged from 18 to 52. The stimulation parameters used in the four trials included a frequency from 2 to 40 Hz, an intensity from 450 μs to 1 ms, and a treatment duration of up 20 to 30 min. Among the four trials, three trials[45,46,49] measured UUI using OAB-V8, and one trial[63] measured UUI using a voiding diary.

The methodological quality of the four trials[45,46,49,63] was moderate to high, and the quality of evidence quality was moderate. A pooled analysis of the four trials (n = 74) revealed a significant reduction in UUI symptoms (SMD: −0.614; 95% CI: −1.023 to −0.206; p = 0.003; Figure 2(a)) in the intervention group compared with the control group.

PFMT versus *no treatment on UUI due to stroke.* Three studies[51–53] examined the effects of PFMT on UUI symptoms compared with a no-treatment control among people with stroke. The PFMT in the three trials consisted of 6 s of maximum contractions, followed by 6 s of rest, for a total of 30 s of maximum contractions and 30 s of rest. All exercises were repeated gradually 6–10 times while lying, standing or seated, 1–2 times each day, 7 days a week. All three trials[51–53] measured UUI with a voiding diary.

The methodological quality of the three trials[51–53] was evaluated as moderate- to high-quality, and the quality of evidence was low. The pooled analysis of the three trials (n = 80) revealed an insignificant reduction in daytime voiding frequency (WMD: −0.751; 95% CI: −2.426 to 0.924; p = 0.380; Figure 2(b)) for the intervention group compared with the control group.

Electrical stimulation versus *no treatment on UUI due to stroke.* Three studies[18,47,48] examined the effects of electrical stimulation (NMES[18] and TENS)[47,48] on UUI compared with a no-treatment

Table 1. Characteristics of included studies ($n = 14$).

First author, year, country of study, PEDro score	Participant characteristics (mean age of participants (SD); sample size of each group)	Intervention	Control	Outcome measure(s)	Pre-treatment results	Post-treatment results
Araujo *et al.*[20] Brazil **8/10**	**Exp**: 64.2 + 2.5 **Con**: 68.2 + 2.3 **Exp**: $n = 15$ **Con**: $n = 15$	**TTNS** **Frequency**: 10 Hz Pulse Duration: 200 μs **Intensity**: 1mA at 1KΩ **Duration**: 20 min for 12 weeks	**TTNS** **Frequency**: <0.5 Hz **Pulse Duration**: 200 μs **Intensity**: not sufficient to trigger rhythmic toe flexion **Duration**: 20 min for 12 weeks	OAB-V8	***UUI symptoms*** **Overactive bladder-V8** Exp: 27.8 ± 8.9 Con: 29.4 ± 8.4	Exp: 15.0 ± 6.9 Con: 25.9 ± 8.1 $p = 0.008$
Ferreira *et al.*[63] Brazil **5/10**	**Exp**: 43.25 ± 10.68 **Con:** 49.8 ± 16.5 **Exp:** $n = 12$ **Con**: $n = 12$	**NMES** **Frequency**: 2 Hz **Pulse Duration**: 1 ms **Intensity**: tolerable for patient. **Duration**: 48 sessions twice weekly for 6 months **PFMT** 3 sets of 10 reps daily for 6 months	**PFMT** 3 sets of 10 reps per day for 6 months	OAB-V8	***UUI symptoms*** **Overactive bladder-V8** **Exp**: 1.69 (0.59) **Con**: 1.58 (0.71)	**Exp:** 0.62 (0.62) **Con:** 0.88 (0.62)
Ferreira *et al.*[45] Brazil **5/10**	Exp: 38.6 ± 13.5 Con: 49.8 ± 16.5 Exp: $n = 15$ Con: $n = 15$	**PFMT** During stimulation, participants perform 20 fast and slow contractions twice weekly for 6 months **IVES** **Frequency**: 2 Hz **Pulse Duration**: 1 ms **Intensity**: tolerable for patient. **Duration**: 30 min 48 sessions twice weekly for 6 months	**PFMT** 3 sets of 8–10 close-to-maximal contractions and 10 s sustenance daily for 6 months	OAB-V8	***UUI symptoms*** **Overactive bladder-V8** **Exp**: 1.1 ± 1.1 **Con**: 0.7 ± 0.7	**Exp:** 0.3 ± 0.3 **Con:** 0.4 ± 0.4 $p = 0.002$
Guo *et al.*[47] China **4/10**	**Exp**: 68.1 ± 7.1 **Con**: 65.1 ± 9.8 Exp: $n = 32$ Con: $n = 29$	**PFMT + TENS** 30 min daily/60 days Pulse duration: 70 μs Frequency: 75 Hz Current: 16 mA (1 kΩ)	**PFMT** Basic therapy	OABSS	***UUI symptoms*** **OABSS** Exp: 5 ± 0.94 Con: 5 ± 0.69	Exp: 2.64 ± 0.98 Con: 4.09 ± 0.71
Guo and Kang[18] China **9/10**	**Exp**: 64.3 (11.8) **Con**: 62.5 (12.2) Exp: $n = 41$ Con: $n = 41$	**NMES** **Frequency**: 50 Hz **Pulse Duration**: 250 μs **Treatment duration**: 30 min (10 second on and 30 second off) Graded intensity based on patient's tolerance. Once daily 5 sessions weekly for 10 weeks	**Sham** NMES without active probe	OABSS	***UUI symptoms*** **OABSS**: Exp: 4.02 ± 0.76 Con: 4.18 ± 0.65 $p > 0.05$	Exp: 1.61 ± 0.32 Con: 3.86 ± 0.74 $p < 0.05$
Liu *et al.*[48] China **7/10**	Exp I: 66.30 (10.84) Exp II: 63.75 (8.92) Con: 67.91 (7.39) Exp I: $n = 27$ Exp II: $n = 27$ Con: $n = 27$	**TENS** **Frequency**: 20 Hz **Pulse Duration**: 150 μs **Treatment duration**: 30 min once daily for 90 days **TENS** **Frequency**: 75 Hz **Pulse Duration**: 150 μs **Treatment duration**: 30 min once daily for 90 days	**No-treatment** Only assessment of OABSS, BI, Urodynamics and Voiding diary on the first day and the 90th day.	Voiding diary	***UUI symptoms*** **Voiding diary: incontinence episodes in 24 h** Exp I: 10.07 (3.98) Exp II: 11.84 (3.05) Con: 10.63 (1.82)	Exp I: 2.10 (0.78) Exp II: 4.69 (1.05) Con: 9.54 (3.51)

(Continued)

Table 1. (Continued)

First author, year, country of study, PEDro score	Participant characteristics (mean age of participants (SD); sample size of each group)	Intervention	Control	Outcome measure(s)	Pre-treatment results	Post-treatment results
Lúcio *et al.*[46] Brazil **5/10**	Exp I: 42 (27–54) Exp II: 45 (22–52) Con: 43.5 (25–51) Exp I: $n = 10$ Exp II: $n = 10$ Con: $n = 10$	**NMS + EMG Biofeedback + PFMT** **Frequency**: 10 Hz **Pulse Duration**: 200 µs **Treatment duration**: 30 min **TTNS + EMG Biofeedback + PFMT** **Frequency**: 10 Hz **Pulse Duration**: 200 µs **Treatment duration**: 30 min	**Sham NMS + PFMT** **Frequency**: 2 Hz **Pulse Duration**: 50 ms **Treatment duration**: 2 s with 60 s rest 30 min once daily for 90 days 30 slow maximal effort followed by 3 min of fast maximal effort	OAB-V8	***UUI symptoms*** **Overactive bladder-V8** Exp I: 5.0 (0–8.3) Exp II: 4.0 (1.7–5.7) Con: 3 (1.7–6.3)	Exp I: 0.2 (0–2.3) Exp II: 0.7 (0–4.3) Con: 0.5 (0–3)
McClurg *et al.*[49] UK **9/10**	Exp: 48.3 (11.5) Con: 52.0 (8.8) Exp: $n = 37$ Con: $n = 37$	**PFMT + Biofeedback + Active NMES** **First Parameter Frequency**: 40 Hz **Pulse Duration**: 250 µs **Treatment duration**: 5 s of stimulation and 10 s of no stimulation with a ramp of 1 s at clinic and home for 30 min **Second Parameter Frequency**: 10 Hz **Pulse Duration**: 450 µs **Treatment duration**: 10 s of stimulation and 3 s of no stimulation with a ramp of 3 s at clinic and home for 30 min	**PFMT + Biofeedback + Placebo NMES** **Frequency**: 2 Hz **Pulse Duration**: 50 µs **Treatment duration**: 2 s of stimulation and 60 s of no stimulation with a ramp of 8 s at clinic and clinic for 30 min	Voiding diary	***UUI symptoms*** **Voiding diary: Incontinence episodes per in 24 h.** Exp: 2.1 ± 4.1 Con: 2.1 ± 4.0	Exp: 0.3 ± 1 Con: 1.1 ± 2.8 $p < 0.001$
McDonald *et al.*[54] UK **8/10**	Exp: 63.6 (1.7) Con: 69.8 (1.8) Exp: $n = 20$ Con: $n = 18$	**Bladder training Programme** • Instructions on urge suppression and distraction techniques • Coaching in PFMT • A personalized voiding schedule • A DVD training • For 12 weeks	Conservative advice	Voiding diary ICIQ-OAB	***UUI symptoms*** **Voiding diary: 72 h.** **Episodes of urgency** Exp: 4.7 (1.1) Con: 6.7 (1.9) $p < 0.366$ ***QoL*** **ICIQ-QOL Score** Exp: 63 (4.7) Con: 60 (6.3) $p < 0.743$	Exp: 2.1 (1.0) Con: 4.7 (1.2) $p < 0.184$ Exp: 50 (7.0) Con: 59 (4.1) $p < 0.224$
Perissinotto *et al.*[50] Brazil **6/10**	Exp: 63.5 (51.0–80.0) Con: 57.0 (50.0–68.0) Exp: $n = 8$ Con: $n = 5$	**TTNS** Pulse Width: 200 µs Frequency: 10 Hz Duration: 30 min for 5 weeks	**Sham** No active electrical stimulation	OAB-V8	***UUI symptoms*** **Overactive bladder-V8** Exp: 18.0 (6.0–27.0) Con: 29 (11.0–33.0)	Exp: 16.0 (6.0–25.0) Con: 21.5 (6.0–21.5)

(Continued)

Table 1. (Continued)

First author, year, country of study, PEDro score	Participant characteristics (mean age of participants (SD); sample size of each group)	Intervention	Control	Outcome measure(s)	Pre-treatment results	Post-treatment results
Tibaek *et al.*[53] Denmark **6/10**	Exp: 59 (56–72) Con: 62 (52–75) Exp: *n* = 12 Con: *n* = 12	**Standardized PFMT** • Close to maximum contraction (6 s contraction/ 6 s rest). • –30% of maximum contraction possible (max 30 s contraction/30 s • rest). • All exercises repeated gradually 6–10 times in lying, standing and sitting positions, 1–2 times daily. • Group treatment in this population	**Normal rehabilitation programme** No specific urinary incontinence treatment	Voiding Diary	***UUI symptoms*** **Voiding diary: Voiding Frequency Totally/24 h** Exp: 11 (6–10) Con: 11 (8–12) p = 0.46	Exp: 7 (5–10) Con: 8 (7–12) *p* = 0.02
Tibaek *et al.*[52] Denmark **7/10**	Exp: 59 (56–72) Con: 62 (52–75) Exp: *n* = 14 Con: *n* = 12	**Standardized PFMT** • Close-to maximum contraction (6 s contraction/ 6 s rest). • 30% of maximum contraction possible (max 30 s contraction/30 s • rest). • All exercises repeated gradually 6–10 times in lying, standing and sitting positions, 1–2 times daily. • Group treatment in this population	**Normal rehabilitation programme** No specific urinary incontinence treatment	Voiding diary	***UUI symptoms*** **Voiding diary: Voiding Frequency Totally/24 h** Exp: 10 (8–12) Con: 9 (8–13)	Exp: 8 (7–9) Con: 8 (7–12) *p* = 0.028)
Tibaek *et al.*[51] Denmark **7/10**	Exp: 68 (57–73) Con: 70 (64–75) Exp: *n* = 15 Con: *n* = 15	**Standardized PFMT** • Close-to-maximum contraction (6 s contraction/ 6 s rest). • 30% of maximum contraction possible (max 30 s contraction/30 s rest). • All exercises repeated gradually 6–10 times in lying, standing and sitting positions, 1–2 times daily. • Group treatment in this population	**General Rehabilitation** No specific urinary incontinence treatment	Voiding Diary	***UUI symptoms*** **Voiding diary: Voiding frequency, total per 24 h** Exp: 11 (6–10) Con: 11 (8–12)	Exp: 7 (5–10) Con: 8 (7–12) ***p* = 0.25**
Vaughan *et al.*[55] US **8/10**	Exp: 71.0 ± 6.1 Con: 69.7 ± 8.2 Exp: *n* = 26 Con: *n* = 21	**Behavioural Therapy** • Isolated PFMT without abdominal muscle recruitment (45 contractions and relaxation divided into 3 sets of 15 with one in each of the three positions: lying, sitting, standing) • Fluid management education (Decrease caffeine, daily drinking 6–8 ounce glasses of fluid) • Constipation management education (increase physical activity, fibre, fruit, and fluid) • Urge suppression strategy	Maintain 7-day bladder diaries for 8 weeks Mirrored-shaped drawing exercises	Voiding diary ICIQ-OAB	***QoL*** **ICIQ-OAB QoL score** Exp: 69.7 ± 23.8 Con: 74.7 ± 23.8 UUI symptoms **Voiding diary: Weekly Frequency** **Exp**: 13.9 ± 9.6 **Con**: 15.1 ± 11.1	Exp: 58.4 ± 21.5 Con: 81.0 ± 24.2 *p* < 0.037 **Exp:** 7.7 ± 10.5 **Con**: 8.5 ± 10.0 *p* = 0.05

Con, control group; Exp, experimental group; ICIQ-OAB, International Consultation on Incontinence Questionnaire – Overactive Bladder; IIQ, Incontinence Impact Questionnaire; IVES, intravaginal electrical stimulation; NMES, neuromuscular electrical stimulation; OABSS, Overactive Bladder Symptom Score; OAB-V8, Overactive Bladder – V8 Questionnaire; PEDro, Physiotherapy Evidence Database; PFMT, pelvic floor muscle training; QoL, quality of life; TENS, transcutaneous electrical nerve stimulation; TTNS, Transcutaneous Tibial Nerve stimulation; UUI, Urge Urinary Incontinence.

Table 2. Summary of methodological quality of the included studies according to the PEDro scale ($n = 21$).

PEDro Scale	Random allocation	Concealed allocation	Baseline Similar	Subject blinding	Therapist blinding	Assessor blinding	Adequate follow-up	Intention-to-treat analysis	Between-group comparison	Points estimate	Total Score/10
Araujo *et al.*[20]	Y	Y	Y	Y	N	Y	Y	N	Y	Y	8
Ferreira *et al.*[63]	Y	N	Y	N	N	N	Y	N	Y	Y	5
Ferreira *et al.*[45]	Y	N	Y	N	N	N	Y	N	Y	Y	5
Guo *et al.*[47]	Y	N	Y	N	N	N	N	N	Y	Y	4
Guo and Kang[18]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9
Liu *et al.*[48]	Y	Y	Y	N	N	Y	Y	N	Y	Y	7
Lúcio *et al.*[46]	Y	N	Y	N	N	Y	N	N	Y	Y	5
McClurg *et al.*[49]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9
McDonald *et al.*[54]	Y	N	Y	Y	N	Y	Y	Y	Y	Y	8
Perissinotto *et al.*[50]	Y	N	Y	Y	N	Y	N	N	Y	Y	6
Tibaek *et al.*[53]	Y	Y	Y	N	N	N	Y	N	Y	Y	6
Tibaek *et al.*[52]	Y	Y	Y	N	N	Y	Y	N	Y	Y	7
Tibaek *et al.*[51]	Y	Y	Y	N	N	Y	Y	N	Y	Y	7
Vaughan *et al.*[55]	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8

N, No; PEDro, Physiotherapy Evidence Database; Y, Yes.

Table 3. Summary of the findings (GRADE) for the effects of interventions compared to control.

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention group**	**Control group**	**Relative (95% CI)**	**Absolute (95% CI)**	
4 McClurg *et al.*[49] Ferreira *et al.*[63] Lúcio *et al.*[46] Ferreira *et al.*[45]	Randomized control trials	Very serious[a]	Not serious	Not serious	Not serious	None	74	74	–	(1.055 lower to 0.208 lower)	⊕⊕◯◯ LOW
3 Tibaek *et al.*[53] Tibaek *et al.*[52] Tibaek *et al.*[51]	Randomized control trials	Very serious[b]	Not serious	Not serious	Not serious	None	41	39	–	(0.628 lower to 0.225 higher)	⊕⊕◯◯ LOW
3 Guo *et al.*[47] Liu *et al.*[48] Guo and Kang[18]	Randomized control trials	Serious[c,d]	Not serious	Not serious	Not serious	None	100	97	–	(4.219 lower to 1.635 lower)	⊕⊕⊕◯ MODERATE
2 Vaughan *et al.*[55] McDonald *et al.*[54]	Randomized control trials	Serious[e]	Serious[f]	Not serious	Not serious	None	46	39	–	(16.015 lower to 8.797 lower)	⊕⊕◯◯ LOW
2 Perissinotto *et al.*[50] Araujo *et al.*[20]	Randomized control trials	Serious[g,h]	Not serious	Not serious	Not serious	None	23	20	–	(14.746 lower to 3.487 lower)	⊕⊕⊕◯ MODERATE
2 Vaughan *et al.*[55] McDonald *et al.*[54]	Randomized control trials	Serious[e]	Serious[f]	Not serious	Not serious	None	46	39	–	SMD 1.365 SD lower (2.598 lower to 0.131 lower)	⊕⊕◯◯ LOW

CI, confidence interval; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; SMD, standardized mean difference.
Explanations:
[a]Lack of intention-to-treat analysis (Ferreira *et al.*,[63] Lúcio *et al.*,[46] and Ferreira *et al.*[45]).
[b]Lack of intention-to-treat analysis (Tibaek *et al.*,[53] Tibaek *et al.*,[52] and Tibaek *et al.*[51]).
[c]Lack of concealed allocation (Guo *et al.*[47]).
[d]Lack of intention-to-treat analysis (Guo *et al.*[47] and Liu *et al.*[48]).
[e]Lack of concealed allocation (McDonald *et al.*[54]).
[f]Evidence of Statistical/Methodology (I^2 value $>$ 50%).
[g]Lack of concealed allocation (Perissinotto *et al.*[50]).
[h]Lack of intention-to-treat analysis (Araujo *et al.*,[20] Perissinotto *et al.*[50]).

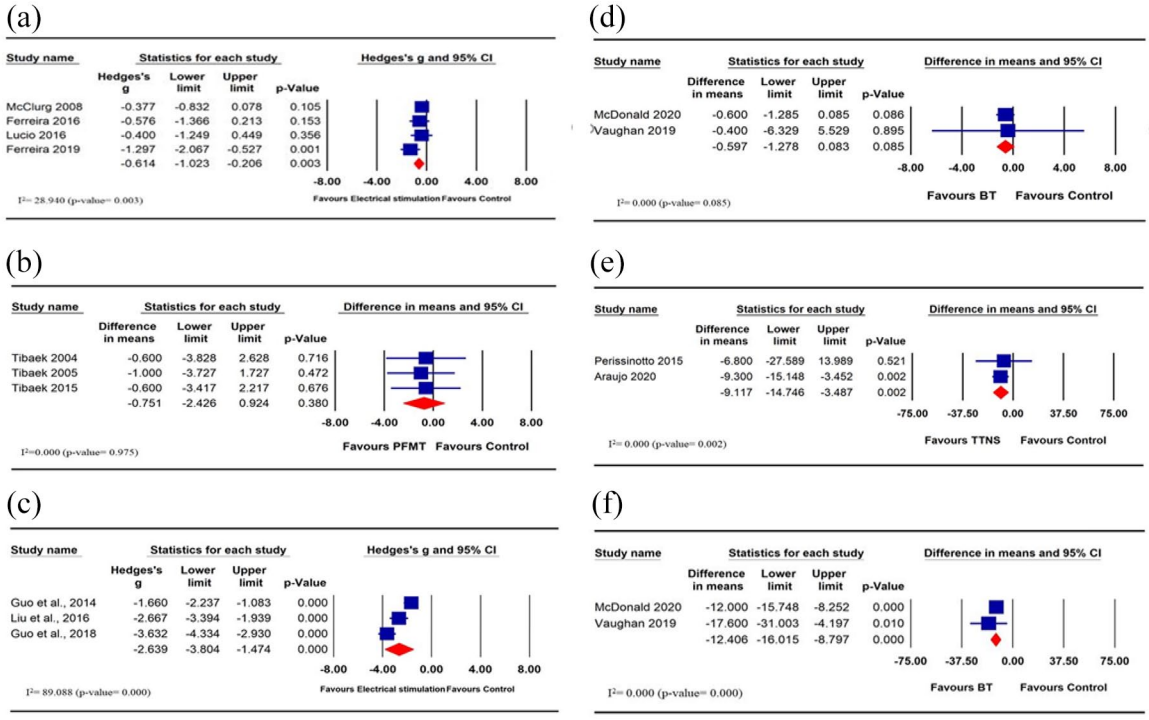

Figure 2. Forest plots. (a) Effect of electrical stimulation compared to PFMT on UUI in people with multiple sclerosis using voiding diary and OAB-V8. (b) Effect of PFMT compared to no treatment in stroke using voiding diary. (c) Effect of electrical stimulation compared to no treatment in stroke using voiding dairy and OABSS. (d) Effect of BT compared with usual treatment on UUI in Parkinson's disease using voiding dairy. (e) Effect of TTNS compared to no treatment in Parkinson's disease using OAB-V8. (f) Effect of BT compared to no treatment on QoL in Parkinson's disease using ICIQ-OAB.
BT, Behavioural Therapy; ICIQ-OAB, International Consultation on Incontinence Questionnaire-Overactive Bladder Module; OABSS, Overactive Bladder Symptom Score; OAB-V8, Overactive Bladder Questionnaire; PFMT, Pelvic Floor Muscle Training; QoL, Quality of Life; TTNS, Transcutaneous Tibial Nerve Stimulation; UUI, Urge Urinary Incontinence.

control group among people with stroke. The stimulation parameters across the three trials ranged from five to seven times each week, for a total of 40–90 treatment sessions, at frequencies ranging from 20 to 75 Hz, with intensities ranging from 70 to 250 μs, and lasting from 20 to 30 min. Of the three trials evaluated, two trials[18,47] measured UUI using the Overactive Bladder Symptom Score, and one trial[48] measured UUI using a voiding diary.

The methodological and evidence qualities of the three trials[18,47,48] were moderate. The pooled analysis of the three trials (n = 224) revealed a significant effect of the intervention on UUI symptoms (SMD: −2.637; 95% CI: −3.804 to −1.474; p = 0.000; Figure 2(c)) compared with the control condition.

BT versus *no treatment on UUI due to Parkinson's disease.* Two studies[54,55] compared the effects of BT against usual care (reduction of alcohol and caffeine intake and advice regarding the management of constipation and available containment products) on UUI symptoms in people with Parkinson's disease. The BT intervention delivered in the included trials include isolated PFMT, without abdominal muscle recruitment (45 contractions and relaxation, divided into 3 sets of 15, with each set performed in a different position: lying, sitting, and standing); fluid management education (decrease caffeine, daily intake of six 8-ounce glasses of fluid); constipation management education (increased physical activity, increased intake of fibre, fruits and fluids); and urge suppression strategies. The two trials[54,55] measured UUI with a voiding diary.

The methodological quality of both trials[54,55] was high, and the quality of evidence was low. The pooled analysis of the two trials (n = 85) revealed

an insignificant effect of the intervention on UUI symptoms compared with the control condition (WMD: −0.597; 95% CI: −1.278 to 0.083; $p = 0.085$; Figure 2(d)).

Effects of interventions on QoL in people with Parkinson's disease

BT versus *no treatment.* Two studies[54,55] compared the effects of BT against usual care (reduction of alcohol and caffeine intake and advice regarding the management of constipation and available containment products) on QoL in people with Parkinson's disease. The two trials[54,55] measured QoL using the ICIQ-SF.

The methodological quality for both trials[54,55] was high, and the quality of evidence was low. The pooled analysis of the two trials ($n = 85$) revealed a significant effect of BT on QoL (WMD: −0.9117; 95% CI: −14.746 to −3487; $p = 0.002$; Figure 2(e)) in the intervention group compared with the control group.

TTNS versus *no treatment.* Two studies[20,50] examined the effects of TTNS on QoL compared with a no-treatment control group in people with Parkinson's disease. The stimulation parameters in the two trials included session lengths ranging from 5 to 12 weeks, a frequency of 10 Hz at an intensity of 200 μs, and a duration of 20–30 min. Both trials[20,50] measured QoL using the OAB-V8.

The methodological quality of the two trials[20,50] ranged from moderate to high, and the quality of evidence was moderate. The pooled analysis of the two trials ($n = 43$) revealed a significant improvement in QoL (WMD: −12.406; 95% CI: −16.015 to −8.797; $p = 0.000$; Figure 2(f)) in the intervention group compared with the control group.

Discussion

The effects of nonsurgical, minimally or noninvasive therapies on UUI symptoms and QoL in people with NGB was evaluated in this review. After review, 14 studies were identified with a total sample size of 804 participants. Our meta-analyses revealed a significant effect of electrical stimulation on UUI due to multiple sclerosis and stroke. The pooled analyses of TTNS revealed significant effects of these interventions on QoL in people with Parkinson's disease. However, meta-analyses revealed nonsignificant effects for PFMT on UUI due to Parkinson's disease.

The pooled analysis of four trials[45,46,49,63] of moderate to high methodological quality and moderate quality of evidence showed a significant effect of electrical stimulations (IVES, NMES, TENS) compared with PFMT on UUI symptoms in people with multiple sclerosis. IVES has been reported to cause a significant increase in pelvic floor muscle strength[64] in women with UUI. IVES depolarizes the somatic lumbar and sacral afferent fibres, thereby inhibiting bladder overactivity.[65] IVES has also been reported to cause profound bladder inhibition in animal models.[66] For the treatment of urge and mixed urinary incontinence, IVES at frequencies below 12 Hz is suggested for beneficial effects,[67] as frequencies below 12 Hz stimulate the pudendal nerve, reducing involuntary detrusor contractions.[68,69] Among the four trials providing evidence for the effects of electrical stimulation in the current review, three trials[45,46,49] utilized IVES at the recommended frequency for maximum benefits.

Considering the procedure of the IVES involving the participants being placed in supine position with 45° of hip and knee flexion, and the intravaginal electrode inserted in the vagina.[70] The acceptance and satisfaction with invasive IVES among women with UUI remain inconclusive, and previous studies[69,71] have reported mixed results. A previous study reported that women experienced pain and discomfort due to the vaginal probe used IVES.[68] However, another study examining women with mixed urinary incontinence reported that 80% of the study participants were satisfied with IVES.[69]

The mean estimated effect size for electrical stimulation when compared with PFMT on UUI symptoms obtained in this review was moderate (0.6).[69,72] However, the effect of electrical stimulation compared to no treatment control condition on UUI symptoms is much larger (2.6). This could be attributed to the effect of PFMT, although not significant in the current meta-analysis of only three pooled studies. The size of the effect, combined with the methodological quality of the included studies, indicated that electrical stimulation might be considered a viable treatment option of UUI due to multiple sclerosis. Future adequately powered studies are required

to investigate the safety and acceptance of electrical stimulation (IVES and TENS) for the treatment of UUI due to NGB.

The pooled analyses of three studies[18,47,48] of moderate methodological quality with moderate quality of evidence revealed a significant effect for electrical stimulation (NMES or TENS) on UUI due to stroke. The mean estimate of the effect was large (SMD: −2.637, $p = 0.000$). A recent review found that NMES is generally safe for the treatment of post-stroke urinary incontinence in women.[73] Considering the safety of the intervention and the size of the effect obtained for this intervention in this review, electrical stimulation may be considered for clinical use.

The pooled analysis of data from three studies[51–53] of moderate to high methodological quality and low quality of evidence identified an insignificant effect of PFMT compared with no treatment on UUI symptoms due to stroke. According to the National Institute for Health and Care Excellence (NICE) guidelines, PFMT is recommended for NGB when voluntary pelvic floor muscle contraction is preserved.[74] PFMT for UUI involves performing a voluntary contraction of the pelvic floor muscles, avoiding a pelvic floor relaxation, until the urination urge is suppressed, an effect known as the 'guard reflex'.[74] According to the NICE guidelines, PFMT must be performed for a minimum of 3 months, consisting of at least eight contractions three times per day.[75] The participants of the three included trials[51–53] performed PFMT 6 to 10 times in lying, standing and sitting positions, one to two times daily, for 3 months. Based on the results of the current review, the efficacy of PFMT for UUI remains inconclusive. Future studies evaluating the effect of PFMT for UUI due to NGB must adhere to the NICE guideline.

The pooled analysis of two Parkinson's disease studies[54,55] of high methodological quality and low quality of evidence found a nonsignificant effect for BT compared with the no-treatment control on UUI symptoms. The rationale underlying BT is based on the premise that a potential precipitant of detrusor instability is the habit of frequent voiding and can be an indicator of uninhibited detrusor contraction and reduced bladder capacity.[76] BT aims to moderate the habit of frequent voiding through practising resisting the urge to void, postponing micturition and increasing the voiding interval, which improves bladder capacity and decreases detrusor instability.[77] BT alone, in the absence of other adjunctive treatments, might not lead to a positive result according to previous findings.[78] Based on the findings in this study, the effects of BT on UUI among individuals with Parkinson's disease remains inconclusive. We recommend future studies integrating BT with other interventions such as electrical stimulations for NGB in other to achieve better effects.

UUI has been reported to impair the QoL of people with Parkinson's disease,[79] and the degree of QoL impairment is associated with social predictors (e.g. age, sex, rural living, the number of household members, and financial problems) and clinical predictors (e.g. disease severity, disability, disease duration, motor impairment, depressive symptoms, complications of therapy, and gait impairment).[80] The pooled analyses of two studies[54,55] of high methodological quality and low quality of evidence revealed a significant effect of BT on QoL in people with Parkinson's disease compared with the no-treatment control. The size of the effect was large (0.9). Pooled analyses[20,50] also found that TTNS was beneficial for improving the QoL of people with Parkinson's disease compared with the no-treatment control. The size of the effect for TTNS was also large (12.4). Based on these results, TTNS and BT may be considered in clinical practice to improve QoL in people with UUI due to Parkinson's disease.

Study strengths and limitations

Our systematic review has several strengths. We adopted a comprehensive search strategy, using relevant search terms to identify RCTs evaluating the effects of nonsurgical, minimally or noninvasive therapies for the management of UUI. A sound, systematic methodology was employed for the identification and evaluation of the included studies. Only RCTs were included in the study to ensure the rigour of the pooled meta-analyses. Psychometrically sound quality assessment tools were employed to evaluate the quality of the methodology and evidence reported by the included studies. Limitations associated with this study include limited size of the pooled analyses and the inability to access some interventions due to lack of RCTs. Although the systematic review of RCTs can provide findings that are considered to represent the highest level of clinical evidence, excluding studies due to study

design could limit the scope of our study. The possibility of language bias could not be eliminated because we did not consider non-English and non-Chinese studies.

Conclusion

Our meta-analysis found that electrical stimulation (IVES and NMES) is beneficial for decreasing the symptoms of UUI among people with multiple sclerosis. Electrical stimulation (NMES and TENS) was also found to be beneficial for reducing the symptoms of UUI among people with stroke. These results were derived from trials of moderate to high methodological quality and moderate quality of evidence. This review also found that TTNS and BT were able to improve QoL in people with NGB due to Parkinson's disease. These results were derived from trials of moderate to high methodological quality and low to moderate quality of evidence. The specific effects of PFMT and BT on UUI remain uncertain. Future studies to evaluate the effects of PFMT and BT and other interventions that have received less attention, such as repetitive transcranial magnetic stimulation, transcranial magnetic stimulation and functional magnetic stimulation, on NGB outcomes are warranted.

Clinical message

- Electrical stimulation has strongest effects. However, might be unpreferable by all patients.
- Electrical stimulation is better than PFMT.

Author contributions

Mohammed Usman Ali: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing-original draft; Writing-review & editing.
Kenneth Nai-Kuen Fong: Conceptualization; Methodology; Supervision; Validation; Writing-review & editing.
Priya Kannan: Conceptualization; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing-review & editing.
Umar Muhammad Bello: Data curation; Formal analysis; Investigation; Methodology; Writing-review & editing.
Georg S. Kranz: Conceptualization; Investigation; Methodology; Supervision; Validation; Writing-review & editing.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Supplemental material

Supplemental material for this article is available online.

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