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Electrical stimulation with non-implanted electrodes for overactive bladder in adults (Protocol)

Stewart F, Gameiro OLF, El Dib R, Gameiro MO, Kapoor A, Amaro JL

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Electrical stimulation with non-implanted electrodes for overactive bladder in adults.
Cochrane Database of Systematic Reviews 2015, Issue 9. Art. No.: CD010098.
DOI: 10.1002/14651858.CD010098.pub2.

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[Intervention Protocol]

Electrical stimulation with non-implanted electrodes for overactive bladder in adults

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Editorial group: Cochrane Incontinence Group.
Publication status and date: Edited (no change to conclusions), published in Issue 9, 2015.

Citation: Stewart F, Gameiro OLF, El Dib R, Gameiro MO, Kapoor A, Amaro JL. Electrical stimulation with non-implanted electrodes for overactive bladder in adults. *Cochrane Database of Systematic Reviews* 2015, Issue 9. Art. No.: CD010098. DOI: 10.1002/14651858.CD010098.pub2.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To determine the effectiveness of electrical stimulation with non-implanted electrodes in comparison with placebo or any other active treatment in adults with overactive bladder with or without urgency urinary incontinence.

BACKGROUND

Description of the condition

Overactive bladder is a chronic disorder with an overall prevalence in the adult population of over 10%, but that may exceed 40% in elderly groups (Irvin 2006). According to the International Continence Society, overactive bladder is characterised by symptoms of urinary urgency (a strong compelling desire to urinate that is difficult to overcome), with or without urinary incontinence. Overactive bladder is usually accompanied by daytime frequency (increased need to urinate) and nocturia (waking during the night to urinate), but without urinary infection or other bladder pathologies (Abrams 2003). Overactive bladder with urinary incontinence is known as overactive bladder wet; overactive bladder without incontinence is known as overactive bladder dry.

Urinary incontinence has many psychosocial implications. It appears that overactive bladder has a greater psychological impact than stress urinary incontinence, with 60% of overactive bladder patients reporting a history of depression compared with 14% of patients with stress urinary incontinence (Zorn 1999).

The aetiology of overactive bladder is multifactorial, with urgency symptoms associated with overactivity of the detrusor muscle. This overactivity can be related to neurogenic, myogenic, or idiopathic origins (Shaw 2011). However, currently its aetiology is unclear.

Description of the intervention

Conservative management, such as bladder training or pelvic floor muscle exercises, has been recommended as a first-line treatment for overactive bladder (Abrams 2003).

The main type of medical treatment for overactive bladder is pharmacotherapy with anticholinergics, which have proven to be effective in several randomised controlled trials (RCTs). However, common side effects such as dry mouth and constipation limit long-term compliance, with discontinuation rates of 70% to 90% within one year (D´ Souza 2008). Intravesical botulinum toxin injections may be an effective and safe option to treat refractory overactive bladder but further controlled studies are required to evaluate its effectiveness (Duthie 2011). This is considered to be a surgical intervention in this review.

In patients for whom conservative or drug treatment is not sufficient, neuromodulation is an alternative. Neuromodulation uses electrical stimulation to target specific nerves in the sacral plexus that control pelvic floor function.

Electrical stimulation can be used to treat overactive bladder via different routes, such as implantable or internal (sacral neuromodulation) and non-implantable electrodes, typically vaginal, rectal (anal) or skin electrodes.

Electrical stimulation can be used on its own or in association with pelvic floor muscle exercises, often indicated in stress urinary incontinence and overactive bladder.

This review includes non-implanted electrodes only; implanted devices are included in another Cochrane systematic review (Herbison 2009).

Intracavitary (vaginal or rectal) electrical stimulation

Intravaginal electrical stimulation

Intravaginal electrical stimulation for treating urinary incontinence was first reported in the literature in the 1960s (Cadwell 1963). Subsequently, it has been shown to achieve satisfactory results with frequencies below 12 Hertz (Hz) stimulating the pudendal nerve, which may inhibit the detrusor muscle, reduce involuntary contractions and, consequently, reduce the number of micturitions (Messelink 1999). Electrical stimulation also works in a passive way, helping patients become conscious of the perineal muscle contraction and this may, in turn, help to inhibit detrusor involuntary contractions (Amaro 2003).

The contraindications to intravaginal electrical stimulation are pregnancy, vaginal infection or lesion, a reduced perception of vaginal sensation, menstruation, and metallic implants (Richardson 1996).

Rectal (anal) electrical stimulation

Electrodes inserted in the rectal canal inhibit detrusor contractions through contact with the pudendal nerve afferent fibres and thus may be effective in the treatment of urgency urinary incontinence and overactive bladder. Rectal electrical stimulation has achieved some favourable results in treating faecal incontinence (Scott 2014). A short-term study of rectal electrical stimulation reported some benefits in treating men with urinary incontinence (Berghmans 2013).

Posterior tibial nerve stimulation

Transcutaneous and percutaneous neuromodulation of the tibial nerve can be delivered over either the sacral outflow or peroneal region of the ankle through surface electrodes (ICI 2012).

Transcutaneous electrical nerve stimulation

Transcutaneous electrical nerve stimulation is a minimally invasive treatment which delivers an electrical current through an electrode placed in the ischiorectal area. Transcutaneous electrical nerve stimulation has been shown to be safe and effective in the treatment of overactive bladder (Bellette 2009). Multimodal treatment could be more effective for improving overactive bladder symptoms. One study has shown better results when transcutaneous electrical nerve stimulation was used with oxybutynin compared to transcutaneous electrical nerve stimulation or oxybutynin alone (Souto 2014).

Percutaneous tibial nerve stimulation

Percutaneous tibial nerve stimulation is a form of neuromodulation that delivers retrograde stimulation to the sacral nerve plexus via a needle electrode inserted into the ankle, cephalad to the medial malleolus, an anatomical area recognised as the bladder centre. A recent multicentre, randomised trial found that percutaneous tibial nerve stimulation was more effective than 4mg extended release tolterodine in the treatment of overactive bladder (Peters 2009). Other authors observed comparable improvement using antimuscarinics; however, fewer side effects were observed when percutaneous tibial nerve stimulation was used (Burton 2012).

How the intervention might work

Electrical stimulation inhibits detrusor contractions, decreasing the number of micturitions and potentially increasing bladder capacity (Wang 2006). Electrodes can be located in the vaginal or rectal canals in such a way as to obtain contact with a significant quantity of afferent nerve fibres of the pudendal nerve. This stimulation of the pudendal nerve activates the skeletal pelvic floor muscles and inhibits detrusor contraction. Partial or total innervation of the pudendal nerve is necessary so that nerve stimulation can occur (Messelink 1999). The anal electrode can be used for men or in cases where the vaginal approach is contraindicated.

Evidence from clinical trials indicates that electrical stimulation may show promise for treating overactive bladder. Ohlsson 1989 studied patients with detrusor overactivity treated with intravaginal electrical stimulation and reported a significant increase in bladder functional capacity, with 30% reporting a reduction in the number of daily micturitions. A randomised controlled study showed that intravaginal electrical stimulation was useful in treating patients with urinary incontinence due to detrusor overactivity (Yamanishi 2000). However, another study observed low effectiveness of intravaginal electrical stimulation on the pelvic floor in elderly women with urinary incontinence (Spruijt 2003).

Why it is important to do this review

Numerous treatment options exist for overactive bladder, including behavioural therapies such as pelvic floor muscle rehabilitation, bladder training, and dietary modification, as well as pharmacological therapy and neuromodulation. Overall, behavioural therapies are considered the mainstay of treatment for urinary incontinence. It is known that overactive bladder can be improved through behavioural therapy or drug treatment but it is not known whether non-invasive electrical stimulation achieves better clinical outcomes. This review aims to present an overview of current evidence related to electrical stimulation in the treatment of overactive bladder.

This systematic review aims to investigate the effects of non-implanted electrical stimulation in patients with overactive bladder or urgency incontinence. It also aims to compare specific subgroups to investigate whether electrical stimulation might be more beneficial for some populations than for others.

OBJECTIVES

To determine the effectiveness of electrical stimulation with non-implanted electrodes in comparison with placebo or any other active treatment in adults with overactive bladder with or without urgency urinary incontinence.

METHODS

Criteria for considering studies for this review

Types of studies

We will include RCTs, quasi-RCTs (RCTs in which allocation to treatment is based on methods such as alternate medical records, date of birth, or other predictable methods) and randomised cross-over trials .

Types of participants

Eligible studies will include adults (≥18 years old, or according to study authors' definitions of adult) with either of the following:

- symptomatic diagnosis of overactive bladder, urgency urinary incontinence or mixed urinary incontinence;
- urodynamic diagnosis of detrusor overactivity in addition to overactive bladder symptoms (urgency, frequency or episodes of urgency incontinence).

Studies including participants with stress urinary incontinence with or without overactive bladder symptoms will be included if data are reported separately for stress urinary incontinence and overactive bladder participants, or if the majority of the population have overactive bladder/urgency urinary incontinence-predominant symptoms.

Types of interventions

Eligible comparators will be any intervention intended to decrease urinary frequency and will include placebo, sham treatment, conservative treatment (including complementary therapies), drugs and surgery. We will also include studies comparing different electrical stimulation methods to each other. There will be no restrictions by type of device, stimulation parameters (such as continuous, interrupted, duration of stimulation), duration of treatment, route of administration (e.g. vaginal, rectal, skin, pretibial area), or other similar factors. We will exclude trials of different combinations of treatments even if one of those is electrical stimulation if it is not possible to identify the effect of this treatment alone (e.g. electrical stimulation plus another treatment versus electrical stimulation plus other combined treatments)

We will consider the following comparisons:

- electrical stimulation versus no active treatment, placebo or sham treatment;
- electrical stimulation versus conservative treatment (e.g. bladder training, pelvic floor muscle training, biofeedback, magnetic stimulation);
- electrical stimulation versus drugs (e.g. anticholinergics);
- electrical stimulation versus surgery (including botulinum toxin);
- electrical stimulation versus electrical stimulation plus another treatment;
- electrical stimulation plus another treatment versus other treatment alone;
- electrical stimulation plus another treatment versus no active treatment, placebo or sham treatment;
- one type of electrical stimulation versus another.

Types of outcome measures

The following outcomes will be considered:

Primary outcomes

- Perception of cure (number of participants with overactive bladder symptoms; number of participants with self-reported urgency urinary incontinence)
- Perception of improvement (number of participants with no improvement in overactive bladder symptoms; number of participants with no improvement in self-reported urgency urinary incontinence)
- Quality of life measures due to overactive bladder or incontinence (however defined by authors or by any validated measurement scales such as International Consultation on Incontinence Questionnaire)

Secondary outcomes

- Quantification of symptoms
  - Number of incontinence episodes (per 24 hours)
  - Number of urgency episodes (per 24 hours)
  - Number of micturitions (per 24 hours)
  - Number of nocturia episodes (per night)
  - Number of pads used per 24 hours
  - Pad tests (weights) (e.g. one hour pad test, 24 hour pad test)
- Clinicians' observations
  - Number of participants with objectively measured incontinence (such as observation of leakage, leakage observed at urodynamics study)
  - Number of participants with detrusor overactivity observed at urodynamic study
  - Bladder capacity measured by urodynamic study
- Socioeconomic measures
  - Costs of interventions
  - Cost-effectiveness of interventions
  - Resource implications
- Procedure outcome measures
  - Duration of procedure
  - Length of hospital stay
  - Time to return to normal activity level
- Adverse effects
  - Skin damage
  - Pain or discomfort
  - Vascular, visceral or nerve injury
  - Voiding dysfunction
  - Other complications
- Other outcomes
  - Non-prespecified outcomes judged important when performing the review

Grading of Recommendations Assessment, Development and Evaluation (GRADE) outcomes

We will include the following outcomes in a 'Summary of findings' table:

- number of participants with no improvement in overactive bladder symptoms or urgency symptoms;
- number of participants with no improvement in self-reported urgency urinary incontinence;
- quality of life measures due to overactive bladder;
- adverse effects (pain or discomfort due to treatment);
- cost-effectiveness of interventions.

Search methods for identification of studies

We will not impose any restrictions, for example language or publication status, on the searches described below.

Electronic searches

This review will draw on the search strategy developed for the Cochrane Incontinence Group. We will identify relevant trials from the Cochrane Incontinence Group Specialised Trials Register. For more details of the search methods used to build the Specialised Register please see the Group's module in *The Cochrane Library*. The Register contains trials identified from the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, MEDLINE in process, ClinicalTrials.gov (https://clinicaltrials.gov/), World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal (http://apps.who.int/trialsearch/) and handsearching of journals and conference proceedings. Most of the trials in the Cochrane Incontinence Group Specialised Register are also contained in CENTRAL. Search terms for the Incontinence Group Specialised Register are given in Appendix 1.

A number of the review authors (OLFG, RE, MOG, AK, JLA) will also search the following databases (Appendix 1):

- PubMed (from inception)
- CENTRAL (*Cochrane Library*);
- Embase on OvidSP (1980 onwards) and the Latin-American and Caribbean Center on Health Sciencies Information (LILACS) (on the Virtual Health Library/Bireme) (1982 onwards). The highly sensitive Embase and LILACS strategies for identification of RCTs (Castro 1997; Castro 1999; Lefebvre 2011) will be combined with search terms relating to the condition and interventions
- Information about ongoing clinical trials will be sought from the clinical trials registries such as ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (WHO ICTRP).

Searching other resources

We will screen reference lists of the identified relevant studies for additional citations. In addition, we will contact clinical specialists and authors of included trials where appropriate to obtain unpublished data.

Data collection and analysis

Selection of studies

Two authors will independently screen the trials identified by the literature search. We will resolve any disagreements by consulting a third author.

Data extraction and management

Two authors will extract data independently. We will resolve any discrepancies by discussion. We will use a pre-standardised data extraction form to extract data pertaining to study characteristics (design, methods of randomisation), participants, interventions and outcomes.

Assessment of risk of bias in included studies

Two authors will independently assess risk of bias in included trials using the Cochrane Collaboration's tool for assessing risk of bias (Higgins 2011), considering the following four domains: random sequence generation, allocation concealment, blinding, and incomplete outcome data. We will resolve any disagreements by consulting a third author.

Measures of treatment effect

We will analyse included trial data as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).
(a) Binary outcomes
For dichotomous data, we will calculate risk ratios (RRs) with 95% confidence intervals (CIs).
(b) Continuous outcomes
For continuous data, we will present mean differences (MDs) with 95% CIs. We will calculate standardised mean differences (SMDs) to combine trials that measure the same outcome but with different methods.

Unit of analysis issues

The unit of analysis will be each participant recruited into the trials.
We will analyse studies with non-standard designs, such as cross-over trials and cluster-randomised trials, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will analyse studies with multiple treatment groups by treating each pair of arms as a separate comparison, as appropriate. Where data from randomised cross-over trials are incomplete we will consider including data from the first period of randomisation only.

Dealing with missing data

We will analyse data on an intention-to-treat (ITT) basis, as far as possible, whereby all participants must be analysed according to the groups to which they were randomised. For individual trials we will report whether or not analysis was performed according to the ITT principle. Where participants are excluded after allocation or withdraw from the trial, we will report any details provided in full. Where data from randomised cross-over trials are incomplete we will include data from the first period of randomisation only.
We will make all reasonable attempts to contact authors for clarification of missing data. Where trials report mean values without standard deviations (SDs) but with P values or 95% CIs, we will use RevMan's calculator to estimate the SDs. Where trials report mean values only, we will assume the outcome to have a SD equal to the highest SD from the other trials within the same analysis.

Assessment of heterogeneity

We will assess clinical heterogeneity by examination of the study details and test for statistical heterogeneity between trial results using the chi-squared test and the I^2 statistic (Higgins 2011), using the following I^2 values:

- < 30% heterogeneity may not be important;
- 30% to 50% may represent moderate heterogeneity;
- > 50% may represent substantial or considerable heterogeneity.

Assessment of reporting biases

We will assess the likelihood of potential publication bias using funnel plots, provided that we identify 10 or more eligible trials.

Data synthesis

We will use Cochrane's statistical software, Review Manager 2014, for data analysis. We will use the fixed-effect model to analyse data. If significant heterogeneity (for example I^2 higher than 50%) is identified, we will compute pooled estimates of the treatment effect for each outcome under a random-effects model (with two or more studies).
If outcomes are reported which are similar to but not precisely the same as pre-specified ones, we will consider whether to use 'surrogate' outcomes to substitute for missing data. For example, if a trial has reported episodes of urinary incontinence without specifying the type of incontinence, e.g. stress urinary incontinence or

urgency urinary incontinence, we could use the data as a substitute for urgency urinary incontinence. Similarly, we could use 'improvement in urgency symptoms' as a substitute for 'improvement in overactive bladder symptoms'. Finally, if a subjective outcome (such as overactive bladder symptoms) is reported as combined with an objective outcome (such as detrusor overactivity) without reporting them separately we will consider using it as a surrogate for the subjective outcome.

Subgroup analysis and investigation of heterogeneity

In the case of substantial heterogeneity (I^2 > 50%), we will investigate the causes of heterogeneity and if data permit, we will carry out the following subgroup analyses:

- participants with idiopathic overactive bladder versus those with neurogenic overactive bladder;
- participants with overactive bladder and urgency urinary incontinence only versus participants with mixed urinary incontinence (urgency urinary incontinence and stress urinary incontinence);
- approaches of electrodes (transcutaneous (e.g. perineal skin, sacral, posterior pretibial nerve), endocavitary (vaginal, rectal, urethral), and percutaneous (posterior pretibial nerve).

Sensitivity analysis

If data permit, we will perform a sensitivity analysis comparing trials with low risk of selection bias to those with high risk of bias.

'Summary of findings' table

We will apply the principles of the GRADE system to assess the quality of the body of evidence associated with specific outcomes (perception of cure, perception of improvement and overactive-related quality of life) (Guyatt 2008). We will construct a 'Summary of findings' table using the GRADEpro (GRADEproGDT) software (http://www.guidelinedevelopment.org/). The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence considers within-study risk of bias (methodological quality), the directness of the evidence, heterogeneity of the data, precision of effect estimates, and risk of publication bias.

ACKNOWLEDGEMENTS

We would like to thank June Cody, Cathryn Glazener, Bronwyn Davidson, Suzanne MacDonald, Sheila Wallace, Muhammad Imran Omar, and Nicola Dean for their relevant help during the preparation of this protocol.

REFERENCES

Additional references

Abrams 2003
Abrams P, Cardoso L, Fall M, Griffith D, Rosier P, Ulmsten U, et al. The standardization of terminology in lower urinary tract function: Report from the standardization subcommittee of International Continence Society. *Urology* 2003;**61**:37–49. MEDLINE: 12559262

Amaro 2003
Amaro JL, Gameiro MOO, Padovani CR. Treatment of urinary stress incontinence by intravaginal electrical stimulation and pelvic floor physiotherapy. *International Urogynecology Journal and Pelvic Floor Dysfunction* 2003;**14**: 204–8.

Bellette 2009
Bellette PO, Rodrigues Palma PC, Hermann V, et al. Posterior tibial nerve stimulation in the management of overactive bladder: a prospective and controlled study. *Actas Urológicas Españolas* 2009;**33**:58-63.

Berghmans 2013
Berghmans B, Hendriks E, Bernards A, de Bie R, Omar MI. Electrical stimulation with non-implanted electrodes for urinary incontinence in men. *Cochrane Database of Systematic Reviews* 2013, Issue 6. DOI: 10.1002/14651858.CD001202.pub5

Burton 2012
Burton C, Sajja A, Latthe PM. Effectiveness of percutaneous posterior tibial nerve stimulation for overactive bladder: A systematic review and meta-analysis. *Neurourology and Urodynamics* 2012;**31**(8):1206–16. [PUBMED: 22581511]

Cadwell 1963
Cadwell KPS. The electrical control of the sphincter incompetence. *Lancet* 1963;**2**:174–5. MEDLINE: 14017856

Castro 1997
Castro AA, Clark OA, Atallah AN. Optimal search strategy for clinical trials in the Latin American and Caribbean Health Science Literature Database (LILACS). *Sao Paulo Medical Journal/ Revista da Associação Paulista de Medicina* 1997;**115**(3):1423–6. MEDLINE: 9532843

Castro 1999
Castro AA, Clark OA, Atallah AN. Optimal search strategy for clinical trials in the Latin American and Caribbean Health Science Literature Database (LILACS database). *Sao Paulo Medical Journal/Revista da Associação Paulista de Medicina* 1999;**117**(3):138–9. MEDLINE: 10511734

Duthie 2011
Duthie JB, Vincent M, Herbison GP, Wilson DI, Wilson D. Botulinum toxin injections for adults with overactive bladder syndrome. *Cochrane Database of Systematic Reviews* 2011, Issue 12. DOI: 10.1002/14651858.CD005493.pub3

D´ Souza 2008
D'Souza AO, Smith MJ, Miller LA, Doyle J, Ariely R. Persistence, adherence, and switch rates among extended-release and immediate-release overactive bladder medications in a regional managed care plan. *Journal of Managed Care Pharmacy* 2008;**14**:291–301. MEDLINE: 18439051

Guyatt 2008
Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ. GRADE Working Group. What is "quality of evidence" and why is it important to clinicians?. *BMJ* 2008;**336**:995–8. MEDLINE: 18456631

Herbison 2009
Herbison GP, Arnold EP. Sacral neuromodulation with implanted devices for urinary storage and voiding dysfunction in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 2. DOI: 10.1002/14651858.CD004202.pub2

Higgins 2011
Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

ICI 2012
Abrams P, Cardozo L, Khoury S, Wein A. *5th International Consultation on Incontinence*. Paris: ICUD-EAU, 2013.

Irvin 2006
Irwin DE, Milsom I, Hunskaar S, Reilly K, Kopp Z, Herschorn S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. *European Urology* 2006;**50**(6):1306–15. MEDLINE: 17049716

Messelink 1999
Messelink EJ. The overactive bladder and the role of pelvic floor muscles. *British Journal of Urology* 1999;**83**:31–5. MEDLINE: 10210602

Ohlsson 1989
Ohlsson BL, Fall M, Frankenberg-Sommar S. Effects of external and direct pudendal nerve maximal electrical stimulation in the treatment of the uninhibited overactive bladder. *British Journal of Urology* 1989;**64**:374–80. MEDLINE: 2819388

Peters 2009
Peters KM, MacDiarmid SA, Wooldridge LS, Leong FC, Shobeiri SA, Rovner ES, et al. Randomized trial of percutaneous tibial nerve stimulation versus extended-release tolterodine:results from the overactive bladder innovative therapy trial. *Journal of Urology* 2009;**182**:1055–66.

Rai 2012
Rai BP, Cody JD, Alhasso A, Stewart L. Anticholinergic drugs versus non-drug active therapies for non-neurogenic overactive bladder syndrome in adults. *Cochrane Database of Systematic Reviews* 2012, Issue 12. DOI: 10.1002/14651858.CD003193.pub4

Reference Manager 2012 [Computer program]
Thomson Reuters. Reference Manager Professional Edition Version 12. New York: Thomson Reuters, 2012.

Review Manager 2014 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Richardson 1996
Richardson DA, Miller KL, Siegel SW, Kavam MM, Blackwood NB, Staskin DR. Pelvic floor electrical stimulation: a comparison of daily and every other day therapy for genuine stress incontinence. *Urology* 1996;**48**:110–8. MEDLINE: 8693630

Schreiner 2013
Schreiner L, dos Santos TG, de Souza ABA, Nygaard CC, da Silva Filho IG. Electrical stimulation for urinary incontinence in women: A systematic review. *International Braz J Urol* 2013;**39**(4):454–64.

Scott 2014
Scott KM. Pelvic floor rehabilitation in the treatment of fecal incontinence. *Clinics in Colon and Rectal Surgery* 2014;**27**(3):99–105.

Shaw 2011
Shaw HA, Burrows LJ. Etiology and treatment of overactive bladder in women. *Southern Medical Journal* 2011;**104**(1):34–9. MEDLINE: 21079535

Souto 2014
Souto SC, Reis LO, Palma T, Palma P, Denardi F. Prospective and randomized comparison of electrical stimulation of the posterior tibial nerve versus oxybutynin versus their combination for treatment of women with overactive bladder syndrome. *World Journal of Urology* 2014;**32**(1):179–84.

Spruijt 2003
Spruijt J, Vierhout M, Verstraeten R, Janssens J, Burger C. Vaginal electrical stimulation of the pelvic floor : A randomized feasibility study in urinary incontinent elderly women. *Acta Obstetricia et Gynecologica Scandinavica* 2003;**82**:1043–8.

Wang 2006
Wang AC, Chih SY, Chen M. Comparison of electric stimulation and oxybutynin chloride in management of overactive bladder with special reference to urinary urgency: a randomized placebo-controlled trial. *Urology* 2006;**68**(5):999–1004. MEDLINE: 17113893

Yamanishi 2000
Yamanishi T, Sakakibara R, Uchiyama T, Suda S, Hattori T, Ito H, et al. Comparative study of the effects of magnetic

versus electrical stimulation on inhibition of detrusor overactivity. *Urology* 2000;**56**(5):777–81.

Zorn 1999
Zorn BH, Montgomery H, Pieper K, Gray M, Steers WD. Urinary incontinence and depression. *Journal of Urology* 1999;**162**:82–4. MEDLINE: 10379745

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategies

Incontinence Group Specialised Register

The terms that will be used to search the Incontinence Group Specialised Register are given below:
({DESIGN.CCT*} OR {DESIGN.RCT*}) AND ({INTVENT.PHYS.ELECTSTIM*}) AND ({TOPIC.URINE.INCON*} OR {TOPIC.URINE.OVERACTIVE*})
(All searches will be of the keyword field of Reference Manager 2012).

PubMed (from inception) and CENTRAL (Cochrane Library) (from inception)

The following search terms will be used:
((Overactive Bladder) OR (Overactive Urinary Bladder) OR (Overactive Detrusor) OR (Overactive Detrusor Function) OR bladder OR (urinary bladder) OR (unstable bladder) OR (urge incontinence) OR (inhibits bladder) OR (Urinary Reflex Incontinence) OR (Urinary Urge Incontinence) OR (Urge Incontinence) OR (Urinary Bladder Disease) OR (Urinary Bladder Diseases) OR (Bladder Diseases) OR (Bladder Disease)) AND ((Electrical Stimulation) OR (Electrical Stimulations) OR (Electric Stimulations) OR (Electric Stimulation) OR (Electric Stimulation Therapy) OR (Therapeutic Electrical Stimulation) OR Electrotherapy OR (Therapeutic Electric Stimulation) OR (Electrical Stimulation Therapy) OR (Transcutaneous Electrical Stimulation) OR (Percutaneous Electric Nerve Stimulation) OR (Percutaneous Electrical Nerve Stimulation) OR (Transdermal Electrostimulation) OR (Transcutaneous Electrical Nerve Stimulation) OR (Transcutaneous Nerve Stimulation) OR (Transcutaneous Electric Stimulation) OR TENS OR Electroanalgesia OR (Analgesic Cutaneous Electrostimulation))

Embase (OvidSP) (from 1980 onwards)

The search strategy that will be used in Embase is given below. The RCT terms (lines 1 and 2) are those recommended by Lefebvre 2011. The search will be limited to those records added to Embase from January 2010 onwards as earlier trials are included in the Specialised Register search of CENTRAL.
1. (random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).tw.
2. (crossover-procedure or double-blind procedure or randomised controlled trial or single-blind procedure).sh.
3. 1 or 2
4. urine incontinence/ or mixed incontinence/ or stress incontinence/ or urge incontinence/
5. overactive bladder/
6. (Detrusor$ or bladder$ or incontinen$ or continen$).tw.
7. 4 or 5 or 6
8. (Electric$ Stimulation$ or Electric Stimulation or Electrotherap$ or TENS or Electroanalgesia or electrostimulation$ or nerve stimulation$).tw.

9. electrostimulation/
10. electrostimulation therapy/
11. transcutaneous nerve stimulation/
12. 8 or 9 or 10 or 11
13. 3 and 7 and 12
14. 2010$.em.
15. 2011$.em.
16. 2012$.em.
17. 2013$.em.
18. 14 or 15 or 16 or 17
19. 13 and 18

LILACS (Virtual Health Library/BIREME) (from 1982)

The terms that will be used to search LILACS are given below. The RCT terms are those developed by Castro and colleagues (Castro 1997; Castro 1999).
(Detrusor$ OR bladder$ OR incontinen$ OR continen$) [Words]
AND
((Electric$ Stimulation$) OR (Electric Stimulation) OR Electrotherap$ OR TENS OR Electroanalgesia OR electrostimulation$ OR (nerve stimulation$)) [Words]
(nb for some reason if remove (electric stimulation) it retrieves less articles!!!)
((Pt randomised controlled trial OR Pt controlled clinical trial OR Mh randomised controlled trials OR Mh random allocation OR Mh
double-blind method OR Mh single-blind method) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Pt clinical trial OR Ex E05.318.760.535$ OR (Tw clin$ AND (Tw trial$ OR Tw ensa$ OR Tw estud$ OR Tw experim$ OR Tw investiga$)) OR ((Tw singl$ OR Tw simple$ OR Tw doubl$ OR Tw doble$ OR Tw duplo$ OR Tw trebl$ OR Tw trip$) AND (Tw blind$ OR Tw cego$ OR Tw ciego$ OR Tw mask$ OR Tw mascar$)) OR Mh placebos OR Tw placebo$ OR (Tw random$ OR Tw randon$ OR Tw casual$ OR Tw acaso$ OR Tw azar OR Tw aleator$) OR Mh research design) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Ct comparative study OR Ex E05.337$ OR Mh follow-up studies OR Mh prospective studies OR Tw control$ OR Tw prospectiv$ OR Tw volunt$ OR Tw volunteer$) AND NOT (Ct animal AND NOT (Ct human and Ct animal))) [Words]
Field = words

ClinicalTrials.gov and WHO ICTRP Search Portal

Ongoing clinical trials will be sought by searching the clinical trials sites from the National Institute of Health (ClinicalTrials.gov) and the WHO International Clinical Trials Registry Platform (WHO ICTRP) using the search term: overactive bladder.

WHAT'S NEW

Date	Event	Description
9 September 2015	New citation required and minor changes	The protocol has been amended.
9 September 2015	Amended	The protocol has been amended.

CONTRIBUTIONS OF AUTHORS

Conceiving the review: Joao Luiz Amaro (JLA).

Co-ordinating the review: JLA, Regina El Dib (RED), Fiona Stewart (FS)

Undertaking manual searches: Luís Felipe Orsi Gameiro (LFOG).

Screening search results: LFOG, FS Mônica Orsi Gameiro (MOG).

Organizing retrieval of papers: LFOG.

Screening retrieved papers against inclusion criteria: LFOG, FS, JLA, MOG, and RED.

Appraising quality of papers: FS, LFOG, JLA, MOG, and RED.

Abstracting data from papers: FS, LFOG.

Writing to authors of papers for additional information: FS, LFOG and Anil Kapoor (AK).

Providing additional data about papers: LFOG, MOG, AK, JLA.

Obtaining and screening data on unpublished studies: LFOG.

Data management for the review: FS, LFOG, JLA, MOG and RED.

Data entry: FS, LFOG and RED.

Statistical analysis using Review Manager 2014: FS, LFOG, JLA, MOG, and RED.

Other statistical analysis not using Review Manager 2014: RED and AK.

Interpretation of data: FS, LFOG, RED, MOG, AK, JLA.

Statistical inferences: FS, LFOG, RED, MOG, AK, JLA.

Writing the review: FS, LFOG, RED, MOG, AK, JLA.

Guarantor for the review: RED.

Reading and checking review before submission: FS, LFOG, RED, MOG, AK, JLA.

DECLARATIONS OF INTEREST

Fiona Stewart: none known.

Luís Felipe Orsi Gameiro: none known.

Regina El Dib: none known.

Mônica Orsi Gameiro: none known.

Anil Kapoor: none known.

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SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- The National Institute for Health Research (NIHR), UK.

This project was supported byNIHR via Cochrane Infrastructure, Cochrane Programme Grant or Cochrane Incentive funding to the Incontinence Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service (NHS) or the Department of Health.

- NHS Grampian Endowment Research Grants, UK.

This project was also supported by NHS Grampian Endowment Research Grants.