Canadian Agency for Drugs and Technologies in Health

RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

TITLE: **The Use of the Electromotive Drug Administration System in Patients with Overactive Bladder: A Review of the Clinical Effectiveness, Safety, and Cost-Effectiveness**

DATE: 24 September 2014

CONTEXT AND POLICY ISSUES

Overactive bladder (OAB) is a urological condition characterized by frequent urination, the need to urinate leading to disruption of sleep (nocturia), and urinating unintentionally with or without urge incontinence.[1] OAB is often associated with overactivity of the bladder detrusor muscle, which represents the most common underlying idiopathic or neurogenic dysfunction.[2] It has been estimated that about one in six adults (17%) have OAB, and the prevalence of OAB increases with age.[3] Approximately 10% of children have symptoms that are severe enough to warrant a diagnosis of OAB.[4] Treatment for OAB includes behavioral modifications, pelvic floor rehabilitation, pharmacological agents (e.g., oral medication, intravesical instillation), electrical stimulation, or reconstructive surgery.[2,5,6] Intravesical instillation is a local drug delivery system though a catheter into the bladder that is widely used to treat bladder cancer and other conditions.[7-9] However, some substances are not readily absorbed through the low permeability of the intact urothelium leading to limited effectiveness of the treatment.[9,10]

Electromotive drug administration (EMDA) represents a minimally-invasive method of intravesical instillation of therapeutic agents without the need of general anesthesia.[10,11] It employs a combination of iontophoresis, electrophoresis, and electroporation to deliver drugs into deep tissue layers using an electrical current created between two electrodes.[10,12] The EMDA system consists of a current generator, catheter-electrodes, and accessories.[12] The Physionizer 30 Mini is a pulse DC generator widely used for EMDA.[12] Lidocaine and epinephrine are used for local anesthesia during the EMDA procedure.[12] EMDA has been used to deliver drugs for a number of conditions including inflammation of the bladder (cystitis), inflammation of the prostate (prostatitis), bladder cancer, and OAB.[11,13,14] Drug administration by EMDA in laboratory studies in the treatment of bladder pathologies and dysfunctions include botulinum toxin A, oxybutynin, mitomycin C, resiniferatoxin, verapamil, and dexamethasone.[10] Botulinum toxin A, an acetylcholine release blocking agent, has been thought to reduce the detrusor overactivity through ephemeral detrusor smooth muscle paralysis.[6] Delivery of verapamil and dexamethasone through EMDA has been used for treatment of Peyronie's disease, an erectile dysfunction.[10]

The aim of this report is to review the clinical effectiveness, safety and cost-effectiveness of EMDA for treatment of OAB.

RESEARCH QUESTIONS

1. What is the clinical effectiveness and safety of the electromotive drug administration system for patients with overactive bladder?
2. What is the cost-effectiveness of the electromotive drug administration system in patients with overactive bladder?

KEY FINDINGS

Clinical evidence on the effectiveness of EMDA for treatment of overactive bladder is limited, and studies on cost-effectiveness could not be identified. EMDA therapy with botulinum toxin A for treatment of refractory neurogenic detrusor overactivity in children appears to be efficacious, while that with dexamethasone for treatment of idiopathic detrusor overactivity in adults does not.

METHODS

Literature search strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 8), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and August 25, 2014.

Selection criteria and method

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to the selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with overactive bladder (all ages)
Intervention	Electromotive drug administration - Of anesthesia (e.g., lidocaine) prior to injection with drug, abolishing need for general anesthesia - Of drug (e.g., Botulinum toxin A)
Comparator	No comparator or Drug administration without electromotive system
Outcomes	Clinical benefit (urodynamic parameters, need for general anesthesia) Clinical harm (adverse events) Cost effectiveness

Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), non-randomized studies, and economic evaluations

Exclusion criteria

Articles were excluded if they did not satisfy the selection criteria in Table 1, if they were published prior to 2009, duplicate publications of the same study, or included in selected health technology assessment of systematic review.

Critical appraisal of individual studies

The Downs and Black checklist for RCTs and non-RCTs were used to for quality assessment of the included studies.[15] Economic studies were assessed using the Critical Appraisal Checklist for Economic Evaluations.[16] A numeric score was not calculated, instead the individual strengths and limitations of the included studies were described narratively.

SUMMARY OF EVIDENCE

Quantity of research available

The literature search yielded 82 citations. Upon screening titles and abstracts, 80 citations were excluded and two potentially relevant articles were retrieved for full-text review. No additional relevant reports were retrieved from grey literature or hand searching. After full-text review, two prospective non-randomized studies (before-and-after design) were included. No economic evaluation studies were identified. The process of study selection is outlined in the PRISMA flowchart (Appendix 1).

Summary of study characteristics

The characteristics of two prospective non-randomized studies[17,18] are presented in Appendix 2.

The study by Kajbafzadeh et al. (2011)[17] included 15 children (11 girls, 4 boys; mean age: 7.8 ± 2.6 years, range 3 to 12 years) with myelomeningocele and refractory neurogenic detrusor overactivity. These patients had urinary/fecal incontinence and had shown no response to clean intermittent catheterization and maximal dose of oral anticholinergics, or had serious side effects from these treatments. Children with coagulopathies and those receiving gentamycin were excluded from the study. Four key outcomes were recorded at baseline and at 1, 4 and 9 months after one treatment of EMDA-therapy. They were daytime incontinence, vesicoureteral reflex, urodynamics (reflex volume, end-fill pressure, maximal detrusor pressure, and maximal bladder capacity), and bowel function. Treatment-related side effects were also recorded. During EMDA therapy, catheterization was performed with a local transurethral anesthesia with 2% lidocaine gel. The intravesical drug solution consisted of botulinum toxin type A at a dose of 10 IU/kg. The catheter and electrode pads were attached to a pulse current generator (Physionizer Mini 30N), which was adjusted to deliver a maximal current of 10 mA (100 µA increments/s) for 15 minutes. The study was conducted at a urology clinic in Iran. The source of funding was not reported.

The study by Bach et al. (2009)[18] included 84 idiopathic detrusor overactivity adult patients (72 women, 12 men; mean age: 63.1 ± 13.0 years). These patients were previously treated with

antimuscarinic (anticholinergic) agents for at least eight weeks with no improvement of urgency. Patients were excluded if they had neural deficiencies or symptoms during physical examination, previous spinal surgery, or an infectious urine sample. Outcome measures included urodynamics (first desire to void volume (FDV), strong desire to void volume (SDV), maximal cystometric bladder capacity (MCBC), patients showing an uninhibited detrusor contraction (UIC), quality of life (using Kings Health Questionnaire), and micturition chart (micturition volume, pads in 24 hours, daytime frequency, and nocturia). The outcomes were recorded at baseline and at four weeks after first EMDA, four weeks after second EMDA, and eight weeks after third EMDA. Complications related to EMDA were also recorded. Intravesical drug solution for EMDA therapy consisted of lidocaine and dexamethasone solution. Epinephrine was added to prolong the anesthetic effect of lidocaine and to prevent the systemic resorption of lidocaine. The two electrodes were connected to a pulse DC generator (Physionizer Mini 30N). The current was increased progressively to a maximum 30 mA for 30 minutes. The study was conducted at a urology clinic in Germany. The source of funding was not reported.

Summary of critical appraisal

The strengths and limitations of the two non-randomized studies are presented in Appendix 3. Both studies were generally well reported, but had limitations in internal and external validity including patient characteristics and generalizability. Both lacked randomization, blinding the patients and assessors, and did not report sufficient power to detect a clinically important effect. Therefore, they were prone to several biases including selection, detection, and estimator biases. In both studies, the length of follow-up was similar for all patients, and patients were recruited in a specified time period. This minimizes the possibility that any changes in care during the study period would differentially affect patients. However, the uncontrolled before-after study design makes it difficult to ascribe treatment affects solely to the intervention and not to other changes that may have occurred during the study period.

Summary of findings

The summary of results of the two included studies is presented in Appendix 4.

In the study by Kajbafzadeh et al. (2011),[17] daytime incontinence had significantly improved at one month, and the effect persisted until 9 months after treatment (2.25 ± 0.7 at baseline versus 1 ± 0.74; $P = 0.03$). The level of incontinency was categorized according to the scoring system defined as: 0, completely dry; 1, wet once daily, usually at night; 2, wet ≤50% of the time between catheterizations; and 3, wet >50% of the time between catheterizations. From 12 patients having vesicoureteral reflux (VUR) of different grades at baseline, there were no patients having VUR of grade 3 or greater, and 7 patients (58.3%) experienced VUR grade reduction at 9 months after treatment. VUR was diagnosed at cystosonography when microbubbles appeared in a ureter or renal pelvis. A VUR of grade 3 indicates mild to moderate dilatation of the pelvicaliceal system. Bowel dysfunction improvement was completely successful in 6 out of 12 (50%), moderately successful in 4 out of 12 (33%), and failed 2 out of 12 (16.6%). All urodynamic variables recorded in this study were statistically significantly improved at all three follow-up sessions (1, 4 and 9 months) compared to baseline values. EMDA-related side effects included transient skin erythema at the site of the skin electrodes (4 patients, 27%) and burning sensation at the urethral orifice (2 patients, 13%). The authors concluded that the EMDA therapy with botulinum toxin A is a feasible, effective and safe method for treatment of refractory neurogenic detrusor overactivity in children.

In the study by Bach et al. (2009),[18] urodynamic variables were significantly improved at 4 weeks after the first and second EMDA treatments. However, the statistically significant differences were abolished at 8 weeks after the third EMDA session. Similar observations were found for Kings Health Questionnaire (measuring quality of life) and the two components in the micturition chart (micturition volume and nocturia). The reduction in the number of pads used in 24 hours and daytime frequency remained statistically significant at 8 weeks after the third EMDA. Two patients discontinued treatment due to development of erythema of the abdominal skin underneath electrodes. The rate of drop-out after two EMDA sessions was 10.7%. Thus, EMDA therapy in this study appears to be effective after the first two sessions only, and the improvements diminished after the third EMDA treatment.

Limitations

Both studies lacked a control group; thus, it was not possible to rule out the placebo effect or the additional beneficiary effect of the electrostimulation induced by EMDA procedure. Additionally, evidence was limited to EMDA with botulinum toxin A or dexamethasone; evidence regarding other drugs that may be used is lacking. Patient reported outcomes in both studies were prone to subjectivity or might not be captured at an ideal time point. The findings could not be extrapolated to the general population since the sample size in the study by Kajbafzadeh et al. (2011)[17] was small (N=15), and the determination of the sample size in Bach et al. (2009) [18] (N=84), as well as how the sample population was selected in the study, was not reported.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Evidence on cost effectiveness of EMDA therapy for overactive bladder could not be identified. Clinical evidence on the effectiveness of EMDA for treatment of overactive bladder is limited to two prospective non-randomized studies. EMDA therapy with botulinum toxin A appears to be efficacious for treatment of refractory neurogenic detrusor overactivity in children, despite small sample size. For adults with idiopathic detrusor overactivity, the short term efficacy of EMDA therapy with dexamethasone could not be maintained after the third procedure. Skin erythema at the site of the skin electrodes was a common EMDA-related side effect. Given the limitations of the current clinical evidence, the findings should be interpreted with cautions when applying to a broader population. Well-designed trials are still needed to evaluate the efficacy and safety of the treatment.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

REFERENCES

1. Kenny T, Tidy C. Overactive bladder syndrome [Internet].Egton Medical Information Systems (EMIS); 2013 Nov 11. [cited 2014 Sep 23]. Available from: http://www.patient.co.uk/pdf/4768.pdf

2. Sacco E, Tienforti D, D'Addessi A, Pinto F, Racioppi M, Totaro A, et al. Social, economic, and health utility considerations in the treatment of overactive bladder. Open Access J Urol [Internet]. 2010 [cited 2014 Sep 23];2:11-24. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3818873/pdf/oaju-2-011.pdf

3. Gormley EA, Lightner DJ, Burgio KL, Chai TC, Clemens JQ, Culkin DJ, et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline. J Urol. 2012 Dec;188(6 Suppl):2455-63.

4. Chen YS, Yang S, Chang SJ. Overactive bladder during childhood: when and how it should be treated. Incont Pelvic Floor Dysfunct [Internet]. 2010 [cited 2014 Sep 8];4(1):13-7. Available from: http://www.tcs.org.tw/issue/Folder/4_1/13_17.pdf

5. Urinary incontinence. The management of urinary incontinence in women [Internet]. London (UK): National Institute for Clinical Excellence; 2013 Sep. [cited 2014 Sep 3]. (NICE clinical guideline 171). Available from: http://www.nice.org.uk/guidance/cg171/resources/guidance-urinary-incontinence-pdf

6. Geoffrion R. Treatments for overactive bladder: focus on pharmacotherapy. J Obstet Gynaecol Can. 2012 Nov;34(11):1092-101.

7. Hsu CC, Chuang YC, Chancellor MB. Intravesical drug delivery for dysfunctional bladder. Int J Urol. 2013 Jun;20(6):552-62.

8. Treatment into the bladder [Internet]. London (UK): Cancer Research UK; 2013 Oct 24. [cited 2014 Sep 3]. Available from: http://www.cancerresearchuk.org/cancer-help/type/bladder-cancer/treatment/early/treatment-into-the-bladder

9. Butte K, Momin M, Kurhade S, Kar S. Intravesical drug delivery system for bladder: an overview. Int J Pharm Chem Biol Sci [Internet]. 2013 [cited 2014 Sep 8];3(3):680-91. Available from: http://www.ijpcbs.com/files/31-3137.pdf

10. Giannantoni A, Di Stasi SM, Chancellor MB, Costantini E, Porena M. New frontiers in intravesical therapies and drug delivery. Eur Urol. 2006 Dec;50(6):1183-93.

11. What is electromotive drug administration? [Internet]. London (UK): Cancer Research UK; 2013 Oct 25. [cited 2014 Sep 3]. Available from: http://www.cancerresearchuk.org/cancer-help/about-cancer/cancer-questions/what-is-electromotive-drug-administration

12. EMDA: electromotive drug administration [Internet]. Dingwall (UK): Albyn Medical Let.; 2011. [cited 2014 Sep 3]. Available from: http://www.albynmedical.com/ImageStore/1982e136-fa04-4079-94a5-1cb3f25eb2ab.pdf

13. Electromotive drug administration of mitomycin-c for non-muscle invasive bladder cancer [Internet]. London (UK): Guy's and St Thomas' NHS Foundation Trust; 2014. [cited 2014

Sep 3]. Available from: http://www.guysandstthomas.nhs.uk/resources/patient-information/urology/bladder/3374-electromotive-mitomycin-c.pdf

14. Gauruder-Burmester A, Biskupskie A, Rosahl A, Tunn R. Electromotive drug administration for treatment of therapy-refractory overactive bladder. Int Braz J Urol. 2008 Nov;34(6):758-64.

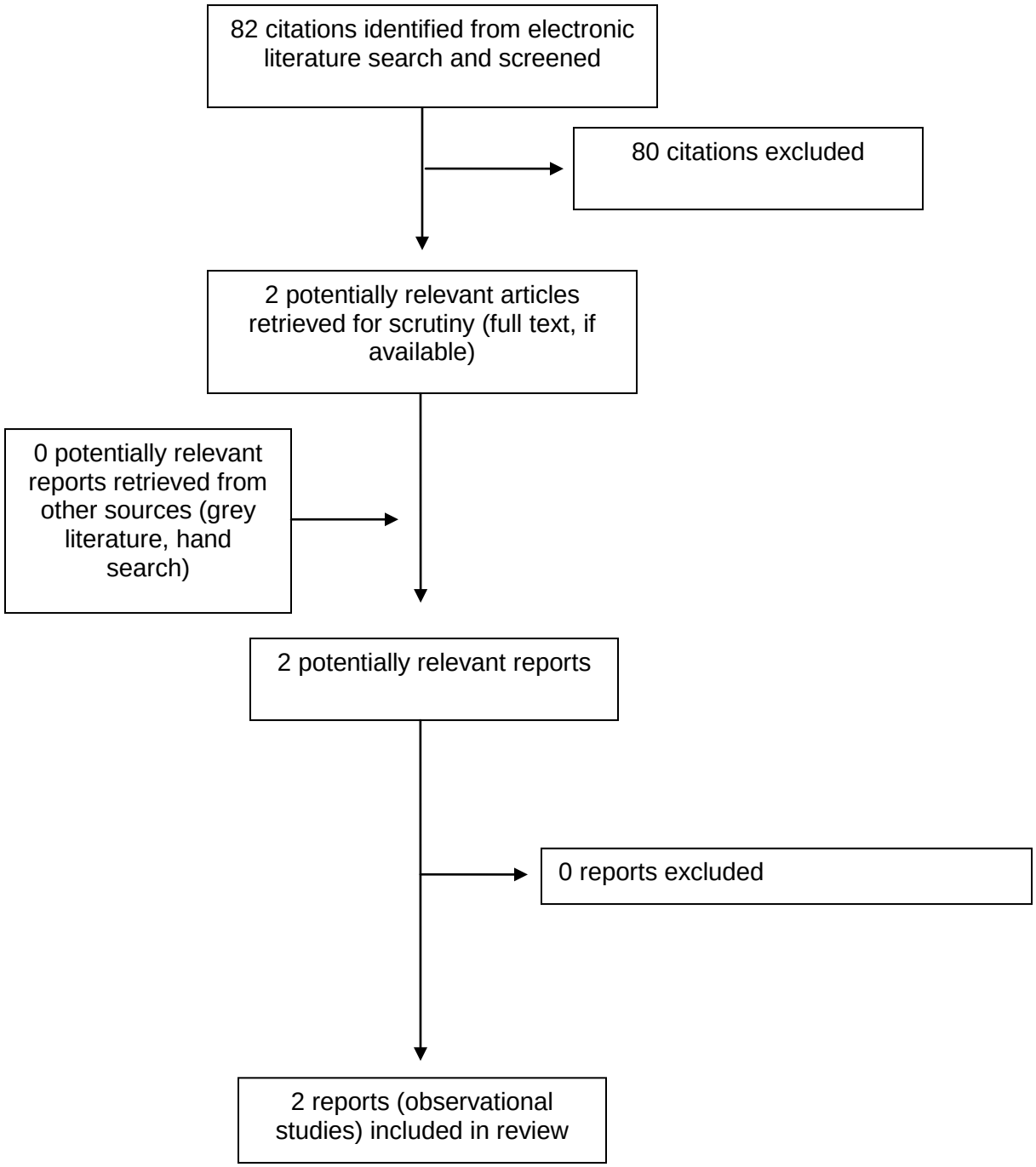
15. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health [Internet]. 1998 Jun [cited 2014 Sep 23];52(6):377-84. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf

16. Critical appraisal checklist for economic evaluations. Study design: any research design incorporating an economic evaluation [Internet]. Glasgow (UK): University of Glasgow; 2014. [cited 2014 Sep 3]. Available from: http://www.gla.ac.uk/media/media_64048_en.pdf

17. Kajbafzadeh AM, Ahmadi H, Montaser-Kouhsari L, Sharifi-Rad L, Nejat F, Bazargan-Hejazi S. Intravesical electromotive botulinum toxin type A administration--part II: Clinical application. Urology. 2011 Feb;77(2):439-45.

18. Bach P, Wormland RT, Mohring C, Goepel M. Electromotive drug-administration: a pilot study for minimal-invasive treatment of therapy-resistant idiopathic detrusor overactivity. Neurourol Urodyn. 2009;28(3):209-13.

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Clinical Studies

Author, year, type of study, country, funding source	Inclusion and exclusion criteria	Interventions	Key Outcomes
Kajbafzadeh et al. (2011)[17] Prospective non-randomized study Iran Source of funding: not reported	*Inclusion*: • Children with myelomeningocele and refractory neurogenic detrusor overactivity (mean age: 7.8 ± 2.6 years, range 3 to 12); N=15 (11 girls, 4 boys) • Had urinary /fecal incontinence • No response to clean intermittent catheterization and maximal dose of oral anticholinergics or had serious side effects from these treatments *Exclusion*: • Children with coagulopathies and those receiving gentamycin	EMDA-therapy (lidocaine [2% gel] and botulinum toxin type A [10 IU/kg]) with two electrodes connected to a pulse DC generator (Mini 30N Physionizer); maximal current 10 mA (100 µA increments/s) for 15 min. Follow-up: 1, 4 and 9 months after treatment using the completed voiding dairy	• Daytime incontinence • Vesicoureteral reflex • Urodynamics (reflex volume, end-fill pressure, maximal detrusor pressure, and maximal bladder capacity) • Bowel function • Side effects
Bach et al. (2009)[18] Prospective non-randomized study Germany Source of funding: not reported	*Inclusion*: • Idiopathic detrusor overactivity adult patients (mean age: 63.1 ± 13 years); N=84 (72 women, 12 men) • Previously treated with antimuscarinic (anticholinergic) agents for at least 8 weeks with no improvement of urgency *Exclusion*: • Patients with neural deficiencies or symptoms during physical examination • Patients with previous final surgery or an infectious urine sample	EMDA-therapy (lidocaine and dexamethasone) with two electrodes connected to a pulse DC generator (Mini 30N Physionizer); maximal current 30 mA for 30 min. Follow-up: • 4 weeks after 1st EMDA • 4 weeks after 2nd EMDA • 8 weeks after 3rd EMDA	• Urodynamics (FDV, SDV, MCBC, UIC) • Micturition chart (micturition volume, pads in 24 hr, daytime frequency, nocturia) • QoL (Kings Health questionnaire) • Side effects

EMDA = electromotive drug-administration; FDV = first desire to void volume; MCBC = maximal cystometric bladder capacity; QoL = quality of life; SDV = strong desire to void volume; UIC = patients showing an inhibited detrusor contraction

APPENDIX 3: Critical Appraisal of Clinical Studies

Author, year, type of study	Strengths	Limitations
Kajbafzadeh et al. (2011)[17] Design: Before-and-after	• The objective of the study was clearly described • The main outcomes were clearly described in the methods section • The lengths of follow-up were similar for all patients • Patients were recruited in a specified time period	• The characteristics of the patients included in the study were not clearly described • Adverse events were not clearly reported • Patients might not be representative of the entire population • No attempt was made to blind the assessors measuring the main outcomes • A power calculation was not reported for the primary outcome • Unclear if the study had sufficient power to detect a clinically important effect • Actual *P* values were not reported
Bach et al. (2009)[18] Design: Before-and-after	• The objective of the study was clearly described • The main outcomes were clearly described in the methods section • The lengths of follow-up were similar for all patients • Patients were recruited in a specified time period • Actual *P* values were reported	• The characteristics of the patients included in the study were not clearly described • Adverse events were not clearly reported • The characteristics of patients lost to follow-up were not reported • Patients might not be representative of the entire population • No attempt was made to blind the assessors measuring the main outcomes • A power calculation was not reported for the primary outcome • Unclear if the study had sufficient power to detect a clinically important effect

APPENDIX 4: Summary of Results of Clinical Studies

Author, year, type of study, country, funding source	Results	Comments
Systematic Review		
Kajbafzadeh et al. (2011)[17] Design: Before-and-after Iran Source of funding: not reported	From baseline to 9 months: Day time incontinence Mean score: 2.25 ± 0.7 to 1.0 ± 0.74 (p = 0.03) Vesicoureteral reflux (VUR) From 12 patients (80%) having VUR of different grades at baseline to no patients having VUR of grade 3 or greater and 7 patients (58.3%) experienced VUR grade reduction. Urodynamics Reflex volume (ml): 99 to 216 (p = 0.005) Maximal bladder capacity (ml): 121 to 262 (p = 0.001) Bladder capacity (ml): 40 to 87.7 (p < 0.001) Maximal detrusor pressure (cm H_2O): 75 to 39 (p < 0.001) End-fill pressure (cm H_2O): 22 to 13 (p = 0.001) Bowel dysfunction improvement Complete success: 6 of 12 (50%) Moderate success: 4 of 12 (33%) Failure: 2 of 12 (17%) Procedure-related side effects Transient skin erythema at the site of the skin electrodes: 4 patients Burning sensation at the urethral orifice: 2 patients	
Authors' conclusions: "…*electromotive botulinum toxin type A administration is a feasible and safe method with no need for anesthesia. This novel delivery system resulted in considerable improvement in the urodynamic parameters, urinary/fecal incontinence, and VUR in patients with refractory neurogenic detrusor overactivity.*" p.439		
Bach et al. (2009)[18] Design: Before-and-after Germany Source of funding: not reported	From baseline to 4 weeks after 2nd EMDA (total 8 weeks): Urodynamics FDV (ml): 94.0 to 142.2 (p = 0.0064) SDV (ml): 155.6 to 199.5 (p = 0.001) MCBC (ml): 192.3 to 239.6 (p = 0.018) UIC (n): 84 to 39 (p = 0.001) Kings Health Questionnaire QoL (Part III): 11.8 to 7.3 (p = 0.018) Micturation chart	Statistically significant differences were showed all outcomes after 2nd EMDA

Author, year, type of study, country, funding source	Results	Comments
	MV (ml): 186.0 to 242.3 (p = 0.043) Pads in 24 hr: 4.5 to 2.5 (p < 0.01) DF: 14.1 to 9.4 (p < 0.0001) Nocturia: 5.1 to 2.5 (p = 0.035) Procedure-related side effect Skin erythema underneath electrodes: 2 patients Pain during EMDA: 2 patients	
	From baseline to 8 weeks after 3nd EMDA (total 16 weeks): Urodynamics FDV (ml): 94.0 to 127.3 ml (*NS*) SDV (ml): 155.6 to 163.0 (*NS*) MCBC (ml): 192.3 to 184.8 (*NS*) UIC (n): 84 to 64 (*NS*) Kings Health Questionnaire QoL (Part III): 11.8 to 10.1 (*NS*) Micturation chart MV (ml): 186.0 to 135.3 (*NS*) Pads in 24 hr: 4.5 to 1.8 (p < 0.0074) DF: 14.1 to 9.3 (p < 0.0001) Nocturia: 5.1 to 4.3 (*NS*)	Most outcome values showed no statistically significant differences compared to those of baseline after 3rd EMDA
Authors' conclusions: "*EMDA significantly improves urodynamic parameters, QoL and pad usages in patients with urge syndrome and therapy-resistant IDO. Therefore, we offer EMDA therapy as an alternative treatment modality to the standard approaches.*" p. 209		

DF = daytime frequency; EMDA = electromotive drug-administration; FDV = first desire to void volume; IDO = idiopathic detrusor overactivity; MCBC = maximal cystometric bladder capacity; MV = micturition volume; n = number of patients; QoL = quality of life; SDV = strong desire to void volume; UIC = patients showing an uninhibited detrusor contraction; VUR = vesicoureteral reflux