Interventional procedure overview of electrically stimulated intravesical therapy for interstitial cystitis or overactive bladder in adults

Contents

Table 1 Abbreviations

Abbreviation	Definition
BPS	Bladder pain syndrome
CI	Confidence interval
DO	Detrusor overactivity
EMDA	Electromotive drug administration
GRA	Global response assessment
HR	Hazard ratio
IC	Interstitial cystitis
IQR	Interquartile range
KHQ	King's Health Questionnaire
MMC	Myelomeningocele
NDO	Neuropathic detrusor overactivity
OAB	Overactive bladder
OR	Odds ratio
QoL	Quality of life
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
UTI	Urinary tract infection
VAS	Visual analogue scale

Indications and current treatment

Interstitial cystitis

Interstitial cystitis, also known as bladder pain syndrome (BPS), is a chronic inflammatory condition of the bladder. The main symptoms are pelvic pain, urinary urgency, urinary frequency and nocturia. Symptoms can last for several months or years. It is diagnosed by exclusion and is challenging to treat.

Current treatment options aim to reduce symptoms and include:

- lifestyle changes, such as dietary changes and stopping smoking
- medication

- intravesical therapy
- intradetrusor botulinum toxin injection
- neuromodulation
- sacral nerve stimulation
- cystoscopy plus hydrodistension.

Overactive bladder

OAB is defined as urinary urgency, usually with urinary frequency and nocturia, with or without urinary incontinence. In some people, it is accompanied by uncontrolled contractions of the detrusor muscle during bladder filling, called detrusor overactivity. It is diagnosed based on symptoms and is challenging to treat.

Current treatment options aim to reduce symptoms and include:

- physical therapies, such as pelvic floor muscle training
- medication
- percutaneous posterior tibial nerve stimulation
- intravesical therapy
- intradetrusor botulinum toxin injection
- sacral nerve stimulation.

Unmet need

Interstitial cystitis

Interstitial cystitis is a chronic condition with unknown aetiology and can have a substantial effect on a person's quality of life. Current treatments are generally aimed at controlling the symptoms. It is challenging to treat and there is an unmet need for other treatments. Bladder removal may be considered for some people

when other treatment options have been ineffective. This procedure aims to offer a more effective option than bladder instillations without electrical stimulation.

Overactive bladder

OAB is a chronic condition that interferes with daily activities and can have a substantial effect on a person's quality of life and mental health. Current treatments are generally aimed at reducing the symptoms. Bladder reconstruction (such as augmentation cystoplasty) and urinary diversion may be an option when symptoms do not respond to conservative treatment. This procedure aims to offer a more effective option than bladder instillations without electrical stimulation.

What the procedure involves

Electrically stimulated intravesical therapy, also known as electromotive drug administration (EMDA), involves using a device to create an electrical field across the bladder tissue. It has 2 mechanisms: transporting ionised molecules through the tissues to apply an electric current to the solution that contains ions (iontophoresis) and transporting non-ionised molecules with the solvent flow (electro-osmosis). This process increases the amount of medicine absorbed compared with only passive diffusion. This procedure is contraindicated for people with a urinary tract infection.

This procedure is done with the person lying in a supine position. It is done using a topical local anaesthetic. An electrode catheter is inserted into the person's bladder through the urethra. The bladder is flushed and drained. A medicine solution is then instilled into the bladder. Electrode pads are placed on the person's skin. The cutaneous and intravesical electrodes are then connected to a generator, which releases electrical current, transmitted to the intravesical

electrode. After the procedure, the bladder is drained, and the catheter is removed.

Outcome measures

Reduction of urinary symptoms, including voiding frequency, and improvement in quality of life were the main outcomes reported for both indications. For interstitial cystitis, reduction of pain was also reported.

The KHQ was used as an outcome measure in 2 studies on OAB. This is a self-reported questionnaire designed to evaluate the impact of urinary incontinence on quality of life. There are 8 domains scored between 0 (best) and 100 (worst) and a symptom severity scale that is scored from 0 (best) to 30 (worst). Decreases in the KHQ domain scores indicate an improvement in quality of life. The minimally important difference has been reported as 3 points for the symptom severity scale and 5 points for all other KHQ domains.

One randomised prospective study on interstitial cystitis assessed the treatment response using the GRA. The GRA was defined as follows:

- 1: worse
- 2: no change
- 3: slightly better
- 4: moderately better
- 5: much better
- 6: completely cured.

People who reported categories 4 to 6 were considered to have had a response to treatment (Gulpinar 2014).

Evidence summary

Population and studies description

Interstitial cystitis

This interventional procedures overview is based on 73 adults from 1 randomised prospective study (Gulpinar 2014), 2 cohort studies (Rosamilia 1997; Riedl 1998a), 1 single-arm trial (Gurpinar 1996), and 1 case report (Hinkel 2004). Of these 73 people, 58 had the procedure. This is a rapid review of the literature, and a flow chart of the complete selection process is shown in figure 1a. This overview presents 4 studies as the key evidence in table 2a and table 3a, and lists 2 other relevant studies in appendix B, table 5a.

The randomised prospective study was the only comparative study (Gulpinar 2014), and was done in Turkey. The other key studies are single-arm cohort studies from Australia (Rosamilia 1997), Austria (Riedl 1998a) and the US (Gurpinar 1996). One case report (Hinkel 2004) described the safety outcome only. The mean age of people with interstitial cystitis considered for efficacy outcomes was between 42 and 62 years. Most of the people who had the procedure were female, as reported by the studies. Follow up was 24 months in the randomised study (Gulpinar 2014). In the 2 cohort studies, mean follow up was 6 months (Rosamilia 1997) and 10 months (Riedl 1998a). Follow up was between 3 months and 18 months in the single-arm trial (Gurpinar 1996). Table 2a presents study details. Follow up was not reported in the case report study (Hinkel 2004).

Overactive bladder

There was evidence from 184 adults from 2 prospective cohort studies done in Germany (Bach 2009, Gauruder-Burmester 2008), 1 prospective cohort study done in Norway (Schiotz 2017) and 1 prospective cohort study done in Austria

(Riedl 1998b). This is a rapid review of the literature, and a flow chart of the complete selection process is shown in figure 1b. This overview presents 4 studies as the key evidence in table 2b and table 3b and 2 other relevant studies in appendix B, table 5b.

Among the studies, the mean age of people with OAB having the procedure was between 60 and 67 years. Most of the people who had the procedure were women. One cohort study had 8 weeks follow up after the third EMDA (Bach 2009). One cohort study had 12 months follow up after the last EMDA treatment (Gauruder-Burmester 2008). One cohort study had 6 months of follow up after 1 outpatient EMDA session (Schiotz 2017). One study did not report the follow-up time (Riedl 1998b).

Figure 1a Flow chart of study selection of electrically stimulated intravesical therapy for interstitial cystitis

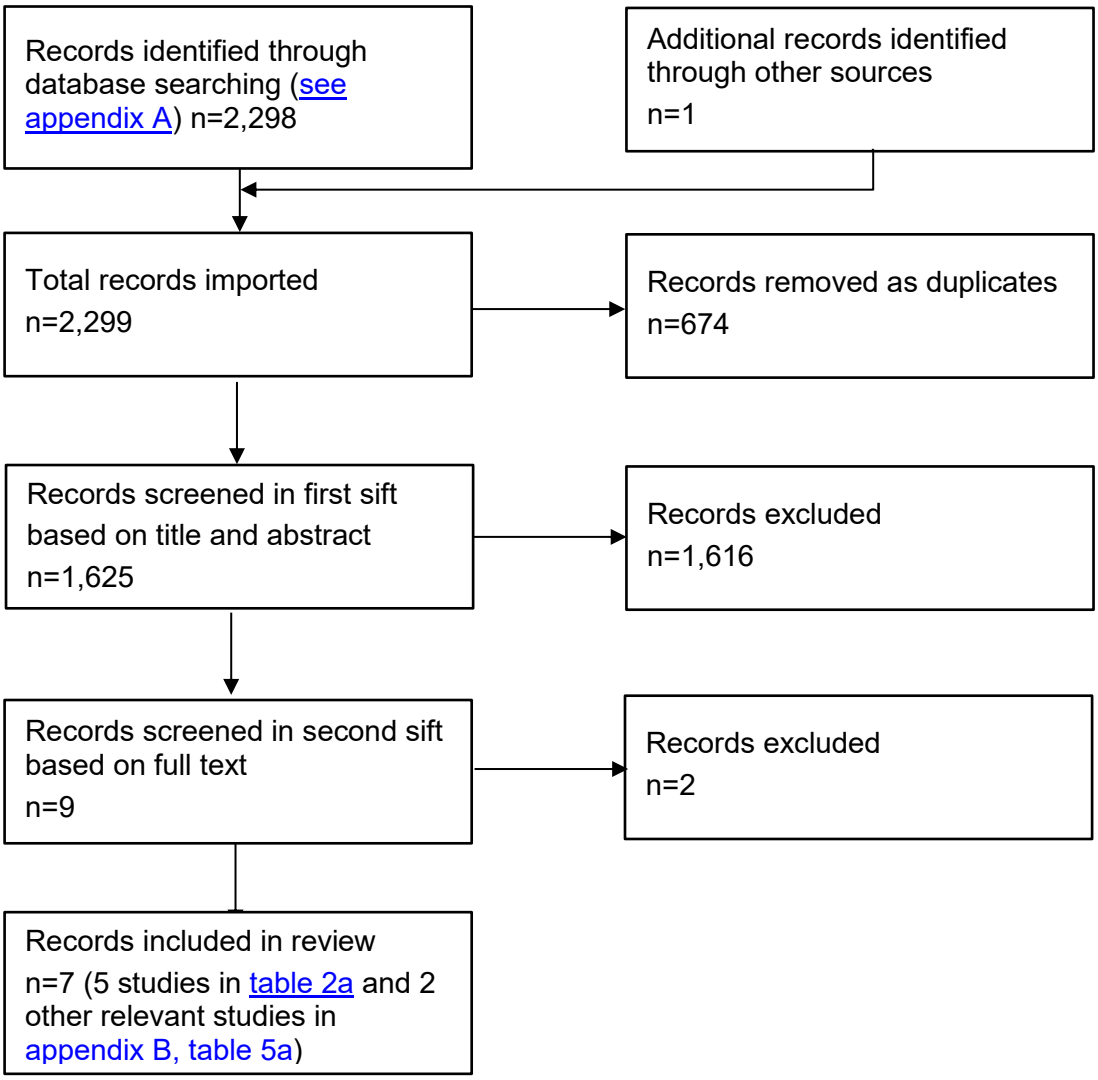

Figure 1b Flow chart of study selection of electrically stimulated intravesical therapy for overactive bladder

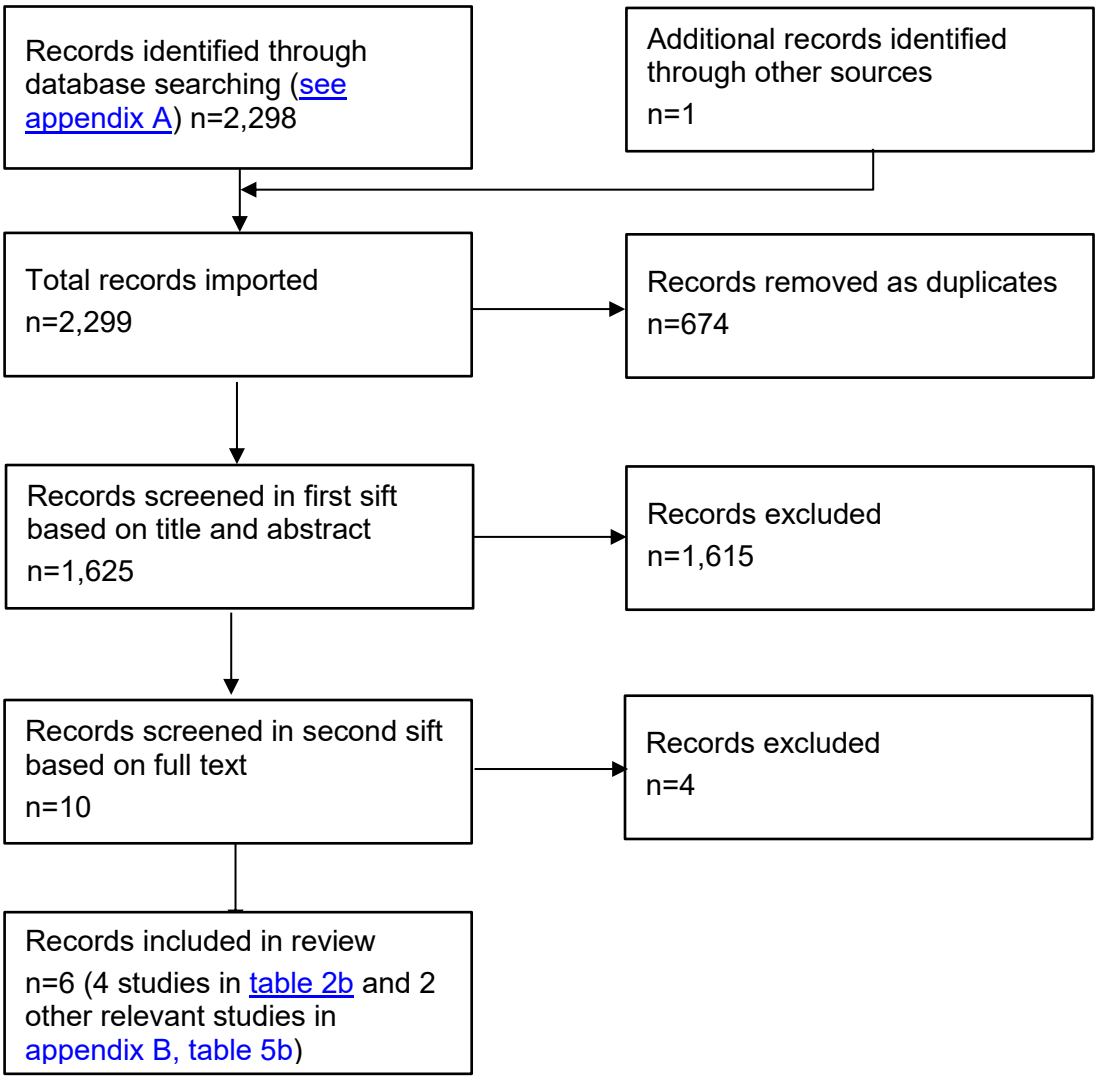

Table 2a Study details of electrically stimulated intravesical therapy for interstitial cystitis

Study no.	First author, date country	Characteristics of people in the study	Age (years)	Study design	Inclusion criteria	Intervention	Follow up
1	Gulpinar, 2014 Turkey	N=31 (male: female as reported by the study = 6:25) 16 intervention (3:13) and 15 comparator (3:12) intravesical hyaluronic acid via catheter	Mean in the EMDA group = 42.8 Mean in the catheter group = 43.5	Randomised prospective study	People who were diagnosed with BPS or IC between 2004 and 2005 according to the National Institute of Diabetes and Digestive and Kidney Diseases criteria for BPS or IC. Exclusion criteria: any other medication for IC during the study period, neurogenic bladder, history of pelvic surgery or trauma to the pelvic region, presence of active urinary tract infection, frequency of urination less	40 mg hyaluronic acid (Cythyal) in 40 ml saline instillation in the bladder administered through a special 16-Fr catheter for EMDA with a spiral silver electrode in the first part with EMDA: polarity positive, rise rate 30 to 60 mA/second, peak current 60 mA, pulsed output, and treatment time 25 minutes. **Comparator:** 40 mg intravesical hyaluronic acid administered through a hydrophilic 12-Fr Foley catheter, retained for at least 60 minutes. Both groups had weekly instillations in the first	24 months

Study no.	First author, date country	Characteristics of people in the study	Age (years)	Study design	Inclusion criteria	Intervention	Follow up
					than 8 times, presence of bladder or lower ureteral calculi, benign or malignant bladder tumours, active genital herpes infection, or chemical or radiation cystitis.	month, and then monthly after 2 months.	
2	Rosamilia, 1997 Australia	N=21 (male: female as reported by the study = 0:21) N=24 procedures; 3 people had a repeat procedure	Median = 48 (range 22 to 80)	Cohort study	Females with IC diagnosed using National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases Workshop	2% sodium chloride-free lidocaine hydrochloride, adrenaline 1.5 mg and dexamethasone 16 mg in 150 ml sterile water. Administered using a 18-Fr catheter commercially fitted with a silver-coated anode, and EMDA with 30 mA current for 20 to 30 minutes	6 months
3	Riedl, 1998a Austria	N=13 (male: female as reported by the study = 2:11) N=42 procedures; between 1 and 7	Mean = 62.2	Cohort study	People who were diagnosed with IC between December 1993 and July 1995 according to the US	People with low capacity-bladders (less than 250 ml): Lidocaine 2% 100 ml, dexamethasone 15 mg,	Mean 10 months (range: 3 to 22 months)

Study no.	First author, date country	Characteristics of people in the study	Age (years)	Study design	Inclusion criteria	Intervention	Follow up
		procedures per person			National Institute of Health criteria	epinephrine 0.5 mg. 15 mA current. People with bladder capacities over 250 ml: Lidocaine 2.6% 150 ml, dexamethasone 20 mg, epinephrine 0.75 mg. 22 mA current. Both groups had EMDA with the pulsed direct current for 20 minutes, followed by hydrodistension of the bladder up to 200% of the cystometric bladder capacity for 1 to 5 minutes. Retreatments performed at the person's request.	
4	Gurpinar, 1996 US	N=6 (men: women = 0:6)	Mean = 44.8 (range 28 to 60)	Single-arm trial	People with long-standing IC who had multiple IC modalities	100 ml lidocaine-epinephrine solution instillation administered using an 18-Fr, intraurinary silver-	Between 3 and 18 months

Study no.	First author, date country	Characteristics of people in the study	Age (years)	Study design	Inclusion criteria	Intervention	Follow up
						coated stainless-steel electrode catheter and through EMDA. A rise of current to 15 mA over 2 minutes, then 15 mA current maintained for additional 38 minutes.	
5	Hinkel, 2004 Germany	N=2 (male: female as reported by the study = 2:0)	Mean = 75 (range 72 to 78)	Case report	People with chronic non-infectious cystitis	100 ml lidocaine 4%, 2 ml epinephrine 1:1,000, 10 ml dexamethasone (40 mg), diluted in 100 ml Aquadest. Positive polarity, rise-rate 50 mA/second, current 22 mA, and pulse modus. Treatment time 30 minutes.	Not reported

Table 2b Study details of electrically stimulated intravesical therapy for overactive bladder

Study no.	First author, date country	Characteristics of people in the study	Age (years)	Study design	Inclusion criteria	Intervention	Follow up
1	Bach, 2009 Germany	N=84 (men: women = 12:72)	Median = 63.1	Prospective cohort study	People with idiopathic detrusor overactivity who had previously had antimuscarinic (anticholinergic) treatment for at least 8 weeks with no improvement of urgency. Exclusion criteria: neural deficiencies or symptoms during physical examination, previous spinal surgery, or an infectious urine sample	2,000 mg lidocaine-hydrochloride 4% (50 ml), 2 mg epinephrine (1:1,000) (2 ml), 40 mg dexamethasone-21-dihydrogen phosphate (10 ml) in a total volume of 100 ml administered via EMDA. 30 mA current for 30 minutes. EMDA was done at least 3 times in 4-weeks during 2-day hospital stays.	8 weeks (after the third EMDA)
2	Gauruder-Burmester, 2008 Germany	N=72 (men: women = 0:72)	Mean = 63 (SD 11.2)	Prospective cohort study	History of persisting OAB for over 24 months and therapeutic	100 ml 4% lidocaine hydrochloride (sodium chloride-free), 100 ml distilled water, 40 mg dexamethasone sodium	12 months (after the last treatment)

Study no.	First author, date country	Characteristics of people in the study	Age (years)	Study design	Inclusion criteria	Intervention	Follow up
					attempts with at least 2 different anticholinergic medicines and at least 6 months of physiotherapy without improvement or cure of symptoms: frequency (voiding more than 8 times a day), nocturia (voiding more than once a night), and urge incontinence	phosphate, and 2 ml epinephrine. 15 to 25 mA current for 20 to 25 minutes. 3 EMDA cycles, each with 3 instillations at 2-week intervals during a 3-day hospital stay.	
3	Schiotz, 2017 Norway	N=14 (men: women = 0:14)	Mean = 59.9 (SD 13.9, range 31 to 79)	Prospective cohort study	Women with severe, treatment resistant OAB, more than 3 months duration, failed conservative and pharmacological treatment and indication for standard cystoscopic	60 ml of normal saline with 200 Allergan units of botulinum toxin A administered via EMDA. 20 mA current for 30 minutes. 1 outpatient session.	6 months

Study no.	First author, date country	Characteristics of people in the study	Age (years)	Study design	Inclusion criteria	Intervention	Follow up
					injection of botulinum toxin. Exclusion criteria: age under 18 years, mixed incontinence with dominant stress incontinence, ongoing UTI, and contraindication to treatment with botulinum toxin.		
4	Riedl, 1998b Austria	N=14 (treatments n=29) (male: female as reported by the study = 4:10)	Mean = 67.3 (range 22 to 84)	Prospective cohort study	People with detrusor hyperreflexia or urge incontinence who did not tolerate or improve on oral anticholinergic medicines.	15 mg to 50 mg oxybutynin hydrochloride in 0.3% saline. 15 mA for 20 minutes.	Not reported

Table 3a Study outcomes of electrically stimulated intravesical therapy for interstitial cystitis

First author, date	Efficacy outcomes	Safety outcomes
Gulpinar, 2014	EMDA treatment associated with significantly higher treatment response (based on the global response assessment), HR: 2.457 (95% CI: 1.458 to 3.897), p=0.011. Overall, there were statistically significant differences in frequency, nocturia, and VAS between the 2 groups at 6 months and 12 months, but no statistically significant difference in any of these outcomes at 1 month and 24 months. **Voiding frequency (per 24 hours):** • 1 month, the EMDA group had a mean absolute change of -1.9 (SD 0.7) compared with -2.1 (SD 0.7) in the catheter group (p=0.152). • 6 months, the EMDA group had a mean absolute change of -7.9 (SD 0.7) compared with -5.1 (SD 0.7) in the catheter group (p=0.012). • 12 months, the EMDA group had a mean absolute change of -8.1 (SD 0.7) compared with -5.0 (SD 0.7) in the catheter group (p=0.022). • 24 months, the EMDA group had a mean absolute change of -3.8 (SD 0.7) compared	No SAE reported. No patients refused treatment because of side effects.

First author, date	Efficacy outcomes	Safety outcomes
	with -4.0 (SD 0.7) in the catheter group (p=0.341). **Nocturia (per night):** • 1 month, the EMDA group had a mean absolute change of -0.5 (SD 0.2) compared with -0.6 (SD 0.2) in the catheter group (p=0.354). • 6 months, the EMDA group had a mean absolute change of -2.5 (SD 0.2) compared with -1.6 (SD 0.2) in the catheter group (p=0.038). • 12 months, the EMDA group had a mean absolute change of -2.4 (SD 0.2) compared with -1.5 (SD 0.2) in the catheter group (p=0.024). • 24 months, the EMDA group had a mean absolute change of -1.5 (SD 0.2) compared with -1.6 (SD 0.2) in the catheter group (p=0.744). **VAS** • 1 month, the EMDA group had a mean absolute change of -1.0 (SD 0.6) compared with -1.1 (SD 0.6) in the catheter group (p=0.565). • 6 months, the EMDA group had a mean absolute change of -4.6 (SD 2.6) compared	

First author, date	Efficacy outcomes	Safety outcomes
	with -3.1 (SD 1.6) in the catheter group (p=0.013). • 12 months, the EMDA group had a mean absolute change of -4.8 (SD 2.4) compared with -3.0 (SD 1.6) in the catheter group (p=0.016). • 24 months, The EMDA group had a mean absolute change of -2.2 (SD 0.8) compared with -2.0 (SD 0.9) in the catheter group (p=0.632).	
Rosamilia, 1997	85% (18 out of 21) had a good response (reduction in pain score by 3 or more and reduction in frequency at 2 weeks). 63% were still having a response at 2 months. 25% (4 out of 16) had an excellent response (pain score of 0) at 6 months. Mean urinary frequency • Baseline: 15.5 (range 9 to 26, n=21) • 2 months: 11.1 (range 6 to 19, n=21), p<0.05 • 6 months: 12.7 (range 7 to 17, n=7), p>0.05 Median pain score • Baseline: 8 (range 2 to 10, n=21) • 2 weeks: 3 (range 0 to 8, n=21), p<0.05 • 2 months: 4 (range 0 to 10, n=21), p<0.05	No SAE reported. Erythema at abdominal electrode site was common but resolved within a few hours. Most people had haematuria at the end of draining the bladder.

First author, date	Efficacy outcomes	Safety outcomes
	• 6 months: 5 (range 0 to 9, n=16), p<0.05	
Riedl, 1998a	8 out of 13 had complete response, 3 out of 13 had partial response, 2 out of 13 deteriorated. Complete response: urgency and bladder pain in combination with a reduction of urinary frequency for at least 1 week. Partial response: reduction of bladder symptom for less than 1 week. Mean duration of symptom improvement: 4.5 months (0.75 to 17 range) 8 out of 13 people reported 'significant' QoL improvement. 12 people said EMDA was tolerable and they would undergo retreatment. 5 people said EMDA was ineffective, including 1 person who had a complete response for 2 months.	No SAE. Everyone had skin erythema observed within hours at abdominal electrode, no skin blistering. Two people showed bladder symptoms deterioration, occurred about 30 minutes after therapy, lasting for 1 to 4 days. Local anaesthesia was incomplete in both.
Gurpinar, 1996	Voiding symptoms decreased. Four people had durable and 'significant' response. Voiding-specific quality of life scores improved. 2 people had temporary improvement but subsequently had additional local bladder treatments	No SAE reported. No one experienced pain or significant discomfort. Some people reported a tingling sensation on the abdominal skin during the treatment.
Hinkel, 2004	Not reported	Both people showed signs of transient ischaemic attack signs, at 3 hours and 6 hours after having EMDA.

Table 3b Study outcomes of electrically stimulated intravesical therapy for overactive bladder

First author, date	Efficacy outcome	Safety outcomes
Bach, 2009	After second EMDA sessions (n=84), Mean voiding frequency per day Baseline= 14.1 (SE 7.7) 4 weeks= 9.4 (SE 6.2), p<0.0001 8 weeks= 9.3 (SE 4.1), p<0.0001 Nocturia per night Baseline= 5.1 (SE 5.1) 4 weeks= 2.5 (SE 2.4), p=0.035 8 weeks= 4.3 (SE 4.1), p>0.1 Impact of QoL Baseline= 11.8 (SE 3.2) 4 weeks= 7.3 (SE 4.1), p=0.018 8 weeks=10.1 (SE 3.5), p>0.1	No SAE reported. 2 people developed abdominal skin erythema underneath electrodes and complained about pain during the second EMDA session, resulting in the treatment being aborted.
Gauruder-Burmester, 2008	Voiding frequency per day decreased from 16 (SD 3) to 7 (SD 2). This was statistically significant (p=0.003). Decreased nocturia from 5 (SD 2) to 2 (SD 1). No statistical significance or p-value was reported.	No SAE reported. 12 women developed reactive hypertension during treatment, which returned to normal without any intervention. 21 people showed signs of dysuria and haematuria. 10 women experienced UTI

First author, date	Efficacy outcome	Safety outcomes
	QoL was improved in 54 people (75%) (p = 0.002). Sexual sensations and sexual satisfaction was improved in 39 people (54%) (p = 0.001)	1 person developed urinary retention, which disappeared after 2 catheterisation procedures.
Schiotz, 2017	Mean voiding frequency per 24 hours • Baseline=11 (SD 2.2, n=14) • 1 month=9.2 (SD 3.2, n=14), p=0.023 • 3 months=11.1 (SD 3.3, n=14), p=0.44 • 6 months=9.4 (SD 0.9, n=5), p=0.37 Mean incontinence episode per 24 hours • Baseline=5.5 (SD 3.8, n=14) • 1 month=2.2 (SD 2.6, n=14), p=0.001 • 3 months=3.3 (SD 3.2, n=14), p=0.01 • 6 months=2.4 (SD 0.9, n=5), p=0.01.	No SAE. Most people had transient, mild, painless abdominal skin erythema for a few hours after treatment. 3 episodes of acute cystitis in 2 people with prior history of recurrent UTI.
Riedl, 1998b	3 people had improved bladder symptoms for more than 1 week, 4 people had improved bladder symptoms for less than 1 week, 4 people had no improvement.	No local or systemic side effects were observed. Treatment was stopped in 3 people because of bladder contractions and leakage.

Procedure technique

Interstitial cystitis

Of the 5 studies, 3 single-arm cohort studies (Riedl 1998a, Rosamilia 1997, Gurpinar 1996), and 1 case report study (Hinkel 2004) named the manufacturer of the current generator device used for EMDA. The randomised prospective study did not name the generator used but mentioned the use of the 16-Fr special catheter designed by the same manufacturer (Gulpinar 2014). The medicine solution and electric current used in EMDA varied within and between studies. The medicine solution included hyaluronic acid, lidocaine hydrochloride with adrenaline and dexamethasone, and lidocaine with adrenaline. The electric current used was between 15 mA and 60 mA. The procedure time varied between studies from 20 to 38 minutes. The number of procedures varied between studies.

Overactive bladder

Of the 4 studies, 3 studies named the same device from the same manufacturer used for EMDA (Bach 2009, Gauruder-Burmester 2008, Schiotz 2017). The medicine solution, electric current and treatment time given in EMDA varied between studies. The medicine solution included lidocaine with dexamethasone and adrenaline, botulinum toxin A in normal saline, and oxybutynin hydrochloride. The electric current used was between 15 mA and 30 mA with 20 to 30 minutes treatment time.

The number of procedures per person varied between studies. Two prospective cohort studies in an adult population did the procedure 3 times with hospital stays (Bach 2009 and Gauruder-Burmester 2008). One prospective cohort study did the procedure once in an outpatient setting (Schiotz 2017).

Efficacy

Interstitial cystitis

Frequency

Two studies reported data on voiding frequency.

In the randomised prospective study comparing the administration of hyaluronic acid via EMDA (n=16) with standard intravesical treatment (n=15), at 6 months the EMDA arm had a mean absolute change of voiding frequency per day of -7.9 (SD 0.7) compared with -5.1 (SD 0.7) in the catheter group. This difference was statistically significant (p = 0.012). At 12 months, The EMDA group had a mean absolute change of -8.1 (SD 0.7) compared with -5.0 (SD 0.7) in the catheter group. This difference was also statistically significant (p=0.022). But, no statistically significant difference was observed at 1 month and 24 months follow up (Gulpinar 2014).

In a single-arm cohort study of 21 people, the mean urinary frequency per 24 hours at 2 months after EMDA was 11.1 compared with 15.5 at baseline (p=0.004). But, at 6 months follow up, the mean urinary frequency per 24 hours was 12.7 (n=7), which was not statistically significantly different (p value not reported; Rosamilia 1997).

Nocturia

The randomised prospective study of 31 people was the only study reporting data on nocturia. At 6 months, the EMDA group had a mean absolute change of nocturia per night of -2.5 (SD 0.2) compared with -1.6 (SD 0.2) in the catheter group. This difference was statistically significant (p=0.038). At 12 months, the EMDA group had a mean absolute change of -2.4 (SD 0.2) compared with -1.5 (SD 0.2) in the catheter group. This difference was also statistically significant

(p=0.024). In line with the frequency outcome, no statistically significant mean difference of nocturia between hyaluronic acid through EMDA compared with a catheter was observed at 1 month and 24 months follow up (Gulpinar 2014).

Pain

Two studies reported data on pain.

In the randomised prospective study of 31 people, pain was measured using VAS. At 6 months, the EMDA group had a mean absolute change of -4.6 (SD 2.6) compared with -3.1 (SD 1.6) in the catheter group. This difference was statistically significant (p=0.013). At 12 months, The EMDA group had a mean absolute change of -4.8 (SD 2.4) compared with -3.0 (SD 1.6) in the catheter group. This difference was statistically significant (p=0.016). Similar to the frequency and nocturia, there was no statistically significant difference in pain at 1-month and 24-month follow up (Gulpinar 2014).

In the single-arm cohort study of 21 people, the pain was measured using a 0 to 10 scale. The median pain score before treatment was 8. The median pain scores were 3 at 2 weeks after EMDA (n=21), 4 at 2 months after EMDA (n=21), and 5 at 6 months after EMDA (n=16). The reductions in pain score in all 3 follow-up periods were statistically significant (p<0.05; Rosamilia 1997).

Treatment response

One randomised prospective cohort study compared the treatment response of hyaluronic acid administered with EMDA compared with a catheter, based on the GRA score. Treatment with EMDA was associated with higher response rates, with HR: 2.457 (95% CI 1.458 to 3.897), p=0.011.

Complete and partial response

One single-arm cohort study described a complete response as the complete resolution of urgency and bladder pain in combination with a reduction of urinary

frequency for at least 1 week. A partial response was defined as the reduction of the bladder symptom for less than 1 week. A total of 8 out of 13 (62%) people had complete response, 3 (22%) experienced partial response, and 2 (16%) had deterioration of symptoms. The mean duration of symptom improvement was 4.5 months (range 0.75 to 17 months; Riedl 1998a).

Quality of Life

One single-arm cohort study reported QoL but no outcome measure was mentioned. Eight out of 13 people (62%) reported 'significant' QoL improvement (p value not reported; Riedl 1998a).

Total voiding symptom

One single-arm cohort study compared the total voiding symptom at 1 week before and 1 week after EMDA. Four out of 6 people experienced 'significant' and durable responses and 2 had temporary responses. The voiding symptom outcome measure used was developed locally (Gurpinar 1996).

Overactive bladder

Frequency

Three studies reported data on voiding frequency.

In the prospective cohort study (n=84), after 2 EMDA sessions, mean daytime frequency decreased from 14.1 (SE 7.7) per day to 9.4 (SE 6.2) per day. This change was statistically significant ($p<0.0001$), and was maintained at 8 weeks follow up, when the mean daytime frequency was 9.3 (SE 4.1; $p<0.0001$; Bach 2009).

In the prospective cohort study (n=72), there was a statistically significant decrease in voiding frequency per day from 16 to 7 ($p=0.003$; Gauruder-Burmester 2008).

In the prospective cohort studies of 14 people, there was a statistically significant decrease in mean voiding frequency per 24 hours from 11 (SD 2.2) at baseline to 9.2 (SD 3.2) at 1 month (p=0.023). There was no statistically significant difference at 3 months (11.1 [SD 3.3], p=0.44), or 6 months (9.4 [SD 0.9], p=0.37, n=5; Schiotz 2017).

Nocturia

Two studies reported data on nocturia.

In the prospective cohort study (n=84), after 2 EMDA sessions, nocturia per night decreased from 5.1 (SE 5.1) per night to 2.5 (SE 2.4) per night. This change was statistically significant (p=0.035). But, it then rose to 4.3 (SE 4.1) at 8 weeks follow up (p>0.1; Bach 2009).

In the prospective cohort study (n=72), there was a decrease of nocturia from 5 to 2. No statistical significance or p-value was reported. (Gauruder-Burmester 2008).

Quality of life

Two studies reported data on QoL, assessed using the validated KHQ.

In the prospective cohort study (n=84), a reduction of impact in QoL was observed from 11.8 (SE 3.2) to 7.3 (SE 4.1; p<0.018) at 4 weeks. But, at 8 weeks follow up, it rose to 10.1 (SE 3.5; p>0.1; Bach 2009).

In the prospective cohort study (n=72), an improvement in QoL was observed in 54 people (75%; p=0.002; Gauruder-Burmester 2008).

Sexual sensation and satisfaction

One prospective cohort study (n=72) reported an improvement in sexual sensations and sexual satisfaction in 39 people (54%; p=0.001; Gauruder-Burmester 2008).

Incontinence

One study reported an incontinence outcome.

In the prospective cohort study (n=14), at 1 month (n=14), mean incontinence episode per 24 hours decreased from 5.5 (SD 3.8) at baseline to 2.2 (SD 2.6). This change was statistically significant (p=0.001). This was maintained at 3 months (n=14), where the mean incontinence episode was 3.3 (SD 3.2; p=0.01), and 6 months (n=5), when the mean incontinence episode was 2.4 (SD 0.9; p=0.01; Schiotz 2017).

Bladder symptoms

In one prospective cohort study in an adult population (n=14), 3 people had improved bladder symptoms for more than 1 week, 4 people had improved bladder symptoms for less than 1 week, 4 people showed no improvement. In this study, the treatment was stopped in 3 people because of bladder contractions and leakage (Riedl 1998b).

Safety

Interstitial cystitis

In a case report of 2 people, both reported signs of transient ischaemic attack within 3 and 6 hours after having EMDA (Hinkel 2004).

In the randomised prospective study of 31 people, no SAEs were reported and no one refused the intervention because of side effects (Gulpinar 2014).

In the single-arm cohort study of 21 females (as reported by the study), no SAEs were reported. Erythema at the abdominal skin was usually present during the procedure and resolved within a few hours. Most experienced haematuria at the end of draining the bladder (Rosamilia 1997).

In the single-arm cohort study of 13 people, no SAEs were reported. All had skin erythema observed within hours at the abdominal electrode site. Two people showed deterioration in bladder symptoms, which occurred about 30 minutes after therapy and lasted for 1 to 4 days. The local anaesthesia was reported as incomplete in both (Riedl 1998a).

In the single-arm cohort study of 6 people, no SAEs were reported. No one experienced pain or significant discomfort. Some people reported tingling sensation on the abdominal skin during the intervention (Gurpinar 1996).

Overactive bladder

No SAEs were reported in the key studies.

In the prospective cohort study, 2 people developed abdominal skin erythema underneath electrodes and complained about pain during the second EMDA session, resulting in the treatment being stopped (Bach 2009).

In the prospective cohort study, 12 people developed reactive hypertension during treatment, which returned to normal without any intervention. 21 people showed signs of dysuria and haematuria. Ten people experienced UTI. One person developed urinary retention, which disappeared after 2 catheterisation procedures (Gauruder-Burmester 2008).

In the prospective cohort study, most people had transient, mild, painless abdominal skin erythema for a few hours after treatment. Three episodes of

acute cystitis was reported in 2 people with prior history of recurrent UTI (Schiotz 2017).

In the prospective cohort study, no local or systemic side effects were observed. Treatment was stopped in 3 people because of bladder contractions and leakage (Riedl 1998b).

Anecdotal and theoretical adverse events

Expert advice was sought from consultants who have been nominated or ratified by their professional society or royal college. They were asked if they knew of any other adverse events for this procedure that they had heard about (anecdotal), which were not reported in the literature. They were also asked if they thought there were other adverse events that might possibly occur, even if they had never happened (theoretical).Two professional expert questionnaires for this procedure were submitted. Find full details of what the professional experts said about the procedure in the specialist advice questionnaires for this procedure.

Validity and generalisability

Interstitial cystitis

- All evidence is from outside the UK.
- There are varying therapeutic agents, electric current, and treatment duration of the intervention.
- The number of EMDA interventions per person varied between studies.
- The maximum follow-up duration was 24 months.
- The outcome measures assessing efficacy were varied across studies.
- The outcome measure in assessing QOL for some studies was neither mentioned nor validated.

- In the Rosamilia (1997) study, pain scores at 6-months were only available for 16 of the 21 subjects. There were incomplete data in 6-month urinary diary, resulting in only 7 out of 16 urinary diaries able to be analysed.
- No randomised controlled trials comparing EMDA with oral therapy or other current standards of care were identified.

Overactive bladder

- All evidence is from outside UK.
- There are varying therapeutic agents, electric current, and treatment duration of the intervention. The number of EMDA interventions per person varied between studies.
- The outcome measure of bladder improvement was not specified in one prospective cohort study (Riedl 1998b).
- The maximum follow-up duration is 12 months.
- No randomised controlled trials comparing EMDA with oral therapy or other current standards of care were identified.

Any ongoing trials

No ongoing trials were identified for either indication.

Existing assessments of this procedure

No recent publications were identified.

Related NICE guidance

Interventional procedures

Electrically stimulated intravesical chemotherapy for non-muscle-invasive bladder cancer (2019) NICE Interventional procedures guidance 638. Recommendation: research only.

Laparoscopic augmentation cystoplasty (including clam cystoplasty) (2009) NICE interventional procedures guidance 326. Recommendation: Standard.

Percutaneous posterior tibial nerve stimulation for overactive bladder syndrome (2010) NICE interventional procedures guidance 362. Recommendation: Standard.

Technology appraisals

Pentosan polysulfate sodium for treating bladder pain syndrome (2019) NICE Technology appraisal guidance 610.

Mirabegron for treating symptoms of overactive bladder (2013) NICE technology appraisal guidance 290.

Medical technologies

Axonics sacral neuromodulation system for treating refractory overactive bladder (2020) NICE medical technologies guidance 50.

Professional societies

- British Association of Urological Surgeons
- British Society of Urogynaecology

Evidence from people who have had the procedure and patient organisations

NICE received 1 submission from a patient organisation about electrically stimulated intravesical therapy for interstitial cystitis. NICE received no questionnaires from people who have had the procedure (or their carers).

Company engagement

NICE asked companies who manufacture a device potentially relevant to this procedure for information on it. NICE received 1 completed submission. This was considered by the interventional procedures technical team and any relevant points have been taken into consideration when preparing this overview.

References

1. Bach P, Wormland RT, Möhring C et al. (2009) Electromotive drug-administration: A pilot study for minimal-invasive treatment of therapy-resistant idiopathic detrusor overactivity. Neurourology and Urodynamics, 28: 209–213. doi:https://doi.org/10.1002/nau.20624
2. Gauruder-Burmester A, Biskupskie A, Rosahl A et al. (2008) Electromotive drug administration for treatment of therapy-refractory overactive bladder. International Braz J Urol 34: 758–764. doi:https://doi.org/10.1590/s1677-55382008000600011
3. Gülpınar Ö, Haliloğlu AH, Gökçe Mİ et al. (2014) Instillation of hyaluronic acid via electromotive drug administration can improve the efficacy of treatment in patients with interstitial cystitis/painful bladder syndrome: a randomized prospective study. Korean Journal of Urology 55: 354–354. doi:https://doi.org/10.4111/kju.2014.55.5.354
4. Gürpinar T, Wong HY and Griffith DP (1996) Electromotive administration of intravesical lidocaine in patients with interstitial cystitis. Journal of Endourology [online] 10: 443–447. doi:https://doi.org/10.1089/end.1996.10.443

5. Hinkel A and Pannek J (2004) Transient ischemic attack after electromotive drug administration for chronic non-infectious cystitis: Report of two similar cases. Neurourology and Urodynamics 23: 180–182. doi:https://doi.org/10.1002/nau.10157

6. Riedl CR, Knoll M, Plas E et al. (1998) Intravesical electromotive drug administration technique: preliminary results and side effects. Journal of Urology 159: 1851–1856. doi:https://doi.org/10.1016/s0022-5347(01)63174-4

7. Riedl CR, Knoll M, Plas E et al. (1998) Electromotive drug administration and hydrodistention for the treatment of interstitial cystitis. Journal of Endourology [online] 12: 269–272. doi:https://doi.org/10.1089/end.1998.12.269.

8. Rosamilia A, Dwyer PL and Gibson J (1997) Electromotive drug administration of lidocaine and dexamethasone followed by cystodistension in women with interstitial cystitis. International Urogynecology Journal and Pelvic Floor Dysfunction [online] 8(3): 142–145. doi:https://doi.org/10.1007/BF02764846.

9. Schiotz HA, Mai HT, Zabielska R (2017) Intravesical electromotive botulinum toxin in women with overactive bladder – a pilot study. ARC Journal of Gynecology and Obstetrics 2(2). doi:https://doi.org/10.20431/2456-0561.0202002.

Appendix A: Methods and literature search strategy

Methods and literature search strategy

NICE has identified studies and reviews relevant to intravesical electrical stimulation for intravesical cystitis or overactive bladder from the medical literature.

Search strategy design and peer review

This search report is informed by the Preferred Reporting Items for Systematic reviews and Meta-Analyses literature search extension (PRISMA-S).

A NICE information specialist ran the literature searches on 29 February 2024. See the search strategy history for the full search strategy for each database. Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The principal search strategy was developed in MEDLINE ALL (Ovid interface). It was adapted for use in each of the databases listed in table 4a, taking into account the database's size, search functionality and subject coverage. The MEDLINE ALL strategy was quality assured by a NICE senior information specialist. All translated search strategies were peer reviewed to ensure their accuracy. The quality assurance and peer review procedures were adapted from the Peer Review of Electronic Search Strategies (PRESS) 2015 evidence-based checklist.

Review management

The search results were managed in EPPI-Reviewer version 5 (EPPI-R5). Duplicates were removed in EPPI-R5 using a 2-step process. First, automated deduplication was done using a high-value algorithm. Second, manual

deduplication was used to assess low-probability matches. All decisions about inclusion, exclusion and deduplication were recorded and stored.

Limits and restrictions

The search was not limited by date.

The CENTRAL database search removed trial registry records and conference material. The Embase search excluded conference material.

English language limits were applied to the search when possible in the database.

The limit to remove animal studies in the searches is standard NICE practice, which has been adapted from Dickersin K, Scherer R, Lefebvre C (1994) Systematic Reviews: Identifying relevant studies for systematic reviews. BMJ 309(6964): 1286.

Main search

Table 4a Main search results

Database	Date searched	Database platform	Database segment or version	Number of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	29/02/2024	Wiley	Issue 2 of 12, February 2024	451
Cochrane Database of Systematic Reviews (CDSR)	29/02/2024	Wiley	Issue 2 of 12, February 2024	34
Embase	29/02/2024	Ovid	1974 to 2024 February 28	931
INAHTA International HTA Database	29/02/2024	https://database.inahta.org/		13
MEDLINE ALL	29/02/2024	Ovid	1946 to February 28, 2024	869

Search strategy history

Medline search strategy

1 Cystitis, Interstitial/ 2675

2 ((interstitial or panmural or submucosal) adj4 cystiti*).tw. 3910

3 ((bladder or hunner* or submucosal or panmural) adj4 (ulcus or ulcer)).tw. 189

4 (pain* adj4 bladder adj4 syndrome*).tw. 1811

5 Urinary bladder, overactive/ 6096

6 Urinary Incontinence/ 24902

7 Urinary Incontinence, Urge/ 1173

8 (urin* adj4 (urge* or frequ* or excessive or overactive or incontinen*)).tw. 38034

9 (inflammat* adj4 (bladder or urinary)).tw. 2726

10 pelvic pain/ 6840

11 (pain* adj4 pelvic).tw. 13556

12 Nocturia/ 1196

13 (nocturia or nycturia).tw. 4194

14 (nocturnal adj4 diuresis).tw. 77

15 or/1-14 76380

16 IVES.tw. 182

17 EMDA.tw. 101

18 (electr* adj4 (administrat* or instillat*)).tw. 3063

19 ((electr* adj4 (therap* or stimulat*)) and intravesical).tw. 208

20 "physionizer".tw. 4

21 administration, intravesical/ 4723

22 ((intravesical or bladder) adj4 (administration* or instillat* or applicat* or dos* or infus*)).tw. 3883

23 or/16-22 10164

24 15 and 23 1262

25 Animals/ not humans/ 5165959

26 24 not 25 996

27 limit 26 to english language 872

Embase search strategy

1 interstitial cystitis/ 6642

2 ((interstitial or panmural or submucosal) adj3 cystiti*).tw. 5943

3 ((bladder or hunner* or submucosal or panmural) adj3 (ulcus or ulcer)).tw. 263

4 (pain* adj3 bladder adj3 syndrome*).tw. 3183

5 urine incontinence/ 57435

6 urge incontinence/ 8165

7 (urin* adj4 (urge* or frequ* or excessive or overactive or incontinen*)).tw. 64980

8 (inflammat* adj4 (bladder or urinary)).tw. 3983

9 pelvic pain/ 11044

10 (pain* adj4 pelvic).tw. 22429

11 nocturia/ 9896

12 (nocturia or nycturia).tw. 7525

13 (nocturnal adj3 diuresis).tw. 116

14 or/1-13 135491

15 "IVES".tw. 266

16 "EMDA".tw. 152

17 (electr* adj4 (administration or instillation)).tw. 4056

18 ((electr* adj3 (therapy or stimulation)) and intravesical).tw. 307

19 "physionizer".tw. 7

20 intravesical drug administration/ 3307

21 ((intravesical or bladder) adj4 (administration* or instillation* or application* or dose* or infusion*)).tw. 11119

22 or/15-21 17278

23 14 and 22 1960

24 nonhuman/ not human/ 5390043

25 23 not 24 1642

26 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. 5851002

27 25 not 26 1022

28 limit 27 to english language 870

CDSR and Central (Wiley) search strategy

#1 MeSH descriptor: [Cystitis, Interstitial] explode all trees 250

#2 ((interstitial or panmural or submucosal) near/3 cystiti*):ti,ab 530

#3 ((bladder or hunner* or submucosal or panmural) near/3 (ulcus or ulcer)):ti,ab 48

#4 (pain* near/3 bladder near/3 syndrome*):ti,ab 330

#5 MeSH descriptor: [Urinary Bladder, Overactive] explode all trees 1204

#6 MeSH descriptor: [Urinary Incontinence] explode all trees 3498

#7 MeSH descriptor: [Urinary Incontinence, Urge] explode all trees 297

#8 (urina* near/4 (urge* or frequ* or excessive or overactive or incontinen*)):ti,ab 7996

#9 (inflammat* near/4 (bladder or urinary)):ti,ab 226

#10 MeSH descriptor: [Pelvic Pain] explode all trees 1752

#11 (pain* near/4 pelvic):ti,ab 2667

#12 MeSH descriptor: [Nocturia] explode all trees 191

#13 (nocturia or nycturia):ti,ab 1265

#14 (nocturnal near/3 diuresis):ti,ab 18

#15 {or #1-#14} 14325

#16 "IVES":ti,ab 29

#17 "EMDA":ti,ab 30

#18 (electr* near/4 (administration or instillation)):ti,ab 385

#19 ((electr* near/3 (therapy or stimulation)) and intravesical):ti,ab 16

#20 "physionizer":ti,ab 2

#21 MeSH descriptor: [Administration, Intravesical] explode all trees 631

#22 ((intravesical or bladder) near/4 (administration* or instillation* or application* or dose* or infusion*)):ti,ab 1136

#23 {or #16-#22} 1873

#24 #15 and #23 329

INAHTA search strategy

1. ((nocturnal AND diuresis)) OR ((nocturia or nycturia)) OR ("Nocturia"[mh]) OR ((pain* AND pelvic)) OR ("Pelvic Pain"[mh]) OR ((inflammat* AND (bladder OR urinary))) OR ((urin* AND (urge* OR frequ* OR excessive OR overactive OR incontinen*))) OR ("Urinary Incontinence, Urge"[mh]) OR ("Urinary Incontinence"[mh]) OR ("Urinary Bladder, Overactive"[mh]) OR ((pain* AND bladder AND syndrome*)) OR (((bladder OR hunner* OR submucosal OR panmural) AND (ulcus OR ulcer))) OR ((((interstitial OR panmural OR submucosal) AND cystiti*))) OR ("Cystitis, Interstitial"[mh])

2. (((intravesical or bladder) AND (administration* or instillation* or application* or dose* or infusion*))) OR ("Administration, Intravesical"[mh]) OR ("physionizer") OR ((intravesical) AND (((electr* AND (therapy OR stimulation)))) OR ((electr* AND (administration OR instillation))) OR ("EMDA") OR ("IVES")

3. 1 AND 2 Limit to English langauge

Inclusion criteria

The following inclusion criteria were applied to the abstracts identified by the literature search:

- Publication type: clinical studies were included with emphasis on identifying good quality studies. Abstracts were excluded if they did not report clinical outcomes. Reviews, editorials, and laboratory or animal studies, were also excluded and so were conference abstracts, because of the difficulty of appraising study methodology, unless they reported specific adverse events not available in the published literature.
- People with interstitial cystitis or overactive bladder.
- Intervention or test: electrically stimulated intravesical therapy.
- Outcome: articles were retrieved if the abstract contained information relevant to the safety, efficacy, or both.

If selection criteria could not be determined from the abstracts the full paper was retrieved.

Potentially relevant studies not included in the main evidence summary are listed in Appendix B: Other relevant studies.

Find out more about how NICE selects the evidence for the committee.

Appendix B: Other relevant studies

Other potentially relevant studies that were not included in the main evidence summary (tables 2a. 2b and 3a, 3b) are listed in table 5a and 5b below.

Table 5a additional studies identified for interstitial cystitis

Study	Number of people and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Riedl CR, Knoll M, Plas E et al. (1997) Intravesical Electromotive Drug Administration for the Treatment of Non-Infectious Chronic Cystitis. International Urogynecology Jurnal 8: 134–137]	Cohort study n=9 Mean follow-up 11.2 months (range 3 to 22 months)	5 out of 9 (55%) had complete response, 3 (33%) had partial response, 1 had no effect.	Overlap with the Riedl (1998a) study.
Riedl CR, Knoll M, Plas E et al. (1998) Intravesical Electromotive Drug Administration Technique: Preliminary Results and Side Effects. The Journal of Urology 159:1851-1856	Cohort study n=16 Mean follow up 10.8 months (range 3 to 22 months)	The result is not separated from the chronic noninfectious cystitis (25). 15 of 25 (60%) had bladder improvement, 3 (12%) had partial response, and 7 (28%) had no improvement. No SAE reported.	13 out of 16 patient population overlap with Riedl (1998a) study

Table 5b additional studies identified for overactive bladder

Study	Number of people and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Di Stasi S, Giannantoni A, Vespasiani G et al. (2001) Intravesical electromotive administration of oxybutynin in patients with detrusor hyperreflexia unresponsive to standard anticholinergic regimens. The Journal of Urology 165: 491–498.	n=10	No side effects reported.	No efficacy outcome reported.
Yune JJ, Shen JK, Pierce MA et al. (2018) Intravesical electrical stimulation treatment for overactive bladder: An observational study. Investigative and Clinical Urology 59:246-251	Cohort study N=17 Follow-up = 3 months	Statistically significant improvement and QOL and reduction of voiding frequency at 12 weeks. One UTI reported. No SAE reported.	Drug solution not mentioned.