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Neuromodulation techniques in the treatment of the overactive bladder

J. GROEN and J.L.H.R. BOSCH
Department of Urology, Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands

Introduction

Symptoms of an overactive bladder often remain a therapeutic problem despite optimal use of conservative treatment methods including drug therapy, behavioural therapy, pelvic floor exercises and biofeedback. In the last decade, sacral nerve neuromodulation has been confirmed as a valuable addition to the therapeutic arsenal. The success of sacral neuromodulation has renewed interest in other neuromodulation techniques. The current techniques of neuromodulation for treating the overactive bladder are:

- anogenital electrical stimulation;
- transcutaneous electrical nerve stimulation (TENS);
- sacral nerve neuromodulation;
- percutaneous posterior tibial nerve stimulation (Stoller afferent nerve stimulation, SANS);
- magnetic stimulation.

Mechanism of action

It is unknown how neuromodulation works; indeed, it is even unknown whether neuromodulation only works at the spinal level or whether supraspinal pathways are involved [1]. The most important spinal inhibitory mechanisms of the micturition reflex are [2]:

- The guarding reflex: increased activity of the striated urethral sphincter in response to bladder filling, reflexively inducing detrusor relaxation;
- Edvardsen's reflex: increased activity of the sympathetic nervous system in response to bladder filling;
- Anal dilatation (afferent pathway: anorectal branches of the pelvic nerve; prevents voiding during defecation);
- Gentle mechanical stimulation of the genital region (afferent pathway: dorsal clitoral or penile branches of the pudendal nerve; prevents voiding during intercourse);
- Physical activity; afferent pathway: muscle afferents from the limbs (but not from the pelvic floor!; prevents voiding during fighting or fleeing);

Most of the afferent fibres involved in the above inhibitory mechanisms reach the spinal cord via the dorsal roots of the sacral nerves. Edvardsen's reflex can also be activated by stimulation of afferent anorectal branches of the pelvic nerve and afferent dorsal clitoral or penile branches of the pudendal nerve, at least in cats. Its role in humans is probably limited [3].

At least two potential mechanisms are possible: (i) activation of efferent fibres to the striated urethral sphincter reflexively cause detrusor relaxation; and (ii) activation of afferent fibres causes inhibition at a spinal or a supraspinal level. Based on experiments in dogs and observations in humans, Tanagho and Schmidt [4], who introduced sacral neuromodulation into the field of urology, adhered to the first theory. However, measurements of the urethral pressure profile and of urethral resistance during voiding do not indicate that the striated sphincter is activated with the stimulation parameters currently used [5]. Interesting studies supporting the second theory are those in which the dorsal clitoral or dorsal penile nerve, purely afferent branches of the pudendal nerve, were electrically stimulated. This induced a strong inhibition of the micturition reflex and detrusor hyper-reflexia in healthy volunteers and patients with a hyper-reflexive bladder [6–8]. Fowler *et al.* [9] measured the latency of the anal sphincter contraction during a peripheral nerve evaluation (PNE) test in women who were candidates for sacral neuromodulation, and concluded that this response was mediated by a polysynaptic reflex rather than the result of efferent stimulation. Experimental work in spinalized rats showed that neuromodulation reduced the degree of hyper-reflexia as well as the expression of *c-fos* after bladder instillation with acetic acid [10] (C-fos protein is expressed in the spinal cord after irritation of the lower urinary tract; this expression is mainly mediated by afferent C fibres). This result shows that inhibition of afferent C fibre activity may be one of the underlying

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mechanisms of neuromodulation. However, it does not explain the beneficial effects of neuromodulation in patients with idiopathic detrusor instability or urgency-frequency. In conclusion, the mechanism of action of neuromodulation remains in debate. Stimulation of afferent pathways seems to play a crucial role.

Electrical parameters

Most devices available for electrical stimulation use bipolar (alternating) square-wave pulses [11]. The rationale of the bipolarity is the minimization of electrochemical reactions at the site of the electrode and thereby of the risk of tissue damage. A pulse duration of 0.2–0.5 ms has been found to be optimal in inhibiting the bladder, but longer pulses (1 ms) are also used. Physiologically, the optimal stimulation frequency is 5–10 Hz or even 5–6 Hz [2]. However, frequencies of <10 Hz soon become unpleasant when the pulse amplitude increases. The possible intensity of stimulation is therefore limited. This may explain why in some clinical testing the degree of bladder inhibition was independent of the stimulation frequency at 5–20 Hz. Some authors use a frequency as high as 50 Hz. The desired pulse amplitude depends on the neuromodulation technique; it should be as high as possible in anogenital electrical stimulation, while a value just above the detection threshold is considered to be sufficient in sacral nerve neuromodulation. Intermittent pulse trains are sometimes used to reduce pelvic floor muscle fatigue, but this mode of stimulation may not be optimal in the treatment of an overactive bladder [11].

Anogenital electrical stimulation

The first publications on anogenital electrical stimulation as a treatment option in the overactive bladder appeared in the 1970s [2]. Good results have been described by mainly Scandinavian and Japanese authors in the 1980s, and the technique can now be considered an established treatment [12]; however, satisfaction is not unanimous. This review focuses on comparative studies of the last decade.

Technique. The method implies the insertion of plugs equipped with electrodes into the anal canal and (or) the vagina (Fig. 1); circular penile electrodes are available for men. Two modes of this type of neuromodulation can be distinguished. 'Long-term' or 'chronic' stimulation implies a home-treatment programme for several months (e.g. 3–12). Stimulation is applied daily for many hours (e.g. 6–8) at a low intensity and may also take place during the night. This way of stimulation is mainly used for patients with stress incontinence and is not discussed here. In 'acute' or 'short-term' maximal stimulation the patient is treated in a limited number of sessions (usually 4–20, sometimes many more) taking 15–30 min each. The intensity is as high as possible, i.e. just below the level of discomfort. Usually, this is about 1.5–2 times the perception threshold [13]. Treatment may take place weekly or during a series of consecutive days (sometimes twice daily) and can be undertaken in the outpatient clinic as well as at home. In addition to patients with an overactive bladder only, it may also be applied in patients with mixed incontinence [14]. Re-treatment may be useful.

Evidence. Anogenital electrostimulation reportedly has a beneficial effect in about half of the patients [14,15], but the published results vary considerably. While Eriksen *et al.* [16] reported a clinical success rate of 85% and 77% immediately after therapy and at 1 year of follow-up, respectively, Kulseng-Hanssen *et al.* [17], also studying women with idiopathic detrusor instability and urge incontinence, found no significant improvement in objective outcome measures, and stopped using the method. A closer examination of the available data is therefore necessary.

A few studies have compared the effect of electro-stimulation with that of treatment with a sham device. Such a device has the same appearance as the normal equipment, but has no stimulus output. Most authors found that active treatment was symptomatically and cystometrically superior to sham treatment [18–20], but Abel *et al.* [21] found no significant differences, possibly because these authors treated postmenopausal women. Smith [22] found that the symptomatic result of intravaginal electrotherapy was at least as good as that of the anticholinergic propantheline bromide.

Suitable patients. Subjective success rates of patients considering themselves cured or improved are as high as 85% [16], but such rates depend heavily on the selection of patients. As an example, Primus and Kramer [23]

Fig. 1. Plugs with electrodes for anal (left) and vaginal (right) stimulation.

obtained a success rate of 64% in a group of patients with idiopathic detrusor instability 2 years after treatment, while all patients with multiple sclerosis who initially had benefited from treatment relapsed within 2 months (although daily treatment of these patients at home was useful). Disappointing results have also been obtained in patients with spinal cord injury and elderly cognitively impaired nursing-home patients [24,25]. Careful patient selection is crucial for good results and maximal electrical stimulation should not be used as a last resort [12]. However, failure of previous pharmacological treatment does not exclude a good response beforehand [16,23].

Treatment scheme and parameters. The intensity of stimulation should be as high as possible. Geirsson and Fall [12] noted that the results obtained with a routine outpatient procedure were far less good than those obtained in their prospective research series. They hypothesized that this was partly because the routine procedure was undertaken by a nurse with no doctor present; in the presence of a doctor, it is usually easier to persuade a patient to accept a high stimulation intensity. These authors also noted that the most successful results published were obtained in series using a stimulation frequency of ≈ 20 Hz, while physiologically frequencies of 5–10 Hz are optimal in inhibiting the bladder. Possibly a higher frequency permits a higher stimulation intensity, as not every single pulse is detected. No data are available on the minimum number of treatments required. Primus and Kramer [23] found that some patients did not improve until the fifth treatment, and recommended treating patients at least 10 times. Intuitively, it may be expected that treatment on a daily basis will be more effective than weekly treatment; this hypothesis has not been tested. Siegel *et al.* [26] found no significant difference between daily and every-other-day treatment.

Long-term effectiveness. Few studies reported success rates after a follow-up of >6 months; of the 17 patients treated by Yamanishi *et al.* [20], seven remained cured for at least 9 months on average after stimulation with no intervention, while another six achieved control with re-treatment. After a 2-year follow-up, 64% of 45 patients with idiopathic detrusor instability [23] still reported subjective satisfaction; several needed re-treatment sessions and the remaining patients had relapsed. The success rate of 85% initially obtained by Eriksen *et al.* [16] in 48 women with idiopathic problems declined to 77% after 1 year. Bratt *et al.* [27] traced these patients after 10 years; 27 were evaluable and symptoms of urge incontinence were reported by 78%. However, 30% leaked only once a week or less; 60% were satisfied with maximal electrical stimulation and would recommend it to a friend.

Side-effects. No severe side-effects have been reported; local pain and diarrhoea disappear after a brief pause in therapy [18]. Mucosal irritation seldom occurs; the lesion quickly heals during a temporary break in the treatment [2].

Transcutaneous electrical nerve stimulation

TENS is used widely in the treatment of pain in a variety of conditions. Fall *et al.* [28] successfully treated patients with interstitial cystitis, using surface electrodes attached over the suprapubic area.

Technique. In treating the overactive bladder, the electrodes are usually attached over the S2 and S3 dermatomes (peri-anal region) or over the sacral foramina S2 and S3 (Fig. 2). Stimulation takes place for 20 min to several hours daily during one or more weeks. The intensity of stimulation should not exceed the level of discomfort.

Evidence. Acute cystometric effects of TENS have been shown in patients with an unstable bladder [29,30]. The effects in patients with sensory urgency were uncertain; the bladder volume at first desire to void increased significantly with TENS over the suprapubic region, but not with TENS over the S2 to S3 sacral foramina. Bladder capacity did not respond at both sites in these patients [30]. However, of the patients treated by Walsh *et al.* [31], 76% and 60% reported an improvement in daytime frequency and urgency, respectively, while 56% noted a reduction of nocturia. Most of these patients had sensory urgency. Hasan *et al.* [29] found that urinary frequency

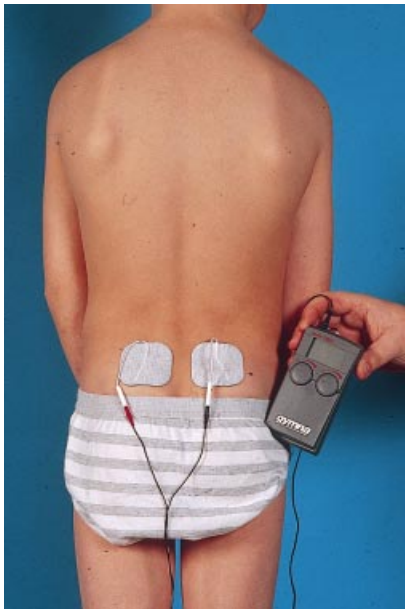

Fig. 2. TENS in a child with electrodes stuck over the sacral foramina.

more than halved in 37% of 59 patients with an unstable bladder. The number of leakages also reduced by half in 69% of those with urge incontinence. Good symptomatic results were also reported in a group of 55 children aged 6–12 years [32]; 57% and 33% of those with daytime incontinence and bedwetting, respectively, became dry, while the voiding frequency became normal in 67%.

Site of stimulation. Beneficial results of TENS at various sites have been reported [33], but few comparative studies have been undertaken. The possible sites of stimulation are:

- Sacral foramina S2 to S3.
- Sacral dermatomes S2 and S3 (peri-anal region).
- Dorsal penile or clitoral nerve.
- Suprapubic region.
- Thigh muscles (quadriceps muscles and hamstrings) [34].
- Common peroneal nerve.
- Posterior tibial nerve.

The published results are conflicting; McGuire *et al.* [35] used traditional acupuncture points for inhibiting bladder activity over the common peroneal and posterior tibial nerve in the treatment of 15 patients with a neurogenic bladder dysfunction, and obtained good symptomatic results in most. However, Hasan *et al.* [29] reported a urodynamic improvement with TENS over the S2 and S3 dermatomes, but not with TENS over the posterior tibial nerve and the suprapubic region. Bower *et al.* [30] obtained comparable urodynamic results with TENS over the suprapubic region and the sacral foramina.

Long-term results. The application of TENS is not useful if the patient is not offered the opportunity for re-treatment, either at the clinic or at home, as the therapeutic effects outlast the period of treatment only for a few months. The symptoms of 25 patients who were successfully treated by Walsh *et al.* [31] returned to pretreatment levels within 2 weeks in 40% of the patients and within 6 months in all; other authors obtained similar results [34,36].

Side-effects. No major complications have been reported after using TENS. Local skin irritation at the site of the electrodes was seen in a third of the patients by Hasan *et al.* [29]. The use of hypo-allergic electrodes and limitation of the daily treatment period was helpful.

Sacral nerve neuromodulation

Sacral nerve neuromodulation (sacral nerve stimulation, SNS, InterStim therapy) has become established within a relatively short period. The method is distinguished from other types of neuromodulation by its continuous stimulation and close nerve contact, while the site of stimulation is closest to the spinal cord. A characteristic feature is the implantation of a pulse generator and an electrode stimulating one of the sacral nerves S3. These nerves have a higher representation in the bladder than the nerves S4 and cause less inconvenience to the legs than the nerves S2. Patients only undergo the implantation procedure if the preceding so-called PNE test was successful, i.e. only pre-selected patients are treated.

Technique. To assess a patient's suitability, a test electrode is placed percutaneously under local anaesthesia, with the patient prone, in one of the S3 foramina and connected to an external pulse generator (Fig. 3a). The typical S3 muscle response, a bellows-like inward movement of the levator ani muscle and flexion of the great toe, is used to verify correct positioning of the electrode and proper functioning of the nerve. Stimulation is normally felt in the perineal area. After this acute PNE test the patient enters the subchronic test phase in which he or she completes a 3–7-day voiding-incontinence diary. Patients in whom the incontinence is

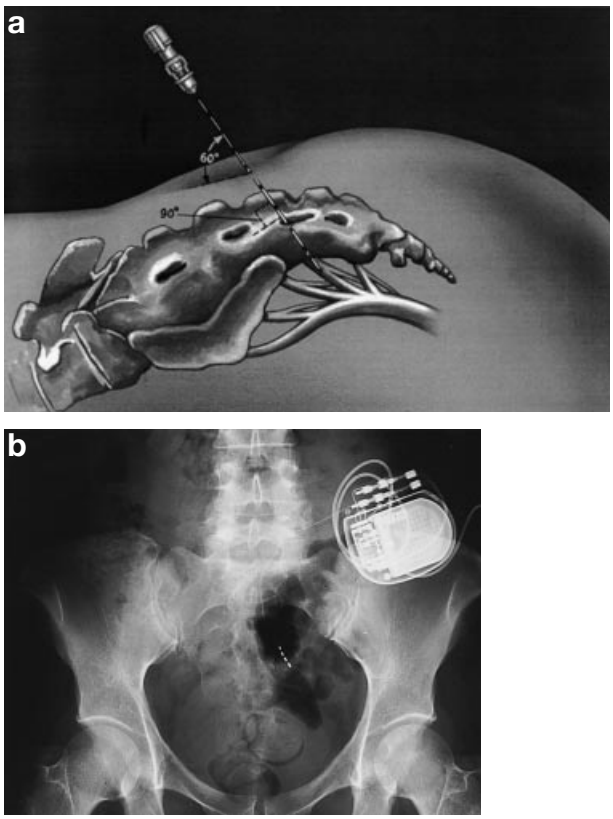

Fig. 3. a, Acute PNE test with a stimulation needle inserted through the left S3 foramen and placed parallel to the nerve S3. **b,** A pulse generator, extension cable and S3 foramen electrode with four stimulation points in a patient.

more than halved may receive the permanent implant, consisting of a foramen electrode fixed to the sacrum, an extension cable and a subcutaneously placed pulse generator (Fig. 3b).

Evidence. The results in patients with an unstable bladder were recently summarized by Bosch [37]; 60–70% of patients respond to a test stimulation. Most studies in implanted patients showed a mean decrease in the grade of instability during cystometry. Symptomatically, about half of patients with urge incontinence and no neurogenic causes had >90% improvement in their incontinence, with 25% having a 50–90% improvement and another 25% <50% improvement. The latter patients should be considered failures, because the results of the permanent implant are apparently worse than those of the test stimulation. As in other types of neuromodulation, the correlation between the urodynamic and the symptomatic improvement is only partial. In two comparative multicentre studies involving patients with refractory urge incontinence and urgency-frequency, respectively (not necessarily with urodynamically confirmed detrusor instability) half of the patients in whom the PNE test was successful were implanted [38,39]. Implantation was delayed for 6 months in the remaining patients, who received standard medical treatment and comprised the control group. The stimulation groups had significantly better symptomatic results than the control groups at 6 months of follow-up.

Suitable patients. At present, the only way to determine whether a patient is a candidate for implantation is a PNE test. Attempts to identify factors predicting the success of SNS failed [39,40]. On average, men do less well than women, probably because men have more severe grades of bladder overactivity than women before they become incontinent [37]. Psychological factors seem to play an important role [37,41]. A neurogenic cause of the bladder overactivity is no reason to exclude a patient from treatment; good results have been reported in patients with a variety of neurogenic lesions [42,43].

Long-term effectiveness. In 45 patients with a mean follow-up of 47 months the cure rate decreased to ≈ 80% and 65% after 1 and 1.5 years, respectively, but subsequently remained constant through the fifth year [44]. The symptomatic results obtained at 6 months remained stable during a mean follow-up of 44 months in seven of nine women with neurogenic urge incontinence [43]. The symptoms return to the baseline level within a few days after discontinuing SNS [38,39].

Side-effects and complications. The need to reposition the electrode after migration is the most frequently reported complication, occurring in ≈ 20% of patients [39,44]. Fracture of the electrode or the extension cable and technical problems with the pulse generator occasionally occur. A few patients complained of pain at the site of the pulse generator, which resolved after repositioning. Pain in the leg can be resolved by reducing the stimulation amplitude. Other complications are rare; nerve damage caused by continuous stimulation has not been reported [39,44].

Current developments

Two-stage implant. Displacement of the electrode during the PNE test may give a falsely negative result. Janknegt *et al.* [45] therefore repeated the test by placing a permanent electrode and an extension cable in patients in whom displacement was suspected, and connecting those to an external pulse generator. The permanent pulse generator was placed at a later stage if the patient had a good response (which was the case in eight of the 10 patients). The current search for better test electrodes will hopefully reduce the need to perform extra surgical procedures [46].

Bilateral stimulation and sacral laminectomy. Bilateral stimulation combined with a small sacral laminectomy to allow optimum electrode placement and fixation was first described by Hohenfellner *et al.* [47]. The value of the increased invasiveness of SNS remains to be determined.

Buttock placement of the pulse generator. The pulse generator is traditionally placed in a lower abdominal pocket. Buttock placement has the advantage that the patient needs no repositioning during the operation and saves ≈ 1 h of operative time [48].

Conditional neuromodulation. Oliver *et al.* [49] found that neuromodulation applied only at moments of an increased level of urge suppressed this sensation. The usefulness of conditional neuromodulation in patients has still to be determined; it will extend the longevity of the pulse generator, which at present is 5–7 years.

Percutaneous posterior tibial nerve stimulation

Intuitively, the pelvic region is the most logical place to seek a site for neuromodulation, but physiological mechanisms permit suppression of bladder overactivity from a more distant location.

Technique. A 34 G stainless steel or other thin needle is inserted 5 cm cephalad from the medial malleolus and just posterior to the margin of the tibia (Fig. 4). This point is known as the Sp-6 point in acupuncture. The needle is advanced to the medial edge of the fibula. A ground pad is usually attached to the medial surface of the calcaneous. Flexion of the great toe upon electrical stimulation indicates the correct positioning of the needle; a tingling sensation is often felt. Treatment usually takes place weekly for 10–12 weeks over 20–30 min.

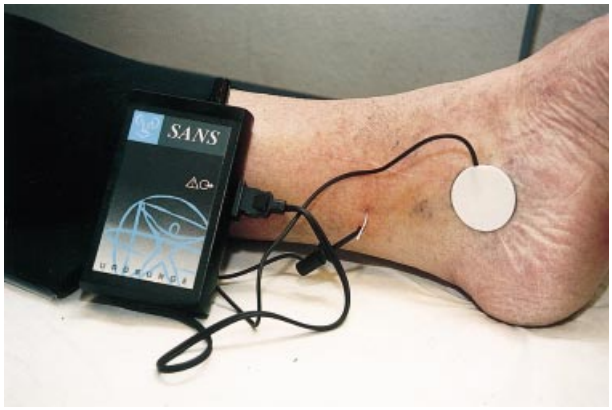

Fig. 4. SANS with stimulation needle and ground pad.

Evidence. McGuire *et al.* [35] used acupuncture points in TENS and obtained good symptomatic results; Chang [50] was the first to report results with the needle technique, showing statistically significant changes in the maximum cystometric capacity and maximum flow rate in a group of 26 women immediately after a 30-min treatment. Such changes were absent in a control group of 26 women. In addition, the proportion of patients who became stable and had subjective symptomatic improvement was greater in the treated group. Despite these promising results from the technique, it did not appear in urological practice until a commercial version (PercSANS™) became available recently. Most of the results of SANS to date are reported only in abstracts. Clinical success rates of 67–81% were reported during the ICS and EAU congresses of 1999 and 2000. Urodynamic results were reported by Klingler *et al.* [51], who found that bladder instability was eradicated in nine of 13 patients and improved in one. The bladder capacity increased significantly from a mean of 197 to 252 mL.

Long-term results. Stoller [52] described an 81% clinical success rate in 90 patients after a mean follow-up of 5.1 years. Patients were treated continuously with increasing intervals between treatments; some patients treated themselves at home. These promising results were a reason to start the development of a minimally invasive peripheral implant device. No side-effects have been reported.

Magnetic stimulation

An electric current, e.g. through a coil, induces a magnetic field, and a changing magnetic field in turn induces an electric field. These physical laws can be applied to stimulate the sacral roots or the pudendal nerves noninvasively using a magnetic field. This is possible because body tissues do not significantly attenuate such a field, but in contrast have a high electrical impedance.

Fig. 5. Commercially available chair for magnetic stimulation.

The advantage of magnetic stimulation over electrical stimulation is therefore that the stimulation intensity at the level of the nerves can be high [53]. Reports of magnetic stimulation in the context of the overactive bladder almost all originate from two groups.

Technique. McFarlane *et al.* [54], who to date have applied magnetic stimulation for research purposes only, place a specially designed coil tangentially over the sacral skin and connect it to a stimulator. The muscle response of the toes (or the EMG response of the toe flexors to single pulses) is used for correct positioning of the coil. The optimal position is usually ≈ 10 cm below the iliac crests and 5 cm lateral to the midline [54]; stimulation lasts for 2–5 s. Yamanishi *et al.* [55] developed a chair with a coil and a cooling system in its seat; patients are instructed to sit so that the anus is positioned at the centre of the coil and so that the highest anal contraction is felt during stimulation (Fig. 5). Patients are treated twice a week for 5 weeks; one session lasts 15 min with cycles of 60 s on/30 s off.

Evidence. The group lead by Craggs was the first to show that magnetic stimulation of S3 acutely suppresses

provoked unstable contractions in idiopathic and neurogenic patients [54,56]. Stimulation also abolished the sensation of urgency. Yamanishi *et al.* [53] compared the acute cystometric effects of magnetic stimulation with those of anogenital electrical stimulation; the inhibition of detrusor overactivity was greater with magnetic stimulation. The same group of authors treated eight patients with urge incontinence, mainly neurogenic [55]. The mean (SD) bladder volume at first desire to void and maximum cystometric capacity increased considerably from 160 (101) to 277 (52) mL, and from 211 (91) to 336 (35) mL, respectively; the latter change was significant. Clinically, six patients were considered cured or improved. Daytime voiding frequency and the number of daytime leakages significantly decreased from 9.5 (2.8) to 8.1 (3.5), and from 3.1 (3.1) to 1.5 (1.2), respectively.

Long-term effectiveness. No data on patients with pure urge incontinence are available. Sand *et al.* [57] treated 76 women with mixed incontinence; considering only those women with no identified risk factors, 11 of 16 had a $>50\%$ improvement in the number of incontinence episodes per day at 2 weeks after therapy, while eight of 14 did so at 18 weeks.

Side-effects. Magnetic stimulation normally causes no serious discomfort; there were two idiopathic patients who found stimulation painful or uncomfortable, while a neurogenic patient had an uncontrolled bowel evacuation [54,56].

Intravesical transurethral electrostimulation

Intravesical electrical stimulation is based on direct activation of receptors in the bladder and aims to enable the patients to recognise urge; it cannot be considered a kind of neuromodulation. However, the method so closely resembles most neuromodulation techniques that a brief description is appropriate.

Technique. A special catheter equipped with a stimulation electrode in its tip is inserted transurethrally into the bladder, which is partially filled with saline, a conducting fluid. A ground pad is placed on an arm or leg. One port of the catheter is connected to a pressure monitor, so that the patient can correlate their sensations with the behaviour of the bladder (biofeedback). Treatment usually takes place five times per week for 3 weeks, with one session taking 60–90 min.

Evidence. Intravesical stimulation was introduced several decades ago with the aim of improving bladder sensation and bladder emptying in patients with a neurogenic bladder, especially children. It follows from this aim that only patients in whom at least some neural pathways between the bladder and the cerebral centres are preserved are suitable candidates. The method is still used in these patients, but it is controversial [58,59]. Application of the method in patients with an overactive bladder is relatively new. The rationale is that these patients may learn to recognize involuntary contractions and inhibit them by squeezing the pelvic floor. Risi *et al.* [60] treated 162 patients, reporting an improvement in urinary continence in 25 of 33 with myelomeningocele, but the treatment failed in 75% of the remaining patients. The authors therefore advised against intravesical electrostimulation in idiopathic cases.

Conclusions

Neuromodulation is a valuable treatment option for patients with an overactive bladder. The non-surgical techniques can be applied as an alternative to standard conservative treatment, or may be tried if such a treatment fails. Sacral neuromodulation should be considered before using a more invasive operation such as bladder augmentation. It is unclear to what extent the various techniques are interchangeable, i.e. it is unknown whether a technique that is or is not effective in a patient can be successfully replaced by another technique, because no variables predictive of success have been identified. The determination of reliable selection criteria would be a major advance; a better understanding of the mechanism of action might contribute considerably to this goal.

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Authors

J. Groen, MD, PhD, Researcher.
J.L.H.R. Bosch, MD, PhD, FEBU, Professor of Urology.
Correspondence: J. Groen, Department of Urology/Urodynamics, Room EE1630, Erasmus University Rotterdam, PO Box 1738, 3000 DR Rotterdam, The Netherlands.
e-mail: groen@udn.fgg.eur nL