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**PERCUTANEOUS TIBIAL NERVE STIMULATION
IN LOWER URINARY TRACT DISORDERS**

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IN LOWER URINARY TRACT DISORDERS

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geboren te Amsterdam

promotor: prof.dr. B.L.H. Bemelmans
copromotor: dr. H. Vergunst

"You speak of signs and wonders, I need something other"
U2, Crumbs from your table

Aan Bianca
Aan mijn kabouters

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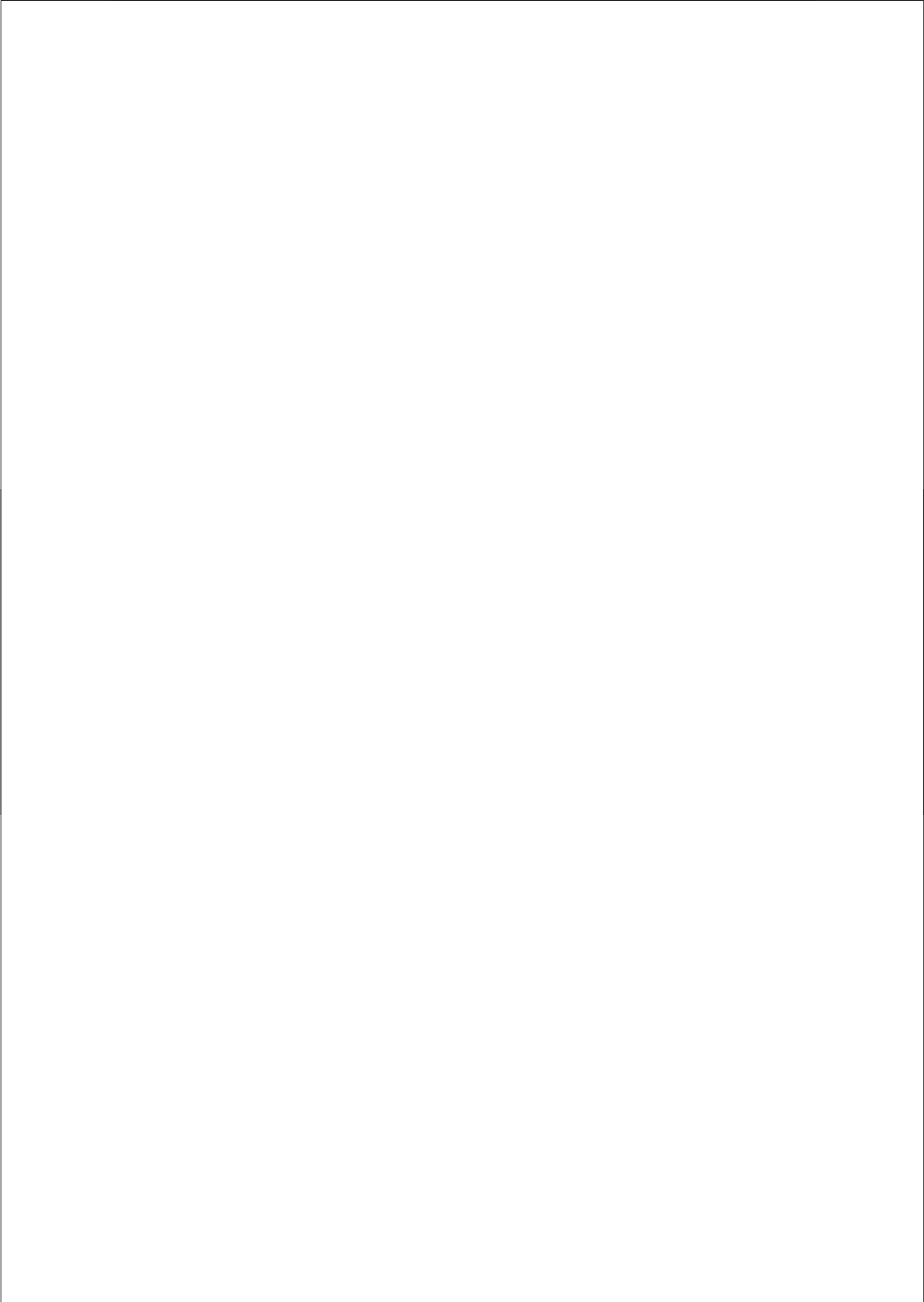
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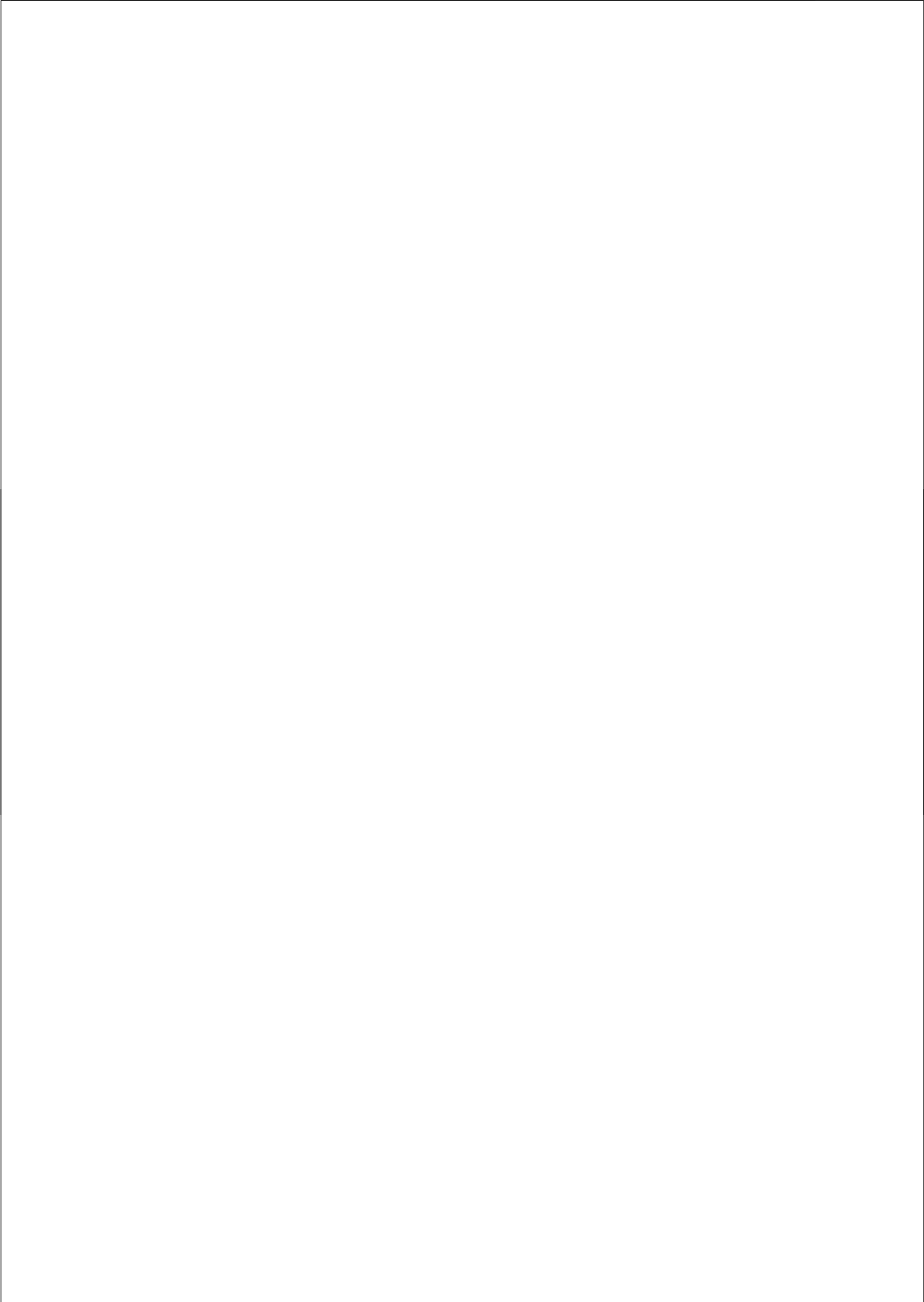
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PROLOGUE

Introduction and outline of the thesis



Introduction

Lower urinary tract dysfunction Non-neurogenic lower urinary tract dysfunction is a common urological problem that strongly affects quality of life. Patients can complain of urgency and frequency, urge incontinence, chronic pelvic pain or present with urinary retention. In most patients the etiology of these complaints remains unclear.¹ Conservative treatment options for bladder overactivity, that is the urgency and frequency syndrome and/or urge incontinence, consist of behavioral techniques with or without biofeedback, bladder re-education, pelvic muscle exercises or pharmacotherapy involving anticholinergics, antispasmodics and tricyclic antidepressants. Patients with non-obstructive urinary retention can perform clean intermittent or permanent catheterization. For refractory cases of overactive bladder more aggressive surgical procedures, including bladder distension, ileocystoplasty or urinary diversion have been advocated. However, high recurrence and complication rates limit the widespread application of these treatments.

Therefore, other treatment modalities, able to fill the gap between conservative measures and surgical procedures, are urgently needed. The increased popularity of intravesical Botulinum toxin injection therapy, first in neurological patients only², but now in non-neurological patients with overactive bladder as well³, can be seen in that light. The same goes for neuromodulation, especially for its most successful representative so far: continuous sacral root stimulation (Medtronic, Inc., Minneapolis, Minnesota).⁴⁻⁶ Although highly effective in selected patients, this technique is expensive and requires explicit surgical skill. Not surprisingly, the quest for better alternatives is ongoing.

Percutaneous tibial nerve stimulation Inspired by previous work on transcutaneous tibial nerve stimulation by McGuire et al.⁷, Marshall Stoller started research on percutaneous tibial nerve stimulation (PTNS) as neuromodulative treatment in lower urinary tract dysfunction. After initial testing in pig-tailed monkeys⁸, PTNS was later investigated in humans with promising results.⁹

PTNS is performed in patients placed in the supine position with the soles of the feet together and the knees abducted and flexed ('frog-position'). A 34 gauge stainless steel needle is inserted approximately 3 to 4 cm, about 3 fingerbreadths cephalad to the medial malleolus, between the posterior margin of the tibia and soleus muscle. A

stick on electrode is placed on the same leg near the arch of the foot. The needle and electrode are connected to a low voltage (9 volts) stimulator (Urosurge, Coralville, Iowa) with an adjustable pulse intensity of 0 to 10 mA., a fixed pulse width of 200 microseconds and a frequency of 20 Hz. The amplitude is slowly increased until the large toe starts to curl or toes start to fan. If the large toe does not curl or pain occurs near the insertion site, the stimulation device is switched off and the procedure is repeated. If the large toe curls or toes start to fan stimulation is applied at an intensity well tolerated by the patient. If necessary the amplitude can be increased during the session. In the original studies patients underwent 12 weekly outpatient treatment sessions, each lasting 30 minutes. If a good response occurred the patient was offered chronic treatment. ¹⁰

After Stoller's presentation of the first clinical data on the European Urological Association in 1999 ⁹, further studies on this new promising treatment option were conducted, especially by research groups in Europe, resulting amongst others in this thesis.

Outline of the thesis

Chapter 1: Historical perspective Neurostimulation and neuromodulation techniques are not new. From the discovery of electricity, its possible use in medicine was explored. Starting from intravesical application, electrical pulses in urology were used to target the bladder, pelvic floor or different nerves in order to improve voiding and/or storage problems. Nevertheless, the many techniques discovered all had their disadvantages. Chapter 1 of this thesis consists of a review on the use of electrical devices in treating bladder dysfunction. It creates a background against which the development of yet another treatment option, namely Percutaneous Tibial Nerve Stimulation (PTNS), as well as its clinical value can be better understood.

Chapter 2: Feasibility and clinical results To explore the possible value of PTNS, a feasibility study was performed in 49 patients with overactive bladder or non-obstructive urinary retention, indications well known from other neuromodulative treatment options. Results were obtained using (micturition) diaries and quality of life questionnaires, while the definition of success was based on subjective parameters.

Next, several indications were studied in more detail. Overactive bladder and non-obstructive urinary retention were evaluated by Vandoninck et al.¹¹⁻¹², the results of which are not included in this thesis. Research on chronic pelvic pain was performed in 33 patients, again using visual analogue scales for pain diaries and quality of life questionnaires, but now also objective parameters for success were included. Finally, the potentially beneficial effect of successful PTNS treatment of lower urinary tract dysfunction on sexual functioning in the three evaluated indication groups combined (121 patients) was investigated. All three studies in this chapter are indicative of the clinical relevance of percutaneous tibial nerve stimulation.

Chapter 3: Urodynamic data Although one can obtain rather objective parameters from especially (micturition) diaries, urodynamic studies may provide more robust data on the effectiveness of percutaneous tibial nerve stimulation. Therefore, studies on urodynamics prior to PTNS as well as after completing treatment were performed in 90 patients with overactive bladder and 39 with non-obstructive urinary retention, respectively. Basic urodynamic parameters in concordance of International Continence Society standards were used as outcome measures, so were special bladder indices. The studies in this chapter further objectively affirm PTNS significance.

Chapter 4: Prognostics and maintenance In chapter 4 two studies are presented regarding refinement of PTNS therapy. First, for all indication groups clinical parameters with prognostic value for successful treatment outcome have been assessed. Amongst others general patient characteristics, stimulation parameters, items like duration of complaints and previous therapies tried, urological symptom measurements, quality of life and psychological issues, but also data regarding a history of sexual and/or physical abuse were evaluated for their predictive value. Thereafter, a study was performed to investigate the necessity for maintenance therapy once successful outcome had been obtained. Both studies lead to recommendations for better patient selection as well as an optimization of PTNS therapy in order to improve treatment outcome.

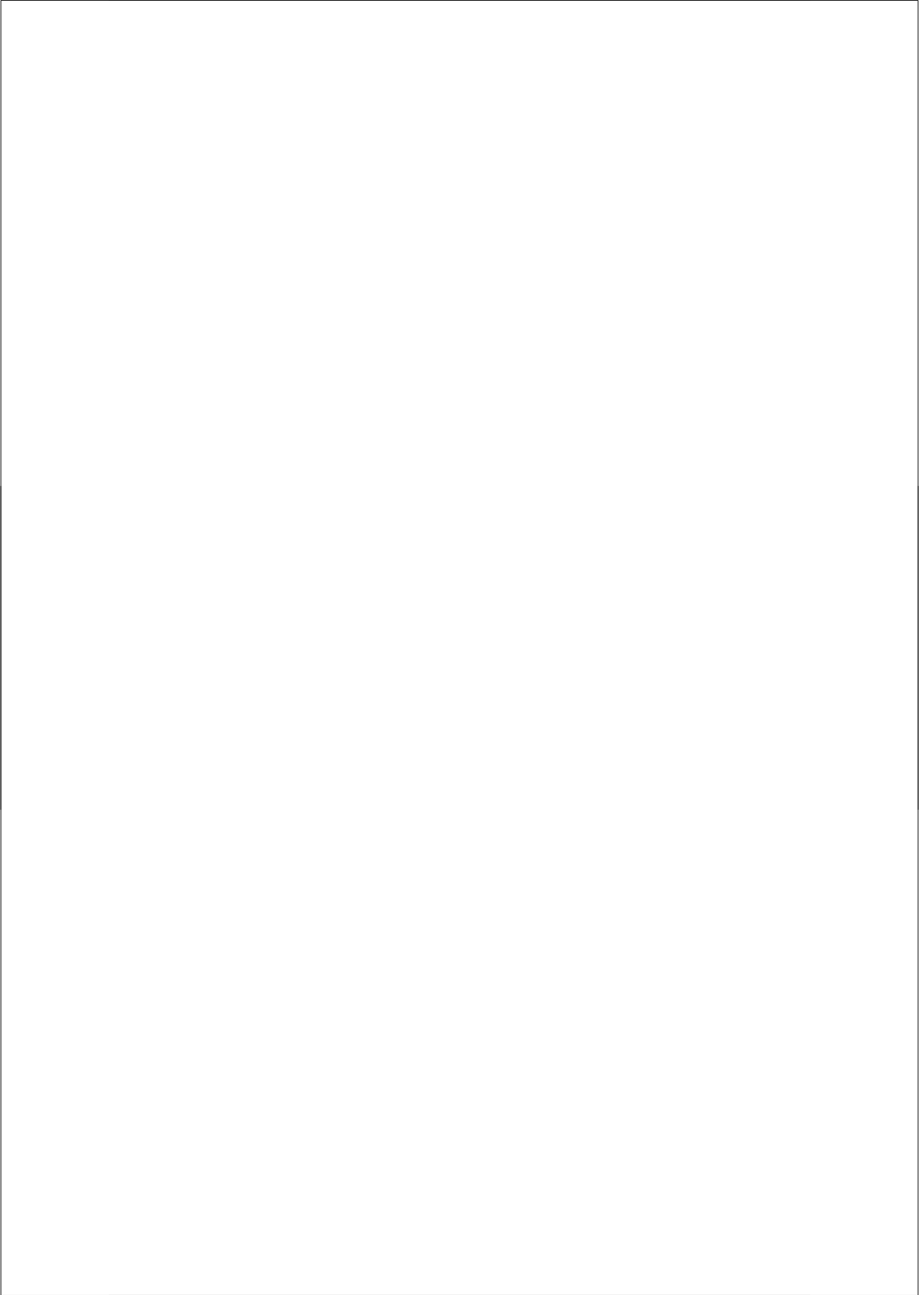
Chapter 5: Towards an implantable device To enable flexible, individualized treatment schedules and chronic maintenance therapy, both independent of

outpatient department support, an implantable device was developed for radiographic subcutaneous tibial nerve stimulation. Chapter 5 presents a feasibility study (follow up: 12 months) regarding this implantable device. It should convince the reader that much effort is made to keep improving tibial nerve stimulation, including its major drawback: maintenance therapy.

Summary and future perspectives In this part of the thesis all studies included are summarized and discussed. Furthermore, the future role of percutaneous tibial nerve stimulation as well as thoughts on further research is reflected upon.

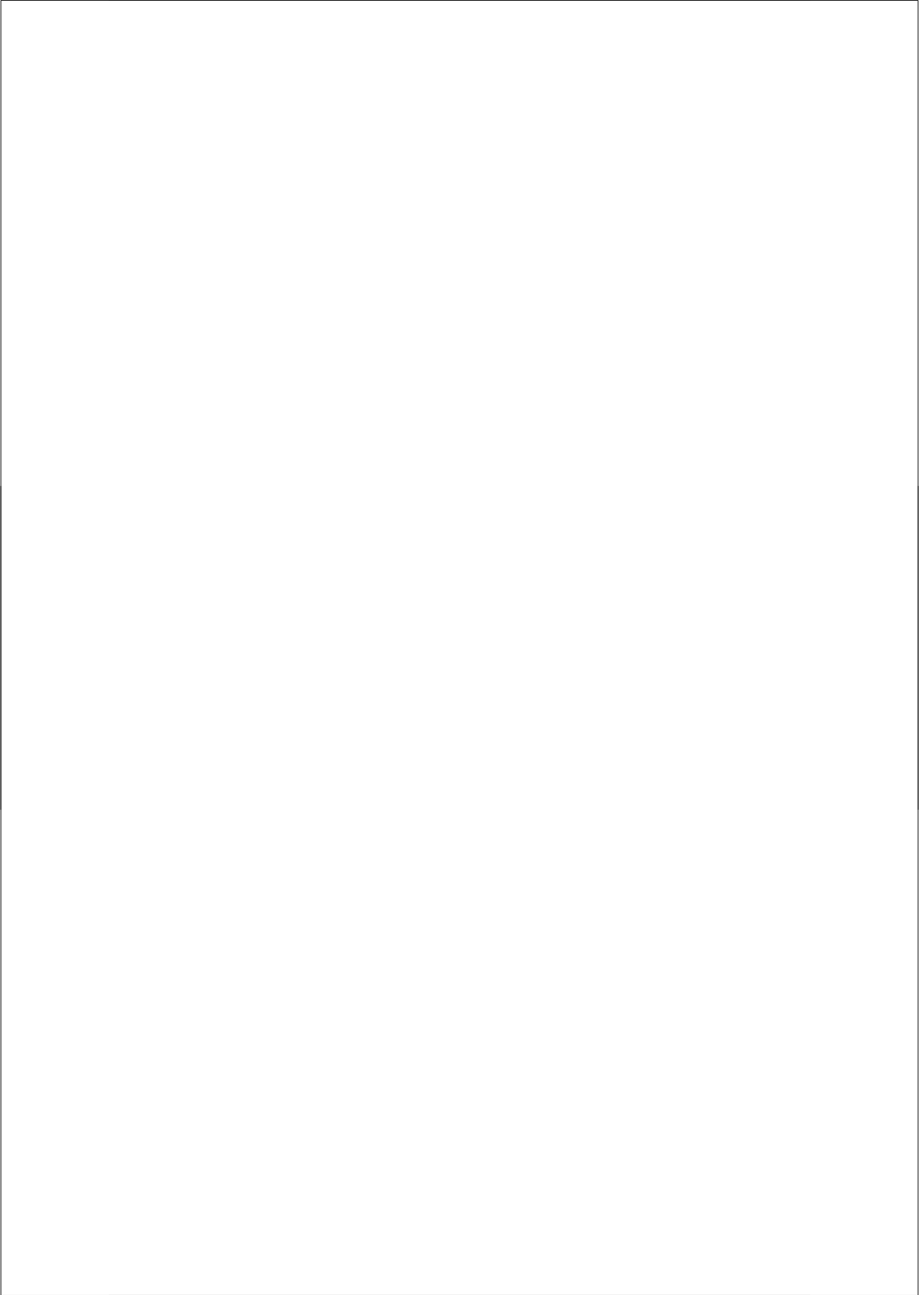
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CHAPTER 1

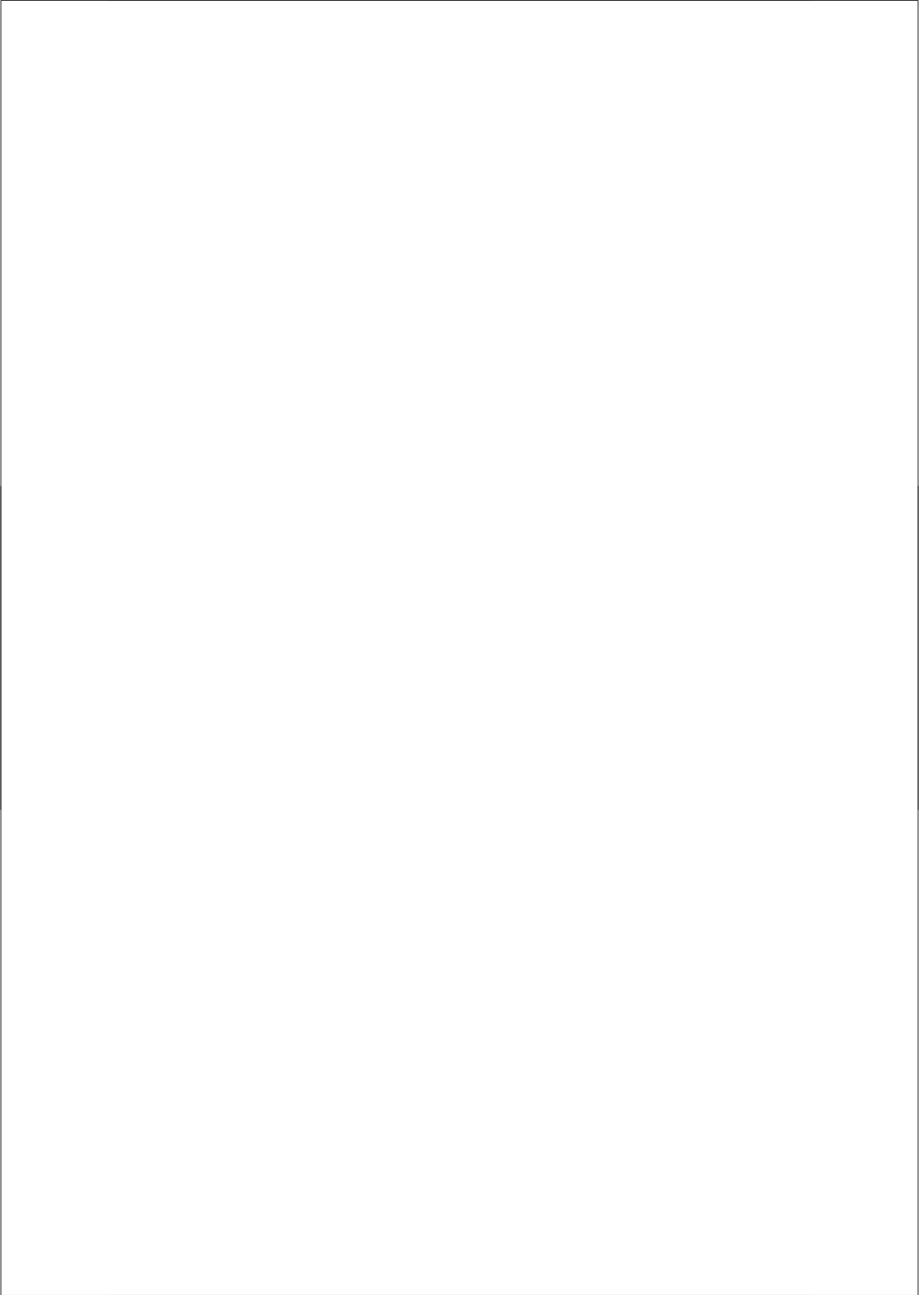
Historical perspective



The use of electrical devices in the treatment of bladder dysfunction: a review of methods

**M.R. van Balken
H. Vergunst
B.L.H. Bemelmans**

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Introduction

In humans, the hypogastric plexus, originating from spinal levels Th10-L2, sympathetically innervates the bladder. Stimulation of these nerves results in relaxation of the detrusor muscle and contraction of the intrinsic sphincter, thereby inhibiting micturition. Stimulation of the pelvic plexus, parasympathetic nerves originating from spinal level S2-S4, has an opposite effect. Pudendal nerves, coming from the same spinal level as the pelvic plexus, innervate the pelvic floor and the external sphincter. In the spine and on the supraspinal level pathways and interactions are much more complex. Especially studies by de Groat ^{1,2} and Blok ³⁻⁵ have given us some insight in the processes involved.

Actual damage of the peripheral or the central nervous system (CNS), like in neurological patients, or disruption of the fine-tuned balance between inhibitory and excitatory stimuli, as occurs in some non-neurological patients, may result in lower urinary tract dysfunction. This dysfunction can lead to voiding disorders (like impaired micturition or urinary retention) and/or storage disorders (like urgency/frequency (UF) and/or urge incontinence(UI)). Both conditions can strongly influence quality of life. Therapeutic options for these patients vary from conservative treatments as pelvic floor training, biofeedback, medical treatment and self-catheterization to invasive surgical procedures, with serious side effects and limited success. ⁶

Over a century, electrical neurostimulation and neuromodulation have been investigated as alternative treatment options. In neurostimulation nerves or muscles are directly stimulated by electrical stimuli to obtain immediate responses. As could be expected, neurostimulation techniques have been used in neurological patients mainly. In neuromodulation electrical stimuli are exerted in order to alter present transmission processes. Neuromodulation therapy is used in patients with non-neurological lower urinary tract dysfunctions. Recently, not only an increasing amount of reports about the application and refining of current stimulation and modulation techniques have been published, but there is also a renewed enthusiasm to develop alternative modalities, like percutaneous tibial nerve stimulation (PTNS) ⁷, magnetic stimulation of the pelvic floor ⁸ or pudendal nerve stimulation (PNS). ⁹ In order to be able evaluate the clinical effectiveness of to these new treatment options we review the application of the various electrical devices for treatment of bladder dysfunction with respect to mechanism of action and clinical outcome.

Electrical stimulation of the bladder

Intravesical electrical stimulation Saxtorph first used Intravesical electrostimulation in 1878 for the treatment of urinary retention. A dedicated catheter was inserted transurethraly in the bladder with a metal-electrode inside and a neutral electrode placed suprapubically.¹⁰ From then time passed till 1959, when Katona et al described a technique of intraluminal electrotherapy for various disorders of the gastrointestinal tract.¹¹ Later on the same technique has been applied for the treatment of neurogenic bladder dysfunction.¹² Since then intravesical electrostimulation has been described by others with inconsistent results (Table 1).

Intravesical electrostimulation involves direct intraluminal electrical stimulation via a catheter with a special stimulation electrode. The bladder is filled with sodium chloride to serve as a cathode and an indifferent electrode is placed on the thigh or arm. The technique has been used mostly in children with incomplete nerve lesions resulting in absence of bladder sensation and/or insufficient detrusor contractions.

Normally micturition is initiated by depolarization of intramural mechanoreceptors, which through complex CNS reflexes elicit detrusor contractions. This is accompanied by the occurrence of sensation.¹⁰ Intravesical current is thought not to activate the detrusor myocytes directly but to stimulate bladder mechanoreceptor afferents, enhancing bladder sensation and subsequent (stronger) detrusor contractions. Supporting this theory are the findings that for direct stimulation of efferent nerves to the bladder much higher (and painful) current intensities are needed, and that intravesical anesthesia by lidocaine abolishes the detrusor response.¹³ Long-term results of intravesical stimulation may be due to potentiation of excitatory synapses in the central micturition reflex pathway.¹⁴

Intravesical electrical stimulation of the bladder remains, however, controversial. Although in most studies enhanced bladder sensation and (stronger) detrusor contractions can be found after intravesical electrotherapy, this does not necessarily result in an improvement of volitional voiding. The increases of bladder capacity widely differ in the aforementioned publications. Besides, there are certain other disadvantages: the technique is time-consuming and requires well-trained personnel and adequate equipment. More importantly, there is no simple test to predict clinical outcome. Therefore, the first 10-15 stimulation sessions are considered as a trial, only to be continued when a positive response is registered. Duration and intensity of

Table 1 Publications on intravesical electrostimulation

Author	y.o.p.	Pts.	Type of study	Indication	Treatment scheme	Treatment parameters			Outcome (%)
						Intensity	Pulses (msec)	Freq. (Hz)	
Adults or age not mentioned:									
Katona ¹⁵	1975	420	NRCT	NBD/VD-SD	90 min. daily, No. of sessions n.m.	1-5 mA	5-10	70-100	75c
Farnsworth ¹⁶	1976	15	NRCT	NBD/VD	n.m.	n.m.	n.m.	n.m.	33i
Madersbacher ¹⁷	1982	29	NRCT	NBD/VD	90 min. daily, 23-132 sessions	1-10 mA	6-8	70-100	59i, 34c
Primus ¹⁸	1996	48	NRCT	NBD/VD	90 min., 5x/week, 10-108 sessions	10 mA	4	20	54c
Children:									
Nicholas ¹⁹	1975	20	NRCT	NBD/SD	90 min., 5 x/week, up to 3 months	1 mA	n.m.	90	0i
Janneck ²⁰	1975	14	NRCT	NBD/VD-SD	30-60 min. daily, No. of sessions n.m.	n.m.	5	50	71i
Berger ²¹	1978	31	NRCT	NBD/VD-SD	90 min. daily, 22-300 sessions	5-6 mA	5-6	50-60	38i, 26c
Seiferth ²²	1978	28	NRCT	NBD/VD	60 min., 2-3x/week, 6-9 months	1-70 V	5	25	43i
Madersbacher ²³	1978	8	NRCT	NBD/VD-SD	90 min., 5x/week, ± 60 sessions	n.m.	n.m.	n.m.	25c
Kaplan ²⁴	1986	24	NRCT	NBD/VD	90 min., 5-6x/week, 1-110 sessions	1-10 mA	2-6	60-90	17c
Kaplan ²⁵	1988	42	NRCT	NBD/VD	90 min., 3-5x/week, ≥ 15 sessions	n.m.	n.m.	n.m.	33-80i
Decter ²⁶	1992	21	NRCT	NBD/VD	90 min. daily, 1-3x 5-30 sessions	1-10 mA	2-6	60-90	5i
Boone ²⁷	1992	31	RBPCT	NBD/VD	90 min., 5x/week, 15 or 30 sessions	1-7 mA	4-6	40-80	0i
Lyne ²⁸	1993	17	NRCT	NBD/VD	90 min., 5x/week, 15-108 sessions	1-10 mA	2-5	60	29i, 0c
Decter (1) ²⁹	1994	25	NRCT	NBD/VD	90 min. daily, 1-6x 15-30 sessions	1-10 mA	2-6	60-90	0i

Y.o.p. = year of publication, Pts. = Patients, Freq. = Frequency, NRCT = Non Randomized Clinical Trial, RBPCT = Randomized Blinded Placebo Controlled Trial, NBD = Neurogenic Bladder Dysfunction, VD = Voiding Disorder, SD = Storage Disorder, No. = Number, n.m. = not mentioned, i = improved, c = cured, (1) = follow-up report on publication of 1992: mostly the same patients are described

the stimulation highly differ between individuals and protocols, thus lacking a standardized treatment scheme. Frequencies used in humans vary between 40 and 100 Hz despite recent data obtained in cats and rats showing that much lower frequencies (≤ 20 Hz) seem to be of more benefit.^{13,14} In patients with neurogenic bladder dysfunction repeated stimulation is often needed, whereas in non-neurogenic bladder dysfunction initial treatment most of the time will be sufficient. Intravesical electrostimulation usually will be combined with intensive bladder training, which may account partly for the successful outcome.¹⁰

Thus far, intravesical electrostimulation has not gained widespread acceptance^{30,31}, reflected by the small amount of clinical reports in recent years. Further research on its precise mode of action continues to be performed.^{13,14}

Direct bladder stimulation Advancing technology resulted in miniature powerful transistorized devices in the early 1960's, which ultimately enabled human use of implantable stimulators.³² In 1962 Bradley described the use of an implantable receiver-stimulator with disk (Grass stimulator) and tape (Medtronic stimulator) electrodes applied directly to the bladder of dogs³³, followed one year later by a less encouraging report on its application in humans.³⁴ Further research resulted in the Avco stimulator using 2-4 silastic coated stainless steel electrodes embedded in the anterior or lateral wall of the bladder, whereas the receiver-stimulator is placed subcutaneously in the lower abdomen.³⁵ In an attempt to decrease the risk of erosion and dislocation of electrodes the Susset stimulator was developed, using 8 platinum disk electrodes placed in two circles on the bladder in pockets made under the superficial muscular layer.³² The Mentor stimulator consists of helical electrodes placed around the vesical neuromuscular pedicle with the bladder wall imbricated over these electrodes, and a bladder stimulator placed subcutaneously in the left lower quadrant of the abdomen.³⁶

The working mechanism of all the abovementioned devices is based on direct stimulation of the detrusor muscle in order to provoke a contraction. The clinical results are summarized in table 2. Stimulation is usually combined with bladder training performed by clamping the indwelling catheter for increasing periods. In this way reflex activity may be provoked in patients with areflexic bladders.

The use of the Avco device in patients with upper motor neuron lesions causes external sphincter spasms during stimulation, thereby preventing effective bladder

Table 2 Publications on direct bladder stimulation

Author	y.o.p.	Pts.	Type of study	Indication	Stimulator	Treatment parameters			Outcome (%)
						Intensity (V)	Pulses (msec)	Freq. (Hz)	
Adults or age not mentioned:									
Bradley ³⁴	1963	7	NRCT	NBD/VD	Grass or Medtronic stimulator	5-15	1-5	n.m.	29i
Boyce ³⁷	1964	3	NRCT	NBD/VD	Grass stimulator	20-40	n.m.	60	33i 33c
Stenberg ³⁵	1967	4	NRCT	NBD/VD	Avco stimulator	2.5-18	4	20	75i
Hald ³⁸	1967	4	NRCT	NBD/VD	Avco stimulator	≤ 15	4	20	75i
Susset ³²	1968	1	NRCT	NBD/VD	Susset stimulator	10-20	1	10-40	100i
Halverstadt ³⁹	1971	8	NRCT	NBD/VD	Avco stimulator	n.m.	n.m.	n.m.	25i, 50c
Merrill ³⁶	1974	5	NRCT	NBD/VD	Mentor stimulator	n.m.	n.m.	n.m.	40i
Merrill ⁴⁰	1975	5	NRCT	(N)NBD/VD	Mentor stimulator	n.m.	n.m.	n.m.	60i
Jonas ⁴¹	1978	11	NRCT	NBD/VD-SD	Mentor or Susset stimulator	n.m.	n.m.	n.m.	67i
Children:									
Kantrowitz ⁴²	1965	3	NRCT	NBD/VD-SD	Avco stimulator	4.4-10	4	20	67i
Merrill ⁴³	1974	2	NRCT	NBD/VD	Mentor stimulator	n.m.	n.m.	n.m.	100i
Wheatley ⁴⁴	1982	8	NRCT	NBD/VD	Mentor stimulator	n.m.	n.m.	n.m.	38i

Y.o.p. = year of publication, Pts. = Patients, Freq. = Frequency, NRCT = Non Randomized Clinical Trial, NBD = Neurogenic Bladder Dysfunction, NNBD = Non Neurogenic Bladder Dysfunction, VD = Voiding Disorder, SD = Storage Disorder, n.m. = not mentioned, i = improved, c = cured

emptying. Neither more cephalad placement of the electrodes on the bladder in order to decrease spread of current to the pelvic floor³⁹, nor using other stimulation devices solved this problem. Therefore, implantation of a bladder stimulator has sometimes been combined with the implantation of a Mentor pelvic floor stimulator and/or a subarachnoidal spinal phenol block³⁶ or with bladder neck incisions and/or sphincter resections to decrease detrusor-sphincter-dyssynergia.⁴¹ Other authors consider upper motor neuron lesions a clear contraindication for extravesical bladder stimulation.³²

Other disadvantages of extravesical bladder stimulators are painful sensations experienced during stimulation, a high technical failure rate usually related to electrode erosion, and in the long term a decreasing response due to bladder fibrosis.³⁸

Notwithstanding acceptable clinical outcome in selected cases the technique of direct bladder stimulation has finally been abandoned because of the occurrence of detrusor-sphincter-dyssynergia in patients with upper motor neuron lesions and the pain accompanying stimulation in patients with incomplete lower motor neuron lesions⁴³ or non-neurogenic hypotonic bladders.⁴⁰

Electrical stimulation of pelvic nerves In an attempt to treat voiding disorders, unilateral pelvic nerve stimulation was tested in dogs as early as in 1957 by Ingersoll et al.⁴⁵ Unfortunately, results of pelvic nerve stimulation appeared to be disappointing because pudendal nerves are stimulated at the same time, resulting in increased outflow resistance by sphincter contractions. Besides, pelvic nerves cannot be stimulated chronically, and early splitting of its fibers in the pelvis, forming a broad plexus, makes the application of an electrode unsuitable.⁴⁶

Electrical stimulation of pudendal nerves

Transvaginal stimulation In 1963 Caldwell reported the successful implantation of an anal sphincter stimulator in a patient with faecal incontinence. Shortly thereafter, a similar stimulator was implanted in another patient for urinary incontinence.⁴⁷ Later on, a plug for intra-anal use was developed⁴⁸ that was subsequently modified.⁴⁹ Based on the experiences with anal stimulation for faecal and urinary incontinence, transvaginal stimulation for urinary incontinence was evaluated by Fall et al in 1977.⁵⁰ Since then, Fall and co-workers have published several reports about transvaginal electrical stimulation in non-neurogenic patients with urinary incontinence and interstitial cystitis (IC).^{51,52} In animal experiments performed to illuminate the working mechanism of this technique⁵³, they demonstrated that bladder inhibition (relaxation of the detrusor) was accomplished by reflexogenic activation of sympathetic hypogastric inhibitory neurons and by central inhibition of pelvic parasympathetic excitatory neurons, the pudendal nerves forming the afferent pathways for these effects.

Although the technique is easily applicable and can be performed by patients at home, there are some disadvantages. Usually, treatment has to be given for a long period of time and eventually not all patients can stop therapy. There are also

considerable discrepancies between symptomatic cure or improvement on one hand and urodynamic findings at follow-up on the other. Overall, the transvaginal way of treatment is not well accepted by most patients. To achieve an acceptable outcome of therapy, stimulation at high intensity is needed which cannot be easily tolerated by women with normal sensation in the pelvic region. Consequently, further reports on this treatment modality are scarce (table 3).⁵⁴⁻⁵⁶

Table 3 Publications on transvaginal stimulation

Author	y.o.p.	Pts.	Type of study	Indication	Treatment scheme	Treatment parameters			Outcome (%)
						Intensity	Pulses (msec)	Freq. (Hz)	
Fall ⁵⁰	1977	15	NRCT	NNBD/SD	Continuously during daytime, ≥ 3 months	≤ 12 V	1	10	100i
Fall ⁵¹	1980	4	NRCT	NNBD/SD	Continuously during daytime, 6 to 23 months	n.m.	2	10	25i
Fall ⁵²	1984	30	NRCT	NNBD/SD	Continuously during day- or night-time or 24 hours, up to 23 months	n.m.	n.m.	10	73i
Bent ⁵⁴	1993	31	NRCT	NNBD/SD	15 min., twice daily, 6 weeks	≤ 30 V	1	20	52-70i
Brubaker ⁵⁶	1997	61	RBPCT	NNBD/SD	20 min., twice daily, 8 weeks	≤ 100 mA	0.1	20	49c
Yamanishi ⁵⁵	2000	68	RBPCT	NNBD/SD	15 min., twice daily, 4 weeks	n.m.	1	10	81i, 22c

Y.o.p. = year of publication, Pts. = Patients, Freq. = Frequency, NRCT = Non Randomized Clinical Trial, RBPCT = Randomized Blinded Placebo Controlled Trial, NBD = Neurogenic Bladder Dysfunction, NNBD = Non Neurogenic Bladder Dysfunction, SD = Storage Disorder, n.m. = not mentioned, i = improved, c = cured

Functional or Maximal Electrical Stimulation In 1967 Moore and Schofield⁵⁷ stimulated anesthetized patients with urinary stress incontinence with faradic 1 msec pulses between an unipolar electrode placed on the perineum and an indifferent electrode on the sacrum with intensities at which the pelvic floor muscles contracted maximally. This was repeated 4-6 times during the session. Godec et al⁵⁸ described their technique to improve the results of this type of stimulation, called chronic Functional Electrical Stimulation (FES). Using an anal plug or needle electrodes, stimulation was performed while measuring EMG responses and vesical as well as urethral pressure changes. In a later report⁵⁹, the same authors changed their technique, calling it Acute Maximal Functional Electrical Stimulation (AMFES). In

AMFES, very high stimulation levels were possible because of sensory losses associated with spinal cord injury.

Other authors⁶⁰⁻⁶⁶ tried to maximize stimulation in a procedure called Maximal Electrical Stimulation (MES), stimulating with an intensity as high as tolerable and also increasing the number of stimulation sites when possible. Women were therefore stimulated anally as well as transvaginally at the same time. Sometimes even needles directed to the pudendal nerve were added.⁶² The results vary considerably, also because different criteria for success were used (Table 4).

Table 4 Publications on functional or maximal electrical stimulation

Author	y.o.p.	Pts.	Type of study	Indication	Treatment scheme	Treatment parameters			Outcome (%)
						Intensity (mA)	Pulses (msec)	Freq. (Hz)	
Godec ⁵⁸	1976	126	NRCT	(N)NBD/SD	Anal or needles, cont., 1-3 months	10-15	1	20	92i
Godec ⁵⁹	1979	18	NRCT	NBD/SD	Anal ± needles, cont. or 15-20 min./2-3 days, 4-10x in total	10-15 or 100-150	1	20	45i, 36c
Merrill ⁶⁷	1979	20	NRCT	NBD/SD	Anal, cont. for 5-12 months	n.s	n.m.	n.m.	20i
Plevnik ⁶⁰	1979	98	NRCT	(N)NBD/SD	Anal or vaginal, 20 min./week, 4 weeks	30-100	1	20	48i
Plevnik ⁶¹	1984	6	NRCT	NBD/VD	Anal ± vaginal, 15-20 min., 2-4x/month	50-90	1	20	83i
Ohlsson ⁶²	1989	29	NRCT	(N)NBD/SD	Anal ± vaginal + needles, 20 min./week, 4 weeks	2-120	1	10	38-100i
Fossberg ⁶³	1990	91	NRCT	NNBD/SD	Anal ± vaginal, 12x 20 min.	≤ 100	1	5-10	56i
Caputo ⁶⁴	1993	57	NRCT	NNBD/SD	Vaginal, 6x 15 min./week	n.m	n.m	20	70-73i
Petersen ⁶⁵	1994	13	NRCT	NBD/SD	Anal, 2x 30 min./day, 12 days	n.m.	0.3	40	17i
Geirsson ⁶⁶	1997	84	NRCT	(N)NBD/SD	Anal ± vaginal or penile, 2x 20 min./week, 4x in total	5-82	0.75	5	54i, 5c

Y.o.p. = year of publication, Pts. = Patients, Freq. = Frequency, Cont. = Continuously, NRCT = Non Randomized Clinical Trial, NBD = Neurogenic Bladder Dysfunction, NNBD = Non Neurogenic Bladder Dysfunction, VD = Voiding Disorder, SD = Storage Disorder, n.m. = not mentioned, i = improved, c = cured

Especially the physical and psychological discomfort of this treatment modality experienced in these studies by many patients who often not finished the studies or were not willing to continue chronic therapy, limited acceptance of functional or maximal electrical stimulation.

Penile and clitoral stimulation Being the most superficial branch of the pudendal nerve the dorsal nerve of the penis is very near to the skin surface.⁶⁸ Squeezing the glans penis has been shown to suppress bladder contractions⁶⁹, but electrical stimulation of the penis did not cause a significant change in intravesical pressure at urodynamics during the filling phase.⁷⁰ The pudendal pelvic nerve reflex has been proposed as a mechanism of bladder inhibition^{1,2} because pudendal nerve afferents from the dorsal nerve of the penis course to sacral cord segments S2 to S4, the same sacral segments from which detrusor afferents, the pelvic nerves, arise.⁷¹ The increase in PNS either stimulates the sympathetic system that suppresses bladder activity via the β -adrenergic system or it stimulates the spinal interneurons that release inhibitory neurotransmitters (such as enkephalins, glycine or γ -aminobutyric acid).^{1,2}

In experimental studies acute effects of dorsal penile nerve stimulation seem promising, especially in improving bladder capacity. However, clinical studies lack significant effects (Table 5) and many patients experience bothersome sensations during stimulation even at threshold levels.⁷² It is believed that chronic low frequency stimulation with high current intensity (up to or even exceeding 99 mA) may improve treatment outcome^{73,74}, but the very unpleasant feeling or pain resulting from this stimulation will limit its application.

Selective pudendal nerve stimulation To deliver more potent electrical stimuli than can be applied by anal or vaginal stimulation, Vodušek et al⁷⁵ introduced selective PNS (Table 6). In this method, a concentric needle electrode is inserted into the periurethral sphincter muscle under auditory and oscilloscopic control, and two teflon-coated bare-tip needle electrodes are introduced ipsilaterally into the proximity of the pudendal nerve (at the ischial spine) through the perineum, 2-3 cm apart. Clear vesicoinhibitory responses could be found, with subsequent increase of micturition thresholds. Although the author proposed the development of an implantable stimulator, no further publications arose.

With the development of the Bion™ device (Advanced Bionics, Sylmar, California, USA)⁹ new interest in selective PNS may be anticipated.

Table 5 Publications on penile/clitoral electrostimulation

Author	y.o.p.	Pts.	Type of study	Indication	Treatment scheme	Treatment parameters			Outcome (%)
						Intensity	Pulses (msec)	Freq. (Hz)	
Nakamura ⁶⁸	1984	22	NRCT	(N)NBD/SD	'continuous' (portable stimulator)	5-50 V	0.5	10-20	18c
Vodušek ⁷⁶	1986	10	AUCE	NBD/SD	Urodynamics before, during and after stimulation	20-37 mA	0.2-0.5	5-10	-
Wheeler ⁷¹	1992	6	AUCE	NBD/SD	Urodynamics before, during and after stimulation	25-70 mA	0.35	5	-
Wheeler ⁷²	1994	9	NRCT	NBD/VD-SD	'continuous' (portable stimulator)	40 mA	0.25	5	22c
Previnaire ⁷⁷	1996	10	AUCE	NBD/SD	Urodynamics during stimulation	14-40 mA	0.5	5	-
Previnaire ⁷³	1998	6	NRCT	NBD/SD	20 min./day, 5 days/week, 4 weeks	35-99 mA	0.5	5	33i
Kirkham ⁷⁴	2001	14	AUCE	NBD/SD	Urodynamics before and after stimulation	20-60 mA	0.2	15	-

Y.o.p. = year of publication, Pts. = Patients, Freq. = Frequency, NRCT = Non Randomized Clinical Trial, AUCE = Acute Urodynamically Controlled Experiment, NBD = Neurogenic Bladder Dysfunction, NNBD = Non Neurogenic Bladder Dysfunction, VD = Voiding Disorder, SD = Storage Disorder, n.m. = not mentioned, i = improved, c = cured

Table 6 Publications on selective pudendal stimulation

Author	y.o.p.	Pts.	Type of study	Indication	Treatment scheme	Treatment parameters			Outcome (%)
						Intensity (mA)	Pulses (msec)	Freq. (Hz)	
Vodušek ⁷⁵	1988	3	AUCE	NBD/SD	Stimulation during urodynamics	1-2	0.2	5	-

Y.o.p. = year of publication, Pts. = Patients, Freq. = Frequency, AUCE = Acute Urodynamically Controlled Experiment, NBD = Neurogenic Bladder Dysfunction, SD = Storage Disorder, i = improved, c = cured

Transcutaneous electrical nerve stimulation (TENS)

Suprapubically In 1980, Fall et al.⁵¹ were the first to report on a study in IC patients using suprapubical transcutaneous electrical nerve stimulation (TENS) to relief pain and symptoms of bladder overactivity. Favorable outcome was considered to be due

to pain relief and thereby the possibility to increase bladder filling and postpone voiding. However, influence of TENS on the autonomic system might be another explanation. As clinical results were promising, especially in relieving pain and decreasing voiding frequency, follow-up studies were performed not only in case of IC, but also in patients with idiopathic lower urinary tract dysfunction⁷⁸⁻⁸¹ (Table 7).

Table 7 Publications on TENS over the suprapubic region

Author	y.o.p.	Pts.	Type of Study	Indication	Treatment scheme	Treatment parameters			Outcome (%)
						Intensity (mA)	Pulses (msec)	Freq. (Hz)	
Fall ⁵¹	1980	9	NRCT	NNBD/SD	2x/day 15 min. to 2 hours for 1-6 months	n.m.	0.2	50	22-100i
Fall (1) ⁷⁸	1987	35	NRCT	NNBD/SD	2x/day 2 hours for 6 weeks, intermittently up to 7 years	n.m.	0.2	2-50	37i, 14c
Fall (1) ⁸²	1994	60	NRCT	NNBD/SD	2x/day 30 min. to 2 hours, to intermittently, up to 10 years	n.m.	0.2	2-50	26-54i
Hasan ⁷⁹	1996	36	AUCE	NNBD/SD	Urodynamic experiment only	n.m.	0.2	50	-
Bower ⁸⁰	1998	? of 79	AUCE	NNBD/SD	Urodynamic experiment only	n.m.	0.2	150	-
Bower ⁸¹	2001	2	NRCT	NNBD/SD	2x/day 1 hour for 1 to 5 months	n.m.	0.2	150	73i

Y.o.p. = year of publication, Pts. = Patients, Freq. = Frequency, NRCT = Non Randomized Clinical Trial, AUCE = Acute Urodynamically Controlled Experiment, NNBD = Non Neurogenic Bladder Dysfunction, SD = Storage Disorder, n.m. = not mentioned, i = improved, c = cured, (1) = extension of original patient group

In this form of TENS two carbon-rubber electrodes are positioned suprapubically, 10-15 cm. apart. Stimulation is given at maximum tolerable intensity up to 2 hours twice daily as there proves to be a carry-over effect, i.e. a lasting improvement after the withdrawal of stimulation. Frequencies used highly differ from 2 Hz, considered to stimulate pudendal nerve afferents to 50 Hz, considered to engage the striated paraurethral musculature.^{53,83} Even 150 Hz has been used, probably having a mainly sensory effect.

Low frequency TENS is reported to give earlier results in some patients, but the muscle twitches are highly unpleasant.⁸² The 150 Hz current may lead to a decrease of detrusor contractility by influencing the anterior cutaneous branch of the iliohypogastric nerve (Lumbar I level), or by inhibiting afferents of the pelvic splanchnic nerves that join the inferior hypogastric plexus.⁸⁰

Compared to placebo there are conflicting publications reporting no significant changes in urodynamics ⁷⁹ versus significant changes in first desire to void, maximum cystometric capacity and threshold volume in the suprapubic TENS group. ⁸⁰ TENS is an easy applicable and non-invasive treatment option, but has to be used intermittently for long periods of time. ^{78,82}

S2 or S3 dermatome As suprapubic TENS proved to be an easy applicable treatment modality with minimal side effects, and direct electrical stimulation of S3 sacral segmental nerve roots by surgically implanted electrodes showed encouraging results ⁸⁴, it was thought that application of TENS over the S2 or S3 dermatome might improve clinical results. This treatment option has been studied extensively using clinical as well as urodynamic parameters. S2-3 TENS was compared to no TENS ^{79,85,86}, sham TENS (just an apparatus with a flashlight ⁸⁰ or TENS on T12 ^{79,85,86}, suprapubic TENS ^{79,80}, TENS on the tibial nerve ⁷⁹, direct S3 stimulation ⁷⁹, and medical treatment with oxybutynin ⁸⁷ (Table 8).

Table 8 Publications on TENS over the S2 and S3 dermatome

Author	y.o.p.	Pts.	Type of study	Indication	Treatment scheme	Treatment parameters			Outcome (%)
						Intensity (V)	Pulses (msec)	Freq. (Hz)	
Adults or age not mentioned:									
Webb ⁸⁵	1992	24	RPCT	NNBD/SD	1 week, scheme n.m.	n.m.	n.m.	n.m.	54i
Hasan ⁸⁶	1994	20	NRCT	NNBD/SD	3 weeks, scheme n.m.	n.m.	0.2	50	71i, 25c
Hasan ⁷⁹	1996	59	NRCT	NNBD/SD	2 to 4 weeks, scheme n.m.	n.m.	0.2	50	37-73i
Bower ⁸⁰	1998	? of 79	AUCE	NNBD/SD	Urodynamic experiment only	n.m.	0.2	10	-
Walsh ⁸⁸	1999	25	NRCT	NNBD/SD	12 hours/day for 1 week	n.m.	0.2	10	56-76i
Soomro ⁸⁷	2001	43	RCT	NNBD/SD	Up to 6 hours/day for 6 weeks	n.m.	0.2	20	2-24i
Children:									
Bower ⁸¹	2001	15	NRCT	NNBD/SD	2x/day 1 hour for 1 to 5 months	n.m.	n.m.	10	73i
Hoebeke ⁸⁹	2001	41	NRCT	NNBD/SD	2 hours/day, for 1 to 6 months	n.m.	0.15	2	76i, 56c

Y.o.p. = year of publication, Pts. = Patients, Freq. = Frequency, RPCT = Randomized Placebo Controlled Trial, NRCT = Non Randomized Clinical Trial, AUCE = Acute Urodynamically Controlled Experiment, RCT = Randomized Clinical Trial, NBD = Neurogenic Bladder Dysfunction, NNBD = Non Neurogenic Bladder Dysfunction, SD = Storage Disorder, n.m. = not mentioned, i = improved, c = cured

The aforementioned studies reveal a positive effect on detrusor instability, delaying the first desire to void and increasing bladder capacity on urodynamics. Some of the patients with detrusor instability become stable on urodynamics, while in others the volume at first contraction improves significantly.^{79,80,85,86} However, for permanent diminishing incontinence, TENS alone appears insufficient.^{81,89} Compared to oxybutynin, TENS has less side effects, but treatment outcome is in favor of medication.⁸⁷ As in suprapubic TENS, continuation of treatment for long periods of time is necessary to prevent recurrence of complaints.⁸⁸ And even in case of a successful outcome, a majority of patients is unwilling to purchase a stimulation device because of the costs or the fear being lost to medical supervision and follow-up.⁸⁸

Electrical stimulation of the sacral spine and roots

Direct sacral spine stimulation In an attempt to achieve micturition by spinal cord stimulation, animal experiments were done by Nashold⁹⁰ and Friedman⁹¹, in which the sacral segments of the conus medullaris were activated directly. It was found that the region of optimal stimulation is at the level of S1-S3 and that the frequency of stimulation determines effectiveness. Stimulation with surface electrodes proved to be of no use, only deep stimulation resulted in high bladder pressures. Unfortunately, simultaneous external sphincter relaxation could not be obtained. Following these reports, stimulators were implanted in humans^{92,93} (Table 9).

Further animal studies by Jonas et al.⁹⁴⁻⁹⁷ with several types of electrodes did not result in successful voiding. Although detrusor contractions arose, they were accompanied by concomitant contractions of the external sphincter, allowing only minimal voiding at the end of the stimulation, the so-called post stimulus voiding. Later research⁹⁸ revealed that at the sacral spinal level the parasympathetic nucleus is located in the vicinity of the pudendal nucleus, which means that it is almost impossible to stimulate the bladder and sphincter separately at this location. Therefore, direct spinal cord stimulation has been abandoned.

Table 9 Publications on direct spinal cord stimulation

Author	y.o.p.	Pts.	Type of study	Indication	Stimulator	Treatment parameters			Outcome (%)
						Intensity (V)	Pulses (msec)	Freq. (Hz)	
Grimes ⁹³	1974	10	NRCT	NBD/VD	n.m.	10-15	n.m.	15-20	60i
Grimes (1) ⁹²	1975	10	NRCT	NBD/VD	n.m.	10-15	0.2	15-20	60i

Y.o.p. = year of publication, Pts. = Patients, Freq. = Frequency, NRCT = Non Randomized Clinical Trial, NBD = Neurogenic Bladder Dysfunction, VD = Voiding Disorder, n.m. = not mentioned, i = improved, (1) = the same patients as in the publication of 1974 are described

Sacral anterior root stimulation after dorsal rhizotomy After several experimental studies in baboons, Brindley first reported in 1982 on the implantation of a sacral anterior root stimulator in paraplegic patients⁹⁹, soon to be followed by the description of a further 50 cases.¹⁰⁰ The sacral anterior root stimulator consists of an implantable receiver with stimulation wires and an external transmitter (Finetech Ltd, Hertfordshire, United Kingdom). The surgical technique has been modified by Sauerwein, who combined sacral anterior root stimulation with complete posterior sacral root rhizotomy to abolish all reflex activity of the detrusor.¹⁰¹ Usually, after laminectomy from L3-4 to S2, the sacral roots are identified intradurally and separated in their anterior and posterior parts using a hook electrode. After transection of the posterior roots S2 to S4(-5), the remaining anterior roots are placed in the electrodes and the dura is closed. The receiver is placed in a ventral subcutaneous pocket.¹⁰² The procedure can also be performed extradurally^{103,104} and may have beneficial effects on erectile function and defecation.¹⁰⁰ Incomplete rhizotomy of the posterior roots results in poor bladder compliance, contrary to patients in which a complete transection has been performed, making patients with intact sacral sensibility less suitable for this procedure.¹⁰² This need for complete dorsal rhizotomy was also confirmed in experimental studies in canines.^{105,106} As stimulation induces simultaneous contractions of the detrusor muscle and the external sphincter, micturition occurs by post stimulus voiding as the relaxation time of the sphincter is shorter than that of the smooth detrusor muscle. Therefore, bursts of impulses are given to empty the bladder to repeat this phenomenon. Variation in

stimulation parameters have been studied to reduce the problem of sphincter contraction.¹⁰⁷ Nevertheless, sometimes a sphincterotomy is still needed.¹⁰⁸

A lot of research has been done by members of the Dutch Study Group on Sacral Anterior Root Stimulation^{102,107,109-112} (Table 10).

Table 10 Publications on sacral root stimulation after dorsal rhizotomy

Author	y.o.p.	Pts.	Type of Study	Indication	Stimulator	Treatment parameters			Outcome (%)
						Intensity (mA)	Pulses (msec)	Freq. (Hz)	
Brindley ⁹⁹	1982	11	NRCT	NBD/VD-SD	Finetech-Brindley stimulator	≤ 20	0.1	8-30	64i
Brindley (1) ¹⁰⁰	1986	50	NRCT	NBD/VD-SD	Finetech-Brindley stimulator	n.m.	n.m.	n.m.	67i
Robinson ¹⁰⁸	1988	22	NRCT	NBD/VD-SD	Finetech-Brindley stimulator	n.m.	n.m.	n.m.	68i
Tanagho ¹⁰⁴	1989	22	NRCT	NBD/VD-SD	n.m.	3-8	0.18-0.2	15-20	45i, 36c
Koldewijn ¹⁰²	1994	27	NRCT	NBD/VD-SD	Finetech-Brindley stimulator	n.m.	n.m.	n.m.	93i
Van der Aa ¹¹²	1995	17	NRCT	NBD/VD-SD	Finetech-Brindley stimulator	n.m.	n.m.	n.m.	71i
Van Kerrebroeck (2) ¹⁰⁹	1996	52	NRCT	NBD/VD-SD	Finetech-Brindley stimulator	n.m.	n.m.	n.m.	91i
Van Kerrebroeck (3) ¹¹⁰	1997	52	NRCT	NBD/VD-SD	Finetech-Brindley stimulator	n.m.	n.m.	n.m.	73-86i
Egon ¹⁰³	1998	96	NRCT	NBD/VD-SD	Finetech-Brindley stimulator	n.m.	n.m.	n.m.	88i
Rijkhoff ¹⁰⁷	1998	12	AUCE	NBD/VD-SD	Finetech-Brindley stimulator	≤ 6	0.2-0.7	25	-
Van der Aa (4) ¹¹³	1999	38	NRCT	NBD/VD-SD	Finetech-Brindley stimulator	n.m.	n.m.	n.m.	63-82i

Y.o.p. = year of publication, Pts. = Patients, Freq. = Frequency, NRCT = Non Randomized Clinical Trial, AUCE = Acute Urodynamically Controlled Experiment, NBD = Neurogenic Bladder Dysfunction, VD = Voiding Disorder, SD = Storage Disorder, n.m. = not mentioned, i = improved, c = cured, (1) = follow-up report on publication of 1982, partly the same patients are described, (2) = follow-up report on publication of Koldewijn, partly the same patients are described, (3) = partly the same patients as in the publication of 1996 are described, (4) = partly the same patients as in the publication of 1995 are described

Cost-effectiveness and quality-of-life analysis is performed, revealing a financial break-even point at about 8 years and significant changes in psychological well-being

and feelings concerning micturition and bladder emptying. General quality-of-life indicators do not significantly change after the implantation.¹¹¹

Sacral anterior root stimulation after dorsal rhizotomy is now a well accepted treatment option in patients with a complete supra-sacral spinal cord lesion leading to incontinence, recurrent urinary tract infections or upper urinary tract deterioration.

Sacral root stimulation by implant In 1981, the urological department of the University of California at San Francisco started a clinical program to evaluate the results of sacral root electrode implantation in humans, leading to the first publications on this subject by Tanagho and Schmidt.^{114,115} Since then a progressive amount of reports has been published as the technique gained popularity. The surgical technique, described in detail by Thon¹¹⁶ and Siegel¹¹⁷, consists of implantation of a wire electrode in one of the sacral foramina, usually S3, which is then connected to a stimulator device (InterStim®, Medtronic, Minneapolis, Minnesota, USA) placed in a subcutaneous pocket in the abdomen. This stimulator device can be controlled radiographically. Because the implantation procedure is expensive and invasive and clear predictors of success are absent¹¹⁸, surgery is preceded by Peripheral Nerve Evaluation (PNE) to select patients who might improve after implantation of a permanent stimulator device. Guided by anatomical landmarks¹¹⁹, a temporary wire electrode is percutaneously inserted in the sacral foramen and connected to an external stimulator for a couple of days.⁹⁷ In case of an improvement in predefined parameters of >50%, implantation of a permanent stimulator is indicated.

Initially it was thought that sacral neuromodulation mainly was effective on the pelvic floor muscles by inducing muscle hypertrophy. A change in histochemical properties¹²⁰ was supposed to lead to improved pelvic floor efficiency.¹²¹ As neuromodulation takes place below the threshold for direct motor responses, this theory is not convincing. Nowadays it is well accepted that effects of sacral root neuromodulation take place at the spinal and supraspinal level, by inhibition of spinal tract neurons involved in the micturition reflex, of interneurons involved in spinal segmental reflexes and of postganglionic neurons.¹²² Furthermore, there may be inhibition of the primary afferent pathway, and indirect suppression of guarding reflexes by turning off bladder input to internal sphincter sympathetic or external urethral sphincter interneurons.⁹⁷ Also in urinary retention, the obtained effects are believed by some

authors to be the result of changed pelvic floor behavior directly ^{123,124}, or as part of retuning of a brainstem 'on-off' switch mechanism. ^{122,125}

Although several authors have reported on mixed groups of patients with chronic voiding disorders ¹²⁶⁻¹³⁰ most publications concern one of the three main indications for sacral neuromodulation: UF syndrome, UI or chronic urinary retention (Table 11). A decrease of pelvic pain as a symptom accompanying UF or UI has been reported by several authors ¹³¹⁻¹³³, but results are disappointing if sacral neuromodulation is performed solely on pelvic pain as a primary complaint. ¹³⁴⁻¹³⁵ With expanding experience also other indications are being explored, like for example sacral neuromodulation in multiple sclerosis patients ^{136,137}, children ¹³⁸ or patients with IC. ^{133,139}

In order to refine the technique and improve treatment results, new stimulation devices are being developed ¹⁴⁰ and modifications to the current technique have been described. To shorten operation time and reduce pain complaints at the stimulator site, buttock placement of the stimulator was advocated by Scheepens et al. ¹⁴¹ Bilateral stimulation with cuff electrodes as well as a tailored laminectomy have been described ¹⁴²⁻¹⁴⁵, but because of progressive improvement of the results of unilateral stimulation treatment outcome during recent years, these techniques never became very popular as they are also more laborious. For patients with repeatedly failed PNE-tests, the two-stage procedure has been described by Janknegt et al. ^{146,147} In this procedure a permanent lead is implanted and connected to an external stimulator for an evaluation period of 4 days. In case a more than 50% improvement occurs, a permanent subcutaneous stimulator is implanted. Oliver et al. ¹⁴⁸ described the use of conditional neuromodulation, that is neuromodulation applied only at moments of an increased level of urge, that might expand battery lifespan. Finally, minimally invasive techniques are being developed, by which the permanent lead can be implanted through a very small paramedian incision, fixing the electrode with the use of bone anchors ¹⁴⁹ or even percutaneously, fixing the lead with the twist-lock ¹⁵⁰ or grip-lock system. Percutaneous implantation of the electrodes is especially desirable in patients with spinal cord injury treated by sacral nerve stimulation as the localization of the skin incision frequently involves decubitus. ¹⁵¹

Table 11 Publications on sacral root stimulation by implant

Author	y.o.p.	Pts.	Type of study	Indication	Stimulator	Treatment parameters			Outcome (%)
						Intensity (V)	Pulses (msec)	Freq. (Hz)	
Thon ¹²⁶	1991	57	NRCT	NNBD/SD	Medtronic stimulator	2-4	0.18-0.21	14-18	75i
Vapnek ¹²⁵	1991	7	NRCT	NNBD/VD	Medtronic stimulator	n.m.	n.m.	n.m.	71c
Dijkema ¹²⁷	1993	23	NRCT	NNBD/VD-SD	Medtronic stimulator	0.5-4	0.15-0.21	5-10	22i, 61c
Elabbady ¹²⁸	1994	17	NRCT	NNBD/VD-SD	Medtronic stimulator in 17 of 50 patients	1.5-5.5	0.21	10-15	37-85i
Koldewijn ¹¹⁸	1994	100	NRCT	(N)NBD/VD-SD	Percutaneous evaluation only, ≥ 3 days	≤ 10 mA	0.20	25	13i, 34c
Bosch ¹⁵²	1995	18	NRCT	NNBD/SD	Medtronic stimulator in 18 of 31 patients	2.7±0.4	0.21	10-15	22i, 61c
Bosch ¹³⁶	1996	6	NRCT	NBD/SD	Medtronic stimulator in 4 of 6 patients	2.8-4.2	0.21	10	25i, 50c
Janknegt ¹⁴⁶	1997	10	NRCT	NNBD/VD-SD	Electrode implantation ('two-stage')	n.m.	n.m.	n.m.	80i
Ishigooka ¹⁵¹	1998	4	NRCT	NBD/VD-SD	Medtronic stimulator, percutaneous implant	≤ 10	0.5	10	50i, 25c
Shaker ¹³¹	1998	18	NRCT	NNBD/VD-SD	Medtronic stimulator	n.m.	n.m.	n.m.	22i, 44c
Shaker ¹⁵³	1998	20	NRCT	NNBD/VD	Medtronic stimulator	n.m.	n.m.	n.m.	100i
Weil ¹²⁹	1998	36	NRCT	NNBD/VD-SD	Medtronic stimulator in 36 of 100 patients	0.5-4	0.21	15	53i
Schmidt ¹⁵⁴	1999	86	RCT	NNBD/SD	Medtronic stimulator in 86 of 155 patients	n.m.	n.m.	n.m.	29i, 47c
Chai ¹³⁹	2000	6	NRCT	NNBD/SD	Percutaneous evaluation only, 5 days	n.m.	n.m.	n.m.	70i
Weil ¹⁵⁵	2000	44	RCT	NNBD/SD	Medtronic stimulator in 44 of 123 patients	≥ 0.1	0.21	15	75c
Hassouna ¹³²	2000	51	RCT	NNBD/SD	Medtronic stimulator	n.m.	n.m.	n.m.	56-88i
Jonas ¹⁵⁶	2001	68	RCT	NNBD/VD	Medtronic stimulator in 68 of 177 patients	n.m.	n.m.	n.m.	14i, 69c
Maher ¹³³	2001	15	NRCT	NNBD/SD	Percutaneous evaluation only, 7-10 days	≤ 10	0.21	15	73i
Janknegt ¹⁵⁷	2001	96	NRCT	NNBD/SD	Medtronic stimulator	n.m.	n.m.	n.m.	36i, 26c
Spinelli ¹³⁰	2001	196	NRCT	(N)NBD/VD-SD	Medtronic stimulator	n.m.	n.m.	n.m.	39-66c
Aboseif ¹⁵⁸	2002	64	NRCT	NNBD/VD-SD	Medtronic stimulator	n.m.	n.m.	n.m.	80i
Aboseif ¹⁵⁹	2002	20	NRCT	NNBD/VD	Medtronic stimulator	n.m.	n.m.	n.m.	90i
Hedlund ¹⁶⁰	2002	14	NRCT	NNBD/SD	Medtronic stimulator in 14 of 53 patients	n.m.	n.m.	n.m.	36i, 57c
Amundsen ¹⁶¹	2002	12	NRCT	NNBD/SD	Medtronic stimulator in 12 of 25 patients	n.m.	n.m.	n.m.	83i, 17c
Spinelli ¹⁵⁰	2003	22	NRCT	(N)NBD/VD-SD	Medtronic stimulator in 22 of 32 patients	n.m.	n.m.	n.m.	5i, 91c

Y.o.p. = year of publication, Pts. = Patients, Freq. = Frequency, NRCT = Non Randomized Clinical Trial, RCT = Randomized Clinical Trial, NBD = Neurogenic Bladder Dysfunction, NNBD = Non Neurogenic Bladder Dysfunction, VD = Voiding Disorder, SD = Storage Disorder, n.m. = not mentioned, i = improved, c = cured

Electrical stimulation of the lower limb

Electrical stimulation of the thigh muscle In 1986, Wheeler et al.¹⁶² reported on urodynamic changes after 4-8 weeks of thigh muscle reconditioning by surface electrical stimulation. Within a year, Shindo et al.¹⁶³ reported on beneficial changes in bladder function allowing effective 'dry' periods in patients treated with thigh muscle stimulation for severe lower limb spasticity (Table 12). More recently, thigh muscle stimulation was studied with the sole purpose to treat detrusor overactivity.¹⁶⁴

Table 12 Publications on thigh muscle stimulation

Author	y.o.p.	Pts.	Type of study	Indication	Treatment scheme	Treatment parameters			Outcome (%)
						Intensity (mA)	Pulses (msec)	Freq. (Hz)	
Shindo ¹⁶³	1987	32	NRCT	NBD/SD	9-35 min. a day, 6 weeks	n.m.	0.2	30-40	50i
Okada ¹⁶⁴	1998	19	NRCT	(N)NBD/SD	20 min. a day, 2 weeks	n.m.	0.2	30	32i

Y.o.p. = year of publication, Pts. = Patients, Freq. = Frequency, NRCT = Non Randomized Clinical Trial, NBD = Neurogenic Bladder Dysfunction, NNBD = Non Neurogenic Bladder Dysfunction, SD = Storage Disorder, n.m. = not mentioned, i = improved, c = cured

The mechanism by which stimulation of the thigh muscles inhibits detrusor overactivity is unclear. Most probably a reflex-mediated central inhibition of the bladder occurs, which normally prevents urine leakage during physical exertion.¹⁶⁵ Manipulation of peripheral input to spinal motor neurons may increase segmental inhibitory tone¹⁶⁶ relieving not only spasticity of limbs in patients with spinal cord injuries, but also regulating micturition reflexes in patients with an overactive bladder.¹⁶⁴ A satisfactory neurophysiological explanation for the carry-over effect could not be given. It is, however, suggested that prolonged electrical stimulation may lead to some reorganization of the neuronal systems controlling the bladder, either peripherally or centrally, and as a result of this plastic change normal reflex patterns may restore.^{165,167}

The treatment is not associated with known adverse effects. If symptoms recur, repeated stimulation again may be effective.¹⁶⁴ Nevertheless, thigh muscle stimulation in the treatment of detrusor overactivity is not commonly performed.

Electrical stimulation of the tibial nerve During experimental studies in non-human primates with spinal cord injury to improve bipolar anal sphincter stimulation, McGuire et al found inhibition of detrusor activity equally achieved by applying a positive current to the anal sphincter, with a negative electrode placed over the posterior tibial nerve. Similar results were obtained by applying current via a transcutaneous positive stick-on electrocardiograph type electrode with a foam backing placed over the common peroneal or posterior tibial nerve and a ground electrode placed over the same nerves contra laterally. The idea of stimulating these nerves was based on the traditional Chinese practice using acupuncture points over the common peroneal or posterior tibial nerves to inhibit bladder activity.¹⁶⁸ Transcutaneous posterior tibial nerve stimulation was then evaluated in clinical trials with variable results¹⁶⁸⁻¹⁷⁰ (Table 13).

Nonetheless, PTNS (Urgent PC™, CystoMedix, Anoka, Minnesota, USA) was FDA approved in 2000. A 34-gauge stainless steel needle is to be inserted approximately 5 cm cephalad from the medial malleolus and just posterior to the margin of the tibia. A stick-on electrode is placed on the medial surface of the calcaneus.^{171,172} Recent reports describe the results after an initial treatment period of 10-12 weeks (Table 5.2). In case of a good response patients are offered tapered chronic treatment. As in sacral root neuromodulation, PTNS seems less effective in treating chronic pelvic pain.¹⁷³

More substantial data, especially on objective parameters and long-term follow-up, are needed, just like studies on the underlying neurophysiological mechanisms of this treatment modality. One possibility might be the reduction of spinal neuronal cell activity, as suggested by Chang et al.¹⁷⁴ Bladder instillation of 1% acetic acid in rats induces expression of the metabolic marker c-fos protein in the spinal micturition center, while PTNS reduces this expression.

Although PTNS is minimally invasive, easily applicable and well tolerated, the main disadvantage seems to be the necessity to pertain chronic treatment. The development of an implantable subcutaneous stimulation device might enlighten this problem.

Table 13 Publications on tibial nerve stimulation

Author	y.o.p.	Pts.	Type of study	Indication	Treatment scheme	Treatment parameters			Outcome (%)
						Intensity (mA)	Pulses (msec)	Freq. (Hz)	
Transcutaneous:									
McGuire ¹⁶⁸	1983	22	NRCT	(N)NBD/SD	n.m.	n.m.	n.m.	n.m.	32i, 55c
Geirsson ¹⁶⁹	1993	8	RCT	NNBD/SD	30 min./day, 4 weeks	n.m.	0.2	1	25i
Hasan ¹⁷⁰	1996	36	AUCE	NNBD/SD	Stimulation during urodynamics	n.m.	0.2	50	-
Percutaneous:									
Stoller ¹⁷¹	1999	90	NRCT	NNBD/SD	10 times 20-30 min., once a week	≤ 10	0.2	20	81i
Govier ¹⁷⁵	1999	n.m.	NRCT	NNBD/SD	12 times 30 min., once a week	≤ 10	0.2	20	80i
Klingler ¹⁷⁶	2000	15	NRCT	NNBD/SD	12 times 30 min., 4 times a week	≤ 10	0.2	20	20i, 47c
Govier ¹⁷²	2001	53	NRCT	NNBD/SD	12 times 30 min., once a week	≤ 10	0.2	20	71i
Vandoninck ¹⁷⁷	2001	8	AUCE	(N)NBD/SD	Stimulation during urodynamics	≤ 10	0.2	20	-
Van Balken ¹⁷⁸	2001	49	NRCT	NNBD/VD-SD	12 times 30 min., once a week	≤ 10	0.2	20	60i
Vandoninck ¹⁷⁹	2003	35	NRCT	NNBD/SD	12 times 30 min., once a week	≤ 10	0.2	20	70i, 46c

Y.o.p. = year of publication, Pts. = Patients, Freq. = Frequency, NRCT = Non Randomized Clinical Trial, RCT = Randomized Clinical Trial, AUCE = Acute Urodynamically Controlled Experiment, NBD = Neurogenic Bladder Dysfunction, NNBD = Non Neurogenic Bladder Dysfunction, VD = Voiding Disorder, SD = Storage Disorder, n.m. = not mentioned, I = improved, c = cured

Conclusions

The use of electrical neurostimulation and neuromodulation to treat patients with lower urinary tract dysfunction has been widely investigated. Nevertheless, in many reports important information is missing and good randomized placebo controlled studies have seldom been performed^{180,181}, even concerning invasive techniques that make use of implantable electrodes and stimulators. Besides this, there are many other problems making it very difficult to judge the different treatment modalities on their true merits.

First of all, there is considerable variety in the treatment parameters and schedules reported, hampering comparison of both studies concerning different and identical techniques. For example, pulse intensity, reported in mA as well as in V, is more or less uniformly set at a well tolerable level, but frequency, known to be optimal at unpleasantly low levels (5-6 Hz)¹⁶⁵, varies from 5-20 Hz and even frequencies up to 150 Hz are reported. The same goes for pulse duration, usually varying from 0.2-0.5 msec, but in some studies set at more than 1 msec. Furthermore, the treatment schedules are highly different, where they vary from continuous stimulation to treatment once daily or once or several times a week, for the duration of mostly some weeks or months.

Secondly, criteria for success differ widely. Cure is sometimes defined as complete disappearance of a predefined parameter, but also as over 90% improvement. Success differs from subjective satisfaction to statistical significant changes of more objective parameters. These outcome measures are rarely uniformly set, consisting of various urodynamic parameters and parameters obtained from micturition diaries and/or questionnaires. Long-term data on the clinical outcome are usually lacking. Finally, patients included in these studies have different characteristics, especially concerning the definition and duration of their symptoms and the various treatments applied before. This not only makes it difficult to compare different trials, but also hampers the determination of prognostic factors that might improve treatment outcome.

However, in general one might say that electrical neurostimulation and neuromodulation on an intention-to-treat basis result in a 30 to 50% clinical success. Influencing lower urinary tract innervation at the level of the sacral root seems to stand the test of time in both neurological and non-neurological patients. It has the advantage of pre-testing possibilities to improve patient selection and thereby treatment outcome, but it has the drawback of invasiveness. Non-invasive techniques lack screening tests and in case of success patients almost always need maintenance therapy.

In conclusion, not only randomized clinical trials to compare different techniques and to evaluate placebo effects overcoming the earlier mentioned methodological flaws are urgently needed, but also further studies to elucidate the mode of action to improve stimulation application and therapy results. The introduction of new stimulation methods may not only provide alternative treatment options, but may also

be of help in answering these more basic questions on electrical neurostimulation and neuromodulation.

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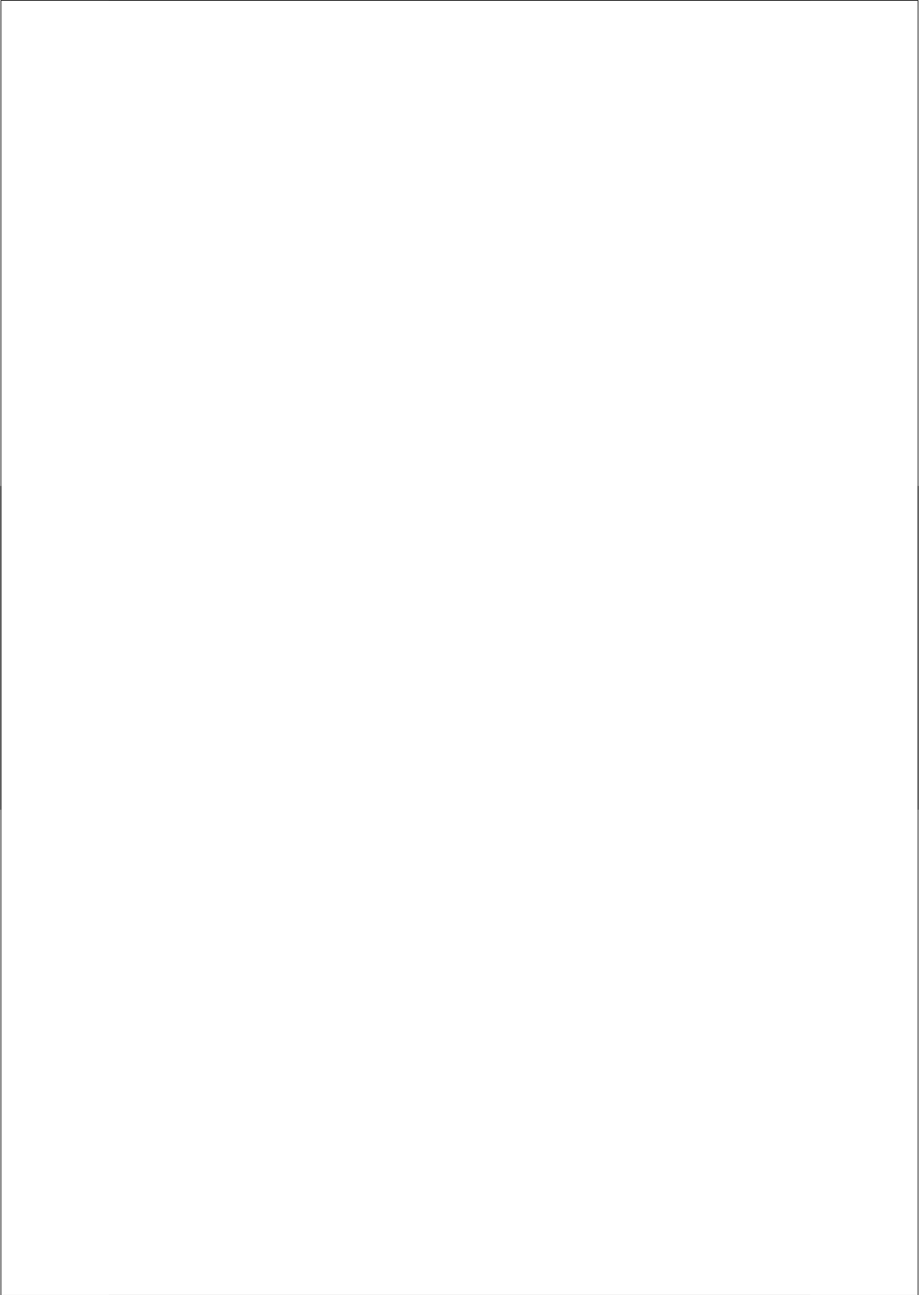
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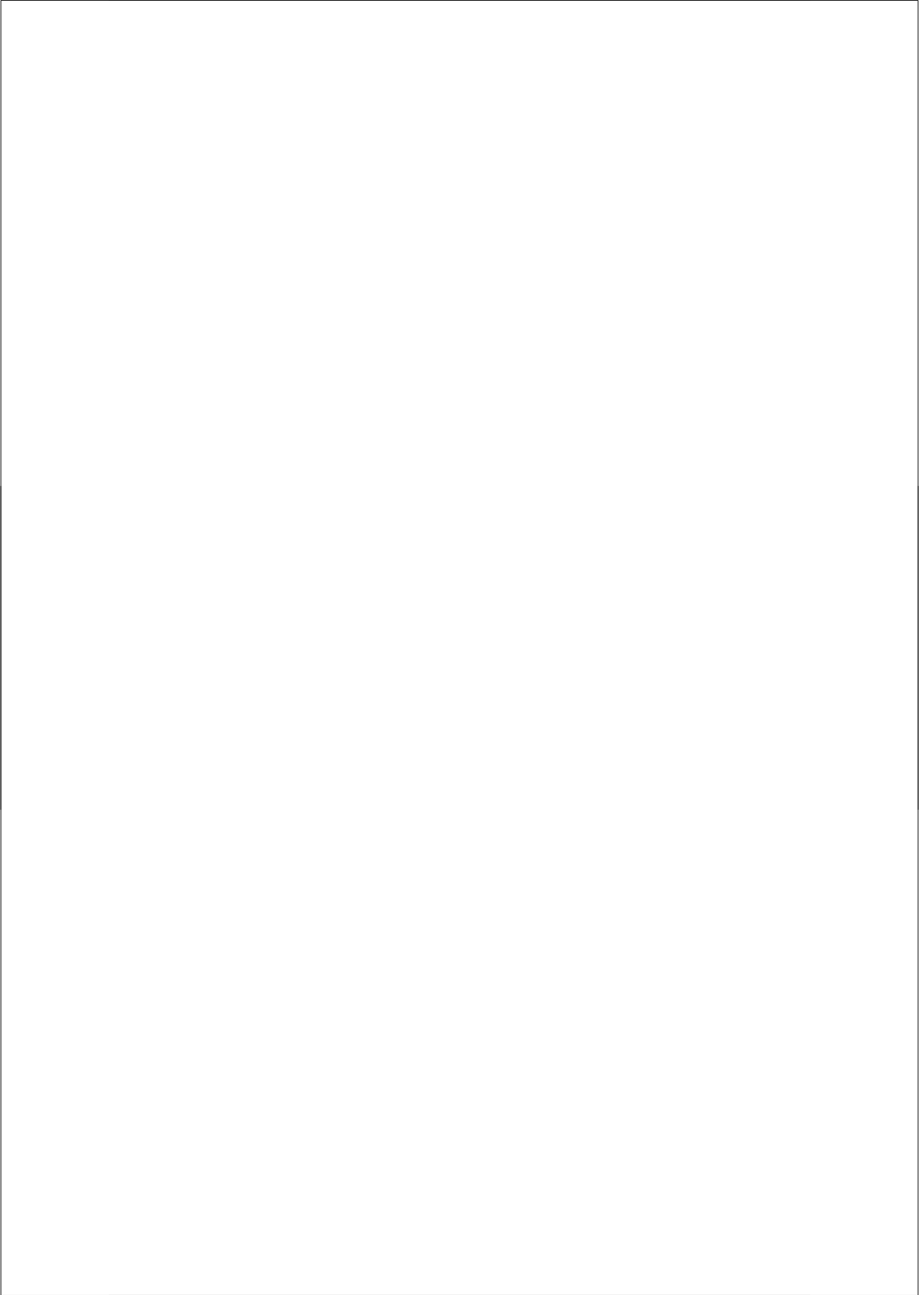
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CHAPTER 2

Feasibility and clinical results



Posterior tibial nerve stimulation as neuro-modulative treatment of lower urinary tract dysfunction

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Abstract

Objective Recently, intermittent percutaneous posterior tibial nerve stimulation was introduced as a treatment modality filling the gap between conservative and surgical therapies in patients with certain types of lower urinary tract dysfunction.

Patients and methods In a prospective multicenter trial posterior tibial nerve stimulation was evaluated in 37 patients who presented with symptoms of bladder overactivity, that is the urgency and frequency syndrome and/or urge incontinence, and 12 with non-obstructive urinary retention. Results were recorded in voiding diaries and on quality of life questionnaires before and after treatment. Patients were classified in responders, including those in whom therapy was successful and chose to continue treatment after the initial 12 weeks, and non-responders, those who chose to stop treatment.

Results Overall, a positive response was seen in 60% of all patients. In patients with bladder overactivity a statistically significant decrease was observed in leakage episodes, number of pads used, voiding frequency and nocturia, and an equal increase in mean and smallest volume voided. Improvements were also seen in non-obstructive urinary retention, including number of catheterisations, total and mean volume catheterized, and total and mean volume voided. Disease specific quality of life and some domains of general quality of life improved, especially of bladder overactivity. Only mild side effects were observed.

Conclusion Posterior tibial nerve stimulation is a minimally invasive and successful treatment option for patients with certain types of lower urinary tract dysfunction.

Introduction

Non-neurogenic lower urinary tract dysfunction is a common urological problem that strongly affects quality of life. Patients can complain of urgency and frequency, urge incontinence or present with urinary retention. In most patients the etiology of these complaints remains unclear.¹ Conservative treatment options for bladder overactivity, that is the urgency and frequency syndrome and/or urge incontinence, consist of behavioral techniques with and without biofeedback, bladder reeducation, pelvic muscle exercise or pharmacotherapy involving anticholinergics, antispasmodics and tricyclic antidepressants. Patients with non-obstructive urinary retention can be treated with clean intermittent or permanent catheterization. For refractory cases more aggressive surgical procedures, including bladder distension, ileocystoplasty or urinary diversion have been advocated. However, a high recurrence and complication rate limits the widespread application of these treatments.

Recently, continuous sacral root stimulation (Medtronic, Inc., Minneapolis, Minnesota) has been proposed as an alternative, less invasive therapeutic option for patients with non-neurogenic lower urinary tract dysfunction, not responding to conservative treatment.² Although highly effective in selected patients, this technique is expensive and requires explicit surgical skill. Posterior tibial nerve stimulation (PTNS) is technically less demanding and probably more cost-effective for management of lower urinary tract dysfunction. We present our initial experience with this new neuromodulation technique in a prospective clinical trial.

Patients and methods

Methods Between November 1999 and March 2000, 15 male and 34 female patients were enrolled in a prospective clinical multicenter trial that received approval by the institutional review board. All patients were evaluated for urgency and frequency, urge incontinence and non-obstructive retention by history, voiding diaries consisting of frequency-volume charts, and physical as well as urological examination, including urodynamics.

Urgency and frequency was defined as greater than 8 voids per 24 hours and the sudden urge to void could hardly be suppressed. Urge incontinence was characterized by urgency leading to urinary leakage occurring at least 3 times weekly and/or phasic involuntary bladder contractions with concomitant incontinence on cystometry. Non-obstructive retention was distinguished by urinary retention, necessitating intermittent catheterization at least 4 times daily without urodynamic signs of outflow obstruction as defined on the Abrams-Griffiths nomogram.³

The use of parasympatholytic medication or other pharmaceuticals influencing bladder function, including antidepressant agents, should have been stopped 2 weeks or longer before PTNS or continued without dose changes during the entire study. Specific exclusion criteria for our study are given in table 1.

Table 1 Exclusion criteria

Younger than 18 years
Symptoms existing for less than 6 months
Pregnancy or intention to become pregnant during the course of the study
Active urinary tract or recurrent urinary tract infection (5 or more recurrent infections during the last 12 months), carcinoma in situ, bladder malignancy, interstitial cystitis
Bladder or kidney stone
Severe cardiopulmonary disease
Use of pentosan polysulfate sodium or bladder installations, including dimethyl sulfoxide, Bacillus Calmette-Guerin, chloropectin or heparin
Uncontrolled diabetes
Diabetes with peripheral nerve involvement
Neurological disease like multiple sclerosis, Parkinson's disease, cerebrovascular accident, bifid spine or spinal cord lesion
Physiotherapy during the study
Bladder outlet obstruction (Abrams-Griffiths nomogram)
Transurethral instrumentation 4 weeks or less before or during the study

Patients A total of 10 men and 27 women with a mean age of 52.5 years (range 23-74) were treated for bladder overactivity. These patients lived with symptoms for a median of 4 years (range 1 to 30). The symptoms were said to be induced by childbirth in 3, pelvic surgery in 9, including 7 hysterectomies, 1 anterior prolapse correction, 1 Burch colposuspension, and other events in 3 patients, including fracture of the coccygeal bone, urinary tract infection, bowel infection. The remaining

patients had no history of any pelvic event before the onset of symptoms. Of the 37 patients 32 (91.4%) received unsuccessful prior medical therapy, including anticholinergics, with a mean number of 1.9 (range 1 to 5) drugs used. Almost half of all (48.6%) patients underwent up to 3 surgical procedures, most frequently colposuspension, for symptoms. Other unsuccessful therapies included physiotherapy and/or biofeedback in 22 (59.4%), electrical stimulation, including Transcutaneous Electrical Nerve Stimulation (TENS) or Peripheral Nerve Evaluation (PNE-tests), in 5 (13.5%) and alternative therapies, such as Chinese herbs in 5 (13.5%) patients. Physical examination did not show overt (neurourological) abnormalities in any of the patients.

There were 5 men and 7 women with a mean age of 50.8 years (range 36 to 64) treated for non-obstructive retention. These patients had symptoms for a median of 3.5 years (range 1 to 36 years). Initiation of symptoms was related to childbirth in 1, pelvic surgery, including Wertheim's-Meighs operation in 1 and Burch colpo-suspension in 1, other surgery, including hip replacement in 1 and inguinal hernia repair in 1 and benign prostate hyperplasia without any effect of transurethral prostatic resection in 1 patient. The remaining 6 patients had no history of any pelvic event before the onset of symptoms. Of the 12 patients 11 (92%) received unsuccessful medical therapy previously, including α -blockers or sympathicomimetics. Almost half the patients (5 of 12) had undergone lower urinary tract surgery, mostly urethradilatation or urethrotomy, for symptoms previously. Other unsuccessful therapies included physiotherapy and/or biofeedback in 3 (25%) and electrical stimulation in 1 patient. All patients had clean intermittent catheterisation. In addition, physical examination did not show overt (neurourological) abnormalities in these patients. Urodynamic investigations revealed hypocontractile detrusors in all patients.

Method of treatment PTNS was applied according to Stoller.⁴ Patients are in supine position with the soles of the feet together, and knees abducted and flexed ('frog-position'). A 34 gauge stainless steel needle is inserted approximately 3 to 4 cm., about 3 fingerbreadths cephalad to the medial malleolus, between the posterior margin of the tibia and soleus muscle. A stick on electrode is placed on the same leg near the arch of the foot. The needle and electrode are connected to a low voltage (9 volts) stimulator (Urosurge, Coralville, Iowa) with an adjustable pulse intensity of 0 to

10 mA., a fixed pulse width of 200 microseconds and a frequency of 20 Hz. The amplitude is slowly increased until the large toe starts to curl or toes start to fan. If the large toe does not curl or pain occurs near the insertion site the stimulation device is switched off and the procedure is repeated. If the large toe curls or toes start to fan stimulation is applied at an intensity well tolerated by the patient. If necessary the amplitude can be increased during the session.

Patients underwent 12 weekly outpatient treatment sessions, each lasting for 30 minutes. If a good response occurred the patient was offered chronic treatment.

Evaluation of results After providing informed consent all patients completed a voiding diary, as well as general and disease-specific quality of life questionnaires at study entry and completion of the 12-week treatment. In the 24-hour voiding diary frequency and voided volumes, number and volume of catheterizations, number of leakage periods, leakage severity as well as the number of pads or diapers used were recorded. The leakage severity was scored on a scale of 0 to 3 and included 0-no leakage, 1-leakage of some drops, 2-loss of a small amount and 3-loss of a massive amount, that is change of clothes. General and disease-specific quality of life questionnaires were evaluated with the 36-item short-form health survey (SF-36) and the (adjusted) I-QOL questionnaire, respectively.^{5,6} The SF-36 consists of 36 items regarding 8 distinct health status concepts and 1 item measuring self-reported health transition, including physical function, role physical, pain, general health, emotional well-being, role emotional, social functioning, energy and fatigue and change in general health. The maximum score of each domain is 100 and a higher score relates to a better quality of life. The I-QOL questionnaire consists of 22 items, each with a 5 point response scale. As with the SF-36, a high score means good quality of life.

Success was defined as the patient request for continued chronic treatment for maintenance. Analysis was done on an intention-to-treat basis. Within group comparisons of parametric results at baseline and 12-week treatment were conducted with the paired sample t-test. Statistical analysis was performed with commercial software.

Results

Bladder overactivity Of the 444 treatment sessions stimulation was performed on the right posterior tibial nerve with a mean pulse intensity of 3.7 mA. (range 1.4 to 6.8) per session in 265 (60%). Complications, including minor bleeding or a temporary painful feeling at the insertion site, were seen only rarely. Of the 37 patients PTNS in 7 men and 15 women (59.4%) was considered successful because they requested continuation of therapy after completion of the 12-week treatment (group 1, responders). In 3 male and 12 female patients treatment was unsuccessful since they did not choose maintenance therapy (group 2, non-responders).

At completion of the 12-week treatment all 33 patients with urgency and frequency had significant improvement of voiding frequency during the day and night (table 2 and figure 1A). When discriminating group 1 (21 responders) from group 2 (12 non-responders), these improvements appeared to be significant only in group 1. The smallest mean values and mean volumes voided also improved, whereas the largest volumes voided did not change in this group.

A statistically significant overall decrease in incontinence was seen in the 30 patients who were urge incontinent (table 3 and figure 1B). When comparing group 1 (18 responders) with group 2 (12 non-responders), improvements found in leakage episodes and number of pads used appeared to be greater in group 1. Leakage severity scores showed improvement in all patients who were urge incontinent, and groups 1 and 2. General quality of life improved in regard to physical and social functioning in all patients with bladder overactivity. Mean physical functioning plus or minus standard deviation (SD) was 53.7 ± 27.9 (mean change +9.1, 95% confidence interval [CI] +14.1, +4, $p < 0.005$) and social functioning 64.7 ± 31.2 (mean change +10.3, +16.5, +4.1, respectively, $p < 0.005$) at 0 weeks. In group 1, both scores also increased. Mean physical functioning plus or minus SD was 61.6 ± 26.3 (mean change +11.2, 95% CI +18.8, +3.5, $p < 0.05$) and social functioning 70.6 ± 26.7 (mean change +11.6, +20.9, +2.3, respectively, $p < 0.05$) at 0 weeks. Only social functioning improved (55.9 ± 35.9 , mean change +8.4, 95% CI +16.6, +0.2, respectively, $p < 0.05$) at 0 weeks in group 2. Disease specific quality of life showed improvement in all patients (60.3 ± 19.3 , mean change +12.3, 95% CI +17.3, +6.8, $p = 0.00004$), as well

Table 2 Voiding parameters in 33 patients with urgency and frequency

	Frequency	Nocturia	Voided volumes		
			Smallest	Largest	Mean
All patients					
Mean ± SD (0 wks.)	16.5 ± 6.8	2.6 ± 2.3	65 ± 49.3	289.8 ± 161	140 ± 82.2
Mean change (95% CI)	-2.8 (-0.8;-4.9)	-1 (-0.2;-1.8)	14.2 (32.8;-4.5)	13.9 (48.7;-20.9)	19.3 (40.3;-1.7)
p- value	p < 0.05	p < 0.05			
Group 1					
Mean ± SD (0 wks.)	16.1 ± 6.1	2.5 ± 2.7	62.6 ± 52.1	268.8 ± 146.4	133 ± 82.8
Mean change (95% CI)	-4.8 (-2.7;-6.8)	-1.4 (-0.4;-2.3)	29.8 (49.2;10.3)	9.5 (50.6;-31.6)	35.1 (62.6;7.7)
p- value	p < 0.0005	p < 0.05	p < 0.005		P < 0.05
Group 2					
Mean ± SD (0 wks.)	17.1 ± 8.3	2.7 ± 1.6	71 ± 44.8	334 ± 188.5	153.6 ± 83.7
Mean change (95% CI)	0.8 (5;-3.3)	-0.2 (1.3;-1.6)	-18.5 (19.4;-56.4)	23 (100.6;-54.6)	-14 (8.5;-36.5)

Group 1 = responders, group 2 = non-responders, SD = standard deviation, CI= Confidence Interval

Table 3 Voiding parameters in 30 patients with urge incontinence

	Leakage episodes	Pads used	Leakage severity
	All patients		
Mean ± SD (0 wks.)	9.8 ± 5.6	6.3 ± 3.2	1.7 ± 0.5
Mean change (95% CI)	-4.8 (-2.2;-7.5)	-2.5 (-1.2;-3.9)	-0.7 (-0.4;-1.0)
p- value	p < 0.005	p < 0.005	p < 0.005
Group 1			
Mean ± SD (0 wks.)	9.8 ± 6.4	5.8 ± 2.6	1.6 ± 0.5
Mean change (95% CI)	-6.2 (-2.9;-9.5)	-3.3 (-1.5;-5.1)	-0.8 (-0.3;-1.3)
p- value	p < 0.005	p < 0.005	p < 0.005
Group 2			
Mean ± SD (0 wks.)	9.8 ± 4.4	7.1 ± 3.9	1.9 ± 0.5
Mean change (95% CI)	-2.4 (2.4;-7.3)	-1.3 (0.9;-3.4)	-0.5 (-0.2;-0.8)
p- value			p < 0.05

Group 1 = responders, group 2 = non-responders, SD = standard deviation, CI= Confidence Interval

Figure 1 Micturition frequency (A) and number of leakage episodes (B) before and after PTNS for all patients, responders and non-responders. Error-bar: standard deviation. n.s.: not significant.

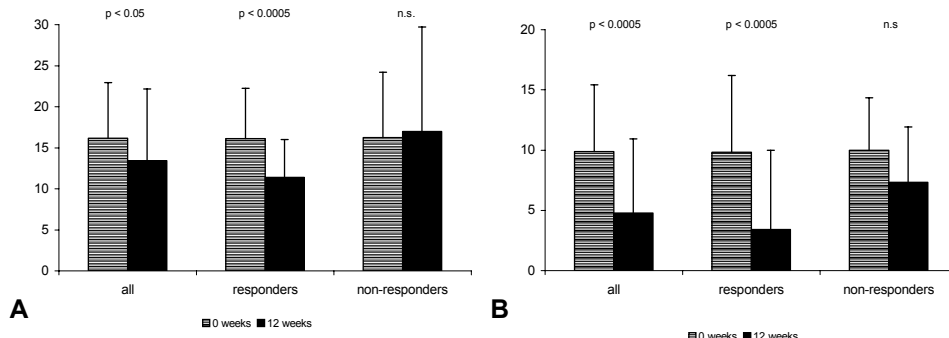
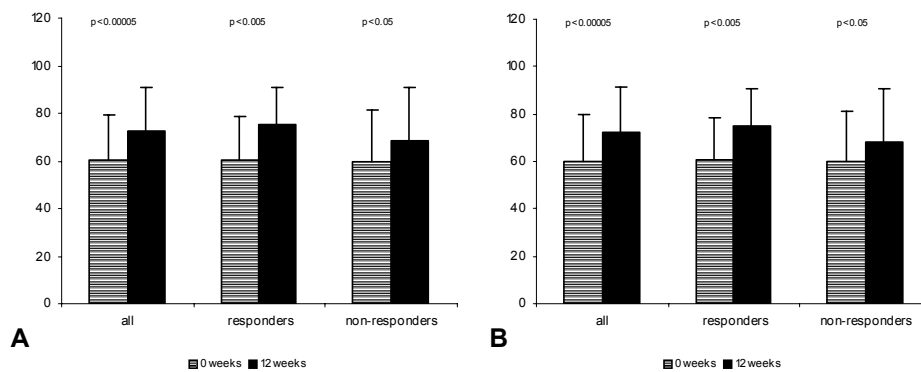


Figure 2 I-Qol scores in patients with bladder overactivity (A) and non-obstructive retention (B) before and after PTNS for all patients, responders and non-responders. Maximum I-Qol score: 110. Error-bar: standard deviation. N.s.: not significant.



as in group 1 (60.6 ± 18.2 , mean change $+14.4$, $+22.3$, $+6.6$, $p < 0.005$) and group 2 (59.9 ± 21.5 , mean change $+8.5$, $+15.1$, $+2$, respectively, $p < 0.05$) at 0 weeks (figure 2A).

Non-obstructive retention Of the 144 treatment sessions stimulation was performed on the right posterior tibial nerve with a mean pulse intensity of 4 mA. (range 2.5 to 7) per session in 87 (60%). As seen in patients treated for urgency and frequency and/or urge incontinence, complications were rarely noted. Of the 12 patients PTNS was considered successful in 1 man and 6 women (58.3%) because they requested continuation of therapy after completion of the 12-week treatment (group 3, responders). Treatment was unsuccessful in 4 men and 1 woman since they did not choose maintenance therapy (group 4, non-responders).

Table 4. Voiding parameters in 12 patients with non-obstructive retention

	All patients		Group 3		Group 4	
	Mean \pm SD (0 weeks)	Mean change (95% CI)	Mean \pm SD (0 weeks)	Mean change (95% CI)	Mean \pm SD (0 weeks)	Mean change (95% CI)
No. catheterizations	5.3 ± 2.4	-0.8 (0.6;-2.3)	5.9 ± 2.6	-1.4 (1.2;-4.1)	4.4 ± 2	0 (0.9;-0.9)
Mean volume catheterized	336 ± 171	-83.3 (27.4;-194)	325 ± 181	-131.9 (63.2;-326.9)	351 ± 176	-15.4 (87.5;-118.4)
Total volume catheterized	1552 ± 776	-537 (175;-1249)	1707 ± 915	-921.4 (284.5;-2127.4)	1335 ± 547	1 (659.7;-657.7)
Mean volume voided	206 ± 192	5.9 (113.2;-101.4)	141 ± 107	94.3 (233.3;-44.7)	297 ± 258	-117.8 (16.5; 252.1)
Total volume voided	919 ± 658	173.8 (639.2;-291.7)	758 ± 567	482.1 (1164.7;-200.4)	1145 ± 774	-258 (374.6;-890.6)

Group 3 = responders, group 4 = non-responders, SD = standard deviation, CI= Confidence Interval

At completion of 12-week treatment all patients clearly had a decrease in the number of catheterizations, and mean and total volumes catheterized, and an increase in mean and total volumes voided. However, statistical significance could not be obtained (table 4). When discriminating group 3 (7 responders) from group 4 (5 non-responders) these changes could also be observed in group 3, but not in group 4.

In regard to quality of life hardly any significant improvement could be found, neither with the adjusted disease specific quality of life questionnaire (I-QOL, figure 2B) or general quality of life questionnaire (SF-36). The only exceptions appeared to be the SF-36 score for emotional well-being, which increased (58.3 ± 12.2 , mean change $+14.3$, 95% CI $+20.6$, $+7.9$, $p < 0.005$) in patients who thought treatment was successful (group 3), and the score for change of health, which significantly increased in all (45.8 ± 27.9 mean change $+22.9$, $+44.9$, $+1$, $p < 0.05$), but not in group 3 or 4 at 0 weeks, respectively.

Discussion

For treatment of refractory urinary tract dysfunction various methods of intermittent neuromodulation have been advocated, including intravesical, anal, vaginal, penile and perineal stimulation, and transcutaneous electrical stimulation (TENS) of the suprapubic or sacral region and the posterior tibial nerve.⁷⁻¹⁵ Because of poor results or uncomfortable stimulation sites, most of the aforementioned treatment modalities did not gain widespread acceptance. In the 1980s implantable neurostimulation electrodes became available for modulation of the sacral spinal nerves, especially S3.¹⁶ Stimulation could be performed continuously, leading to better results but drawbacks included invasiveness of the procedure, the high costs involved and the limited service life of the stimulation device, which was 7 to 10 years. In addition, symptoms appear to recur almost immediately after discontinuation of the stimulation.² Therefore, the development of an easy applicable, non-invasive or minimally invasive, cost-effective neuromodulation device, with good treatment outcome was anticipated. The recent advent of PTNS may offer urologists a treatment modality that meets the aforementioned criteria.^{4,17}

Stimulation of the tibial nerve was first described by McGuire et al in 1983.¹⁵ In studies of non-human primates with spinal cord injury bipolar anal sphincter stimulation resulted in the inhibition of detrusor activity. Similar results could be obtained by applying current through a transcutaneous electrode over the common peroneal or posterior tibial nerve, with a ground electrode being contralaterally placed over the same nerves. The idea of stimulating these nerves was based on the traditional Chinese practice of using acupuncture points over the common peroneal

or posterior tibial nerves to affect bladder activity.¹⁵ Electrical stimulation of the tibial nerve was subsequently performed in 22 patients with detrusor instability, interstitial or radiation cystitis or neurological diseases with promising results, including continence in 12 and urodynamic improvement in 7. However, in a prospective study by Geirsson et al in patients with interstitial cystitis, transcutaneous tibial nerve stimulation or traditional Chinese acupuncture treatment revealed no difference in voiding frequency, mean and maximal voided volumes and visual analogue symptom scores before or after either treatment modality.¹⁸

In our study percutaneous stimulation resulted in a success rate of about 60% of 49 patients with bladder overactivity or non-obstructive urinary retention. Although our definition of success was a subjective one, responders differed significantly from non-responders in almost every semi-objective parameter. The same result was observed in disease specific and several domains of general quality of life scores.

Because our study was not placebo-controlled, the observed improvements might theoretically be the result of regression to the mean, synchronous other treatment or placebo effect, rather than a positive response to PTNS. Regression to the mean is not likely as all patients included had to present with symptoms for at least 6 months (median 4 years). To prevent interference of other treatment modalities, concomitant physiotherapy during PTNS was not permitted as was the case with starting parasympatholytic medication or other pharmaceuticals influencing bladder function, including antidepressant agents, within 2 weeks before treatment. In patients who were already using any of the aforementioned drugs, medication had to be stopped 2 weeks before beginning PTNS or continued without dose changes during the entire 12 weeks. In placebo controlled studies success rates in the placebo group are usually much lower than the response rate of about 60% in our study. Because most patients had symptoms for a long period and undergone various treatments before trying neuromodulation, it is not likely that they were highly susceptible to the placebo effect of this treatment modality. Nevertheless, to validate these data a properly designed placebo controlled study is warranted. However, it can be anticipated that the feasibility of such studies will be difficult.

Notwithstanding the promising results and only mild complications of this neuromodulation technique found in our study, this therapy also has some disadvantages, including percutaneous insertion of the stimulation electrode, necessity of regular visits to the outpatient clinic and, thus far, unknown results of

chronic treatment of initially successful cases. In the near future most aforementioned problems may be solved with an implantable subcutaneous electrode, which can be radiographically stimulated by the patients themselves at home and on a regular basis. Studies regarding long-term results are ongoing, but results are not yet available.

In conclusion, although thorough research is anticipated to improve patient selection criteria, optimize the technique and help learn more about the precise mode of action, PTNS is a promising, cost-effective and easily applicable treatment option for patients with lower urinary tract dysfunction.

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Percutaneous tibial nerve stimulation as neuromodulative treatment of chronic pelvic pain

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Abstract

Objective Neuromodulative therapies have been used with moderate success in patients with chronic pelvic pain. Intermittent Percutaneous Tibial Nerve Stimulation (PTNS) is a new, minimally invasive treatment option, which has shown to significantly decrease accompanying pain complaints in patients with lower urinary tract dysfunction, such as urge incontinence or urgency/frequency. In our study we evaluate the objective results of PTNS in patients with chronic pelvic pain as their main complaint.

Patients and methods In a prospective multicentre trial PTNS was evaluated in 33 patients with chronic pelvic pain. Effects were recorded by Visual Analogue Scale (VAS) for pain diaries, the McGill pain questionnaire and the SF-36 general quality of life questionnaire at baseline and after 12 weeks of treatment. Subjective (patients' request to continue chronic treatment to keep the obtained success) and objective responses (decrease in mean VAS >50% and VAS <3 after treatment) were evaluated.

Results A subjective response was seen in 42% of all patients. In 7 patients (21%) mean VAS decreased >50%, in 6 cases (18%) the decrease was >25%. After 12 weeks of treatment 7 patients (21%) ended up with a mean VAS <3. In all patients quality of life (SF-36) significantly improved, as did the total pain rate intensity (McGill)

Conclusions Despite very modest overall success rates and the need for placebo controlled studies, PTNS may have a place in the treatment of patients with chronic pelvic pain who have already tried many other therapies and are left with no further options.

Introduction

Chronic pelvic pain is a common problem with a high impact on patients' quality of life. Unfortunately, pelvic pain is hard to measure, assess or localize, causing great difficulties in diagnosis and treatment ¹, as well as frustration in both patients and physicians. The use of descriptive 'diagnoses' and the high referral rate amongst medical specialties covering only certain aspects of the pelvic region furthermore illustrate our difficulties coping with this complex problem.

As aetiology and pathophysiology are mostly unknown, treatment is often empirical and polypragmatic. Non-steroidal anti-inflammatory drugs, steroids, benzodiazepines, anti-depressants, anti-convulsants, α -blockers, local anaesthetics, GABA- and NMDA-receptor agonists ² and antibiotics all have been described to have some effect. When faulty pelvic floor behaviour is suspected physiotherapy may be of use. Neuromodulation has been reported in reducing pelvic pain by means of sacral nerve stimulation ^{3,4}, while there are also reports on positive effects of neuromodulation in pain complaints accompanying conditions like interstitial cystitis (TENS ⁵, vaginal stimulation ⁶ or maximal electric pelvic floor stimulation ⁷).

Recently Percutaneous Tibial Nerve Stimulation (PTNS) has come to use for the treatment of lower urinary tract dysfunction, e.g. urge incontinence, urgency/frequency and non-obstructive retention. ⁸⁻¹¹ Although accompanying pain complaints were reported to decrease ^{9,10}, this minimally invasive treatment option has not yet been described for the use in distinct pelvic pain syndromes. In our study we evaluate the objective results of PTNS in patients with chronic pelvic pain as their main complaint.

Patients and methods

Methods Between November 1999 and August 2000 33 patients (22 men, 11 women) with chronic, therapy resistant pelvic pain were enrolled in a prospective clinical multicentre trial after approval by the Institutional Review Boards. All patients were evaluated for chronic pelvic pain by history, Visual Analogue Scale (VAS) for pain and physical as well as urological examination.

Chronic pelvic pain was defined as complaints of pain for at least 6 months in the bladder, groin, genitals or lower abdomen and/or perineal or (peri)anal pain without clear abnormalities on urological examination. On the Visual Analogue Scale for pain (0-10), the score should be over 5. The use of analgesics should have been stopped two weeks or longer prior to Percutaneous Tibial Nerve Stimulation (PTNS) or had to be continued without dose changes during the entire study. Physiotherapy or electrotherapy like Transcutaneous Electrical Nerve Stimulation (TENS) should have been stopped for at least 3 months prior to the PTNS treatment. Specific exclusion criteria for this study are given in table 1.

Table 1 Exclusion criteria

Age under 18
Symptoms existing for less than 6 months
Pregnancy or intention to become pregnant during the course of the study
Active urinary tract or recurrent urinary tract infections (recurrent infections: ≥ 5 during the last 12 months)
Bladder or kidney stone
Bacterial prostatitis, sexually transmitted disease
Carcinoma in situ, bladder malignancy, interstitial cystitis
Uncontrolled diabetes or diabetes with peripheral nerve involvement
Severe cardiopulmonary disease
Neurological disease like MS, M. Parkinson, CVA, bifid spine or spinal cord lesion
Use of Elmiron or bladder installations like DMSO, BCG, Chloropectin or Heparin
Change in analgesics within 2 weeks prior to or during the study
Physiotherapy at the same time as the study
Electrotherapy (for example TENS) at the same time as the study

Patients 22 men and 11 women with a mean age of 51.6 years (range 25-79) were treated for chronic pelvic pain (see table 2). These patients had their complaints for a median period of 5 years (range 2-30). Twenty-eight of 33 patients (85%) reported unsuccessful previous medical therapies, mostly analgesics and α -blockers, with a mean number of drug types used of 2.3 (range 1-4). Eight patients (24%) underwent up to two surgical procedures like (partial) epididymectomy, bladder neck incision, transurethral resection of the prostate or transurethral microwave therapy for their complaints. Other unsuccessful therapies included physiotherapy and/or biofeedback

Table 2 Patient characteristics

Patient number	Sex	Age	Main localization pain	Surgical procedures (abdomen, pelvis, genitals) prior to PTNS
1	Male	33	Lower abdomen	None
2	Male	34	Lower abdomen, scrotum	None
3	Male	39	scrotum, groin (left)	None
4	Male	54	Lower abdomen, scrotum (left)	Epididymectomy ¹
5	Male	34	Perineum	None
6	Male	34	scrotum, groin (left)	Vasectomy, epididymectomy ¹
7	Male	40	scrotum, groin (left)	Varicocele correction
8	Male	43	Perineum, perianaly, suprapubic/bladder region	TW ¹ , TURP ¹
9	Male	43	Perineum, scrotum	Inguinal hernia repair, varicocele correction
10	Male	46	Perineum, scrotum	Dorsal penile vene ligation, epididymectomy
11	Male	48	Suprapubic/bladder region	Vasectomy, inguinal hernia repair, TUMT ¹
12	Male	49	Suprapubic/bladder region, perineum	Vasectomy, nephrectomy
13	Male	49	Perineum, scrotum	None
14	Male	50	Suprapubic/bladder region	Appendectomy, inguinal hernia repair, varicocele correction, TW ¹ , Otis ¹
15	Male	50	scrotum, groin (left)	Inguinal hernia repair
16	Male	53	Perineum, lower abdomen	Vasectomy, chemonucleolysis L5-S1
17	Male	56	Suprapubic/bladder region	Cholecystectomy, Sachse urethrotomy ¹
18	Male	62	Perineum, perianaly	TUMT ¹
19	Male	67	Suprapubic/bladder region	None
20	Male	70	Perineum, perianaly	Inguinal hernia repair, TURP ¹
21	Male	77	Perineum, scrotum	TURP
22	Male	79	Suprapubic/bladder region	Appendectomy, TURP
23	Female	30	Vagina	None
24	Female	54	Groin (left)	None
25	Female	66	Vagina	None
26	Female	72	Lower abdomen, vagina	None
27	Female	25	Lower abdomen, groin (right)	None
28	Female	41	Suprapubic/bladder region	Hysterectomy, Mitrofanoff
29	Female	50	Perineum, vagina	None
30	Female	55	Suprapubic/bladder region	None
31	Female	60	Suprapubic/bladder region	None
32	Female	61	Perineum, vagina	None
33	Female	79	Perineum, vagina	Hysterectomy, excision coccyx, ileocaecal resection ¹ , rectal prolapse repair ¹

¹operations were performed after the complaints had already started

in 17 (52%), electrical stimulation like TENS in 8 (24%) and alternative therapies like local injection therapy, corsets, sexuological evaluation, acupuncture, aura-therapy

and hot water baths in 18 patients (55%). Physical examination did not show overt (neuroulogical) abnormalities in any of the patients.

Method of treatment PTNS was applied according to Stoller⁸ and Govier et al.¹⁰ Patients lie in supine position with the soles of the feet together and their knees abducted and flexed ('frog-position'). A 34-gauge stainless steel needle is inserted for approximately 3 to 4 cm cephalad to the medial malleolus, between the posterior margin of the tibia and the soleus muscle tendon. A stick-on electrode is placed on the same leg near the arch of the foot. Both needle and electrode are connected to a stimulator (Urgent PC[®], CystoMedix, Anoka, Minnesota, USA) with an adjustable pulse intensity (0-10 mA). Fixed parameters are a pulse width of 200 µsec and a frequency of 20 Hz. The stimulator contains a battery of 9 V. The amplitude is slowly increased until plantar flexion of the large toe or fanning of the other toes occur. If this response can not be obtained or pain occurs near the insertion site the stimulation device is switched off and the procedure is repeated. In most patients the motor response was accompanied by a sensory response as a radiating sensation spreading in the sole of the foot. The current was set at a well-tolerable level. Elevation of the current was allowed whenever fading of this sensation was experienced due to adaptation. Patients underwent 12 weekly outpatient treatment sessions, each lasting for 30 minutes. In case of a good response patients were offered chronic treatment.

Evaluation of results After informed consent, all patients had to fill out pain diaries as well as general and disease-specific quality of life questionnaires at study entry and at completion of treatment at 12 weeks. Pain diaries consisted of 7 Visual Analogue Scales for pain, one for every day of the week, recording the maximum pain felt during the day. The lowest, highest and mean VAS were calculated from these diaries. General and disease-specific quality of life was evaluated using the SF-36 questionnaire¹² and the McGill Pain Questionnaire (Dutch Language Version) respectively.^{13,14} The SF-36 questionnaire consists of 36 items covering eight distinct health status concepts and one item measuring self-reported health transition: physical function, role-physical, pain, general health, emotional well-being, role-emotional, social functioning, energy/fatigue and change in general health. The maximal score of each domain is 100. A higher score relates to a better quality of life.

The McGill Pain Questionnaire uses 20 sets of descriptive words for pain, which can either be sensoric, affective or evaluative. One is allowed to choose maximal 1 word out of every set, resulting in a 'number of words chosen' score and a 'pain rate intensity' score. The higher the scores, the worse the condition.

Subjective success was defined as the request of the patient to continue chronic treatment to keep the obtained outcome, objective success as a decrease in mean Visual Analogue Scale for pain of over 50%. A decrease of over 25% was considered to be a partial response. Moreover, the number of patients with a VAS below 3 after 12 weeks of treatment was recorded. Within-group comparisons of parametric results at baseline and twelve weeks of treatment were conducted using the paired-samples T-test (5% level statistical difference). Statistical analysis was performed using SPSS 9.0 software (SPSS, Chicago, USA).

Results

After 12 weeks of PTNS, 14 (10 men, 4 women) out of 33 patients (42%) were considered subjective responders, as these patients requested continuation of therapy. An objective response occurred in 7 patients (21%) of all patients and almost only in the subjective responder group (see table 3). Mean VAS for pain changed from 6.5 (range 5.3-7.7) at baseline to 5.4 (range 4.2-6.8) after 12 weeks of treatment (95% Confidence Interval (CI): -0.2, -2.0, $p < 0.05$). Seven patients (21%) ended up with a mean VAS below 3. In the subjective responder group, mean VAS decreased from 5.9 (range 4.5-7.3) at baseline to 3.8 (range 2.7-5.2) after 12 weeks of treatment (95% CI: -0.5, -3.7, $p < 0.05$). No changes were seen in the subjective non-responders.

In patients with an objective improvement of $\geq 25\%$ as well as in patients without an objective response certain patient characteristics were recorded that may have an influence on treatment outcome (see table 4). Although we did not try to statistically identify prognostic factors, a high number of previous tried treatment modalities, a long period of complaints and a more superficial localization of the pain seem to have a negative influence on PTNS results.

Table 3 Decrease of mean VAS for pain (1 week) after 12 weeks of PTNS

	All patients (%) N=33	Subjective responders (%) N=14	Subjective non-responders (%) N=19
≥ 50%	7 (21%)	6 (43%)	1 (5%)
≥ 25%, < 50%	6 (18%)	3 (21%)	3 (15%)
No improvement	20 (61%)	5 (36%)	15 (80%)

Table 4 Characteristics in patients with and without a ≥ 25% decrease of the mean VAS for pain

	≥ 25% decrease		No response	
Sex	6 f	(46%)	8 f	(40%)
	7 m	(54%)	12 m	(60%)
Mean age in years (range)	55,2	(25-79)	49,1	(33-79)
Median duration of symptoms in years (range)	4	(2-15)	5,5	(2-30)
Mentioned localizations of pain ¹				
groin/scrotum	2	(15%)	10	(50%)
lower abdomen/suprapubic-/bladder region	5	(38%)	11	(55%)
perineal/(peri)anal/vaginal region	8	(62%)	7	(35%)
Mean VAS before PTNS	65	(range 60)	65	(range 77)
Mean number of drug types used (range)	2,82	(1-4)	2	(1-4)
Number of patients having had an operation for pain complaints	1	(8%)	7	(35%)
Number of patients having used physiotherapy	5	(38%)	12	(60%)
Number of patients having used electrotherapy	3	(23%)	5	(40%)
Number of patients having used alternative therapy	5	(38%)	12	(60%)

¹more than one localization per patient possible

The SF-36 quality of life questionnaire showed statistically significant changes in the domains 'physical functioning' (51.5 to 57.1 (95% CI: +0.9, +10.3, p<0.05)), 'role physical' (15.2 to 28 (95% CI: +0.1, +25.6, p<0.05)), 'pain' (37.4 to 47.8 (95% CI: +2.3, +18.5, p<0.05)) and 'change of health' (37 to 57 (95% CI: +7, +33, p<0.05)) as well as in the total score (46.1 to 52.7 (95% CI: +2.6, +10.5, p<0.05)).

In the McGill Pain Questionnaire (MPQ) 8 domains were evaluated: Number of Words Chosen (NWC) sensoric, affective, evaluative and total, and Pain Rate Intensity (PRI) sensoric, affective, evaluative and total. Changes after 12 weeks of

PTNS were not significant with the exception of PRI total: a decrease was seen from 21.5 to 17.2 (95% CI: -0.3, -8.3, $p < 0.05$).

Discussion

Posterior tibial nerve stimulation was first described in 1983 by McGuire et al.¹⁵ in 22 patients with incontinence, using a transcutaneous electrode over the common peroneal or posterior tibial nerve and a contralaterally placed ground electrode over the same nerve. Later on, Stoller⁸ adjusted this method by using a percutaneous needle electrode and placing the ground electrode on the ipsilateral extremity. Since then, several publications report promising early results regarding urge incontinence, urgency/frequency and non-obstructive urinary retention.⁹⁻¹¹ As a positive side effect, pain reduction has been described in a group of 15 patients, with a decrease in VAS from a mean (standard deviation) of 7.6 (5 to 10) to 3.1 (1 to 7) ($P < 0.0005$)⁹, as well as in a group of 53 patients, with a reduction in pelvic pain intensity of 30% ($p < 0.05$).¹⁰ This decrease in pelvic pain as a symptom accompanying urgency/frequency or urge incontinence is also well known in sacral neuromodulation: in many reports there is, alongside relief of other symptoms, a significant decrease in Visual Analogue Scale for pain or likewise pelvic pain scores.¹⁶⁻¹⁸

When looking at neuromodulation in patients with chronic pelvic pain as their main symptom, only a few reports can be found. In a prospective, non-randomized feasibility study sacral nerve stimulation resulted in a substantial clinical benefit in 6 of 10 patients with chronic, intractable pelvic pain.⁴ Everaert et al.³ describe the implantation of a sacral neuromodulator in 11 of 26 PNE tested patients with therapy-resistant pelvic pain syndromes. Nine patients were satisfied and one needed an explantation because of infection of the prosthesis, reducing the success rate to 8 out of 11 and the intention to treat percentage to 31%. At a follow-up of 36 ± 8 months no further failures were seen. Other neuromodulation modalities reported are intrarectal or vaginal electrostimulation in deep pelvic pain syndromes and TENS in superficial pelvic pain. Results are very modest and fail to reach statistical significance. The same treatment options^{5,6} as well as maximal electric pelvic floor stimulation⁷, are described for the more specific cases of interstitial cystitis, in which pain cure rates vary between 26 and 54%.

The mechanism of action of neuromodulation is still unknown, although many theories exist. In lower urinary tract dysfunction neuromodulation most probably causes rebalancing of inhibitory and excitatory impulses that govern bladder function in the central nervous system.¹⁹ For pain it can be suggested that, according to the gate control theory, stimulation of large somatic fibres could modulate/inhibit the thinner afferent A-delta or C fibres, thus decreasing pain perception.²⁰ Another mode of action may be the elevation of endorphins at a spinal level, as can be seen in TENS and acupuncture.^{21,22} However, the most important evidence of effects of neuromodulation on nociceptive pathways in the spinal cord comes from Chang et al.²³: after instillation of acetic acid in rat bladders, a rise in c-fos, a neurotransmitter for pain in the central nervous system, was seen in the sacral micturition centre. Rats that underwent acetic acid installation as well as PTNS, showed a significant lower c-fos expression.

In our study PTNS had a positive effect in 39% of 33 pelvic pain patients (objective success and partial response together), who were refractory to all other previous treatments. A subjective response was seen in 42% of all cases. As can be suspected, most patients with objective changes considered themselves a subjective success as well (69%). Not all patients with an objective response were satisfied enough to continue treatment after the initial 12 weeks. On the other hand, five patients, with no objective response on pelvic pain whatsoever, considered themselves a therapeutic success. All had experienced some pain relief after several PTNS sessions, which disappeared at the end of the course.

To minimize the effects of regression to the mean, only patients who had had complaints for over 6 months (median 5 years) were included in our study. On the other hand, cyclic changes in pain patterns could not completely be ruled out, although quick changes were met by keeping diaries during one week and recording not only highest and lowest VAS, but also the mean VAS over 7 days. To prevent interference by other treatment modalities, concomitant physiotherapy was not allowed as was the case with starting probable influencing medication. When drugs were already in use, patients had to stop 2 weeks prior to PTNS or to continue this medication during the entire 12 weeks. As our study was not placebo-controlled, a placebo effect cannot be ruled out. Percutaneous stimulation of the tibial nerve is prone to these effects because of a great deal of personal attention and care within many outpatient clinic visits. Unfortunately, it is most likely that a good placebo

controlled PTNS study is not feasible. We found patients with years of medical history and many failed therapies very well informed on new treatment techniques, making any placebo too different from PTNS useless. Also, placement of a percutaneous needle alone, without electrical stimulation may already have some effect. Maybe placebo acupuncture needles will provide a future possibility for placebo controlled studies.²⁴

An important way to improve treatment results in the future is the determination of clear selection criteria. Although 33 patients is too small a number to reliably determine prognostic factors, evaluating some characteristics in patients with or without a $\geq 25\%$ objective improvement of the mean VAS for pain seems to reveal that age, sex or mean VAS for pain prior to PTNS is not of great importance. Patients with a shorter period of complaints and less failed therapies in the past tend to do better. Also, in patients with an objective improvement, deep pain (perineal, (peri)anal and vaginal) seemed to be the most present feature, whereas patients without objective improvement primarily seemed to suffer from more superficial pain (suprapubic region, groin, scrotum). This seems not surprising as the visceral organs neurologically overlap better with stimulated level S3 than the superficial regions do.

Furthermore, the technique may be improved by changing the treatment schedule. In patients with an overactive bladder, Klingler et al⁹ stimulated 12 times at a rate of 4 per week, obtaining much better results than other authors stimulating once a week for 12 weeks.^{10,11} And, as in sacral nerve stimulation bilateral stimulation seems to improve results^{25,26}, stimulating both posterior tibial nerves concomitantly is an interesting future study objective.

Conclusions

Although success rates found in our study are very modest, they are comparable with what has been found in other forms of neuromodulative treatment. Nevertheless, there is a clear need for placebo-controlled data, however difficult a placebo study design. Furthermore, research is needed on the mode of action, optimal treatment scheme, long term effects of the treatment and selection criteria, to increase the benefit of percutaneous tibial nerve stimulation in patients with chronic pelvic pain. In

our study, PTNS was found to be minimally invasive and easy applicable in pelvic pain patients. In this patient group PTNS might be effective, but the lack of a controlled study cannot allow any larger assessment.

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Sexual functioning in patients with lower urinary tract dysfunction improves after percutaneous tibial nerve stimulation

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Abstract

Objective In this study we evaluated the effect of lower urinary tract dysfunction and its neuromodulative therapy on sexual functioning.

Patients and methods We studied 121 patients with an overactive bladder (N=83), chronic pelvic pain (n=23) and non-obstructive retention (n=15) which were treated with neuromodulation (i.e. percutaneous tibial nerve stimulation, PTNS). To obtain information on their sexual function a self-administered standardized questionnaire was filled out prior to therapy as well as after 12 weeks of treatment.

Results Prior to therapy different aspects of sexual life were considered not normal in 25.3 to 45.6% of the cases. This improved significantly after treatment. Patients most likely to benefit were women, patients with an overactive bladder and subjective responders. The aspects of sexual life which mostly improved were overall satisfaction, libido and the frequency of sexual activities.

Conclusions Sexual dysfunction is observed in a lot of patients with lower urinary tract disorders and may improve on successful therapy for the latter.

Introduction

Non-neurogenic lower urinary tract dysfunction (LUTD) is a common urological problem that strongly affects the quality of life. Although, in general quality of life issues gain more attention in studies performed, effects of disorders and therapies on sexual life are only rarely investigated. This is particularly true for patients with an overactive bladder (OAB), chronic pelvic pain (CPP) and non-obstructive urinary retention. Most publications that do consider sexual impairment in incontinence patients regard female patients only and describe groups suffering from stress or mixed incontinence.^{1,2}

For our study, we hypothesized that a considerable amount of patients with LUTD has impaired sexual life and that patients with impaired sexual life benefiting from therapy for their urological complaints also improve with regard to sexual functioning. Therefore, patients with OAB, CPP and non-obstructive urinary retention undergoing Percutaneous Tibial Nerve Stimulation (PTNS) were to be evaluated with self-administered standardized questionnaires regarding sexual functioning prior to and after finishing therapy.

Patients and methods

Between November 1999 and August 2001 121 patients (45 male, 76 female) with CPP, non-obstructive urinary retention or OAB were enrolled in a prospective clinical multicenter trial to evaluate the effect of PTNS on these lower urinary tract disorders. The trial got approval by the Institutional Review Boards. Reports on clinical outcome were published recently.³⁻⁶ As part of this study sexual functioning has been evaluated as well as possible effects of PTNS on sexual impairment.

Patients A total of 45 male and 76 female patients, mean age 53.6 years (range 21 to 82) have been treated for LUTD. Mean age of male (54.4 years, range 21 to 76) and female patients (53.1 years, range 23 to 82) did not differ significantly. Fifteen patients (6 male, 9 female) were treated for non-obstructive retention, 23 (17 male, 6 female) for CPP and 83 (22 male, 61 female) for OAB. Median duration of lower urinary tract complaints was 4 years (range 1 to 56 years). No statistical significant

differences in median duration of symptoms were seen between sexes or subgroups. Physical examination did not show overt (neuromuscular) abnormalities in any of these patients (see table 1).

Table 1 Patient characteristics

	All N=121	OAB N=83	CPP N=23	NOUR N=15
Men/women	45/76	22/61	17/6	6/9
Mean age ¹	53.6 (21-82)	54.4 (21-82)	52.7 (25-79)	50.9 (25-68)
Median history ¹	4 (1-56)	4 (1-56)	5 (2-30)	3 (1-36)
Previous medications ²	2 (0-5)	2 (0-5)	2 (1-4)	1 (0-2)
Previous operations ²	0 (0-3)	0 (0-3)	0 (0-2)	0 (0-1)
Previous physiotherapy	60 (49.6%)	39 (47.0%)	18 (78.3%)	3 (20.0%)
Previous electrotherapy	18 (14.9%)	9 (10.8%)	8 (34.8%)	1 (6.7%)
Frequency ³		15.0 (4-41)		
Incontinence episodes ³		6.4 (0-22)		
Catheterizations ³				4.9 (2-10)
VAS for Pain ⁴			64.9 (22-100)	
I-QoL ⁴		60.8 (22-100)		
Adjusted I-QoL ⁴				81.8 (38-100)
PRI-total (McGill) ⁴			21.7 (5-50)	
Mean stimulation ⁵	3.4 (1.3-7)	3.4 (1.4-6.8)	3.1 (1.3-5.5)	3.7 (1.3-7)
Subjective response	51.2%	55.4%	39.1%	46.7%
Objective response	35.5%	41.0%	21.7%	26.7%

OAB = Overactive Bladder, CPP = Chronic Pelvic Pain, NOUR = Non-obstructive Urinary retention, VAS = Visual analogue Scale, I-QoL = Incontinence Quality of Life, PRI = Pain Rate Intensity, ¹years (range), ²number (range), ³mean number/24 hours (range), ⁴mean score (range), ⁵mA (range)

Method of treatment PTNS was applied according to Stoller⁷ and Govier.⁸ A percutaneous inserted 34 gauge needle approximately 3-4 cm cephalad to the medial malleolus and a stick-on electrode placed on the same leg near the arch of the foot have been used for electrical stimulation with an adjustable pulse intensity (0-10 mA), a fixed pulse width of 200 μ sec and a frequency of 20 Hz. The stimulator contained a battery of 9 V (Urgent PC[®], CystoMedix, Anoka, MN, USA). In case of a

good motor response, generally accompanied by a specific sensory response, stimulation current was set at a well-tolerable level. Patients underwent 12 weekly outpatient treatment sessions of half an hour each without in-between stimulations. In case of a good response on their lower urinary tract symptoms patients were offered chronic treatment.

Evaluation of results After informed consent, all patients had to fill out micturition or pain diaries as well as general (SF-36⁹) and disease-specific quality of life questionnaires (McGill Pain Questionnaire Dutch Language Version¹⁰ and I-QoI¹¹) at study entry and at completion of treatment at 12 weeks. Subjective response was defined as the request of patients to continue chronic treatment to keep the obtained response, objective success as a decrease in symptoms (i.e. number of voids/24 hours, number of incontinence episodes/24 hours, number of catheterizations/24 hours or score on the Visual Analogue Scale for pain) of over 50%.

The sexual functioning prior to PTNS as well as after 12 weeks of treatment was studied by means of a standardized questionnaire to be filled out by the patients. This 'Nine questions regarding Sexual Functioning, Dutch language version' (NSF-9) was constructed by Vroege¹², has been described in English literature by Francken et al¹³ and is available in equally constructed versions for men and women. In the NSF-9 sex is considered as 'coitus, but also other forms of contact that you find sexually arousing'. (See also appendix).

Within group analysis of results have been conducted by the non-parametric Wilcoxon signed ranks test for two related samples, subgroup analysis by the non-parametric Mann-Whitney U-test for two independent samples. Tests have been performed on a two-tailed basis and the level of significance was set at 5%. Statistical analyses have been performed using Statistical Package for the Social Sciences version 9.0 software (SPSS, Chicago, ILL, USA).

Results

After 12 weeks of PTNS treatment, 62 out of 121 patients (51.2%) were considered subjective responders as these patients requested continuation of therapy. For OAB this was 55.4% (46 out of 83 patients), for CPP 39.1% (9 out of 23 patients) and for

non-urinary retention 46.7% (7 out of 15 patients). An objective response was seen in only 35.5% of all patients with 41% for OAB, 21.7% for CPP and 26.7% for non-urinary retention (see table 1).

At baseline, 88.4%% filled out the NSF-9, after 12 weeks of PTNS this percentage decreased to 86%. To the question, prior to PTNS, to what extent patients were satisfied with their current sex life, 40 patients answered 'dissatisfied' or 'very dissatisfied'.

In this group satisfaction over all improved significantly ($p < 0.005$). Improvement was mainly seen in female patients ($N=22$, $p < 0.005$), OAB patients ($N=22$, $p < 0.05$) and subjective responders ($N=16$, $p < 0.05$) (see table 2). Patients answering (prior to PTNS) 'neutral' to 'very satisfied' with their sex life remained as satisfied after the treatment ($p=0.2$).

Table 2 Change in dissatisfaction with current sexual life

Patient group	Number	p-value overall satisfaction whole (sub-)group	Prior to PTNS	After PTNS	p-value
			Pts (very) dissatisfied / respondents	Pts still (very) dissatisfied / pts that felt so before PTNS	
All	N=121	ns	40/103	20/35	p=0.002
Women	N=76	p=0.024	22/60	9/19	p=0.003
Men	N=45	ns	18/43	11/16	ns
OAB	N=83	ns	22/68	8/18	p=0.017
CPP	N=23	ns	11/23	9/11	ns
Retention	N=15	ns	7/12	3/6	ns
Subjective responders	N=62	ns	16/52	6/14	p=0.008
Objective responders	N=43	ns	8/37	4/7	ns

OAB = Overactive Bladder , CPP = Chronic Pelvic Pain, PTNS = Percutaneous Tibial Nerve Stimulation, ns = not significant, Pts = Patients

The improved satisfaction with their current sex life also resulted in a change in frequency of 'feeling like having sexual contact' as well as 'actually having sexual contact' ($p < 0.005$ in 46 and 47 patients respectively, formerly answering these

questions with 'not at all' and 'once in the past month'). As in the question on satisfaction, changes were predominantly observed in female patients (N=30 and N=29, p<0.005). The same applies to OAB patients (N=34, both) and subjective responders (N=20 and N=22): all p<0.05 (see table 3). Patients that 'felt like having sexual contact' at least several times a month or 'actually had sexual contact' at least several times a month prior to PTNS, remained doing so afterwards (p=0.3 and p=0.8).

Table 3 Change in frequency of 'feeling like' or 'actually having sex'

Patient group	Number	p-values overall frequency feeling like/ having sex whole (sub)group	Prior to PTNS		After PTNS		p-value	p-value
			Pts that wanted sex ≤ once a month / respon-dents	Pts that had sex ≤ once a month / respon-dents	Pts still wanting sex ≤ once a month / pts that did so before PTNS	Pts still having sex ≤ once a month / pts that did so before PTNS		
All	N=121	ns/ns	46/104	47/103	26/42	31/47	p=0.003	p=0.001
Women	N=76	ns/p=0.042	30/62	29/61	14/26	17/29	p=0.003	p=0.002
Men	N=45	ns/ns	16/42	18/42	12/16	14/18	ns	ns
OAB	N=83	ns/ns	34/68	34/67	21/31	22/34	p=0.021	p=0.005
CPP	N=23	ns/ns	7/22	7/22	3/7	5/7	ns	ns
Retention	N=15	ns/ns	5/14	6/14	2/4	4/6	ns	ns
Subjective responders	N=62	ns/ns	20/54	22/53	10/19	13/22	p=0.006	p=0.006
Objective responders	N=43	ns/ns	13/38	14/37	7/12	7/14	ns	p=0.048

OAB = Overactive Bladder, CPP = Chronic Pelvic Pain, PTNS = Percutaneous Tibial Nerve Stimulation, ns = not significant, Pts = Patients

The aforementioned improvements could not be related to changes in pain in the genital regions during sexual contact or disturbances in vaginal lubrication or erectile functioning. However, together with changes in frequency of wanting or having sex

and sexual satisfaction, significant improvements were seen in OAB patients never having reached an orgasm during sexual activity in the past month, as well as in female patients reaching orgasms too fast or too slowly. 17 out of 29 OAB patients that, prior to PTNS, did not reach orgasms although being sexually active, did so afterwards ($p < 0.05$), whilst 11 out of 26 female patients reaching orgasms too fast and 21 out of 32 female patients reaching orgasms too slowly significantly improved (both: $p < 0.05$).

Discussion

In a recent review by Shaw on the prevalence of sexual impairment in female patients with urinary incontinence ¹ figures widely varied between 0.6 and 64%. Most studies dealt with female patients with stress incontinence only, mixed groups or patients with 'any involuntary urine loss'. In the few cases clear detrusor instability has been regarded, impairment mostly was found in 10-35% of patients, depending on the way impairment was defined. More recent reports reconfirm the negative way in which OAB may affect sexual function in female patients. ^{2,14} For other forms of LUTD, especially non-urinary retention, as well as for male patients with urinary symptoms, data on sexual impairment are very scarce. In a Danish survey in over 7,000 people Hansen showed recently that lower urinary tract symptoms are an independent risk factor for sexual dysfunction in both women and men. ¹⁵

In our study, questions of the NSF-9, a standardized Dutch-language questionnaire dealing with different aspects of sexual functioning, revealed abnormal sexual functioning in 25.3-45.6% of all cases. In patients with OAB, sexual dysfunction has been observed in about a quarter to one third of cases being in accordance to the above mentioned literature. It should be noted that sexual dysfunction in our study might be underreported, as about 12% of the treated patients did not fill out the questionnaires. However, due to widely differing definitions of impairment of sexual function, urinary incontinence as well as sexual activity in different reports, useful comparisons can not be made. This is further hampered by the fact that in the Netherlands, validated questionnaires on sexual functioning hardly exist, let alone questionnaires that can be used for female as well as male patients. The NSF-9 is equally constructed for male and female patients. It is short, enhancing compliance,

and especially suitable for the Dutch language, but we are aware of the fact that it does not contribute to uniformity in international research.

Our intent was not only to establish some indication on the prevalence of sexual impairment in patients with LUTD, but also to find out whether improvement of the latter improved sexual functioning as well. One of the difficulties regarding this subject is the possibility that complaints of urinary symptoms may be the result of sexual dysfunction rather than the cause. In that case treating the sexual problem itself, instead of the LUTD, might be of more importance.¹

In this study, treatment of the LUTD has been performed by means of PTNS. Our earlier studies revealed PTNS' success rates on lower urinary tract symptoms up to 70%³⁻⁵, much higher than was observed here. It should be mentioned that those studies were performed in only a few high volume centers. The data presented in this paper are pooled data from our own center with those from several low volume hospitals in the Netherlands, that all used the same protocol. Results in these added centers were worse, although not statistically significant. Furthermore, a discrepancy was observed between the number of subjective and objective responders. One should bear in mind that most patients underwent many therapies before using PTNS as a final option. Small changes, not enough for objective success, may therefore have been considered enough to pursue chronic treatment. Besides, especially in OAB-patients, not only the number of voids/24 hours and the number of incontinence episodes/24 hours are of importance. The urge severity and the time patients can postpone micturition also play a role. Patients experiencing the most improvement of these items, more than of objective criteria, may be subjectively successful, objectively they are not.

Although compliance to the NSF-9 was rather high, the above mentioned low objective response rate to PTNS and the also rather small number of patients in each investigated subgroups, like, amongst others gender and indication for PTNS, made it difficult to obtain fair statistics on separate NSF-9 items per subgroup. It was therefore chosen to perform the other way around: separate NSF-9 items have been investigated and its changes correlated to the subgroups.

However, bearing these shortcomings in mind, we still feel our study proved that in particular sexually impaired female patients suffering from OAB, subjectively responding to PTNS, also benefited from LUTD treatment with regard to their sexual functioning. They were more satisfied and were more frequently sexually active than

before PTNS. A possible explanation might be the positive effects on the fear for involuntary urine loss or actual incontinence during sexual activity. Female patients with involuntary urine loss frequently feel dirty, fear smells and therefore have a low self-esteem, emotions likely to disappear with resolving urinary symptoms. Male patients, in whom sexual functioning is highly related to the way erectile functioning is experienced and not so much to urinary symptoms during sexual activity, may therefore not have the same positive outcome on successful LUTD therapy.

Conclusions

In conclusion, sexual dysfunction was observed in about one third of patients with lower urinary tract disorders and improved significantly on successful therapy for the latter. Female patients, patients with OAB and subjective responders were most likely to improve.

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Appendix (NSF-9)

Please read the questions carefully. After you have done so, please select the answer that best describes your situation. Do not choose more than one answer for every question

1. During the past month, how often have you wanted to have sexual contact? (By sexual contact do not only think of intercourse, but also of other sexual activities with a partner)

- 1 never
- 2 once
- 3 a couple of times
- 4 once a week
- 5 a couple of times a week
- 6 once a day
- 7 a couple of times a day

2. During the past month, how often have you had sexual contact? (By sexual contact do not only think of intercourse, but also of other sexual activities with a partner)

- 1 never —————→ go to question 9
- 2 once
- 3 a couple of times
- 4 once a week
- 5 a couple of times a week
- 6 once a day
- 7 a couple of times a day

3. During the past month, how often your penis has been less erected / your vagina has been less lubricated than you wanted?

- 1 not once
- 2 occasionally
- 3 several times
- 4 often
- 5 every time

4. During the past month, how often your penis has been not as long erected / your vagina has been not as long lubricated as you wanted?

- 1 not once
- 2 occasionally
- 3 several times
- 4 often
- 5 every time

5. During the past month, how often have you had an orgasm during sexual contact?

- 1 not once
 - 2 occasionally
 - 3 several times
 - 4 often
 - 5 every time
-
- go to question 8

6. During the past month, how often have you had an orgasm not as fast as you wanted?

- 1 not once
- 2 occasionally
- 3 several times
- 4 often
- 5 every time

7. During the past month, how often have you had an orgasm faster than you wanted?

- 1 not once
- 2 occasionally
- 3 several times
- 4 often
- 5 every time

8. During the past month, how often have you experienced pain in your genitals before, during or after sexual contact? (instead of pain, you can also think of itching or a burning sensation)

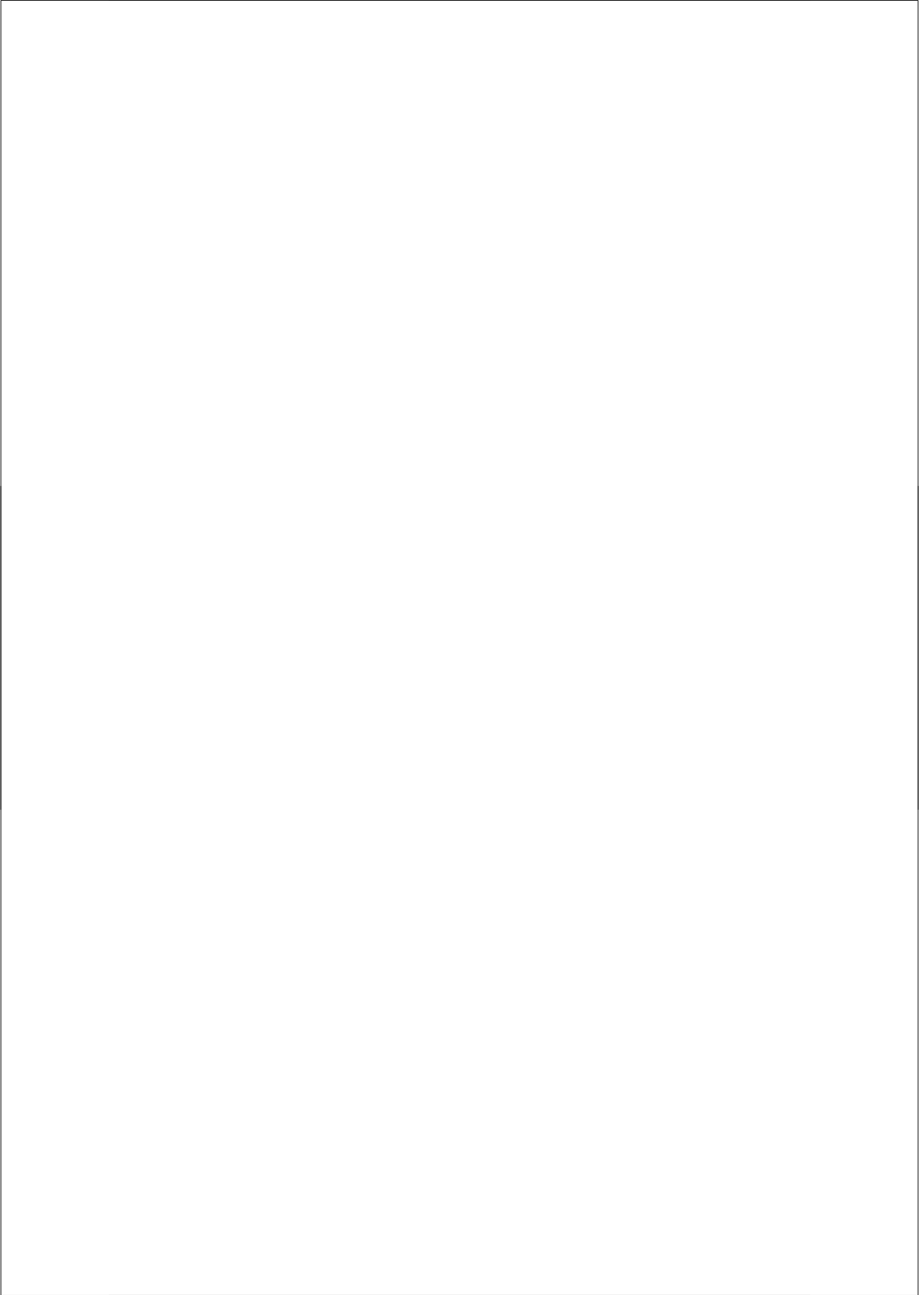
- 1 not once
- 2 occasionally
- 3 several times
- 4 often
- 5 every time

9. How satisfied with your current sex life are you?

- 1 very dissatisfied
- 2 dissatisfied
- 3 neutral
- 4 satisfied
- 5 very satisfied

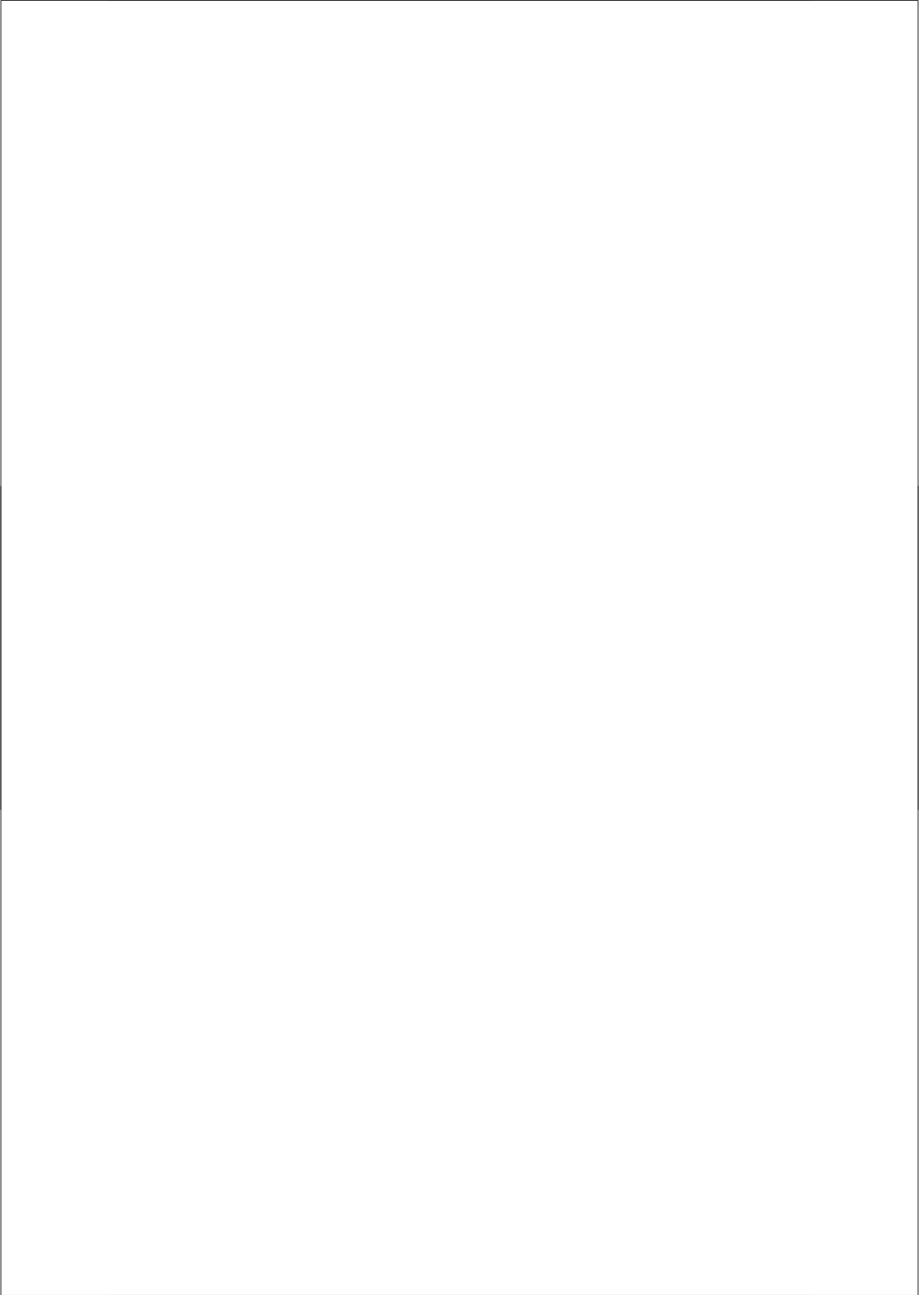
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CHAPTER 3

Urodynamic data



Posterior tibial nerve stimulation in the treatment of overactive bladder: urodynamic data

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Abstract

Objective The aim of this study was to evaluate urodynamic changes after percutaneous tibial nerve stimulation (PTNS) for the treatment of complaints related to the overactive bladder syndrome and to search for urodynamic-based predictive factors.

Patients and methods Ninety consecutive patients with symptoms related to overactive bladder syndrome were enrolled in this study. Patients underwent 12 PTNS sessions. For evaluating objective success, the primary outcome measure was a reduction in number of urinary leakage episodes of 50% or more per 24 hours. Patients' request for continuation of therapy was considered subjective success. This study focussed on urodynamic features at baseline and on changes found after 12 PTNS treatments.

Results The objective success rate was 56% (leakages/24h). Subjective success rate was 64%. Frequency/volume chart data and quality of life scores improved significantly ($p < 0.01$). Pre- and posturodynamic data were available from 46 participants. Detrusor instabilities (DI) could be abolished in a few cases only. Increments in cystometric bladder capacity and in volume at DI were significant ($p = 0.043$ and 0.012 , respectively). Subjects without detrusor instabilities at baseline were 1.7 times more prone to respond to PTNS (Odds Ratio (OR): 1.75; 95% Confidence Interval (CI): 0.67- 4.6). The more the bladder overactivity was pronounced, the less these patients were found to respond to PTNS, the area under the receiver operating characteristic curve was 0.644 (95% CI: 0.48-0.804).

Conclusions PTNS could not abolish DI. PTNS increased cystometric capacity and delayed the onset of DI. Cystometry seemed useful to select good candidates: patients without DI or with late DI onset showed to be the best candidates for PTNS.

Introduction

Electrostimulation has been exploited both for overactive bladder and for hypocontractile bladder alike. Recently, percutaneous posterior tibial nerve stimulation (PTNS) has been introduced for the treatment of lower urinary tract dysfunction. The tibial nerve is a mixed nerve containing L4-S3 fibres, and originates from the same spinal segments as the innervation to the bladder and pelvic floor. Therefore, it is not surprising that efforts were made to stimulate these fibres to treat bladder disturbances.¹⁻⁴ In previous studies, we have discussed extensively subjective success, quality of life scores and frequency/volume charts.⁴⁻⁵ Therefore, this article presents the urodynamic features found in patients who underwent PTNS for symptoms of overactive bladder syndrome. Three issues will be addressed: First, the primary outcome measures based on charts and questionnaires will be described briefly. Second, the urodynamic changes after PTNS treatment will be discussed and lastly, the predictive value of baseline urodynamic parameters on treatment outcome will be reported.

Patients and methods

Between November 1999 and August 2001, a total of 90 consecutive patients with a diagnosis of overactive bladder syndrome were enrolled in an international multicentre prospective clinical trial in five sites in the Netherlands and one site in Italy. Patients underwent 12 sessions of PTNS.

Definition and criteria Overactive bladder syndrome was defined as urgency, frequency and/or urge incontinence. For urgency and urge incontinence International Continence Society (ICS) definitions were used.⁶ For this study, an increased urinary frequency was defined as eight voids or more per 24 hours. Stress urinary incontinence was excluded through urodynamic investigation.

Inclusion and exclusion criteria as well as the PTNS technique have been extensively described in a previous study.⁴ In short, the procedure was as follows: the posterior tibial nerve was located through percutaneous insertion of a needle a few inches above the medial malleolus. After connection to a low voltage stimulator

(Cystomedix, Anoka, MN, USA) and placement of a ground surface electrode on the ipsilateral calcaneus, the tibial nerve was stimulated. This resulted in a tickling sensation in the sole of the foot and flexion of the toes.

Primary outcome measure, positive response rate and quality of life Following the considerations of Blaivas on how to assess new treatment modalities, the subsequent parameters were evaluated: the number of leakage episodes, the amount of urine loss, urinary frequency and subjective patient assessment.⁷ A reduction in the number of leakage episodes of at least 50% on 24-hour frequency/volume charts was taken as primary outcome measure. Furthermore, a reduction in leakage severity of at least 50% was a secondary outcome measure (scale score 1, some drops; 2, small amount; 3, severe urine loss necessitating change of clothing). A reduction in urinary frequency was regarded clinically significant when a normal voiding pattern of less than 8 voids per 24 hours could be obtained. Patients' request for continuation of treatment was regarded a subjective success, and these patients were called "positive responders". In addition, quality of life was determined at week 0 and at week 12. For incontinence specific Quality of Life the I-QoL was used.⁸ For the estimation of generic functional status and well-being, the MOS 36 items Short-Form health survey (SF-36) was completed.⁹ Higher scores indicate better quality of life. All patients gave their informed consent.

Urodynamic data Both at baseline and after 12 sessions, urodynamic investigations were performed in all patients. For urodynamic analysis, a standard transurethral subtraction cystometry was done in the supine position. Sterile saline at room temperature was infused through a double-lumen 8 F catheter at a filling rate of 50 ml/min. The volume at which detrusor instabilities (volume at DI) occurred was noted. DI was defined as an increase of 15 cm water pressure or of lower amplitude if accompanied with a distinct sensation of urgency. Methods, definitions and units conform to the standards recommended by the International Continence Society, except where specifically noted.⁶

Statistical analysis and predictive factors Descriptive data were reported as median values and range and with a median change and range. Within-group comparisons of results were conducted by the nonparametric Wilcoxon signed ranks

test. Tests were performed on a two-tailed basis, and level of significance was set at 5%. To evaluate whether it is possible to predict subjective success with urodynamic characteristics, we performed univariate and multivariate logistics regression analyses. The dependent variable was “subjective success”, because this is the clinically most relevant outcome measure: despite good improvement in frequency/volume charts, a patient can experience the net effect as unsatisfactory and vice versa. Odds ratios (OR) with their 95% confidence intervals (95%CI) were calculated as a measure for the predictive power of each characteristic. Based on the outcome of the multivariate analyses, a Receiver Operating Characteristic (ROC) curve was constructed in order to visualize the predictive power of the combination of the variables. The area under the ROC curve quantified this predictive power. Statistical analysis was performed using SPSS 9.0 software (SPSS, Chicago, IL, USA).

Results

Baseline characteristics Ninety patients (67 females and 23 males) with a median age of 51 years (range: 19-82) were enrolled in this study (table 1). Duration of symptoms ranged between 1 and 56 years with a median of 4.5 years. A total of 80 of 90 frequency/volume charts were completed correctly and used for further analysis (10 of 90: 11% missing values). Sixty of 80 (75%) of these patients were incontinent and leaked at least once a day. From those patient who filled in correctly the frequency/volume chart, 73 of 80 (91%) patients had an increased frequency at baseline and 7 of 80 (9%) had a normal voiding frequency of less than 8 voids per 24 hours. Eighty-one I-QoL and 82 SF-36 surveys were found suitable for further examination. At baseline, 82 urodynamic reports were suitable for evaluation. DI occurred in 48 of 82 (59%) patients.

Reduction in leakage episodes, severity of urine loss and urinary frequency:

After 12 PTNS treatments, 78 complete voiding charts were available for evaluation (12 of 90:13% missing values). All parameters improved significantly (see table 1). Seventy-five percent of the subjects with daily incontinence at baseline was reduced to 44% (35 of 80) of subjects after 12 PTNS (35 of 78 incontinent; 43 of 78 not incon-

Table 1 F/V chart, urodynamic data and Quality of Life results (all 90 patients)

Parameter	M	N	Baseline	N	End	Change	p-value*
24h F/V chart							
Leakages	30	60	5 (1;19)	59	2 (0;16)	-3 (-19;+7)	<0.01
Incontinence severity	30	60	2 (1;3)	58	1 (0;3)	-1 (-3;+1)	<0.01
Urinary frequency	10	80	13 (4;41)	75	10 (4;53)	-3 (-18;+12)	<0.001
Mean Voided Volume	11	79	135 (20;327)	74	191 (47;410)	+27 (-96;+200)	<0.001
Quality of Life scores							
I-QoL	9	81	49 (20;100)	80	67 (20;100)	+10 (-31;+88)	<0.001
SF-36	11	79	57(10;93)	82	67 (13;93)	+4 (-42;+56)	<0.001
Cystometric data							
Cystometric capacity	7	82	263 (30;745)				
Subjects with DI	42	48	59%				
Volume DI	42	48	150 (30;350)				
Pdet DI	42	48	41 (4;123)				

M = missing values at baseline because not complete or not relevant, N = number of valid values, * = Wilcoxon signed ranks test, significance level set at 5%, F/V = Frequency/Volume, DI = Detrusor Instability, CC = Cystometric Capacity, Pdet DI = Detrusor pressure at DI

tinent, 12 of 90 missing values). End evaluation considered 23 of 60 (38%) patients dry, that is cured. However, four of these wished to discontinue treatment. An additional 11 of 60 (18%) incontinent subjects achieved at least 50% reduction in the number of leakage episodes. This resulted in a success rate of 56% (primary outcome measure). In positive responders a median reduction of 100% (+50; -100) was found whereas non-responders obtained a median reduction of 33% (+77; -100). An at least 50% reduction in incontinence severity was found in 31 of 60 (52%) subjects. Positive responders and non-responders achieved a median reduction of 100% and 23%, respectively. At baseline, 7 of 80 (9%) had a normal voiding frequency of less than 8 voids per day, 12 subjects voided 8 to 10 times a day (15%). After 12 PTNS sessions 20/80 (25 %) subjects achieved a voiding frequency of less than 8 times (primary outcome measure) and another 25 voided 8 to 10 times (31%).

Patients' assessment: subjective response and quality of life scores Fifty-eight of 90 (64%) patients requested continuation of the therapy. I-QoL and SF-36 scores improved significantly as shown in table 1.

Urodynamic profiles In only 46 patients, urodynamic investigations were performed at baseline and after 12 PTNS sessions. Therefore, post-PTNS treatment urodynamic findings are based on data of 46 participants only (36 females, 10 males; median age: 51 years). Comparable subjective success rates in this subgroup were found: 32 of 46 (70%) versus 58 of 90 (64%); this finding reduces the possible bias of having only successful patients undergoing a second urodynamic investigation. Baseline and end evaluation data are summarised in table 2: a significant increment was seen in cystometric bladder capacity and in volume at which first instable detrusor contraction occurred. At baseline, DI's were noted in 34 of 46 participants (74%), 31 subjects continued to have DI; however, these instabilities occurred at larger bladder volumes. In three patients DI was eliminated and in three others, de novo DI was noticed. Detrusor pressures recorded during the instabilities decreased only slightly.

Table 2 F/V chart, urodynamic data and Quality of Life results (46 patients)

Parameter	Baseline	End	Change	p-value*	Change in responders N = 32/46 (70%)	p-value*
24h F/V chart						
Leakages	4 (1;19)	3 (1;16)	-2 (-19;+7)	0.001	-2(-19;+2)	<0.01
Severity of leakages	2 (1;3)	1.85 (1;3)	-1(-3;+1)	<0.001	-1 (-3;+1)	<0.01
Urinary frequency	13 (4;32)	9 (5;19)	-3(-18;+8)	<0.001	-3 (-18;+8)	<0.01
Mean Voided Volume	135 (28;275)	205 (76;300)	+50(-50;+200)	<0.001	+62 (-50;+200)	0.001
Quality of Life scores:						
I-QoL	39 (22;94)	66(20;100)	+9(-19;+88)	<0.001	+19(-14;+88)	<0.01
SF-36	54 (17;93)	64 (19;89)	+5 (-42;+55)	0.003	+6 (-18;+56)	<0.01
Cystometric data:						
Cystometric Capacity	243 (30;745)	340 (70;500)	+30 (-324;+450)	0.043	+36 (-324;+450)	0.14
Subjects with DI	34/46 (70%)	34/46 (70%)			23/32 (72%)	
Volume DI	133 (30;350)	210 (50;375)	+60 (-183;+333)	0.012	+115(-183;+333)	0.031
Pdet DI	35 (4-120)	41 (10-93)	-5 (-63; 74)	0.67	-6.5(-46;+64)	0.69

* = Wilcoxon signed ranks test, significance level set at 5%, F/V = Frequency/Volume, DI = Detrusor Instability, CC = Cystometric Capacity, Pdet DI = Detrusor pressure at DI

Influencing factors on outcome Taking the small number of participants into account (n=82, although in only 48 patients the features of DI could be analysed),

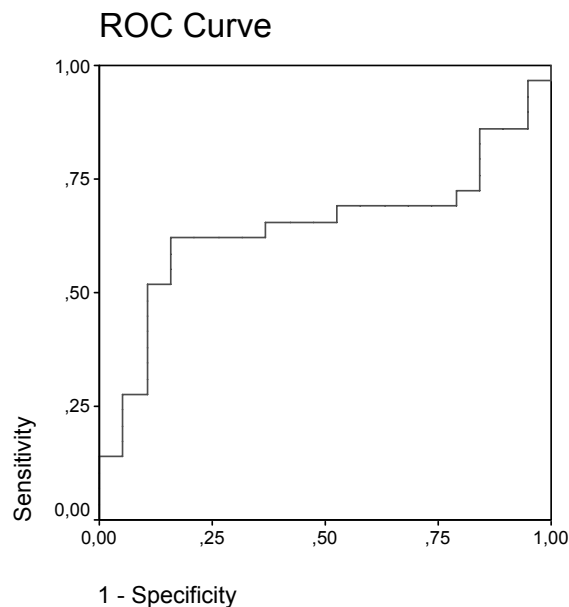
analysis of potential predictive factors among baseline characteristics revealed one strong prognostic factor: subjects having detrusor instabilities at baseline (n=48) were less likely to respond to PTNS. A stable bladder enhanced the chance for a successful outcome of the PTNS therapy by 1.75 times (OR: 1.75; 95%CI: 0.669-4.57).

Univariate logistic regression analysis showed that none of the baseline characteristics (cystometric capacity, volume at DI, detrusor pressure at DI) proved to be a significant predictor for subjective success. This finding may also be due to the small number of participants with unstable detrusor (n=48). There was some suggestion that the volume at DI can predict outcome to a certain extent. For example, for each 100 ml "delay in DI onset", chance for success increased 1.5 times (OR: 1.0043; 95% CI: 0.997, 1.012). However, the three baseline characteristics showed no statistical significance, a multivariate analysis combining these three factors revealed a predictive power of 0.64 (OR: 0.644; 95% CI: 0.484, 0.804), see figure 1. Also a slight tendency was seen that could support the idea that stronger stimulation inhibit detrusor overactivity: a participant having a 5 mA higher mean stimulation intensity had 1.8 times more change for success (OR: 1.13; 95% CI: 0.81; 1.6).

Discussion

The primary outcome measures that were taken to assess PTNS, were obtained in 56% of the patients with urinary leakage at baseline; 38% of them showed micturition charts without any leakages, 52% of the patients noticed significant reduction in urine loss. Only 25% of all participants achieved a normal micturition pattern (less than 8 voids/24 hours). Patients treated by PTNS seem to regain their control on involuntary urine loss, but achievement of a normal micturition pattern is hardly feasible in most of them. Additionally, patients' assessment was determined through QoL questionnaires ($p < 0.001$) and the number of requests to continue the treatment (64%). All together, it seems that PTNS can be considered as a new treatment modality that can be offered to patients with intractable OAB symptoms; nearly 60% of such patients will benefit from PTNS.

Figure 1 ROC curve constructed to visualize the predictive power for success (cystometric capacity, volume at and pressure at detrusor instability combined)



This study was mentioned to detect the impact of PTNS by looking to these patients in a more objective way, namely by determining urodynamic changes. Examination of 46 patients with overactive bladder syndrome who underwent 12 PTNS sessions revealed significant urodynamic changes, namely increment of total bladder capacity and volume at DI. For positive responders the increment in cystometric capacity was not significant; this could be due to the rather large baseline capacity positive responders already had, which only increased slightly. Non-responders started with a median baseline capacity of 155 ml (range: 77-550) and ended up with a capacity of 250 ml (range: 70-500). For positive responders, this change was 300ml (range 30-745) at week 0 and 340 ml (range: 103-500) after 12 PTNS sessions. These figures strongly suggest that patients with small cystometric capacity were more prone to fail. Even though the cystometric capacity of non-responders increased, the resultant capacity seemed of small clinical value for this group as they choose not to continue with PTNS. Remarkably, logistic regression analysis could not point out baseline capacity as a prognostic factor for success (OR: 1.0008; 95%CI: 0.998-1.004). The patient group that underwent pre- and posturodynamic evaluation contained more patients with an instable bladder than the baseline group did. The reason for this can

be sought in the fact that mainly academic centres, that participated, received more second opinion patients often with intractable detrusor instabilities. Investigating the DI features revealed a significant delay in onset of DI. The clinical relevance of 60 ml increment in volume at which the first DI occurs seems perhaps questionable but assuming a physiological filling rate of 1 ml/min, such an increment would delay the onset of urge or urge-incontinence provoked by the DI, with nearly one hour or in case of responders (+115ml) with nearly two hours! ¹⁰ The reductions found in detrusor pressures during unstable contractions were of minor size and presumable of minor clinical relevance. Furthermore, repetitive PTNS could not substantially decrease the number of subjects in whom detrusor instabilities were detected. Disappearance of DI was only seen in 3/90 patients. This is in contrast with Klingler et al. reporting an elimination of DI in 77% of the cases after 12 sessions of PTNS. ³ It is questionable how relevant the finding of persistent DI is in evaluating therapeutic effects of neuromodulation. In fact, many neuromodulation studies reported failures to suppress DI. ¹¹⁻¹⁴ Nevertheless, the presence of DI at baseline was found to be a strong predictive factor for therapeutic failure, especially when it occurred early in the filling phase. So, stable bladders were more prone to respond well to PTNS. In conclusion, it seems advisable to include only those patients with stable bladders, or those with late onset bladder instability.

A common remark questions how intermittent stimulation in PTNS possibly can succeed, comparing with the continuous stimulation patients receive when a sacral root neuromodulator is implanted. The inhibitory and long-lasting effect through PTNS can be explained by experiments performed in Macaca monkeys. It was shown that repetitive tibial nerve stimulation powerfully inhibits nociceptive spinothalamic tract cells through A- δ fibres, provided a high enough intensity was applied. ¹⁵ This inhibition was thought to act on a spinal level. Although these experiments were not focused on the complex micturition system, extrapolation of these findings to voiding dysfunction can be made. Hypothetically, repetitive PTNS inhibits pathologic afferent information from the bladder to supraspinal levels, resulting in a decreased awareness of pathological sensations (less urge) and delayed onset of detrusor instability. Similar studies on these spinothalamic cells, demonstrated long-lasting inhibition for 30 minutes. Inhibition occurred more strongly as stimulation intensity increased. ¹⁶ This finding can explain a carry-over effect found upon intermittent stimulation. To our knowledge, no research has been

performed investigating how long this inhibition occurs in humans, or how strongly this nerve has to be stimulated. Determination of the exact intensity applied through PTNS stimulation is troubled because of the inhomogeneous character of each nerve, recruitment of fibres by size, physical environment and type of stimulated nerve.¹⁷ A stronger stimulation will surely be more effective as has been already proved in human experiments using supramaximal stimulation in spinal cord patients.¹⁸ Also, this study provided some evidence for better therapy outcome in those patients in whom stronger stimulation currents were used. Even though the real stimulation intensity that reached the tibial nerve remains unknown, a slight tendency was seen that could support the former ideas: a participant receiving a 5 mA higher mean stimulation intensity, had 1.8 times more change for success. Unfortunately, application of higher current intensity through percutaneous needling is hardly feasible in individuals with intact sensation. Finding a more adequate way to stimulate the posterior tibial nerve, with better placement of the electrode and controlled applied intensity should be aimed and searched for.

Many factors seem to influence the outcome of PTNS. Presumably, complex interaction of several factors, such as bladder retraining by frequently completed voiding diaries, release of enkephalines or other neurotransmitters through needling, decreased c-fos expression by tibial nerve stimulation and attribution of some placebo effect, will play important roles and finally add up resulting in a successful outcome. The urodynamic results refute, however, the possibility of a placebo effect being the only explanation for the positive results found in this study.

Conclusions

PTNS sessions could not eliminate DI but resulted in increased bladder capacity and delayed onset of DI to such an extent that the patients experienced a clinical relevant decrease in leakage episodes, severity of incontinence and voiding frequency. The latter parameters can all be calculated from frequency/volume charts. Therefore, the value of urodynamic investigations to evaluate therapeutic effect of neuromodulation is debatable. On the other hand, predictive factors related to cystometric parameters were found: patients with stable bladders are good candidates for PTNS treatment. When bladder instability is present, it seems advisable to exclude those patients with

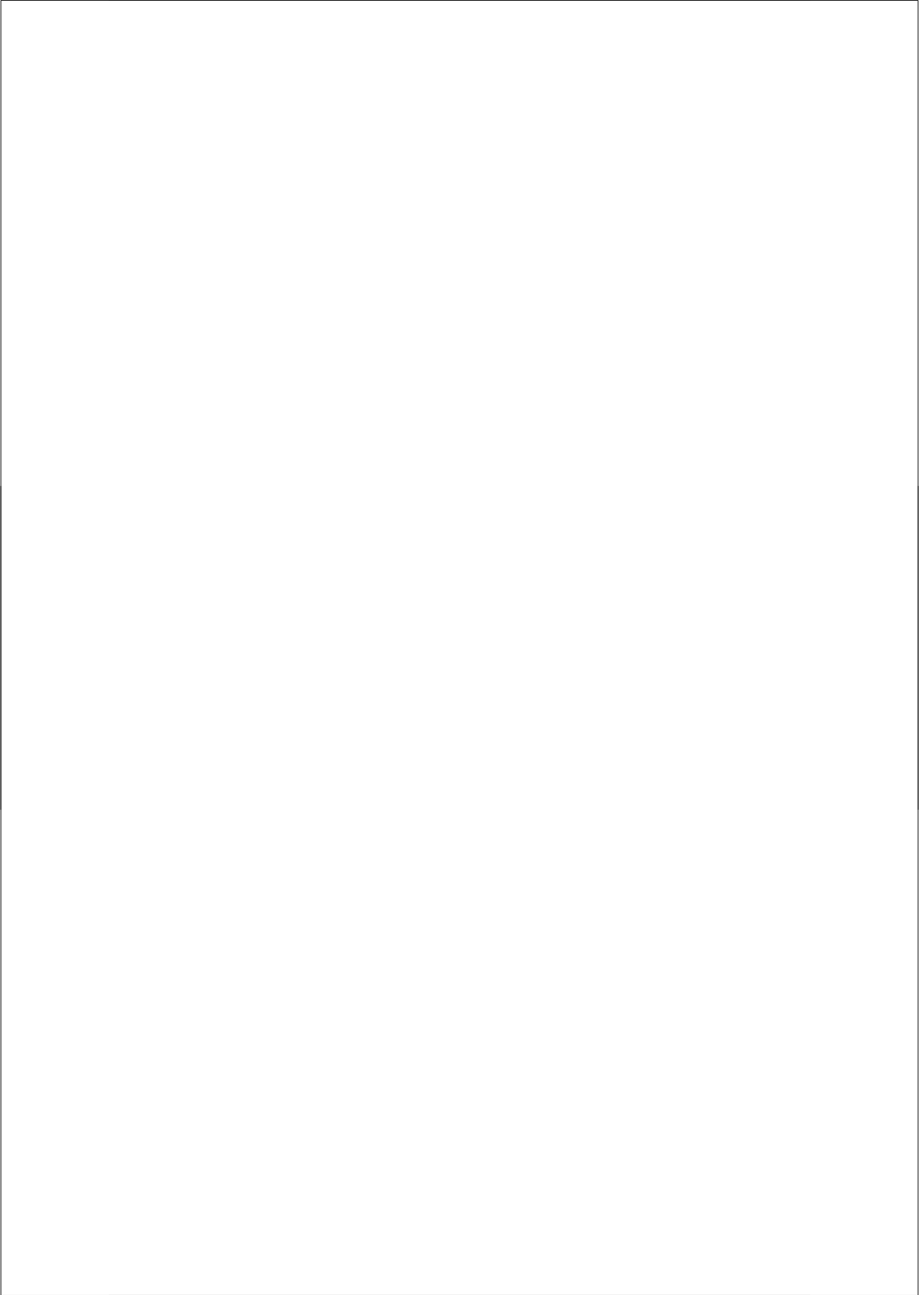
severe forms of bladder overactivity (i.e. early onset of DI) from PTNS treatment. In view of the facts that PTNS is an inexpensive treatment modality that is minimally invasive and simple to perform, it is an attractive first-line option for patients with overactive bladder syndrome before proceeding towards surgical interventions such as bladder augmentation or replacement. PTNS is a young therapy requiring further research, analysing predictive factors and optimal stimulation parameters.

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Posterior tibial nerve stimulation in the treatment of voiding dysfunction: urodynamic data

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Abstract

Objective To determine urodynamic changes and predictive factors in patients with voiding dysfunction who underwent 12 percutaneous tibial nerve stimulations.

Patients and methods Thirty nine patients with chronic voiding dysfunction were enrolled in a prospective multicentre trial in the Netherlands (n=19) and in Italy (n=20). A 50% reduction in total catheterized volume per 24 hr was taken as a primary objective outcome measure. Patients' request for continuation of treatment was regarded as subjective success. Objective urodynamic parameters and bladder indices were determined. Odds ratios and their 95% confidence interval were computed as a measure for predictive power in order to reveal predictive factors (Pdet at Qmax, Qmax, BVE and BCI).

Results Primary outcome measure was obtained in 41%, an additional 26% reduced their 24 hr residuals with more than 25%. Fifty nine percent of patients chose to continue treatment. Detrusor pressure at maximal flow, cystometric residuals and bladder indices improved significantly for all patients ($p < 0.05$). Patients with minor voiding dysfunction were more prone to notice success (Odds ratio: 0.73; 95% CI: 0.51-0.94).

Conclusions PTNS is a young treatment modality, minimally invasive and easily accessible. It might be an attractive first line option for patients with (minor) voiding dysfunction.

Introduction

Voiding dysfunction can be caused by neurological disorders, post surgical conditions, infravesical obstruction, bladder overdistention, inflammation, drugs, psychogenic factors, learned voiding dysfunction, detrusor myopathy and pelvic floor dysfunction.¹ Therapeutic lower urinary tract rehabilitation includes pelvic floor training, biofeedback, behavioral modification, catheterization, electrical stimulation or bladder expression and bladder reflex triggering in case of neurogenic disorders.² Patients might benefit clinically from cholinergic agents.^{3,4} Other treatment modalities are urethral dilatation, insertion of intraurethral device or surgery to relieve anatomic obstruction. Often clean intermittent self-catheterization is the most effective therapy for chronic bladder emptying problems. Unfortunately catheterization is at the expense of patients' quality of life. During the last decades neuromodulation has gained interest as an alternative treatment for difficult to treat voiding dysfunction before proceeding towards more invasive surgical procedures. One of the newest modalities is percutaneous tibial nerve stimulation (PTNS). The posterior tibial nerve is a mixed nerve containing L5-S3 fibres, originating from the same spinal segments as the parasympathic innervation to the bladder. The first results of PTNS for patients with voiding dysfunction were already extensively reported in previous papers.^{5,6} This paper focuses on urodynamic changes found in these patients and on determination of urodynamic predictive factors.

Patients and methods

Between November 1999 and July 2000, 39 consecutive patients with idiopathic non-obstructive voiding dysfunction were enrolled in an international prospective multicentre clinical trial in the Netherlands (n=19) and Italy (n=20). Patients underwent 12 weekly percutaneous stimulations of the posterior tibial nerve.

Definition and criteria Idiopathic non-obstructive voiding dysfunction: all patients with abnormal detrusor function (detrusor underactivity or acontractile detrusor and postvoidal residual) conform the definitions from the standardisation report 2002.²

Prior to the study, all patients failed in achieving complete bladder emptying, two of them had complete urinary retention and thus all patients catheterized.

In all patients extensive medical history was taken focussing on urinary symptoms, previous and present treatments, neurological disease, and medications. Physical examination was done to rule out any relevant pathology such as uro-gynaecological or neurological abnormalities. Symptoms existed for a minimum of 6 months. Exclusion criteria were bladder outlet obstruction related to benign prostatic hyperplasia (using the Abrams-Griffiths nomogram), any uro-gynaecological, central or peripheral neurological disorders including dysfunctional voiding due to pelvic floor overactivity, pregnancy, age under 18 and severe cardiopulmonary disease.

PTNS procedure was extensively described in a previous paper.⁵ In short, through percutaneous needling the posterior tibial nerve was stimulated above the medial malleolus. After connection to a low voltage stimulator (CystoMedix, Anoka, MN) and a ground electrode, this nerve was electrically stimulated which resulted in a sensory response (tickling sensation in the sole of the foot) and a typical motor response (plantar flexion of digit I or fanning of all toes). Treatment consisted of 12 weekly sessions of 30 minutes each. All patients gave their informed consent.

Primary outcome measure, positive response rate and quality of life In line with Blaivas' proposals concerning how to assess efficacy of neuromodulation, 50% reduction in total catheterized volume per 24 hr was taken as primary objective outcome measure. Additionally the positive response rate and Quality of Life scores displayed patients' assessment.⁷

Request for continuation of treatment was regarded a subjective success and these patients were called "positive responders". Quality of Life scores were determined at week 0 and at week 12. For incontinence specific quality of life the I-QoL was used.⁸ For the estimation of generic functional status and well-being, the MOS 36 items Short-Form health survey (SF-36) was completed.⁹ Higher scores indicate better quality of life.

Urodynamic data Objective assessment of the efficacy of PTNS was done through urodynamic investigation and through calculating bladder indices. At baseline and after 12 PTNS sessions, a standard transurethral subtraction cystometry was performed in the supine position whereas the pressure flow study was carried out in

the sitting position. Sterile saline at room temperature was infused through a double lumen 8 F catheter at a filling rate of 50 ml/min. The volume at which detrusor instabilities (DI) occurred was noted. DI was defined as an increase of 15 cm water pressure or of lower amplitude if accompanied with a distinct sensation of urgency. Methods, definitions, and units conform to the standards recommended by the International Continence Society, except where specifically noted.²

Bladder indices based on frequency/volume charts and urodynamics An effort to measure bladder contractility and voiding efficacy was made. Bladder Contractility Index (BCI) was derived from the formula: $BCI = P_{det} \times Q_{max} + 5 \times Q_{max}$; such that a strong bladder contractility is a BCI of >150, normal contractility a BCI of 100-150, and a weak contractility a BCI of <100.¹⁰ BCI was thus calculated from the urodynamic measurements. Bladder Voiding Efficiency (BVE) reflects bladder contractility against urethral resistance and is measured according to the degree of bladder emptying: $BVE = 100 \times (\text{voided volume} / \text{total bladder capacity})$. Total bladder capacity is defined as the summation of voided volume and postvoidal residual volume.¹⁰ BVE was computed both from urodynamic and voiding/frequency chart data. Both bladder indices were determined at baseline and at week 12.

Statistical analysis and predictive factors Efficacy of PTNS was analysed for all patients on an intention-to-treat basis. Descriptive data were reported as median values and range, and as mean change with 95% confidence interval (CI).¹¹ Within-group comparisons of results were conducted by the non-parametric Wilcoxon signed rank test. Tests were performed on a two-tailed basis and level of significance was set at 5%. In order to evaluate whether it is possible to predict subjective success with baseline characteristics we performed univariate and multivariate logistics regression analyses. In our opinion, the clinically most relevant outcome measurement is patients' perception of the PTNS effect on their voiding disorder: despite good improvement in frequency/volume charts, a patient can experience the net effect as unsatisfactory and vice versa. Odds ratios with their 95% CIs were calculated as a measure for the predictive power of each characteristic. Statistical analysis was performed using SPSS 9.0 software (SPSS, Chicago).

Results

Thirty nine patients (12 men, 27 women) with a median age of 53 years (range: 28-77) were enrolled in this study. Patients' baseline characteristics and their medical history are summarised in Table 1.

Table 1 Patient characteristics

(% of patients)	All (39)	
Patient characteristics:	Median	Range
Male/female	12/27	
Age in years (y)	53	28-77
Duration of symptoms (y)	3	1-36
Current intensity (mA)	4	1.4-7.6
Treatments prior to PTNS (%):	Number	Percent
Medication for complaints ¹ :	31	80
One	19	49
Two	12	31
Pelvic floor/bladder retraining:	8	21
Electrotherapy:	5	13
Surgical intervention ² :	11	29
One	8	21
Two	3	8
Baseline voiding parameters:	Median	Range
Total catheterized volume	800	210-3000
Mean catheterized volume	241	74-675
Number of catheterizations	2.5	1-10
Total voided volume	1000	95-2700
Bladder Contractility Index	63	37-160
Bladder Voiding Efficiency (urodynamics)	64	40-96
Bladder Voiding Efficiency (frequency/volume chart)	56	8-91
Baseline QoL score:	Median	Range
I-QoL	62	26-99
SF-36	65	19-92

¹Medication used: parasympathomimetica, alpha-blockers, ²Surgical intervention for urinary complaints were: urethral dilatation, suspension- and prolaps surgery, transurethral prostatic resection (TURP) and bladder neck incision.

At baseline, one patient had a mean of 74 ml residual, catheterising 4 times a day on frequency/volume charts. All others had residuals larger than 100 ml.

Primary outcome measure: more than 50% decrement in 24 hr total catheterized volume Frequency/volume charts were completed after 12 weeks by 38 patients. All patients improved significantly in all frequency/volume chart data (See table 2). In 16/39 (41%) patients' 24 hr total catheterized volume reduced with 50% or more (= primary outcome measure). Another 10/39 (26%) participants noticed a 25-50% decrement of their residuals. Thus, 26 (67%) patients noticed a reduction of 25% or more in 24 hr total catheterized volume. A tendency to increment of the total voided volume was found (p=0.053). PTNS resulted in 15/39 patients with a mean catheterized volume smaller than 100 ml (13 patients) or zero (2 patients). Nobody became catheterization free, even the 2 patients that had zero residual after catheterization, still continued catheterizing themselves once a day.

Table 2 Frequency/volume chart and Quality of Life results

	Week 0			Week 12			Median change			p-value
	N	Median	Range	N	Median	Range	N	Median	Range	
F/V chart data:										
Tot CV(ml)	37	800	210-3000	38	450	0-2450	37	-200	-2700;700	<0.01
Mean CV(ml)	38	241	74-675	38	163	0-163	38	-80	-375;247	<0.01
No of cath.	38	2.5	1-10	38	2	1-7	38	0	-7;2	0.024
Tot VV (ml)	37	1000	95-2700	36	1260	50-310	36	275	-500;1720	0.053
BE	37	64	40-96	38	77	0-100	37	9.5	-38;78	<0.01
Quality of Life:										
I-QoL	39	62	26-99	39	86	29-100	39	11	-2;60	<0.01
SF-36	39	65	19-92	38	70	17-91	38	3	-18;50	<0.01

Tot CV: total catheterized volume, Mean CV: mean catheterized volume, Tot VV: total voided volume, BCI: Bladder Contractility Index, BVE: Bladder Voiding Efficiency index based on the Frequency/volume charts

Subjective success: positive responders Twenty three out of thirty nine patients (59%) chose to continue treatment. In 13 out of these 23 patients the primary outcome measure (more than 50% reduction) was obtained, another eight subjects noticed a reduction of their 24 hr residual volume with more than 25%. For non-responders (n=16) the primary outcome measure was obtained in only two patients: two patients had more than 50% reduction in 24 hr catheterized volume and another

two revealed more than 25% reduced residual volume. From these four patients, one patient stopped because of personal reasons, though she had nearly zero residuals. The other three persons noticed a good decrease in total amount of catheterized volume but they still had the same catheterization rate and were thus not satisfied (e.g. from 5x 340 to 4x 220ml times a day). One patient dropped out of the study after six sessions because of aggravation of pre-existing cardiac arrhythmia, assumed not to be related to PTNS.

Urodynamic data At baseline, 37 urodynamic investigations were performed (60% of these patients wanted to continue treatment: positive responders), after 12 PTNS sessions 27 patients (63% positive responders) underwent a cystometry and pressure flow study (Table 3). Patients' cystometric capacity remained the same, detrusor pressure at maximal flow increased statistically significant and a decrement in patient's residual volume after the pressure flow study was seen. Urodynamic examination revealed five patients (5/37, 14%) with unstable detrusor activity at baseline. After 12 treatment sessions unstable detrusor contractions were seen in three participants, DI disappeared in two subjects and seven patients developed de novo DI. Added up, 10 participants had DI after 12 PTNS sessions (10/27= 37%). Eight out of these 10 patients requested continuation of PTNS, mostly with a 2–3 weekly interval. Their total catheterized volume decreased with a mean of 51% (range: -26%, -87%).

Bladder index based on frequency/volume charts Bladder voiding efficiency increased significantly with a median change of +9.5% (range: -38; +78%). For responders this was +18.2% (range: -16; +78%).

Bladder indices based on urodynamic data For all patients both BCI and bladder voiding efficiency increased significantly. The urodynamically based bladder voiding efficiency improved in a similar way (median change: +6%, range: -9; +18%). Responders noticed a median percentage increase of +11% (range: -8; +18%). Baseline bladder voiding efficiency was not different among responders (median BVE: 62; range: 40-83) and non-responders (median BVE: 64; range: 50-96) (p=0.6). The BCI rose with 20 points (range: -52, + 70) for all patients. Responders revealed an addition of 20 points (range: -15; +70) whereas non-responders noticed a median

improvement of 15 points (range: -52; +25). At baseline, 23 patients had a weak (BCI <100), two a normal (BCI 100-150) and one participant had a strong detrusor contractility (BCI >150). After 12 PTNS sessions this was respectively seen in 20, 3 and 2 patients. The median baseline BCI score was not significantly different between responders (median BCI: 65; range: 37-120) and non-responders (median BCI: 59; range: 40-160) (p=0.8).

Table 3 Urodynamic results

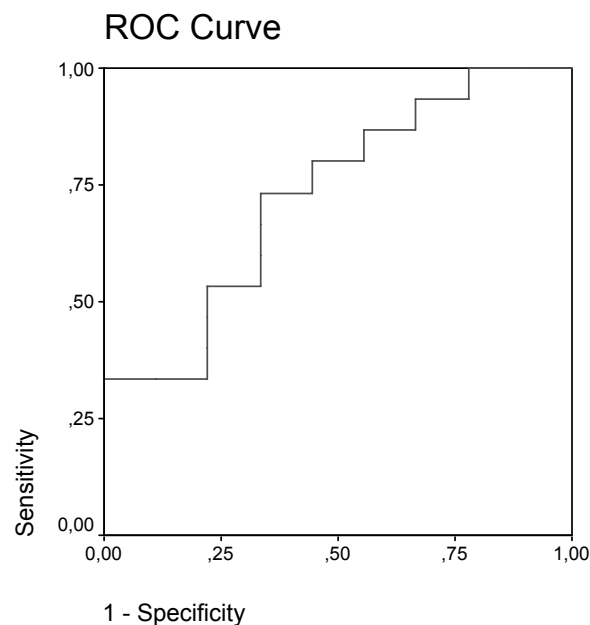
	Week 0			Week 12			Median change			p-value
	N	Median	Range	N	Median	Range	N	Median	Range	
All patients:										
CC	37	500	165-835	27	500	149-800	27	0	-225;300	0.930
Pdi	5	37	16-60	10	26.5	10-48	3	1	-2;3	0.59
Vdi	5	150	50-450	10	245	175-480	3	70	-30;130	0.29
Pdet at Qmax	27	25	10-70	24	33	10-83	21	8	-5;68	<0.01
Qmax	25	7	2-27	25	10	4-29	20	1	-12;13	0.13
Res. volume	31	270	35-755	19	220	50-450	19	-80	-280;100	0.01
BCI	26	63	37-160	25	83	5-178	20	20	-52;70	<0.01
BE	31	56	8-91	19	67	56-86	19	6	-8.8;18.1	<0.01
Subj. responders:										
CC	22	500	165-835	17	500	149-650	17	0	-225;300	0.9
Pdet at Qmax	16	25	10-70	16	34	15-59	13	8	-5;31	<0.01
Qmax	16	8.5	2-16	16	10	4-29	13	1	-4;13	0.1
Res. volume	18	285	80-755	9	130	50-400	9	-100	-200;10	0.01
BCI	16	65	37-120	16	85	55-178	9	11	-1.5;18.1	<0.01
BVE	18	62.5	40-83	9	73	60-86	13	20	-15;70	0.011

CC: Cystometric Capacity in ml, Pdi: Pressure of detrusor instability in cm H₂O, Vdi: Volume at first detrusor instability in ml, Pdet at Qmax: Detrusor pressure at maximal Flow in cm H₂O, Qmax: Maximal Flow in ml/sec, Res. volume: Residual volume in ml, BCI: Bladder Contractility Index, BVE: Bladder Voiding Efficiency index

Predictive factors Univariate logistic regressions analysis showed that none of the baseline urodynamic characteristics or bladder indices proved to be a significant predictor for subjective success. This may be due to the small number of study participants. There was some suggestion that certain characteristics can predict outcome to a certain extent. For example, for each 10 cm water increment in baseline detrusor pressure at maximal flow rate, the chance of subjective success

increased with a factor 1.3 (Odds Ratio (OR): 1.028; 95%CI: 0.977-1.083). Per 10 ml/sec increments in maximal flow rate, the change for success increased with 1.7 (OR: 0.947; 95%CI: 0.804-1.112). A 30% higher baseline bladder voiding efficiency score was found to result in 1.7 times more chance for patients to notice success. A multivariate analysis combining four urodynamic factors (maximal detrusor pressure, maximal flow rate, bladder voiding efficiency, and BCI) revealed a predictive power of 0.73 (OR: 0.73; 95% CI 0.51, 0.94) (See Figure 1).

Figure 1 Univariate logistic regression analysis of baseline characteristics to calculate predictive value for subjective success



Side-effects No serious side-effects were reported. Transient pain at the stimulation site was noticed. Diarrhoea, headaches, calf cramps and low back pain were reported. One patient did not complete the treatment because of aggravating pre-existent heart rhythm problems. However these adverse effects were considered not to be related to PTNS.

Discussion

The primary outcome measure was obtained in 41% of all patients (percentage based on intention-to-treat). An additional 26% of patients noticed a reduction in 24 hr total catheterized urine by 25-50%. The total of these 2 figures (67%) is comparable with the subjective response rate (59%). Nearly all responders also diminished their 24 hr residual volume with more than 25%. PTNS resulted in 15/39 patients with a mean catheterized volume smaller than 100 ml and even the two patients that had zero residual after catheterization, still continue catheterization. Presumably these patients wanted to be on the safe side by checking once daily their residuals. Since PTNS is a young treatment modality, optimal stimulation parameters still have to be searched for. More adequate stimulation specified for voiding dysfunctional patients and directly placed on the tibial nerve, could hopefully lead to catheterization free results. The intention of this study was to determine more objective indicators of a successful outcome, namely, derived from urodynamic investigations. The total cystometric capacity in patients did not change at all, most patients had a normal bladder capacity before entering the study and this remained unchanged.

Surprisingly more DI were detected in patients with voiding dysfunction after the 12 weekly sessions (from 14 to 37% of patients urodynamically investigated). Perhaps DI is an essential feature for a good outcome in PTNS for bladder emptying problems; the perception of DI may result in an accentuated awareness of bladder filling and this is believed to “train” the complex neural regulation system of voiding. Although eight out of the 10 patients with DI considered their treatments as successful, the number of participants is too small to draw conclusions from these DI-related data. Moreover, the value of the presence or absence of DI should be further investigated as some even question the whole concept of DI since this phenomenon can be seen in asymptomatic persons.¹² This study found improvement in detrusor pressure at maximal flow, maximal flow rate, cystometric residual volume and bladder indices. The BCI increased for most participants but left the main part of patients in the “weak detrusor” classification, suggesting that PTNS is not acting strongly on the detrusor muscle itself. Unfortunately EMG records of the pelvic floor and urethral striated sphincter were not available, it might be possible that PTNS also improves the detrusor-sphincter coordination. Uni- and multivariate analysis revealed

no spectacular results: participants with only minor voiding dysfunction were more prone to be successful. It seems therefore that patients with minimal voiding dysfunction are good candidates for PTNS. PTNS results in improved voiding parameters, higher quality of life and a high subjective response rate.

PTNS is believed to relieve symptoms related to bladder over- and underactivity, a phenomenon also seen in Sacral Nerve Stimulation SNS.^{5,13-15} The underlying neurophysiological mechanisms of such a bi-polar effect have not yet been elucidated. The result achieved by SNS returns to baseline values after switching off the device, as opposed to long-term effect of a few weeks after stimulation by PTNS.^{5,15,16} Schultz-Lampel et al.¹⁷ confirmed by cat experiments the hypothesis of a rebound phenomenon as mechanism of action for induction of spontaneous voiding in patients with chronic retention.

The long-term effect through PTNS could be explained by the carry-over effect found in cat experiments where a 5-min stimulation of afferent nerves resulted in more than 1 hr lasting effect.¹⁸ In rats, PTNS exerted its influence on c-fos expression suggesting neuromodulating action.¹⁹ Presumably the combination of needling (resulting in a higher concentration of certain neurotransmitters), bladder retraining by completing voiding charts and induction of DI in some patients, and to some extent the attribution of a placebo-effect (meeting fellow sufferers, having a very intensive guidance and attention given by medical care-givers) finally results in a higher voiding efficacy.

PTNS is a cheap treatment modality, minimally invasive, and with a simple accessible stimulation site. However, in daily practise some logistic problems appeared, PTNS is a time consuming procedure both for clinicians and for patients. Positive responders need to have PTNS on a regular basis, hereby occupying precious out patient clinical time to treat new patients. Most investigators limit the number of sessions for this reason. In our clinic we started to train positive responders how to insert the needle themselves and how they can apply the stimulator at home. Besides more basic research investigating optimal parameters, development of an implantable stimulator might be very useful and every effort to conduct a placebo controlled or sham study should be encouraged.

In conclusion, PTNS is an attractive young treatment modality for patients with minor chronic voiding disorders, requiring further research to establish optimal stimulation parameters.

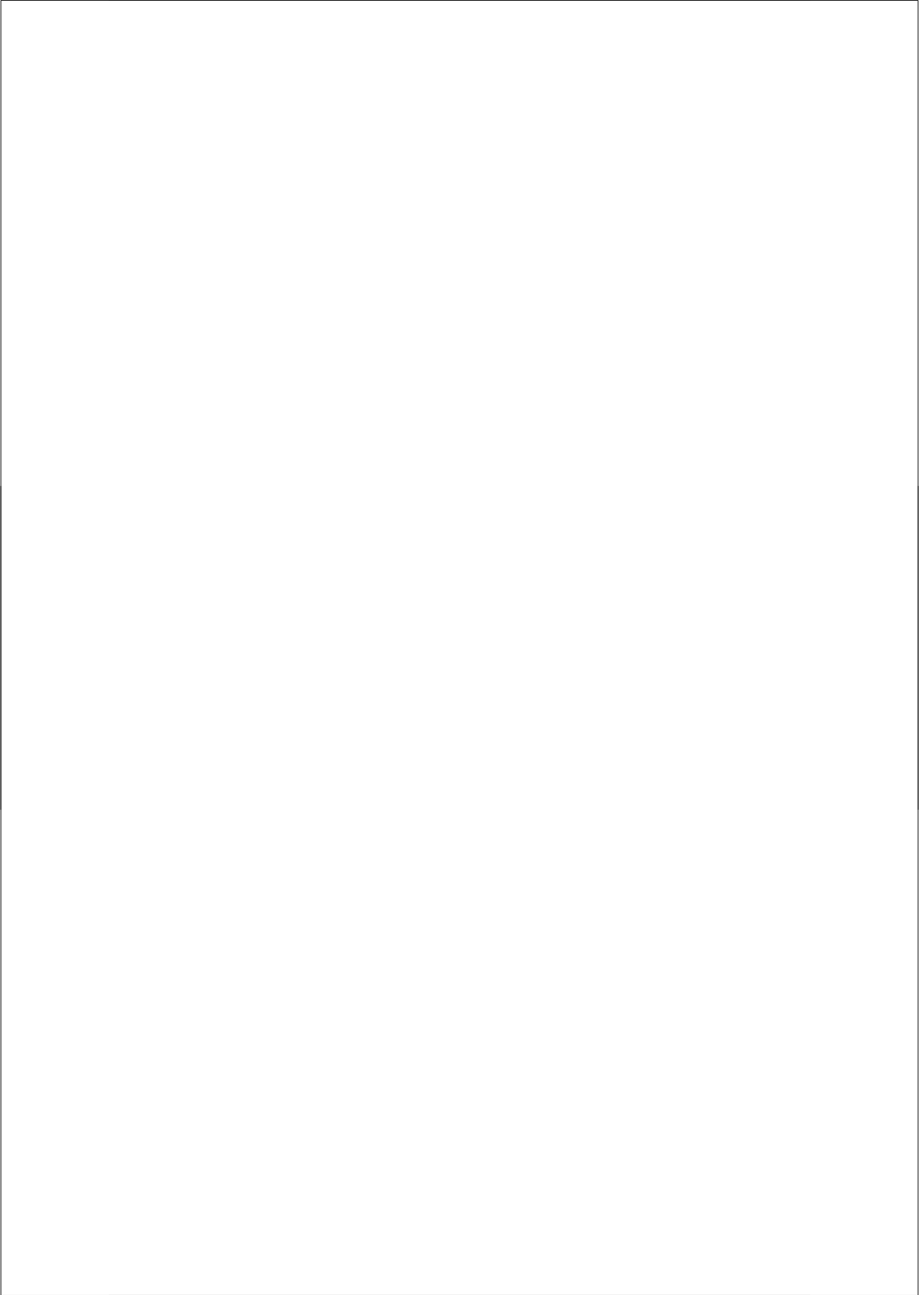
Acknowledgments

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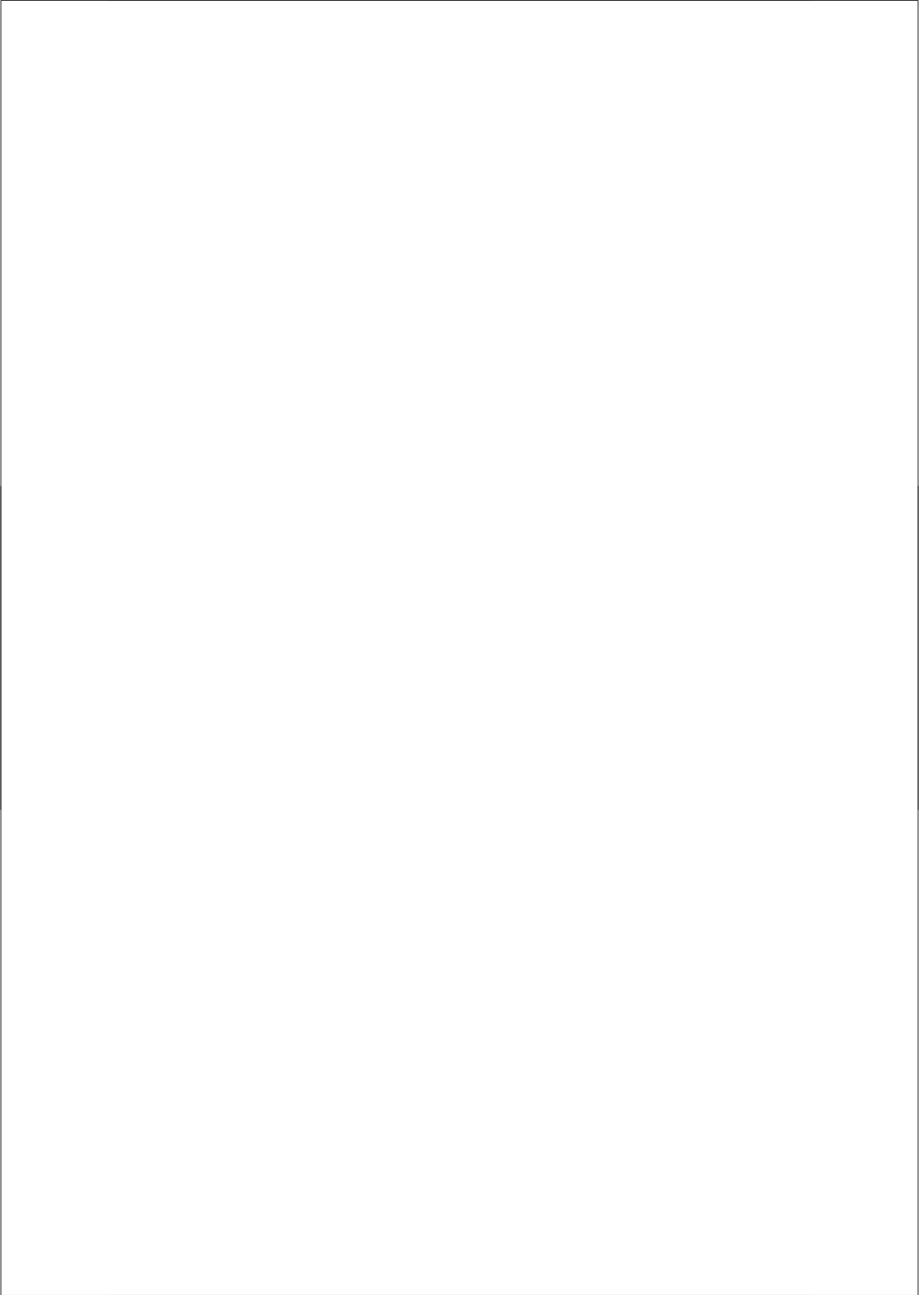
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CHAPTER 4

Prognostics and maintenance



Prognostic factors for successful percutaneous tibial nerve stimulation

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Abstract

Objective In sacral as well as tibial nerve stimulation test stimulation is the main prognostic factor for success. In our study we tried to identify prognostic patient characteristics to improve patient selection for neuromodulation therapy.

Patients and methods PTNS was applied to 132 patients in 8 study centers (51 men, 81 women, mean age of 53 years (range: 21-82)). 83 patients were treated for overactive bladder, 16 for non-obstructive urinary retention and 33 for chronic pelvic pain. All patients had to fill out micturition or pain diaries, as well as quality of life questionnaires before and after treatment. Patient characteristics were evaluated for their prognostic value for successful outcome of neuromodulation therapy with use of logistic regression.

Results Objective success was seen in 32.6% of patients, subjective success in 51.5%. Most evaluated clinical parameters proved not to be of prognostic value. A history of sexual and/or physical abuse was found in 12 of 103 interviewed patients, but did not alter PTNS treatment outcome.

However, a low total score at baseline in the SF-36 questionnaire proved to be predictive for not obtaining objective (OR 0.444 [95% CI: 0.198-0.996], $p=0.04$) or subjective success (OR 0.424 [CI: 0.203-0.887], $p=0.02$). Especially patients with a low SF-36 Mental Component Summary were prone to fail neuromodulation therapy: OR 0.123 (95% CI: 0.273-0.552), $p=0.006$ for objective success. These patients also scored worse on disease-specific quality of life questionnaires, although they had no different disease severity compared to patients with good mental health.

Conclusions Bad mental health as measured with the SF-36 Mental Component Summary does not depend on symptom severity and is a negative predictive factor for success of percutaneous tibial nerve stimulation. It therefore might be used as a tool for better patient selection in neuromodulation therapy.

Introduction

In Sacral Neurostimulation (SNS), the result of Percutaneous Nerve Evaluation (PNE) prior to definitive implantation is the most important prognostic factor for success. Efforts to establish other predictive parameters were not very successful, why at present most is expected from refining the PNE technique. Likewise in Percutaneous Tibial Nerve Stimulation (PTNS), the justification of chronic treatment (e.g. by implantation of a subcutaneous stimulation device) is also evaluated through test stimulations. In our study we tried to identify prognostic patient characteristics to improve patient selection for neuromodulation therapy in the future.

Patients and methods

Patients After approval of the ethical committee, PTNS was applied to 132 patients in 8 study centers. The study group consisted of 51 men and 81 women, with a mean age of 53 years (range: 21-82). Mean age of men (53.2 years, range: 21-79) and women (53.2 years, range: 23-82) did not differ significantly. Sixteen patients (7 male, 9 female) were treated for non-obstructive urinary retention, 33 (21 male, 12 female) for Chronic Pelvic Pain (CPP) and 83 (23 male, 60 female) for Overactive Bladder (OAB). Median duration of lower urinary tract complaints was 4 years (range: 1-56). No statistical significant differences in median duration of symptoms were seen between sexes or treatment indications. Physical examination did not show overt (neurourological) abnormalities in any of these patients. More detailed patient characteristics are given in table 1.

Method of treatment PTNS was applied according to Stoller and Govier.^{1,2} A 34 gauge needle percutaneously inserted approximately 3-4 cm cephalad to the medial malleolus and a stick-on electrode placed on the same leg near the arch of the foot were used for electrical stimulation with an adjustable pulse intensity (0-10 mA), a fixed pulse width of 200 μ sec and a frequency of 20 Hz. The stimulator contained a battery of 9 V (Urgent PC[®], CystoMedix, Anoka, MN, USA). When an adequate motor response, mostly accompanied by a specific sensory response, was obtained,

Table 1 Patient characteristics

	All N=132	OAB N=83	CPP N=33	NOUR N=16
Men/women	51/81	23/60	21/12	7/9
Mean age ¹	53.3 (21-82)	54.1 (21-82)	51.9 (25-79)	51.3 (25-68)
Median history ¹	4 (1-56)	4 (1-56)	4 (2-30)	3 (1-36)
Previous medications ²	2 (0-5)	2 (0-5)	2 (1-4)	1 (0-2)
Previous operations ²	0 (0-3)	0 (0-3)	0 (0-2)	0 (0-1)
Previous physiotherapy	60 (45.5%)	39 (47.0%)	18 (54.5%)	3 (18.8%)
Previous electrotherapy	18 (13.6%)	9 (10.8%)	8 (24.2%)	1 (6.3%)
Frequency ³		15.0 (4-41)		
Incontinence episodes ³		6.4 (0-22)		
Catheterizations ³				4.9 (2-10)
VAS for Pain ⁴			64.9 (22-100)	
I-QoL ⁴		60.8 (22-100)		
Adjusted I-QoL ⁴				81.8 (38-100)
PRI-total (McGill) ⁴			21.7 (5-50)	
Mean stimulation ⁵	3.4 (1.3-7)	3.4 (1.4-6.8)	3.1 (1.3-5.5)	3.7 (1.3-7)
Subjective response	51.5%	55.4%	32.4%	50%
Objective response	32.6%	37.3%	24.2%	25%

OAB = Overactive Bladder, CPP = Chronic Pelvic Pain, NOUR = Non-obstructive Urinary retention, VAS = Visual analogue Scale, I-QoL = Incontinence Quality of Life, PRI = Pain Rate Intensity, ¹years (range), ²number (range), ³mean number/24 hours (range), ⁴mean score (range), ⁵mA (range)

stimulation current was set at a well-tolerable level. Patients underwent 30-minutes outpatient treatment sessions weekly for a period of 12 weeks. In case of sufficient improvement of their lower urinary tract symptoms patients were offered chronic treatment.

Evaluation of results After informed consent, all patients had to fill out micturition or pain diaries as well as general (SF-36 ³) and disease-specific quality of life questionnaires (McGill Pain Questionnaire Dutch Language Version ⁴ and (adjusted) I-QoL ⁵) at study entry and at completion of treatment at 12 weeks. Furthermore, patient characteristics at baseline were collected as history of complaints, earlier treatment modalities, weight and Body Mass Index. To determine a history of sexual

and/or physical abuse, patients were interviewed by their investigating urologist according to a standardized question form. Also parameters as stimulation intensity and center of treatment were evaluated.

Subjective response was defined as the request of patients for continuous chronic treatment to keep the obtained response, objective success as a decrease in symptoms (i.e. number of voids/24 hours, number of incontinence episodes/24 hours, number of catheterizations/24 hours or score on the Visual Analogue Scale for pain) of over 50%.

Within-group analysis of results were conducted by the non-parametric Wilcoxon signed ranks test for two related samples, subgroup analysis by the non-parametric Mann-Whitney U-test for two independent samples. Patient characteristics were evaluated for their prognostic value for successful outcome of neuromodulation therapy with use of logistic regression (Odds ratio, 95% Confidence Interval, (OR [95% CI]). Tests were performed on a two-tailed basis and the level of significance was set at 5%. Statistical analysis was performed using Statistical Package for the Social Sciences version 9.0 software (SPSS, Chicago, ILL, USA).

Results

Objective success was seen in 32.6% of all patients, subjective success in 51.5%. For OAB these figures were 37.3% and 55.4%, for CPP 24.2% and 42.4% and for non-obstructive urinary retention 25% and 50%, respectively. Gender, age, weight, Body Mass Index, indication for PTNS, duration of complaints, number and kind of treatments used before, PTNS study center and stimulation parameters all statistically proved not to be of prognostic value. The same goes for number of incontinence episodes per 24 hours, frequency per 24 hours, number of catheterizations per 24 hours, pain intensity (Visual Analogue Scale for pain) and total scores at the (adjusted) I-QoL and McGill disease-specific quality of life questionnaires.

As one study center did not wish to participate in the collection of data on a possible history of sexual and/or physical abuse (SPA), only data on 103 patients were available (table 2). Of these 103 patients, 12 (11.7%) confirmed a history of abuse. Sexual abuse was more likely to have serious impact on patients' lives at present

(87.5%), compared to cases in which only physical abuse was involved (25%, $p < 0.05$). Nevertheless, a history of sexual and/or physical abuse did not negatively influence PTNS treatment results.

Table 2 Patient characteristics of victims of sexual and/or physical abuse

	Sex	Age (years)	Form of abuse	Age at onset sexual abuse	Current impact of abuse	Form of LUTD	Subjective Response	Objective Response
Patient 1	M	40	Physical		No	Pain	No	No
Patient 2	M	30	Physical		No	OAB	No	Yes
Patient 3	M	57	Physical		Yes	OAB	Yes	No
Patient 4	F	74	Physical		No	OAB	No	No
Patient 5	M	61	Sexual	18	Yes	OAB	No	No
Patient 6	F	29	Sexual	8	Yes	OAB	Yes	Yes
Patient 7	F	43	Sexual	18	No	OAB	Yes	No
Patient 8	F	54	Sexual	12	Yes	OAB	No	No
Patient 9	F	53	Sexual	Not known	Yes	Retention	No	No
Patient 10	M	49	Physical/sexual	10	Yes	Pain	Yes	Yes
Patient 11	F	25	Physical/sexual	11	Yes	Pain	No	No
Patient 12	F	48	Physical/sexual	7	Yes	Retention	Yes	Yes

When evaluating the SF-36 questionnaires, a low total score at baseline (≤ 50 out of a maximum of 100 points) proved to be predictive for not obtaining objective (OR 0.444 [95% CI: 0.198-0.996], $p=0.04$) and/or subjective success (OR 0.424 [95% CI: 0.203-0.887], $p=0.02$). The SF-36 questionnaire can also be divided in Physical and Mental Component Summaries (PCS and MCS). The PCS did not prove to be of prognostic value, but patients with a low MCS (≤ 30 out of a maximum of 50 points) were very likely to objectively fail neuromodulation therapy (OR 0.123 [95% CI: 0.273-0.552], $p=0.006$) (table 3). Although disease-specific quality of life questionnaires themselves proved not to be of prognostic value, OAB and CPP patients with a low MCS scored significantly worse on the I-QoL and McGill questionnaires respectively. In OAB patients with a low MCS the I-QoL score was 46.5 +/- 13.69 versus 64.69 +/- 19.51 in patients with a good mental health (the higher, the better, $p < 0.005$). CPP patients with a MCS ≤ 30 scored a total Pain Rate Intensity on the McGill questionnaire of 32.63 +/- 6.02 versus 16.25 +/- 8.58 for CPP patients with a

high MCS (the lower, the better, $p < 0.05$). However, patients with a bad mental health had no statistical worse disease severity when measured by number of voids, incontinence episodes, catheterizations or the VAS for pain.

Table 3 Prognostic value of tested parameters

Parameter	Subjective response (OR (95% CI) significance)	Objective response (OR (95% CI) significance)
Gender (male/female)	0.748 (0.370-1.509) ns	0.729 (0.341-1.560) ns
Age ($\leq 70 / > 70$ years) ¹	2.917 (0.865-9.832) ns	1.267 (0.373-4.305) ns
Weight ($\leq 70 / > 70$ kg) ¹	0.915 (0.398-2.101) ns	0.754 (0.313-1.817) ns
Body Mass Index ($< 25 / \geq 25$) ¹	0.821 (0.362-1.862) ns	0.846 (0.357-2.003) ns
Duration of complaints ($< 1 / \geq 1$ year) ¹	0.698 (0.227-2.143) ns	0.584 (0.151-2.251) ns
Previous medication (y/n)	0.349 (0.065-1.872) ns	0.740 (0.137-3.988) ns
Previous operations (y/n)	0.972 (0.477-1.978) ns	0.547 (0.257-1.165) ns
Previous physiotherapy (y/n)	1.110 (0.555-2.220) ns	1.058 (0.504-2.218) ns
Previous electrotherapy (y/n)	0.912 (0.336-2.474) ns	0.678 (0.224-2.049) ns
Previous alternative therapies (y/n)	0.759 (0.335-1.722) ns	0.499 (0.194-1.280) ns
Indication (OAB/rest)	1.526 (0.750-3.104) ns	1.991 (0.902-4.398) ns
Indication (CPP/rest)	0.614 (0.277-1.361) ns	0.549 (0.223-1.347) ns
Indication (retention/rest)	1.071 (0.377-3.048) ns	1.603 (0.484-5.303) ns
VAS score in CPP ($\leq 50 / > 50$) ¹	0.667 (0.135-3.303) ns	1.056 (0.167-6.679) ns
Frequency in OAB ($\leq 8 / > 8$) ^{1,2}	1.000 (0.999-1.001) ns	1.000 (0.999-1.002) ns
Incontinence in OAB ($\leq 3 / > 3$) ^{1,2}	1.161 (0.697-1.935) ns	1.746 (0.610-5.000) ns
CIC in retention ($\leq 4 / > 4$) ^{1,2}	2.222 (0.280-17.63) ns	2.750 (1.258-6.010) ns
PRI-totaal in CPP ($\leq 30 / > 30$) ¹	1.001 (0.999-1.002) ns	1.000 (0.998-1.002) ns
I-QOL in OAB ($\leq 50 / > 50$) ¹	2.071 (0.724-5.927) ns	0.752 (0.256-2.212) ns
I-QOL in retention ($\leq 50 / > 50$) ¹	1.000 (0.999-1.001) ns	1.000 (0.997-1.002) ns
SF-36 total score ($\leq 50 / > 50$)	0.424 (0.203-0.887) $p = 0.02$	0.444 (0.198-0.996) $p = 0.04$
SF-36 PCS ($\leq 30 / > 30$)	1.719 (0.779-3.797) ns	1.797 (0.746-4.328) ns
SF-36 MCS ($\leq 30 / > 30$)	1.835 (0.771-4.372) ns	0.123 (0.273-0.552) $p = 0.006$

OR = Odds Ratio, CI = Confidence Interval, Ns= not significant, y/n = yes/no, OAB = Overactive Bladder, CPP = Chronic Pelvic Pain, VAS = Visual Analogue Scale (≤ 100), CIC = Clean Intermittent Catheterization, I-QOL = Incontinence Quality Of Life (≤ 100), PRI = Pain Rate Intensity (McGill) (≤ 50), PCS = Physical Component Summary (≤ 50), MCS = Mental Component Summary (≤ 50), ¹other border values were also tested, proven not significant as well, and therefore not shown in this table, ²number/episodes per 24 hours

Discussion

To refine the PNE technique, the results of which mainly determine the success of SNS, the two-stage procedure⁶ is developed. In this procedure, a permanent lead is implanted and temporarily connected to an external stimulator for an evaluation period of 4 days. Subsequently, a permanent subcutaneous stimulator is implanted in case of success. In patients considered a failure of conventional PNE-testing, an improvement of 60-90% could be achieved by the two-stage procedure.

Various clinical parameters were evaluated for their prognostic value. However, age, duration of complaints, number and kind of former treatments, indication for neuromodulation therapy and different neurostimulation parameters were not proven to be predictive for treatment outcome.⁷⁻⁹ Although some studies suggest the opposite^{7,10}, overall, neither gender seems to influence treatment outcome.^{8,9} The only factor rather consistently reported to predict poor treatment outcome is the history or presence of psychological disorders or poor mental health.^{9,11,12}

As PTNS is a relatively new neuromodulation modality, only scarce data are available on parameters influencing its therapy success. Therefore, as in SNS, trial sessions are recommended to evaluate the justification of maintenance therapy. Especially regarding the development of a subcutaneous implant¹³, accurate prognostic parameters to predict success of treatment minimizing unnecessary laborious trial sessions will be helpful.

In our recent international multicenter studies on PTNS, overall baseline urodynamic features failed to reach statistical significant predictive power in univariate analysis.^{14,15} This may be due to rather small study groups. Nevertheless, in OAB patients it was strongly suggestive that patients with detrusor instability (DI) do worse on PTNS compared to those with stable bladders, as did patients with low bladder volumes at DI or with very small bladder capacity at baseline.¹⁴ In patients with voiding dysfunction only multivariate analysis combining maximal detrusor pressure, maximal flow rate, bladder voiding efficacy and bladder contractility index at baseline showed statistical significant predictive power.¹⁵

In this study on various clinical parameters in a much larger group of patients, most parameters did not influence the outcome of neuromodulation therapy. This is in concordance with what is known in SNS¹⁶ and earlier studies on PTNS.^{17,18} It means that old patients, patients with severe symptoms and patients with a long

history of complaints should not be ruled out for therapy, like patients with a high Body Mass Index, because even in those patients the tibial nerve can well be reached for stimulation. Stimulation intensity probably is not of prognostic value because high intensity parameters are more indicative for less well positioning of the stimulation needle than for actual higher stimulation of the nerve itself. Although it is generally accepted that OAB and non-obstructive urinary retention are better indications for neuromodulation than CPP, in this study the actual indication for therapy proved not to be a prognostic factor, possibly caused by the relatively small number of patients with non-obstructive urinary retention and CPP respectively.

Our earlier studies revealed success rates up to 70%^{17,18}, much higher than was found here. It should be mentioned that those studies were performed in only a few high volume centers. The data presented in this paper are pooled data from our own center with those from several low volume hospitals in the Netherlands, that all performed PTNS using the same protocol. Results in this added centers were worse, although not statistically significant. Nevertheless, these low success rates emphasize the need for pre-PTNS selection criteria investigated in our study to increase overall success rates and decrease the number of unnecessarily treated patients.

In our selected group of patients, almost 12% admitted a history of sexual and/or physical abuse. For the Dutch population comparable figures are only available from patients for the first time visiting a gynecological outpatient clinic, revealing former sexual abuse in 15.4% and physical abuse in 7.4% of patients. Whether there was some degree of overlap was not mentioned.¹⁹ Comparison of our data with general data from the Dutch population is hampered by major discrepancies between frequencies found in national registration systems, surveys in an open population and studies in general practice, respectively.²⁰ Data of few international reports dealing with former SPA are neither useful to evaluate our findings as they are mainly restricted to patients with CPP in which prevalences of sexual abuse merely may be as high as 64%.^{21,22} Despite what one might expect however, a history of SPA did not influence the chances for a successful outcome of PTNS in a negative way, not even in patients still experiencing consequences of this abuse at present.

Nevertheless, the results of our study corroborates with general clinical experience that patients who mentally suffer the most from their complaints are less susceptible to successful outcome of treatment. These patients proved not to have more severe symptoms, but they considered their disease-specific quality of life worse than did

patients with good mental health. Whether bad mental health is caused by the complaints or contributes to their origin remains unanswered, but measuring mental health with the SF-36 Mental Component Summary may be a useful tool for better patient selection for neuromodulation therapy. We recommend further studies on this particular issue to reaffirm our findings so that in the future patients with bad mental health can be informed about the poor chances for success or even can be excluded from neuromodulative therapy.

Conclusions

Bad mental health is a negative predictive factor for success of percutaneous tibial nerve stimulation and depends not on symptom severity. As the same was suggested in an earlier study on sacral neurostimulation, the SF-36 Mental Component Summary might be used as a tool for better patient selection in neuromodulation therapy.

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**Percutaneous Tibial Nerve Stimulation (PTNS)
in the treatment of refractory overactive
bladder syndrome: is maintenance treatment a
necessity?**

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Abstract

Objective To determine the effect of pausing Percutaneous Tibial Nerve Stimulation (PTNS) in successfully treated patients and the reproducibility of successful treatment.

Patients and methods 11 patients (mean age 51 years) with refractory overactive bladder syndrome (> 7 voids and/or ≥ 3 urge incontinence episodes per day) were successfully treated with PTNS and continued treatment. Patients filled out bladder diaries and quality of life questionnaires (SF-36 and I-QoL) before (T1) and after a 6-week pause (T2) of maintenance PTNS and again after re-treatment (T3). The first objective was defined as $\geq 50\%$ increase of the number of incontinence episodes and/or micturition frequency on bladder diary after the 6-week pause of maintenance PTNS. The second objective was defined as a $\geq 50\%$ reduction of the number of incontinence episodes and/or micturition frequency on bladder diary after re-treatment.

Results At T2, 7/11 patients (64%) had a $\geq 50\%$ increase of the number of incontinence episodes and/or micturition frequency on bladder diary after the 6-week pause of maintenance PTNS. Mean voided volume, nocturia, number of incontinence episodes and incontinence severity had significantly ($p < 0.05$) deteriorated. At T3, 9/11 patients (82%) had a $\geq 50\%$ reduction of the number of incontinence episodes and/or micturition frequency on bladder diary after re-treatment. Nocturia, number of incontinence episodes, incontinence severity, mean voided volume and quality of life had significantly ($p < 0.05$) improved.

Conclusions Continuous therapy is a necessity in successfully PTNS treated patients. The efficacy of PTNS can be reproduced in formerly successfully treated patients.

Introduction

Percutaneous Tibial Nerve Stimulation (PTNS) is an alternative therapy for refractory non-neurogenic lower urinary tract dysfunction.¹ After successful treatment patients are put on maintenance therapy.² So far there have been no reports on long-term results in treatment of patients with overactive bladder syndrome (OAB), nor are any data available on the effect of prolonged interruption of the maintenance treatment, nor concerning the question if the efficacy of the therapy can be reproduced.

The present study was performed to evaluate the effect of prolonged interruption of the maintenance therapy on the complaints of patients with overactive bladder syndrome. A second goal was to investigate whether the efficacy of the therapy can be reproduced.

Patients and methods

Methods Between November 2003 and January 2004, 11 patients were enrolled in a clinical trial. Patients were evaluated at the outpatients' clinic for overactive bladder syndrome (OAB) by history and physical and urological examination, including urodynamic evaluation. Methods, units and definitions used in this study meet the standard recommended by the International Continence Society,³ except for the 24-hour bladder diaries.⁴ These bladder diaries are sufficient to evaluate the patients' micturition complaints.⁵⁻⁷

OAB was defined as more than 7 voids per day and/or a sudden insuppressibly urge to void, culminating in urinary leakage at least 3 times per day on bladder diary. All medication that could influence bladder function was stopped at least 2 weeks before treatment or continued without dosage changes during the entire study. Specific exclusion criteria for PTNS as described by van Balken et al. were used (see table 1).¹

Patients All patients, 5 men and 6 women with a mean age of 51 years (range 33-66), were diagnosed with OAB (2 patients had urgency/frequency syndrome and 9 patients had urge urinary incontinence). All patients were refractory to conservative

Table 1 Exclusion criteria

Younger than 18 years
Symptoms existing for less than 6 months
Pregnancy or intention to become pregnant during the course of the study
Active urinary tract or recurrent urinary tract infection (5 or more recurrent infections during the last 12 months), carcinoma in situ, bladder malignancy, interstitial cystitis
Bladder or kidney stone
Severe cardiopulmonary disease
Use of pentosan polysulfate sodium or bladder installations, including dimethyl sulfoxide, Bacillus Calmette-Guerin, chloropectin or heparin
Uncontrolled diabetes
Diabetes with peripheral nerve involvement
Neurological disease like multiple sclerosis, Parkinson's disease, cerebrovascular accident, bifid spine or spinal cord lesion
Physiotherapy during the study
Bladder outlet obstruction (Abrams-Griffiths nomogram)
Transurethral instrumentation 4 weeks or less before or during the study

treatment. Oral medication was unsuccessful in all and patients had had mean 3 prescriptions (range 1-8) for their complaints. Mostly anticholinergics, alpha-blockers, antidepressants, antibiotics, and desmopressin were prescribed. 6 patients were treated with physiotherapy or bladder training, 5 with sacral nerve stimulation and 4 with other treatments, all unsuccessfully. 4 patients had had unsuccessful surgical treatment (range 1-2 operations). The performed surgical therapies were colposuspension, urethra dilatation, bladder distension, bulk injections and transurethral resection of the prostate.

All patients were previously successfully treated with PTNS ($\geq 50\%$ reduction of incontinence episodes and/or micturition frequency on bladder diary) and had continued treatment. 5 patients had maintenance PTNS in an outpatients setting, and all were diagnosed with urge urinary incontinence. 6 patients performed self-administrated home treatment, either by transcutaneous stimulation with 2 surface electrodes (5 patients) or percutaneous tibial nerve stimulation (1 patient). Of these patients 4 were diagnosed with urge urinary incontinence and 2 patients with urgency/frequency syndrome. Maintenance therapy was performed during a mean period of 13 months (range 1-36 months).

Method of treatment All patients paused maintenance PTNS for a period 6-week, and were re-treated after this period in outpatients' setting. PTNS was performed as described by van Balken et al. ¹ A low-voltage (9V) stimulator (Urgent-PC™, CystoMedix Inc, Anoka, MN, USA) was used. The stimulator had an adjustable stimulation intensity 0-10 mA and fixed stimulation parameters: pulse width 200 microseconds, stimulation frequency 20 Hz. All patients had a sensory response to the stimulation: a radiating sensation at the sole of the foot and in the toes. Stimulation at the intensity of the motor response was too painful for almost all patients, so the current was set at a well-tolerable level resulting in the sensory response. If patients had adapted to the stimulation the current was adjusted, usually as soon as the sensation faded away. Patients were treated with 30-minute treatment sessions 3 times a week during a 4-week period. PTNS was performed on Monday, Wednesday and Friday of each week.

Evaluation of results At baseline (before the 6-week pause of maintenance PTNS, T1) patients were evaluated by 24-hour bladder diaries, as well as general (36-item short-form health survey, SF-36) ⁸ and disease specific quality of life (incontinence-specific quality of life assessment, I-QoL) questionnaires. ⁹ This procedure was repeated after the 6-week pause (T2), and after PTNS re-treatment (T3). In the bladder diary micturition frequency, voided volume (cc), number of incontinence episodes, severity of urine loss and the number of used pads were recorded. The severity of urine loss was described on a scale of 0-3 (i.e. 0– no urine loss, 1– loss of some drops, 2– loss of small amount and 3– change of clothes due to urine loss). The first objective was defined as $\geq 50\%$ increase of the number of incontinence episodes and/or number of voids on bladder diary after the 6-week interruption of the maintenance PTNS. The second objective was defined as $\geq 50\%$ reduction of the number of incontinence episodes and/or number of voids on bladder diary after PTNS re-treatment. Comparison of the results before and after pausing maintenance PTNS and re-treatment were conducted with the Wilcoxon signed Ranks Test; the statistical analysis was performed with commercial software (SPSS version 10, Chicago, IL, USA).

Results

At T1 (before the 6-week interruption of maintenance PTNS), the patients who performed self-administrated home treatment (i.e. self-treatment group, 6 patients) tended to have lesser voiding parameters and quality of life compared to the patients who received maintenance treatment in an outpatient setting (i.e. outpatient group, 5 patients) (table 2 and 3). However statistical significance could not be determined since the patient groups were too small.

At T2 (after 6-week pause of maintenance PTNS) 7 out of the 11 patients (64%) met the first objective and had $\geq 50\%$ increase of the number of incontinence episodes and/or number of voids on bladder diary. 2 patients, who performed self-administrated home treatment, had a deterioration of their symptoms but did not meet the first objective and 2 patients had no change of their symptoms on bladder diary, of which 1 performed self-treatment and another had maintenance treatment in an outpatient setting. All patients experienced a subjective deterioration of their symptoms. There was an objective significant deterioration ($p < 0.05$) of nocturia, mean voided volume, and number incontinences episodes and the SF-36 domain pain (table 2 and 3).

The self-treatment group tended to still have slightly lesser voiding and quality of life parameters, compared to the outpatient group. However, statistical significance could again not be determined due to the small patient groups.

During PTNS a mean pulse intensity of 3.8 mA (range 1.6-7.8) was used. Complications of the therapy – minor bleeding or a temporary painful/numb feeling at the insertion site or under the sole of the foot – rarely occurred.

At T3 (after PTNS re-treatment) 9 out of the 11 patients (82%) met the second objective and had a $\geq 50\%$ reduction of the number of incontinence episodes and/or number of voids on bladder diary. 2 patients had no improvement on bladder diary, of which 1 patient performed self-treatment and another had maintenance PTNS in an outpatient setting. 8 patients (73%) did again subjectively improve and wanted to continue the treatment. There was a significant ($p < 0.05$) improvement of nocturia, mean voided volume, number of incontinence episodes, incontinence severity, I-QoL score and the SF-36 domains physical, role emotional, social function, pain and mental health (table 2 and 3).

At T3 (after PTNS re-treatment) the difference with the data at T1 (before the 6-week interruption) tended to be the largest in the self-treatment group. Again statistical significance could not be determined due to the small patient groups.

Table 2 Voiding parameters at T1 to T3 in 11 patients

Parameters per 24 hour	Mean (SD)		
	T1 ¹	T2 ²	T3 ³
Number of voids			
Home ¹	12.5 (7.3)	13.0 (8.3)	8.5 (1.9)
Clinic ²	9.2 (2.9)	10.8 (4.1)	10.0 (3.9)
All patients	11.0 (5.8)	12.0 (6.5)	9.2 (2.9)
Nocturia			
Home ¹	1.7 (1.4)	3.7 (4.2)	0.7 (0.5)
Clinic ²	1.0 (0.7)	2.2 (1.3)	0.6 (0.9)
All patients	1.4 (1.1)	3.0 (3.2)*	0.6 (0.7)*
Mean voided volume (cc)			
Home ¹	190.3 (123.3)	95.8 (62.0)	222.0 (124.2)
Clinic ²	174.0 (60.1)	121.6 (37.1)	146.0 (45.4)
All patients	182.9 (95.5)	107.6 (51.5)*	187.5 (100.6)*
Number of incontinence episodes			
Home ¹	1.3 (2.4)	3.5 (4.5)	1.0 (1.5)
Clinic ²	2.6 (2.7)	12.0 (16.8)	5.6 (6.4)
All patients	1.9 (2.5)	7.4 (12.0)*	3.1 (4.9)*
Incontinence severity³			
Home ¹	0.3 (0.5)	1.2 (1.2)	0.8 (0.5)
Clinic ²	1.0 (0.7)	1.4 (0.5)	0.6 (0.5)
All patients	0.6 (0.7)	1.3 (0.9)	0.6 (0.5)*
Number of used pads			
Home ¹	1.5 (2.0)	2.2 (2.9)	0.7 (1.5)
Clinic ²	2.0 (1.0)	3.6 (2.4)	2.6 (1.5)
All patients	1.7 (1.6)	2.8 (2.6)	1.6 (1.5)*

¹Baseline, ²After 6-week pause of maintenance PTNS, ³After PTNS-retreatment, *p<0.05, ¹6 patients who performed self-administrated maintenance PTNS at home, ²5 patients who had maintenance PTNS in an outpatient setting, ³0= no urine loss, 1= loss of some drops, 2= loss of small amount and 3= change of clothes due to urine loss

Table 3 Quality of life parameters at T1 to T3 in 11 patients

Parameters per 24 hour	Mean (SD)		
	T1 ¹	T2 ²	T3 ³
SF-36 Physical			
Home ¹	80.8 (16.9)	75.8 (28.4)	96.7 (4.1)
Clinic ²	79.0 (21.0)	70.0 (22.1)	81.0 (19.5)
All patients	80.0 (5.4)	73.2 (7.4)	89.5 (4.5)*
SF-36 Role physical			
Home ¹	62.5 (49.4)	45.8 (51.0)	95.8 (10.2)
Clinic ²	55.0 (51.2)	55.0 (51.2)	70.0 (44.7)
All patients	59.1 (14.4)	50.0 (14.7)	84.1 (9.7)
SF-36 Role emotional			
Home ¹	94.5 (13.6)	61.1 (39.0)	94.5 (13.6)
Clinic ²	73.3 (43.5)	66.8 (40.8)	93.3 (14.9)
All patients	84.9 (9.4)	63.6 (11.4)	93.9 (4.1)*
SF-36 Social function			
Home ¹	66.7 (20.4)	58.3 (30.3)	81.3 (19.0)
Clinic ²	75.0 (23.4)	50.0 (15.3)	80.0 (14.3)
All patients	70.5 (6.4)	54.5 (7.2)	80.7 (4.9)*
SF-36 Pain			
Home ¹	79.5 (27.9)	64.3 (30.7)	82.8 (18.8)
Clinic ²	73.4 (30.6)	51.2 (16.8)	75.0 (25.4)
All patients	76.7 (8.4)	58.4 (7.6)*	79.3 (6.4)*
SF-36 Mental health			
Home ¹	61.3 (12.08)	58.0 (18.5)	72.0 (13.4)
Clinic ²	72.0 (17.2)	69.6 (16.4)	80.0 (14.7)
All patients	66.2 (4.6)	63.3 (5.4)	75.6 (4.2)*
SF-36 Vitality			
Home ¹	60.0 (23.2)	46.7 (24.2)	67.5 (12.9)
Clinic ²	65.0 (25.5)	67.0 (20.8)	71.0 (20.4)
All patients	62.3 (7.0)	55.9 (7.3)	69.1 (4.8)
SF-36 General health			
Home ¹	61.8 (27.8)	56.0 (24.1)	66.3 (12.6)
Clinic ²	64.4 (14.1)	58.4 (26.5)	66.2 (20.5)
All patients	63.0 (6.5)	57.1 (7.2)	66.3 (4.7)
I-QoL			
Home ¹	67.3 (19.7)	61.0 (15.9)	88.0 (15.7)
Clinic ²	80.2 (14.7)	67.0 (23.7)	77.8 (18.3)
All patients	73.2 (18.1)	63.7 (19.0)	83.4 (16.9)*

¹Baseline, ²After 6-week pause of maintenance PTNS, ³After PTNS-retreatment, *p<0.05, ¹6 patients self-administrating maintenance PTNS at home, ²5 patients who had maintenance PTNS in an outpatient setting

Discussion

The present study stresses that maintenance treatment is a necessity in successfully PTNS treated patients. All patients had subjective and 9 out of 11 patients an objective deterioration of complaints after the 6-week pause of maintenance therapy. Moreover, there was a significant deterioration of mean voided volume, nocturia, number of incontinence episodes and quality of life (table 2 and 3). The observation that not all parameters did significantly change is obviously caused by the small patient population. Furthermore, 2 patients did not respond to the interruption of maintenance PTNS or re-treatment. In retrospect, PTNS was probably not effective in these patients.

Another explanation could be that 6 out of the 11 patients who performed self-administrated home therapy – either percutaneous or transcutaneous tibial nerve stimulation – could have done this suboptimally. This is supported by the tendency that the voiding and quality of life parameters of the self-treatment group seemed to be lesser than the outpatient group. Moreover, the difference between the voiding and quality of life parameters at T1 and T3 seemed to be the larger for the self-treatment group than for the outpatient group, however not significant.

The difference between both groups was to be expected, since all patients of the self-treatment group, except one, performed transcutaneous maintenance PTNS. Up till now, no comparing study has been performed to determine whether transcutaneous stimulation is as effective as percutaneous treatment. PTNS seems to be more effective, since the electrical field is created between a stick-electrode and a needle, which is close to the tibial nerve. Low current is needed for the motor response (flexing the big toe and/or fanning of the other toes) and sensory response (a radiating sensation is felt at the sole of the foot and in the toes) to occur. In the case of transcutaneous stimulation, the electrical field is created between two surface stick-electrodes. The current has to overcome the impedance of the skin before it has its effect on the tibial nerve. Therefore, is in theory, for transcutaneous stimulation a larger current needed to evoke the motor and sensory responses compared to the percutaneous needle stimulation. When larger amplitude is applied, more afferent nerves located in the skin are recruited and stimulated, which can lead to a painful sensation. This could result in suboptimal stimulation when patients stimulate themselves at a well-tolerable level.

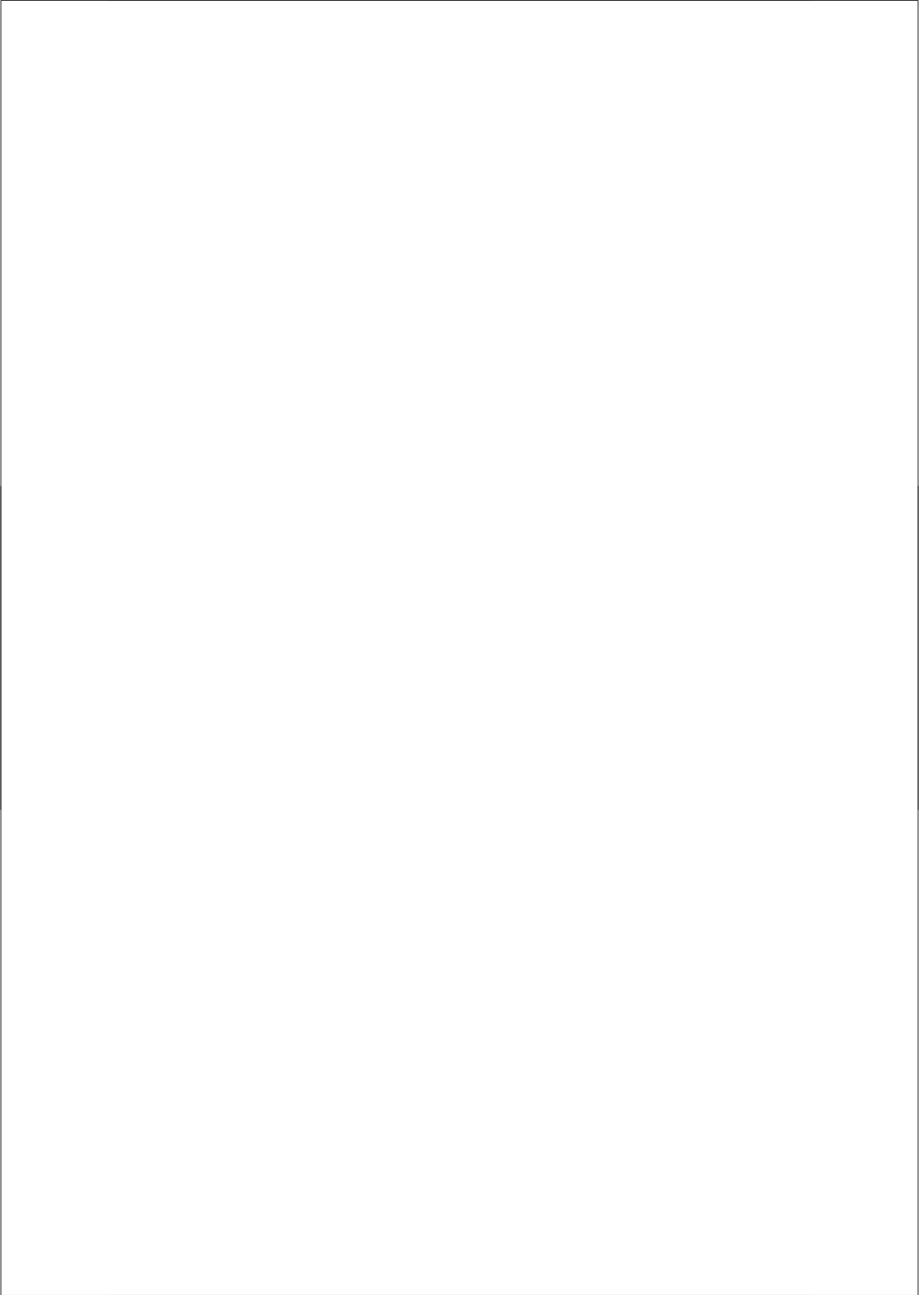
Our results have implications beyond the basic idea that maintenance therapy is indispensable to keep up positive clinical results. Obviously, such maintenance programs put great strains on caregivers and hospital facilities. Each patient that is put on a maintenance schedule will visit the outpatients department at least 20 to 30 times per annum. This problem was the basis for new developments in the field of tibial nerve stimulation. Currently clinical work is undertaken to develop an implantable device that allows a patient to stimulate himself at home as frequently as the individual situation requires. In prospect, this implantable device will lessen the burden on medical professionals and institutions.

Conclusions

Maintenance treatment is to be a necessity in successfully PTNS treated patients, since they experience a subjective and objective deterioration of their complaints when it is not provided. The efficacy of PTNS is reproducible in these patients.

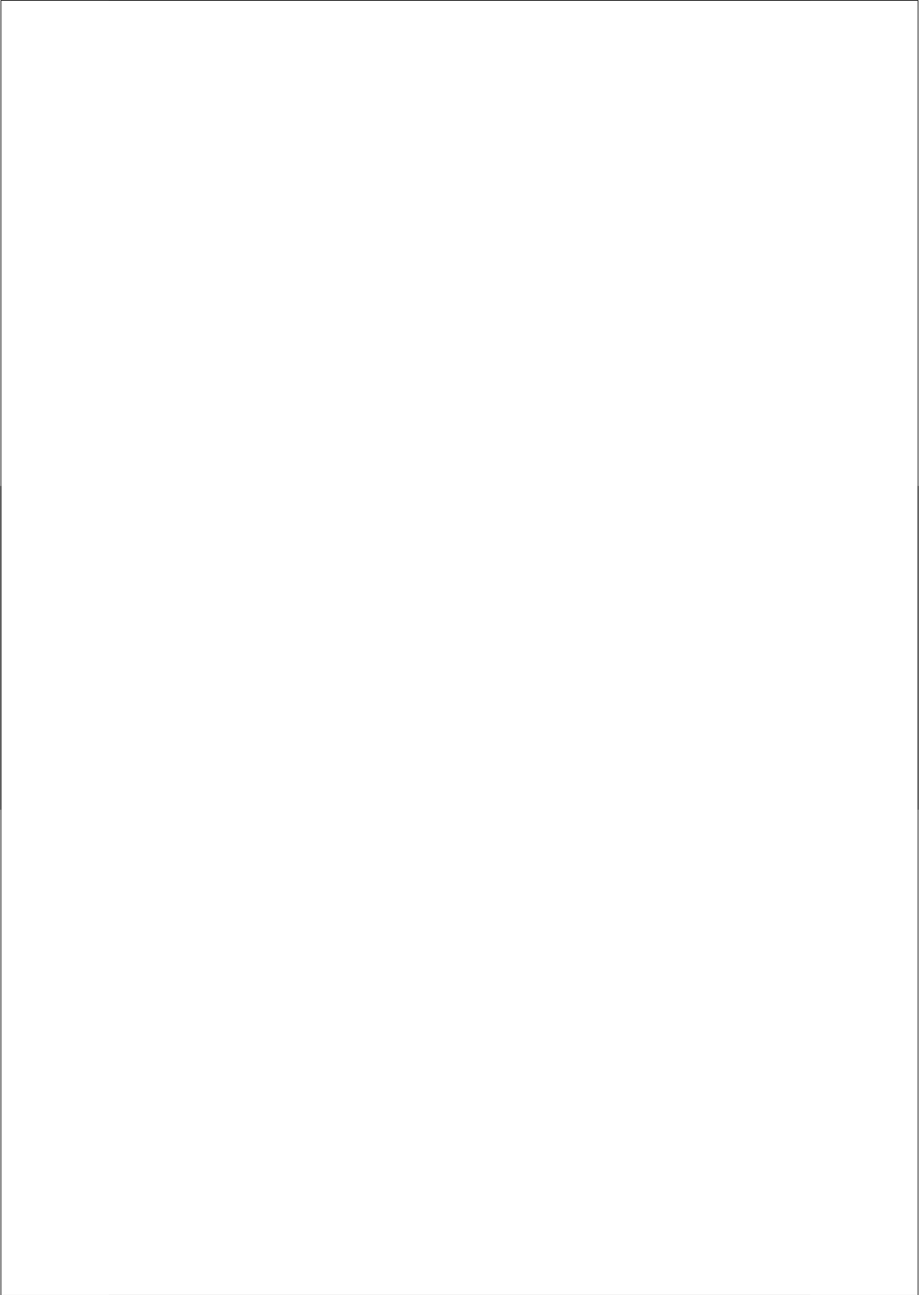
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CHAPTER 5

Towards an implantable device



Implant driven tibial nerve stimulation in the treatment of refractory overactive bladder syndrome: 12-month follow up

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Abstract

Objective To investigate feasibility and safety of implant driven tibial nerve stimulation.

Patients and Methods 8 patients with refractory overactive bladder (OAB) were successfully treated with Percutaneous Tibial Nerve Stimulation and implanted. Patients were evaluated with bladder diaries, quality of life questionnaires, and physical examination before implantation, and at 3, 6 and 12 months of follow up. The primary objective was $\geq 50\%$ reduction of the number of incontinence episodes and/or voids on bladder diary. The Wilcoxon Signed Ranks Test was used.

Results At 3, 6 and 12 months respectively 5, 6 and 4 patients met the primary objective. At 3 and 6-month follow up voiding and quality of life parameters had significantly ($p < 0.05$) improved. Urinary tract infection, temporarily walking difficulties, and spontaneous radiating sensations were reported as adverse events and no local infection, erosion or dislocation.

Conclusions Implant driven tibial nerve stimulation seems to be feasible and safe.

Introduction

Overactive bladder syndrome (OAB, overactive bladder wet and dry) is a common urological problem in many countries. It has been estimated that OAB affects approximately 17% of the adult population in Europe and the United States ^{1,2}, with an estimated worldwide prevalence of 50-100 million. ³ The economic burden of OAB can only be estimated since the disorder is underreported and often overlooked by physicians. ⁴ Total annual costs, including treatment and diagnosis, absorbent products, related medical conditions, assisted living or nursing home care, lost wages and cleaning expenses are estimated to range from \$16 billion to \$26 billion each year in the United States, depending on the studied age group. ^{5,6} In the future the impact of OAB will probably increase even further, since the world population is aging ⁴ and the prevalence increases with age. ⁷

OAB is initially treated with conservative therapy. If refractory, irreversible surgery can be advocated. However, this is not widespread due to high recurrence and complication rates. ⁸ Percutaneous Tibial Nerve Stimulation (PTNS) is an alternative therapy in the treatment of refractory OAB, with reported clinical success rates of 63-71%. ⁸⁻¹⁰ It is known that PTNS maintenance therapy is a necessity in successfully treated patients ¹¹, usually once every 2-3 weeks. ⁹ This is demanding for both patients and outpatient departments. Therefore, it would be advantageous if the patients themselves at the location and time of their choice could perform maintenance therapy. Surface electrodes can be used for tibial nerve stimulation, as has been demonstrated by Andrews. ¹² However, there are indications transcutaneous tibial nerve stimulation may be less effective than percutaneous stimulation. ¹³

Ongoing research has led to the design and development of an innovative subcutaneous implant – Urgent-SQ™ (CystoMedix Inc., Anoka, MN, USA) – that enables self-treatment. This pilot study presents results concerning the feasibility and safety at 12 months of follow up in 8 patients with refractory OAB.

Patients and methods

Methods With the approval of the institutional review board 8 patients with refractory OAB were enrolled in a prospective pilot study between November 2002 and January 2004. All patients gave written informed consent to the study. Implantations were performed in either November 2003 or January 2004.

Methods, units and definitions used in this study all conform to the standards recommended by the International Continence Society ¹⁴, except for the 24-hour bladder diary. ¹⁵ A 24-hour bladder diary is sufficient to evaluate the patients' micturition complaints. ¹⁶⁻¹⁸ OAB was defined as more than 7 voids and/or a sudden compelling urge to void, culminating in urinary leakage at least 3 times per 24 hours on bladder diary. All medication that could influence bladder function was stopped at least 2 weeks before treatment or continued without dose changes during the entire study. For this study specific exclusion criteria as described by van Balken et al. were used. ⁸

The primary objective of the study was defined as $\geq 50\%$ reduction of the number of incontinence episodes and/or voids on bladder diary after implant driven tibial nerve stimulation. Apart from feasibility a secondary objective was to evaluate the safety of the implant.

Patients 2 male and 6 female patients (mean age 56 years, range 46-66) had had OAB complaints for a mean period of 10 years (range 1-30) and were enrolled in the study. Prior to enrolment, patients were evaluated for OAB by history, physical examination and urological examination, including urodynamic investigation. All patients had an urodynamic evaluation without abnormalities, except for one patient who showed late onset detrusor overactivity. All patients had been unsuccessfully treated with conservative treatment. 3 patients had had unsuccessful surgery (range 1-2 operations) for their symptoms. Colposuspension, Botulinum toxin A injections in the bladder and urethral dilatation were performed. All patients had been successfully treated with PTNS ($\geq 50\%$ reduction of the number incontinence episodes and/or voids on bladder diary).

Method of treatment PTNS was performed as described by van Balken et al. ⁸ Patients were treated with 30-minute sessions 3 times a week during a 4-week

period. Until implantation no maintenance PTNS was provided for a mean period of 8 months (range 3-12).

The Urgent-SQ™ consists of an external electromagnetic pulse generator with radio frequency (RF) transmission capability (figure 1a) and an internal electromagnetic pulse receiver, the body, with two leads and monopolar electrodes, which are covered by medical grade silicones with the leads having platinum electrodes (figure 1b). The electrodes are approximately 1 cm². The body has a diameter of approximately 4 cm and receives RF electromagnetic pulses from the generator transforming them into current pulses. Stimulation parameters are: 0-19 mA amplitude, 12 or 20 Hz pulse rate and 200 microseconds pulse width. The maximum amplitude was not altered during follow up. The pulses are biphasic and symmetrical. The 12 Hz pulse rate was chosen, since 1 patient did only respond to PTNS at 12 Hz. The external stimulator has to be placed directly on the skin over the internal body in order to activate it. Therefore, the amplitude will not be influenced by the coil position and the internal body will not be activated by other frequency devices, like mobile phones.

Pre- and postoperatively prophylactic oral antibiotics (500 mg amoxicilline) were given. Patients were implanted in the supine position and were covered with sterile drapes after an antiseptic scrub of the lower leg. After spinal or general anaesthesia an incision of 5-7 cm was made approximately 5 cm above the medial malleolus, parallel to the tibia. Muscle relaxants were avoided in order not to blur a motor response of the foot musculature. After incising the fascia of the flexor tendons the electrodes were placed near the neurovascular bundle that contains the tibial nerve, without exposing it. The electrodes were parallel placed and the distance between them was approximately 1 cm. The internal body was placed in a subcutaneous pocket overlying the tibia. During the procedure the implant was activated at regular intervals to confirm correct functioning and placement. Similar to percutaneous stimulation, hallux flexion can be observed when positioned correctly. If correct placement was confirmed the implant was fixed, and the wound was closed.

Motor and sensory responses were evaluated postoperatively at day 10 and at follow up at 3, 6 and 12 months. The responses were tested by a physician, who correctly placed the external stimulator and slowly increased the amplitude until the sensory response was present. The amplitude was further increased until the motor response occurred or to maximum amplitude (19 mA), which was not painful for the patients.

There were no limitations to test the responses. Therapy was started at home postoperatively at day 10, each session lasting 30 minutes 3 times a week. The stimulation was performed at the amplitude resulting in the sensory response and adjusted when it had faded, as has been described for PTNS.⁸

Patients were evaluated by 24-hour bladder diaries, and quality of life questionnaires: SF-36 (social function¹⁹) and I-QoL (index of quality of life²⁰) before implantation and at follow up of 3, 6, and 12 months of implant driven tibial nerve stimulation. Physical examination and urinalysis were performed at all visits. X-rays in 2 directions of the medial ankle were made 1 day and 1 month postoperatively to verify the position of the implant. During follow up no urodynamic evaluations were performed, nor was sham stimulation performed, nor were the stimulators turned off. Furthermore, it was not possible to determine whether the patients had actually treated themselves, nor changed the stimulation frequency and amplitude.

Changes in the voiding and quality of life parameters were tested on statistical significance using the Wilcoxon Signed Ranks Test.

Results

After cessation of the PTNS treatment in all patients voiding and quality of life parameters returned to baseline values as before PTNS.

The surgical procedure was straightforward without complications. Mean operating time was 25 minutes (range 20-30). Patients were discharged after 2 days of bed rest and leg elevation. The implant was not visible from the outside.

The individual results during follow up are presented in table 1 and 2. The motor responses were present intra-operatively in all patients and in none at postoperative day 10. The sensory response (i.e. a radiating sensation at the sole of the foot and toes) was present 10 days postoperatively in 6 patients. 7 patients were treated with a frequency setting at 20 Hz and 12 Hz in 1 patient.

At the 1-month follow up, X-rays showed no dislocation of the implant and no cable breach in all patients. For home-based stimulation, patients adjusted the stimulation schedule to their individual needs.

At the 3-months follow up, 5 patients met the primary objective and were considered a success. There was a significant improvement in number of voids, incontinence

Table 1 The individual results during follow up in 8 patients

	Patient							
	1	2	3	4	5	6	7	8
Sex	M ¹	F ¹	F ¹	F ¹	M ¹	F ¹	F ²	F ¹
Age (years)	49	65	66	46	50	48	62	64
Postoperative day 10	*		*	*				
Responses	m-	m-	m-	m-	m-	m-	m-	m-
	s+	s+	s+	s+	s-	s+	s-	s+
Stimulation frequency	b	c	a	b	a	b	c	c
3 months of STNS								
Responses	m+	m+	m+	m+	m+	m-	m+	m-
	s+	s+	s+	s+	s+	s+	s+	s+
Successful treatment	-	+	-	-	+	+	+	+
6 months of STNS								
			‡					
Responses	m+	m+	m+	m+	m+	m-	m+	m-
	s+	s+	s+	s+	s+	s+	s+	s+
Successful treatment	+	+	-	+	+	- [¶]	+	+
12 months of STNS								
Responses	m+	m+	m+	m+	m+	#	m+	m-
	s+	s+	s+	s+	s+		s+	s-
Successful treatment	-	+	-	+	+	-	+	- [¶]

+ = present, - = absent, ¹ = 20 Hz pulse rate, ² = 12Hz pulse rate, M = male, F = female, * = walking difficulties, ‡ = urinary tract infection, [¶] = unexplainable loss of efficacy, # = dropped out of the study, a = daily stimulation, b = stimulation 3 times a week, c = weekly stimulation, m = motor response, s = sensory response

episodes and I-Qol score (table 3). The motor and sensory responses were respectively present in 6 and 8 patients. 3 patients still performed implant driven tibial nerve stimulation 3 times per week, 2 patients once per week and 3 patients daily. At the 6-month follow up, 6 patients met the primary objective. Compared to the 3-month follow up, voiding and quality of life parameters had not significantly changed except for the SF-36 domain general health ($p < 0.05$). Compared to before

Table 2 Individual voiding and quality of life parameters in 8 patients at baseline, 3 and 6 months of follow up and in 7 patients at 12 months of follow up

Parameters per 24 hour	Patient number							
	1	2	3	4	5	6	7	8
Number of voids								
Baseline	16	9	15	12	23	14	8	18
3-month follow up	10	9	9	8	9	13	6	11
6-month follow up	7	13	13	9	11	17	8	9
12-month follow up	9	12	16	10	9		10	15
Nocturia								
Baseline	5	1	3	3	3	2	1	5
3-month follow up	5	1	0	0	2	3	0	3
6-month follow up	3	2	1	0	1	3	1	2
12-month follow up	3	3	2	2	2		1	2
Mean voided volume (cc)								
Baseline	104	209	120	170	17	90	127	153
3-month follow up	135	242	233	123	27	65	117	145
6-month follow up	114	174	133	206	32	49	114	133
12-month follow up	156	158	222	190	44		167	142
Number of incontinence episodes								
Baseline	0	3	0	12	0	40	6	13
3-month follow up	0	1	0	5	0	17	2	6
6-month follow up	0	0	0	6	0	21	0	2
12-month follow up	0	1	0	4	0		0	8
Incontinence severity¹								
Baseline	0	2	0	2	0	1	2	2
3-month follow up	0	1	0	1	0	1	2	2
6-month follow up	0	0	0	1	0	1	0	2
12-month follow up	0	1	0	1	0		0	2
Number of used pads								
Baseline	0	3	2	4	0	6	6	2
3-month follow up	0	2	1	2	0	5	2	3
6-month follow up	0	2	2	0	0	6	1	2
12-month follow up	0	2	2	2	0		2	7
I-QoL score								
Baseline	69	88	68	62	51	47	80	48
3-month follow up	84	97	98	71	96	61	101	52
6-month follow up	84	105	89	80	96	52	105	81
12-month follow up	82	99	76	81	97		99	51

¹ 0= no urine loss, 1= loss of some drops, 2= loss of small amount, 3= need for change of clothes

Table 3 Voiding and quality of life parameters before implantation, at 3 and 6 months of implant driven tibial nerve stimulation in 8 patients, and at 12 months in 7 patients

Parameters per 24 hours	Mean (SD)			
	Before Implantation	3-month follow up	6-month follow up	12-month of follow up
Number of voids	14.4 (4.9)	9.4 (2.1)*	10.9 (3.3)	11.6 (2.9)
Nocturia	2.9 (1.6)	1.8 (1.8)	1.6 (1.1)	2.1 (0.7)
Mean voided volume (cc)	123.8 (57.6)	135.9 (73.9)	119.4 (58.0)	154.1 (55.3)
Number of incontinence episodes	9.3 (13.5)	3.9 (5.8)*	3.6 (7.3)*	1.9 (3.0)
Number of used pads	2.9 (2.4)	1.9 (1.6)	1.6 (2.0)	2.1 (2.3)
I-QoL score	64.1 (15.1)	82.5 (18.9)*	86.5 (17.1)*	83.6 (17.2)

* = compared to before implantation and $p < 0.05$

implantation, number of incontinence episodes, I-QoL score (table 3), and SF-36 (social function and vitality) had significantly ($p < 0.05$) improved. Compared to the results after PTNS, voiding and quality of life parameters were similar, except for mean voided volume, which was significantly decreased ($p < 0.05$). Patients had not changed their treatment schedule.

At the 12-month follow up, 5 patients had improved on bladder diary and 4 of these patients met the primary objective. Compared to the data before implantation and at 6-month follow up there were no significant changes in the voiding and quality of life parameters. Compared to the results of PTNS, voiding and quality of life parameters were similar as well and without significant differences. The motor response was present in 6 and the sensory response in 7 patients. Patients had not changed their treatment schedule. All patients who completed the 1-year follow up were satisfied with the results of the implant.

Directly after the operation 3 patients reported difficulties when walking or standing on the operated leg due to wound pain. Two of these patients received physiotherapy for their complaints, which had disappeared within 2-3 weeks without further intervention. Moreover, these patients had not used the prescribed analgesics. Postoperatively, 7 patients reported spontaneous radiating sensations (i.e. sensory response without activation of the implant), which disappeared without any

intervention within 3 months in all patients except one. Before the 3-month follow up and at 6 months one patient had a urinary tract infection, which was treated with antibiotics. During follow up no other adverse events were reported, such as local infection, dislocation or erosion. The adverse events are summarised in table 4.

Table 4 Reported adverse events

Adverse events	Number of patients
Walking difficulties	3
Spontaneous sensory response	7
Urinary tract infection	2

At 6 months of implant driven tibial nerve stimulation, one patient had an unexplainable loss of efficacy though still having the sensory response (the motor response had been present only intra-operatively). Technical problems like lead dislocation were ruled out on X-ray. However, lead wire breakage can not be ruled out since no surface mapping was performed. Switching the stimulation frequency to 12 Hz had no result; neither had PTNS re-treatment. Afterwards the patient dropped out of the study and was considered unsuccessfully.

At 12-month follow up, another patient had an unexplainable loss of efficacy. This patient had lost the sensory response to the implant driven tibial nerve stimulation (the motor response had only intra-operatively been present). Technical (dislocation) and physical causes were ruled out on respectively X-ray and physical examination, including neurological examination. However, since no surface mapping was performed, lead wire breakage can not be ruled out. The patient was successfully re-treated with PTNS. Afterwards, the UrgentSQ™ was explanted at the patients' request. During explantation the implant was activated, which did not result in a motor response. The device was examined; however no results are available yet.

Discussion

Implant driven tibial nerve stimulation is feasible, since both sensory and motor responses were present postoperatively. The occurring loss of the motor response at maximal amplitude (temporarily in 6 and lasting in 2 patients) may have been caused by edema and/or fibrosis around the electrodes, since after the edema had disappeared the response occurred in 6 out of the 8 patients.

At 3, 6 and 12 months of follow up, respectively 5, 6 and 4 patients were successfully treated. The fact that not all voiding and quality of life parameters improved significantly at follow up can most probably be explained by the small number of patients included in this pilot study, the fact that at the 6-month evaluation one patient had a urinary tract infection (the patient was not re-evaluated after treatment) and by the unexplainable loss of stimulation efficacy in 2 patients at 6 and 12 months of follow up. Moreover, when the data at 6 months of implant driven tibial nerve stimulation are corrected for the urinary tract infection and the unexplainable loss of efficacy, these are similar to the data after PTNS.

Due to the small patient population it was impossible to determine whether the preoperative urodynamic outcome correlates with the efficacy of the implant. However, it is to be expected that patients with urodynamic stable bladders or late onset detrusor overactivity are the best candidates for implant driven tibial nerve stimulation, as has been described for PTNS.²¹

Also, because of the small patient population, it was impossible to determine whether the presence of the motor and/or sensory responses correlates with the efficacy of the implant. To date this has not been determined for PTNS either. Percutaneous tibial nerve stimulation is performed at an amplitude resulting in the sensory response with adjustment of the amplitude when the response has faded.^{8,9} Moreover, stimulation at an amplitude resulting in the motor response is too painful for most patients. Therefore, implant driven tibial nerve stimulation was performed similar to PTNS. As with PTNS, implant driven stimulation at the level of the motor response is too painful for most patients.

The observation that not all patients who respond well on percutaneous stimulation do the same on subcutaneous stimulation, is known from studies concerning sacral nerve stimulation; the same goes for loss of efficacy.²²⁻²⁴ The difference between percutaneous and implant driven tibial nerve stimulation could be that for implant

driven stimulation is was impossible to determine whether the patients had actually treated themselves or not. Moreover the stimulation amplitude was not recorded, so it is possible that the patients had treated themselves at too low amplitude. Another possibility is that the placebo effect is larger for implant driven tibial nerve stimulation than for PTNS. For the latter a randomized double-blind placebo-controlled study is being performed to determine whether PTNS is more than a placebo effect, however results are not available yet. It seems likely that the PTNS placebo effect is similar to that of pharmacotherapy in the treatment of OAB. Pharmacotherapeutic placebo-controlled trials have reported placebo-effects of 28-43% in patients with urge urinary incontinence.²⁵⁻²⁷ A larger study is needed to make conclusions concerning the efficacy of the implant.

Patients were discharged after 2 days, which is a relatively long period for such a procedure. This was caused by the fact that these patients were the first to be operated on, which led to increased caution. Probably we were too careful and we anticipate that future patients will be discharged at the same day.

During the 12-month follow up implant driven tibial nerve stimulation proved to be safe. No local infection, spontaneous dislocation or erosion of the Urgent SQ™ equipment had occurred during follow up; one stimulator unit failed. Postoperatively, 3 patients had walking difficulties due to pain caused by the surgery. These complaints had disappeared completely within 2-3 weeks. Moreover, these patients used no prescribed analgesics. During the 12-month follow up 2 patients had a urinary tract infection. These patients were known to have had some recurrent urinary tract infections in the past. 7 patients did mention postoperatively a sudden radiating sensation, which disappeared without intervention within 3 months in all patients except one. In this patient the sudden radiating sensations are still present, but occur rarely. Long-term follow up is needed to determine the safety of the implant during chronic use.

Other implantable devices are available for neuromodulative treatment of lower urinary tract dysfunction.²⁸⁻³⁰ For all devices a pre-operative eligibility test is performed to determine whether the patient is a deemed candidate. Of these implantable devices sacral nerve stimulation (SNS) is proven to be effective and safe. 30-33 Side effects have been reported such as pain in the buttocks, pelvic area, lower extremities and at the pulse generator (Interstim®, Medtronic, Minneapolis, Minnesota, USA) site, lead migration, infection at test stimulation lead site, transient

electric shock, re-operations due to technical problems and adverse change of urinary, bowel or sexual function.³⁰⁻³⁶ For pudendal nerve stimulation by the Bion[®] rechargeable battery-powered microstimulator (Advanced Bionic Corp., Valencia California, USA) vaginal fungus infection, allergic reaction, vaginal dryness during intercourse, mechanical irritation during bicycle riding and altered bowel functions have been reported²⁸, as is skin erosion at the connection site between lead and extension cable for pudendal nerve stimulation by definitive quadripolar tined lead, as is used for SNS.²⁹ For PTNS minimal hematoma and transient pain at the insertion site have been described.^{9,37} The Urgent SQ[™] could be an alternative. Implant driven tibial nerve stimulation is minimal invasive and adverse events like infection or dislocation did not occur in this study. Furthermore, the internal body contains no internal battery that has to be replaced in time, as is the case with SNS and the devices for pudendal nerve stimulation. Patients experience no mechanical problems due to the implant, which is invisible at the outside. Finally, during the 12-month follow up only urinary tract infection, transient walking difficulties and spontaneous sensory responses were reported as adverse events. All patients, who completed the 1-year follow up, were satisfied with the result. In order to define the proper place of the Urgent SQ[™] in the treatment of lower urinary tract dysfunction, comparative studies are needed.

Conclusions

Implant driven tibial nerve stimulation with the Urgent SQ[™] device seems to be feasible and safe during short-term follow up in patients with refractory OAB. A study with a larger population and long-term follow up has to be performed to determine the efficacy and long-term safety of the implant.

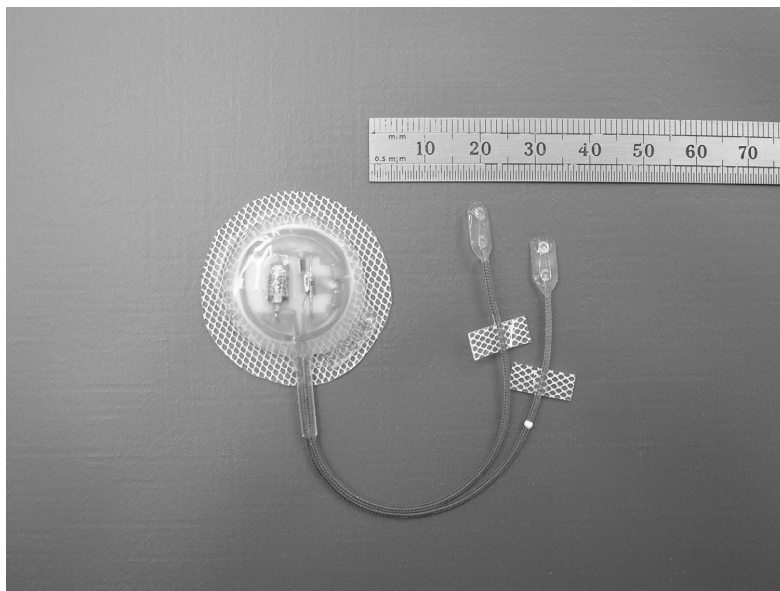
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Figure 1 External stimulator (A) and the internal body with cables and electrodes of the Urgent SQ™ (B)



A



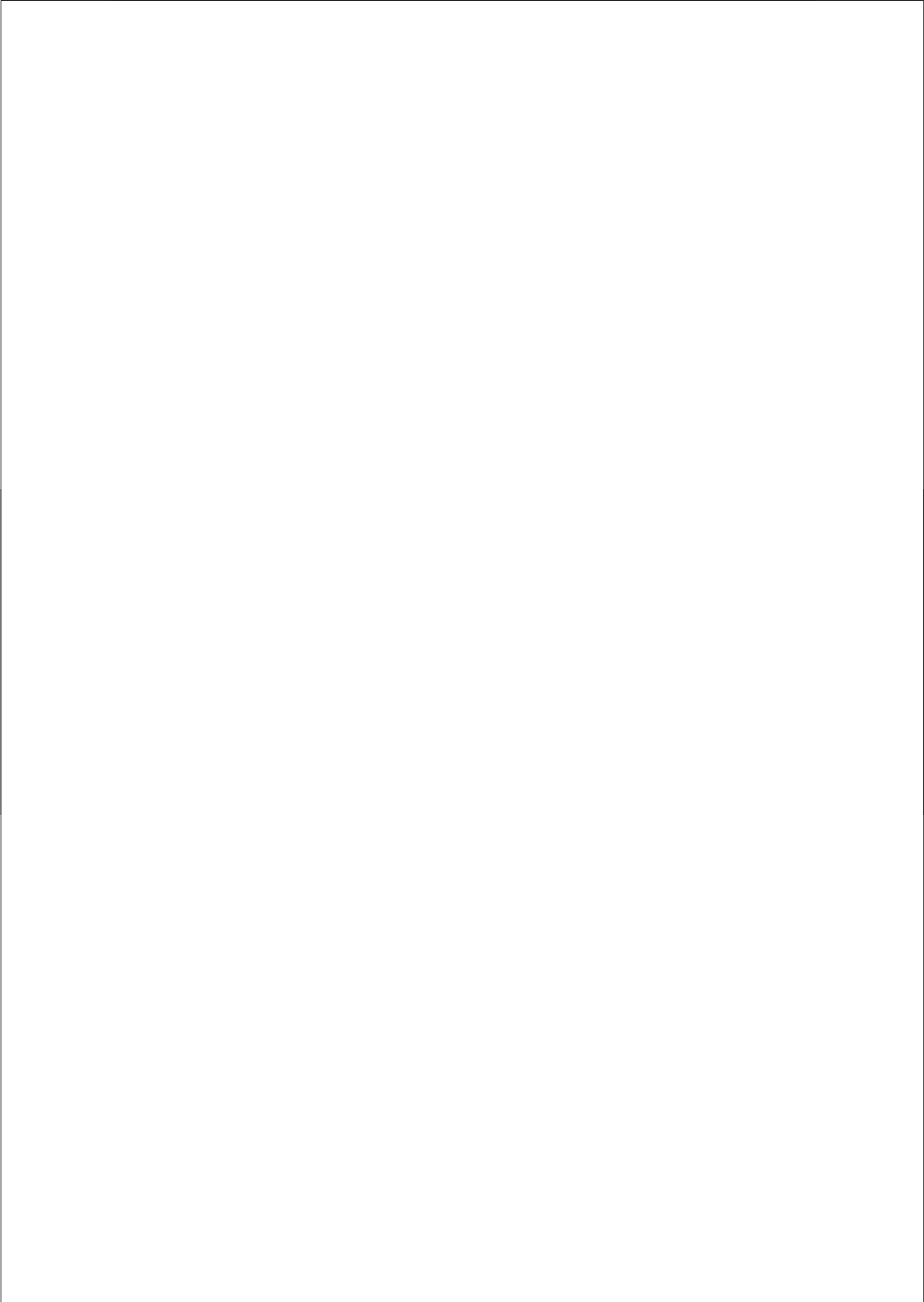
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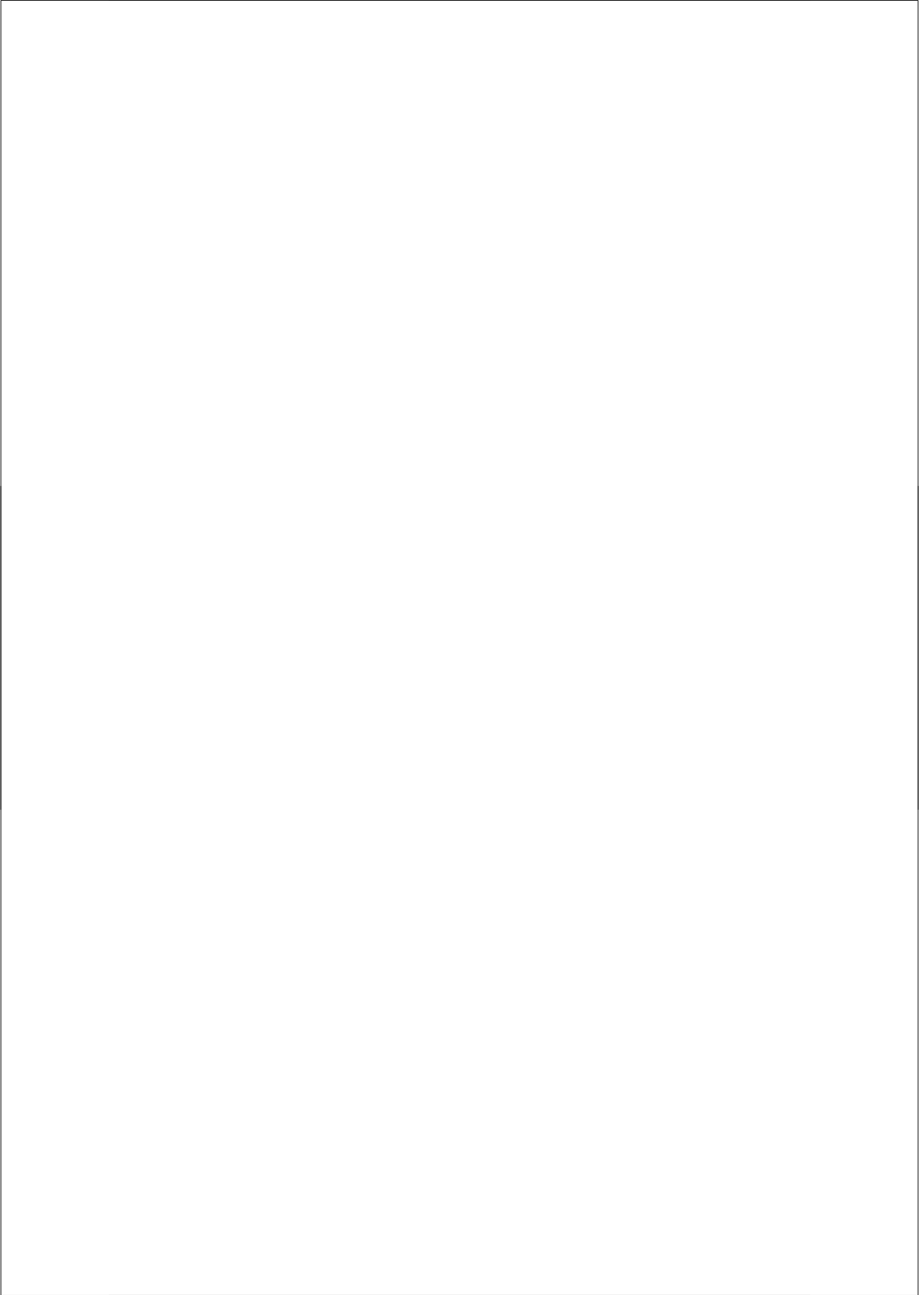
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EPILOGUE

Synopsis and future perspectives



Synopsis

In case lower urinary tract dysfunction fails conservative treatment and surgical therapy with all its disadvantages looms to the horizon, neuromodulation may be a welcome alternative. So far, of many methods investigated over the years, sacral neuromodulation still is the most successful. However, this technique is expensive and requires explicit surgical skill. Not surprisingly, the search for even better alternatives is ongoing. This thesis focuses on a currently developed neuromodulative treatment modality, percutaneous tibial nerve stimulation or PTNS.

Chapter 1 Neurostimulation and neuromodulation techniques are not new. From the discovery of electricity, its possible use in medicine was explored. In this chapter the use of electrical stimulation and neuromodulation to treat patients with lower urinary tract dysfunction as investigated over the years, is reviewed. Data are given on treatment procedures, stimulation parameters and clinical results as well as on particular advantages and disadvantages. Various forms of electrical stimulation of the bladder, the pudendal nerves, transcutaneous electrical nerve stimulation or TENS, electrical stimulation of the sacral spine or roots and finally the electrical stimulation of the lower limb, including its most recent variant, PTNS, are described in detail.

It can be concluded from this chapter that in many reports important information is missing and good randomized placebo controlled studies have seldom been performed. Therefore, it is very difficult to compare different treatment modalities or to judge them on their true merits. Furthermore, there is considerable variety in the treatment parameters and schedules reported as well as in criteria for success, hampering comparison of both studies concerning different and identical techniques. Finally, patients included in the studies often differ, especially with regard to the definition and duration of their symptoms and the various treatments applied before. This also hinders the determination of prognostic factors for successful treatment outcome.

However, in general one might say that different forms of electrical neurostimulation and neuromodulation on an intention-to-treat basis result in a 30 to 50% clinical success. Influencing lower urinary tract innervation at the level of the sacral roots seems to stand the test of time in both neurological and non-neurological patients. It

has the advantage of pre-implant testing possibilities to improve patient selection and thereby treatment outcome, but it has the drawback of invasiveness. Non-invasive techniques lack screening tests and in case of success patients almost always need maintenance therapy. It is with this information in mind that one should regard the development and possible clinical value of the new treatment option of PTNS.

Chapter 2 To explore the possible value of PTNS, first a feasibility study was performed in 49 patients with overactive bladder or non-obstructive urinary retention, indications well known from other neuromodulative treatment options. PTNS was evaluated in a prospective multicenter trial in 37 patients who presented with symptoms of bladder overactivity, that is the urgency and frequency syndrome and/or urge incontinence, and 12 with non-obstructive urinary retention. Data were collected by means of voiding diaries and quality of life questionnaires before and after treatment. Patients were classified in responders, those in whom therapy was successful and chose to continue treatment after the initial 12 weeks, and non-responders, those who chose to stop treatment. Overall, a positive response was seen in 60% of all patients. In patients with bladder overactivity a statistically significant decrease was observed in leakage episodes, number of pads used, voiding frequency and nocturia, and an equal increase in mean and smallest volume voided. Improvements were also seen in patients with non-obstructive urinary retention, where the number of catheterizations, total and mean volume catheterized, and total and mean volume voided changed. Disease specific quality of life and some domains of general quality of life improved, especially in patients with bladder overactivity. Besides, only mild side effects were observed.

Encouraged by these results, subsequently several indications were studied in more detail. Overactive bladder and non-obstructive urinary retention were evaluated by Vandoninck et al.¹⁻² This chapter presents the research on chronic pelvic pain (CPP) as the main indication for PTNS. In a prospective multicentre trial PTNS was evaluated in 33 patients. Effects were recorded by Visual Analogue Scale (VAS) for pain diaries, the McGill pain questionnaire and the SF-36 general quality of life questionnaire at baseline and after 12 weeks of treatment. Subjective response was defined as in earlier studies (patients' request to continue chronic treatment to keep the obtained success), but now also more objective responses (decrease in mean VAS >50% and VAS <3 after treatment) were included. A subjective response was

seen in 42% of all patients. In 7 patients (21%) mean VAS decreased >50%, in 6 cases (18%) the decrease was >25%. After 12 weeks of treatment 7 patients (21%) ended up with a mean VAS <3. In all patients quality of life (SF-36) significantly improved, as did the total pain rate intensity (McGill). These very modest results in CPP, however, are in concordance with the results of other neuromodulation techniques.

Finally, the potentially beneficial effect of successful PTNS treatment of lower urinary tract dysfunction on sexual functioning in the three indication groups combined was investigated. Therefore, 121 patients with an overactive bladder (N=83), chronic pelvic pain (n=23) and non-obstructive retention (n=15) which were treated with PTNS were evaluated. To obtain information on their sexual function a self-administered standardized questionnaire was filled out prior to therapy as well as after 12 weeks of treatment. Prior to therapy different aspects of sexual life were considered not normal in 25.3 to 45.6% of the cases. This improved significantly after treatment. Patients most likely to benefit were women, patients with an overactive bladder and subjective responders, whereas the aspects of sexual life which mostly improved were overall satisfaction, libido and the frequency of sexual activities.

Chapter 2 leads to the conclusion that clinical success through PTNS can safely be obtained in especially overactive bladder and non-obstructive urinary retention, while the outcome in chronic pelvic pain is only modest. Apart from positive effects on lower urinary tract dysfunction itself, PTNS may also improve sexual dysfunction, observed in a lot of these patients as well.

Chapter 3 Stimulated by the promising results in especially overactive bladder and voiding disorders further research was done to affirm the value of PTNS. Although one can obtain rather objective parameters from (micturition) diaries in particular, urodynamic studies may provide more robust data on the effectiveness of percutaneous tibial nerve stimulation. Therefore, studies on urodynamics prior to PTNS as well as after finishing treatment were performed in patients with overactive bladder and non-obstructive urinary retention, respectively.

In the first study, 90 consecutive patients with symptoms related to overactive bladder syndrome each underwent 12 PTNS sessions. Objective success, the primary outcome measure defined as reduction in the number of urinary leakage episodes of 50% or more per 24 hours, could be obtained in 56%. Patients' request

for continuation of therapy, considered subjective success, was seen in 64% of cases. Furthermore, frequency/volume chart data and quality of life scores improved significantly ($p < 0.01$). Of 46 participants with pre- and post-treatment urodynamic data, only a few showed complete abolishment of detrusor instabilities (DI). Nevertheless, increments in cystometric bladder capacity ($p = 0.043$) and in volume at DI ($p = 0.012$) were significant. Subjects without DI at baseline appeared 1.7 times more prone to respond to PTNS (OR: 1.75; 95% CI: 0.67-4.6). The more the bladder overactivity was pronounced, the less these patients were found to respond to PTNS (area under the ROC curve 0.64 (95% CI: 0.48-0.80)).

In the second study, 39 patients with chronic voiding dysfunction were enrolled in a comparable prospective trial. In this group, a $\geq 50\%$ reduction in total catheterized volume per 24 hr, the primary objective outcome measure, was obtained in 41% of patients. An additional 26% reduced their 24 hr residuals with more than 25%, while 59% of patients chose to continue treatment. Pre- and post-treatment urodynamic data were available in 27 cases. Detrusor pressure at maximal flow, cystometric residuals and various bladder indices (bladder contractility index and bladder voiding efficiency) improved significantly for all patients ($p < 0.05$). Patients with minor voiding dysfunction were more prone to notice success (OR: 0.73; 95% CI: 0.51-0.94).

From this chapter it can be concluded that PTNS not only results in clinical, but also in more objective urodynamic changes. In overactive bladder patients PTNS increases cystometric capacity and delays the onset of, but not abolishes detrusor instability. In patients with voiding disorders PTNS improves parameters regarding more effective bladder emptying. In addition, this chapter shows that urodynamics can provide some helpful criteria for PTNS candidate selection. These data should further objectively affirm PTNS significance.

Chapter 4 In chapter 4 two studies are presented regarding refinement of PTNS therapy. First, in addition to the urodynamic parameters with predictive importance shown in chapter 3, it was tried to establish clinical parameters with prognostic value for successful treatment outcome.

For this purpose, PTNS was applied to 51 men and 81 women with a mean age of 53 years (range: 21-82). Of them, 83 were treated for overactive bladder, 16 for non-obstructive urinary retention and 33 for chronic pelvic pain. All patients had to fill out micturition or pain diaries as well as quality of life questionnaires before and after

treatment. Also data on history, physical examination and stimulation specifics were collected. Objective success ($\geq 50\%$ improvement of specified symptoms) was seen in 32.6% of patients, subjective success in 51.5%. Unfortunately, most evaluated clinical parameters proved not to be of prognostic value. Even a history of sexual and/or physical abuse, found in 12 of 103 interviewed patients did not alter PTNS treatment outcome. However, a low total score at baseline in the SF-36 questionnaire proved to be predictive for not obtaining objective (OR 0.44; 95% CI: 0.2-1, $p=0.04$) nor subjective success (OR 0.42; 95% CI: 0.20-0.89, $p=0.02$). Especially patients with a low SF-36 Mental Component Summary were prone to fail neuromodulation therapy: OR 0.12 (95% CI: 0.27-0.55), $p=0.006$ for objective success. These patients also scored worse on disease-specific quality of life questionnaires, although they had no different disease severity compared to patients with good mental health.

Apart from evaluating which patients may be best suited to start therapy, it is also important to evaluate how, if possible, positive results can be sustained. The second study in this chapter was performed to investigate whether maintenance therapy once successful outcome had been obtained is really necessary.

Eleven patients (mean age: 51 years) with refractory overactive bladder syndrome (> 7 voids and/or > 3 urge incontinence episodes per day) were successfully treated with PTNS and started maintenance therapy. Patients filled out bladder diaries and quality of life questionnaires (SF-36 and I-QoL) before and after a 6-week pause of maintenance PTNS and again after re-treatment. The first objective was defined as $>50\%$ increase of the number of incontinence episodes and/or micturition frequency after the 6-week pause of maintenance PTNS. The second objective was defined as a $>50\%$ reduction of the same parameters after re-treatment. After the 6-week pause, 7/11 patients (64%) met the first objective. Mean voided volume, nocturia, number of incontinence episodes and incontinence severity significantly deteriorated ($p<0.05$). The second objective was reached in 9/11 patients (82%). Nocturia, number of incontinence episodes, incontinence severity, mean voided volume and quality of life significantly ($p<0.05$) improved.

It can be concluded from this chapter that most clinical parameters are of no value in predicting PTNS treatment outcome. Only bad mental health as measured with the SF-36 Mental Component Summary proved a negative predictive factor for success and may therefore be used as a tool for better patient selection. In case patients are treated successfully, they do need continuous therapy to maintain their results.

Chapter 5 After it became clear that in case of successful PTNS treatment maintenance therapy proved to be a necessity, ways were looked at to ease this problem as it is demanding for both patients and outpatient departments. In concordance with other neuromodulation techniques an implantable device was designed. It resulted in an implant for radiographically controlled subcutaneous tibial nerve stimulation (STNS).

In this chapter the first results on feasibility and safety of STNS are presented. Eight patients with refractory overactive bladder successfully treated with PTNS received a subcutaneous implant after a washout period of 3 to 12 months. Evaluation was done by means of bladder diaries, quality of life questionnaires and physical examination before implantation and at 3, 6 and 12 months of follow up. At the three consecutive postimplantation evaluation points the primary objective of $\geq 50\%$ reduction of the number of incontinence episodes and/or voids on bladder diary was met by 5, 6 and 4 patients respectively. Furthermore, at 3 and 6-month follow up voiding and quality of life parameters had significantly ($p < 0.05$) improved. STNS proved to be safe as the only adverse events reported were urinary tract infection, temporarily walking difficulties and spontaneous radiating sensations. There were no reports on local infection, erosion or dislocation.

It can be concluded from this chapter that implant driven STNS seems to be both feasible and safe. In addition, it should convince the reader that much effort is made to keep improving tibial nerve stimulation, including its major drawback: maintenance therapy.

Future perspectives

The studies presented in this thesis are only few; so many questions remain unanswered. The near future of PTNS is therefore most probably dedicated to further research, which will not only clarify the many dark areas left behind, but may also shine a light on ongoing mysteries in other neuromodulation techniques. A widespread application of PTNS as ready to use neuromodulation therapy, at least in Europe seems less likely as the percutaneous route necessitates maintenance therapy too demanding for patients as well as outpatient departments. As PTNS is reimbursed in the United States, financial stimuli to develop an implantable device to

overcome these drawbacks are almost completely absent. Not surprisingly, many enthusiastic urologists that started PTNS shortly after its introduction a few years ago, slightly disappointed in the further developments abandoned the technique. What are the main issues in percutaneous tibial nerve stimulation that have to be resolved?

Does PTNS work? Despite changes in symptoms, quality of life items, urodynamic features and LUTD accompanying sexual functioning, there are also central nervous system changes all very indicative for the action of PTNS. However, a placebo effect can not completely ruled out. Although the issue has already been discussed in some of the articles in this thesis a placebo controlled trial still needs to be performed. However, because of the very specific features of the PTNS technique, a blinded (let alone a double blinded) randomized controlled trial is almost impossible to conduct. In addition it should be noted that almost none of the even most established neuromodulation techniques have been properly ran against placebo. This issue is one of the most challenging for the nearby future.

How does PTNS work? Nowadays it is well accepted that effects of especially sacral root neuromodulation take place at the spinal and supraspinal level. Spinal tract neurons involved in the micturition reflex are inhibited, as are interneurons involved in spinal segmental reflexes and postganglionic neurons.³ Furthermore, there may be inhibition of the primary afferent pathway, and indirect suppression of guarding reflexes by turning off bladder input to internal sphincter sympathetic or external urethral sphincter interneurons.⁴ In urinary retention, the obtained effects are believed by some authors to be the result of changed pelvic floor behavior directly^{5,6}, or as part of retuning of a brainstem 'on-off' switch mechanism.^{3,7} However, a lot of the assumptions made above need to be evidenced further. Although many investigators mainly focus on clinical results, basic research is as evenly important. Clarifying the many unsolved issues will eventually lead to a better understanding of how neuromodulation really works and ultimately will improve therapy outcome. This is especially true for a new treatment modality as percutaneous tibial nerve stimulation. One way to explore basic issues is by means of animal experiments. For example it is shown that PTNS actually changes spinal neuronal cell activity in rats by reducing the metabolic marker c-fos protein in the

spinal micturition center.⁸ In another experiment in anesthetised cats, arguments were found that PTNS works through sacral reflex pathways instead of through activation of pain, sympathetic or cervico-thoracic reflex pathways.⁹ In addition to animal experiments new exciting ways to study central nervous processes have become available, especially functional PET scanning. It has already shown some effects in sacral neuromodulation for urinary retention¹⁰, but much more research is awaited for.

What is the best way to perform PTNS? Almost all research done on PTNS used the same stimulation protocol: PTNS was performed in 10 to 12 weekly sessions, each lasting for 30 minutes. Stimulation parameters were preset and rather fixed and every time only one needle was inserted. It may be well anticipated that changes in treatment scheme and/or stimulation parameters could lead to a different, possibly even better outcome. The same goes for bilateral instead of unilateral therapy.

Compared to the once-a-week protocol, an accelerated scheme of 3 to 4 times a week for example seems not to significantly influence treatment outcome, although there are some conflicting reports on its effect on the necessity of maintenance therapy afterwards.^{11,12} On the other hand, it is evident that an accelerated scheme has the advantage of achieving clinical results faster.¹³

Regarding stimulation parameters, it is rather widely agreed that pulse intensity in neuromodulation should be set at a well tolerable level. Frequency however, for PTNS set at 20 Hz, has been varied in the different neuromodulation techniques from 5-20 Hz, but even frequencies up to 150 Hz are reported. As it is suggested that frequency is optimal at more unpleasantly low levels (5-6 Hz)¹⁴, studies on PTNS with pulse frequencies below 20 Hz may produce interesting results. The same goes for changes in pulse duration, in PTNS set at 0.2 msec, but in other techniques also up to 0.5 or even over 1 msec.

Besides research on stimulation scheme and parameters it may also be interesting to evaluate the possible beneficial effect of stimulating both legs at the same time. At least in sacral neuromodulation there is some evidence that bilateral stimulation may improve results not so much in relieving symptoms better than unilateral stimulation once successful, as well in improving the chance that patients react at all.¹⁵⁻¹⁷ Of course a positive outcome of bilateral stimulation in PTNS would create some new problems with regard to a possible implantable device.

And this will eventually be the way we are heading: a readily available subcutaneous implantable device, easily controllable by patients themselves in flexible, individualized treatment schemes. Unnecessary to state that there is still a long way to go.

In whom should PTNS be performed? As percutaneous tibial nerve stimulation with its 10 to 12 half-an-hour sessions before results are obtained is elaborative, predictive factors for successful outcome are urgently needed. Some studies in sacral as well as tibial nerve stimulation have now been performed (see chapter 4 of this thesis), resulting in the best candidates being psychological sound patients with not too severe bladder overactivity or non-obstructive urinary retention. More research should be done to tighten these criteria for neuromodulation therapy increasing positive results. As soon as a subcutaneous implant for chronic tibial nerve stimulation is readily available, by analogy with sacral neuromodulation additional efforts should be undertaken to refine the pre-implant testing phase in order to decrease the amount of unnecessarily treated patients.

In contrast, optimizing the success of PTNS treatment will without a doubt lead to the exploration of its value in other indication groups, something that can already be seen in sacral neuromodulation. Most likely to be subject of further investigation seem to be children, neurologic patients and patients with fecal incontinence.

Till now, almost all stimulation and neuromodulation techniques were tested in adults only, with the exception of intravesical electrostimulation in children with neurogenic voiding disorders and TENS in non-neurogenic incontinence. The majority of neuromodulation techniques namely seem less suitable to children because of their invasive nature and the necessity to apply current in the anal and/or genital area. Although percutaneous tibial nerve stimulation is not 'non-invasive', its focus on the ankle might be less threatening to children, offering a possibility for PTNS use in this young age group. Promising results reported in the first two studies in 31 and 23 children respectively^{18,19} warrant further evaluation.

The second challenging patient group consists of neurological patients. In most neuromodulative therapies this group is not included. However, it can be argued that neuromodulation treatment in selected cases, especially in multiple sclerosis, may be of benefit as well. Up to now, experience in this field is very limited and contradictive²⁰⁻²², but results are encouraging enough to justify more research.

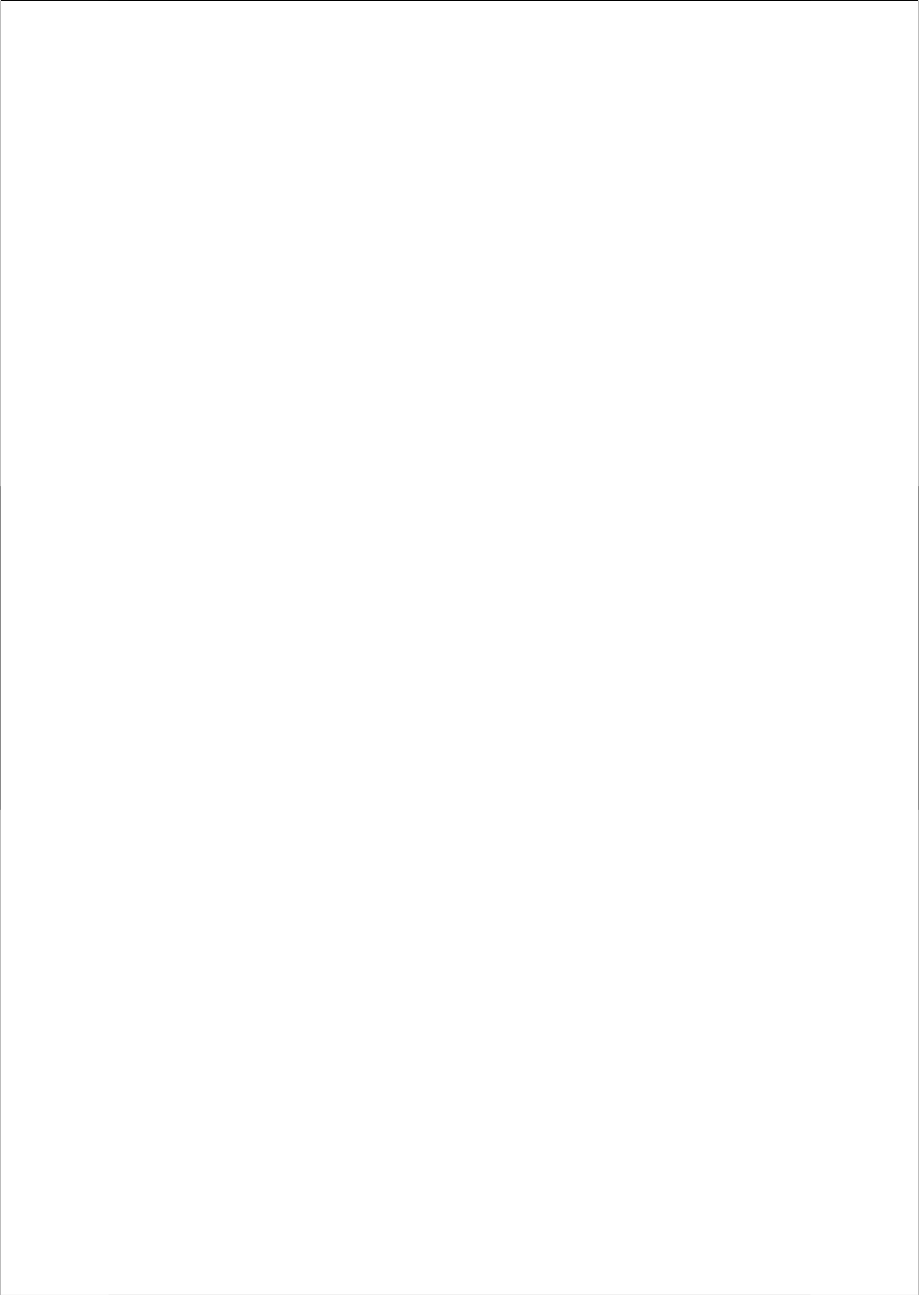
Finally, an area generally spoken beyond the interest of most urologists but in many ways comparable to lower urinary tract dysfunction, is that of fecal incontinence. As goes for urinary leakage, fecal incontinence has a high impact on patients' quality of life but seems even more difficult to discuss for both patients and care-givers. As the first steps are taken in exploring the value of sacral neuromodulation in this field ²³, it can be anticipated that research on PTNS for this indication will also be performed. ²⁴

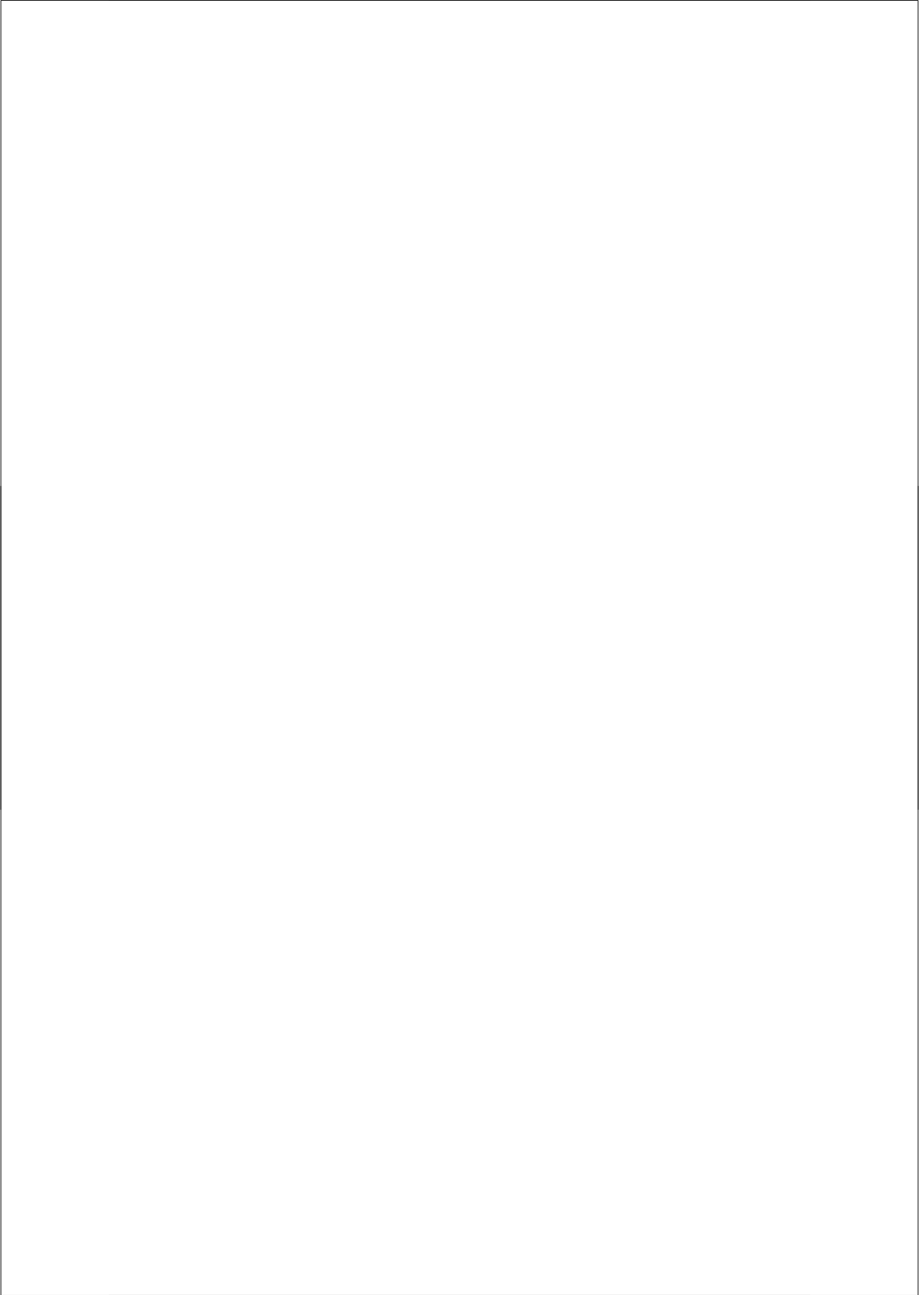
It is the fate of science: with every question answered, even more questions arise. With this thesis I hope I've been able to raise a lot of new questions.

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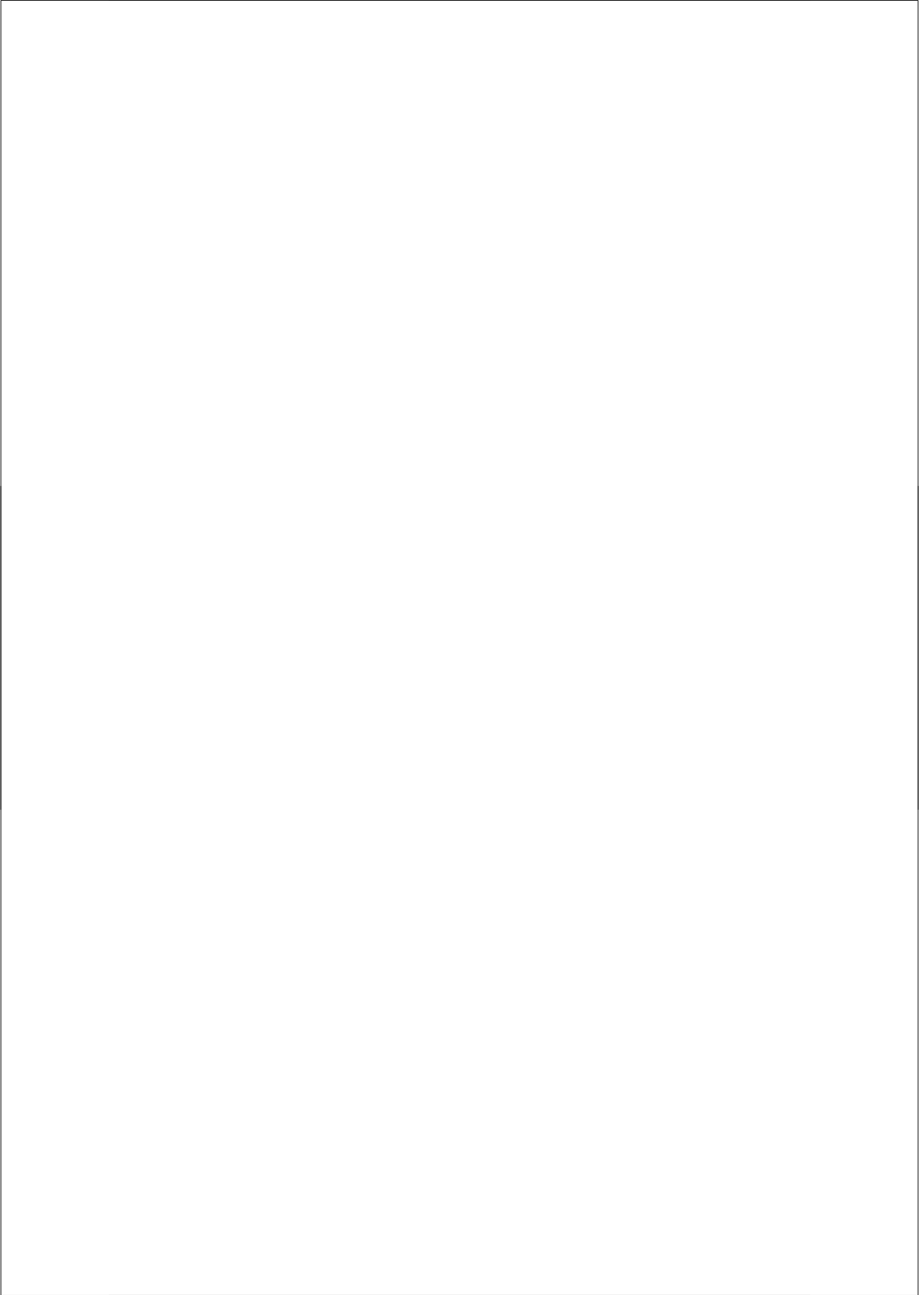
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EPILOOG

Synopsis en toekomstverwachtingen



Synopsis

Wanneer bij disfunctie van de lagere urinewegen conservatieve behandeling faalt en operatieve therapie met al haar nadelen opdoemt aan de horizon, kan neuromodulatie een welkom alternatief zijn. Tot nu toe is sacrale neuromodulatie van de vele methoden onderzocht in de laatste jaren het succesvolst gebleken. Het betreft hier echter een dure techniek die speciale vaardigheden vereist. Het zal dan ook niemand verbazen dat de zoektocht naar nog betere alternatieven voortgaat. Dit proefschrift richt zich op een van de meest recente neuromodulatievormen: de percutane stimulatie van de nervus tibialis ofwel Percutaneous Tibial Nerve Stimulation (PTNS).

Hoofdstuk 1 Neurostimulatie- en -modulatietechnieken zijn niet nieuw. Spoedig na de ontdekking van elektriciteit werden de mogelijkheden voor toepassing binnen de geneeskunde al onderzocht. In dit hoofdstuk wordt het gebruik van elektrische stimulatie en neuromodulatie voor de behandeling van patiënten met disfunctie van de lagere urinewegen door de jaren heen beschreven. Informatie over behandelprocedures, stimulatieparameters, klinische resultaten, maar ook specifieke voor- en nadelen passeren de revue. Dientengevolge kan men lezen over verscheidene vormen van elektrische stimulatie van de blaas, van de nervi pudendi, over transcutane elektrische zenuwstimulatie of TENS en over elektrische stimulatie van het sacrale ruggenmerg of zijn wortels en tenslotte over elektrische stimulatie van de onderste extremiteit inclusief haar modernste variant, PTNS.

Uit dit hoofdstuk kan worden geconcludeerd dat in veel publicaties relevante informatie ontbreekt en dat goede, gerandomiseerde en placebogecontroleerde studies zeldzaam zijn. Hierdoor is het amper mogelijk de verschillende modulatie-technieken met elkaar te vergelijken dan wel naar waarde te schatten. Bovendien bestaat er een aanzienlijke variatie in gerapporteerde behandelprogramma's en -parameters, maar ook in criteria voor succes, wat een verdere barrière vormt voor een goede vergelijking van studies zowel over verschillende neuromodulatievormen als over identieke technieken onderling. Tenslotte zijn patiëntengroepen in de studies beschreven niet uniform, voornamelijk waar het gaat om definitie en duur van de klachten en de eerder toegepaste therapieën. Buiten het feit dat dit de onderlinge

vergelijking nog eens verder bemoeilijkt, staat het ook de determinatie van prognostische factoren voor een succesvol behandelresultaat in de weg.

Desalniettemin kan men in het algemeen stellen dat neuromodulatie resulteert in een 30-50% kans op klinisch succes ('intention to treat'). Het beïnvloeden van de innervatie van de lagere urinewegen op het niveau van de sacrale wortels blijkt tot op heden het meest solide, zowel bij neurologische als bij niet-neurologische patiënten. Het heeft het voordeel van een testmogelijkheid vóór definitieve implantatie, waardoor een striktere patiëntselectie kan plaatsvinden met als gevolg een verbetering van het behandelresultaat, het nadeel is echter de invasiviteit. Niet-invasieve technieken ontberen screeningsmogelijkheden en in geval van succes zijn patiënten vrijwel altijd gebonden aan een onderhoudsbehandeling. Het is tegen deze achtergrond dat de ontwikkeling en de mogelijk klinische waarde van de nieuwe neuromodulatietechniek PTNS dient te worden gezien.

Hoofdstuk 2 Om de mogelijke waarde van PTNS te onderzoeken werd allereerst een haalbaarheidsstudie uitgevoerd bij 49 patiënten met overactieve blaas of niet-obstructieve urineretentie, indicaties bekend van andere neuromodulatievormen. PTNS werd in een prospectieve, multicentrische studie geëvalueerd bij 37 patiënten met symptomen van een overactieve blaas (dat wil zeggen: urgency/frequency syndroom en/of urge incontinentie) en 12 met niet-obstructieve urineretentie. Data werden verzameld met behulp van mictiedagboeken en 'kwaliteit van leven'-vragenlijsten voor en na behandeling. Patiënten werden ingedeeld in responders, zij die succesvol reageerden op de therapie en na de initiële 12 weken verkozen door te gaan, en niet-responders, zij die de behandeling staakten. Een positieve respons werd gezien bij 60% van de patiënten. Bij patiënten met overactieve blaas werd een statistisch significante daling gezien van het aantal incontinentie-episodes, gebruikte verbandjes, mictiefrequentie en de nycturie, terwijl een vergelijkbare stijging werd gezien in het gemiddelde en het kleinste geplaste volume. Bij niet-obstructieve urineretentie werden eveneens veranderingen gezien in het aantal katheterisaties, het gemiddelde en totale gekatheteriseerde volume en het gemiddelde en totale geplaste volume. Ziektespecifieke 'kwaliteit van leven'-vragenlijsten en enkele domeinen van de algemene 'kwaliteit van leven'-vragenlijst verbeterden, vooral bij blaasoveractiviteit. Slechts zeer milde bijwerkingen werden waargenomen.

Aangemoedigd door deze resultaten werden verschillende indicatiegebieden meer in detail bestudeerd. Evaluatie van blaasoveractiviteit en niet-obstructieve urineretentie vond plaats door Vandoninck et al.^{1,2} Dit hoofdstuk presenteert de uitkomsten van PTNS als behandeling van chronische bekkenpijn. In een prospectieve, multicentrische studie werd PTNS geëvalueerd bij 33 patiënten met deze aandoening. Effecten werden gevolgd middels Visual Analogue Scale (VAS) voor pijn dagboeken, de McGill pijn vragenlijst en de SF-36 vragenlijst voor de algemene kwaliteit van leven, afgenomen voor en na 12 weken therapie. Subjectieve respons was gedefinieerd als boven beschreven (het verzoek van patiënt het behaalde resultaat te behouden middels onderhoudsbehandeling), maar nu werd ook een meer objectief responscriterium (daling van het gemiddelde VAS van meer dan 50% en een VAS van minder dan 3 na behandeling) geïnccludeerd. Een subjectieve respons werd bij 42% van de patiënten gezien. Bij 7 patiënten (21%) daalde de gemiddelde VAS meer dan 50%, in nog eens 6 gevallen (18%) met meer dan 25%. Na 12 weken therapie eindigden 7 patiënten (21%) met een VAS onder de 3. In de gehele patiëntengroep verbeterde de kwaliteit van leven (SF-36) significant, net als de totale pijn intensiteit (McGill). Deze zeer bescheiden resultaten zijn in overeenstemming met uitkomsten van andere neuromodulatievormen bij chronische bekkenpijn.

Tenslotte werd onderzocht in hoeverre, voor de drie indicatiegebieden gecombineerd, een succesvolle PTNS therapie ook een verbetering van het seksueel functioneren tot gevolg had. Hiertoe werden 121 met PTNS behandelde patiënten met een overactieve blaas (N=83), chronische bekkenpijn (N=23) of niet-obstructieve urineretentie (N=15) geëvalueerd. Om informatie te verkrijgen over het seksueel functioneren werd een gestandaardiseerde vragenlijst door patiënten ingevuld voor en na 12 weken PTNS. Voorafgaand aan de therapie werden diverse aspecten van het seksueel functioneren als afwijkend beschouwd in 25,3 tot 45,6% van de gevallen. Dit verbeterde significant na behandeling. Patiënten die het meest profiteerden waren vrouwen, patiënten met een overactieve blaas en subjectieve responders. De aspecten van het seksueel functioneren die het best reageerden bleken de tevredenheid over en de frequentie van de seksuele activiteiten, alsmede het libido.

Hoofdstuk 2 leidt tot de conclusie dat klinisch succes middels PTNS veilig kan worden verkregen bij vooral overactieve blaas en niet-obstructieve urineretentie,

terwijl het succes bij chronische bekkenpijn slechts bescheiden is. Naast positieve effecten op disfunctie van de lagere urinewegen kan PTNS ook een verbetering geven van de hiermee nogal eens gepaard gaande seksuele disfunctie.

Hoofdstuk 3 Aangemoedigd door de veelbelovende uitkomsten bij vooral overactieve blaas en mictiestoornissen werd verder onderzoek ingezet om de waarde van PTNS te bevestigen. Hoewel men redelijk objectieve parameters kan onttrekken uit met name (mictie)dagboeken is het urodynamisch onderzoek waarschijnlijk meer geschikt om hardere data over de effectiviteit van PTNS te verzamelen. Derhalve werden urodynamische onderzoeken uitgevoerd voor en na PTNS bij zowel overactieve blaas als niet-obstructieve urineretentie patiënten.

In de eerste studie ondergingen 90 patiënten met symptomen gerelateerd aan overactieve blaas elk 12 PTNS sessies. Objectief succes, het primaire onderzoeksdoel gedefinieerd als een reductie in het aantal incontinentie-episodes van meer dan 50% per 24 uur, werd gezien in 56% van de gevallen. Een verzoek tot onderhoudsbehandeling, beschouwd als subjectief succes, werd gedaan door 64% van de patiënten. Daarnaast verbeterden parameters uit de mictiedagboeken en de kwaliteit van leven vragenlijsten significant ($p < 0,01$). Van 46 patiënten met urodynamische data van voor en na PTNS lieten slechts enkele een volledig verdwijnen van de detrusor instabiliteiten (DI) zien. Desalniettemin bleken toename in cystometrische blaascapaciteit ($p = 0,043$) en het volume waarbij DI optrad ($p = 0,012$) significant. Patiënten zonder DI voor PTNS bleken een 1,7 maal grotere kans op respons te hebben dan zij met DI (OR: 1,75; 95% CI: 0,67- 4,6). Daarnaast: hoe meer uitgesproken de blaasoveractiviteit was, hoe kleiner de kans bleek op een succesvol resultaat (oppervlakte onder de ROC curve 0,64 (95% CI: 0,48-0,80)).

In de tweede studie werden 39 patiënten met chronische mictieproblemen opgenomen in een vergelijkbare prospectieve studie. In deze groep werd een $\geq 50\%$ afname van het totaal gekatheteriseerde volume per 24 uur -het primaire einddoel- gezien bij 41% van de patiënten. Nog eens 26% verbeterde zijn residuen met meer dan 25%, terwijl 59% van de patiënten verzocht om onderhoudsbehandeling. Urodynamische data van voor en na PTNS waren beschikbaar van 27 patiënten. Detrusordruk bij maximale flow, cystometrische residuen en blaas indices ('bladder contractility index' en 'bladder voiding efficiency') verbeterden significant voor de gehele groep ($p < 0,05$). Patiënten met een beperkte mictiestoornis bleken een grotere

kans op succes te hebben dan zij met meer uitgesproken problematiek (OR: 0,73; 95% CI: 0,51-0,94).

Vanuit dit hoofdstuk kan worden geconcludeerd dat PTNS niet alleen resulteert in klinische, maar ook in –meer objectieve- urodynamische veranderingen. Bij patiënten met een overactieve blaas verbetert PTNS de cystometrische capaciteit en vertraagt (maar onderdrukt niet) het moment van detrusor instabiliteit. Bij patiënten met niet-obstructieve urineretentie verbetert PTNS parameters die betrekking hebben op een effectievere blaasleiding. Verder laat dit hoofdstuk zien dat urodynamica behulpzaam kan zijn bij het opstellen van criteria voor een betere patiëntselectie. Voornoemde data zouden verdere ondersteuning moeten bieden aan de betekenis van PTNS.

Hoofdstuk 4 In hoofdstuk 4 worden twee studies gepresenteerd die betrekking hebben op verfijning van de PTNS therapie. Allereerst werd, volgend op enkele urodynamische parameters met mogelijk prognostische betekenis getoond in hoofdstuk 3, gezocht naar klinische parameters met een voorspellende waarde voor een succesvolle uitkomst van de behandeling.

Hiertoe werd PTNS toegepast bij 51 mannen en 81 vrouwen met een gemiddelde leeftijd van 53 jaar (bereik: 21-82 jaar). Van hen werden er 83 behandeld voor een overactieve blaas, 16 voor niet-obstructieve urineretentie en 33 voor chronische bekkenpijn. Alle patiënten moesten mictie- of pijn dagboeken invullen, evenals 'kwaliteit van leven'-vragenlijsten, zowel voor als na behandeling. Ook werden data verzameld betreffende voorgeschiedenis, lichamelijk onderzoek en stimulatie-bijzonderheden. Objectief succes (meer dan 50% verbetering van specifieke symptomen) werd gezien bij 32,6%, subjectief succes bij 51,5% van de patiënten. Helaas bleken de meeste geëvalueerde parameters niet van prognostische waarde. Zelfs een voorgeschiedenis van seksueel en/of lichamelijk misbruik, gevonden bij 12 van 103 onderzochte patiënten, bleek de uitkomst van PTNS niet te beïnvloeden. Daarentegen bleek een lage totaalscore voor PTNS behaald met de SF-36 algehele 'kwaliteit van leven'-vragenlijst voorspellend voor het niet behalen van een objectieve (OR 0,44; 95% CI: 0,2-1, p=0,04), noch een subjectieve respons (OR 0,42; 95% CI: 0,20-0,89, p=0,02). Vooral patiënten met een lage SF-36 Mental Component Summary liepen risico op falen van neuromodulatie therapie: OR 0,12 (95% CI: 0,27-0,55), p=0,006 voor objectief succes. Deze patiënten scoorden eveneens slechter op

de ziektespecifieke 'kwaliteit van leven'-vragenlijsten, ofschoon ze qua ernst van hun ziekte niet verschilden van patiënten met een goede mentale gezondheid.

Behalve onderzoek naar welke patiënten het meest geschikt zijn om therapie te starten dient ook te worden bestudeerd hoe, als mogelijk, behandeling kan worden beëindigd. De tweede studie in dit hoofdstuk werd verricht met als vraagstelling of onderhoudsbehandeling in geval van een positief behandelresultaat werkelijk noodzakelijk is.

Elf patiënten (gemiddelde leeftijd: 51 jaar) met refractaire blaasoveractiviteit (meer dan 7 micties en/of meer dan 3 urge incontinentie-episodes per dag), succesvol behandeld met PTNS, startten onderhoudstherapie. Patiënten vulden mictiedagboeken in, net als kwaliteit van leven vragenlijsten (SF-36 en I-Qol), voor en na een pauze van zes weken in de onderhoudstherapie en ook weer na herstart van de PTNS. De eerste doelstelling bestond uit een meer dan 50% toename van het aantal incontinentie-episodes en/of de mictiefrequentie na 6 weken behandelingspauze. De tweede doelstelling bestond uit een meer dan 50% reductie van de symptomen na herstart van de therapie. Na de 6 weken onderbreking voldeden 7 van de 11 patiënten (64%) aan de doelstelling. Het gemiddelde geplaste volume, de nycturie, het aantal incontinentie-episodes en de incontinentie-ernst verslechterden significant ($p < 0,05$). De tweede doelstelling werd gehaald in 9 van de 11 gevallen (82%). Nycturie, het aantal incontinentie-episodes, de incontinentie-ernst, het gemiddeld geplaste volume en de kwaliteit van leven verbeterden significant ($p < 0,05$).

Vanuit dit hoofdstuk kan worden geconcludeerd dat de meeste klinische parameters van geen waarde zijn voor het voorspellen van het behandelresultaat. Slechts een slechte mentale gezondheid, zoals gemeten via de SF-36 Mental Component Summary bleek negatief voorspellend voor succes en zou derhalve gebruikt kunnen worden voor een betere patiëntselectie. Wanneer patiënten met succes behandeld zijn blijkt onderhoudstherapie noodzakelijk.

Hoofdstuk 5 Nadat duidelijk werd dat in geval van een succesvolle PTNS behandeling onderhoudstherapie noodzakelijk bleek, werden wegen gezocht dit probleem te verlichten aangezien het veel vraagt van zowel de patiënten als de poliklinische praktijk. Overeenkomstig andere neuromodulatie-technieken werd een implantaat ontwikkeld, resulterend in een apparaatje voor radiografisch gecontro-

leerde subcutane stimulatie van de nervus tibialis ofwel Subcutaneous Tibial Nerve Stimulation (STNS).

In dit hoofdstuk worden de eerste resultaten betreffende haalbaarheid en veiligheid van STNS gepresenteerd. Acht patiënten met refractaire blaasoveractiviteit die succesvol behandeld werden met PTNS ontvingen na een pauze van 3 tot 12 maanden een subcutaan implantaat. Evaluatie vond plaats middels mictiedagboeken, 'kwaliteit van leven'-vragenlijsten en lichamelijk onderzoek, afgenomen voor implantatie en 3, 6 en 12 maanden nadien. Op de drie opvolgende evaluatiemomenten haalden respectievelijk 5, 6 en 4 patiënten de primaire objectieve doelstelling van minstens 50% vermindering van het aantal incontinentie-episodes en/of micties in het mictiedagboek. Daarnaast bleken bij 3 en 6 maanden follow up, mictie en kwaliteit van leven parameters significant verbeterd ($p < 0,05$). Ook bleek STNS veilig aangezien de enige bijwerkingen die gevonden werden bestonden uit urineweginfecties, tijdelijke moeilijkheden met lopen en spontane, uitstralende sensaties. Er werden geen lokale infecties, erosies of dislocaties gevonden.

Er kan vanuit dit hoofdstuk worden geconcludeerd dat STNS middels een implantaat zowel mogelijk als veilig is. Daarenboven zou dit hoofdstuk de lezer moeten overtuigen van de vele inspanningen die geleverd worden om PTNS verder te verbeteren, inclusief het belangrijkste nadeel: onderhoudstherapie.

Toekomstverwachtingen

In dit proefschrift worden slechts enkele studies gepresenteerd; veel vragen blijven onbeantwoord. Voor PTNS zal de nabije toekomst daarom vooral bestaan uit verder onderzoek, niet alleen naar zaken over PTNS die onderbelicht bleven, maar ook naar nog steeds bestaande onduidelijkheden betreffende neuromodulatie in het algemeen. Een opkomst van PTNS als een makkelijk toegankelijke en veelgebruikte neuromodulatie techniek is -vooral in Europa- niet voor de hand liggend, aangezien de percutane route een onderhoudsbehandeling vraagt met een te grote belasting voor patiënten en poliklinieken. Daar PTNS wel vergoed wordt in de Verenigde Staten ontbreken financiële prikkels om een implantaat te ontwikkelen dat dit nadeel het hoofd biedt vrijwel volledig. Het is dan ook niet verwonderlijk dat veel urologen

die enthousiast startten met PTNS vlak na de introductie enkele jaren geleden teleurgesteld raakten in de verdere ontwikkelingen en de techniek verlieten.

Wat zijn de belangrijkste kwesties binnen percutaneous tibial nerve stimulation die opgelost dienen te worden?

Werkt PTNS? Hoewel verbeteringen kunnen worden aangetoond in symptomen, kwaliteit van leven, urodynamische parameters en met disfunctie van de lagere urinewegen gepaard gaand seksueel disfunctioneren, zijn er ook veranderingen in het centrale zenuwstelsel die duiden op de werking van PTNS. Toch is het waar: tot op heden kan een placebo-effect niet geheel worden uitgesloten. Hoewel dit onderwerp reeds enige malen werd bediscussieerd in artikelen opgenomen in dit proefschrift, is een placebogecontroleerde studie nog niet verricht: de specifieke kenmerken van de PTNS techniek maken een geblindeerde (laat staan een dubbelblinde), gerandomiseerde, gecontroleerde trial bijna onmogelijk om uit te voeren. Daarbij, bijna geen van zelfs de meest gevestigde neuromodulatietechnieken werd in het verleden serieus vergeleken met placebo. Dit onderwerp zal een van de meest uitdagende zijn voor de nabije toekomst.

Hoe werkt PTNS? Tegenwoordig is het algemeen geaccepteerd dat effecten van vooral sacrale zenuwstimulatie plaatsvinden op spinaal en supraspinaal niveau door inhibitie van spinale neuronen betrokken bij de mictiereflex, van interneuronen betrokken bij spinale segmentale reflexen en van postganglion neuronen.³ Verder spelen mogelijk de inhibitie van de primaire banen richting ruggenmerg en indirecte suppressie van 'guarding reflexes' -door middel van het uitschakelen van signalen vanuit de blaas naar sympathische interne sphincter of externe urethrale sphincter interneuronen- een rol.⁴ Bij niet-obstructieve urineretentie worden de verkregen resultaten door sommige auteurs toegeschreven aan directe veranderingen in de bekkenbodem^{5,6}, dan wel aan hernieuwde afstemming van het 'on/off switch'-mechanisme in de hersenstam.^{3,7} Veel van de voornoemde aannames dienen echter nog nader te worden onderbouwd.

Hoewel de meeste onderzoekers zich vooral richten op klinische resultaten is basaal onderzoek minstens zo belangrijk: verheldering van de vele onopgeloste vraagstukken zal uiteindelijk leiden tot een beter begrip van de echte werking van neuromodulatie en van daar naar de verbetering van behandelresultaten. Eén van

de mogelijkheden om basaal onderzoek te verrichten is met behulp van dierenexperimenten. Zo is bijvoorbeeld bij ratten aangetoond dat PTNS de activiteit in spinale neuronale cellen beïnvloedt door middel van verlaging van de metabole marker c-fos in het spinale mictiecentrum.⁸ In een ander experiment uitgevoerd op katten onder anesthesie, werden argumenten gevonden om aan te nemen dat PTNS werkt via sacrale reflexbanen in plaats van via pijn-, sympathische of cervicothoracale reflexbanen.⁹ Naast dierenexperimenten zijn nieuwe, veelbelovende afbeeldingstechnieken beschikbaar gekomen om het centrale zenuwstelsel te bestuderen, met name 'functional PET-scanning'. PET heeft reeds effecten aangetoond van sacrale neuromodulatie voor niet-obstructieve urineretentie¹⁰, maar er is veel meer onderzoek noodzakelijk.

Wat is de beste manier om PTNS toe te passen? Bijna al het onderzoek tot op heden uitgevoerd maakte gebruik van het zelfde stimulatieprotocol: PTNS werd toegepast in 10 tot 12 wekelijkse sessies van 30 minuten elk. Stimulatieparameters waren vooraf ingesteld en vrijwel gefixeerd en iedere keer werd via één naald gestimuleerd. Het is niet onaannemelijk dat verandering in behandelingschema en/of stimulatieparameters resulteert in andere, misschien zelfs betere therapie-uitkomsten. Hetzelfde geldt voor bilaterale stimulatie.

Met betrekking tot één keer per week PTNS kan gesteld worden dat een versneld schema van 3 tot 4 maal per week stimuleren de behandeluitkomst niet duidelijk beïnvloedt, hoewel er tegenstrijdige uitkomsten zijn betreffende de noodzaak tot onderhoudstherapie nadien.^{11,12} Natuurlijk heeft een versneld schema wel het voordeel van eerdere duidelijkheid over het klinisch resultaat.¹³

Voor wat betreft stimulatieparameters: het is alom geaccepteerd dat de pulsintensiteit bij neuromodulatie wordt ingesteld op een nog goed te verdragen niveau. De puls frequentie echter, bij PTNS 20 Hz, varieert voor verschillende neuromodulatie technieken van 5 tot 20 Hz, hoewel zelfs frequenties tot 150 Hz zijn beschreven. Aangezien gesteld wordt dat de meest optimale frequentie op een voor patiënten onaangenaam laag niveau ligt (5-6 Hz)¹⁴ kunnen studies naar PTNS bij frequenties onder de 20 Hz interessante resultaten opleveren. Hetzelfde geldt voor verandering in pulsduur, 0,2 msec bij PTNS, en hoger (0,5 tot zelfs 1 msec) bij andere technieken.

Naast onderzoek naar behandelingschema en stimulatie parameters kan het ook interessant zijn de mogelijke additionele effecten te onderzoeken van gelijktijdige stimulatie van beide benen. Voor sacrale stimulatie is beschreven dat bilaterale stimulatie in geval van succes misschien niet zo zeer symptomen beter bestrijdt dan unilaterale behandeling, maar wel de kans doet toenemen dat een patiënt überhaupt reageert.¹⁵⁻¹⁷ Uiteraard zouden uitkomsten ten gunste van bilaterale stimulatie nieuwe obstakels opwerpen ten aanzien van de ontwikkeling van een implantaat. En dat is toch waar we uiteindelijk naar toe zullen gaan: een vrij beschikbaar subcutaan implantaat, makkelijk te bedienen door patiënten zelf volgens flexibele, geïndividualiseerde behandelingschema's. Onnodig te zeggen dat er nog een lange weg te gaan is.

Bij welke patiënten zou PTNS moeten worden toegepast? Aangezien PTNS, met 10 tot 12 sessies van een half uur voordat resultaat kan worden gezien, bewerkelijk is, worden voorspellende parameters voor een succesvolle behandeling nog gemist. Enkele onderzoeken hiernaar zijn gedaan voor zowel sacrale als tibialis stimulatie (zie hoofdstuk 4 van dit proefschrift), met als beste kandidaten mentaal gezonde patiënten met een matig ernstige overactieve blaas of niet-obstructieve urineretentie. Verder onderzoek dient plaats te vinden om de criteria voor neuromodulatietherapie te verfijnen ten einde tot betere therapieresultaten te komen. Zodra een subcutaan implantaat voor chronische tibialis stimulatie beschikbaar komt, dienen naar analogie van de sacrale neuromodulatie verdere inspanningen te worden verricht om de testfase vóór implantatie te optimaliseren met als doel verdere vermindering van het aantal onnodig behandelde patiënten.

Hier tegenover staat dat met een verbetering van de resultaten van PTNS behandeling ongetwijfeld gezocht zal worden naar de mogelijke waarde voor andere indicatiegroepen, iets wat ook al gezien wordt bij sacrale neuromodulatie. De meest waarschijnlijk nader te bestuderen groepen zijn: kinderen, neurologische patiënten en patiënten met faecale incontinentie.

Tot op heden zijn vrijwel alle stimulatie- en neuromodulatietechnieken uitgetest op volwassenen, met als uitzondering intravesicale stimulatie bij kinderen met neurogene mictiestoornissen en TENS bij kinderen met niet-neurogene incontinentie. De meerderheid van de neuromodulatietechnieken is namelijk minder geschikt voor kinderen vanwege het invasieve karakter en de noodzaak met stroom te werken in

de anale en/of genitale regio. Hoewel PTNS niet 'niet-invasief' is, kan het feit dat het via de enkel werkt toch minder bedreigend zijn voor kinderen, zodat zich een mogelijkheid voordoet PTNS toe te passen in een jonge leeftijdscategorie. Veelbelovende resultaten uit de eerste twee studies onder respectievelijk 31 en 23 kinderen^{18,19} nodigen in ieder geval uit tot nadere evaluatie.

De tweede patiëntengroep die nader onderzoek waard is, is die van de neurologische patiënten. In veel studies naar neuromodulatie zijn deze patiënten niet opgenomen. Toch kan, in geselecteerde gevallen van vooral multiple sclerose, worden verondersteld dat ook bij hen positief resultaat kan worden behaald. Momenteel is ervaring op dit gebied beperkt en tegenstrijdig²⁰⁻²², maar resultaten zijn bemoedigend genoeg om verder onderzoek te rechtvaardigen.

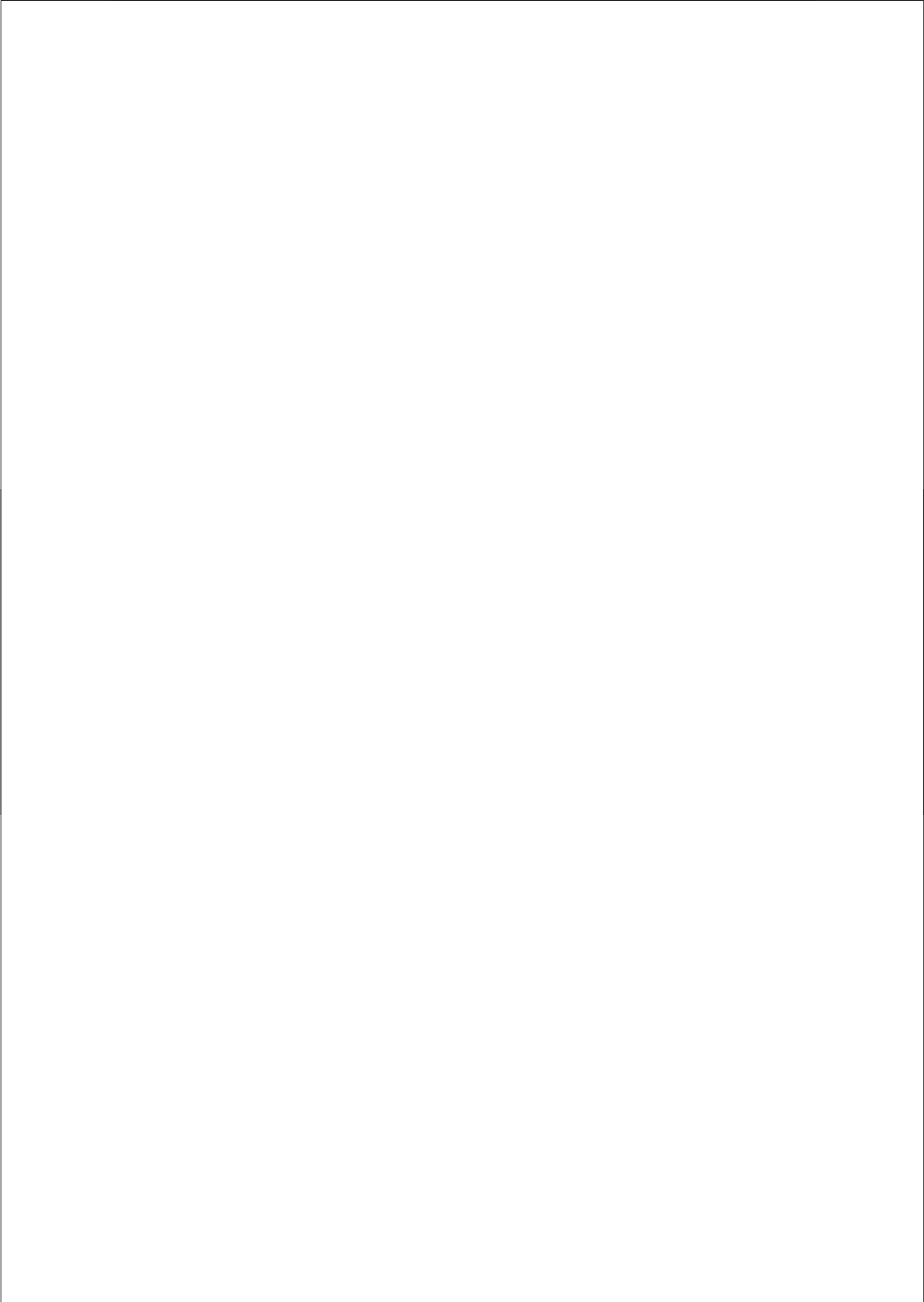
Een gebied tenslotte waarin veel urologen niet geïnteresseerd zijn, maar dat veel gemeen heeft met disfunctie van de lagere urinewegen is dat van de faecale incontinentie. Net als urineverlies heeft faecale incontinentie een grote invloed op de kwaliteit van leven, maar het onderwerp is zo mogelijk nog moeilijker bespreekbaar voor zowel patiënten als zorgverleners. Aangezien de eerste stappen worden gezet in de evaluatie van sacrale neuromodulatie ter bestrijding van deze aandoening²³ kan worden verondersteld dat ook onderzoek naar PTNS zal worden uitgevoerd.²⁴

Het is het lot van de wetenschap: elk antwoord op een vraag levert weer meer nieuwe vragen op. Met dit proefschrift hoop ik in staat te zijn geweest vele nieuwe vragen op te roepen.

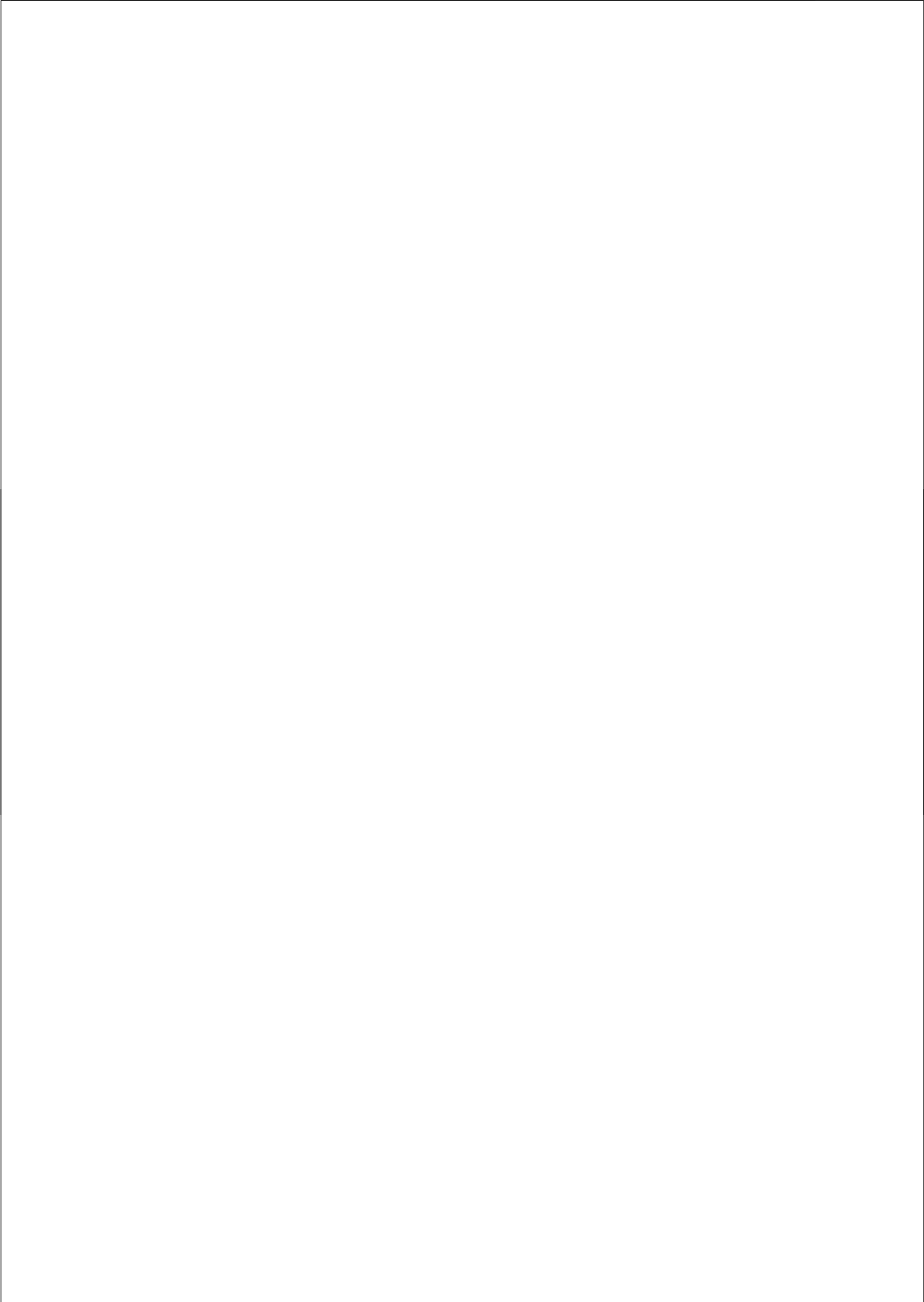
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APPENDICES



Abbreviations

AMFES	Acute Maximal Functional Electrical Stimulation
BCI	Bladder Contractility Index
BVE	Bladder Voiding Efficiency
CI	Confidence Interval
CNS	Central Nervous System
CPP	Chronic Pelvic Pain
DI	Detrusor Instability
EMG	ElectroMyoGraphy`
FES	Functional Electrical Stimulation
GABA	Gamma Amino Butyric Acid
IC	Interstitial Cystitis
ICS	International Continence Society
I-QoL	Incontinence Quality of Life
LUTD	Lower Urinary Tract Dysfunction
MCS	Mental Component Summary (subgroup SF-36 questionnaire)
MES	Maximal Electrical Stimulation
MPQ	McGill Pain Questionnaire
NMDA	N-Methyl D-aspartic Acid
NOUR	Non-Obstructive Urinary Retention
NSF-9	Nine questions regarding Sexual Functioning
NWC	Number of Words Chosen (subgroup McGill pain questionnaire)
OAB	OverActive Bladder
OR	Odds Ratio
PCS	Physical Component Summary (subgroup SF-36 questionnaire)
Pdet	Detrusor Pressure
PNE	Peripheral/Percutaneous Nerve Evaluation
PNS	Pudendal Nerve Stimulation
PRI	Pain Rate Intensity (subgroup McGill pain questionnaire)
PTNS	Percutaneous Tibial Nerve Stimulation
Qmax	Maximal Flow rate
RF	Radio Frequency
ROC	Receiver Operating Characteristic (Curve)

SD	Standard Deviation
SF-36	Short Form 36 (quality of life questionnaire)
SNS	Sacral Nerve Stimulation
SPA	Sexual and/or Physical Abuse
STNS	Subcutaneous Tibial Nerve Stimulation
TENS	Transcutaneous Electrical Nerve Stimulation
UF	Urgency/Frequency
UI	Urge Incontinence
VAS	Visual Analogue Scale

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Curriculum vitae

Michael Rogier van Balken werd op 6 mei 1971 geboren in Amsterdam. Hij behaalde het gymnasium diploma cum laude aan het Serviam College in Sittard in 1989 en startte datzelfde jaar met de studie Geneeskunde aan de Katholieke Universiteit Nijmegen. Tijdens zijn studie werd onderzoek verricht naar semenkwaliteit en bevruchting bij de humane in vitro fertilisatie (begeleider: Dr. L.A. Bastiaans). Na het behalen van zijn doctoraal in 1993 bracht hij de zomer door op de afdeling Pathologie van het Universitair Medisch Centrum Nijmegen als obducent en verrichtte hij onderzoek naar het plasminogeen activator systeem in uvea melanomen (promotie onderzoek Dr. Ir. T.J. de Vries). Aan het einde van zijn co-schappen werd het enthousiasme, opgedaan voor de urologie, vormgegeven in een keuze co-schap en een onderzoek naar inverted papilloma's (begeleider: Prof. Dr. J.A. Witjes).

In 1996 werd het artsexamen behaald en startte Michael als arts-assistent niet in opleiding verbonden aan de afdeling Urologie van het Canisius-Wilhelmina Ziekenhuis te Nijmegen, alwaar na twee jaar chirurgie in het Deventer Ziekenhuis (opleider: Dr. M. Eeftinck Schattenkerk) vanaf 1999 ook de twee perifere jaren van de opleiding urologie werden doorgebracht (opleider: Dr. H.F.M. Karthaus). Hier werd voor het eerst kennisgemaakt met de percutane tibialis stimulatie. De laatste jaren van de opleiding vonden plaats aan het Universitair Medisch Centrum Nijmegen (opleider: Prof. Dr. F.M.J. Debruyne). In deze periode werden de eerste stappen gezet die leidden tot de totstandkoming van dit proefschrift. De nazomer van 2002 werd doorgebracht aan de Clinica Urologica Policlinico G. Rossi, het universiteits-ziekenhuis van Verona, onder bezielende begeleiding van Prof. Dr. W. Artibani en Dr. F. Pesce.

Michael is sedert 1-1-2003 geregistreerd als uroloog en werkzaam aan het Rijnstate Ziekenhuis Arnhem, met als aandachtsgebied de functionele en reconstructieve urologie. Hij is getrouwd met zijn jeugdliefde Bianca en is de meer dan trotse vader van twee prachtige zonen, Wouter en Jochem.

