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Implementation of sacral neuromodulation for urinary indications. A Danish prospective study during the initial 15 months of a new service in a tertiary referral hospital

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ABSTRACT

Objective: Sacral neuromodulation (SNM) is a well-established treatment modality for idiopathic overactive bladder and urgency incontinence, idiopathic fecal incontinence and non-obstructive urinary retention. This study describes the start-up phase of establishing the SNM service. *Primary objective:* To investigate the patient-reported outcome measures of SNM on lower urinary tract dysfunction symptoms. *Secondary objectives:* To investigate bowel function, sexual satisfaction and to monitor SNM safety.

Materials and methods: Twenty-two patients with refractory idiopathic and neurogenic lower urinary tract dysfunction were offered a two-stage test-phase procedure and SNM device implantation. On completing the study, the patients rated their satisfaction with the treatment using a five-point Likert scale and a bother score of urinary, bowel and sexual symptoms on a scale of 1–10 (the worst). Their complications were assessed.

Results: Nineteen patients (86%) were responders during the test phase and had the pulse generator implanted. Seventeen patients were very satisfied/satisfied. A statistically significant change in urinary symptoms bother score was observed in the idiopathic and neurogenic patients, a reduction from 10 to 4 ($p = .0057$) and 10 to 3 ($p = .014$), respectively. Eleven patients (58%) had symptoms from two or three pelvic compartments. Nine patients (47%) had complications. All but one event was resolved.

Conclusions: SNM is safe in this heterogeneous group of patients with refractory lower urinary tract dysfunction of various etiologies. A substantial improvement was observed in the pelvic organ dysfunction, demanding a multidisciplinary approach. More studies are required to standardize the evaluation of the subjective and objective outcomes of SNM.

Abbreviations: SNM: Sacral neuromodulation; PROM: Patient-reported outcome measures; CIC: clean intermittent catheterization; LS: Likert scale; IPG: Implantable pulse generator; PTNS: Percutaneous tibialis nerve stimulation; OAB-wet: Idiopathic overactive bladder – with urgency urinary incontinence; OAB-dry: Idiopathic overactive bladder-dry – without urgency urinary incontinence; nOAB-wet: Neurogenic overactive bladder – with urgency urinary incontinence; nOAB-dry: Neurogenic overactive bladder-dry – without urgency urinary incontinence; NOUR: idiopathic non-obstructive urinary retention; nNOUR: Neurogenic non-obstructive urinary retention; BPS: Bladder pain syndrome; LUTD: Idiopathic lower urinary tract dysfunction; nLUTD: Neurogenic lower urinary tract dysfunction; DanPSS: Danish Prostate Symptoms Score; ICIQ-UI SF: International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form; GRA: Global response assessment

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Introduction

In daily urological practice, patients with refractory lower urinary tract dysfunction (LUTD) often present a challenge due to difficulty establishing the etiology and managing voiding and storage symptoms of this chronic disorder [1,2]. These patients are a heterogeneous and highly prevalent group, inflicting a significant socioeconomic burden owing to the many contacts made to the health care system and the need for assistive devices. Furthermore, the impact on their quality of life is severe [3,4].

LUTD may be secondary to clinically diagnosed neurologic disorders, such as Parkinson's disease, spinal cord injury, or

multiple sclerosis [5]. These patients often suffer from bowel and sexual dysfunction concomitant with an impact on the central nervous system, further increasing morbidity and decreasing quality of life [6–8]. Patients with neurogenic LUTD (nLUTD) might mimic idiopathic LUTD; however, the mechanism behind the neurogenic syndrome is more complex. The symptoms are related to the site and nature of the nervous system lesion, implying that conditions affecting the nervous system may cause bladder function alteration [8].

Tanagho and Schmidt developed the sacral neuromodulation (SNM) therapy in 1982, and the technique has improved significantly [9]. SNM is a well-established treatment modality

for refractory overactive bladder, wet and dry, urinary and fecal incontinence [10–12]. SNM is currently not approved for patients with neurological disorders; however, several studies indicate its efficiency and safety in these patients [13]. The SNM implantation procedure is reversible and minimally invasive with a low rate of adverse events. The InterStim™ II and Micro System for SNM became compatible with magnetic resonance imaging (MRI) in 2020. Consequently, SNM is an attractive alternative for patients with nLUTD, where only major surgery remains a treatment option [14,15]. SNM is incorporated in the European and American urological guidelines and is an option for the former indications if more conservative treatments have failed [16,17].

SNM's mechanism of action is not fully understood. According to different imaging studies, SNM seems to involve the modulation of spinal cord reflexes and brain networks by peripheral afferent nerve fibers. Motor effects mediated *via* efferent nerve fibers on direct stimulation might also be involved [18].

In 2020, SNM was established at a tertiary hospital in Denmark. This prospective study describes our first clinical experience with patients offered SNM within 15 months. The primary objective was to investigate subjective satisfaction of SNM using patient-reported outcome measures (PROM) on refractory LUTD symptoms. The secondary objective was to investigate the subjective satisfaction of SNM on the bowel and sexual function and to monitor SNM safety.

Material and methods

Patient selection

This single-center prospective study was performed between February 2020 and June 2021. Patients were referred to a tertiary Health Care Center due to refractory LUTD or nLUTD and evaluated for SNM. No formal inclusion or exclusion criteria were applied, as the study was intended to reflect real-life clinical practice. Concerns prior to the treatment were discussed with experienced external consultants familiar with SNM treatment, and they attained a consensus. Patients with neurological disorders had to be in a stable cognitive and physical state to manage the procedure precautions. They were presented to the local neurologists for certainty in doubtful cases. The patients provided informed consent. They consented to be the first patients to receive the

treatment at the department despite the procedure's inherent challenges.

Most patients had undergone extensive investigations and treatments, including oral antimuscarinics, beta3-adrenergic agonists, repeated intradetrusor Onabotulinum toxin A injections, percutaneous tibial nerve stimulation (PTNS), clean intermittent catheterization (CIC) and indwelling transurethral or suprapubic catheter. The symptoms included dry overactive bladder (OAB-dry), wet overactive bladder (OAB-wet) or non-obstructive urinary retention (NOUR). Patients with nLUTD and LUTD were classified into the same group according to the predominant symptom; however, nLUTD might comprise storage and voiding symptoms and detrusor sphincter dyssynergia. In this situation, the treatment would be the same.

Patients with anatomic sacral anomalies, pathologic urological conditions related to existing LUTD, cognitive impairment with inability to manage and process precautionary information, or a non-compliance history were not offered SNM. Patients unable to refrain from intense physical activity such as horse riding, biking or physiotherapy for five weeks were omitted.

All the patients were assessed using the following investigations at baseline (Table 1). Imaging of the kidneys and the renal function was primarily done to exclude other urinary system pathologies. The course of patients offered SNM is further described in Figure 1.

Test phase – first step

The implantable pulse generator (IPG) candidates were initially evaluated in a test phase. During this test phase, the SureScan MRI systems tined lead electrode model for InterStim II non-rechargeable and InterStim Micro rechargeable IPG (Medtronic Inc., Minneapolis, MN, USA) were utilized. The patients could choose between the non-rechargeable and rechargeable IPG based on preference.

The test phase followed the standardized electrode placement technique and was conducted under sedation and local anesthesia with the patient in the prone position [15]. The first 12 patients were administered cefuroxime, metronidazole and hexamycine as prophylaxis. On the advice of the microbiologist, the other patients were administered cloxacillin preoperatively. Additionally, a solution of 160 mg hexamycine in 250 ml sterile water was used to rinse the devices and the cavity for the IPG.

Table 1. Examinations and investigations of patients undergoing sacral neuromodulation at baseline.

| | Detailed medical history Physical and neurological examination |
|-------------------------------------|---|
| Clinical examination | |
| Urinary data | Bladder diary recording fluid intake, number of micturitions, voided volumes, degree of incontinence, numbers of CIC, pad tests |
| Questionnaires | DanPSS and ICIQ-UI SF |
| Urological objective investigations | Free flow/rates including post-void residual volume Urodynamics including electromyography Cystoscopy |
| Biochemistry | Blood tests and urinary analysis |
| Imaging | Ultrasound examination of the kidneys Radionuclide imaging for renal function |

CIC: clean intermittent catheterization; DanPSS: Danish Prostate Symptoms Score; ICIQ-UI SF: International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form.

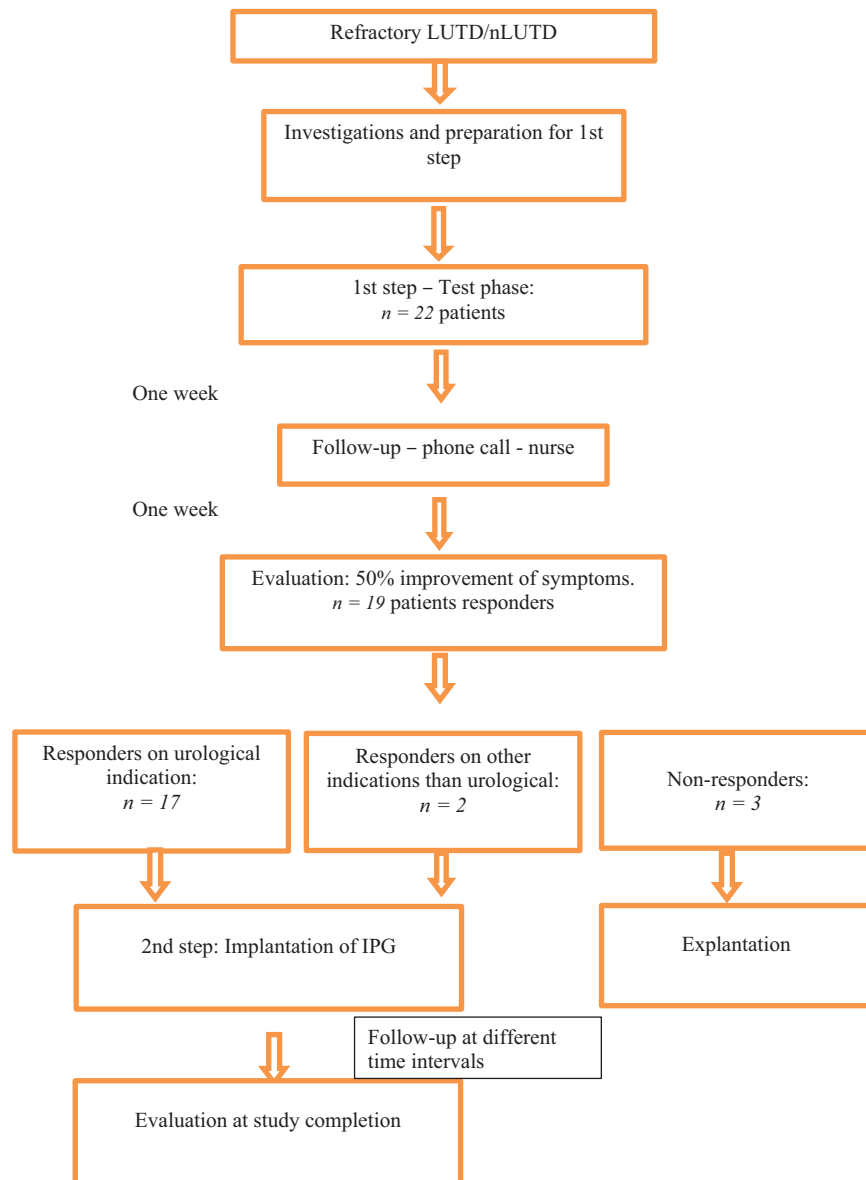


Figure 1. Course of patients undergoing sacral neuromodulation at a tertiary Health Care Center.

The permanent quadripolar tined lead electrode was positioned under fluoroscopic guidance. The foramen with a motor response corresponding to S3 or S4 with the lowest amplitude was chosen. A specialized SNM nurse programmed the system postoperatively. The programs inducing a light sensory vibration from the midline of the anus to the external genitals were chosen and discussed between the nurse and the patient. The nurse performed a follow-up telephone interview after a week. Two weeks postoperatively, the patient was followed up in the outpatient clinic by the operating surgeon. The efficacy was evaluated in a dialogue between patients and surgeons. When over 50% improvement in urinary symptoms was reported, the patient proceeded with the IPG. When the effect was unclear, the test phase was extended for another two weeks to make a final decision.

Implantation of the IPG – second step

After confirming the treatment effect, the patients proceeded with the temporary external wire exchanged for the IPG

under local anesthesia. The cavity for the IPG was rinsed using 160 mg hexamycine in 250 ml sterile water, as used in the first step, and the wound was closed. A specialized SNM nurse, in dialogue with the patient, programmed the system again. The electrode with the best sensory response, defined as midline sensation with no side effects, and with the lowest sensory stimulation level was established [19]. We used uni- and bipolar stimulation modes.

Patient-related outcomes

The intention was to follow up with the patients with a bladder diary and International Consultation on Incontinence Short Form (ICIQ-SF). For practical reasons, the questionnaires were printed on the same sheet as the bladder diary. At the time of documentation for this study, all data were not consistently available, and consequently, there were not enough data for statistical analysis. Therefore, at the end of the study, the patients filled a questionnaire using a

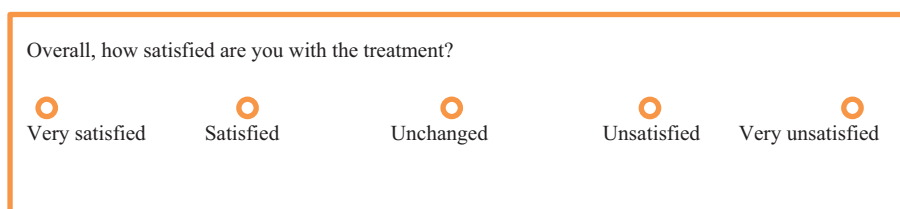


Figure 2. Five-point Likert Scale rating overall satisfaction with the treatment.

| | |
|--|---|
| <p>Urinary symptoms:</p> <p>We want to know about your urinary symptoms BEFORE and AFTER the treatment</p> | <p>On a scale from 1 – 10 (worst) how much did your voiding symptoms affect you BEFORE the treatment?</p> <p>On a scale from 1 – 10 (worst) how much did your voiding symptoms affect you AFTER the treatment?</p> |
| <p>Bowel symptoms:</p> <p>We want to know about your bowel symptoms BEFORE and AFTER the treatment</p> | <p>Did you have or do you still have problems with the bowel function? Yes or no.</p> <p>On a scale from 1 – 10 (worst) how much did your bowel symptoms affect you BEFORE the treatment?</p> <p>On a scale from 1 – 10 (worst) how much did your bowel symptoms affect you AFTER the treatment?</p> |
| <p>Sexual symptoms:</p> <p>We want to know about your sexual symptoms BEFORE and AFTER the treatment.</p> | <p>Did you have or do you still have problems with the sexual function? Yes or no.</p> <p>On a scale from 1 – 10 (worst) how much did your sexual symptoms affect you BEFORE the treatment?</p> <p>On a scale from 1 – 10 (worst) how much did your sexual symptoms affect you AFTER the treatment?</p> |

Figure 3. Questionnaire for rating bother scores of urinary, bowel and sexual symptoms before and after the treatment.

five-point Likert Scale, rating their satisfaction with the treatment (Figure 2). Afterwards, they rated the urinary, bowel and sexual functions on a bother score from 1–10 (worst) before and after the treatment (Figure 3).

Statistical analysis

Urinary, sexual and bowel symptom scores at baseline and study completion were compared using a paired Wilcoxon non-parametric test. R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses. Statistical significance was set at $p < .05$.

Results

Twenty-two patients were offered SNM, and 15 were females (70%). The median age at IPG implantation time was 50.5 years (range, 29–67 years). Fourteen and eight patients were categorized into the LUTD and nLUTD groups, respectively. Further demographic data are presented in Tables 2 and 3.

Response after the test phase – first step

Seventeen patients (77%) were responders with a 50% improvement in urinary symptoms. Two patients (9%) with nLUTD did not report a 50% improvement; however, they experienced

Table 2. Underlying diagnosis of patients undergoing sacral neuromodulation.

| Diagnosis | Number of patients |
|---|--------------------|
| Idiopathic (no known neurological or urological cause for refractory lower urinary tract symptoms) | 9 |
| Bladder pain syndrome | 3 |
| Fowlers syndrome | 1 |
| Complication after obstetric procedure | 1 |
| Multiple sclerosis | 3 |
| Other neurologic diagnosis (Guillan Barré, adrenoleukodystrophy, neuromyelitis optica, stroke, tethered cord) | 5 |
| Total | 22 |

Table 3. Characteristics of patients undergoing sacral neuromodulation grouped by sex and symptom syndromes.

| Primary symptom syndrome | Female – LUTD | Male – LUTD | Female – neurogenic LUTD | Male – neurogenic LUTD |
|--------------------------|---------------|-------------|--------------------------|------------------------|
| OAB-wet | 6 | 2 | 2 | 1 |
| OAB-dry | 3 | | | 3 |
| NOUR | 2 | 1 | 2 | |
| Total: (n = 22) | 11 | 3 | 4 | 4 |

OAB-wet: overactive bladder with urgency urinary incontinence; OAB-dry: overactive bladder without urgency urinary incontinence; NOUR: non-obstructive urinary retention.

improvements in sexual and bowel functions and opted to proceed with IPG. Three patients (14%), two with NOUR and one with BPS did not experience any change in symptoms, and the electrode was explanted. Two of them proceeded to urinary diversion, and the last patient continued with CIC. Consequently, 19 patients (86%) had the IPG implanted, 4 rechargeable neurostimulators and 15 recharge-free systems.

Overall satisfaction after the IPG – second step

At study completion, 15 months after study initiation, the overall satisfaction with the treatment was rated on a five-point Likert scale: 5 – very satisfied, 4 – satisfied, 3 – unchanged, 2 – unsatisfied and 1 – very unsatisfied (Figure 2).

Seventeen (90%) of the 19 patients were very satisfied or satisfied with the treatment; ten patients with LUTD and seven with nLUTD.

One patient had no change in symptoms, and another was unsatisfied with the treatment (Table 4).

A significant change in bother score of urinary symptoms was observed in LUTD and nLUTD patients: a reduction from 10 to 4 ($p = .0057$) and 10 to 3 ($p = .014$), respectively. There was no significant change in bowel and sexual symptoms; however, a trend toward improvement was observed (Figure 4).

Regarding overall changes in symptoms from the pelvic organs, eight patients (42%) had exclusively urinary symptoms and five (26%) had additional symptoms from two other pelvic compartments: the urinary tract and the bowel or sexual organs. Six patients (32%) had symptoms from all three pelvic compartments.

Complications

Nine patients (47%) reported reversible electrode or IPG implantation complications. At study completion, only one

Table 4. Overall satisfaction of patients undergoing sacral neuromodulation at study completion.

| | LUTD | Neurogenic LUTD | % |
|------------------------|-----------|-----------------|------------|
| Very satisfied | 2 | 2 | 21 |
| Satisfied | 8 | 5 | 69 |
| Unchanged | | 1 | 5 |
| Unsatisfied | 1 | | 5 |
| Very unsatisfied | | | |
| Total: (n = 19) | 11 | 8 | 100 |

complication was unresolved. Six patients (32%) experienced events related to the electrode implantation (first step), two experienced bleeding from the electrode implantation site, and the procedure was interrupted. The electrode was successfully implanted months later, and they proceeded to IPG implantation without further complications. Two patients had a displaced electrode in the test phase, and they had correct S3 or S4 motor response during the operation. However, after heavy physical activities, the electrode was displaced, stimulation changed and revisions were successfully performed. Another two patients reported post-operative pain requiring opioids for three days and had no symptoms afterwards.

The last three complications were related to the IPG implantation (second step): Two patients had infected IPG implantation sites. The electrodes and the IPGs were explanted, and after four months, new systems were successfully implanted without complications. The last patient had the rechargeable IPG implanted, and a month later, she still complained of pain from the IPG implantation site and recharging the IPG. Despite all extensive tests to resolve the problem, including IPG replacement, the pain persisted when recharging the IPG at the end of the study. Nevertheless, she wanted to continue with the SNM despite the pain owing to the positive effects of the treatment and the improved quality of life.

Discussion

In our study, we observed that 19 patients with implanted IPG had overall satisfaction with the treatment.

Establishing a new treatment entails a lot of considerations and practical challenges. A crucial point is evaluating the effect of treatment from the patients' point of view and obtaining quantifiable data; also, the data must be reliable and reproducible [1].

The limitations of our study included the inability to obtain data from voiding diaries and validated questionnaires, and several studies focused on the same problem. Tutolo et al., in a systematic review, revealed that studies investigating the efficacy and safety of sacral and percutaneous tibial neuromodulation in non-neurogenic LUTD and chronic pelvic pain did not use a comprehensive evaluation of subjective and objective outcomes combined with satisfaction assessment systematically [20]. A voiding diary can be bothersome for the patient; consequently, data are often not reported or are inadequate [1]. Furthermore, a correlation between the patient's satisfaction and the clinician's outcome assessment is not always significant [1,21]

In a prospective, longitudinal, observational study, Peters et al. demonstrated a relationship between responders to

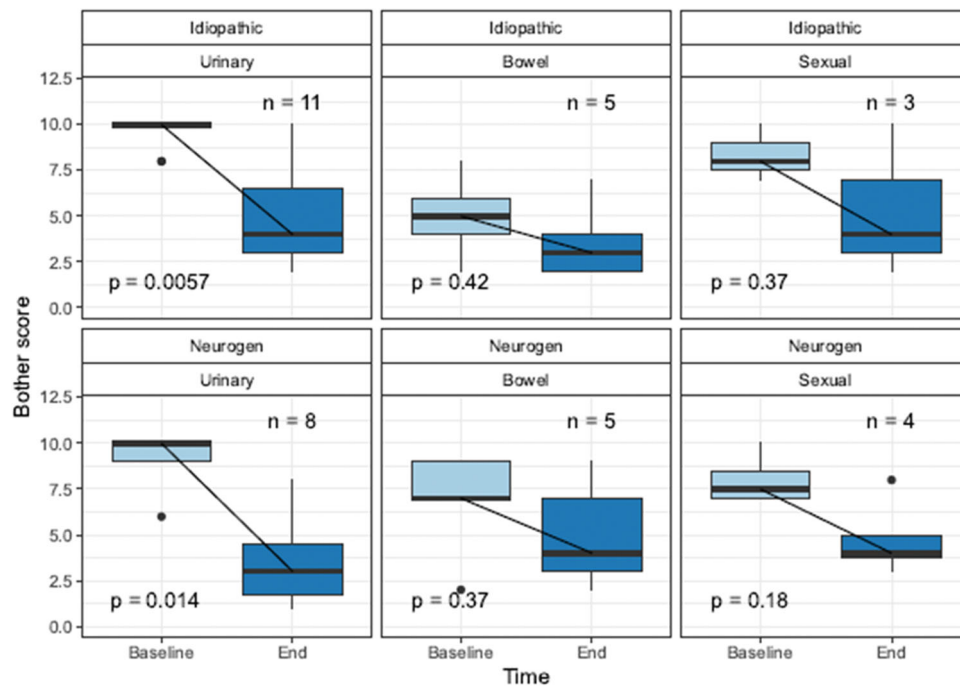


Figure 4. Overall results of changes in bother score 1–10 (worst) of urinary, bowel and sexual symptoms before and after the treatment for patients undergoing sacral neuromodulation.

SNM, objective changes and reduction of bothersome symptoms. They used voiding diary parameters, measured voided volumes, rated urgency and pelvic pain on a 10-point scale and symptom-specific global response assessments (GRA). They observed that the GRA responder group demonstrated significant reductions in bothersome symptoms and that GRA were able to assess changes identified by the voiding diary data [1].

Hence, we valued obtaining a direct measure of the patient-reported outcome (PROM) [22]. We wanted a quick, easy and simple way for the patients to monitor the treatment efficacy and their satisfaction. Hence, we used a simple questionnaire, a five-point Likert Scale and a bother score for the corresponding urinary, bowel and sexual functions before and after the treatment.

There is no consensus on which objective parameters to use for predicting SNM outcome and how to follow up. In this context, the value of urodynamics remains unclear. It cannot predict SNM outcome, and urodynamics results do not change SNM indication [14,23]. The test phase of SNM remains the best approach to predict the potential therapeutic success of SNM for urinary indications [14]. SNM can be applied to various symptom-based conditions with different etiologies. A heterogeneous group of patients might present with the same clinical phenotype; however, SNM response might differ due to the underlying etiology [20]. Urodynamics might help reveal the underlying pathophysiology and treatment response. Switching off the IPG returns the symptoms and urodynamic results to the baseline, suggesting that it is not a curative but a symptomatic treatment [24,25].

In our study, over half of the patients complained of bowel or sexual dysfunction, combined with urinary symptoms.

Various symptoms underline the complexity of treating patients presenting with LUTD of different etiology and the

need for a multidisciplinary approach. Berghmans et al. conducted two extensive epidemiological studies concerning the prevalence and triage of first-contact complaints on pelvic floor dysfunctions. The study included male and female patients referred from other hospitals for a second or third opinion, which is comparable with the status of our department [26,27]. The patients were asked about their pelvic floor dysfunction during the last six months, and the severity was registered on a scale of 0 to 10. They concluded that females and males presented multifactorial problems, needing more than one specialist. Our results reflect the same tendency with an equal distribution between LUTD and nLUTD.

Two of our patients were known with bladder pain syndrome (BPS) without pathology. SNM is not approved for treating BPS; however, a systematic review on SNM treating chronic pelvic pain revealed that SNM is effective in treating the storage symptoms in patients with BPS (frequency, urgency and nocturia) [26,28]. The main complaints of both our patients with BPS were urgency and nocturia, which considerably improved after treatment, and they also experienced less pain.

Our study revealed that SNM could be done without life-threatening side effects. The overall complication rate is rather high compared to other studies and most complications were related to the electrode implantation and the learning curve around the SNM set-up [29]. Due to IPG-site infection requiring revision under local anesthesia, the most severe complication was classified as Grade IIIa according to Clavien-Dindo. There are no evidence-based recommendations for antibiotic prophylaxis to avoid infections from implanting sacral devices [15,30]. The local microbiologist was consulted for the appropriate perioperative antibiotic regimen. The regimen of antibiotics for the rest of the patients in the study was changed from cefuroxime, metronidazole and hexamycine to dicloxacillin. *Staphylococcus aureus* is the most cultured organism and is sensitive to

prophylactic antibiotics. No other study has reported intestinal bacteria as a causative agent [30].

Our study reflects a real-life situation of establishing a new service. Based on the experiences during the process, we have some recommendations:

The patients referred for SNM are a heterogeneous and complex group, with most having a long history of investigations and unsuccessful treatments. Consequently, they are eager for the treatment; however, not all of them are appropriate candidates. Medical doctors must make accurate diagnoses and discuss expectations with patients; moreover, a bladder diary is crucial.

On the other hand, many urologists remain unfamiliar with SNM. Thus, implementing a new service like SNM requires considerable investigation and research effort, learning about the procedure and learning how to plan patient follow-up. It requires learning at all levels: colleagues, operation staff and staff at the outpatient clinic. Selecting dedicated teams at every step of the setup is crucial.

Finally, discussing the cost-benefit of the treatment is essential. The SNM devices are expensive, and the longer lasting effect of SNM compared to other treatments for patients with refractory LUTD must be considered a strong argument.

Conclusions

This study describes the start-up phase and learning curve of establishing SNM primarily for urological indications.

The complexity of patients with refractory LUTD is multifactorial. SNM is safe and effective for selected patients with refractory LUTD of various etiologies. A trend toward improving bowel and sexual dysfunctions was observed, indicating a beneficial effect on pelvic organ function, thus, demanding a multidisciplinary approach to improving quality of life.

Clinical studies with prolonged follow-up are required to standardize the evaluation of the subjective and objective outcomes of SNM to provide the right treatment to the right patient at the right time.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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