Systematic Literature Review and Meta-Analysis of Sacral Neuromodulation (SNM) in Patients with Neurogenic Lower Urinary Tract Dysfunction (nLUTD): Over 20 Years’ Experience and Future Directions

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ABSTRACT

Introduction: Sacral neuromodulation (SNM) has been used in carefully selected patients with neurogenic lower urinary tract dysfunctions (nLUTD) for over two decades.

Methods: The aim of the current work was to perform a systematic literature review and meta-analysis of studies reporting the safety and effectiveness of SNM in patients with nLUTD (neurogenic detrusor overactivity, non-obstructive urinary retention, or a combination of both). For this purpose a systematic literature research was conducted using Embase (OvidSP), MEDLINE (OvidSP), MEDLINE In-Process Citations & Daily Update (OvidSP), MEDLINE (OvidSP) e-Pub ahead of print, Cochrane Central Register of Controlled Trials (CENTRAL), NIH Clinicaltrials.gov, and WHO International Clinical Trials Registry Platform (ICTRP) between 1998 and March 2020, supplemented by a hand search.

Results: Forty-seven studies were included in the systematic literature review. Twenty-one studies comprising a total of 887 patients were included in the meta-analysis of test SNM. The pooled success rate of SNM test stimulation was 66.2% (95% CI 56.9–74.4). Depending on neurogenic conditions test success rates varied greatly. Twenty-four studies with a total of 428 patients were included in the meta-analysis of permanent SNM. The success rate of pooled permanent SNM was 84.2% (95% CI 77.8–89.0). Among the identified studies, the most common adverse events (AEs) were loss of effectiveness, infection, pain at implant site, and lead migration with AE rates of 4.7%, 3.6%, 3.2%, and 3.2%, respectively. Limitations entail lower level of evidence (Oxford classification 3–4) of included studies, significant risk of bias, small sample sizes in some studies, the inclusion of retrospective case series, substantial

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between-study heterogeneity, heterogeneous patient populations, insufficient disease classification, and variations in terms of outcome parameters as well as techniques. Furthermore, long-term data are limited.

**Conclusion:** This meta-analysis supports not only the benefits of permanent SNM for various nLUTDs but also high overall success rates, similar to idiopathic patients. Current data of the analyzed studies showed that SNM is safe for these patients. However, more vigorous studies and/or registries are needed before definitive conclusions can be drawn.

**Keywords:** Implantable neurostimulators; Magnetic resonance imaging; Meta-analysis; Neurogenic lower urinary tract dysfunction; Sacral neuromodulation

| Key Summary Points |
| --- |
| **Why carry out this study?** |
| Sacral neuromodulation (SNM) has been used for more than 20 years in patients with neurogenic lower urinary tract dysfunctions (nLUTD). |
| With new MRI-safe devices available, there is an increasing interest in these indications. However, clinical data are limited. |
| **What was learned from the study?** |
| This systematic literature review supports the effectiveness and safety of SNM in patients with nLUTD. |
| More vigorous studies are needed. |

**INTRODUCTION**

With more than 325,000 implantations worldwide, sacral neuromodulation (SNM) has become a widely adopted treatment modality for non-neurogenic urge urinary incontinence (UUI), urgency-frequency syndrome, non-obstructive urinary retention, and fecal incontinence since its US Food and Drug Administration (FDA) approval in 1997, 1999, 1999, and 2011, respectively [1–5]. Although the pioneering preclinical and clinical research by Tanagho et al. on sacral nerve stimulation was based on neurological subjects [6], clinical evidence in this subpopulation is still limited.

Neurogenic lower urinary tract dysfunctions (nLUTD) comprise storage and voiding symptoms or a combination of both. These conditions can be subdivided into three categories: injury/trauma [i.e., spinal cord injury (SCI), cerebrovascular injury, pelvic surgeries], degenerative [i.e., multiple sclerosis (MS), Parkinson disease (PD)], and congenital (i.e., spina bifida, cerebral palsy). These neurologic patients show a wide spectrum of bladder pathologies depending on the level and extent of neuronal lesions. In addition, bladder symptoms may be accompanied by bowel or sexual dysfunctions [7]. The armamentarium of the bladder management encompasses anticholinergic drugs, beta-3-adrenergic receptor agonists, injections of botulinumtoxinA, intermittent catheterization, augmentation cystoplasty, and urinary diversion with a limited level of evidence for many of these treatment options in these often-difficult-to-treat patients [8]. Since at least 40% of the neurologic patients are unsatisfied with their therapy regimen over the long term [9–11], there has been an intensive search for more therapeutic options.

In 2010, Kessler et al. reported promising results of SNM in patients with nLUTD: in a meta-analysis the pooled success rate for test SNM was 68% and the permanent SNM success rate was 92% [12].

In the current guidelines of the European Association of Urology (EAU) SNM has been described as a treatment for nLUTD, but without concrete guidance or recommendations.
The recently introduced new full-body magnetic resonance imaging (MRI)-safe SNM devices [14] will offer broader access to a patient group that has often been considered as a contraindication due to the need for regular MRI investigations. For example, in a population-based study of patients with MS, prevalence rates of lower urinary tract symptoms or fecal incontinence were high, at 75% and 29%, respectively [15]. With modern 3-T scanners widely available, MRI has become a commonly used tool for the evaluation of patients with MS, with many patients undergoing frequent MRI screenings for optimal therapeutic guidance [16, 17]. Similarly, MRI is also used as surveillance in many patients with chronic SCI, which represents another group with a high prevalence of nLUTD [18, 19].

Since the meta-analysis by Kessler et al. many further studies have investigated SNM in nLUTD. This review aims to update the findings of the Kessler analysis and will address knowledge gaps in this challenging and often very heterogeneous patient population. A systematic literature search was conducted to collate effectiveness and safety evidence as primary and secondary outcome, and a meta-analysis was performed to determine the overall success rates of SNM test stimulation and chronic SNM with the permanent implant in the treatment of patients with nLUTD.

METHODS

Data Sources and Searches for Systematic Literature Review

The systematic literature review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [20]. A search strategy was developed; the PICOS elements and search strings are provided in the supplementary material. The following databases were searched: Embase (OvidSP), MEDLINE (OvidSP), MEDLINE In-Process Citations and Daily Update (OvidSP), MEDLINE (OvidSP) e-Pub ahead of print, Cochrane Central Register of Controlled Trials (CENTRAL), NIH Clinicaltrials.gov, and WHO International Clinical Trials Registry Platform (ICTRP). Electronic searches for identifying literature included a time period between January 1998 and March 31, 2020. The electronic searches were supplemented by a manual search. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Study Selection

Inclusion and exclusion criteria of the systematic literature review are summarized in Table 1. Records retrieved during the searches were stored in a reference library and duplicate records were removed before screening (deduplication). After de-duplication, every record retrieved in the search was marked as “include” or “exclude” after review of the study title and abstract (if available) by two independent reviewers. Full-text articles were obtained for citations that met the inclusion criteria or in cases in which it was unclear if the record met the inclusion criteria. The full-text review was also carried out by the two independent reviewers. Disagreements were resolved through discussion.

Data Extraction and Quality Assessment

The study variables recorded were year of publication, level of evidence, number of patients with nLUTD, sex, age, underlying neurological disorder, length of follow-up, and the success rates of test and permanent SNM. Criteria for success were based on the reviewer’s judgment. Treatment success was generally defined as ≥ 50% improvement of symptoms, including other cutoff thresholds such as ≥ 70%, ≥ 75% improvement, and cure, but other parameters such as significant symptom improvement, positive treatment outcome, patient satisfaction, non-failures, non-explants, or non-dropouts have also been used (see Table 2S in the supplementary material).

Percentage and type of adverse events (AEs) were analyzed to assess safety. AEs were assigned
to one of the following categories: infection, pain at implant, adverse stimulation, lead migration, lead breakage, hardware issues, adverse change in bowel function, loss of effectiveness, and other. Battery replacements were not considered a therapy revision or failure if due to battery depletion [21].

Quality appraisal of the included studies was carried out through classification of the level of evidence and type of study according to the Oxford Centre for Evidence-Based Medicine criteria reported by Howick et al. [22]. Furthermore, the methodological quality of the non-randomized studies included in the meta-analysis was assessed using the ROBINS-I tool [23]. Risk of bias due to confounding factors, selection of participants, classification of interventions, deviations from interventions, missing data, measurement of outcomes, and selection of reported results was determined. Risk of bias graphs were generated by the online robvis tool [24].

Data Synthesis and Analysis

For this meta-analysis studies with at least four patients were included. Meta-analyses were conducted to generate pooled estimates for test and permanent success rates. Sensitivity analyses were conducted to assess the impact of including very small studies (≥ 4 patients) versus larger studies (≥ 10 patients) in the analyses. The pooled success rate estimates and corresponding 95% confidence intervals were calculated using the DerSimonian–Laird random-effects model to account for between-study heterogeneity. The analyses were conducted in
| References                  | Publication year | Level of evidence | Study type | No. of neurogenic patients | No. of women (% female) | Mean age, year (of neurogenic patients) | Mean follow-up (range)* | Study includes data on |
|----------------------------|------------------|-------------------|------------|----------------------------|-------------------------|----------------------------------------|-------------------------|-------------------------|
| Al-Azzawi et al.           | 2018             | 4                 | PCS        | 11                         | 14 (58%)*               | 32.8*                                  | 12 months (median)       | T + P                   |
| Amundsen et al.            | 2005             | 3                 | PCoS       | 23                         | 91 (87%)*               | 60*                                    | 29 months (8–48)*        | P                       |
| Andretta et al.            | 2014             | 4                 | RCS        | 17                         | 13 (76%)*               | 49.8                                   | 52 months                | P                       |
| Arlen et al.               | 2011             | 3                 | RCoS       | 32                         | 16 (50%)                | 56.03                                 | 2.3 years                | T + P                   |
| Bartley et al.             | 2017             | 3                 | PCS        | 109                        | 84 (77.1%)              | 63                                     | 2.3 years                | T + P                   |
| Bertapelle et al.          | 2008             | 4                 | PCS        | 30                         | 68 (71%)*               | NR                                    | NR (12–48 months)        | T + P                   |
| Bosch et al.               | 1998             | 4                 | CS         | 7                          | 7 (100%)                | 46*                                   | 6 months                 | T + P                   |
| Bosch et al.               | 2000             | 4                 | PCS        | 11                         | 70 (82%)*               | 46.2*                                 | 47.1 months              | T + P                   |
| Bross et al.               | 2003             | 4                 | PCS        | 24                         | NR                      | 46*                                   | NR                      | T                       |
| Carone et al.              | 1999             | 4                 | RCS & PCS  | 12                         | NR                      | NR                                    | 13.3 months              | T + P                   |
| Chaabane et al.            | 2011             | 4                 | RCS        | 62                         | 47 (76%)                | 50.5                                  | 4.3 years                | T + P                   |
| Chartier-Kastler et al.    | 2000             | 4                 | PCS        | 32                         | 9 (100% at permanent implant) | 42.6                                 | 43.6 months (7–72)       | T + P                   |
| Chartier-Kastler et al.    | 2001             | 4                 | PCS        | 14                         | 7 (50%)                 | 41.7                                  | 18 months                | T                       |
| Chen et al.                | 2015             | 4                 | RCS        | 23                         | 6 (26%)                 | 37.3                                  | 17.5 months              | T + P                   |
| Daniels et al.             | 2010             | 4                 | RCS        | 32                         | 27 (84%)                | 61.8 (27–83)                         | 29.3 months              | T + P                   |
| References               | Publication year | Level of evidence | Study type | No. of neurogenic patients | No. of women (% female) | Mean age, year (of neurogenic patients) | Mean follow-up (range)* | Study includes data on |
|-------------------------|-----------------|-------------------|------------|---------------------------|------------------------|-----------------------------------------|------------------------|------------------------|
| Denzinger et al.        | 2012            | 4                 | PCS        | 8                         | 6 (75%)                | 46.5                                    | 12 months*             | T + P                  |
| Dobberfuhl et al.       | 2017            | 4                 | RCS        | 121                       | (77.2%)                | NR                                      | NR                     | T + P                  |
| Engeler et al.          | 2015            | 4                 | PCS        | 17                        | 13 (76%)               | 46.3                                    | 3 years                | T + P                  |
| Garg et al.             | 2007            | 4                 | CR         | 1                         | 1 (100%)               | 58                                      | 8 months               | T + P                  |
| Groen et al.            | 2012            | 4                 | PCS        | 5                         | 15 (83%)*              | 15 (9–17)                               | 28.8 months            | T + P                  |
| Hohenfellner et al.     | 1998            | 4                 | PCS        | 11                        | 9 (81%)                | 43.4                                    | 13 months (9–28)       | T + P                  |
| Hohenfellner et al.     | 2001            | 4                 | CS         | 27                        | 19 (70%)               | 44.9                                    | 54 months (11–96)      | T + P                  |
| Ishigooka et al.        | 1998            | 4                 | CS         | 4                         | 1 (25%)                | 36.8                                    | 36 weeks               | P                      |
| Lansen-Koch et al.      | 2012            | 4                 | PCS        | 10                        | 4 (40%)                | 26.4                                    | 1, 3, 6, & 12 months   | T + P                  |
| Lavano et al.           | 2004            | 4                 | CS         | 6                         | NR                     | NR                                      | Max. 26 months         | T + P                  |
| Lombardi et al.         | 2008            | 3                 | PCoS       | 17                        | 17 (100%)              | 39.4                                    | 22 months (median)     | P                      |
| Lombardi et al.         | 2009            | 4                 | RCS        | 24                        | 10 (42%)               | 46                                      | 61 months (median)     | T + P                  |
| Lombardi et al.         | 2011            | 4                 | RCS        | 37                        | 0                      | NR                                      | > 3 years (median)     | T + P                  |
| Lombardi et al.         | 2013            | 4                 | RCS        | 77                        | 27 (35%)               | Non-responders: 41.7 Responders: 40.1   | 54 months              | T + P                  |
| References   | Publication year | Level of evidence | Study type | No. of neurogenic patients | No. of women (% female) | Mean age, year (of neurogenic patients) | Mean follow-up (range)* | Study includes data on |
|--------------|------------------|-------------------|------------|-----------------------------|-------------------------|----------------------------------------|------------------------|--------------------------|
| Lombardi et al. | 2014             | 4                 | RCS        | 85                          | 33 (39%)                | Non-responders: 39.3 Responders: 38.2 | 50 months (6–95)        | T + P                    |
| Marinkovic et al. | 2010             | 4                 | RCCS       | 14                          | 14 (100%)               | 46                                    | 4.32 years             | T + P                    |
| Marinkovic et al. | 2011             | 4                 | RCS        | 7                           | 7 (100%)                | 51                                    | 3.87 years             | T + P                    |
| Minardi et al. | 2005             | 4                 | RCS & PCS  | 5                           | 3 (60%)                 | 48.6                                  | 30.4 months (24–38)    | T + P                    |
| Minardi et al. | 2012             | 4                 | RCS        | 25                          | 15 (60%)                | 45.2 (31–68) (at permanent implant)   | 49.4 months            | T + P                    |
| Peters et al. | 2013             | 3                 | PCoS       | 71                          | 47 (75%, at permanent implant) | 63 (at permanent implant)          | NR                     | T + P                    |
| Roth         | 2007             | 4                 | CR         | 1                           | 1 (100%)                | 45                                    | 5 months               | T + P                    |
| Schurch et al. | 2003             | 4                 | CS         | 3                           | 2 (66%)                 | 31                                    | NR                     | T                        |
| Seif et al.  | 2004             | 3                 | RCoS       | 41                          | NR                      | 53.6*                                 | NR                     | T                        |
| Sharifaghdas | 2019             | 4                 | RCS        | 4 (≥ 16 years)              | 2 (50%)                 | 16.75 (successfully treated patients) | 14.25 months*          | T + P                    |
| Sievert et al. | 2010             | 3                 | PCoS       | 10                          | 0 (0%)                  | 31                                    | 26.2 months            | P                        |
| Spinelli et al. | 2003             | 4                 | PCS        | 5                           | 12 (80%)*               | 49*                                   | 11 months (5–19)       | T + P                    |
| Wallace et al. | 2007             | 4                 | RCS        | 33                          | 31 (94%)                | 54                                    | 12.4 months (4–32)     | T + P                    |
| Wöllner et al. | 2016             | 4                 | RCS        | 50                          | 30 (60%)                | 46                                    | 1.3 years              | T + P                    |
| Wosnitzer et al. | 2009             | 4                 | CR         | 1                           | 1 (100%)                | 20                                    | 5 months               | T + P                    |
R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria; 2019) [25] and used a logit transformation and inverse variance weighting.

Search Results

The search of the electronic databases retrieved 1522 records and 4 by additional hand search. This total was reduced to 1177 after de-duplication. A total of 993 records were excluded, leaving 184 records for a full review. Studies that only included children (aged < 16 years) were excluded, as were non-human studies, non-original or non-English articles, studies not published as full-text articles or published before 1998 or later than March 31, 2020. In addition, studies without any relevant outcome parameter in the neurologic patient population were excluded. As the assumptions of a meta-analysis require studies to be independent (i.e., no overlap of patients), the most recent or relevant study was selected for inclusion in the analysis to avoid an overlap of patients.

RESULTS

Included Studies

A total of 47 records were identified for inclusion in the systematic literature review (Table 2). The level of evidence ranged from 3 to 4 according to the Oxford Centre for Evidence-Based Medicine [22]. Risk of bias graphs are presented in Figs. 1, 2. A flow diagram of the included/excluded records at each stage is shown in Fig. 3.

Study and Patient Characteristics

The identified studies included retrospective or prospective clinical studies, cohort studies, and case reports. Two studies (Carone et al. 1999; Minardi et al. 2005) [26, 27] were both a prospective and retrospective clinical trial. The level of evidence of all included studies was 3 or 4 according to the Oxford level of evidence table of 2011. In total 887 patients presenting
with nLUTD across all included studies were identified. The mean patient age of the analyzed patient population ranged from 16.75 to 63 years (mean ± standard deviation (SD), 47.7 ± 12.6 years) and the proportion of women in the analyzed, purely neurological patient population was 59.9%. Most of the studies (38/47) reported both test and permanent SNM outcomes.

**Effectiveness of SNM**

**Test Success Rates by Underlying Condition**

The neurogenic conditions underlying LUTD in patients in the included studies are shown in Table 3 for the test stimulation. The conditions were reported for varying degrees of thoroughness. For example, the proportion of patients with a particular condition is not clearly stated in all studies, nor is the number of patients with a particular condition who successfully responded to the therapy. The imprecise nature of the reporting makes it difficult to estimate precise success rates of SNM in individual conditions. Moreover, there was a significant variation in the classification of the underlying conditions in the included studies.

The underlying conditions affecting most patients were back surgery, incomplete SCI, and MS, with at least 151, 116, and 94 patients undergoing test SNM, respectively. Test success rates for back surgery and MS were significantly higher than those for incomplete SCI (84.1% and 76.6% versus 48.3%). Lower test success rates of about 50% were also observed in patients with spina bifida/myelomeningocele, cerebral vascular disease, and PD, although the patient numbers in the last group was small ($n = 11$).

Complete SCI has long been considered a contraindication for SNM [28], since pioneering studies in this patient group failed to demonstrate any clinical benefit [29, 30]. In contrast, early treatment with bilateral SNM during the spinal shock phase has shown promising results with 8 out of 10 patients benefiting from SNM [31].

**Test Success Rates by Type of nLUTD**

Dividing nLUTD in the three subgroups (neurogenic detrusor overactivity (nDO), neurogenic non-obstructive urinary retention, or a combination of both) revealed test success rates of 61%, 52%, and 69%, respectively.

**Meta-Analysis**

Twenty-one studies comprising a total of 887 patients were included in the meta-analysis of test SNM and the pooled test SNM success rate was 66.2% (95% CI 56.9–74.4) (Fig. 4a) [21, 29, 32–50]. Twenty-four studies with a total of 428 patients were included in the meta-analysis of permanent SNM [21, 26, 29, 31–38, 40, 42–45, 48, 49, 51–56]. The success rate of pooled permanent SNM was 84.2% (95% CI 77.8–89.0) according to a per-protocol analysis (Fig. 4b). The likelihood of receiving a permanent, definitive SNM device is approximately 55% (intention-to-treat analysis).

Sensitivity analyses were performed excluding studies with fewer than 10 patients in order
### Fig. 2 Risk of bias assessment of included studies for permanent SNM

| Study                        | D1 | D2 | D3 | D4 | D5 | D6 | D7 |
|------------------------------|----|----|----|----|----|----|----|
| Al-Azzawi 2018               | -  | -  | +  | +  | +  | +  | -  |
| Amundsen 2005                | ?  | -  | +  | +  | -  | +  | -  |
| Andretta 2014                | ?  | x  | +  | +  | x  | -  | x  |
| Arlen 2011                   | -  | x  | +  | +  | -  | -  | x  |
| Bertapelle 2008              | ?  | x  | +  | -  | -  | -  | x  |
| Carone 1999                  | ?  | !  | +  | ?  | -  | !  | x  |
| Chaabane 2011                | +  | +  | +  | +  | +  | -  | -  |
| Chartier-Kastler 2000        | +  | -  | +  | +  | +  | +  | +  |
| Chen 2015                    | +  | x  | +  | +  | +  | +  | +  |
| Daniels 2010                 | -  | x  | +  | +  | -  | -  | -  |
| Denzinger 2012               | -  | -  | +  | -  | -  | -  | x  |
| Engeler 2015                 | +  | -  | +  | -  | +  | -  | x  |
| Hohenfellner 1998            | +  | -  | +  | +  | +  | +  | +  |
| Hohenfellner 2001            | -  | ?  | +  | +  | x  | -  | -  |
| Ishigooka 1998               | !  | !  | +  | -  | -  | x  | x  |
| Lavano 2004                  | !  | !  | +  | -  | +  | +  | -  |
| Lombardi 2014                | +  | x  | +  | -  | +  | +  | -  |
| Marinkovic 2010              | +  | x  | +  | +  | x  | x  | x  |
| Minardi 2012                 | -  | -  | +  | +  | -  | x  | x  |
| Peters 2013                  | -  | -  | +  | +  | ?  | -  | -  |
| Sharifiaghdas 2019           | +  | x  | +  | +  | +  | +  | +  |
| Sievert 2010                 | +  | -  | +  | +  | +  | +  | +  |
| Wallace 2007                 | -  | x  | +  | +  | -  | -  | -  |
| Wöllner 2016                 | +  | -  | +  | -  | -  | -  | -  |

**Domains:**
- D1: Bias due to confounding.
- D2: Bias due to selection of participants.
- D3: Bias in classification of interventions.
- D4: Bias due to deviations from intended interventions.
- D5: Bias due to missing data.
- D6: Bias in measurement of outcomes.
- D7: Bias in selection of the reported result.

**Judgement**
- Critical
- Serious
- Moderate
- Low
- No information

△ Adis
to assess the sensitivity of the results when including very small sample sizes (online supplementary material). The pooled success rates for test SNM and permanent SNM were 64.2% (95% CI 54.6, 72.8) and 82.9% (95% CI 75.8, 88.2), respectively. Therefore, the results were comparable to the analyses including at least four patients.

**Safety of SNM (Chronic Implant)**

Following permanent SNM, AEs were reported by less than 25% of 494 patients with nLUTD. For comparison, Kessler et al. reported a similar pooled AE rate (24%) in their meta-analysis from 2010 [12]. The results presented in Table 4 only include patients from studies in which AEs were reported, or in which it was specifically stated that no AEs occurred. The most common AEs were loss of effectiveness, infection, pain at implant site and lead migration with AE rates of 4.7%, 3.6%, 3.2% and 3.2% respectively. Adverse stimulation was reported in 2.0% of patients.

**DISCUSSION**

SNM is an established treatment modality for idiopathic (non-neurogenic) overactive bladder and non-obstructive urinary retention. However, its value for neurological patients seems to be less clear. In this meta-analysis of neurological patients pooled success rates for test SNM...
(66.2%) as well as for permanent SNM (84.2%) seem to be comparable to SNM outcomes in idiopathic patient populations (test, 57–72% and 82% for permanent SNM) [39, 57]. Likewise, in a prospective cohort study by Peters et al. comparing 71 neurogenic with 269 idiopathic patients it was concluded that the clinical benefits of SNM were equivalent for both groups [45]. The mean (SD) age of the neurological patient in this meta-analysis (47.7 ± 12.6 years) is lower than in the typical idiopathic patient population (INSITE trial, 57.0 ± 14.2 years) [57]. The percentage of women in the purely neurological patient population was only 59.9% compared with 91% in the INSITE trial. AE rates were similar or even lower than those observed in the idiopathic population [57, 58]. At a rate of 2.0% adverse stimulation was a relatively rare AE in comparison with the recent large INSITE study (22%) [57].

Our meta-analysis, based on more than triple or double the patient sizes, respectively, are in line with Kessler et al. (2010) reporting a test success rate of 68% (256 patients) and a permanent success rate of 92% (206 patients) [12]. Since 2010 six prospective studies have been published that further strengthen Kessler et al.’s conclusions [32, 38, 40, 41, 45, 59]. For the majority of neurological patients, clinical

**Table 3** Success rate of test SNM by underlying dysfunction

| Dysfunction                      | Total no. of patients with dysfunction | No. of patients with successful testing | Success rate (%) | Exact 95% confidence intervalc |
|----------------------------------|----------------------------------------|----------------------------------------|------------------|-------------------------------|
| Incomplete SCI                   | 116                                    | 56                                     | 48.3             | (38.9%, 57.7%)                |
| Multiple sclerosis               | 94                                     | 72                                     | 76.6             | (66.7%, 84.7%)                |
| Back surgerya                    | 151                                    | 127                                    | 84.1             | (77.3%, 89.5%)                |
| Diabetes/ polynephropathy        | 47                                     | 31                                     | 66.0             | (50.7%, 79.1%)                |
| Spina bifida/MMC                 | 25                                     | 12                                     | 48.0             | (27.8%, 68.7%)                |
| Cerebral vascular disease        | 8                                      | 4                                      | 50.0             | (15.7%, 84.3%)                |
| Parkinson disease                | 11                                     | 6                                      | 54.5             | (23.4%, 83.3%)                |
| Pelvic surgery                   | 9                                      | 7                                      | 77.8             | (40.0%, 97.2%)                |
| Complete SCI                     | 9                                      | 0                                      | 0.0              | (−, −)                        |
| Complete SCI (early stim)b       | 10                                     | 8                                      | 80.0             | (44.4%, 97.5%)                |
| Cerebral palsy                   | 3                                      | 3                                      | 100.0            | (−, −)                        |
| Other neurological condition     | 15                                     | 13                                     | 86.7             |                               |
| Not clearly reported             | 239                                    | 145                                    | 60.7             |                               |
| Total                            | 737                                    | 484                                    |                  |                               |

SCI spinal cord injury, MMC myelomeningocele

a Including disc disease

b Complete SCI (early stimulation): since there was no SNM test [31], a virtual test phase during the chronic phase has been assumed

c For the calculation of the exact 95% confidence interval data was pooled per indication across all applicable studies
outcomes remained stable for a follow-up of up to 61 months [44, 60]. The results from this large meta-analysis can be interpreted as real-world data providing significant real-world evidence for such a heterogeneous group of patients [61].
Test success rates varied greatly depending on the type of neurologic condition. The highest test success rates were achieved in patients with back surgery, MS, and pelvic surgery (84.1%, 76.6%, and 77.8%, respectively), suggesting a higher likelihood for preservation of nerve plasticity or reversibility.

Test success rates in patients with neurogenic non-obstructive urinary retention were slightly lower than for patients with nDO (52% versus 61%), consistent with the data reported by Kessler et al. (56% versus 61%) [12]. Test success rates for combined lower urinary tract symptoms (nDO and voiding difficulties) were 69% and thereby almost identical to those reported by Hennessey et al. for detrusor hyperactivity with impaired contractility (70%) [62].

| Adverse event          | No. of patients with adverse event/total no. of permanently implanted patients | Percentage of adverse events | No. of studies reporting type of AE |
|------------------------|---------------------------------------------------------------------------------|------------------------------|----------------------------------|
| Infection              | 18/494                                                                           | 3.6%                         | 8                                |
| Pain at implant        | 16/494                                                                           | 3.2%                         | 8                                |
| Adverse stimulation    | 10/494                                                                           | 2.0%                         | 5                                |
| Lead migration         | 16/494                                                                           | 3.2%                         | 7                                |
| Lead breakage          | 6/494                                                                            | 1.2%                         | 4                                |
| Hardware issues        | 14/494                                                                           | 2.8%                         | 6                                |
| Adverse change in bowel function | 2/494 | 0.4% | 1 |
| Loss of effectiveness  | 23/494                                                                           | 4.7%                         | 9                                |
| Other                  | 9/494                                                                            | 1.8%                         | 6                                |

Chaabane et al. concluded that the type of nLUTD (retention or DO) has no impact on the test success rate [34]. Three studies reported an improvement of detrusor–sphincter dyssynergia (DSD) with SNM [31, 34, 44].

Patients with MS are an interesting population for SNM because of the high prevalence of nLUTD or fecal incontinence (75% and 29%, respectively) [15]. SNM seems to be an attractive option because it can be evaluated for all those conditions. However, its usage has previously been limited by the lack of full-body MRI compatibility. Since new full-body MRI-safe devices have become recently commercially available for 1.5 T and 3 T (Axonics, Irvine, CA and Medtronic, Minneapolis, MN), more patients with MS could gain access to this minimally invasive, reversible treatment. New SNM technologies with smaller rechargeable devices (Axonics r-SNM, 5.5 cm³; Medtronic InterStim Micro, 2.8 cm³) with an expected battery life of up to 15 years [14] offer significant advantages for patients with a need for high stimulation amplitudes, which is not rare among the neurological patient population. In their case series, Minardi et al. observed a mean amplitude of 3.6 V (range 2.3–5.8 V) for patients with MS [44] resulting in a mean battery life of approximately 5 years. For example, in a standard, mostly non-neurogenic SNM patient population, effective modulation can nowadays be achieved by a mean amplitude of 0.95 V with optimized lead placement [63]. In addition, small buttock-placed rechargeable SNM devices are expected to be advantageous in wheelchair-bound (neurological) patients [64].

OnabotulinumtoxinA with a level of evidence 1a is the standard treatment for refractory nDO due to MS or SCI according to current guidelines [13]. Nevertheless, the discontinuation (ca. 40%) is significant and can be up to 86% in patients with MS [11]. Therefore, alternative treatment options are urgently needed, despite the momentary weaker evidence for SNM.

There are legitimate concerns for using SNM in patients with a progressive neurological condition. Chaabane et al. reported that three out of seven patients with MS (43%) failed SNM because of disease progression [34]. On the
other hand, in their prospective cohort study, Peters et al. suggested that neurological patients with a progressive condition as well as those with a nonprogressive condition benefited from SNM. No significant differences in terms of revisions, explants, complications, or reprogramming have been observed between the two groups [45]. In fact, another prospective study showed that SNM can be effective in patients with progressive MS [40]. Nevertheless, it is common practice to consider SNM only in patients with disease stability over the last 6–12 months. New medications for MS may also prevent a relapse or progression of symptoms and help to prolong the benefit of SNM [40].

SNM has also demonstrated durable long-term results in patients with incomplete SCI [43]. These patients and other neurological patients may suffer from nDO. In these cases, the protection of the upper urinary tract is of utmost importance in order to prevent renal failure [8]. Hohenfellner et al. reported a reduction in maximum detrusor pressure (maxPdet) by SNM (from 48 to 24 cmH2O) [54] and can range from 12.1% to 60.0% [49, 65, 66]. Although the exact mechanism of action of SNM has not been fully elucidated, it is generally thought that SNM plays a key role in modulating pathological afferent signals at spinal and supraspinal levels [67]. On the basis of these considerations the impact of SNM on reduction of Pdet may be limited. Regular urodynamic examinations are therefore recommended in patients with significant nDO. However, this applies also for pharmacological treatments. It is noteworthy that apart from the pressure level, the frequency of DO contractions and the duration of elevated detrusor pressures can also gradually harm the upper urinary tract [8]. The reduction of detrusor pressures by SNM can be comparable with other treatment modalities [68, 69], although such indirect comparisons have methodological weaknesses. Furthermore, nDO often requires concomitant therapies because of the complex nature of the condition.

In the context of the absence of a reliable predictor, a prior test SNM, even over a prolonged period of time, has a high prognostic value for the therapeutic effect of chronic SNM. Although complete SCI is commonly considered as a general contraindication for SNM, Sievert et al. showed that early bilateral SNM, while still in spinal shock phase, prevents nDO by potentially involving hypogastric-sympathetic nerves [31]. However, until these promising early results for SNM in complete SCI are confirmed, this indication remains investigational. The potential significance of an earlier application of SNM has also been suggested in other studies [70]. In two small retrospective case series on patients with PD, success rates for permanent SNM varied greatly with follow-up periods of up to 18 months and longer (8/8 [100%] and 7/13 [54%]) [71, 72]. Test success rates for patients with PD seem to be lower than for idiopathic LUTD [34]. Joussain et al. suggested that SNM could be a good alternative for patients with PD and nDO because of the risk of urinary retention with onabotulinumtoxinA [73].

Limitations

When comparing test success rates for various conditions, confounding factors must be taken into account, such as variations in techniques (basic test with a temporary wire versus advanced test with the permanent tined lead or unilateral versus bilateral modulation). Permanent implants and implant techniques have evolved significantly over the last 25 years [2, 6, 58, 74]. Further limitations of some of the included studies and therefore this meta-analysis are related to heterogeneous patient populations, insufficient disease classification, substantial between-study heterogeneity, and variations in terms of outcome parameter (success rates). Nevertheless, several studies have demonstrated that a symptom improvement of at least 50% during the test phase correlates favorably with patient-reported outcomes (such as a high patient satisfaction or quality of life improvement) in up to 94% of patients during the chronic SNM phase [21, 44, 45, 48, 49, 57]. Moreover, a small number of explants can also be interpreted as a clinically meaningful patient satisfaction [48, 75].
Further limitations include significant risk of bias, small sample sizes in some studies, retrospective case series with potential reporting bias, or in part poor reporting and publication quality. Publication bias seems to be of lesser importance, since only one study included in the meta-analysis for permanent SNM reported unrestricted industry funding (Table 2S in the supplementary material). It is noteworthy that randomized controlled studies of SNM in nLUTD are lacking [76].

In 2016 a framework for the product life cycle of medical devices has been developed [77]. The IDEAL concept (Idea, Development, Exploration, Assessment, Long-term study) aims at enabling patient access to devices with adequate clinical evidence but without excessive delay or resource use [77]. SNM in patients with nLUTD could be categorized according to IDEAL stage 3 or 4, since prospective studies are available, randomized trials are underway [76], and long-term data exists [44, 60]. Cooperative registries could provide further insights into patient selection for this very heterogeneous group of patients. It is noteworthy that SNM in patients with nLUTD is neither a new surgical technique nor does it relate to an entirely new indication, albeit bladder behavior may be very different between neurogenic and non-neurogenic conditions.

Last but not least the differentiation between neurogenic and non-neurogenic etiologies is not always straightforward, as in the cases of SCI, MS, PD, or cerebral vascular disease. Classification of patients with previous pelvic or back surgeries or concomitant diabetes is not without ambiguity. Moreover, the term “non-neurogenic” may be inappropriate with regards to the following well-known, clinically observed paradox: “in SNM modulating the nervous system of patients referred to as ‘idiopathic’, and of obtaining favorable results in a number of different, and often contradictory, clinical situations is a paradox.” [78].

CONCLUSIONS

This systematic literature review showed that there is growing evidence for the effectiveness of SNM in neurological patients. Although this indication has been investigated since the early days of SNM, it was not a realistic option in routine clinical practice, because full-body MRI-approved devices were lacking. Consequently, SNM was either not offered or devices had to be even explanted. With the recent approval of full-body MRI-certified devices a new era of SNM has begun. This meta-analysis supports not only the benefits of permanent SNM for various neurogenic conditions but also high overall success rates. The overall chance to receive a chronic implant with long-term benefit is approximately 55% (intention-to-treat analysis).

Finally, the evidence of this meta-analysis in an overall large heterogenous neurological patient population should ignite further prospective trials with more vigorous study designs (including validated patient-reported outcomes such as quality of life) that focus on specific subgroups. Moreover, a central registry on SNM in patients with nLUTD would be helpful to shed more light onto clinical outcomes of such a heterogeneous patient population before definitive conclusions can be drawn.

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**Compliance with Ethics Guidelines.** This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

**Data Availability.** The database analyzed during the current study is available from the corresponding author on reasonable request.

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