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REVIEW BODY REPORT

Title	Systematic review of the efficacy and safety of sacral nerve stimulation for urinary urge incontinence and urgency-frequency.
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'Home unit' details

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1. To study or evaluate clinical activities with a view to improving effectiveness and efficiency in health care;
2. To work for the implementation of proven changes in clinical activities;
3. To encourage and support similar work thoughout Scotland;
4. To train NHS staff in Scotland, and others, in the principles and practice of health services research in general, and health care evaluation in particular.

The Unit has an established portfolio of health services research focusing on two main programmes – health care assessment and delivery of care. The Unit is one of the three research groups that make up the 'Review Body' for the National Institute for Clinical Excellence Interventional Procedures Programme. The others are based at the Universities of Sheffield and Leeds.

Contributions of authors

Miriam Brazzelli wrote the initial protocol, screened the search results, assessed full text papers for inclusion, undertook data abstraction and quality assessment of studies, and drafted the majority of the review. Alison Murray contributed to the writing of the protocol, screened the search results, assessed full text papers for inclusion, undertook data abstraction and quality assessment of studies, and drafted parts of the review. Cynthia Fraser developed and ran the literature search strategies, obtained papers and formatted the references. Adrian Grant was involved in scoping the review, commented on the protocol, and contributed to the writing of the review.

Conflict of interest

None

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EXECUTIVE SUMMARY

Background

Sacral nerve stimulation therapy involves the use of mild electrical pulses to stimulate the sacral nerves located in the lower back. It has been proposed as a potential option for the management of patients with severe urge urinary incontinence or urgency-frequency symptoms for whom non-surgical treatments have failed. Electrodes are placed next to a sacral nerve, usually S3, by inserting the electrode leads into the corresponding foramen of the sacrum. Adequate electrode placement is confirmed by obtaining appropriate motor and sensory responses. The electrodes are inserted subcutaneously and are subsequently attached to an implantable pulse generator. The procedure is reversible. Prior to 'permanent' implantation responsiveness is tested using a temporary stimulator.

Number and quality of included studies

From the initial 1562 reports identified by the search strategy, 54 primary studies (including 22 reported just in abstracts) published in 103 reports were included in the review. For studies with multiple publications only the most up-to-date report was considered. Seven of the 54 primary studies were randomised controlled trials and 47 were case series. Randomised controlled trials could potentially have been affected by performance and attrition biases. The methodological quality of the case series studies was less robust. In addition to the limitations of not including a comparison group, they did not take into account possible confounding factors, and often did not provide information on non-responders or dropouts.

Summary of evidence of efficacy

Evidence from the randomised controlled trials showed that about 70% of patients achieved continence or exhibited an improvement of >50% in their main incontinence symptoms after sacral nerve stimulation. This compared with about 4% of patients in the control groups who were receiving conservative treatments while waiting for an implant. Case series studies had similar results with 68% of patients becoming dry or

achieving a >50% improvement in their symptoms post-implantation. Incontinence episodes, severity of leakage, frequency of voids, and pad usage were all significantly lower after implant. Benefits of sacral nerve stimulation were reported to persist at follow-up 3-5 years after implantation.

Summary of evidence of safety

Adverse events were documented in 27 studies. Overall, the re-operation rate for implanted patients was 33%. The most common reasons for surgical revision were relocation of the generator because of pain at the implant site, adjustment and modification of the lead system, and infection. Common complications were pain at the implant or lead site (24%); lead related problems such as lead migration (16%); replacement and repositioning of the implanted pulse generator (15%); wound problems (7%); adverse effects on bowel function (6%); infection (5%); and generator problems (5%). Permanent removal of the electrodes was reported in 9% of patients. No cases of long-lasting neurological complication were identified. Technical changes over time have been associated with reduced rates of complications.

Conclusions

Results from randomised controlled trials and case series studies are consistent with sacral nerve stimulation reducing symptoms in patients with urge urinary incontinence and urgency-frequency. The impact of sacral nerve stimulation on patients' quality of life is still to be demonstrated.

Adverse events occurred in about half of the implanted patients and surgical revision was performed in 33%. No major irreversible complications have been reported. The long-term safety of sacral nerve stimulation has not yet been established.

1. OBJECTIVE OF THE REVIEW

To systematically review the evidence for efficacy and safety of sacral nerve stimulation (SNS) for the management of urinary urge incontinence and urgency-frequency symptoms in adults.

2. BACKGROUND

2.1 The interventional procedure under review

2.1.1 Description of the interventional procedure

SNS therapy involves the use of mild electrical pulses to stimulate the sacral nerves located in the lower back. Electrodes are placed next to a sacral nerve, usually S3, by inserting the electrode leads into the corresponding foramen of the sacrum. Adequate electrode placement is confirmed by obtaining appropriate motor and sensory responses. The electrodes are inserted subcutaneously and are subsequently attached to an implantable pulse generator (IPG).

The technique of SNS normally has three stages:

(a) Phase I or acute phase - a percutaneous nerve evaluation test, under local anaesthesia, prior to implantation of the permanent device. Usually, a temporary lead is placed near to one of the sacral nerves and connected to an external stimulator in order to evaluate the integrity of the sacral nerves and identify the optimal lead location.

(b) Phase II or sub-chronic phase - a sub-chronic test stimulation, involving the monitoring and adjustment of the external stimulator to assess the optimal comfort level of individual patient stimulation and identify suitable candidates for the permanent implant.

(c) Phase III or chronic/permanent implant phase - implantation of the stimulation system if the sub-chronic phase is successful.

The sub-chronic phase typically lasts from three to seven days and is usually considered successful when there is an improvement of at least 50% in the main incontinence symptoms. Phases I and II are referred to as peripheral nerve evaluation (PNE).

SNS is designed to be completely reversible and the implanted pulse generator can be removed at any time. At present the SNS implanted device is exclusively produced by Medtronic Inc., a worldwide medical technology company, under the name: InterStim Therapy.

2.1.2 *Proposed clinical indications/contraindications and putative impact of the procedure*

The use of SNS has been investigated since the early 1980s. Tanagho and Schmidt published the results of the first ten patients, who had electrodes implanted on the sacral roots for the treatment of neuropathic voiding dysfunction, in 1986.[1] Since then in excess of 8000 implant procedures have been performed to treat a number of voiding conditions refractory to standard conventional treatment.[2]

The use of SNS - InterStim therapy - was initially marketed in Europe, Canada, and Australia in 1994 and subsequently received Food and Drug Administration (FDA) approval in the USA - for the treatment of urge incontinence in 1997 and for urgency-frequency and non-obstructive urinary retention in 1999. In February 2002, the FDA approved inclusion of the term "overactive bladder" amongst the indications for InterStim therapy. In September 2002, the FDA approved the use of a minimally invasive lead implant technique.

SNS is currently being suggested as a treatment for the symptoms of overactive bladder, including urge urinary incontinence and urgency-frequency alone or in combination, in patients who have failed or cannot tolerate conservative treatments. It is thought not to be appropriate in the following categories of patients: those who have failed to demonstrate a positive response to the peripheral nerve evaluation test; those unable to operate the neurostimulator; those with primary stress incontinence or mechanical obstructions due to benign prostatic hypertrophy, cancer, or urethral strictures.

The manufacturer reports that "diathermy (e.g. shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy) is contraindicated because diathermy's energy can be transferred through the implanted system, which can cause tissue damage, and can result in severe injury or death". The SNS system can also be affected by (or can adversely affect) cardiac pacemakers, defibrillators, ultrasonic equipment, radiation therapy, magnetic resonance imaging, theft detectors, and screening devices.[3]

2.1.3 Personnel involved (e.g. surgeons, anaesthetists, nurses) and skill/experience required

In the UK, the current National Institute for Clinical Excellence (NICE) provisional guidance on SNS for urge urinary incontinence recommends its use only under special arrangements for consent and for audit or research, due to the uncertainty about its efficacy and safety.[4] At present, clinicians who want to perform SNS procedures for urge urinary incontinence are asked to inform the clinical governance leads in their trusts and ensure that appropriate arrangements are in place for audit and research.

The physician performing the implant must be trained in the use of the SNS device produced by Medtronic Inc. The company has organised training courses specifically designed for urologists and urogynecologists since 1997 and these take place twice a year in the Maastricht University Hospital in the Netherlands, with more advanced courses also organised biannually in various other centres in Europe.

Phase I or `acute phase' of SNS is usually performed in an operating theatre under local anaesthesia. This phase can require up to one hour and the patient is preferably observed overnight.

Implantation of the pulse generator in phase III is usually undertaken under general anaesthesia and requires between two and two and a half hours. In general three surgical incisions are required: one over the lower back to insert the lead into the selected sacral foramen; one in the lower abdomen or upper buttock area to shape a subcutaneous pocket for positioning of the pulse generator; and a small one in the flank to allow connection of the lead and extension lead, tunnelled under the skin, to the pulse generator.

Variants or modifications of the procedure include the use of a percutaneous lead implant with fascial fixation, implantation of bilateral electrodes, and the newly developed 'tined lead' technique. The tined lead technique requires fewer incisions and less surgical time. A small incision is made over the sacrum for implantation of the lead and a second incision in the upper buttock creates a pocket in the layer of tissue to fit the pulse generator. Essentially this technique represents a percutaneous implant using a

two-stage approach and offers the possibility of a longer screening period during the evaluation phase.

2.1.4 Current use in the UK

Clinicians in six centres in the UK are currently undertaking the procedure for urinary voiding dysfunctions (Medtronic personal communication, 2003):

- National Hospital of Neurology and Neurosurgery, London.
- New Hall Private Hospital, Salisbury
- Leicester General Hospital, Leicester
- Freeman Hospital, Newcastle-upon-Tyne
- Hope Hospital, Salford, Manchester
- Pinderfields General Hospital, Wakefield

In 2002 a total of 12 SNS procedures were performed in the UK for urinary voiding dysfunctions (Medtronic personal communication, 2003).

2.1.5 Equipment or devices required

A sacral nerve test stimulation system consists of a test stimulation lead pack, test stimulation cables and a test external stimulator. The test stimulation lead pack includes foramen needles (20 gauge), test stimulation leads, patient cable, and preparation supplies (e.g. syringe, gauze, bandages).

The implantable SNS system consists of a pulse generator, a patient programmer, an extension cable, and a lead with quadripolar electrodes. Details of the components of the InterStim Implantable System are provided by Medtronic Inc.[3] Two implantable pulse generators are currently available: i) InterStim model 3023 which uses a single lead and provides unilateral stimulation, and ii) InterStim TWIN model 7427T which offers bilateral stimulation and the possibility to connect two leads. Compatible extensions and leads are available in different sizes, lengths, and models,[3] the most recently developed being tined leads (model 3889 with four equally sized electrodes and model 3093 with three equally sized electrodes and one extended electrode). The pulse generator battery runs for about five years, and can be replaced during an outpatient procedure.

The techniques actually used vary between clinicians especially in terms of the number and type of electrodes.

2.2 Description of the underlying health problem

2.2.1 Epidemiology

Urge urinary incontinence is one of the most commonly encountered forms of urinary incontinence. It may be defined as the involuntary leakage of urine accompanied by, or immediately preceded by, a sudden desire to void.

Urgency-frequency syndrome is a form of voiding dysfunction characterised by an uncontrolled urge to void, resulting in frequent, small amounts of urine voided many more times than is normally expected (as often as every 15 minutes).

Prevalence studies of urge urinary incontinence caused by an overactive bladder vary considerably partly because of differences in the definitions of clinically significant urinary symptoms and in the survey methods used. Many studies focus on patients with incontinence and overlook people, particularly men, with urgency-frequency symptoms.[5] In general, urinary incontinence, frequency and urgency are more often observed in women than in men and the prevalence of symptoms tends to increase with age. In the UK urinary incontinence affects an estimated 14.9% of adults over 40 years of age living in the community. Urgency and frequency symptoms were observed respectively in 7.3% and 7.8% of the same sample population.[6] Prevalence of incontinence is higher among people living in institutional settings.[7] In the USA the overall prevalence of symptoms of overactive bladder in adults over 18 years of age has been recently estimated to be 16.9% in women and 16.0% in men. Across all age groups, overactive bladder without urge incontinence but with persistent urgency-frequency symptoms was more common in men than in women.[8]

2.2.2 Aetiology, pathology and prognosis

Overactive bladder symptoms are most often caused by instability of the lower urinary tract where there is involuntary contraction of the bladder wall muscle (detrusor overactivity) resulting in urinary leakage. Detrusor overactivity may be idiopathic, due to urinary tract infection, outflow tract obstruction (in men), neurological conditions (neurogenic detrusor overactivity) or precipitated by concomitant disease (e.g. cancer, bladder stones, polyps, emotional disorders).

SNS has been proposed as an option for the management of severe urge urinary incontinence and urgency-frequency syndrome. The rationale for its use is that electrical stimulation of sacral nerves (pudendal nerves) can modulate neural reflexes that influence bladder and pelvic floor behaviour. The exact physiological mechanism of action by which electrical nerve stimulation works is not yet fully understood.[9]

2.3 Population

2.3.1 Suitable candidates and relevant subgroups

Patients suggested as suitable for SNS are those suffering from urge urinary incontinence and urgency-frequency symptoms who have failed to respond to conservative treatments.

Clinical parameters for selection of the best candidates for SNS implants have yet to be defined and no predictive factors have yet been identified. The current way to assess the potential success of a permanent implant is by a peripheral nerve evaluation (PNE) test. Patients who show a positive response to a PNE test are considered suitable candidates for implantation.

2.4 Current management and alternative procedures

Urge urinary incontinence and urgency-frequency symptoms are typically managed conservatively by means of behavioural techniques (e.g. bladder training) physical therapies (e.g. electrical stimulation using vaginal or anal electrodes) or pharmacotherapy (antimuscarinic – anticholinergic – drugs). When these approaches are unsuccessful more invasive and irreversible surgical procedures are considered. These include bladder reconstruction (for example, augmentation cystoplasty) and urinary diversion.

3. EFFICACY AND SAFETY

3.1 Methods for reviewing evidence on efficacy and safety

3.1.1 Search strategy

Electronic searches were conducted to identify both published and unpublished reports of studies evaluating the efficacy and safety of SNS for urinary urge incontinence and urgency-frequency syndrome. The following databases were searched and full details of the searches are documented in Appendix 1:

MEDLINE (1966 to Week 2 May 2003)
MEDLINE Extra (29th May 2003)
EMBASE (1980 to Week 21 2003)
CINAHL (1985 to May 2003)
BIOSIS (1985 to May 2003)
Science Citation Index (1981 to June 2003)
Web of Science Proceedings (1990 to June 2003)
Cochrane Controlled Trials Register (Cochrane Library Issue 2 2003)
Cochrane Database of Systematic Reviews (Cochrane Library Issue 2 2003)
Database of Abstracts of Reviews of Effectiveness (May 2003)
HTA Database (May 2003)
National Research Register (Issue 2 2003)
Clinical Trials (May 2003)
Current Controlled Trials (May 2003)
Research Findings Register (May 2003)

In addition, the reference lists of all included studies were scanned and experts were contacted for further potentially eligible references. Selected websites (for listing see Appendix 1) were also searched for eligible evidence-based reports.

A total of 1562 reports were identified from the literature search. Titles and, where possible, abstracts were screened for inclusion, independently by two reviewers. A total of 245 reports were identified as potentially relevant and, where possible, full papers were obtained. In addition, 45 potentially relevant non-English language papers (42 full-

text papers and three abstracts) were noted but copies of full-text papers were not retrieved. Full-text papers were obtained and assessed independently for inclusion by two reviewers and any disagreements that could not be resolved through discussion were referred to an arbiter. One hundred and twelve papers met the criteria for inclusion in the review (four reports from commissioning bodies or health technology assessment agencies, 41 full-text papers, and 67 abstracts).

3.1.2 Inclusion and exclusion criteria

Types of studies

Systematic reviews of the literature, randomised controlled trials, controlled clinical trials, comparative observational studies, case series studies, and population-based registries assessing the efficacy and/or safety of SNS.

Types of participants

Adults with urinary urge incontinence and/or urgency-frequency symptoms (a systematic review of SNS for patients with faecal incontinence has been undertaken separately for the NICE Interventional Procedures Programme).

Types of intervention

Sacral nerve stimulation.

Transcutaneous electrical nerve stimulation (TENS), magnetic sacral nerve stimulation, and sacral anterior root stimulation (Brindley technique), were not considered in this review.

Other clinical indications for SNS such as urinary retention, pelvic pain, interstitial cystitis, and neurogenic overactive bladder were included in the scope of the search strategy but subsequently not considered in the review.

Types of outcomes

Efficacy

Three categories of outcome measures were considered for the assessment of efficacy: a) main clinical outcomes, b) quality of life measurements, c) surrogate outcomes.

a) Main clinical outcomes:

- Cure/improvement
- Number of leakage episodes per day
- Number of pads used per day
- Frequency of voiding
- Severity of leakage
- Degree of urgency

b) Quality of life measurements:

- General health status instruments (e.g. Short Form-36 Health Survey)
- Condition-specific instruments (e.g. questionnaires for patients with incontinence)

c) Surrogate outcomes:

- Bladder capacity
- Volume per void

In the included studies measures of efficacy were derived from patients' voiding diaries, physiological measurements (urodynamic tests), and published questionnaires and checklists. Physiological measurements such as urodynamics were regarded as surrogate outcomes as they are reported to correlate poorly with symptoms and severity of incontinence. The definitions of the various measures were those used in the reports of the studies. 'Cure' was usually defined as no incontinence or a clinical improvement >90% and 'improvement' as 50% or greater reduction in main incontinence or urgency-frequency symptoms.

Safety

The frequency and type of adverse events were tabulated to assess the safety of SNS. Safety endpoints were considered in the following categories:

- Re-operations

- Permanent explants
- Implants replaced or relocated
- Infection
- Pain (all types of pain including pain at the pulse generator site, pain at the lead implant site, and new pain or discomfort)
- Lead problems (e.g. lead migration, lead breaks)
- Generator problems (e.g. battery exhaustion)
- Wound problems other than infection (e.g. seroma)
- Adverse bowel function

3.1.3 Quality assessment strategy

Two reviewers independently assessed the methodological quality of all included full-text reports. Two separate quality assessment checklists were used in the review. The 16-question checklist used to assess the quality of the case series studies (Appendix 2) was adapted from the NHS Centre for Reviews and Dissemination's guidance for those carrying out or commissioning reviews(2001) and from Downs and Black.[10] The 11-question checklist used to assess randomised controlled trials is a modified version of the Delphi List, a criteria list developed using Delphi consensus methods by Verhagen and colleagues[11] to assess the quality of randomised controlled trials (Appendix 3). The methodological quality of the included abstracts was not assessed as not enough information was provided. .

3.1.4 Data extraction strategy

A data extraction form was specifically developed to record details of the design of included studies, characteristics of participants, technical aspects of both PNE and SNS, and outcome measures (Appendix 4). Data were independently extracted by two reviewers and cross-checked. Where possible, for each reported outcome, data were sought on every patient studied. Differences of opinion between reviewers were resolved by discussion or arbitration. Reviewers were not blinded to the names of study authors, institutions, and publications.

3.1.5 Data analysis

For randomised controlled studies, data were tabulated and within-group comparisons were presented for the stimulation group and the delay group at last follow-up. Data from case series studies were tabulated and presented as comparisons between the baseline and last follow-up after implantation.

3.2 Results

3.2.1 Type and quantity of available evidence

Only studies that focused on urge urinary incontinence, urgency-frequency symptoms or both these clinical indications were considered. Studies including patients with a mixture of voiding or other dysfuntions (e.g. urge incontinence, urgency-frequency, urinary retention, pelvic pain) were considered only if data were presented separately for each clinical condition or adverse events were reported. Four studies – published in five abstracts - in which the indication for SNS was not clearly stated and no safety data were reported were initially included but subsequentely not incorporated in the review. The characteristics of these studies are presented in Appendix 5. For studies with multiple publications, the most up-to-date report was considered.

3.2.2 Number and type of included studies

Four reports from commissioning bodies and health technology assessment agencies, and 54 primary studies published in 103 reports were included in the review. Thirty-two of the 54 primary studies were reported in full-text papers and 22 were abstracts. Seven of the studies were randomised controlled trials and 47 were case series. The primary studies along with their related references are listed in Appendix 6.

The four reports from commissioning bodies and health technology assessment agencies did not provide any references that our search strategy had not already identified. They were utilised for general and background information but their methodological quality was not assessed and their results were not summarised in this review.[12-15]

Tables 1 and 2 show respectively the lists of full-text studies and of studies reported only in abstract format. The detailed characteristics of included primary studies are shown in Appendix 7.

Table 1 Included studies – full-text studies

Study id	RCT/Case Series	Mean age	Enrolled (all diagnoses)	Received PNE	Received implant	Months of follow-up (range)
Aboseif 2002[16,17]	case series	47	160*	160*	64*	24[a] (6-36)
Amundsen 2002[18]	case series	69	25	25	12	7.8[a] (1-16)
Benson 2000[19]	case series	51.3	15	15	-	-
Bosch 2000[20-30]	case series	46.2	85	85	45	47.1[a] (6-96)
Braun 1999[31-35]	case series	49	9*	NR	9*	12.5[a] (7-18)
Cappellano 2001[36-38]	case series	51.1	113*	NR	113*	18
Cappellano 1998[39]	case series	47	47*	47*	10	23.1[a] (3-47)
Carey 2001[40,41]	case series	49	12	12	-	-
Chai 2001[42]	case series	NR	20*	20*	-	8[a] (1-14)
Edlund 2000[43]	case series	59.8	30*	30*	9*	19.9[a] (8-39)
Everaert 2000[44,45]	case series	43	53*	177*	53*	24[a] (13-39)
Grünewald 2000[46-49]	case series	49	184*	184*	55*	44.3[a] (1-89)
Hasan 1996[50]	case series	48	35	35	-	-
Hassouna 2000[51-56]	RCT	39	51	NR	25	24
Hassouna 1991[57]	case series	NR	36*	32*	7*	NR
Hedlund 2002[58,59]	case series	54	53	53	14	18[a] (9-32)
Hohenfellner 1998[60,61]	case series	43.4	11*	NR	10*	13[a] (9-28)
Ishigooka 1999[62]	case series	40.2	40	NR	40	12
Janknegt 2001[63,64]	case series	NR	96	NR	96	30.8 (12-60)
Janknegt 1997[65]	case series	46	10*	10*	8*	16 (4-36)
Ratto 2003[66]	case series	50.4	10*	10*	10*	NR
Scheepens 2003[67,68]	case series	53	34	10	31	11[a] (0-56)
Scheepens 2002a[69-71]	case series	53	15*	15*	15*	59[a] (30-90)
Scheepens 2002b[72,73]	RCT	45.5	33*	33*	-	-
Scheepens 2001[74]	case series	51	39*	NR	39*	5.3[a] (1-10)
Schmidt 1999[75-77]	RCT	46.6	155	155	34	14.7[a] (0.9-39.7)
Schmidt 1988[78]	case series	NR	19	19	-	-
Shaker 1998[79-82]	case series	42.3	18	NR	18	18.8[a] (3-83)
Siegel 2000[83,84]	case series	43	581*	581*	219*	(18-36)
Spinelli 2003[85,86]	case series	43	32*	13*	22*	11[a] (2-25)
Weil 2000[87]	RCT	43	123*	123*	44	18[b] (6-36)
Weil 1998[88-90]	case series	36	36*	NR	36*	37.8[a] (12-60)
Total			**2180***	**1844***	**1038***	

* including patients with urinary retention

[a] mean

[b] median

NR not reported

Table 2 Included studies - abstracts

Study id	RCT/Case Series	Mean age	Enrolled (all diagnoses)	Received PNE	Received implant	Months of follow-up (range)
Bristow 1997[91]	case series	44	29*	29*	-	-
Bryan 1999[92]	case series	NR	57*	57*	10	-
Carabello 2001[93]	case series	60.6	17	NR	17	13.4[a] (3-22)
Das 2002a[94]	RCT	56.8	45*	45*	-	-
Das 2002b[95]	case series	47	256*	NR	256*	26[a] (15-46)
Dijkema 1994[96,97]	case series	NR	25	NR	25	≥6
Everaert 2002[98]	RCT	48	22	NR	22	12
Groenendijk 2002a[99]	case series	NR	111	NR	111	6
Groenendijk 2002b[100]	case series	NR	19	NR	19	6
Heesakkers 2003[101-104]	case series	NR	259*	NR	259*	>12
Kiss 2002[105]	case series	NR	13*	13*	12*	-
Koldewijn 1999[106]	case series	40	40*	NR	40*	29[a] (5-46)
Light 1992[107]	case series	52	17*	14*	5*	(10-24)
Oliver 2001[108-110]	case series	NR	10	10	-	-
Peters 2002[111]	case series	NR	30*	30*	14*	-
Ruffion 2003[112]	case seires	48.8	166*	166*	33*	37[a] (3-87)
Ruiz-Cerdá 2003[113]	case series	47	204*	204*	69*	6.8[a] (2-30)
Spinelli 2002[114]	case series	34	9*	9*	6*	NR
Thon 1992[115]	case series	NR	114*	NR	41*	4.2[a] (1-12)
Weil 1996[116]	RCT	NR	18*	NR	9*	6
Winters 2003[117]	case series	44.9	12*	NR	12*	NR
Zermann 2001[118]	case series	NR	81*	81*	-	-
Total			**1554***	**658***	**960***	

***** including patients with urinary retention
[a] mean
NR not reported

Eleven of the primary studies were set in the USA, two in Canada, one in Australia and 31 in Europe (12 in the Netherlands, five in Italy, four in the UK, three in Germany, two in Belgium and one each in Sweden, Norway, France, Spain, and Austria). In addition, there were seven multicentre studies with centres in North America and Europe, one multicentre study in Europe and one based in Germany, Japan and the USA. The manufacturer funded eight of the studies, including six of the multicentre studies,[51,63,75,83,95,99] four studies were funded by governments, one by the author's institution, and one received no funding. The remaining studies did not declare their source of funding.

In total, the 54 studies included in this review enrolled 3734 patients with a mean or median age for each study between 34 and 69 years (age range 15 to 81 years). Overall, 2502 patients were reported to undergo PNE testing and 1998 to receive the implanted SNS. Sample sizes ranged from nine to 581 patients and the percentage of women ranged from 50% to 100% with three studies[40,98,100] including only women. The recruitment periods ranged from one year[74] to eight years and six months[20] and took place between 1981 and 2002. Average follow-up was between 5.3 months[74] and 47.1 months[20] and ranged up to 96 months.[20]

Ten studies[19,40,42,50,72,78,91,94,108,118] limited their investigation to the evaluation test of SNS. These include one randomised cross-over trial comparing unilateral versus bilateral PNE[72] and one randomised controlled trial evaluating the addition of an electrodiagnostic technique to PNE.[94]

The remaining 44 studies investigated patients receiving both the PNE test and the implant. In 20 of these studies, however, only patients who had had a positive response to the test stimulation and subsequently received implanted SNS were included, and the total number of patients who had received the PNE test at the start of these studies was not reported. Five studies were randomised controlled trials and 39 were case series of implanted SNS. Four of the randomised trials[51,75,87,116] compared implanted SNS with conservative treatment; patients receiving conservative treatment were given the option of SNS after six months follow-up. The fifth randomised controlled trial[98] compared 1-stage with 2-stage SNS.

Clinical indications for SNS included urinary urge incontinence, urgency-frequency, urinary retention, pelvic pain, interstitial cystitis, neurogenic overactive bladder or mixed voiding dysfunctions. In the review, efficacy outcomes were only considered for patients with urinary urge incontinence and urgency-frequency. Studies did not distinguish between different clinical indications in reporting adverse events, and hence the safety data considered in this review come from the total study populations.

3.2.3 Number and type of excluded studies; reasons for exclusion

One hundred and thirty three reports, originally identified as being potentially relevant were judged to be unsuitable for inclusion in the current review. Commonest reasons for exclusion were: inappropriate type of intervention (i.e. no SNS); inappropriate study design (e.g. letters, editorials, discussion papers), no efficacy and/or safety data reported. Studies that focused on patients with other clinical indications (e.g. urinary retention, interstitial cystitis, neurogenic overactive bladder) were also excluded. Potentially eligible non-English language studies were noted but not incorporated into the review (see Appendix 8).

3.2.4 Quality of available evidence

The methodological quality was assessed only for those 32 primary studies that were reported in full since abstracts alone did not usually provide enough information on which to assess the reliability of the methods employed.

Randomised controlled trials

The results of the quality assessment of the four randomised controlled trials are summarised in Table 3. Three studies compared implanted SNS with conservative treatment.[51,75,87] One study was a randomised cross-over trial comparing unilateral with bilateral PNE test.[72] Treatment assignment was deemed to be adequately randomised in one trial, which used a computerised random number generator.[87] The remaining trials[51,72,75] stated that patients were randomly assigned to treatment groups but did not provide any information on the method of randomisation. It was unclear whether the treatment allocation was adequately concealed in any of the trials.

Aside from the randomised cross-over trial,[72] only one of the remaining randomised trials[87] compared prognostic factors in each group of patients at baseline. Two trials included patients with refractory urinary urge incontinence,[75,87] one included patients with refractory urgency-frequency,[51] and the remaining trial included patients with chronic voiding disorders.[72] Other eligibility criteria were similar for all four trials. Both patient groups within each trial were treated in the same way apart from the intervention received.

Implanted SNS cannot be blinded to the care provider or the patients as it is an invasive procedure. Moreover, the crossover trial of the PNE test was not blinded because patients needed to be instructed to adjust the stimulation amplitude of each electrode.[72] No information was provided on whether the outcome assessor was blinded in any of the trials.

All four randomised controlled trials presented point estimates and measures of variability for the primary outcome measures. Only two trials lost patients to follow-up and it was unclear whether the number of dropouts was likely to have caused bias.[75,87]

Table 3 Summary of the quality assessment of the four randomised controlled trials (excluding abstracts)

Criteria	Yes	No	Unclear
1. Was the assignment to the treatment groups really random?	1	0	3
2. Was the treatment allocation concealed?	0	0	4
3. Were the groups similar at baseline in terms of prognostic factors?	2	0	2
4. Were the eligibility criteria specified?	4	0	0
5. Were the groups treated in the same way apart from the intervention received?	4	0	0
6. Was the outcome assessor blinded to the treatment allocation?	0	0	4
7. Was the care provider blinded?	0	4	0
8. Were the patients blinded?	0	4	0
9. Were the point estimates and measures of variability presented for the primary outcome measures?	4	0	0
10. Was the withdrawal/drop-out rate likely to cause bias?	0	3	1
11. Did the analyses include an intention-to-treat analysis?	2	2	0

Case series

A summary of the quality assessment of the 28 full-text case series studies is presented in Table 4.

It was not possible to determine if participants were a representative sample of a relevant population for any of the studies as the manner in which patients were selected for SNS was not clear. Only five studies[20,44,63,65,79] properly described the criteria for inclusion or exclusion of patients to the study. None of the studies reported whether or

not patients were entering the study at a similar point in their disease progression. Important prognostic factors were clearly identified in only two studies.[18,88]

Enrollment of patients was reported to be consecutive in two studies.[39,88] In one retrospective study[67] patients entered the study only if they previously underwent urodynamic investigations. In the remaining studies it was unclear from the information provided how patients were selected. Data collection was retrospective in six studies,[18,44,62,65,67,74] prospective in four,[36,40,63,83] and unclear in the remaining studies. The recruitment period was stated in only half of the studies.

Eighteen studies involved standard SNS therapy or PNE test. A further three[36,67,78] appeared to involve standard SNS therapy but details of the procedure were not specified. Seven studies reported modifications to the standard procedure: electrodiagnostic testing added to PNE;[19] use of permanent electrodes for PNE or 2-stage implantation;[42,65,69,85] tailored laminectomy;[31] and a minimally invasive implant technique.[66] None of the studies detailed the experience of surgeons undertaking the procedure or the staff and facilities where the operations were performed.

In four studies[42,57,66,74] only subjective outcome measures were used or only safety data reported. Most studies did not report all the outcome measures pre-identified in the protocol for this review; quality of life and patient satisfaction were considered or reported in only six studies.[16,18,20,36,69,79] After permanent implant average follow-up was at least six months where clearly stated. Information on dropouts and non-respondenrs was provided in only seven studies.[16,18,40,43,58,60,65] Nevertheless, participants lost to follow-up were considered likely to introduce bias in only one study.[20]

Table 4 Summary of the quality assessment of the 28 case series studies (excluding abstracts)

Criteria	Yes	No	Unclear
1. Were participants a representative sample selected from a relevant patient population?	0	0	28
2. Are the inclusion/exclusion criteria of patients in the study clearly described	5	23	0
3. Were participants entering the study at a similar point in their disease progression?	0	0	28
4. Was selection of patients consecutive?	2	1	25
5. Were all important prognostic factors identified?	2	25	1
6. Was data collection undertaken prospectively?	4	6	18
7. Was the recruitment period clearly stated?	14	14	0
8. Was the intervention that which is being considered in the review?	18	7	3
9. Was the operation undertaken by someone experienced in performing the procedure?	0	0	28
10. Did the staff, place, and facilities where the patients were treated provide an appropriate environment for performing the procedure?	0	0	28
11. Were objective (valid and reliable) outcome measures used?	23	4	1
12. Were all the important outcomes considered?	6	22	0
13. Was the follow-up long enough to detect important effects on outcomes of interest?	23	0	5
14. Was information provided on non-respondents, dropouts?	7	19	2
15. Were participants lost to follow-up likely to introduce bias?	1	16	11
16. Were the main findings clearly described?	16	12	0

3.2.5 Overview of efficacy findings

Only results from primary studies have been considered in the assessment of the efficacy and safety of SNS. Results of the PNE test are presented separately from results of the permanent implant phase, and results of randomised trials separately from results of case series studies. The results of the included studies are presented for each outcome measure according to the clinical indications for SNS: a) urge urinary incontinence; b) urgency-frequency; or c) a combination of these two conditions.

Peripheral nerve evaluation (PNE)

The numbers of patients in case series studies who exhibited a satisfactory response during PNE are presented in Table 5. Only studies that clearly stated the number of patients who initially underwent PNE were tabulated.

Amongst the 15 case series studies of patients with urge incontinence or urgency-frequency symptoms, two reported a PNE success rate of 100% (but each had only six patients) and the PNE success rates in the others ranged from 22% to 88%. In the five studies that did not differentiate between patients with urge incontinence and urgency-frequency symptoms the reported success rates ranged from 50% to 83%.

Success rates were not reported in a cross-over randomised trial of 12 patients with urge incontinence in which unilateral PNE was compared to bilateral PNE.[72]

In a randomised controlled trial (published as an abstract) comparing PNE testing based on visual observations of motor responses (control group) with PNE testing based on compound muscle action potentials (CMAP group) reported success rates were 5/10 (50%) and 4/9 (43%) respectively for patients with urge urinary incontinence and 4/9 (43%) and 0/10 (0%) for patients with urgency-frequency.[94]

A case series study, published in an abstract format, reported a success rate of 42.1% for unilateral PNE and 63.2% for bilateral PNE in patients with urge urinary incontinence but total numbers of patients in each group were not provided.[118]

Another case series study reported results after implantation of SNS in 15 patients who demonstrated an appropriate sensory and motor response during the acute phase of SNS but failed in the sub-chronic phase.[69] However, the total number of patients who initially undertook PNE was not specified.

Table 5 Success rates of PNE test (case series)

Study id	Success rate	Technical aspects
Urge incontinent patients		
#Ruffion 2003[112]	19/88 (22%)	
#Ruiz-Cerdá 2003[113]	25/89 (28%)	
Amundsen 2002[18]	12/25 (48%)	Bilateral PNE
Hedlund 2002[58]	19/49 (39%)	
#Kiss 2002[105]	6/6 (100%)[a]	Use of a permanent electrode
Bosch 2000[20]	46/85 (54%)	
Edlund 2000[43]	9/26 (35%)	
Weil 2000[87]	44/65 (68%)	
#Bryan 1999[92]	12/44 (27%)	
Schmidt 1999[75]	98/155 (63%)	
Cappellano 1998[39]	20/34 (59%)	
#Bristow 1997[91]	15/17 (88%)	
Janknegt 1997[65]	6/6 (100%)	Use of a permanent electrode
Hasan 1996[50]	16/21 (76%)	
Schmidt 1988[78]	14/19 (74%)	
Total	**361/729 (50%)**	
Urgency-frequency patients		
#Ruiz-Cerdá 2003[113]	19/46 (41%)	
Hasan 1996[50]	10/31 (32%)	
Total	**29/77 (38%)**	
Urge incontinent and urgency-frequency patients (undifferentiated)		
Scheepens 2003[67]	7/10 (70%)	
#Oliver 2001[108]	2/4 (50%)	
Carey 2001[40]	10/12 (83%)	
Chai 2001[42]	15/20 (75%)	Use of a permanent electrode
Benson 2000[19]	11/15 (73%)	Electrodiagnostic testing (CMAP) added to PNE
Total	**45/61 (74%)**	

#Abstract only

a. One patient required bilateral stimulation

Sacral nerve stimulation permanent implant

Results of randomised controlled trials

Urge urinary incontinence

Cure and improvement rates at the six months follow-up in patients with urge incontinence randomised to a stimulation or a delayed group are shown in the top section of Table 6.

About 50% of patients in the stimulation group achieved complete continence or an improvement >90% in the main incontinence symptoms compared with 2.5% of patients in the delay group.[75,87] A 50% improvement in main incontinence symptoms was observed in about 87% and 5% of patients in the stimulation and delay groups respectively.[75,87]

In the trials by Weil and colleagues[87] and Schmidt and colleagues[75] the number of leakage episodes per day, severity of leakage, and number of pads used per day were significantly lower six months after implantation compared with baseline in the stimulation group (Table 7). In contrast, patients in the delay group showed either no significant improvement or worsening of their incontinence symptoms. Weil and colleagues also observed that the mean bladder capacity significantly increased at six months compared with baseline in the stimulation group. Changes in urodynamic parameters were not reported for the delay group.[87]

Urgency-frequency

A 50% improvement in number of voids was observed in 56% of the patients in the stimulation group and 4% of the patients in the delay group (see bottom part of Table 6).[51]

Hassouna and colleagues[51] reported a significant decrease in the frequency of void (from 16.9 to 9.3, $p<0.0001$) and degree of urgency (from 2.2 to 1.6, $p=0.01$) at six months compared to baseline in the stimulation group. Mean volume voided (from 118ml to 226 ml, $p<0.001$) and mean bladder capacity (from 234ml to 325ml, $p=0.008$) were also

significantly higher compared with baseline values (see Table 8). In contrast, none of these parameters changed significantly in the delay group.

Urge incontinence and urgency-frequency symptoms

One randomised controlled trial compared the efficacy of a 2-stage implant with a 1-stage implant procedure in 22 patients with overactive bladder symptoms (urge incontinence and urgency-frequency).[98] No significant differences were observed in main clinical symptoms and quality of life between the two procedures.

Table 6 Success rates at six months in randomised controlled trials

Study id	Stimulation group				Delay group			
	Cured		Improved (including cured)		Cured		Improved (including cured)	
	Rate	%	Rate	%	Rate	%	Rate	%
Urge incontinent patients								
Weil 2000[87]	9/16	56	NR	85	1/22	5	1/22	5
Schmidt 1999[75]	16/34	47	26/34	76	0/42	0	2/42	5
#Weil 1996[116]	NR	NR	5/5	100	NR	NR	NR	0
Urgency-frequency patients								
Hassouna 2000[51]	NR	NR	14/25	56	NR	NR	1/25	4

NR not reported

Table 7 Leakage episodes, pad usage, severity of leakage, and bladder capacity in urge incontinent patients in randomised controlled trials

Study id	Stimulation group				Delay group			
	n	Baseline	6 months	p value	n	Baseline	6 months	p value
Mean leakage episodes per day (SD)								
Weil 2000[87]	21	13.5 (7.5)	1.4 (3.3)	<0.0005	22	13.5 (7.8)	11.2 (5.6)	n.s.
Schmidt 1999[75]	34	9.7 (6.3)	2.6 (5.1)	<0.0001	42	9.3 (4.8)	11.3 (5.9)	0.002
Mean pad use per day (SD)								
Weil 2000[87]	21	8.7 (6.8)	0.7 (1.3)	<0.0005	22	8.7 (7.1)	6.8 (4.0)	n.s.
Schmidt 1999[75]	34	6.2 (5.0)	1.1 (2.0)	<0.0001	42	5.0 (3.7)	6.3 (3.6)	0.003
Mean severity of leakage (SD)								
Weil 2000[87]	21	2.1 (0.6)	1.6 (1.7)	0.047	22	2.1 (0.6)	2.1 (0.6)	n.s.
Schmidt 1999[75]	34	2.0 (0.7)	0.8 (0.9)	<0.0001	42	1.8 (0.6)	2.0 (0.6)	0.006
Mean bladder capacity (ml) (SD)								
Weil 2000[87]	21	266 (112)	370 (91)	0.013	23	NR	NR	-

Severity of leakage was assessed on a 0-3 scale (0 dry, 1 loss of a few drops of urine, 2 loss of 1-2 tablespoons of urine, 3 complete wetting/soaked pad or outer clothing).
n.s. not significant
NR not reported

Table 8 Frequency of voiding, degree of urgency, volume per void, and bladder capacity in urgency-frequency patients in randomised controlled trials

Study id	Stimulation group				Delay group			
	n	Baseline	6 months	p value	n	Baseline	6 months	p value
Mean frequency of voiding per day (SD)								
Hassouna 2000[51]	25	16.9 (9.7)	9.3 (5.1)	<0.0001	26	15.2 (6.6)	15.7 (7.6)	n.s.
Mean degree of urgency (0 none, 1 mild, 2 moderate, 3 severe) (SD)								
Hassouna 2000[51]	25	2.2 (0.6)	1.6 (0.9)	0.01	25	2.4 (0.5)	2.3 (0.5)	n.s.
Mean voided volume per void (ml) (SD)								
Hassouna 2000[51]	25	118 (74)	226 (124)	<0.001	26	124 (66)	123 (75)	n.s.
Mean bladder capacity (ml) (SD)								
Hassouna 2000[51]	23	234 (128)	325 (185)	0.008	25	253 (93)	227 (104)	n.s.

n.s. not significant

Table 9 Quality of life results at six months follow-up in randomised controlled trials

Study id			SF-36 mean score (SD)							
			Physical Health					Mental Health		
		n	Physical functioning	Physical role	Bodily pain	General health	Vitality	Social functioning	Emotional role	Mental health
Urge incontinent patients										
Weil 2000[87]	Implant	16	67 (25)	60 (28)	59 (25)	62 (23)	59 (23)	54 (9)	90 (15)	69 (24)
	Control	23	51 (28)	59 (23)	55 (23)	56 (22)	56 (25)	55 (13)	77 (23)	67 (23)
	p value		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	0.037	n.s.
Schmidt 1999[75]	Implant	28		46				47		
	Control	32		36				45		
	p value			0.0008				n.s.		
Urgency-frequency patients										
Hassouna 2000[51]	Implant	23	77	51	60	61	55	77	62	71
	Control	20	48	30	64	46	36	43	48	62
	p value		<0.0001	0.01	0.01	0.003	0.01	0.002	0.17	0.01

n.s. not significant

Quality of life

Urge incontinence

Two randomised controlled trials used the SF-36 short-form Health Survey to assess the impact of SNS on patients' quality of life.[75,87] Weil and colleagues[87] found a significant difference in only the emotional role score (Table 9). They also reported that, for the stimulation group at six months, the physical functioning score (67; 95% CI, 55-78) and the overall score for the physical component of the scale (42; 95% CI, 37-57) were significantly higher (p=0.034 and p=0.019 respectively) than the corresponding baseline values (52; 95% CI, 41-64 and 36; 95% CI, 30-41). Schmidt and colleagues[75] observed a significant between-group difference six months after implantation in the physical health component of the questionnaire (p=0.0008) but no significant difference between the treatment groups in the mental health component (Table 9).

Urgency-frequency

Hassouna and colleagues[51] used the SF-36 Health Survey to assess the physical and mental health in 23 stimulation and 20 delay group patients at six months (Table 9). Significantly higher scores were observed in the stimulation group for all the subscales of SF-36 with the exception of the emotional role score.

Results of case series studies

Urge incontinence

Twenty-two studies provided data on the efficacy of SNS in patients with urge urinary incontinence.

- *Success rate*

Seventeen studies reported cure and/or improvement rates in patients with urge incontinence (top part of Table 10). Length of follow-up varied amongst the studies. Cure rates ranged from 7% to 64% and in total 139 out of 361 patients (39%) were reported to be cured. Overall a $\geq$50% improvement in incontinence symptoms was observed in 338 out of 501 patients (67%).

- *Leakage episodes*

Fourteen case series studies measured the change in the average number of leakage episodes at follow-up compared to baseline in patients with urge incontinence alone (Table 11). Overall, the frequency of leakage was 4.5-11.6 episodes per day at baseline and 0.8-5.0 at last follow-up after implantation of the pulse generator (reduced by 53%-92%). The change was reported to be statistically significant in 11 of the 14 studies ($p<0.05$).

- *Pad usage*

Fourteen studies compared the number of pads used per day at six months or last follow-up after implantation with the number of pads used at baseline in patients with urge incontinence alone (Table 12). The average number of pads decreased from 4.0-8.3 to 0.4-3.4 (reduced by 75%-94%) and the change was statistically significant in ten studies ($p<0.05$).

- *Severity of leakage*

The severity of incontinence episodes in patients with urge urinary incontinence was assessed on a scale from 1 to 3 (1=mild, 2=moderate, 3=severe) in four studies (Table 13). On average, severity of leaks reduced from 1.4-2.0 at baseline to 0.8-1.6 at 18 months or last follow-up (reduced by 16%-40%). The reduction was statistically significant in three of the four studies ($p<0.05$).

- *Degree of urgency*

The degree of urgency was assessed by means of a scale from 0 to 3 (0=none, 3=strong) in two studies (Table 14). The scale used by Weil and colleagues 1998[88] was not specified. No significant differences were observed in mean urgency scores from baseline to last follow-up in patients with urge urinary incontinence.

- *Frequency of void*

Frequency of void in patients who had urge incontinence was assessed in eight studies (Table 15). Mean number of voids per day decreased from 10.0-15.0 at baseline to 7.0-9.2 at last follow-up after implantation (reduced by 30%-41%). The change was statistically significant in six studies ($p<0.05$).

- *Urodynamic parameters*

Voided volume per void was measured in nine studies of incontinence patients at baseline and at last follow-up (top part of Table 16). On average the total voided volume increased from 99-195 ml per void to 176-402 ml per void (34%-288% change). The increase was significant in eight of the nine included studies ($p<0.05$).

Bladder capacity was considered in nine studies in this patient group (Table 17). Total bladder capacity increased from 122-400 ml at baseline to 273-596 ml at six months or last follow-up (15%-197% change). The change from baseline was statistically significant in six studies.

Urgency-frequency

Four case series studies assessed the efficacy of SNS in patients with urgency-frequency symptoms.

- *Success rate*

All four studies reported improvement rates but different definitions of success were used to define improvement (Table 10). Overall 22 out of 54 patients (41%) were reported to be cured whilst 75 out of 116 patients (65%) had an improvement of at least 50% in their symptoms.

- *Degree of urgency*

The degree of urgency was assessed on a scale from 0 to 3 (0=none, 3=strong) in one study published as an abstract (bottom of Table 14). The average degree of urgency decreased from 2.2 at baseline to 1.9 at the 35-month follow-up ($p=0.002$).

- *Frequency of void*

Frequency of void was assessed in three studies (middle section of Table 15). Number of voids per day was significantly reduced from baseline to last follow-up in each study ($p<0.05$) with the differences being more significant in the two larger studies ($p<0.0001$).

- *Urodynamic parameters*

Two studies reported changes in voided volume from baseline to last follow-up after implantation (middle section of Table 16). Both Heesakkers and colleagues[101] and Siegel

and colleagues[83] reported a statistically significant increase in voided volume per 24 hours (74% and 69% respectively, p<0.001). Heesakkers and colleagues[101] also observed an increase of 47% in total bladder capacity from baseline (p<0.0001) (Table 17).

Urge incontinence and urgency-frequency

Three studies included patients with various forms of voiding dysfunctions whose results could not be separated into urge urinary incontinence and urgency-frequency. The results of these studies are therefore presented for both clinical conditions together.

- *Success rate*

Three studies reported a 50% or greater improvement in patients' symptoms at six months or at last follow-up (bottom of Table 10). Overall, 63 out of 85 patients (74%) reported improvement in their main clinical symptoms after SNS.

- *Leakage episodes, frequency of voids, and pad usage*

One study provided data on the changes in the average number of incontinence episodes, voids per day, and pads used.[16] The number of incontinence episodes was significantly lower at last follow-up compared with baseline (from 6.4 to 2.0, p<0.05). Similarly the frequency of voids was reduced from 17.9 per day at baseline to 8.6 post-implantation (p<0.05). The average number of pads used in 24 hours was also significantly fewer after the procedure (from 3.5 at baseline to 1.0, p<0.05) (Tables 11, 12, 15).

- *Urodynamic parameters*

Voided volume was measured in one study after sacral nerve implant.[16] The average voided volume was significantly higher at follow-up - from 130 ml at baseline to 248 ml post-implantation (p<0.05) (bottom of Table 16).

Quality of life

Four instruments were used in three studies to assess the impact of SNS on patients' quality of life: a quality of life index questionnaire, the Incontinence Impact Questionnaire, the Beck Depression Inventory, and the Short-Form-36 Health Survey (Table 18).

Capellano and colleagues[36] reported the results of 47 patients assessed using a 22-item, domain specific, questionnaire developed to detect modifications in self-perceived incontinence severity. The score of the questionnaire was calculated on a scale 0-100 (0=poor self-perceived quality of life; 100=incontinence did not negatively impact quality of life). The average quality of life index score was significantly higher after implantation - 34.4 compared with 83.8 ($p<0.01$).

Amundsen and colleagues[18] observed a significantly higher total score on the Incontinence Impact Questionnaire at last follow-up compared to baseline (from 250 at baseline to 62 at last follow-up, $p=0.03$).

Shaker[79] used both the SF-36 and the Beck Depression Inventory (BDI) to assess the impact of SNS on the quality of life of 18 patients with refractory urge incontinence (Table 18). An improvement of 10%-40% was detected in the BDI (but it was not specified whether it was statistically significant). No significant differences were observed in the scores of any SF-36 subscales with the exception of change of health perception that was reported to be significantly higher at six months compared to baseline (significance level not given).

Table 10 Cure and improvement rates at last follow-up in case series studies

Study id	Follow-up (months)	Patients cured		Patients improved (including cured)	
		Rate	%	Rate	%
Urge incontinent patients					
#Ruiz-Cerdá 2003[113]	6.8*	14/25	55	16/25	66
#Heesakkers 2003[101]	60	NR	NR	27/43	63
Amundsen 2002[18]	7.8*	2/12	17	12/12	100
#Everaert 2002[98]	12	NR	NR	4/5	80
#Groenendijk 2002a[99]	6	NR	NR	55/84	65
Hedlund 2002[58]	18*	8/14	57	13/14	93
#Spinelli 2002[114]	NR	NR	NR	3/3	100
#Carabello 2001[93]	13.4*	1/15	7	12/15	80
Janknegt 2001[63]	30.8*	25/96	26	60/96	62
Bosch 2000[20]	47*	18/45	40	27/45	60
Grünewald 2000[46]	6	6/26	23	19/26	73
Siegel 2000[83]	36	19/41	46	24/41	59
#Koldewijn 1999[106]	29*	18/28	64	21/28	75
Hohenfellner 1998[60]	13*	NR	NR	5/5	100
Shaker 1998[79]	18.8*	8/18	44	12/18	67
Weil 1998[88]	37.8*	14/24	58	17/24	71
#Dijkema 1994[96]	17	6/17	35	11/17	65
Total	**-**	**139/361**	**39**	**338/501**	**67**
Urgency-frequency patients					
#Ruiz-Cerdá 2003[113]	6.8*	10/19	52	11/19	58
#Heesakkers 2003[101]	35*	NR	NR	41/56	73
Siegel 2000[83]	24	9/29	32	16/29	56
Weil 1998[88]	37.8*	3/6	50	3/6	50
Total	**-**	**22/54**	**41**	**75/116**	**65**
Urge incontinent and urgency-frequency patients (undifferentiated)					
Aboseif 2002[16]	24*	NR	NR	33/44	75
#Groenendijk 2002b[100]	6	NR	NR	13/19	68
Ishigooka 1999[62]	12	NR	NR	17/22	77
Total	**-**	**-**	**-**	**63/85**	**74**

#Abstract only
* mean follow-up
NR not reported

Table 11 Mean leakage episodes per day in case series studies

Study id	n	Length follow-up (months)	Baseline (SD)	Follow-up (SD)	p-value	Change (%)
Urge incontinent patients						
#Heesakkers 2003[101]	105	45*	10.9	4.3	<0.0001	-6.6 (-61)
#Ruiz-Cerdá 2003[113]	25	6.8*	4.5	0.8	<0.02	-3.7 (-82)
Amundsen 2002[18]	12	7.8*	7 (3)	2 (1)	n.s.	-
Scheepens 2002a[69]	7	59*	9.0 (4.3)	3.2 (3.4)	n.s.	-
Cappellano 2001[36]	47	12	5.8 (4.2)	0.9 (1.5)	<0.01	-4.9 (-84)
Janknegt 2001[63]	96	30.8*	10.9 (6.5)	4.2 (4.9)	<0.0001	-6.7 (-61)
Bosch 2000[20]	44	6	7.1[a]	1.3[a]	0.0001	-5.8 (-82)
Edlund 2000[43]	8	12	5.9 (2.2)	2.8 (1.5)	0.01	-3.1 (-53)
Siegel 2000[83]	41	36	11.6 (6.6)	5.0 (6.1)	<0.0001	-6.6 (-57)
Braun 1999[31]	6	12.5*	7 (7.3)	1 (0.7)	<0.05	-6 (-86)
Cappellano 1998[39]	10	23.1*	13	1	NR	-12 (-92)
Shaker 1998[79]	18	1	6.5	2.0	<0.05	-4.5 (-69)
Weil 1998[88]	24	6	4.9 (7.1)	1.1 (3.4)	0.0039	-3.8 (-78)
#Dijkema 1994[96]	17	18	8.5	2.7	<0.001	-5.8 (-68)
Urge incontinent and urgency-frequency patients (undifferentiated)						
Aboseif 2002[16]	43	24*	6.4	2.0	<0.05	-4.4 (-69)

#Abstract only
* mean follow-up
[a] median
n.s. not significant
NR not reported

Table 12 Mean pad usage per day in case series studies

Study id	n	Length follow-up (months)	Baseline (SD)	Follow-up (SD)	p-value	Change (%)
Urge incontinent patients						
#Heesakkers 2003[101]	105	45*	6.5	2.4	<0.0001	-4.1 (-63)
Amundsen 2002[18]	12	7.8*	7 (3)	2 (1)	n.s.	-
Hedlund 2002[58]	7	24	8.3 (1.3)	0.6 (0.4)	<0.05	-7.7 (-93)
Scheepens 2002a[69]	7	59*	5.0 (2.4)	1.0 (1.3)	0.003	-4 (-80)
Janknegt 2001[63]	96	30.8*	6.6 (5.2)	2.7 (3.8)	<0.0001	-3.9 (-59)
Bosch 2000[20]	45	6	5.4[a]	1.2[a]	0.0001	-4.2 (-78)
Edlund 2000[43]	8	12	3.0 (2.5)	1.9 (1.8)	n.s.	-
Siegel 2000[83]	41	46	6.7 (4.6)	3.4 (4.9)	<0.0001	-3.3 (-49)
Braun 1999[31]	6	12.5*	4 (4.9)	1 (0.7)	0.05	-3 (-75)
Cappellano 1998[39]	10	23.1*	9.0	0.5	NR	-8.5 (-94)
Hohenfellner 1998[60]	5	13*	5 (4.5)	1 (1.3)	n.s.	-
Weil 1998[88]	24	6	6.6 (5.4)	2.3 (4.4)	0.0011	-4.3 (-65)
Janknegt 1997[65]	4	6	7.2	0.4	<0.05	-6.8 (-94)
#Dijkema 1994[96]	17	18	6.1	2.5	<0.001	-3.6 (-59)
Urge incontinent and urgency-frequency patients (undifferentiated)						
Aboseif 2002[16]	43	24*	3.5	1.0	<0.05	-2.5 (-71)

#Abstract only
* mean follow-up
[a] median
n.s. not significant
NR not reported

Table 13 Mean severity of leakage in case series studies

Study id	n	Length follow-up (months)	Baseline (SD)	Follow-up (SD)	p-value	Change (%)
Urge incontinent patients						
Scheepens 2002a[69]	7	59*	1.8 (0.3)	1.3 (0.3)	0.041	-0.5 (-28)
Janknegt 2001[63]	96	30.8*	2.0 (0.6)	1.2 (0.9)	<0.0001	-0.8 (-40)
Edlund 2000[43]	8	19.9*	1.9 (0.4)	1.6 (0.4)	0.02	-0.3 (-16)
Shaker 1998[79]	7	18	1.4 (0.7)	0.8 (0.8)	NR	-0.6 (-43)

* mean follow-up
NR not reported

Table 14 Mean degree of urgency in case series studies

Study id	n	Length follow-up (months)	Baseline (SD)	Follow-up (SD)	p-value	Change (%)
Urge incontinent patients						
Janknegt 2001[63]	80	30.8*	2.0 (0.9)	2.0 (0.7)	n.s.	-
Shaker 1998[79]	18	18	2.1 (1.4)	1.9 (1.3)	n.s.	-
Weil 1998[88]	24	6	3.1 (1.5)	3.1 (1.0)	n.s.	-
Urgency-frequency patients						
#Heesakkers 2003[101]	74	35*	2.2 (0.6)	1.9 (0.7)	0.002	-0.3 (-14)

* mean follow-up
n.s. not significant

Table 15 Mean frequency of void (voids per day) in case series studies

Study id	n	Length follow-up (months)	Baseline (SD)	Follow-up (SD)	p-value	Change (%)
Urge incontinent patients						
Amundsen 2002[18]	12	7.8*	11 (2)	7 (1)	n.s.	-
Hedlund 2002[58]	7	24	10.0 (1.1)	7.0 (0.7)	n.s.	-
Scheepens 2002a[69]	7	59*	12.9 (5.8)	7.9 (2.2)	0.05	-5.0 (-39)
Janknegt 2001[63]	85	30.8*	13.2 (6.8)	9.2 (4.5)	<0.0001	-4 (-30)
Bosch 2000[20]	44	6	13.2[a]	8.3[a]	0.0001	-4.9 (-37)
Hohenfellner 1998[60]	5	13*	14 (2.2)	7 (2.2)	<0.05	-7 (-50)
Shaker 1998[79]	10	1	15.0 (6.2)	8.8 (2.7)	<0.05	-6.2 (-41)
Weil 1998[88]	24	6	13.7 (6.7)	8.7 (12.7)	0.0063	-5.0 (-36)
Urgency-frequency patients						
#Heesakkers 2003[101]	74	35*	17 (8)	11 (6)	<0.0001	-6 (-35)
#Ruiz-Cerdá 2003[113]	19	6.8*	15.3	6.6	<0.04	-8.7 (-57)
Siegel 2000[83]	29	24	17.7 (8.6)	10.6 (6.6)	<0.0001	-7.1 (-40)
Urge incontinent and urgency-frequency patients (undifferentiated)						
Aboseif 2002[16]	43	24*	17.9	8.6	<0.05	-9.3 (-52)

#Abstract only
* mean follow-up
[a] median
n.s. not significant

Table 16 Mean voided volume (ml) per void in case series studies

Study id	n	Length follow-up (months)	Baseline (SD)	Follow-up (SD)	p-value	Change (%)
Urge incontinent patients						
Hedlund 2002[58]	7	24	195 (25)	289 (37)	<0.05	94 (48)
Scheepens 2002a[69]	7	59*	99 (62)	313 (121)	0.004	214 (216)
Janknegt 2001[63]	85	30.8*	149 (99)	200 (100)	<0.0001	51 (34)
Bosch 2000[20]	44	6	129	176	0.0001	47 (36)
Grünewald 2000[52]	21	6	208	292	<0.05	84 (40)
Hohenfellner 1998[60]	5	13*	86 (47)	334 (193)	<0.05	248 (288)
Shaker 1998[79]	10	12	182 (162)	402 (503)	n.s.	-
Weil 1998[88]	24	6	158 (90)	228 (128)	0.0117	70 (44)
#Dijkema 1994[96]	17	18	158	220	<0.001	62 (39)
Urgency-frequency patients						
#Heesakkers 2003[101]	57	35*	117 (79)	204 (144)	<0.001	87 (74)
Siegel 2000[83]	29	24	133 (94)	225 (162)	<0.0001	92 (69)
Urge incontinent and urgency-frequency patients (undifferentiated)						
Aboseif 2002[16]	43	24*	130	248	<0.05	118 (91)

#Abstract only
* mean follow-up
n.s. not significant

Table 17 Mean bladder capacity (ml) in case series studies

Study id	n	Length follow-up (months)	Baseline (SD)	Follow-up (SD)	p-value	Change (%)
Urge incontinent patients						
Hedlund 2002[58]	7	24	400 (35)	596 (36)	n.s.	-
Grünewald 2000[46]	21	6	278	306	n.s.	-
Braun 1999[31]	6	12.5*	198 (127)	352 (120)	<0.05	154 (78)
Capellano 1998[39]	10	23.1*	122	330	NR	208 (170)
Hohenfellner 1998[60]	5	13*	130 (103)	386 (128)	<0.05	256 (197)
Shaker 1998[79]	10	6	292 (153)	336 (161)	NR	44 (15)
Weil 1998[88]	24	6	187 (144)	273 (153)	0.0108	86 (46)
#Dijkema 1994[96]	17	18	182	291	<0.001	109 (60)
#Thon 1992[115]	36	6	267	330	n.s.	-
Urgency-frequency patients						
#Heesakkers 2003[101]	74	35±12	315 (208)	462 (246)	<0.0001	147 (47)

#Abstract only
* mean follow-up
n.s. not significant
NR not reported

Table 18 Quality of life results from case series studies

Study id		Quality of Life Index (SD)	Incontinence Impact Questionnaire (SD)	Becks Depression Inventory	SF-36							
					Physical functio-ning	Physical role	Bodily pain	General health	Vitality	Social functio-ning	Emotional role	Mental health
Amundsen 2002[18]	Baseline	-	250 (64)	-	-	-	-	-	-	-	-	-
	Follow-up	-	62 (45)	-	-	-	-	-	-	-	-	-
	p value	-	0.03	-	-	-	-	-	-	-	-	-
Cappellano 2001[36]	Baseline	34 (23)	-	-	-	-	-	-	-	-	-	-
	Follow-up	84 (17)	-	-	-	-	-	-	-	-	-	-
	p value	<0.01	-	-	-	-	-	-	-	-	-	-
Shaker 1998[79]	Baseline	-	-	-	72	62	50	50	62	62	67	76
	Follow-up	-	-	10%-40% improved	95	100	78	50	75	56	100	80

3.2.6 Overview of safety findings

Adverse events relating to the permanent implant phase of SNS are detailed for individual studies in Table 19. Full details were not provided in some of the studies that discussed adverse events. In most of the studies safety data were not provided separately for each clinical indication with the safety profile of SNS being based on pooling of data from all patients under investigation (including, in some studies, patients with urinary retention). A few studies reported safety data based on a comprehensive patient population for whom efficacy information had been reported separately according to patients' clinical diagnosis. In these only the report with the most complete account of adverse events was considered.

Adverse events were documented amongst a total of 1015 patients in 27 studies. A summary of the adverse event rates is shown in Table 20. Among 860 patients 283 (33%) underwent surgical revision of the SNS implant. The most common reasons for re-operation were relocation of the neurostimulator because of pain at the implant site; revision of the lead system for suspected or detected lead migration; and infection.

Pain, lead related complications, and pulse generator replacement or relocation appeared to be the most frequently observed adverse events, followed by removal of the pulse generator, wound problems, bowel problems, and infection.

Pain was reported in 162 out of 663 tested patients (24%) and included pain at the generator site, pain at lead site, stimulation related pain, and new pain. Pain at the generator site was often treated by adjustment of the current amplitude and frequency of the stimulation or by relocation of the generator.

Lead related complications were observed in 130 out of 807 (16%) patients and were mainly lead migration, lead breakage, loosened connection between extension lead and electrode, and electrode insulation defects.

Forty-two out of 279 patients (15%) required replacement or relocation of the pulse generator mainly because of pain at the implant site, upgrade or reprogramming of an early pulse generator (Itrel I), battery failure, infection, or technical failure.

Overall, wound problems (e.g. seroma, hematoma, partial wound dehiscence) occurred in 20 out of 283 tested patients (7%).

Modification of bowel function or adverse bowel function were documented in 20 out of 353 implanted patients (6%).

Infection was reported in 35 out of 739 of patients (5%). It was usually managed with antibiotics but deep infection in some patients required explantation of the pulse generator. The implanted pulse generator was also removed in cases of aversion (i.e. psychological rejection) or when the treatment failed. The overall permanent explant rate was 9% (44 out of 514 patients).

Problems related to the implanted pulse generator (e.g. battery exhaustion) occurred in 5% of the patients who received SNS.

No major neurological complications were documented apart from a suspected case of nerve injury[83] and a case of generalised fasciculation whose aetiology could not be established.[44]

A study by Das and colleagues[95] reviewed 256 patients to compare upper buttock with lower abdomen placement of the pulse generator. Pain at the implant site or infection occurred in 16% and 42% of patients respectively (p=0.005).

Table 19 Adverse events in patients with implanted SNS

Study id	Implants (n)	Re-operations	IPG replaced/ relocated	Permanent explants	Generator problems	Electrode & lead problems	Pain	Infection	Wound problems	Adverse bowel function	Other
#Heesakers 2003[101]	105	-	-	14	-	-	-	-	-	-	-
Ratto 2003[66]	10*	-	-	-	-	0	0	-	1	-	-
#Ruffion 2003[112]	33*	-	-	4[a]	-	-	1	1	-	-	-
#Ruiz-Cerdá 2003[113]	69*	5	1	1[b]	-	3	-	0	-	-	20[c]
Spinelli 2003[85]	22*	5	-	1[d]	-	4	-	0	-	-	-
Aboseif 2002[16]	64*	5	-	1	2	2	-	4	6	-	-
Amundsen 2002[18]	12	1	-	-	-	1[e]	2	0	0	-	-
Hedlund 2002[58]	14	2	-	-	-	2	0	-	1	2	-
#Peters 2002[111]	14*	4	-	0	-	-	3	0	-	-	1[f]
#Caraballo 2001[93]	17	2	1	-	1	-	1	3	2	-	-
Scheepens 2002a[69]	15*	5	1	2	-	1	11	0	-	1	-
Scheepens 2001[74]	39*	2	0	-	-	-	6	0	2	-	-
Bosch 2000[20]	45	25	7	0	7	15	5	0	4	-	-
Edlund 2000[43]	9*	1	-	-	-	1	-	-	-	5	3[g]
Everaert 2000[44]	54*	15	-	-	3	2	27	1	-	3	15[h]
Grünewald 2000[46]	55*	14	-	-	-	4	3	5	1	-	1[i]
¡Siegel 2000[83]	219*	73	-	-	5	22	65	13	-	7	38[k]
Weil 2000[87]	42	21	-	1	-	8	24	-	-	2	5[l]
Braun 1999[31]	9*	1	-	-	-	1	-	-	1	-	-
#Koldewijn 1999[106]	40*	26	9	6	-	20	8	4	-	-	-
Cappellano 1998[39]	10	1	-	-	-	1	-	-	-	-	-
Hohenfellner 1998[60]	11*	3	-	1[m]	-	2	-	5	-	-	-
Shaker 1998[79]	18	7	2[n]	1[b]	-	2	2	0	2	-	-
Weil 1998[88]	36*	57	21[o]	12[p]	-	24	4	-	-	-	-
Hassouna 1991[57]	7*	-	-	-	-	0	-	0	-	-	-
#Light 1992[107]	5*	1	-	-	-	1	-	0	-	-	-
#Thon 1992[115]	41*	7	-	-	-	14	-	-	-	-	8[q]

* includes patients with urinary retention
#Abstract only

Notes for Table 19 Adverse events in patients with implanted SNS

Notes:

a. one ineffective and one functional but removed due to pregnancy
b. explanted due to psychological rejection
c. seroma, electro induced pain, constipation, anal fissure
d. IPG damage secondary to magnetic resonance imaging
e. earlier type of electrode without a fixed anchor used in this patient
f. revised generator pocket
g. stimulator was unintentionally turned off in three patients
h. current-related problems (6), disturbing toe flexion (4), operation related problems (1), generalised fasciculation (1), other stimulation related symptoms (4) (e.g. difficulty swallowing, heavy sweating and fatigue)
i. polyurethane allergy
j. Siegal 2000,[83] Janknegt 2001,[63] Schmidt 1999[75] and Hassouna 2000[51] all report safety data for the same pooled population. The data from Siegel 2000 were used in this table as this was the only one of these studies to report data for adverse events with a rate of below 5%
k. transient electric shock (5.5%), change in menstrual cycle (1.0%), adverse change in voiding function (0.6%), persistent skin irritation (0.5%), suspected nerve injury (0.5%), other (9.5%)
l. leg stimulation (2), urinary retention (1), vaginal cramps (1), skin irritation at implant site (1)
m. functioning implant removed as patient complained of being constantly aware of the disease during stimulation
n. battery failure
o. replace Itrel I stimulator with Itrel II or Itrel III, change programme of stimulation in Itrel I, or reposition stimulator
p. the stimulator was removed when the patient required it, in cases of aversion, or when it was considered that the treatment had completely failed
q. complications of surgical origin

Table 20 Rates of adverse events

Type of adverse event	Rate[a] (%)
Re-operations	283/860 (33%)
IPG replaced/relocated	42/279 (15%)
Permanent explants	44/514 (9%)
Generator problems	18/399 (5%)
Electrode and lead problems	130/807 (16%)
Pain	162/663 (24%)
Infection	35/739 (5%)
Wound problems	20/283 (7%)
Adverse bowel function	20/353 (6%)

a. Number of events/number of implanted patients in studies reporting that type of adverse event

4. DISCUSSION

4.1 The main findings

Efficacy data from both randomised controlled trials and case series studies show that about 70% of the patients who received SNS became dry or showed improvement in their main incontinence symptoms. This compared with 4% in the control groups in randomised studies. Fewer episodes of leakage per day, fewer pads used per day, and fewer voids per day were also reported post-implantation. The degree of urgency changed significantly in patients with urgency-frequency syndrome but not in patients with urge incontinence. There was a relatively small change in volume per void and bladder capacity in patients with urge urinary incontinence.

There was no evidence that the safety profile of SNS differs according to patients' clinical indications (e.g. urge urinary incontinence, urgency-frequency, and retention). The overall surgical revision rate for the implanted patients (283/860) was 33%. Most common complications were pain at the implant site (24%), lead migration (16%), wound problems (7%), adverse effect on bowel function (6%), infection (5%), and generator problems (5%). In 42 out of 279 patients (15%) the implanted pulse generator was replaced or relocated and 44 out of 514 patients (9%) required permanent explantation of the pulse generator.

There were no reports of long-lasting neurological adverse events. However, a suspected case of nerve injury was mentioned in one study[83] and a case of generalised fasciculation of unknown aetiology was reported in another study.[44] No further details on the severity and duration of these two complications were provided.

4.2 Assumptions, limitations, and uncertainties

SNS has been proposed as a possible treatment for patients with voiding problems due to a range of underlying clinical conditions where conservative treatments have failed. The commonest group is patients with severe urge urinary incontinence or urgency-frequency and this is the focus of this review. However, most of the studies in this review were not limited to patients with urge incontinence or urgency-frequency

symptoms alone and did not always report the breakdown of results by type and aetiology of the urinary symptoms. For efficacy data we considered only studies reporting findings in patients with urge urinary incontinence or urgency-frequency symptoms, either presented separately or lumped together. Efficacy of SNS in patients with other indications such as urinary retention or pelvic pain, even when reported, was not considered in the present review. Safety data were often only reported for a whole population entering a study regardless of the clinical conditions of individual patients or subgroups of patients. However, for the purpose of assessing safety, studies that did not differentiate patients with urge incontinence or urgency-frequency symptoms from patients with other clinical diagnoses but which reported safety data were included in this review.

Available evidence on the efficacy and safety of SNS came from four randomised, manufacturer-sponsored, multicentre trials, three additional randomised trials, and 47 case series studies published in 88 reports. Although we tried to identify all duplicates it may be possible that some degree of overlap has been overlooked especially for studies reporting on the outcomes of SNS over time.

SNS is intended for patients with severe incontinence symptoms refractory to conventional treatments. However, there was great discrepancy in the range of treatments patients had received before implantation and the severity of their incontinence was often not described. In most studies patients were previously treated with pharmacological therapy and/or surgical operations; in some instances they had received only conservative, non-surgical treatments, such as behavioural therapy.

The range of median or mean age of the patients considered in the studies included in this review varied between 34 and 69 years. Consequently it is uncertain whether the results can apply to an older population. It is interesting to note that modification of bowel function or adverse effects on bowel function were side effects more often reported in studies that included patients over 75 years of age.

The best evidence in this review should come from the four full-text reports of randomised trials. However, none of these four trials was of high quality. In none was it stated how allocation of patients to treatment groups was concealed: in three of the trials

it was unclear whether the outcome assessors were blinded to treatment allocation, and none of the trials provided an intention-to-treat analysis of data. It is also worth mentioning that the multicentre trial was sponsored by Medtronic, the manufacturer of the SNS device. Another problem concerning the analysis of data of randomised controlled trials was that they presented within-group comparisons (pre- and post-implant results in each treatment group) but did not formally compare differences between groups (stimulation group versus control group). The direction and magnitude of differential effects was however consistent across the trials.

Most of the remaining evidence consisted of case series studies, which are known to be more prone to biases than randomised controlled trials. In particular, selection bias (patients treated and cases reported both chosen by investigators), findings not adjusted for confounding factors (e.g. age, duration of symptoms, previous pelvic surgery); likelihood of some spontaneous improvement because patients were treated at their worst; and dropout/withdrawal rates may affect the reliability and magnitude of the treatment effect in case series studies. The majority of case series studies were also small, failed to identify important patient prognostic factors, and did not provide information on non-responders and dropouts. Furthermore, it was unclear in most studies whether data had been collected prospectively. However, the direction and size of the pre- and post-treatment differences were consistent across studies and with those of the randomised trials.

Patients' quality of life was rarely measured in the studies included in this review. Only three randomised trials and three case series studies reported some quality of life measures. Amongst those tending to suggest improvement after SNS the findings were not consistent across studies.

It is only the most recently published studies that tended to quantify adverse events, whilst earlier studies either discussed them in a more narrative way or did not report them. Most of the complications observed in the included studies were technical problems related to the implantation of the device. The clinical experience and skill of the clinician performing the procedure could have a major impact on the success of the procedure and subsequent incidence of 'technical' complications. For neither randomised trials nor case series was information provided about the level of expertise

of the clinician(s) undertaking the procedure. Furthermore, the back-up facilities of the hospital/clinic where the procedures were performed were never described.

4.3 Other considerations

No factors (other than the peripheral nerve evaluation test) have been identified to predict which patients with voiding dysfunctions would benefit from SNS. It has been suggested that the presence of neurogenic bladder dysfunction and long-lasting symptoms may negatively affect the likelihood of success.[119] However, further evidence is needed to corroborate these results. The PNE test is the method used to select suitable candidates for SNS. Yet, its success rate is approximately 50% and varies considerably across studies. Furthermore, the test evaluation may produce inconclusive results because of lead migration or inappropriate site of stimulation and in many occasions it needs to be repeated several times. It has been observed that patients who show a positive response during the acute phase of the test evaluation, but fail the sub-chronic phase because of technical problems, might still be suitable candidates for permanent implant.[65,69]

Long-term safety of SNS has yet to be documented. Current data extend up to two/three years of follow-up and only two studies provide results at five years post-intervention in a small sample of patients.[20,69] Safety in children and pregnant women has yet to be established.

SNS techniques have evolved over time and rates of adverse effects have followed as a consequence. The pulse generator is now positioned in the upper buttock region rather than in the abdominal wall and this has reduced episodes of pain. The test evaluation to select patients for permanent implant can now be performed as a needle test stimulation or as a staged implant (i.e. use of a surgically implantable lead as test lead). Novel lead systems have been developed for the staged implant evaluation test to reduce the occurrence of infection and prevent lead migration. The feasibility of a percutaneous lead placement under local anaesthesia and with fascial fixation has recently been evaluated in a series of 22 patients.[85] The technique is considered to be less invasive, offers the possibility of testing the sensory response during implant, and allows the implant to be performed under local anaesthesia. A similar method that has recently

gained attention is a complete percutaneous implant in a two-stage approach. A new tined permanent lead is utilised for this technique and no incision or additional fascial fixation is required. The correct placement and identification of lead and electrode position is confirmed by fluoroscopy. The main disadvantage of the latter two procedures is the need of an additional procedure for lead removal in patients who do not respond to stimulation.[120]

4.4 Aspects of the procedure that might be improved

The peripheral nerve evaluation test is the only method currently used to select suitable candidates for SNS. Almost 50% of the patients tested do not then have implantation because of an unsatisfactory response to the test. However, this non-response may be due to both technical problems as well as lack of response. Methods to improve the accuracy of the PNE test (e.g. by adding electrodiagnostic techniques, use of a permanent lead) have the potential for further development.

SNS has evolved over time to limit the incidence of adverse effects and reduce the invasiveness of the procedure. The placement of a permanent lead during the evaluation phase of SNS and in particular the use of permanent tined leads seem to be the current method of choice for clinicians who are undertaking the procedure. It is possible that these specific techniques might be refined over time.

The protocol for patients undertaking SNS is not properly defined. It is still unclear which other interventions should be attempted before proceeding to SNS. In particular, further clarification is required to determine at which stage of disease patients should be offered SNS and whether they should have failed both pharmacological and non-surgical treatments beforehand. Otherwise there is the risk that patients who have only failed non-surgical treatments such as behavioural interventions, which represent the first line of treatments for urinary incontinence, are enrolled for the procedure before all other options have been exhausted.

5. CONCLUSIONS

SNS for urge urinary incontinence or urgency-frequency symptoms has generally been reserved for patients who have failed conservative, non-surgical treatments. Alternative surgical treatments include urinary diversion or bladder augmentation surgery. SNS is currently little used in the UK. According to information provided by the manufacturer, only 12 SNS operations were performed for voiding dysfunctions in the UK in 2002.

5.1 Efficacy of SNS

Results from randomised controlled trials provide evidence of some benefit from SNS in reducing incontinence episodes, pad usage, and frequency of voids, and in improving bladder capacity and voided volume. Evidence from case series studies is less reliable because of the risk of potential bias in this type of study design. Their findings are however broadly similar to those of randomised trials. Benefits of SNS were reported to persist at follow-up three to five years after implantation of the pulse generator. Although the few data available suggest improvement, the impact of SNS on quality of life of patients with urge incontinence or urgency-frequency is still to be established.

5.2 Safety of SNS

SNS was followed by surgical revision in 33% of cases. Most common reasons for re-operation were relocation of the implantable pulse generator because of pain, revision of the lead system, and infection. Overall, adverse events occurred in almost half of the tested patients. The most common complications were: pain at the implant site, lead migration, relocation, replacement or permanent explant of the implanted pulse generator, and wound problems.

At present there is no evidence about the long-term efficacy safety (i.e. ten years) of the procedure and it is likely that revisions will be required to maintain clinical benefits over time.

6. NEED FOR FURTHER AUDIT OR RESEARCH

6.1 Collection of further data

At present in the UK there is no registry or database for SNS for patients with urge urinary incontinence and urgency-frequency. Establishment of a registry of cases would provide a useful way to monitor further technical developments, update efficacy and safety findings, and ascertain effectiveness and cost-effectiveness of the procedure.

6.2 Further investigation (new data collection/trials)

Currently the use of SNS is indicated (and licensed in Europe and USA) for refractory urge incontinence, urgency-frequency syndrome, and urinary retention. A number of emerging indications are, however, under consideration. These include: neurogenic urge incontinence, pelvic pain, interstitial cystitis, faecal incontinence, and constipation. For these clinical indications a limited number of studies have been carried out and their initial findings seem to support the use of SNS as a treatment modality for patients suffering from these conditions. However, further investigations are needed to clearly define the spectrum of indications for SNS. In particular, research into the aetiology of voiding dysfunctions (e.g. interstitial cystitis) and into the mechanism of action of neuromodulation would help to explain the therapeutic effect of SNS and provide more precise clinical indications and hence patient selection.

The use of bilateral sacral stimulation has been suggested when unilateral stimulation is not successful but warrants further research.

7. REFERENCES

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APPENDIX 1Literature search strategy

1. MEDLINE (1966- May Week 2 2003) EMBASE (1980 – Week 21 2003)
Ovid Multifile Search URL: http://gateway.ovid.com/athens

1 ((sacral or s3) adj3 (stimulat$ or modulat$)).tw.
2 ((sacral or s3) adj3 (neurostimulat$ or (neural adj1 stimulat$) or (nerve adj1 stimulat$))).tw.
3 ((sacral or s3) adj3 (neuromodulat$ or (neural adj1 stimulat$) or (nerve adj1 stimulat$))).tw.
4 ((sacral or s3) adj3 (electrostimulat$ or electrical stimulat$)).tw.
5 sacral nerve stimulation/ use emez
6 or/1-5
7 electric stimulation therapy/
8 transcutaneous electric nerve stimulation/
9 electrodes,implanted/
10 neuromodulation/ use emez
11 nerve stimulation/ use emez
12 (stimulat$ or modulat$).tw.
13 (neurostimulat$ or (neural adj1 stimulat$) or (nerve adj1 stimulat$)).tw.
14 (neuromodulat$ or (neural adj1 modulat$) or (nerve adj1 modulat$)).tw.
15 (electrostimulat$ or electrical stimulat$).tw.
16 ((implant$ or insert$) adj3 (neuroprosthes$ or neural prosthes$)).tw.
17 ((implant$ or insert$) adj3 (neurostimulat$ or neural stimulat$)).tw.
18 ((implant$ or insert$) adj3 (electrostimulat$ or electrical stimulat$)).tw.
19 ((implant$ or insert$) adj3 pulse generator?).tw.
20 or/7-19
21 (sacral$ or sacrum or sacro$).tw.
22 sacrum/
23 lumbosacral plexus/
24 Sacrococcygeal region/ use mesz
25 sacral spinal cord/ use emez
26 spinal root/ use emez
27 lumbosacral spine/ use emez
28 or/21-27
29 6 or (20 and 28)
30 animal/ or nonhuman/
31 human/
32 30 not 31
33 29 not 32
34 ae.fs. use mesz
35 co.fs
36 i.fs. use emez
37 equipment failure/
38 equipment safety/
39 (lead adj (migrat$ or avulsion)).tw.
40 ((surgical or surgery) adj3 (revision or interven$ or reinterven$)).tw.
41 (implant adj3 (remov$ or replac$)).tw.
42 re operat$.tw.
43 or/34-42

44 33 and 43
45 urinary incontinence/
46 urge incontinence/ use emez
47 urination disorders/
48 urinary retention/
49 bladder,neurogenic/
50 detrusor dyssynergia/ use emez
51 ((urge or urinary) adj incontinence).tw.
52 ((detrusor or bladder or urethral or sphincter) adj1 (instability or unstable or overactiv$ or hyperactiv$ or hyperflex$ or activ$ or function or control$)).tw.
53 (neurogenic adj1 (bladder or detrusor or shincter or overactive$ or hyperactive$ or hyperflex$)).tw
54 (urin$ adj1 (retain or retention)).tw
55 (voiding adj1 (dysfunction$ or disorder?)).tw.
56 (micturition adj1 (dysfuction$ or disorder?)).tw.
57 (lower urinary tract adj1 (dysfunction or instability)).tw.
58 or/45-57
59 33 and 58
60 44 or 59
61 Remove duplicates from 60

2. CINAHL 1985 – May 2003
Ovid URL: http://gateway.ovid.com/athens

1 ((sacral or s3) adj3 (stimulat$ or modulat$)).tw.
2 ((sacral or s3) adj3 (neurostimulat$ or (neural adj1 stimulat$) or (nerve adj1 stimulat$))).tw.
3 ((sacral or s3) adj3 (neuromodulat$ or (neural adj1 stimulat$) or (nerve adj1 stimulat$))).tw.
4 ((sacral or s3) adj3 (electrostimulat$ or electrical stimulat$)).tw.
5 or/1-4
6 electric stimulation/
7 electric stimulation,neuromuscular/
8 transcutaneous electric nerve stimulation/
9 electrodes,implanted/
10 (stimulat$ or modulat$).tw.
11 (neurostimulat$ or (neural adj1 stimulat$) or (nerve adj1 stimulat$)).tw.
12 (neuromodulat$ or (neural adj1 modulat$) or (nerve adj1 modulat$)).tw.
13 (electrostimulat$ or electrical stimulat$).tw.
14 ((implant$ or insert$) adj3 (neuroprosthes$ or neural prosthes$)).tw.
15 ((implant$ or insert$) adj3 (neurostimulat$ or neural stimulat$)).tw.
16 ((implant$ or insert$) adj3 (electrostimulat$ or electrical stimulat$)).tw.
17 ((implant$ or insert$) adj3 pulse generator?).tw.
18 or/6-17
19 (sacral$ or sacrum or sacro$).tw.
20 sacrum/
21 lumbosacral plexus/
22 spinal nerve roots/
23 spinal nerves/
24 or/19-23

25 5 or (18 and 24)
26 animal/
27 human/
28 26 not 27
29 25 not 28
30 ae.fs.
31 co.fs.
32 equipment failure/
33 equipment safety/
34 (lead adj (migrat$ or avulsion)).tw.
35 ((surgical or surgery) adj3 (revision or interven$ or reinterven$)).tw.
36 (implant adj3 (remov$ or replac$)).tw.
37 re operat$.tw.
38 or/30-37
39 urinary incontinence/
40 urge incontinence/
41 urination disorders/
42 urinary retention/
43 bladder,neurogenic/
44 ((urge or urinary) adj incontinence).tw.
45 ((detrusor or bladder or urethral or sphincter) adj1 (instability or unstable or overactiv$ or hyperactiv$ or hyperflex$ or activ$ or function or control$)).tw.
46 (neurogenic adj1 (bladder or detrusor or sphincter or overactiv$ or hyperactiv$ or hyperflex$)).tw.
47 (urin$ adj1 (retain or retention)).tw.
48 (voiding adj1 (dysfunction$ or disorder?)).tw.
49 (micturition adj1 (dysfuction$ or disorder?)).tw.
50 (lower urinary tract adj1 (dysfunction or instability)).tw.
51 or/39-50
52 29 and 38
53 29 and 51
54 52 or 53

3. BIOSIS 1985 – 28th May 2003
Edina URL:http://edina.ac.uk/biosis/

(((((((al: (sphincter n1 function)) or al: (sphincter n1 control*)) or (((al: (sphincter n1 hyperflex*)) or al: (sphincter n1 dyssynergia)) or al: (sphincter n1 activ*))) or (((al: (sphincter n1 instab*)) or al:(sphincter n1 overactiv*)) or al: (sphincter n1 hyperactiv*))) or (((al:(bladder n1 function)) or al: (bladder n1 control*)) or al: (bladder n1 spastic))) or (((al: (bladder n1 activ*)) or al: (bladder n1 dyssynergia)) or al: (bladder n1 hyperflex*))) or (((al: (bladder n1 instab*)) or al: (bladder n1 overactiv*)) or al: (bladder n1 hyperactiv*))) or ((((((((((al: (detrusor n1 function)) or al: (detrusor n1 control*)) or (((al: (detrusor n1 activ*)) or al: (detrusor n1 dyssynergia)) or al: (detrusor n1 hyperflex*))) or (((al: (detrusor n1 instab*)) or al: (detrusor n1 overactiv*)) or al: (detrusor n1 hyperactiv*))) or (((al: (neurogenic n1 overactiv*)) or al: (neurogenic n1 hyperflex*)) or al:(neurogenic n1 hyperactiv*))) or (((al: (neurogenic n1 bladder)) or al: (neurogenic n1 detrusor)) or al:(neurogenic n1 sphincter))) or ((al: (micturition n1 dysfunction)) or al: (micturition n1 disorder*))) or ((al: (voiding n1 dysfunction)) or al: (voiding n1 disorder*))) or (((al: (urinary n1 disorder*)) or al: (urinary n1 dysfunction)) or al: (urinary

n1 urgency))) or (((al: (urinary n1 incontinence)) or al: (urge n1 incontinence)) or al: (urinary n1 retention)))))
or
(((((((al: (surg* n3 revision)) or al: (surg* n3 interven*)) or al: (surg* n3 reinterven*)) or (((al: (implant n3 remov*)) or al: (implant n3 replac*)) or al: (re n operat*))) or ((al: (lead n1 migration)) or al: (lead n1 avulsion))) or ((al: (equipment n1 failure)) or al: (equipment n1 safety))) or (((al: (adverse n1 effect*)) or al: (adverse n1 event*)) or al: (complication*)))
and
(((((((((al: (pulse n1 generator)) or al: (electrostimulat*)) or al: (electrical n1 stimulat*)) or (((al: (neuromodulat*)) or al: (neural n1 modulat*)) or al: (nerve n1 modulat*))) or (((al: (implant)) or al: (neuroprosthes*)) or al: (neural prosthes*))) or (((al: (neurostimulat*)) or al: (neural n1 stimulat*)) or al: (nerve n1 stimulat*))) and ((al: (lumbosacral)) or (((al: (sacral)) or al: (sacro*)) or al: (sacrum))))) or
((((((al: (sacral n3 stimulat*)) or al: (s3 n3 stimulat*)) or ((al: (sacral n3 modulat*)) or al: (s3 n3 modulat*))) or (((al: (s3 n3 neurostimulat*)) or al: (s3 n3 neuromodulat*)) or al: (s3 n3 electrostimulat*))) or (((al: (sacral n3 neurostimulat*)) or al: (sacral n3 neuromodulat*)) or al: (sacral n3 electrostimulat*))) or ((mq: (sacral)) or ((mq: (interstim)) or (((mq: (sacral nerve stimulat*)) or mq: (neurostimulat*)) or mq: (neuromodulat*))))))
and (su: (humans)))

4. Science Citation Index 1981 – 8th June 2003
Web of Science Proceedings 1990 – 8th June 2003
Web of Knowledge URL: http://wok.mimas.ac.uk/

((((sacral or s3) SAME (stimulat* or modulat*)) or neurostimulat* or neuromodulat* or electrostimulat* or neuroprosthes*)) and (((urinary or urge) same incontinence) or detrusor or bladder or urinary or voiding or micturition)

5. Cochrane Library Issue 2,2003
URL: http://www.update-software.com/clibng/cliblogon.htm

1. SR-Incont
2. Sacral
3. S3
4. #1 and (#2 or #3)
5. SACRUM single term (MeSH)
6. LUMBOSACRAL PLEXUS single term (MeSH)
7. SACROCOCCYGEAL REGION single term (MeSH)
8. (neurostimulat* or neuromodulat* or stimulat* or electrostimulat*)
9. ELECTRIC STIMULATION THERAPY single term (MeSH)
10. TRANSCUTANEOUS ELECTRIC NERVE STIMULATION single term (MeSH)
11. ELECTRODES IMPLANTED single term (MeSH)
12. (#2 or #3 or #5 or #6 or #7)
13. (#8 or #9 or #10 or #11)
14. (#12 and #13)
15. (#4 or #14)

6. **DARE and HTA Database (May 2003)**
   NHS Centre for Reviews & Dissemination
   URL:http://nhscrd.york.ac.uk/welcome.htm

   Sacral and stimulat*
   or electrostimulat*
   or neurostimulat*
   or neuromodulat*
   or urinary incontinence
   or urge incontinence

7. **National Research Register (May 2003)**
   URL: http://www.update-software.com/National/

   Sacral nerve stimulation
   or
   Sacral or stimulat* or electrostimulat* or neurostimulat* or neuromodulat* or incontinent*

8. **Clinical Trials (May 2003)URL: http://clinicaltrials.gov/ct/gui/c/r**
   Current Controlled Trials (May 2003) URL: http://www.controlled-trials.com/
   Research Findings Register (May 2003) URL:
   http://tap.ukwebhost.eds.com/doh/refr_web.nsf/Home?OpenForm

   Sacral or stimulat* or electrostimulat* or neurostimulat* or neuromodulat* or incontinence

9. **Meeting Abstracts:**
   International Continence Society 2000-2002
   URL: http://www.continet.org/
   American Urogynecologic Society 2001-2003
   URL: http://www.augs.org/public/articles/details.cfm?id=190

Sacral or stimulat or electrostimulat or neurostimulat or neuromodulat

In addition the following Websites were searched for evidence-based reports (accessed May 2003):

Alberta Heritage Foundation for Medical Research URL: http://www.ahfmr.ca/
American Urogynecologic Society: URL:http://www.augs.org/
ASERNIP-S URL: http://www.surgeons.org/asernip-s/
Blue Cross Blue Shield Technology Evaluation Center URL:
http://www.bcbs.com/tec/tecassessments.html
Canadian Urological Association URL: http://www.cua.org/
CCOHTA URL: http://www.ccohta.ca/
Centers for Medicare & Medicaid Services URL:
http://cms.hhs.gov/mcd/index_list.asp?list_type=tech
ECRI URL: http://www.ecri.org/

European Association of Urology
URL:http://www.uroweb.nl/index.php?structure_id=1
FDA Center for Devices & Radiological Health URL: http://www.fda.gov/cdrh/
International Continence Society URL: http://www.continet.org/
Medicines & Healthcare Products Regulatory Agency URL: http://www.medical-devices.gov.uk/
Medtronic URL: http://www.medtronic.com/
SUMSEARCH URL: http://sumsearch.uthscsa.edu
TRIP database URL:
http://www.updatesoftware.com/scripts/clibng/usauth.exe?Server=TRIPUSER&Product=TRIP&Guest=YES

APPENDIX 2 Checklist for quality assessment of case series studies on intervention

(adapted from CRD's Guidance for those Carrying out or Commissioning Reviews, 2001 and from Downs and Black, 1998[10])

Criteria	Yes	No	Unclear	Comments
1. Were participants a representative sample selected from a relevant patient population?				
2. Are the inclusion/exclusion criteria of patients in the study clearly described?)				
3. Were participants entering the study at a similar point in their disease progression?				
4. Was selection of patients consecutive?				
5. Were all important prognostic factors identified?				
6. Was data collection undertaken prospectively?				
7. Was the recruitment period clearly stated?				
8. Was the intervention that which is being considered in the review? (or was it a significant modification?)				
9. Was the operation undertaken by someone experienced in performing the procedure?				
10. Did the staff, place, and facilities where the patients were treated provide an appropriate environment for performing the procedure? (e.g. was the intervention undertaken in a centre with the necessary back-up facilities?)				
11. Were objective (valid and reliable) outcome measures used?				
12. Were all the important outcomes considered?				
13. Was follow-up long enough to detect important effects on outcomes of interest?				
14. Was information provided on non-respondents, dropouts?				
15. Were participants lost to follow-up likely to introduce bias? (e.g. high drop-out rate; no description of those lost)				
16. Were the main findings clearly described? (to allow replication)				

APPENDIX 3 Checklist for quality assessment of randomised controlled trials on intervention *(adapted from Verhagen et al., 1998[11])*

Criteria	Yes	No	Unclear	Comments
1. Was the assignment to the treatment groups really random? *Adequate approaches to sequence generation* • computer-generated random tables • random number tables *Inadequate approaches to sequence generation* • use of alternation, case record numbers, birth dates or week days				
2. Was the treatment allocation concealed? *Adequate approaches to concealment of randomisation* • centralised or pharmacy-controlled randomisation • serially-numbered identical containers • on-site computer based system with a randomisation sequence that is not readable until allocation • other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients *Inadequate approaches to concealment of randomisation* • use of alternation, case record numbers, birth dates or week days • open random numbers lists • serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)				
3. Were the groups similar at baseline in terms of prognostic factors?				
4. Were the eligibility criteria specified?				
5. Were the groups treated in the same way apart from the intervention received?				
6. Was the outcome assessor blinded to the treatment allocation?				
7. Was the care provider blinded?				
8. Were the patients blinded?				
9. Were the point estimates and measures of variability presented for the primary outcome measures?				
10. Was the withdrawal/drop-out rate likely to cause bias?				
11. Did the analyses include an intention-to-treat analysis?				

APPENDIX 4 Sacral Nerve Stimulation for Urinary Incontinence

Data extraction form

Administration details	
Study ID:	**Paper No:**
Extractor initials:	**Date Extracted:**
Paper type: journal article/abstract/conference paper/unpublished/other _____	
Source of funding: Government/manufacturer/private/unfunded/unclear/other _____	
Other papers this study may link with:	

Study design

- ☐ **Systematic Review**
- ☐ **RCT**
- ☐ **Pseudo-RCT**
- ☐ **Comparative study with concurrent controls, allocation not randomised (cohort study), case-control studies or interrupted time series with control group**
- ☐ **Two or more single arm studies or interrupted time series without a parallel control group**
- ☐ **Case series, either post-test or pre-test and post-test**
- ☐ **Other** _____

Other comments:

Aim of study:

Interventions

A:

B:

Characteristic of the participants						
Source of participants/setting/geographic location of treatment centres:						
Method of recruitment:						
Recruitment/treatment dates:						
Inclusion criteria:						
Exclusion criteria:						
Diagnosis:	Urge incontinence	Urgency-frequency	Retention (+Fowler's)	Pelvic pain	Neurogenic bladder	Other
Number:						
Are urge incontinent patients identified throughout?						

	Group A	**Group B**	**All**
Definition of Group			
Number enrolled in trial			
Number receiving PNE			
Number of successful PNE			
Number receiving implant			

	Group A	Group B	All
Number lost to follow-up **PNE** **Implant** **___ months** **___ months** **___ months** **___ months**			
Number analysed **PNE** **Implant** **___ months** **___ months** **___ months** **___ months**			
Baseline data: ☐ **Patients receiving PNE** ☐ **Only patients receiving implant**			
Age (range)			
Gender	M: F:	M: F:	M: F:
Duration of symptoms (range)			
Spinal cord injury			
Co-existing faecal incontinence			
Previous lower urinary tract or pelvic surgery			
Other			

Characteristics of the intervention
Test stimulation (PNE)
Make and model of PNE equipment (inc. needle size)**:** **Stimulation parameters:** Width: Rate: Amplitude: Frequency: **Sacral nerves used:** ☐ S2 ☐ S3 ☐ S4 ☐ Unilateral ☐ Bilateral **Duration of test:** **Definition of a positive test result:** **Was a positive test stimulation result required before permanent implantation?** **Additional information** (inc. how site identified)**:**
Permanent implantation of SNS
Make and model of SNS equipment: **Stimulation parameters:** Width: Rate: Amplitude: Frequency: **Sacral nerves used:** ☐ S2 ☐ S3 ☐ S4 ☐ Unilateral ☐ Bilateral **Position of IPG:** ☐ Abdominal wall ☐ Buttock **Length of follow-up:** **Definition of a positive result:** **Additional information** (inc. incision type/size)**:**

Outcome - Efficacy			
	Group A	**Group B**	**All**
Number receiving PNE			
Number receiving permanent implant			
Number cured (dry)**:** **PNE** **Implant** **___ months** **___ months** **___ months** **___ months**			
Number improved (>50% improvement)**:** **PNE** **Implant** **___ months** **___ months** **___ months** **___ months**			
Incontinent episodes (over 24 hours): **Baseline** **PNE** **Implant** **___ months** **___ months** **___ months** **___ months**			

	Group A	Group B	All
Leakage severity: **Baseline** **PNE** **Implant** **___ months** **___ months** **___ months** **___ months**			
Pad use (over 24 hours)**:** **Baseline** **PNE** **Implant** **___ months** **___ months** **___ months** **___ months**			
Incontinence Score: **Baseline** **PNE** **Implant** **___ months** **___ months** **___ months** **___ months**			

	Group A	Group B	All
_____ **Baseline** **PNE** **Implant** **___ months** **___ months** **___ months** **___ months**			
_____ **Baseline** **PNE** **Implant** **___ months** **___ months** **___ months** **___ months**			
_____ **Baseline** **PNE** **Implant** **___ months** **___ months** **___ months** **___ months**			

	Group A	Group B	All
Quality of life (state instrument): _____			
Generic health status (state instrument): _____			
Other results:			

Outcome - Safety		
Test stimulation (PNE)		
Adverse event	**Frequency**	**Treatment**
Permanent implant of SNS		
	Frequency	**Treatment**
Other comments:		

Additional information/Other comments

APPENDIX 5 Characteristics of studies with unclear diagnosis

Author(s)	Design/ Patients	Inclusion/ exclusion criteria	PNE	SNS	No. of procedures	Results
Rosier 1997[121] **Location:** international multicentre study **Funding:** unclear	**Design:** case series study/ randomised control trial **Patients:** 35 **Diagnosis:** urgency/frequency (4), urge incontinence (23), urinary retention/ voiding difficulties (8) **Follow-up**: 3, 6, 12 and 18 months in 28 patients that had a follow-up of ≥6 months at time of analysis	**Inclusion:** Patients enrolled by the centre into an international multicentre study to evaluate the efficacy of sacral neuromodulation on urgency/frequeny urge incontinence or urinary retention/voiding difficulty.	*Information on PNE not reported*	**Positivity criterion:** adequate (normal lower urinary tract function); mixed (much improved not perfectly normal); inadequate (almost no change in lower urinary tract function)	**35 SNS** (28 analysed)	**Efficacy:** **Improvement:** 17/28 (60.7%) adequate, 5/28 (17.9%) mixed, 6/28 inadequate/non-responder **SF-36** Control group (delayed implant) showed no significant change at 3 and 6 months delay. **Physical component score:** Baseline: 37.8 (35.9 responders (R) vs 42.3 non-responders (NR)) 3 months: 40.7 (41.0 R vs 44.8 NR) 6 months: 41.3 (41.1 R vs 43.2 NR) 12 months: 43.4 (46.2 R vs 33.9 NR) 18 months 44.7 (46.5 R) 14/23 patients improved after 3 months, 11/18 after 6 months, 7/13 after 1 year, and 7/7 after 18 months. **Mental component score:** Baseline: 49.6 (52.3 R, 40.6 NR) 3 months: 50.9 (53.7 R, 39.1 NR) 6 months: 50.4 (51.4 R, 40.0 NR) 12 months: 50.7 (50.5 R, 40.9 NR) 18 months: 55.2 (55.0 R) This score did not show a tendency to change however, after 18 months 6/7 patients had improved

Author(s)	Design/ Patients	Inclusion/ exclusion criteria	PNE	SNS	No. of procedures	Results
Rueff 2003[122] **Location:** single centre, USA **Funding:** none	**Design:** case series study **Patients:** 25 **Diagnosis:** voiding dysfunction, 22 also had pelvic pain **Gender:** M: 2 W: 23 **Mean age:** 46.7 (range 24-85) **Mean follow-up**: 19.5 months (6-43 months)	**Inclusion:** Patients with chronic voiding dysfunction and pelvic pain who were refractory to conservative therapies	*Information on PNE not reported*	**Type:** Combination of sacral nerve stimulation and behavioural and physical therapy **Model:** Medtronic Interstim **Positivity criterion:** patients perception: patients asked to rank their improvement in pain and voiding symptoms as >75% improved, 50-75% improved, 25-50% improved and <25% improved.	**25 SNS**	**Efficacy:** Improvement in pelvic pain (in patients with pelvic pain): >75% improvement: 8 50-75% improvement: 6 25-50% improvement: 5 <25% improvement: 3 Improvement in voiding dyfunction: >75% improvement: 7 50-75% improvement: 10 25-50% improvement: 6 <25% improvement: 2
van Kerrebroeck 2002[123,124] **Location:** multicentre, USA **Funding:** unclear	**Design:** prospective randomised clinical trial **Patients:** 89 **Diagnosis:** urinary incontinence (28), urinary retention (12), urinary frequency (49) **Gender:** M: 16 W: 73 **Mean age:** 38 (10.1) **Recruitment period:** until 1999 **Follow-up:** 3 and 6 months	**Inclusion:** patients refractory to standard medical therapies in the general urologic population	*Information on PNE not reported*	*Information on SNS not reported*	**56 SNS** group, 33 delayed implant group	**Efficacy:** ***Implant group vs delayed group*** **Becks Depression Index:** Baseline: 17.0(9.5) vs 16.2(11.3) 3 months: (10.3(9.1) vs 18.0 (13.0) 6 months: 11.1(9.1) vs 17.2(14.6) There was a significant difference (p<0.01) in average score between groups at 3 months, but not at 6 months

Author(s)	Design/ Patients	Inclusion/ exclusion criteria	PNE	SNS	No. of procedures	Results
Woo 2001[125] **Location:** single centre **Funding:** unclear	**Design:** case series study **Patients and Diagnosis:** 7 patients with chronic pelvic pain, of whom: 5 urgency/frequency, 2 intermittency, 2 straining, 2 incomplete voiding, 1 urinary retention, 1 urge incontinence **Gender:** M: 2 W: 5 **Mean age:** 44.1 (range 26-81) **Duration of symptoms:** >6 months pelvic pain **Previous surgery:** most patients underwent surgical procedures **Follow-up**: 1 week, 1 month, 3 months, and thereafter as needed	**Inclusion:** Patients with chronic pelvic pain and lower urinary disorders refractory to standard therapy such as biofeedback, medication or surgical procedures, and required chronic usage of pain medications to control their pain symptoms	**Type:** Temporary electrode placed percutaneously into the sacral nerve forament **Identification of sacral nerves:** bellows movement of levator ani and great toe dorsoflexion plus X-ray Lead location*: **S3*** **Duration:** 1 week **Positivity criterion:** ≥50% decrease in the urinary symptoms and pelvic pain	**Type:** InterStim Therapy **Model:** implantable quadrapolar electrode and neurostimulator with an extension **Positivity criterion:** Refractory symptoms of urinary frequency and urgency normalized; chronic pelvic pain decreased >50%, urinary retention resolved	**7 PNE** **5 SNS**	**Efficacy:** PNE successful in 5 patients All 5 patients with permanent implant experienced successful and satisfactory outcomes in treatment of their urinary symptoms as well as pelvic pain

APPENDIX 6 List of included studies with related references

(a) Primary studies published as full text papers

Aboseif 2002

Primary reference:
Aboseif S, Tamaddon K, Chalfin S, Freedman S, Kaptein J. Sacral neuromodulation as an effective treatment for refractory pelvic floor dysfunction. Urology 2002;60(1):52-6.

Related reference:
Tamaddon K, Bellman G, Aboseif S. Sacral nerve stimulation as an effective treatment of refractory pelvic floor dysfunction. J Endourol 2000;14(Suppl 1):A76.

Amundsen 2002

Amundsen CL, Webster GD. Sacral neuromodulation in an older, urge-incontinent population. Am J Obstet Gynecol 2002;187(6):1462-5.

Benson 2000

Benson JT. Sacral nerve stimulation results may be improved by electrodiagnostic techniques. Int Urogynecol J Pelvic Floor Dysfunct 2000;11(6):352-7.

Bosch 2000

Primary reference:
Bosch JL, Groen J. Sacral nerve neuromodulation in the treatment of patients with refractory motor urge incontinence: long-term results of a prospective longitudinal study. J Urol 2000;163(4):1219-22.

Related references:
Bosch JL, Groen J. Sacral (S3) segmental nerve stimulation as a treatment for urge incontinence in patients with detrusor instability: results of chronic electrical stimulation using an implantable neural prosthesis. J Urol 1995;154(2 Pt 1):504-7.

Bosch JLHR, Groen J, Essink-Bot ML, Krabbe P, Seerden R, van Hout B. Sacral segmental (S3) nerve stimulation as a treatment for urge incontinence due to detrusor instability: quality of life analysis and cost-effectiveness. J Urol 1996;155(5 Suppl):594A.

Bosch JLH. Dissappointing results of neuromodulation in men with urge incontinence due to detrusor instability. Neurourol Urodyn 1997;16(5):347-9.

Bosch JL, Groen J. Seven years of experience with sacral (S3) segmental nerve stimulation in patients with urge incontinence due to detrusor instability or hyperreflexia. Neurourol Urodyn 1997;16(5):426-7.

Bosch JL, Groen J. Complete 5-year follow-up of sacral (S3) segmental nerve stimulation with an implantable electrode and pulse generator in 36 consecutive patients with refractory detrusor overactivity incontinence. Neurourol Urodyn 2002;21(4):390-1.

Groen J, Bosch JL, Schroder F. Neuromodulation (sacral segmental nerve stimulation) as a treatment for urge incontinence in patients with bladder instability. J Urol 1993;149(4 Suppl):367A.

Groen J, Van Mastrigt R, Bosch JL. Computerized assessment of detrusor instability in patients treated with sacral neuromodulation. J Urol 2001;1656(1):169-73.

Groen J, Bosch JL, Van Mastrigt R. Sacral neuromodulation in women with idiopathic detrusor overactivity incontinence: reduced overactivity but unchanged bladder contraction strength and urethral resistance. Neurourol Urodyn 2002;21(4):392-3.

Ruud Bosch JL, Groen J. Treatment of refractory urge urinary incontinence with sacral spinal nerve stimulation in multiple sclerosis patients. Lancet 1996;348(9029):717-9.

Ruud Bosch JL, Groen J. Neuromodulation: urodynamic effects of sacral (S3) spinal nerve stimulation in patients with detrusor instability or detrusor hyperflexia. Behav Brain Res 1998;92(2):141-50.

Braun 1999

Primary reference:
Braun PM, Boschert J, Bross S, Scheepe JR, Alken P, Juenemann P. Tailored laminectomy: a new technique for neuromodulator implantation. J Urol 1999;162(5):1607-9.

Related references:
Braun PM, Seif C, Bross S, Boschert J, Alken P, Juenemann KP. Tailored laminectomy for neuromodulator implantation. Eur Urol 2001;39(Suppl 5):199.

Braun PM, Seif C, Bross S, Scheepe JR, Alken P, Junemann KP. Tailored laminectomy: long-term results of bilateral neuromodulation. Eur Urol 2001;39(Suppl 5):15.

Christoph S, Braun PM, Bross S, Weil J, Martinez Portillo F, Alken P et al. Longterm results after 36 months for chronic bilateral neuromodulation. Proceedings of the International Continence Society, 32nd Annual Meeting; Heidelberg, Germany: 2002.

Juenemann P, Boschert J, Braun PM, Wipfler G, Schumacher S, Zendler S, Kohrmann KU. Tailored laminectomy for neuromodulator implantation in patients with bladder dysfunction. Eur Urol 1998;33(Suppl 1):62.

Cappellano 1998

Cappellano F, Ciotti MG, Pizzoccaro M, Catanzaro M, Santambrogio S, Catanzaro F. Sacral root neuromodulation in the treatment of female urge and mixed urinary incontinence. Urogynaecol Int J 1998;12(3):111-21.

Cappellano 2001

Primary reference:
Cappellano F, Bertapelle P, Spinelli M, Catanzaro F, Carone R, Zanollo A et al. Quality of life assessment in patients who undergo sacral neuromodulation implantation for urge incontinence: an additional tool for evaluating outcome. J Urol 2001;166(6):2277-80.

Related references:
Cappellano F, Bertapelle P, Spinelli M, Catanzaro F, Carone R, Zanollo A et al. Quality of life improvement during chronic neuromodulation of sacral roots: a prospective study with an incontinence domain specific instrument (QOL-I). Neurourol Urodyn 1999;18(4):379.

Cappellano F, Cantanzaro F, Bertapelle P, Carone R, Spinelli M, Zanollo A et al. Quality of life improvement following sacral neuromodulation; a prospective study with an incontinence specific instrument (QOL-I). J Urol 2001;165(5 Suppl):249.

Carey 2001

Primary reference:
Carey M, Fynes M, Murray C, Maher C. Sacral nerve root stimulation for lower urinary tract dysfunction: overcoming the problem of lead migration. BJU Int 2001;87(1):15-8.

Related reference:
Fynes M, Carey M, Murray C, Maher C. Sacral nerve root stimulation for lower urinary tract dysfunction: overcoming the problem of lead migration. Neurourol Urodyn 2000;19(4):523-4.

Chai 2001

Chai TC, Mamo GJ. Modified techniques of S3 foramen localization and lead implantation in S3 neuromodulation. Urology 2001;58(5):786-90.

Edlund 2000

Edlund C, Hellstrom M, Peeker R, Fall M. First Scandinavian experience of electrical sacral nerve stimulation in the treatment of the overactive bladder. Scand J Urol Nephrol 2000;34(6):366-76.

Everaert 2000

Primary reference:
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APPENDIX 7 Characteristics of the included studies

(a) Full text papers

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Aboseif 2002[16,17] **Location:** three different medical centers. USA **Funding:** manufacturer	**Design:** case series study. **Patients:** 160 **Diagnosis:** frequency, urgency, urge incontinence, and idiopathic, non-obstructive chronic urinary retention. **Gender:** M: 10 W: 54 **Mean age:** 47 (range 22-76) **Duration of symptoms:** 5.6 years (1– 20) **Recruitment period:** Oct 1996 – Jan 2001. **Mean follow-up:** 24 months (6-36)	**Inclusion:** patients with frequency, urgency and urge incontinence refractory to standard behavioural and pharmacological management.	**Type:** unilateral PNE under local anaesthesia (outpatient procedure) **Identification of sacral nerves:** by fluoroscopy **Duration:** 3-5 days **Positivity criterion:** >50% objective improvement (voiding diaries)	**Type:** SNS under general anaesthesia **Identification of sacral nerves:** by both functional response and fluoroscopy. **Needle:** 22-gauge insulated needle was inserted in the S3 foramen. **Sacral nerves:** S3 **Incision:** lead inserted through a 14-gauge angiocatheter. Small incision. **Position of neurostimulator:** upper part of the buttocks. **Model:** Implantable Pulse Generator Itrel II model 3023	**160 PNE** **64 SNS** (44 urge incontinence, 20 retention).	**Efficacy:** **Incontinence episodes per day:** from 6.4 to 2.0 **Pads used per day:** from 3.5 to 1; P<0.05 **Voids per day:** from 17.9 to 8.6 **Voiding volume (ml):** from 4.4 to 8.4 All statistically significant **Quality of life:** 33 patients (77%) reported an improvement in their >50%. **Safety:** 1 removal of the device due to infection 2 wound infections 2 wire migrations 2 device mulfunctions

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Amundsen 2002[18] **Location:** single centre. USA **Funding:** unclear.	**Design:** retrospective case series study **Patients and setting:** 25 community-dwelling patients. **Mean age:** 69 (range 55-78). **Mean follow-up:** 7.8 months (1-16).	**Inclusion:** community-dwelling patients older than 55 years with severe lower urinary tract symptoms who had failed behavioural and pharmacological management. No patients had a known central or peripheral nervous system abnormality. All patients completed an urogynecologic evaluation.	**Type:** bilateral percutaneous test stimulation under local anaesthesia **Needle:** 22-gauge spinal needle into each S3 foramen **Identification of sacral nerves:** tactile and fluoroscopic identification **Duration:** 7 days **Positivity criterion:** >50% reduction in incontinent episodes.	**Type:** SNS under general anaesthesia. (as described by Schmidt el al, 1990) **Identification of sacral nerves:** fluoroscopic identification of S3 foramen **Incision:** 5-cm incision parallel to the midline of the sacral spine, 4 electrodes tested until 2 gave desired response. **Position of neurostimulator:** patients' buttock through a subcutaneous pocket.	**25 PNE** **12 SNS** *No statistically significant differences between responders (12) and non-responders (13) to the PNE in terms of length of incontinence, incontinent episodes, pads used, voided volume and frequency of voids.*	**Efficacy:** **Cured:** 2 patients achieved total dryness. **Incontinence episodes**: no statistically significant difference between pre-implant and post-implant evaluations **Heavy incontinence episodes:** no statistically significant difference between pre-implant and post-implant evaluations **Pad usage:** no statistically significant difference between pre-implant and post-implant evaluations **Voided volumes:** no statistically significant difference between pre-implant and post-implant evaluations **Frequency of voids:** no statistically significant difference between pre-implant and post-implant evaluations **Incontinence Impact Questionnaire**: statistically significant improvement (P = 0.03). **Safety:** 2 patients had mild discomfort on neuromodulation site 5 patients required reprogramming because of continued urgency/urge –incontinence or worsening of symptoms 1 revision after lead migration

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Benson 2000[19] **Location:** single center. USA **Funding:** unclear	**Design:** case series study **Patients:** 15 **Mean age:** 51.3 (range 28-78).	**Inclusion:** patients with urge incontinence or urgency/frequency who had failed standard behavioural and/or pharmacological management.	**Type:** unilateral PNE under local anaesthesia **Specific technical aspects:** electrodiagnostic response was monitored by ring electrodes located on a Foley catheter inserted into the urethra. Response was called the compound muscle action potential (CMAP). **Sacral nerves:** S3 or S4. Nerve site producing the best response selected **Duration:** 3-7 days **Positivity criterion:** reduction of ≥50% for urge incontinent group or reduction of voiding frequency by ≥50%in urgency/frequency group.		**15 PNE**	**Efficacy:** 11 patients (73%) had a positive response. 3 patients had a negative response and were denied surgical implantation. 1 patient had a questionable response and was planned for retesting.

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Bosch 2000[20-30] **Location:** The Netherlands **Funding:** government	**Design:** case series study. **Patients and setting:** 85 patients with bladder overactivity: 11 neurogenic, 74 idiopathic **Gender:** M: 15 W: 70 (Neurogenic: M: 2 W: 9 Idiopathic: 13 W: 61) **Mean age:** 46.2. **Diagnosis:** urge incontinence and detrusor instability. **Mean duration of pad usage:** 7.7 years. **Mean duration of drug therapy for incontinence:** 2.7 years. **Previous surgery:** average 1.3 previous operative procedures for incontinence including: hysterectomy (22), and bladder neck suspension (24). **Recruitment period:** Jun 1990 – Dec 1998. **Follow-up:** 1 month, every 3 months between 3 and 18 months, and 6 months thereafter. **Mean follow-up:** 47 months (6-96).	**Inclusion:** patients with refractory urge incontinence and urodynamically demonstrated detrusor overactivity (refractory to bladder retraining and drug treatment) with a bladder capacity of 150-500ml. **Exclusion:** stress incontinence, untreated urinary tract infection, stone disease, diabetes mellitus, psychiatric disturbance, pregnancy or cerebrovascular accident in the last 6 months, anatomical abnormalities or skin infection in the future operative area.	**Type:** unilateral PNE **Sacral nerves:** S3 **Duration:** 3-5 days. **Positivity criterion:** >50% improvement (voiding diaries).	**Type:** unilateral SNS (as described by Siegel, 1992). Patient retained an external magnet to switch the pulse generator on and off. **Model:** Medtronic **Sacral nerves:** S3 Stimulation parameters: *Pulse width:* 210µsec. *Rate:* 10 pps *Amplitude:* 2.6 (0.2) V. **Positivity criterion:** Cure: >90% clinical improvement. Partial success: 50-90% improvement.	**85 PNE** (46 successful, 1 woman refused surgery) **45 SNS** (34 women and 5 men with idiopathic incontinence; 5 women and 1 man with neurogenic bladder). **Mean age:** 44.5 (16-65).	**Efficacy:** **Cured:** 18/45 patients (including 4/5 with neurogenic bladder). **Partial success:** 9/45 had a 50-90% decrease in pad usage and incontinence episodes. **Incontinence episodes:** significantly less incontinence episodes (p=0.0001) **Pad usage:** significant fewer pads used (p=0.0001) There was a discrepancy between symptomatic improvement and urodynamic findings. Of the successfully treated patients without bladder instability (40.9%) 72% were cured at the 6-month follow-up .However, only 45% of successfully treated patients who still had bladder instability (45.4%) were cured. **Safety:** 19 re-operations in 17 patients. 12 repositioning of electrodes (due to dislocation in 9 and suboptimal initial positioning in 3) 2 extension cables changed because of fracture. 2 patients had pain at the pulse generator site. 1 pulse generator replaced 1 lead dysfunction 1 seroma 1 wound of sacral incision 3 pain in the buttock or leg No infection, no implant removed, and no permanent nerve damage. Empty pulse generator replaced in first 6 patients after an average of 5.3 years.

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
	Withdrawals/dropouts: 2 at 1 year 13 at 2 years 5 at 3 years 3 at 4 years 2 at 5 years (total 25)					

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Braun 1999[31-35] **Location:** single centre. Germany **Funding:** government	**Design:** case series study **Diagnosis:** Group I: 6 patients with urge incontinence (including: chronic pelvic pain (1), detrusor instability (4), and low compliance (2)). Group II: 3 patients with urinary retention **Gender:** M: 3 W: 3 **Mean age:** 49 (range 28-68). **Mean follow-up:** 12.5 months (7-18).	**Inclusion:** patients with urge incontinence, urodynamic examination and PNE.	*Information on PNE not reported.*	**Type:** sacral laminectomy and bilateral electrode implantation through the sacral canal. **Sacral nerves:** S2, S3 **Incision:** 6 to 10 cm. midline skin incision. **Specific technical aspects:** dorsal face of the sacrum perforated on both sides using Rosen bur drill. **Position of the neurostimulator:** subcutaneous pouch on one side of the lower abdominal wall. **Model:** Medtronic system with an Interstim model 3023 generator, 2 model 3886 quadripolar electrodes and model 7495 extension cords. **Stimulation parameters:** *Pulse width:* 180-280 microseconds. *Frequency:* 15 to 20 Hz. *Amplitude:* 1.7 V (range 0.5 to 2.5).	**6 SNS**	**Efficacy:** **Mean leakage episodes per day:** from 7 (SE 3) to 1 (SE 0.3), $p<0.02$ **Mean pads used per day:** from 4 (SE 2) to 1 (SE 0.3), $p<0.05$ **Mean bladder capacity (ml):** from 198 (SE 52) to 352 (SE 49), $p<0.05$ **Mean bladder compliance:** from 15 (SE 4) to 31 (SE 8), $p<0.05$ **Safety:** 1 patient had a seroma near the pulse generator 1 failure due to disrupted leads (functioning restored by exchanging leads).

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Cappellano 2001[36-38] **Location:** multicentre study (national prospective registry). Italy **Funding:** unclear	**Design:** case series study **Patients and setting:** 113 enrolled in a national prospective registry. **Gender:** M: 31 W: 82 **Mean age:** 51.1 (range 17-79) **Diagnosis:** urge incontinence (63), urgency/frequency (5), voiding disturbance (41), and pelvic pain (4). Only the 63 patients with urge incontinence (47 with detrusor instability and 16 with detrusor hyperreflexia) were asked to complete the questionnaire. (44 women and 19 men. Mean age: 59.2, range 27-79) **Concomitant conditions:** trauma to L1 (2) and to C6 (1), myelitis and multiple sclerosis (5), herniated disc at L4, L5 (1), Parkinson disease (1), cerebral ischemia (1). **Recruitment period:** May 1998 - Dec 2000 **Follow-up:** 9 and 18-month.	**Inclusion:** patients with urge incontinence, urgency/frequency, voiding disturbance, and pelvic pain resistant to conservative treatment who underwent urological evaluation including urodynamics, cystoscopy, and urine culture.		SNS as described by Siegel, 1992. *Details not reported.*	**PNE** numbers not reported. **63 SNS**	**Efficacy:** ***Detrusor instability group (18-month follow-up)*** **Quality of life index:** from 34.4(22.8) to 83.8(16.6) ($p<0.001$) **Mean incontinence episodes per day:** from 5.8(4.2) to 1.2(1.5) **Patient satisfaction:** 90% **Percentage of patients who would recommend the operation:** 100% ***Hyperreflexia group (9-month follow-up)*** **Quality of life index** from 37.3(16.6) to 62.9(10.8) ($p<0.001$) **Mean incontinence episodes per day:** from 6.3(6.9) to 1.2(1.6) *Positive correlation between quality of life scores and incontinence episodes ($p<0.001$).* **Safety:** 2 Surgical revisions for lead migration and lead breakage

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Cappellano 1998[39] **Location:** single centre. Italy **Funding:** unclear	**Design:** case series study **Patients:** 47 **Gender:** M: 13 W: 34 **Mean age:** 47 (range 18-71). **Diagnosis:** urge incontinence (30), mixed urinary incontinence (7), urgency/frequency (4 including 2 interstitial cystitis), pelvic pain (2) and urinary retention (4). **Recruitment period:** Apr 1994 – Jun 1998. **Mean follow-up:** 23.1 months (3-47). **Withdrawals/dropouts:** 3 patients refused surgery, 2 patients had a permanent improvement in symptoms, and 1 had a neoplastic recurrence that contraindicated permanent implant.	**Inclusion:** patients with therapy resistant lower urinary tract dysfunction for over 6 months refractory to standard behavioural and pharmacological management. All patients underwent physical, urodynamic, and neurophysiological investigations.	**Type:** 63 unilateral PNE of S3 performed in 47 patients under local anaesthesia (as described by Schmidt et al., 1990). **Needle:** 20-gauge spinal needle into each S3 foramen. **Incision:** one finger lateral to the midline of the sacrum. **Sacral nerves:** S3 or S2 – S4 **Model:** external stimulator (Medtronic 3625). **Stimulation parameters:** *Width:* 210µsec. *Amplitude:* 0-10 mA *Frequency:* 15 Hz **Duration:** 3-5 days. **Positivity criterion:** >50% reduction in incontinent episodes.	**Positivity criteria:** cure: >90% improvement. Moderate success: 50-90% improvement. Slight success: 10-50% improvement. No success: no improvement.	**47 PNE** Only results of the female group were reported. Out of 34 women, 16 had a complete response, 4 moderate response, 3 slight response, and 11 no response **10/16 SNS**	**Efficacy:** **Mean leakage episodes (per day):** from 13 pre to 2 PNE to 1 SNS **Mean pads used per day:** from 9 pre to 1 PNE to 0.5 SNS **Mean volume per void (ml):** from 42 pre to 114 PNE to 140 SNS Mean bladder capacity (ml): from 122 pre to 314 PNE to 330 SNS *Patients with urodynamic documented urethral instability were reported to have the best outcomes.* **Safety:** 1 devise revision due to electrode breaking.

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Carey 2001[40,41] **Location:** single centre. Australia **Funding:** unclear	**Design:** prospective case series study **Diagnosis:** 12 patients with severe sensory urgency and/or urge incontinence (6 had detrusor instability and 5 interstitial cystitis). **Gender:** women **Mean age:** 49 (range 23-79) **Duration of symptoms:** mean 3.5 years (2.5 – 10) **Follow-up:** none	**Inclusion:** patients with low urinary tract symptoms who underwent voiding cystometry. Patients with bladder hypersensitivity at urodynamic assessment underwent cysto-urethroscopy and biopsy and had both macroscopic and histological evidence of interstitial cystitis.	**Type:** bilateral PNE under local anaesthesia **Needles:** in the right and left S3 foramina **Identification of sacral nerves:** by functional response **Sacral nerves:** S3 **Model:** Electrodes: old 041830-002 and new 3057, Medtronics. Pulse generator: Screener 3625, Medtronics. **Stimulation parameters:** *Width:* 210µsec. *Amplitude:* 10 V (0.5-20mA) *Frequency:* 20 Hz **Duration:** 7 days **Positivity criterion:** ≥50% reduction in the mean number of incontinent episodes and/or urinary frequency per day.	No implants.	**12 PNE** 10 women responded positively	**Efficacy:** **Mean incontinence episodes per day** (6 women with detrusor instability)**:** from 4 to 1 **Urinary frequency during the day** (10 women)**:** from 10.9 to 5.5 **Urinary frequency during the night** (10 women)**:** from 5.1 to 0.1 **Safety:** 1 lead replacement at the time of insertion.

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Chai 2001[42] **Location:** single centre. USA **Funding:** government /manufacturer	**Design:** discussion paper that reports results of a series of 20 patients **Mean follow-up:** 8 months (1-14).		**Type:** PNE with implanted S3 lead, rather than percutaneous temporary lead, under local anaesthesia. **Needle:** S3 finder needle (Medtronic 041829) and a 14-gauge Angiocath sheath (Gelco, Johnson & Johnson, Tex) to direct permanent lead. **Incision:** paramedian minimal incision. **Identification of sacral nerves:** by fluoroscopy. **Sacral nerves:** S3 **Model:** Medtronic InterStim kit. External stimulator: Medtronic 3625 Test Stimulator. **Duration:** 1-2 weeks. **Positivity criterion:** ≥50% reduction in mean number of incontinent episodes, voiding frequency, and pad usage.	No implants.	**20 PNE** with implanted S3 lead. 5 non-responders.	**Efficacy:** 15/20 positive responses during test period. **Safety:** No short-term complications.

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Edlund 2000[43] **Location:** single centre (part of a large multicentre study). Sweden **Funding:** unclear.	**Design:** case series study **Diagnosis:** urge incontinence and overactive bladder (26), hypotonic bladder and retention (4). **Gender:** M: 11 W: 19 **Mean age:** 59.8 (range 21-79) **Duration of symptoms:** 12.4 years (2-46 years). **Mean follow-up:** 19.9 months (range 8-39 months). Efficacy data available only at the 8-12 month follow-up. **Withdrawal/dropouts:** 1	**Inclusion:** patients with urodynamically proven urge incontinence or retention refractory to pharmacological measures and external electrical stimulation. All patients with incontinence had a unstable detrusor. None had neurological disease or trauma.	**Type:** PNE under local anaesthesia. In 11 patients 2 electrodes were introduced through S3 bilaterally or S3 and S4 unilaterally. **Identification of sacral nerves:** by palpation for anatomical landmarks **Needle:** 20 gauge, 9cm. **Sacral nerves:** S2, S3 or S4. **Model:** Medtronic screener 3625 external neurostimulator. **Technical aspects:** new spiral (coiled) electrode designed to prevent migration was used in 6 patients **Stimulation parameters:** *Width:* 210µsec. *Frequency:* 20 Hz **Duration:** 4 days **Positivity criterion:** ≥50% reduction in incontinent episodes, voiding frequency, and urge symptoms.	**Type:** SNS under general anaesthesia **Identification of sacral nerves:** best response of the levator ani or flexion of the great toe. **Incision:** midline incision to the fascia and exposure of the selected sacral foramen by dissecting the muscle off the sacral periosteum. **Sacral nerves:** S3 or S4. **Lead fixation:** sacral periosteum. **Electrode position:** determined by X-ray and CT. **Position of the neurostimulator:** abdominal wall. **Model:** Medtronic Itrel II pulse generator. **Stimulation parameters:** On/off stimulator *Width:* 210µsec. *Frequency:* 20 Hz	**30 PNE** **9 SNS** 1 woman cured after PNE. 20 patients were non-responders to PNE: 9 had an 'inadequate sensation' probably due to electrode displacement; 1 did not complete the voiding diaries; amongst the 11 non-responders with adequate sensation, 3 had retention and 7 had an uninhibited overactive bladder.	**Efficacy:** **Incontinence episodes per day:** from 5.9(2.2) to 2.8(1.5) **Severity of leakage:** from 1.9(0.4) to 1.6(0.4) **Pads usage:** from 3.0(2.5) to 1.9(1.8) **Safety:** Changes in stimulation frequency in most patients. 1 surgical repositioning. 3 loss of sensation (stimulator was unintentionally turned off). 4 increased frequency of bowel emptying.

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Everaert 2000[44,45] **Location:** multicentre study. Belgium **Funding:** unclear	**Design:** retrospective case series study **Patients and setting:** 53 patients from 3 university centres. **Gender:** M: 8 W: 45 **Mean age:** 43 **Diagnosis:** refractory urgency and/or urge incontinence (22) , dysuria and/or urinary retention (38), and perineal pain (19). **Co-existing pathologies:** diabetes (2), thyroid (1), lung disease (3), hepatitis (1), cardiac disease (1), psychiatric symptoms (2), and severe depression (6). **Previous surgery:** some patients had hysterectomy or underwent previous surgery for stress incontinence (numbers not specified). **Recruitment period:** Mar 1994 – Apr 1998. **Mean follow-up:** 24 months (13-39).	**Inclusion:** patients with therapy resistant symptoms of urgency, urge incontinence, dysuria, urinary retention and/or perineal pain and with a follow-up of at least 12 months. **Exclusion:** pregnant women and prepubertal children.	*Information on PNE not reported here but available from a previous publication (Everaert et al., 1997).* **Type:** PNE under local or general anaesthesia as described by Siegel, 1992. **Sacral nerves:** S3 **Model:** Medtronic screener and Flexon wire (Davis & Geck). **Stimulation parameters:** *Width:* 210µsec. *Amplitude:* 1-10 V. *Frequency:* 20 Hz **Positivity criterion:** dramatic improvement in symptoms and an objective confirmation of normal micturition (i.e. a normal flow pattern, a residual urine volume of <50 ml and a bladder capacity of <600 ml).	**Type:** SNS. 49 unilateral leads and 4 bilateral leads. **Sacral nerves:** S3 or S4 **Model:** quadripolar electrode: Medtronic Interstim 3886 (6 patients) and 3080 (47 patients). Pulse generator: Medtronic Interstim Itrel 2 (8) or IPG (45). **Position of neurostimulator:** abdominal wall. **Positivity criterion:** >50% reduction in incontinent episodes in patients with urgency/urge incontinence; >50% increase on the visual analogue scale in patients with perineal pain; and normalization of the uroflow patterns and/or decrease of residual urine <50 ml in patients with dysuria and/or retention.	**177 PNE** **53 SNS**	**Efficacy:** **Positive responses:** 45/53 had a positive response. **Cured/improved**: 30/53 were considered cured and 15/53 improved. Patients with a history of incontinence surgery were more likely to be treated efficiently with the implant (P=0.001). **Patient satisfaction:** 68% and 66% would repeat the procedure if necessary. **Safety:** 8 late failures (mean failure delay of 9 $\pm$5 months) 18 device related pain 9 pain not related to device 6 current-related problems 4 disturbing toe flexion 3 diarrhoea (in patients with a contractile bladder) 3 technical device problems 2 lead migration (model 3886) 1 operation-related problem 1 infection 4 stimulation-related symptoms (e.g. difficulty in swallowing, heavy sweating, fatigue) **Revisions:** 15 in 12 patients. 2 were successful.

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Grüenewald 2000[46-49] **Location:** single centre. Germany **Funding:** unclear	**Design:** case series study **Patients and setting:** 184 **Diagnosis:** urge incontinence or urinary retention. **Gender** (implanted patients)**:** M: 6 W: 49 **Mean age** (implanted patients)**:** 49 (range 24-77) **Recruitment period:** Since May 1990. **Mean follow-up:** 44.3 months.	**Inclusion:** patients with urge incontinence or urinary retention refractory to conventional treatment.	**Type:** PNE under local anaesthesia. **Lead location:** S3 or S4 **Duration:** 3-7 days **Positivity criterion:** ≥50% reduction in incontinence symptoms.	**Type:** SNS **Model:** Pisces Quad Lead Medtronic and Itrel II Medtronic pulse generator. **Lead location**: S3 or S4. **Position of neurostimulator:** abdominal wall	**184 PNE** **55 SNS** (idiopathic motor urge incontinence (21), urinary retention (28), sensory urge incontinence (5), and stress incontinence (1)).	**Efficacy :** ***Urge incontinence data at 6-month follow-up*** **Cured:** 6/21 **Improved** (>50%)**:** 16/21 **Volume at first sensation:** from 80 to 109 ml. N.S. **Bladder capacity:** from 278 to 306 ml. N.S. **Mean voided volume:** from 208 to 292 ml. ($p<0.05$) ***Sensory urge incontinence data at 6-month follow-up*** **Improved** (>50%)**:** 3/5 ***Stress incontinence data at 6-month follow-up*** The one patient did not respond to treatment. **Safety:** ***6-month follow-up data*** 14/55 surgical revisions due to: 5 infection 2 lead migration 3 pain at the site of the implanted generator 1 lead fracture 1 electrode insulation defect 1 skin erosion at the site of the implanted generator 1 polyurethane allergy

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Hasan 1996[50] **Location:** two medical departments. UK **Funding:** government	**Design:** case series study **Patients:** 35 **Gender:** M: 13 W: 22 **Mean age:** 48 (rane 22-77) **Diagnosis:** frequency/urgency, urge incontinence, and enuresis. **Recruitment period:** Jan 1993 - Dec 1994	**Inclusion:** patients with idiopathic detrusor instability with increased frequency, urgency, urge incontinence, and enuresis refractory to conservative medical treatment.	**Type:** unilateral PNE (as described by Siegel et al., 1992) under local anaesthesia. **Mean duration:** 6 (4-8) days **Stimulation parameters:** *Width:* 200µsec. *Frequency:* 25 Hz. *Amplitude:* to patient maximum tolerable level.		**35 PNE** 31 completed the test	**Efficacy:** **Cured** (>75% improvement): Urgency/frequency 2/31 Urge incontinence 12/21 Enuresis 7/14 **Improved** (50-75% improvement): Urgency/frequency 8/31 Urge incontinence 4/21 Enuresis 4/14 **Frequency of voids:** from 13(10) to 9(4) **Nocturia** (14 patients)**:** from 3(2) to 0(0) **Urgency:** 29 patients reported moderate to severe urgency before study compared to 25 who reported mild to moderate urgency during test stimulation and 2 who reported no urgency. **Incontinence episodes** (21 patients)**:** from 6(7) to 1(1) **Pad usage** (17 patients)**:** from 5(4) to 1(2) **Urinary symptoms score:** from 10(3) to 5(2) ***Urodynamics*** **Mean voided volume:** from 184(81) to 277(107) ml. $p<0.05$ **Mean voiding pressure:** from 57(29) to 58(23) cm water N.S. **Mean residual volume:** from 24(27) to 28(35) N.S. **No. unstable contractions:** from 20(15) to 9(11) $p<0.05$

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
						Frequency of unstable contractions/hours: from 5(3) to 2(3) $p<0.05$ **Max amplitude of unstable contractions:** from 75(49) to 59(49) N.S. **Mean volume of urge incontinence:** from 21(23) to 15(26) N.S. 3/31 patients were urodynamically stable. **Safety:** 4 electrode displacement/ intolerance to electrical stimulation 1 haemorrhage from the puncture site

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Hassouna 2000[51-56] **Location:** multicentre. USA, Canada and Europe **Funding:** manufacturer.	**Design:** randomised controlled trial. **Patients and setting:** 51 enrolled from the general urological population at 12 worldwide centres. **Gender:** M: 5 W: 46 **Mean age:** 39(11.8) **Duration of symptoms:** 8.1(9.2) years. **Previous surgery**: 125 surgical procedures: hydrodistension (76), bladder/sphincter surgery (13), prostate surgery (1), urethral stricture repair (1), suspension/sling (6), denervation (4), cystocele repair 92), and other procedures such as hysterectomy and laparoscopy (22). **Recruitment period:** database closure June 1998. **Follow-up:** at 6, 12, and 24 months.	**Inclusion:** patients older than 16 years with refractory voiding dysfunction but normal upper urinary tract function, bladder capacity ≥100 ml. **Exclusion:** neurological conditions. Primary stress incontinence and primary pelvic pain symptoms.	**Type:** PNE **Sacral nerves:** S3 or S4. **Duration:** 3-7 days. **Positivity criterion:** ≥50% reduction in main incontinent symptoms.	*Information on SNS not given*	**PNE** total number not reported. **51 SNS** **Randomisation:** 25 implant group and 26 control group. Controls allowed to cross-over after 6 months.	**Efficacy:** **Cured/improved:** 14/25 had ≥50% reduction in number of voids at 6 months. 2/25 patients had no improvement or deterioration of symptoms. **Frequency of voids:** *Implant group:* from 16.9(9.7) to 9.3(5.1) at 6 months (p<0.0001). *Control group:* from 15.2(6.6) to 15.7(7.6) at 6 months N.S. **Voided volume:** *Implant group:* from 118(74) to 226(124) p<0.001 *Control group:* from 124(66) to 123(75) N.S. **Degree of urgency:** *Implant group:* from 2.2(0.6) to 1.6(0.9) p=0.01 *Control group:* from 2.4(0.5) to 2.3(0.5) N.S. **Bladder volume at first sensation:** *Implant group (23):* from 107(97) to 161(119) p=0.01 *Control group (25):* from 104(77) to 92(69) **Bladder volume at max filling:** *Implant group (23):* from 234(128) to 325(185) p=0.008 *Control group (25):* from 253(93) to 227 (104) **Peak detrusor pressure during cystometry:** *Implant group (22):* from 27.4(28.6) to 16.5(21.8) p=0.01 *Control group (23):* from 7.3(4.9) to 9.8(10.2) Detrusor pressure at first sensation and max filling were not significant different between-group comparisons and within-group comparisons.

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
						SF-36 Quality of Life questionnaire. Implant group (23) showed significant improvements compared to the control group (20) in various aspects of quality of life (mean values): Physical function 77 vs 48 p<0.0001 Physical Role 51 vs 30 p=0.01 Bodily pain 60 vs 34 p=0.01 General health 61 vs 46 p=0.003 Vitality 55 vs 36 p=0.01 Social function 77 vs 43 p=0.002 Mental health 71 vs 62 p=0.01 ***12-month results*** **Frequency of voids** (33)**:** from 16.6(8.5) to 9.0(4.5) p<0.0001 **Voided volume (ml)** (33)**:** from 132(89) to 233(141) p<0.0001 **Degree of urgency (scale 0-3)** (33)**:** from 2.2(0.6) to 1.8(0.8) p=0.005 **Total volume voided/day** (27)**:** from 1834(1072) to 1792(927) N.S. **Max voided volume** (27)**:** from 334(223) to 440(231) p=0.001 **% Felt empty** (27)**:** from 44(43) to 81(33) p=0.0002 **Pelvic /bladder discomfort** (26)**:** from 2.0(1.0) to 0.9(1.0) p<0.0001 **Strength of flow - scale 1-4** (27)**:** from 2.7(0.8) to 1.9(0.9) p=0.0005 **Safety:** 1 explant due to bowel dysfunction before 6-month follow-up. Pain at implant site: 15.3%

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
						Surgical revisions of the implanted neurostimulator or lead system: 33.3% New pain: 9% Lead migration: 8.6% Infection: 6.1% Electrical shock sensation: 5.5% Pain at the lead site: 5.4%

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Hassouna 1991[57] **Location:** single centre. Canada **Funding:** unclear	**Design:** case series study **Patients and setting:** 36 **Diagnosis:** urgency frequency, urge incontinence, urinary retention, pain. 8 patients had spinal cord lesions. **Recruitment period (date of implant):** Jun 1989 - Nov 1990	**Inclusion:** patients with refractory voiding dysfunction.	**Type:** PNE under local anaesthesia. **Needle:** a 20-gauge, 2-in. angiocatheter replaced by 22-gauge spinal needle mounted trough the sheath of the angiocatheter. **Lead position:** S3 (3-0 Flexon wire) **Position of the lead:** confirmed by lateral x-ray. **Model:** Urys 800 external stimulator **Stimulation parameters:** *Rate:* 33 pps *Amplitude:* 20 V **Positivity criterion:** >75% reduction in main incontinent symptoms.	**Type:** SNS **Model:** Pisces-Quad model 3487A, Medtronic. Extension lead 7493. **Lead location:** S2-S3 **Sacral incision:** over the lower two-thirds of the sacrum in the midline. **Position of neurostimulator:** subcutaneous pouch in the abdominal wall.	**32 PNE** **7 SNS** 14 showed adequate response to PNE. 7 patients (3 urgency/ frequency and 4 pain/retention) received SNS 1 patient underwent anterior root neuromodulation.	**Efficacy:** ***Patients with urgency/frequency*** 60% improvement in voiding symptoms

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Hedlund 2002[58,59] **Location:** single centre. Norway **Funding:** unclear	**Design:** case series study **Patients and setting:** 53 **Gender:** M: 8 W: 45 **Mean age:** 54 (range 17-76) **Previous surgery:** 11 patients underwent incontinence surgery and 12 patients gynaecological surgery. 2 further patients had enterocystoplasty before entering the programme. **Recruitment period:** Sept 1998 - October 2001 **Mean follow-up:** 18 months (range 9-32). 12 patients available at the 6-month follow-up; 9 at the 1-year follow-up; and 7 at the 2-year follow-up.	**Inclusion:** patients with non-neurogenic refractory urge incontinence.	**Type:** PNE under local anaesthesia **Model:** Medtronic screener 3625 external stimulator. **Lead location:** S3 **Needle:** 20-gauge needle **Confirmation of lead location: by** plain x-ray. **Stimulation parameters:** *Frequency:* 20 Hz *Width:* 210 µsec. **Duration:** 3 days **Positivity criterion:** ≥50% reduction in target symptoms.	**Type:** SNS **Model:** Medtronic quadripolar lead, model 3080. Implantable pulse generator, Medtronic Interstim, Model 3031. Lead extension Medtronic, Model 3095. **Sacral incision:** midline incision **Lead location:** S3 (11 cases) and S4 (3 cases) **Position of neurostimulator:** lower part of the abdominal wall in the first 2 patients and lateral-superior quadrant of the buttock in the remaining patients. **Stimulation parameters:** *Frequency:* 20 Hz *Width:* 210 µsec. *Amplitude:* 0.5-3.5 V. *Mode of operation:* continuous	**109 PNE in 53 patients** 19 patients were declared responders and 30 non-responders. In 1 patient an open procedure followed 2 technically unsuccessful tests. Responders are still under evaluation. Overactive detrusor was diagnosed in all responders expect 1 female with sensory urgency. **14 SNS** (12 women and 2 men, mean age 47 (33-73)).	**Efficacy:** **Cured:** 8/14 **Improved:** 5/14 **Failures:** 1/14 (woman with urgency) **Leakage per day (g):** from 579(176) to 93(60) at 6 months p<0.01 16(8) at 1 year p<0.01 9(1) at 2 years p<0.05 **Pad usage:** from 8.3(1.3) to 2.1(0.7) at 6 months p<0.01 1.3(0.4) at 1 year p<0.01 0.6(0.4) at 2 years p<0.05 **Frequency of voids:** from 10(1.1) to 8.6(0.6) at 6 months 8.0(0.6) at 1 year 7.0(0.7) at 2 years **Mean voided volume:** from 195(25) to 256(30) at 6 months p<0.05 255(27) at 1 year p<0.05 289(37) at 2 years p<0.05 **Mean residual urine:** from 132(71) to 143(46) at 6 months 130(59) at 1 year 151(69) at 2 years **Bladder capacity:** from 400(53) to 479(54) at 6 months 512(59) at 1 year 596(36) at 2 years **Urgency:** from 278(163) to 430(62) at 6 months 436(56) at 1 year 519(19) at 2 years

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
						Safety: 2 repositioning of the lead 1 seroma (punctured and evacuated without any infection) 2 bowel problems

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Hohenfellner 1998[60,61] **Location:** two university departments. Germany **Funding:** unclear	**Design:** case series study **Patients:** 11 **Gender:** M: 2 W: 9 **Mean age:** 43.4 (range 21-70). **Diagnosis:** 5 patients had a confirmed diagnosis of neurogenic bladder. **Mean follow-up:** 13 months (range 9-28).	**Exclusion:** sacral dermal pathological conditions, congenital or other anatomical sacral anomalies (e.g. spina bifida, sacral agenesis, trauma sequelae), stress incontinence, bladder capacity <150 ml., other pathological urological conditions related to existing voiding dysfunction, or pregnancy.	**Type:** unilateral or bilateral PNE under local anaesthesia. **Lead location:** S3 **Duration:** 3 to 4 days. **Positivity criterion:** ≥50% reduction in main symptoms.	**Type:** bilateral SNS **Lead location:** S2-S4 through a sacral laminectomy. **Position of neurostimulator:** abdominal wall. **Mode of operation:** continuous in 5 patients and cyclic in 5. **Stimulation parameters:** *Frequency:* 10 Hz. *Width:* 210 µsec.	**11 PNE** **11 SNS** Neurostimulator was post-operatively activated in 10 patients.	**Efficacy:** ***5 patients with incontinence*** **Incontinence episodes per day:** from 14(2.2) to 6(2.2) during PNE p<0.05, to 7(2.2) post-implant p<0.05 **Nocturia:** from 3(0.5) to 1(0.7) during PNE p<0.05, to 1(0.7) post-implant p<0.05. **Pad usage:** from 5(4.5) to 1(0.9) during PNE, to 1(0.6) post-implant. **Voided volume:** from 86(47) to 303(116) during PNE p<0.05, to 334(193) post-implant p<0.05. **Bladder capacity:** from 130(103) to 342(130) during PNE p<0.05, to 386(128) post-implant p<0.05. **Filling at first sensation:** from 76(69) to 141(69) during PNE N.S., to 225(87) post-implant. **Max detrusor pressure during filling:** from 48(11) to 22(4.5) during PNE p<0.05, to 24(6.7) post-implant p<0.05. **Safety:** 1 removal of the device 5 wound infection (superficial and not endangering the implant in 4, stimulator could not be activated in 1) 1 reconnection of electrode 1 wire break of the extension lead (fixed)

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Ishigooka 1999[62] **Location:** single centre, USA **Funding:** unclear	**Design:** retrospective case series **Patients and setting:** 40 **Gender:** M: 3 W: 37 **Mean age:** 40.2 (range 18-65) **Diagnosis:** urgency/frequency (22) or urge incontinence (17). **Follow-up:** 1, 3 and 6 months after implantation and every 6 months thereafter. Long-term follow-up include 22 women (37.4 years (18-61)).	**Inclusion:** patients with urgency/frequency and/or urge incontinence and no history of major neurological events.	**Type:** PNE **Duration:** 3-4 days	**Type:** SNS as described by Thon et al., 1991. **Model:** Itrel, Medtronic.	**40 PNE** **40 SNS**	**Efficacy:** ***Chronic effect (22 patients)*** **Increase in the average volume per void:** 21/22 **Decrease in frequency of void:** 17/22 **Pelvic pain and/or urethral burning sensation improved in** 17/22 patients. Symptoms improved in all (22/22) patients.

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Janknegt 2001[63,64] **Location:** worldwide multicentre trial **Funding:** manufacturer	**Design:** prospective clinical trial and case series study **Patients:** 96 **Gender:** M: 11 W: 85 **Age:** range 22-78 **Diagnosis:** urge incontinence. **Mean duration of symptoms:** 9.1(7.0) years. **No. of previous surgical procedures:** 177 for the treatment of urinary problems. **Recruitment period:** Dec 1993 – Sept 1999 **Mean follow-up:** 30.8 months (12-60).	**Inclusion:** patients older than 16 years with a bladder capacity of ≥100 ml and normal upper tract who were refractory to standard medical therapies. All patients underwent urodynamic testing and completed two 3-day baseline voiding diaries. **Exclusion:** neurological conditions, primary stress incontinence, and primary pelvic pain symptoms.	**Type:** PNE **Lead location:** S3 or S4 **Positivity criterion:** ≥50% reduction in incontinent symptoms.	**Type:** SNS **Model:** InterStim Medtronic.	**PNE** (total number not reported) **96 SNS**	**Efficacy:** **Cured:** 25/96 **Improved:** 35/96 **Mean incontinence episodes per day:** from 10.9(6.5) to 4.2(4.9) ($p<0.0001$) at an average of 30.8 months. **Severity of leaks** (scale 0-3)**:** from 2.0(0.6) to 1.2(0.9) ($p<0.0001$) **Mean pad usage** (90)**:** from 7.1(5.1) to 2.9(3.8) per day ($p<0.0001$) **Frequency of voids** (85)**:** from 13.2(6.8) to 9.2(4.5) ($p<0.0001$) **Voided volume** (85)**:** from 149(00) ml to 200(100) ml. **Degree of urgency** (scale 0-3) (80)**:** 2.0(0.9) to 2.0(0.7) N.S. **Pelvic/bladder discomfort** (69)**:** from 1.6(1.1) to 0.9(1.1) ($p<0.0001$) **Safety:** Explanted due to: 9 lack of efficacy 1 chronic leg pain 1 bowel dysfunction

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Janknegt 1997[65] **Location:** single centre. The Netherlands **Funding:** unclear	**Design:** case series study **Patients:** 10 **Mean age:** 46 (range 32-56) **Diagnosis:** urge incontinence (4), urinary retention (4), urgency/ frequency (2). **Duration of incontinence symptoms:** 3.6 years **Previous surgery:** suspension procedures in 3 patients with mixed incontinence and prostate resection in 2 with retention. **Mean follow-up:** 4 to 36 months.	**Inclusion:** patients with refractory voiding dysfunction who failed the chronic PNE were selected for the two-stage procedure.	**Type:** PNE **Model:** Pice-Quad electrode, Medtronic. **Lead location:** S3, S2 or S4. **Duration:** 4-7 days **Positivity criterion:** ≥50% improvement in the main symptoms. **Specific technical aspects:** implant of a permanent electrode during PNE	**Type:** SNS **Model:** Itrel II, Medtronic	PNE 99: *52 implanted, 47 nonresponders.15 of the non-responders fulfilled the criteria but 5 patients did not consent to the two-stage implant* *During the acute phase all patients had appropriate sensory and motor reactions, but failed in the PNE subchronic phase.* **10 PNE** **8 SNS**	**Efficacy:** 8/10 patients had an improvement >50% in their symptoms (60% to 90%). **Pad usage:** from 7.2 to 0.4 at 6 months **Safety:** Repositioning of the electrode from S4 to S3 in 1 of the 2 failures proved to be successful.

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Ratto 2003[66] **Location:** single center, Italy. **Funding:** government (and manufacturer?)	**Design:** case series **Patients:** 10 **Gender:** M: 5 W: 5 **Mean age:** 50.4 **Recruitment period:** May 2000 – Nov 2001		**Type:** PNE **Needle:**insulated needle. **Lead location:** S3 **Positioning of the needle:** observable contraction of the levator ani and flexion of the homolateral big toe. Radioscopy of the pelvis. **Duration:** 14 days.	**Type**: SNS **Model:** electrode model 3080, Medtronic; Rotator Cuff Easy Anchor, Mitek Products); neurostimulator Medtronic InterStim 3023 for unilateral SNS; neurostimulator Medtronic Synergy 7427 for bilateral SNS. **Lead location:** S3 **Sacral incision:** directly on the sacral foramen. Longitudinal incision, 3 cm. Application of a catheter cannula beside the insulated needle. Electrode is introduced into the catheter cannula, which is then removed. **Fixation location:** with anchors at the medullar layer of the sacral bone. **Final position of implanted electrode:** by x-ray of the pelvis. **Position of the neurostimulator:** subcutaneous pocket in the gluteal region or in the anterior abdominal wall. **Operative time:** 1 vs 1.5 hours.	**10 PNE** **10 SNS** 4 unilateral and 6 bilateral implants	**Efficacy:** No efficacy data reported. **Safety:** 1 seroma (successfully drained without need for antibiotic therapy or major procedures). No cases of lead displacement or suboptimal position of the electrode. No complaints of pain at the neurostimulator site.

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Scheepens 2003[67,68] **Location:** two university departments. The Netherlands **Funding:** manufacturer	**Design:** retrospective case series **Patients:** 34 **Gender:** M: 7 W: 27 **Mean age:** 53 (34-75) **Diagnosis:** all patients had an overactive bladder, 28 with urge incontinence and 6 with urgency/frequency. **Mean follow-up:** 11 months post-implant (0-56).		*Information on PNE not given.*	*Information on SNS not given.*	**24 Implanted group** **10 PNE group:** 3 patients did not respond to stimulation. 7 received SNS implant. Results were not provided separately for the PNE phase and the SNS implant phase.	**Efficacy:** **Cured/improved:** 18/34 (53%) had >50% improvement. ***Baseline values versus values during SNS*** **Incontinence episodes:** from 3.3(3.1) to 2.1(2.3) p=0.008 **Urge events:** from 4.6(3.4) to 2.9(3.0) p=0.036 **Number of voids:** from 4.6(2.2) to 3.4(2.3) p=0.011 **Bladder contractions:** from 15.1(18.6) to 10.9(12.7) N.S. **Max amplitude of bladder contraction (cmH_2O):** from 66.4(64.4) to 71.5(80.0) N.S. **Max duration of bladder contraction (s):** from 11.5(2.9) to 10.5(4.4) **Voided volume (g):** from 691.1(539.4) to 608.8(632.2) N.S. **Total urine loss:** from 121.8(301.3) to 111.2(359.1) N.S. **No. of drinks:** from 6.1(3.2) to 6.1(3.4) N.S. **Total drinking volume (ml):** from 1089.4(611.4) to 1204(606.9) N.S. **Detrusor Activity Index (22):** from 0.7(0.3) to 0.5(0.4) p=0.017 *Reduction in DAI correlated significantly (p=0.03) with the effect of sacral neuromodulation (subjective effect and voiding diaries).*

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Scheepens 2002a[69-71] **Location:** single center. The Netherlands. **Funding:** unclear	**Design:** case series study. **Patients:** 15 **Gender:** M: 2 W: 13 **Mean age:** 53 (range 44-66) **Recruitment period:** 1991-1998 **Mean follow-up:** 4.9 years (range 2.5-7.5) **Withdrawals/dropouts/lost at follow-up:** 3		**Type:** PNE **Duration:** 4-7 days **Positivity criterion:** ≥50% improvement in the main symptoms.	**Type:** SNS **Sacral incision:** median incision over the sacrum **Lead location:** right side S3 foramen (10) left side S3 foramen (5) **Position of neurostimulator:** buttock	**15 PNE** During the acute phase all patients had appropriate sensory and motor reactions, but failed in the PNE subchronic phase. Reasons of failure: repeated lead migration (7); insufficient objective response (3); contradictory test (3); technical failures (3). SNS was undertaken in patients who failed subchronic PNE phase but in whom success was anticipated because of good objective variables in the acute phase of PNE (15 patients).	**Efficacy:** **Incontinence episodes per day:** from 9.0(4.3) to 3.2(3.4) N.S. **Pad usage** from 5.0(2.4) to 1.0(1.3) p=0.003 **Severity of leakage (scale 0-3)** from 1.8(0.3) to1.3(0.3) p=0.041 **Frequency of voids from** 12.9(5.8) to 7.9(2.2) p<0.05 **Voiding volume** from 99.1(62.5) to 313.0(121.4) ml; p=0.004 **Patient satisfaction:** 91% (50-100%) **Safety:** 1 explant of lead during PNE 2 explant IPG because ineffective 1 replacement of empty IPG 1 abdominal pain 1 flank pain 1 replacement of broken lead 1 replacement of lead due to adverse bowel function 3 leg pain 3 perineal pain 2 pain at IPG site

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Scheepens 2002b[72,73] **Location:** single centre. The Netherlands **Funding:** manufacturer	**Design:** prospective randomised cross-over trial **Patients:** 33 **Gender:** M: 6 W: 27 **Mean age:** 45.5 (range 28-65) **Diagnosis:** urge incontinence (18), voiding difficulty (8), urinary retention (7). **Previous surgery:** Burch suspension (1), sling suspension (6), bladder dilatation (2), urethral dilatation (3). **Recruitment period:** from Jan 1999 to May 2001.	**Inclusion:** patients older than 16 years with chronic voiding dysfunction refractory to standard medical therapy but normal upper urinary tract function, and with bladder capacity $\geq$100 ml. **Exclusion:** neurogenic voiding disorders (multiple sclerosis, diabetes with peripheral involvement, spinal cord injury), stress urinary incontinence, primary pelvic pain symptoms, Reiter's syndrome, cerebrovascular accident less than 6 months ago, malignancy of the urinary tract, pelvic prolapse, cystocele, urethrocele, enterocele, proven interstitial cystitis.	**Type:** bilateral test stimulation as described by Siegel 1992. **Model:** Medtronic Dualscreen 3628 external stimulator. **Duration:** two 4 –day periods with a wash-out period of 2 days. Patients were randomly assigned to start with bilateral (17) or unilateral (16) test stimulation. **Lead location:** S3 (31) and S4 (2) **Lead position:** confirmed by x-ray.	**Type:** SNS **Model:** Medtronic Synergy 7427 implantable pulse generator.	**33 PNE** Two patients with urinary retention underwent bilateral implant. No details given.	**Efficacy:** *Urge incontinence* **Number leakages per day:** significantly decreased from baseline to stimulation baseline vs unilateral: p=0.006 baseline vs bilateral: p=0.004 unilateral vs bilateral p=0.594 **Severity of leakages:** significantly reduced from baseline to stimulation baseline vs unilateral: p=0.005 baseline vs bilateral: p=0.009 unilateral vs bilateral p=0.102 **Pad usage:** significantly reduced from baseline to stimulation baseline vs unilateral: p=0.048 baseline vs bilateral: p=0.016 unilateral vs bilateral p=0.594 **Frequency of voids:** significantly decreased from baseline to stimulation baseline vs unilateral: p=0.001 baseline vs bilateral: p=0.001 unilateral vs bilateral p=0.865 **Voided volume per void:** significantly increased from baseline to stimulation baseline vs unilateral: p=0.001 baseline vs bilateral: p=0.001 unilateral vs bilateral p=0.460 No significant differences between unilateral and bilateral stimulation. **Patient satisfaction (questionnaire):** no significant difference between unilateral and bilateral stimulation p=0.541. **Safety**:8 lead migration

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Scheepens 2001[74] **Location:** single centre. The Netherlands **Funding:** unclear	**Design:** case series study. **Patients:** 39 **Mean age:** 51 (range 33-72) **Diagnosis:** urge incontinence (22), urgency-frequency 6, urinary retention (9), pelvic pain (1), faecal incontinence (1). **Recruitment period:** Aug 1999 – Jul 2000 **Mean follow-up:** 5.3 months (range 1-10).			**Type:** SNS under general anaesthesia. **Model:** Medtronic quadripolar lead, model 3080; Medtronic quadripolar IPG, model 3023; Medtronic lead extension, model 3095. **Position of the neurostimulator:** buttock. **Incision:** 2 incisions required, a short subcutaneous tunnel is required to connect the lead at the level of the sacrum to the IPG at the level of the buttock. **Operative time** for implantation of the IPG in the buttock: 1-1.5 hours.		**Safety:** 4 pain at implant site: 3/18 pain at the level of the IPG 2 post-operative haematoma (treated conservatively). 2 repositioning of the IPG from the abdominal wall to the buttock

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Schmidt 1999[75-77] **Location:** multicentre trial. USA, Canada, Europe **Funding:** manufacturer	**Design:** prospective randomised trial **Patients and setting:** 155 urge incontinence patients enrolled from the general urological population at 16 worldwide centres. **Gender:** M: 30 W: 125 **Mean age:** 46.6 (range 20.2-78.9) **Mean duration of symptoms:** 9.0±7.4 **Previous surgery:** 208 procedures in 88 patients. **Recruitment period:** from Dec 1993 to Apr 1997. **Follow-up:** 1, 3 and 6 months after implantation and every 6 months thereafter. **Mean follow-up:** 14.7 months (0.9-39.7).	**Inclusion:** patients older than 16 years with voiding dysfunction refractory to standard medical therapy but normal upper urinary tract function, and with bladder capacity ≥100 ml. **Exclusion:** neurological conditions (multiple sclerosis, diabetes with peripheral involvement, spinal cord injury, stroke). Stress urinary incontinence and primary pelvic pain symptoms.	**Type:** PNE **Sacral nerves:** S3 or S4. **Duration:** 3-7 days. **Positivity criterion:** ≥50% reduction in voiding symptoms.	**Type:** SNS **Model:** InterStim neurostimulator system, Medtronic. **Lead location:** targeted sacral nerve (S3). **Position of neurostimulator:** pocket in the lower quadrant of the abdomen.	**155 PNE** 57 non-responders 98 randomised to implant group and control/delayed group. 6-month follow-up data available from 76 patients (34 in implant group and 42 in control group). Controls received standard medical treatment and were allowed to cross-over after 6 months.	**Efficacy:** ***6-month follow-up*** **Cured:** 16/34 in the implant group **Failures:** 3/34 **Mean incontinence episodes/day:** *Implant group:* from 9.7(6.3) to 2.6(5.1) p<0.0001 *Control group:* from 9.3(4.8) to 11.3(5.9) p=0.002 **Heavy incontinence episodes/day:** *Implant group:* from 3.4(3.8) to 0.3 to (0.9) p<0.0001 *Control group:* from 2.6(3.5) to 3.9(3.8) **Severity of leakage** (scale 0-3)**:** *Implant group:* from 2.0(0.7) to 0.8(0.9) p<0.0001 *Control group:* from 1.8(0.6) to 2.0(0.6) p=0.006 **Pad usage:** *Implant group:* from 6.2(5.0) to 1.1(2.0) p<0.0001 *Control group:* from 5.0(3.7) to 6.3(3.6) p=0.003 **Bladder volume at first sensation:** 222 in the implant group versus 79 cc in the control group p=0.017 **Bladder volume at first contraction:** 151 in the implant group compare with 70 cc in the control group. **Stable detrusor function at 6 months:** 19/34 in the implant group compared with 7/42 in the control group p=0.014

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
						Clinical benefits at the 18-month follow-up **Dry** (11) **or >50% reduction in symptoms** (5)**:** 16/21, 76% **Elimination of heavy incontinent episodes:** 18/21, 84% **Elimination** (12) **or >50% reduction in pad usage** (4)**:** 16/21, 79% **Safety:** 1 device explantation due to pain with stimulation 2 worsening of symptoms ***Safety data based on study population of 157 patients*** Adverse events occurred in 51 of the 157 cases (32.5%) and resolved in all but 3 at the time database closure. Pain at neurostimulator site 15.9% Pain at implant site 19.1% Lead migration 7.0% Infection 5.7% Surgical revisions of the implanted neurostimulator or lead system 32.5%, including: 6 permanent explants (due to pain at implant site, change in bowel function, infection); 4 temporary explants/ reimplantations (due to pain at implant site, infection, allergic reaction to implanted material) ; 14 device exchanges (due to technical problems, lead migration, change in bowel function**,** pain at implant site); 16 reposition lead/extension (due to pain at implant site, change in bowel function, technical problems, lead/extension migration, transient electric shock); 23 reposition (due to pain at the pulse generator site):

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Schmidt 1988[78] **Location:** single centre. USA **Funding:** unclear	**Design:** case series study **Patients:** 19 **Diagnosis:** urge incontinence **Recruitment period:** 1981 – 1986	**Inclusion:** patients with voiding dysfunction.	**Type:** PNE **Needle:** 22-gauge spinal needle insulated with a 20-in cath sheath. A 3-0 flexon pacer wire is passed down through the sheath. **Lead location:** S3 **Duration:** 3-5 days **Position of the lead:** confirmed on a lateral spinal x-ray	**Type:** SNS (unilateral or bilateral) **Lead location:** S3		**Efficacy:** **Cured/improved:** 14/19 **Failures:** 5/19

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Shaker 1998[79-82] **Location:** single centre. Canada **Funding:** unclear	**Design:** case series study **Patients:** 18 **Gender:** M: 2 W: 16 **Mean age:** 42.3 (range 22-67) **Diagnosis:** urge incontinence (18). In 8 patients urge incontinence was associated with idiopathic non-obstructive chronic urinary retention. **Duration of symptoms:** 6.6 years (range 1.2-18.8) **Mean follow-up:** 18.8 months (range 3-83)	**Inclusion:** patients with urge incontinence, urgency/frequency or non-obstructive chronic urinary retention refractory to all conservative measures. All patients underwent urodynamic study and cystoscopy. **Exclusion:** multiple sclerosis, severe uncontrolled diabetes or diabetes with peripheral neuropathy, pregnancy, anatomical limitations which would prevent successful placement of an electrode such as meningomyelocele, active degenerative disk disease, spinal cord injury or cerebrovascualr accident in the past 6 months, urinary tract infection until treated, stress incontinence, pelvic pain associated with voiding dysfunction, severe psychological problems and	**Type:** PNE as described by Siegel, 1992. **Model:** Medtronic 3625 mobile pulse generator. **Lead location:** S3 **Duration:** 4 days **Positivity criterion:** $\geq$50% reduction in the number of incontinent episodes.	**Type:** SNS **Model:** Medtronics Itrel I, II or Interstim. **Stimulation parameters:** *Width:* 210µsec. *Amplitude:* 2 V *Frequency:* 2-15 Hz	**104 PNE** 41 with a positive response (20 with urge incontinence and 21 with urinary retention) **38 SNS** (only the results of the 18 with urge incontinence are reported here)	**Efficacy:** ***All patients*** **Cured:** 8/18 **Improved:** 4/18 (one leakage episode per day) **Mean number of incontinence episodes per day:** from 6.49 to 1.98 after 1 month of the implant and remained significant thereafter ($p<0.05$). **Degree of urgency** (score 0-3)**:** from 2.15(0.32) to 1.91(0.30) at 18-month follow-up. **Post-void sensation (%):** from 38.18(10.80) to 93.92(5.37) at 18-month follow-up ($p<0.05$). **Pain and discomfort** (score 0-3)**:** from 1.78(0.31) to 0.64(0.44) at 18-month follow-up ($p<0.05$). **SF36 quality of life:** non-significant different from baseline apart from the 'health perception' item at 6 months. **Beck Depression Index:** improvement between 10 to 40%. **Severity of leakage** (patients who complete the 18-month follow-up (7 in each group)**:**from 1.43(0.28) to 0.78(0.30) ***Patients with pure urge incontinence*** **Frequency of voids** from 15.02(1.96) to 8.77(0.86) after 1 month of the implant and stayed within that range thereafter ($p<0.05$).

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
		mechanical infra-vesical obstruction.				**Voided volume:** from 182.44(51.23) to 402.50(159.10) at 12- month follow-up. **Bladder volume:** from 133.17(25.31) to 203.75 (42.29) ml at 6 months. **Bladder capacity:** from 291.93(48.32) to 335.83(51.05) ml at 6 months. ***Patients with associated urinary retention*** **Voided volume:** from 600 ml to 1500 ml (statistically significant). **Safety:** Lead migration during PNE (number not reported). Skin irritation, change of bowel habits and pain during PNE (number not reported). 2 wound dehiscence 2 repositioning of the extension cable due to erosion 2 change of implant site due to severe pain 1 explant for patient psychological disturbance 2 replacement for battery failure 1 atrial fibrillation unrelated to implant

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Siegel 2000[83,84] **Location:** multicentre. USA, Canada, Europe. **Funding:** manufacturer.	**Design:** prospective muticentre trial. **Patients:** 581 **Diagnosis:** urge incontinence (184), urgency/frequency (220), and urinary retention (177). **Gender:** M: 127 W: 453 **Mean age:** 43 (17-81) **Duration of symptoms:** 8 years. **Previous surgery:** in 106 patients with urge incontinence, 145 with urgency/frequency, 83 with urinary retention. **Follow-up:** 1, 3, 6 months after implant and every 6 months thereafter. **Long-term follow-up (112 patients):** 1.5-3 years.	**Inclusion:** patients with urge incontinence, urgency/frequency, and urinary retention refractory to standard medical treatment.	**Type:**PNE **Lead location:** by motor and sensory response. **Duration:** 3-7 days. **Positivity criterion:** ≥50% reduction in target symptoms.	**Type:** SNS **Model:** InterStim system, Medtronic. **Sacral incision:** 2.5 to 4.0 cm deep. **Lead position:** checked by motor response. **Position of neurostimulator:** either the abdominal wall or the upper buttock area. **Mode of operation:** cyclic.	**581 PNE** 260 responders. **219 SNS**	**Efficacy:** ***Urge incontinence (41) at 3 year follow-up*** **Mean incontinence episodes/day:** from 11.6(6.6) to 5.0(6.1) p<0.0001 **Heavy episodes:** from 3.56(4.0) to 1.3(3.5) p<0.0001 **Pad usage/day:** from 6.7(4.6) to 3.4(4.9) p<0.0001 ***Urgency/frequency (29) at 2-year follow-up*** **Mean voids/day:** from 17.7(8.6) to 10.6(6.6) p<0.0001 **Mean volume per void:** from 132.5(93.6) ml to 225(162) ml p<0.0001 *Average degree of urgency improved in 20 (69%) patients.* **Safety:** From entire study population of 581 patients who underwent PNE **PNE** 181 adverse events occurred in 166/914 procedures. Lead migration: 108 events, 11.8% of procedures Technical problems: 24 events, 2.6% of procedures Pain: 19 occurrences, 2.1% of procedures. 1 Surgical revision was required to remove a test lead electrode that became dislodged during routine lead removal.

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
						SNS Adverse events at 12-month follow-up for the 219 patients who received implanted SNS Pain at neurostimulator site: 15.3% of cases New pain: 9.0% Lead migration: 8.4% Infection: 6.1% Transient electric shock 5.5% Pain at lead site: 5.4% Adverse change in bowel function: 3.0% Technical problems: 1.7% Suspected device problems: 1.6% Change in menstrual cycle 1.0% Adverse change in voiding function: 0.6% Persistent skin irritation: 0.5% Suspected nerve injury: 0.5% Device rejection: 0.5% Other 9.5% Surgical revisions of the implanted neurostimulator or lead system: 33% of cases (73/219)

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Spinelli 2003[85,86] **Location:** single centre. Italy **Funding:** unclear	**Design:** case series study **Patients:** 32 **Gender:** M: 10 W: 22 **Mean age:** 43 **Diagnosis:** chronic urinary retention (19), urge incontinence (10), urgency/frequency (2), pelvic pain (1). 8 patients had incomplete neurogenic lesions. **Recruitment period:** since Dec 1999. **Mean follow-up:** 11 months (range 2-25 months). **Withdrawals/dropouts:** 1 (IPG damage secondary to MRI)		**Type:** unilateral PNE with permanent lead under local anaesthesia. **Model:** Medtronic 3886 lead **Lead location:** S3 **Confirmation of lead placement:** fluoroscopy or X-rays **Fixation location:** fascia layer **Type of fixation:** no fixation in 4 patients; twist-lock anchor in 20; silicon anchor in 6. **Site of implant:** based on the best sensory response **Duration:** 3-4 weeks ***Specific technical aspects:*** percutaneous positioning of a permanent quadripolar lead. A guide wire is inserted through the needle. The needle is then removed and a permanent lead inserted. **Positivity criterion:** $\geq$50% reduction in main incontinence symptoms	**Type:** unilateral SNS under local (30) or general anaesthesia (2).	**13 PNE** 6 non- responders 4 are still under screening **22 SNS** (19 patients underwent implantation without performing the preliminary test stimulation)	**Efficacy:** **Cured** (>90% improvement)**:** 20/21 **Improved** (50-70% improvement)**:** 1/21 **Safety:** 4 lead displacements (2 when the silicone anchoring was used and 2 when no anchoring was used)

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Weil 2000[87] **Location:** two centres. The Netherlands **Funding:** unclear	**Design:** prospective randomised trial **Patients:** 123 **Diagnosis:** urge incontinence, urinary retention, severe or protracted urgency/frequency in the absence of incontinence **Recruitment period:** from Dec 1992 to Jan 1997 ***Implanted patients:*** **Gender:** M: 4 W: 40 **Mean age:** 43 (range 20-66). **Duration of symptoms:** 9 years (range 2-34) **Previous surgery:** 20/44 (most frequently urethrosuspension or hysterectomy). **Follow-up:** at 6 months (controlled phase of the trial). After evaluation at 6 months stimulation was discontinued for at least 72 hours until regression to baseline symptoms. **Long-term follow-up** all patients completing voiding	**Inclusion:** patients older than 16 years with refractory voiding dysfunction but normal upper urinary tract function, detrusor storage capacity ≥100 ml. **Exclusion:** stress incontinence, multiple sclerosis, Reiter's syndrome, severe or uncontrolled diabetes or diabetes with peripheral nerve involvement, pregnancy, anatomical contraindications to implant of an IPG, spinal cord injury or cerebrovascular accident within the preceding 6 months, active degenerative disc disease, or bleeding complications, moderate to severe ureteral reflux or moderate to severe hydronephrosis, symptomatic urinary tract infection, and pelvic pain of unknown etiology.	**Type:** PNE as described by Dijkema et al., 1993 and Schmidt et al., 1990. **Sacral nerves:** S3 or alternatively S2 or S4. **Needle:** insulated needle **Model:** neurostimulator 3625 Screener, Medtronic **Duration:** 3 days **Positivity criterion:** ≥50% reduction in main incontinent symptoms.	**Type:** SNS under general anaesthesia. **Model:** 3886 PISCES-Quad Lead, Medtronic. 7424 Itrel II, Implantable Pulse Generator, Medtronic. **Lead location:** sacral foramen successfully stimulated during PNE. **Fixation location:** sacral periosteum or bone. **Position of neurostimulator:** lower abdominal pocket. **Stimulation parameters:** *Width:* 210µsec. *Rate:* 15 s^{-1} *Amplitude:* 0.1 V increments.	**123 PNE** 56 failures. 44 patients enrolled in the randomised trial. No information provided on the 23 remaining patients. **44 SNS** **Randomisation:** 21 patients in the implant group and 23 in the control group. Detrusor instability was evident in 6 patients in the control group and in 5 patients in the implant group.	**Efficacy:** **Cured:** 1/16 at 6 months in the implant group and 1/22 in the control group. **Mean incontinence episodes:** from 13.5 (95% CI 10.3 to 16.7) to 1.4 (95% CI 0.0 to 3.2) p<0.0005 **Severity of leakage** (scale 0-3)**:** from 1.6 (95% CI 0.7 to 2.4)to 2.1 (95% CI 1.9 to 2.4) N.S. **Pads usage:** from 8.7 (95% CI 5.8 to 11.6) to 0.7 (95% CI 0.0 to 1.3) p<0.0005 No significant change from baseline in the control group in the mean values of the following outcome measures: mean incontinence episodes 11.2 (95% CI 8.9 to 13.5), severity of leakage 2.1 (95% CI 1.9 to 2.4), and pad usage 6.8 (95% CI 5.2 to 8.5). ***SF-36 quality of life questionnaire (significant results only):*** *Physical functioning score* from 52.1 (95% CI 40.7- 63.5) to 66.6 (95% CI 55.4 to 77.7) p=0.037 for between-group comparison versus controls at 6 months *Standardized physical scale* from 35.8 (95% CI 30.4- 41.3) to 41.6 (95% CI 36.6- 46.5) p=0.019 for within-group comparison versus baseline at 6 months. No significant improvement in the control group versus baseline. **Mean bladder volume at first sensation:** from 92.6 (95% CI 66.6- 118.6) to 167.2 ml (95% CI 59.2 to 275.2) N.S.

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
	diaries at 6-month intervals. **Mean follow-up:** 18 months (6-36). **Withdrawals/dropouts:** 2 patients declined to undergo implantation (one in each group). 4 patients lost at follow-up. 30 patients evaluated at 6 months.					**Mean bladder volume at first contraction:** from 115.8 (95% CI 75.7 to 155.8) to 370.2 ml (95% CI 324.9-415.4) p<0.0005 **Mean bladder volume max fill:** from 265.9 (95% CI 218.0 to 313.8) to 370.2 ml (95% CI 324.9-415.4) p=0.013 Mean values of detrusor pressure were not significantly different at 6 months that at baseline. **Treatment failures:** 13/44 (?) at 36-month follow-up. **Safety:** (42 patients) 1 explant due to intractable pain at implant site 16 pain at implant site in 12 patients (8 surgical revisions) 8 surgical revisions to correct lead migration in 7 patients 7 leg pain 2 leg stimulation 2 bowel function disturbance 1 urinary retention 1 vaginal cramps 1 anal pain 1 skin irritation at implant site

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
Weil 1998[88-90] **Location:** single center. The Netherlands. **Funding:** unclear	**Design:** case series study **Patients:** 36 **Gender:** M: 9 W: 27 **Median age:** 45 (range 23-67) **Diagnosis:** urge incontinence (24), urgency-frequency (6), urinary retention (6). **Duration of symptoms:** 6 years **Previous surgery:** 16 patients had a previous history of at least one operation of the lower urinary tract (e.g. urethrosuspension, urethral dilatation, bladder neck incision, artificial sphincter, clam ileocystoplasty) and/or pelvic surgery (e.g. hysterectomy, herniorraphy, uteropexy, anus dilatation, rectal amputation). **Recruitment period:** Jan 1991 – Mar 1993. **Average follow-up period:** 37.8 months (range 12-60). 19 patients were followed up to 5 years after the implantation.	**Inclusion:** patients with urgency, frequency, urine retention, urge incontinence, and pelvic pain. Urodynamic investigation was performed at baseline and repeated at 6 months after implantation.	**Type:** PNE as described by Dijkema et al., 1993 and Schmidt et al., 1990. **Lead location:** S3 , S2 or S4. **Needle:** insulated needle (Medtronic 041828). **Lead model:** Medtronic 041830 **Stimulation parameters:** *Pulse width:* 210µsec. *Rate:* 15 pps *Amplitude:* 0.5-5 V. **Duration:** 3-5 days **Positivity criterion:** ≥50% reduction in main incontinent symptoms.	**Type:** SNS under general anaesthesia. **Model:** PICE-Quad electrode 3886 or 3080, Medtronic. Lead extension 7495, Medtronic. Itrel I IPG 7421 (15 patients), Itrel II IPG 7424, Medtronic (21 patients). **Lead location:** sacral foramen successfully stimulated during PNE. **Fixation location:** sacral periosteum or bone. **Position of neurostimulator:** lower abdominal pocket. **Stimulation parameters:** *Width:* 210µsec. *Rate:* 15 pps *Amplitude:* 0.5-4 V **Mode of operation:** continuous or cyclic. **Positivity criteria:** good if improvement in baseline symptoms >90%; partial if >50% and <90%, and poor if <50%.	**PNE** number of eligible patients unclear. **36 SNS**	**Efficacy:** **Good success:** 17/36 **Partial success:** 3/36 **Failures:** 16/36 **Frequency:** from 13.7(8.22) to 8.7(15.6) at 6 months p=0.0063 **Major leakage episodes:** from 4.9(8.64) to 1.1(4.2) at 6 months p=0.0039 **Minor leakage episodes:** from 5.1(7.2) to 1.1(4.2) at 6 months p=0.0111 **Minor leakage episodes:** from 5.1(7.2) to 1.3(9) at 6 months p=0.0111 **Pad usage:** from 6.6(6.6) to 2.3(5.4) at 6 months p=0.0011 **Urgency:** from 3.1(1.8) to 3.1(1.2) at 6 months p=0.3911 **Volume voided:** from 158.0(111) to 228.0(157.2) at 6 months p=0.0117 **Bladder capacity:** from 273(187.8) to 187.0(175.8) at 6 months p=0.0108 **Volume at first sensation:** from 101(145.8) to 194(169.2 at 6) months p=0.0025 **Volume at first unstable contraction:** from 114(472.2) to 179(546) at 6 months p=0.0581 **Maximal detrusor pressure at unstable contraction:** from 56(63) to 42(72) at 6 months p=0.3488 **Postvoid residual:** from 110(342) to 66(249) at 6 months p=0.9164

Study id	Design/patients	Inclusion/exclusion criteria	PNE	SNS implanted	No. procedures	Results
						Safety: 12 Removal of IPG due to lack of effect or lack of patient satisfaction regarding the implant. 11 Loss of therapeutic effect 19 lead repositioning 3 lead replacement 4 change Itrel I stimulator with Itrel II 1 change Itrel II stimulator with Itrel III 8 change programme of stimulation in Itrel I 7 repositioning of IPG 2 replacement of extension cable

(b) Abstracts

Study id	Design/ Patients	Inclusion/ exclusion criteria	PNE	SNS	No. procedures	Results
Bristow 1997[91] **Location:** single centre, UK **Funding:** Unclear	**Design:** case series study **Diagnosis:** multiple sclerosis (12), idiopathic detrusor instability (17) **Gender:** multiple sclerosis: M: 4 W: 8 idiopathic detrusor instability: M: 5 W 12 **Mean age:** multiple sclerosis: 43, idiopathic detrusor instability: 44	**Inclusion:** Patients with multiple sclerosis or idiopathic detrusor instability	**Type:** Bipolar pacing electrode inserted under local anaesthetic **Lead location:** S3 foramen **Stimulation parameters:** *Width:* 0.2ms*:* *Amplitude:* patient controlled to produce a tingling sensation Frequency: *25 Hz* **Duration:** max 6 day **Positivity criterion:** 25% increase in capacity at first unstable contraction on cystometry; halving of magnitude of instability on cystometry or ambulatory monitoring; or halving in volume of urge incontinence during ambulatory monitoring	*PNE only*	**17 PNE** of which electrode placement was unsatisfactory in 4.	**Efficacy:** Beneficial outcome in 10 patients with multiple sclerosis and 15 patients with idiopathic detrusor instability. Urge incontinence on cystometry resolved in 1/7 patients with multiple sclerosis and 2/9 patients with idiopathic detrusor instability. On ambulatory monitoring, 5/7 patients with MS and 9/10 with idiopathic detrusor instability became dry

Study id	Design/ Patients	Inclusion/ exclusion criteria	PNE	SNS	No. procedures	Results
Bryan 1999[92] **Location:** single centre, UK **Funding:** None	**Design:** case series study **Patients:** 57 **Diagnosis:** detrusor overactivity (44 -7 neurological cause-), urgency/frequency or detrusor hypofunction (13)	*Not stated*	**Identification of sacral nerves:** bellows contraction of pelvic floor **Lead location:** adjacent to the anterior 3rd sacral root **Duration:** 3 to 4 days **Positivity criterion:** >25% rise in mean volume voided or an increase in the mean volume voided and reduction in subjective leakage/urgency by >50%	*PNE only*	**57 PNE** **10 SNS** or waiting for SNS Many patients required repeat PNE due to electrode slippage. Mean number of tests per patient was 1.72	**Efficacy:** PNE successful in 12 (27.3%) of 44 patients with detrusor over activity, 9 of whom await of have had implant. PNE successful in 1(7.7%) of 13 patients with urgency/frequency or detrusor hypofunction, patient implanted. Urodynamics did not provide additional information **Safety:** Repeat PNE required due to electrode slippage

Study id	Design/ Patients	Inclusion/ exclusion criteria	PNE	SNS	No. procedures	Results
Carabello 2001[93] **Location:** three centres, USA **Funding:** Unclear	**Design:** Case series study **Patients:** 17 **Diagnosis:** refractory urge incontinence (15), pelvic pain (10), urgency/frequency and pain (17), faecal incontinence (2), constipation (5), and diarrhoea (3). **Gender:** M: 2 W: 15 **Mean age:** 60.6 (range 38-81) **Recruitment period:** Electrode implanted Jun 1998 – Dec 1999 **Mean follow-up**: 13.4 months (3-22)	**Inclusion:** Patients with predominantly bladder related symptoms and other pelvic floor disorders.	*Information on PNE not reported*	**Type:** Unilateral sacral foramen electrode **Model:** Interstim, Medtronics **Lead location**: S3 **Stimulation parameters:** *Amplitude:* mean 3.1V (0.7-7.2) Mean number of reprogramming events per patient 9.3 (2-22). Highest mean reprogramming events was for those patients with pelvic pain at 15.8. **Positivity criterion:** Patient perception of improvement: Failure: 0 Mild failure: 25% Moderate: 50% Significant: 75% Cured: >75%	**17 SNS**	**Efficacy:** ***Patients with urge incontinence:*** 3 (20%) failures 11 (73%) markedly improved 1 (6.7%) cured. **Safety:** 3 mild cellulites (resolved) 2 wound dehiscence (resolved) 1 pain secondary to medial migration to the vertebral column (lateral mobilisation of the impulse generator) 1 malfunctioning IPG requiring surgical exchange

Study id	Design/ Patients	Inclusion/ exclusion criteria	PNE	SNS	No. procedures	Results
Das 2002a[94] **Location:** four centres, USA **Funding:** Unclear	**Design:** prospective randomised control study **Patients:** 45 **Diagnosis:** refractory urge incontinence (19), urgency/frequency (19), non-obstructive urinary retention (7) **Gender:** M: 2 W: 43 **Mean age:** 56.8 **Duration of symptoms:** average 13 years	**Inclusion:** Patients with refractory voiding dysfunction	**Type:** Control group: traditional test stimulation with visual observations of motor response. CMAP group: compound muscle action potential testing utilizing a urethral and a rectal sponge electrode. **Positivity criterion:** ≥50% improvement in the appropriate parameter (e.g. number incontinence episodes)	PNE only	**45 PNE** 23 Control group, 22 CMAP group	**Efficacy:** **Successful test stimulation:** *Urge incontinence:* 5/10 (50%) vs 4/9 (43%) (Control vs CMAP) *Urgency/frequency:* 4/9 (43%) vs 0/10 (0%) (Control vs CMAP) **Mean leaks:** *Control:* 7.2 baseline, 3.8 PNE *CMAP:* 8.5 baseline, 3.5 PNE **Number of voids:** *Control:*12.8 baseline, 8.5 PNE *CMAP:* 17.7 baseline, 12.3 PNE No statistically significant differences noted
Das 2002b[95] **Location:** Patient data from the Medtronic MDT-103 post market study **Funding:** Unclear	**Design:** comparative study **Patients:** 31 patients who underwent upper buttock placement (UBP) of IPG, 225 patients who underwent abdominal placement (AP) of IPG **Gender:** Upper buttock placement: M: 4 W: 27 Abdominal placement: M: 28 W: 197 **Mean age:** Upper buttock placement: 45.0 (10.3), Abdominal placement: 47.1 (11.3) **Mean follow-up**: 26 months (range 15-46)	*Not stated*	*Information on PNE not reported*	**Position of neurostimulator:** upper buttock or lower abdomen	**256 SNS**	**Efficacy:** Efficacy rates were similar in both groups **Safety:** ***Upper buttock placement vs abdominal placement*** **Pain at IPG site or infection:** No. events: 5/31 vs 95/225 (p=0.005). No. surgical interventions: 1/31 vs 62/225 (p=0.003) **All adverse events:** No. events: 31/31 vs 378/225 (p=ns). No. surgical interventions: 8/31 vs 174/225 (p=ns) Probability at 12 months of revision surgery: upper buttock placement 7.9%, Abdominal placement 19.8%.

Study id	Design/ Patients	Inclusion/ exclusion criteria	PNE	SNS	No. procedures	Results
Dijkema 1994[96,97] **Location:** single centre, The Netherlands **Funding:** Unclear	**Design:** case series study **Patients:** 25 **Follow-up**: ≥6 months (>18 months for 17)	**Inclusion:** Patients with urge incontinence	**Positivity criterion:** therapeutic efficacy	**Model:** Itrel pulse generator with Pisces Quad lead (Medtronic)	**25 SNS** (patients with successful PNE)	**Efficacy:** 6 months: 10 complete relief, 10 substantial improvement 18 months: 6 complete cure, 5 partially improved 2 failed primarily, 5 relapsed but in 1 complete response regained after replacement of lead to another sacral foramen. **Pads usage:** 6.1 to 2.5 ($p<0.001$) **Voiding volumes:** 158 ml to 220 ml ($p<0.001$) **Times of urine loss:** 8.5 to 2.7 per day ($p<0.001$) **Detrusor instability:** cured in 6/17, in other 11 first unstable contraction increased from 112 ml to 182 ml ($p<0.05$) **Cystometric capacity:** 182ml to 291 ml ($p<0.001$) **First desire to void:** 104 ml to 211 ml ($p<0.001$) Ambulatory measurements not significantly different

Study id	Design/ Patients	Inclusion/ exclusion criteria	PNE	SNS	No. procedures	Results
Everaert 2002[98] **Location:** single centre, Belgium **Funding:** Unclear	**Design:** randomised controlled trial **Patients:** 22 **Diagnosis:** urge incontinence (12), urgency/frequency (10) **Gender:** M: 0 W: 22 **Mean age:** 1-stage implant: 47±13 2-stage implant: 49±18 **Recruitment period:** Oct 2000 to Jan 2002 **Follow-up**: 3 and 12 months	**Inclusion:** Women with overactive bladder symptoms	**Duration:** 4-7 days **Positivity criterion:** >50% improvement in incontinence (pad weight – urge incontinence) or functional bladder capacity (urgency/frequency or urge incontinence)	**Type:** 1-stage vs 2-stage implant **Model:** sacral (s3) foramen lead (model 3080) and pulse generator (Interstim) **Specific technical aspects:** 2-stage implant evaluated during 3-5 weeks	**22 SNS** (patients with successful PNE) randomised according to symptoms and age: 11 1-stage implant (6 urge incontinence, 5 urgency/ frequency), 11 2-stage implant (6 urge incontinence, 5urgency/frequency)	**Efficacy:** ***Subjective improvement on a VAS bladder symptoms*** At 3 months 4 patients have <50% subjective improvement (1 1-stage, 3 2-stage). At 12 months all 11 patients had a >50% subjective improvement. **1-stage vs 2-stage implant:** Baseline: 11(9) vs 16(15) PNE: 81(13)* vs 72(16)* Stage 2: - vs 70(12)* 3 months: 72(21)* vs 62(30)* 12 months: 79±19* vs 70(12)* (*p<0.0001 vs baseline) No significant difference between 1-stafe and 2-stage. Lower subjective improvement seen at 3 months compared to PNE or 12 months for all patients (p=0.048) **Objective improvement** At 3 months, lack in objective improvement of >50% was seen in 3/12 urge incontinence and 3/10 urgency/frequency patients. At 12 months this was 1/5 and 2/6 respectively. **Functional bladder capacity (1-stage vs 2-stage):** Baseline: 162(83) vs 122(84) PNE: 238(58)* vs 192(76)** Stage 2: - vs 223(106)** 3 months: 254(114)* vs 194(101)** 12 months: 249(147) vs 294(110)** (*p<0.05 vs baseline, **p<0.01 vs baseline)

Study id	Design/ Patients	Inclusion/ exclusion criteria	PNE	SNS	No. procedures	Results
						Frequency (1-stage vs 2-stage): Baseline: 10(5) vs 9(4) PNE: 6(1)** vs 9(5) Stage 2: - vs 7(2) 3 months: 6(1)* vs 7(2)* 12 months: 7(5) vs 6(2)** (*p<0.05 vs baseline, **p<0.01 vs baseline) **Leakage episodes (1-stage vs 2-stage):** Baseline: 2(0-5) vs 2(0-5) PNE: 0(0-0)* vs 1(0-3) Stage 2: - vs 0(0-1)* 3 months: 0(0-1) vs 0(0-1) 12 months: 0(0-0) vs 0(0-0) (*p<0.05 vs baseline) **Pad weight (1-stage vs 2-stage):** Baseline: 17(0-15) vs 88(0-128) PNE: 0(0-0)* vs 1(0-103) Stage 2: - vs 0(0-14) 3 months: 0(0-1)* vs 0(0-95) 12 months: 0(0-0) vs 0(0-0) (*p<0.05 vs baseline) No significant differences were found between 1-stage and 2-stage procedure

Study id	Design/ Patients	Inclusion/ exclusion criteria	PNE	SNS	No. procedures	Results
Groenendijk 2002a[99] **Location:** MDT-103 population **Funding:** Unclear (one author Medtronic)	**Design:** case series study **Patients:** 111 **Diagnosis:** sensory urge incontinence (44), motor urge incontinence (67) **Follow-up**: 6 months **Withdrawals/dropouts:** 6 patients with sensory urge incontinence and 6 patients with motor urge incontinence exited study prior to 6 month follow-up and some patients had missing data.	**Inclusion:** MDT-103 population	**Positivity criterion:** >50% improvement in urge incontinence behaviour	**Positivity criterion:** ≥50% improvement in primary voiding diary parameters	**111 SNS** (Patients with successful PNE) Complete data available for 26 sensory urge incontinence patients and 39 motor urge incontinence.	**Efficacy:** **Bladder volumes at first sensation of fullness and max fill prior to void:** statistical improvement for both sensory and motor urge incontinence compared to baseline. 50% motor urge incontinence patients achieved stable bladder at follow-up but were not clinically more successful than those who kept bladder instability (P=0.73). **Clinical benefit:** 55/84 patients. (Sensory urge incontinence: 22/30, motor urge incontinence: 33/54)
Groenendijk 2002b[100] **Location:** single centre, The Netherlands **Funding:** Unclear	**Design:** case series study **Patients:** 19 **Diagnosis:** refractory urge incontinence (15), urgency/frequency (4) Of these: 9 bladder instability, 16 type III (>31cm H_2O) urethral instability, 2 type II (16-30cm H_2O) urethral instability, 1 no urethral instability **Gender:** M: 0 W: 19 **Follow-up**: 6 months	**Inclusion:** Patients with refractory micturition symptoms	**Positivity criterion:** >50% improvement in main symptoms	**Model:** Neurostimulator (Medtronic) **Positivity criterion:** >50% improvement	**19 SNS** (Patients with successful PNE)	**Efficacy:** **Successful:** 13 patients (68%), 4 patients <50% improvement, 2 underwent device explant. All patients had urethral instability at baseline, bladder instability present in 4. Urethral instability decreased or disappeared in 9, bladder instability disappeared in 2 **First sensation of fullness:** from 98 to 235 ml (p=0.002) (n=17)

Study id	Design/ Patients	Inclusion/ exclusion criteria	PNE	SNS	No. procedures	Results
Heesakkers 2003[101-104] **Location:** 16 sites worldwide **Funding:** Unclear	**Design:** case series study **Diagnosis:** urge incontinence (126), urgency/frequency (74), urinary retention (59) **Mean follow-up**: min 12 months. Urge incontinence: 45(16) months, urgency/frequency: 35(12) months	*Not stated*	*Information on PNE not reported*	**Type:** Interstim implant **Clinical success** urge incontinence: >50% reduction in leaks/day. Urgency/frequency: increased volume voided per void with a corresponding sense of urgency	***Urge incontinence*** **126 SNS**, 105 analysed as reached min follow-up ***Urgency/ frequency*** **74 SNS**, 57 analysed as reached min follow-up	**Efficacy:** ***Urge incontinence*** 14/105 explanted due to adverse events or lack of efficacy **Leaking episodes/day**: 10.9 to 4.3 (p<0.0001) **Severity of leaks:** 97/105 experienced heavy leaks at baseline, 65 of these (67%) had ≥50% improvement or heavy or moderate leaks. **Pad use/day:** Of 96 patients using pads at baseline, 61 (64%) had a reduction of >50% in pad replacement **Clinical success:** 6 months: 67% (n=86) 12 months: 72% (n=93) 18 months: 61% (n=66) 24 months: 59% (n=81) 36 months: 54% (n=71) 48 months: 55% (n=58) 60 months: 63% (n=43) **Urgency/frequency** 10 patients explanted or exited the study due to lack of efficacy or an adverse event **Voids/day**: 17(8) to 11(6) (p<0.0001) **Voided volume/void (ml):** 117(79) to 204(144) (p<0.001). **Max void volume:** 315(208) to 462(246) (p<0.0001). 48% experienced a reduction of ≥50% in number of voids per day, 53% had an increase of >50% in volume voided per void

Study id	Design/ Patients	Inclusion/ exclusion criteria	PNE	SNS	No. procedures	Results
						Degree of urgency (0 none – 3 severe)**:** 2.2(0.6) to 1.9(0.7) (p=0.002). **Clinical success:** 41 (73%) of patients Of the 20 patients who also had urge incontinence at baseline, reduction in number of moderate or heavy leaks per: 1.1(1.8) to 0.2(0.1) (p<0.02). Severity of leaks (4 point scale): 1.3(0.5) to 0.6(0.5) (p=0.001). Pad use: 2.1(2.9) to 0.3(0.6) (p=0.01)

Study id	Design/ Patients	Inclusion/ exclusion criteria	PNE	SNS	No. procedures	Results
Kiss 2002[105] **Location:** single centre Austria **Funding:** unclear	**Design:** case series study **Patients:** 13 **Diagnosis:** urge incontinence (6), chronic urinary retention (7)	*Not stated*	**Type:** Permanent electrodes were used for PNE testing and implanted bilaterally, stimulating uni- and/or bilaterally **Model:** External dual stimulator (Medtronic) **Lead location:** S3 bilaterally **Duration:** 5-7 days **Positivity criterion:** ≥50% improvement according to the micturition protocol	**Type:** Stimulator implanted and connected to the already positioned electrodes Model: In patients responding to bilateral stimulation only: 2 implanted with a Synergy-IPG which stimulates the roots on both sides separately, 2 stimulated bilaterally via a Y-connector **Sacral incision:** small	**13 PNE** **12 SNS** (IPG implanted) 1 woman with severe spinal hyperreflexia showed no effect with PNE and permanent electrodes removed	**Efficacy:** PNE positive in 12/13 patients (7 also showed response with urodynamics), IPG implanted in these patients. 4 patients (3 urinary retention, 1 urge incontinence) PNE successful only with bilateral stimulation.

Study id	Design/ Patients	Inclusion/ exclusion criteria	PNE	SNS	No. procedures	Results
Koldewijn 1999[106] **Location:** two centres, The Netherlands **Funding:** unclear	**Design:** case series study **Patients:** 40 Diagnosis: urge incontinence (28), detrusor hypoactivity (12) **Gender:** M: 2 W: 38 **Mean age:** 40 (range 21-58) **Duration of symptoms:** mean 5 years **Recruitment period:** Nov 1994 - Jun 1998 **Mean follow-up:** 29 months (5-46)	**Inclusion:** Patients unsuccessfully treated by several other conservative and surgical treatment options	**Positivity criterion:** >50% improvement	**Model:** Medtronic sacral nerve stimulator system	**40 SNS** (patients with successful PNE)	**Efficacy:** **Improvement:** 64% urge incontinence patients stopped using pads, 25% had <50% improvement 58% detrusor hypoactivity group stopped using ICC, in remainder ≥1 ICC necessary per day **Safety:** **Operation time:** mean 133 min (60-225) **Hospital stay:** 1-5 days No major or minor hospital morbidity 36 re-operations in 20 (50%) patients (2 in 11, 3 in 5): 4 explantation due to infection, 3 explantation due to failure 8 replacement of IPG due to pain 18 refixation of lead 2 lead replacement (breakage) 1 re-implantation after infection.

Study id	Design/ Patients	Inclusion/ exclusion criteria	PNE	SNS	No. procedures	Results
Light 1992[107] **Location:** single centre, USA **Funding:** unclear	**Design:** case series study **Patients:** 17 **Diagnosis:** detrusor hyperreflexia (9) idiopathic detrusor instability (8) **Gender:** M: 2 W: 15 **Mean age:** 52 (range 30-80) **Follow-up**: range 10-24 months	**Inclusion:** Patients with urodynamically proven detrusor instability, non-responsive to maximum pharmacological therapy	**Type:** Continuous stimulation with percutaneous wire electrodes **Identification of sacral nerves** (for lead location)**:** **Lead location:** *S3* **Duration:** 2-6 days **Positivity criterion:** improved significantly on basis of voiding diary comparisons	**Type:** Urosystems, Inc. Protocol USI-101 **Model:** Medtronic PISCES-Quad lead electrode, ITREL IPG **Stimulation parameters:** each patients required multiple adjustments of the stimulation parameters, best results obtained with stimulus just above sensory threshold	**17 acute PNE** **14 subacute PNE** **5 SNS**	**Efficacy:** 6/14 subacute PNE patients improved significantly 4 SNS patients obtained significant symptomatic improvements, total failure occurred in 1 patient **Safety:** Migration of implanted electrode occurred in 1 patient and required surgical repositioning. No device infections.

Study id	Design/ Patients	Inclusion/ exclusion criteria	PNE	SNS	No. procedures	Results
Oliver 2001[108-110] **Location:** single centre, UK **Funding:** unclear	**Design:** case series study **Patients:** 10 **Diagnosis:** overactive bladder (10)	**Inclusion:** Patients with overactive bladder	**Type:** temporary S3 neuoromodulation **Lead location:** S3 **Duration:** 7 days	*PNE only*	10 PNE	**Efficacy:** 6/10 tests invalid due to technical difficulties **Bladder volume at each urge score:** 2/4 patients had a good acute response **Improvement:** 2/4 had improvement in symptoms
Peters 2002[111] **Location:** single centre, USA **Funding:** unclear	**Design:** case series study **Patients:** 30 **Diagnosis:** urge incontinence (7), retention (2), interstitial cystitis (21)		**Type:** temporary electrode or staged technique using a permanent implant. **Duration:** temporary electrode: 5-7 days, permanent electrode: 2 weeks	*Information on SNS not given*	**30 PNE with temporary electrode** **16 PNE with permanent electrode**	**Efficacy:** ***Temporary electrode*** 15/30 positive, 12/15 implanted, overall test to implant rate 40% Permanent electrode 14/16 positive, 14/14 implanted, overall test to implant rate 88% **Safety:** 4 reoperations required: 3 lead adjustment due to sensory discomfort 1 revise generator pocket No infections, no adverse events, no units explanted

Study id	Design/ Patients	Inclusion/ exclusion criteria	PNE	SNS	No. procedures	Results
Ruffion 2003[112] **Location:** single centre, France **Funding:** Unclear	**Design:** case series study **Patients:** 166 **Diagnosis:** urge incontinence (88), urinary retention (56), chronic pelvic pain (22) **Gender:** M: 66 W: 100 **Mean age:** 48.8 (range 16-77) **Recruitment period:** May 1995 – May 2002 **Median follow-up**: 37 months (3-87)	*Not stated*	**Type:** sacral root neuromodulation tests **Positivity criterion:** strongly positive (complete resolution of urinary symptoms)	**Type:** Sacral neuromodulator implantation	***188* PNE** on 166 patients (1 in 149 patients, 2 in 14 patients, 3 in 2 patients, and 4 in 1 patient) **33 SNS** (4 of the positive PNE patients chose a different procedure)	**Efficacy:** Positive PNE in 37/166 (22.3%) patients: 19/88 (21.5%) urge incontinence, 13/56 (23%) urinary retention, 5/22 (22.7%) chronic pelvic pain. Neuromodulation functional in 28/32 (88%) patients at follow-up **Safety:** Repeat PNE required in 7 patients Explantation performed in 4/32 (12%) patients: 1 intractable local pain, 1 infection, 1 inefficiency, 1 pregnancy (although implant functional)
Ruiz-Cerda 2003[113] **Location:** GENS group (6 centres), Spain **Funding:** unclear	**Design:** case register **Patients:** 204 **Diagnosis:** urge incontinence (89), non-obstructive urinary retention (50), urgency/frequency (46), mixed symptoms (19) **Gender:** M: 35 W: 139 **Mean age:** 47 (range 15-81) **Mean follow-up**: 6.8 months (range 2-30)	*Not stated*	**Positivity criterion:** improvement in voiding diary during temporary stimulation >50%	**Type:** Definitive implant	**263 PNE** on 204 patients (1 in 157 patients, 2 in 37 patients, 3) in 10 patients **69 SNS**	**Efficacy:** Positive PNE in 69/204 (34%) patients: 25/89 (28%) urge incontinence, 16/50 (32%) urinary retention, 19/46 (41%) urgency/frequency, 9/19 (47%) mixed. ***Urge incontinence*** **Episodes per day:** 4.5 to 0.8 ($p<0.02$), 66% patients >50% improvement, 55% dry ***Urgency/frequency*** **Daytime frequency:** 15.3 to 6.6 ($p<0.04$), 58% patients >50% improvement, frequency <7 in 52% **Bedtime frequency:** 5.7 to 1.5 ($p<0.03$), 66% patients >50% improvement, frequency =1 in 46% **Safety:** 1 explantation due to psychological rejection 3 lead foramen location changed 1 IPG relocated 20 minor complaints (seroma, electro induced pain, constipation and anal fissure)

Study id	Design/ Patients	Inclusion/ exclusion criteria	PNE	SNS	No. procedures	Results
Spinelli 2002[114] **Location:** single centre; Italy **Funding:** Unclear	**Design:** case series study **Patients:** 9 consecutive **Diagnosis:** urinary retention (4 (2 neurogenic)), urge incontinence (5 (1 neurogenic)) **Gender:** M: 3 W: 6 **Mean age:** 34 (range 27-56) **Recruitment period:** Sept 01 onwards **Mean follow-up:** 5 months		**Type:** two-stage SNS using tined lead implanted under local anaesthesia **Model:** tined lead, with introducer kit **Duration:** 12-36 days	*Information on SNS not given*	**9 PNE** (first stage SNS) **6 SNS** (second stage SNS)	**Efficacy:** 2 improvement <50% and lead removed 1 in screening phase Continence restored in 3/3 patients with urge incontinence at SNS **Safety:** No displacement of lead

Study id	Design/ Patients	Inclusion/ exclusion criteria	PNE	SNS	No. procedures	Results
Thon 1992[115] **Location:** European Study Group (7 centres), Germany and The Netherlands **Funding:** unclear	**Design:** case series study **Patients and diagnosis:** 114 patients, mostly with combined voiding dysfunction: urge incontinence due to detrusor instability (71%), urgency/frequency (78%), and/or pain (68%) **Recruitment period:** Up to Aug 1991 **Mean follow-up**: 4.2 months (1-12).Urodynamics at 6 months	**Inclusion:** Patients with non-neurogenic voiding dysfunctions such as urgency, frequency, pathological flow patterns, retention and urinary incontinence secondary to detrusor and/or urethral instability.	**Type:** Percutaneous acute and temporary stimulation testing	**Model:** Sacral foramen electrode and an impulse generator (Medtronic inc)	**41 SNS** (patients with successful PNE)	**Efficacy:** **Subjective improvement:** 90% of patients. Symptom scores showed significant improvement **Urodynamics** (urge incontinence patients (n=36))**:** only volume at first sense changed significantly: 10ml to 195ml ($p<0.05$). Patients with detrusor instability: unstable contractions partially or totally suppressed in 62%, no change or deterioration in 38% Patients with voiding dysfunctions (n=26): pressure and flow parameters did not differ significantly. **Safety:** 22 (54%) complications: 64% device related, 36% surgical origin. Most associated with electrode migration or badly positioned electrodes. Reoperation rate: 32%
Weil 1996[116] **Location:** single centre, The Netherlands **Funding: u**nclear	**Design:** randomised controlled trial **Patients & diagnosis:** 18 patients: in SNS arm of study 5 urge incontinence, 3 urinary retention, 1 urgency/frequency **Follow-up**: 6 months	**Inclusion:** Patients with a long history of refractory urgency/frequency, urge incontinence or urinary retention **Exclusion:** Spinal or cerebral disease and elongated evoked responses	**Duration:** 4-5 days **Positivity criterion:** >50% improvement	**Type:** direct definitive implant	18 patients with successful PNE included in study: **9 SNS**; 9 delayed SNS with conservative treatment of pelvic floor exercises, external vaginal stimulation or medication for 6 months	**Efficacy:** ***Conservative arm*** None of the patients improved ***Treatment arm*** All 9 patients showed considerable improvement 5 patients with urge incontinence had reduced leaks/day and pads/day 4/6 patients with unstable bladder showed no bladder instability at follow-up

Study id	Design/ Patients	Inclusion/ exclusion criteria	PNE	SNS	No. procedures	Results
Winters 2003[117] **Location:** single centre, USA **Funding:** institutional	**Design:** case series study **Patients:** 12 **Diagnosis:** refractory detrusor instability (7), non-obstructive urinary retention (4), interstitial cystitis (1). **Gender:** M: 3 W: 9 **Mean age:** 44.9 (28-67)	*Not stated*	*Information on PNE not reported*	**Type:** Interstim (Medtronic) implantation **Positivity criterion:** >50% reduction in symptoms by voiding diary, and/or resumption of voiding	**12 SNS**	**Efficacy:** 10/12 (83%) implant successful, 2/12 patients did not have a satisfactory result. **Detrusor instability (n=7):** 4 no change in urodynamic findings, 3 increase in cystometric capacity, 2 decrease in amplitude of unstable bladder contractions. **Interstisial cystitis (n=1):** mild improvement in sensory urgency, no increase in cystometric capacity *In many patients, subjective improvement in symptoms was not associated with an improvement in urodynamic findings*
Zermann 2001[118] **Location:** three centres, Germany, Japan and USA **Funding:** unclear	**Design:** case series study **Patients:** 81	*Not stated*	**Type:** temporary uni- and bilateral SNS **Duration:** mean 8.4 days	*PNE only*	**81 PNE**	**Efficacy:** 65/81 (80.2%) tested successfully. 71.6% of all patients benefited from unilateral stimulation, 8.6% needed bilateral stimulation: ***Urge incontinence*** 42.1% success vs 63.2% (uni vs bilateral)

APPENDIX 8 List of identified papers in non-English language

Czech:

Dolezel J, Cejpek P, Miklanek D. [Sacral deafferentation and neurostimulation of anterior spinal roots in the treatment of neurogenic bladder in patients with complete transverse spinal lesions--initial clinical experience]. Rozhl Chir 2002;81(4):203-9.

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