SACRAL NERVE STIMULATION FOR REFRACTORY URINARY URGE INCONTINENCE OR URINARY RETENTION

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MSAC application 1009

Assessment report

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The Medicare Services Advisory Committee is an independent committee which has been established to provide advice to the Commonwealth Minister for Health and Aged Care on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform Government decisions about which medical services should attract funding under Medicare.

This report was prepared by the Medicare Services Advisory Committee (MSAC) with the assistance of Ms Elizabeth Burrows from the Centre for Clinical Effectiveness, Monash Institute of Public Health and Health Services Research, and Mr Anthony Harris and Ms Elena Gospodarevskaya from the Health Economics Unit, Monash University. The report was endorsed by the Commonwealth Minister for Health and Aged Care on 6 March 2000.

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MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

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The therapy is based on the observation that electrical stimulation of sacral nerves can influence bladder, sphincter and pelvic floor behaviour. The mode of action has not been fully elucidated but is probably through restoration of the correct balance between excitatory and inhibitory impulses from and to the pelvic organs at a sacral and supra-sacral level (Bemelmans et al 1999).

Medicare Services Advisory Committee—role and approach

The Medicare Services Advisory Committee (MSAC) is a key element of a measure taken by the Commonwealth Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health and Aged Care on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of the available evidence is thus the basis of decision-making when funding is sought under Medicare. The medical literature available on the technology is searched and the evidence assessed and classified according to the National Health and Medical Research Council (NHMRC) four-point hierarchy of evidence (NHMRC 1999). A supporting committee with expertise in this area then evaluates the evidence and provides advice to MSAC.

MSAC's assessment of sacral nerve stimulation for refractory urinary urge incontinence or retention

MSAC's assessment is based primarily on two randomised controlled trials (RCTs) (NHMRC Level II): one on patients with urge incontinence and the other on patients with urinary retention. However, another 17 studies which were uncontrolled case series comparing the clinical symptoms of patients and before and after implantation (NHMRC Level IV) and a patient satisfaction survey were also included in the assessment.

Clinical need

Urinary frequency, urgency and urge incontinence impact negatively on patients' physical, social and emotional well-being (Lenderking et al 1996) and are costly to both the individual and society (Dowell et al 1999). While urinary incontinence affects both women and men, over 85 per cent of sufferers are women aged between 30 and 59.

Most patients can be treated successfully with conservative therapy (drug therapy, bladder training, pelvic floor muscle exercise, and external electrical stimulation), but a small percentage of patients do not respond to, or cannot tolerate, these treatments and must manage their incontinence with catheterisation or absorbent pads. Treatments available to these patients are sacral nerve stimulator implantation, which is reversible, and more invasive and often irreversible surgical procedures such as bladder muscle transection, bladder reconstruction and urinary diversion.

Up to 200 Australian patients per year are expected to be candidates for a sacral nerve stimulator implant (SNSI).

Safety

There is a relatively high incidence of adverse events associated with sacral nerve stimulator implants. More than half of the permanent implant patients (51.6%) experienced an adverse event (NNH=2) based on the pooled results of the RCTs of patients with urge incontinence and urinary retention. Among the 10 studies that reported complications, one in three patients required further surgery and in 9 per cent of cases the device had to be removed (NNH=11). The most commonly reported adverse events and reasons for revision surgery were pain at the pulse generator or lead implant site and lead migration.

MSAC noted that the SNSI procedure is complex, and the experience and skill of the service provider have a significant impact on the success of the procedure and the related adverse events. There have been technical refinements to the device and operative procedure which the manufacturers claim are reducing the incidence of the most common adverse effects and causes of re-operation. The risks associated with SNSI also need to be balanced against the fact that it is indicated only for patients who have not responded to, or not tolerated, other available pharmacological and physiological interventions. The available operative alternatives are more invasive, may also require revision and, unlike SNSI, are usually not reversible if unsuccessful.

Effectiveness

The best available evidence is provided by two RCTs, both of which have methodological deficiencies which limit the strength of their results. On the basis of this evidence, sacral nerve stimulation appears to have treatment benefits for female patients with urge incontinence in terms of reducing the incidence of urinary incontinence, reducing pad consumption, and regaining of bladder control. The reported durability of the response is 18 months (Schmidt et al 1999) to at least five years post-implant (a and Groen 1997a). For patients with urinary retention, treatment benefits have been seen at six months follow-up in the majority of patients in eliminating or reducing catheterisation use and improving voiding parameters. The reported durability of response in this group

is 18 months (Siegel, in press). Evidence from the case series is of lower quality as there is increased potential for bias in the results, but it supports the findings of the RCTs.

The impact on the quality of life of patients is uncertain. Many of the quality-of-life measurements performed did not demonstrate a significant improvement in the quality of life of patients undergoing sacral nerve stimulation, and the results of the Medtronic patient satisfaction survey do not lend themselves to generalisation due to the low response rate (34 patients of whom 24 had implants for urge incontinence or retention). However, the patients surveyed did report significant improvements in their ability to perform certain physical activities, their feelings of self-esteem and their satisfaction with overall health and quality of life. Approximately two-thirds were satisfied with their implant.

Cost-effectiveness

Sacral nerve stimulation has an estimated cost per patient of approximately $11,000 over six months**.** These costs include the device, medical treatment and re-surgery costs arising from complications for both indications.

The cost saving in appliances and laundry per patient is between $277.70 and $574.20 for urge incontinence and approximately $245 for urinary retention, over six months. It is not possible to project costs and cost savings over a longer period because of the lack of available data.

The indicative cost-effectiveness ratio for sacral nerve stimulation treatment for urge incontinence is estimated to be approximately $35,000 per additional patient free of incontinence at six months follow-up. However there are a number of areas of uncertainty in the data available that need further clarification for a more complete cost-effectiveness analysis to be done.

For the small number of patients who undergo the major alternative procedures (bladder reconstruction or urinary diversion) costs are also high: $4,822 for public hospital treatment in patients without complications and $9,448 for those with catastrophic or severe complications.

Other considerations

MSAC noted that obtaining high level data on this procedure is problematic as it is difficult to randomise these patients to other interventions. Pre/post studies using delayed treatments may be the best option for collecting data. For a quality of life study, a condition-specific measure such as the Urinary Distress Inventory (UDI-6) may be more appropriate than a generic measure to assess or track current symptom distress in incontinent patients (Dugan et al 1998).

Further research is required on the results of recent refinements to the device and procedure, in particular the impact on safety, long-term effectiveness and quality of life.

Recommendation

MSAC found that, on the strength of the evidence pertaining to sacral nerve stimulation:

- the intervention is associated with a relatively high rate of adverse events (NNH=2);
- the long-term effectiveness is uncertain; and
- the cost-effectiveness ratios associated with the intervention are unfavourable.

MSAC therefore recommended that public funding for sacral nerve stimulator implantation should not be supported at this time.

Introduction

The Medicare Services Advisory Committee (MSAC) has reviewed the use of the sacral nerve stimulation for the treatment of refractory urinary urge incontinence or urinary retention. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer affairs and health administration.

This report summarises the assessment of current evidence for sacral nerve stimulation for the treatment of refractory urinary urge incontinence or urinary retention.

Background

The procedure

Sacral nerve stimulation for the treatment of refractory urinary urge incontinence or urinary retention involves the application of electrical stimulation to the sacral nerve via a totally implantable system which consists of an electrode placed extradurally close to the third sacral nerve (S3), an implantable pulse generator (IPG) and an extension which connects the lead to the pulse generator.

The therapy is based on the observation that electrical stimulation of sacral nerves can influence bladder, sphincter and pelvic floor behaviour. The mode of action has not been fully elucidated but is probably through restoration of the correct balance between excitatory and inhibitory impulses from and to the pelvic organs at a sacral and supra-sacral level (Bemelmans et al 1999).

The procedure is carried out in three phases:

- Phase I—'acute phase': a percutaneous test stimulation is performed via a temporary electrode. The electrode is inserted through the skin of the lower back and into the S3 sacral foramen. Small electrical pulses from an external pulse generator are used to test for a satisfactory response and identify the optimal location for the electrode. The procedure is usually done in an operating theatre, with the patient conscious so he or she can identify where the test stimulation is felt. The procedure can take up to one hour and the patient is usually observed overnight;

- Phase II—'subchronic phase': the subchronic test is conducted by connecting the temporary electrode to an external pulse generator, over a period of 3–5 days. During this time, the maximum comfortable level of stimulation is identified and maintained, as well as a comprehensive record of symptoms and voiding function; and

- Phase III—'permanent implantation phase': patients who have demonstrated improvement of at least two major symptoms by greater than 50 per cent are considered for permanent implantation of the sacral nerve pulse generator and electrode. The major symptoms or associated measures of voiding function are urinary frequency and urgency, voided volumes, and episodes and volumes of urinary incontinence.

Phases I and II are referred to as percutaneous nerve evaluation (PNE). The proportion of patients eligible for permanent implantation is approximately 50 per cent. The procedure is usually conducted under general anaesthetic and takes 2–2½ hours. It involves up to three incisions: one over the lower back to insert the lead into the selected sacral foramen, place it near the appropriate sacral nerve and anchor it; one in the lower abdomen or upper buttock to create a subcutaneous pocket for placement of the IPG; and a small flank incision to allow connection of the ends of the lead and extension, which the surgeon has tunnelled under the skin from the lead and IPG sites. The

procedure is normally performed by a urologist or urogynaecologist with training in test stimulation and implantation.

The patient remains hospitalised for 4–5 days after the operation, during which time the IPG stimulation settings are adjusted and the patient is instructed in the control of the device.

Intended purpose

Sacral nerve stimulation is indicated for the treatment of refractory urinary urge incontinence or urinary retention. It is also used for the treatment of intractable chronic pelvic pain, but this indication was not included in the application to MSAC and has not been assessed.

Sacral nerve stimulation is intended for use as a second-line treatment for those in whom conservative treatment (ie drug therapy, bladder training, pelvic floor muscle exercise, and external electrical stimulation) has failed. The procedure is an alternative to more invasive surgery, which is considered to be unsuitable for most of these patients.

Clinical need/burden of disease

Urge incontinence is involuntary urinary leakage preceded by a sudden desire to void. This condition is frequently caused by instability of the lower urinary tract where there is involuntary contraction of the bladder resulting in urinary leakage. In the majority of patients there is no obvious underlying cause (idiopathic), although an unstable bladder can be secondary to neurological abnormalities, for example multiple sclerosis (MS), outlet obstruction or urinary tract infection. While urinary incontinence affects both women and men, over 85 per cent of sufferers are women aged between 30 and 59. The prevalence could be as high as 59 per cent in women over 75 years of age.

Urinary frequency, urgency and urge incontinence have been shown to impact negatively on patients' physical, social and emotional well-being (Lenderking et al 1996). A study by Dugan et al (1998) of 435 incontinent adults aged 60 years and older found that quality of life as measured by the Urinary Distress Inventory (UDI-6) and Incontinence Impact Questionnaire was particularly affected in those who are younger and those with the most urine leakage per incident. Urinary incontinence is also costly to both the individual and society. A recent Australian study by Dowell et al (1999) in community-dwelling ambulatory women found that the median total direct (personal and treatment) incontinence cost was $12.89 ($5.26–22.67) per week. This cost was significantly correlated with the number and volume of urine leaks and a measure of the impact of leakage on lifestyle.

Up to 200 Australian patients per year are expected to be candidates for a sacral nerve implant. This is the manufacturer's estimate based on current experience that about 2 per cent of patients attending a major urology clinic are suitable for the procedure—that is, do not benefit from conservative treatment and have a satisfactory response on test stimulation. As there are about 20 urogynaecologists and urologists in Australia who can provide such a service, and expert advice is that they would have an average of 10 suitable patients each per year, the annual utilisation of the procedure could be up to 200.

On the basis of the trial and demographic data, the majority of patients are expected to be in the 35 to 60 year age group.

Existing procedures

The current clinical management includes conservative treatment with anticholinergic drugs, intermittent catheterisation, and pelvic muscle exercise. In addition, electrical stimulation of pelvic floor muscles, the detrusor muscle, pelvic nerves, spinal cord or sacral nerves has been used in an effort to identify the most effective way of achieving bladder control. The other treatments available are more invasive and often irreversible surgical procedures; for example, intravesical instillation of capsaicin, bladder muscle transection, bladder reconstruction and urinary diversion.

Comparator

The appropriate comparator for sacral nerve stimulation is standard clinical management—that is, best supportive care—for patients who have not benefited from conservative treatment and are managing their urinary condition with catheterisation or absorbent pads. The more invasive surgical procedures specified above were not used as comparators because expert advice indicated that only a small number of this patient group would be eligible for them.

Marketing status of the device/technology

The Medtronic Itrel® I and Itrel® II pulse generators and sterile electrodes (leads) are currently registered and listed, respectively, on the Australian Register of Therapeutic Goods.

The US Food and Drug Administration (FDA) granted approval for the Medtronic InterStim® System for Urinary Control 'for the treatment of urinary urge incontinence in September 1997, and for urinary retention and significant symptoms of urgency/ frequency in patients who have failed or could not tolerate more conservative treatments' in April 1999. FDA approval for its use in cases of intractable chronic pelvic pain has not yet been sought by Medtronic. InterStim® is also marketed in Canada and Europe for the treatment of urge incontinence.

The US Health Care Financing Administration (HCFA) is currently evaluating whether the literature supports a national coverage policy on SNSI for treatment of urge urinary incontinence (Health Care Financing Administration 2000).

Current reimbursement arrangement

Sacral nerve stimulation is not covered for use in any indication under existing Medicare Benefits Schedule arrangements. Another type of neuromodulation using a similar implantable system (spinal cord stimulation for chronic pain relief) is covered under MBS items 39140, 39133 and 39134.

Approach to assessment

Review of literature

Literature search

The medical literature was searched to identify relevant studies and reviews for the period between 1998 and October 1999. Searches were conducted via Medline and HealthStar.

The search terms used were:

> 'sacral nerve' or 'neuroprosthesis' or 'electric stimulation therapy', 'neurostimulation' or 'neuromodulation' or 'neurotransmitter'
> and
> 'urinary incontinence' or 'urinary disorder' or 'voiding dysfunction', or 'detrusor instability'.

As a result of the literature search, 270 publications were identified, from which 22 articles were included in the review.

Inclusion and exclusion criteria

Inclusion criteria were:

- study conducted on sacral nerve stimulator implantation;
- patients had incontinence, regardless of aetiology or gender; and
- patients had failed previous conservative treatment (drug, pelvic exercise etc.)

Exclusion criteria were:

- study conducted on electronic stimulation of other than the sacral nerve—for example, the pelvic muscle, detrusor muscle and pelvic nerves; and
- patients had not received more conservative treatment.

Where it was obvious that there was duplication in reporting of results on the same patients, the earlier study was excluded: for example, Bosch and Groen (1996) reported results on four patients and included them again, with the addition of one other patient, in a section of Bosch and Groen (1998).

The susceptibility to bias of the studies selected for inclusion was assessed and classified according to the National Health and Medical Research Council (NHMRC) revised hierarchy of evidence (Table 1).

Table 1 Designation of levels of evidence

I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly designed randomised controlled trial.
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case–control studies or interrupted time series with control group.
III-3	Evidence obtained from comparative studies with historical control, two and more single arm studies or interrupted time series without a parallel control group.
IV	Evidence obtained from case series, either post-test or pre-test and post-test.

Source: National Health and Medical Research Council 1999, A guide to the development, implementation and evaluation of clinical practice guidelines, NHMRC, Canberra.

The design of the selected studies and their classification by level of evidence are provided in Table 2.

Table 2 Characteristics of studies

Level of Evidence	Study, setting, duration	Study design	Patient characteristics	Treatment	Follow-up
II	Schmidt et al 1999 Multicentre trial Study years: 1993–1997	RCT	PNE: (randomised + not randomised): n = 155 male: 30, female: 125 mean age: 46 (range 20-79) Implanted patients: n=46 (excludes delay arm.) No demographic details Indication: urge incontinence refractory to standard medical therapy	Implants: n = 34 Controls: n = 42 Treatment: sacral S3 stimulator implant (multiprogrammable neurostimulator)	6 months
II	Grünewald 1999 (a) Multicentre trial Study years: 1993–1997	RCT	PNE: n=177 Implanted patients: n=37, No demographic details Indication: severe voiding dysfunction due to detrusor sphincter dyssynergia—refactory to standard therapy	N=68 randomised: Implants: n= 37 Controls: n= 31 Treatment: sacral S3 stimulator implant (Itrel® II pulse generator)	6 months
IV	Grünewald 1999 (b) Hanover Study years: 1991–?	Case series: pre/post	PNE: n=154 Implanted patients: n=43 male: 5, female: 38 mean age: 49 (range 23–76) Indications: urge incontinence: n=22; retention: n=21 conventional treatment modalities had been unsuccessful	Implants: n=43 Treatment: sacral S3 stimulator implant (Itrel® II pulse generator)	Mean: 44 months (range 2–77)
IV	Koldewijn 1999 Nijmegen/ Maastricht Study years: 1994–1998	Case series: pre/post	PNE: n=? Implanted patients: n=40 male: 2, female: 38 mean age: 40 (range 21–58) Indications: Urge incontinence: n=28 detrusor underactive: n=12 unsuccessfully treated by other treatment options	Implants: n=28 Treatment: sacral S3 stimulator implant (Medtronic neuromodulation system)	Mean: 29 months (range 5–46)
IV	Bosch 1998 Rotterdam Study years: ?	Case series: pre/post 2 arms	PNE: n=70 (male:14 , female: 56) Implanted patients: n = 35 male: 5, female: 30 mean age (n=24):46 (range 25–65) Indications: Detrusor instability: n=30 Detrusor hyperreflexia: n=5 (*5 patients with MS, 1 partial spinal cord lesion)—refractory to conservative treatment	Implants: n=35 Treatment: sacral S3 stimulator implant (Itrel® 1/Itrel® II pulse generator)	Mean:37 months (24 patients with detrusor instability) Mean:33 months (5 patients with detrusor hyperreflexia)

Level of Evidence	Study	Study design	Patient characteristics	Treatment	Follow-up
IV	Hohenfellner 1998 Mainz Study years: ?	Case series: pre/post	PNE subjects: n=?, Implanted patients: n=11 male: 2, female: 9 mean age: 43 (range 21–70) Indications: incontinence: n=5, retention: n=6 - not responsive to conservative treatment	Implants: n=11 Treatment: bilateral sacral S3 stimulator implant (4-channel neurostimulator)	Mean:13 months Range: 9–28
IV	Shaker 1998a Toronto Study years: ?	Case series: pre/post	PNE: n=? Implanted patients: n=20, male: 1, female: 19 mean age: 34 (range 19 to 56) Indication: urinary retention—previous treatment: Intermittent catheterisation	Implants: n=20 Treatment: sacral S3 stimulator implant (pulse generator)	Mean:15 months Range: 1–74
IV	1998b Toronto Study years ?	Case series: pre/post	PNE: n=? Implanted patients: n=36 male: 2, female:16 mean age 42.3 (range 22-67) Indication: urge incontinence (7 patients also with urinary retention) - refractory to all conservative measures	Implants: n =18 Treatment: sacral S3 stimulator implant (not described)	Mean: 19 months Range: 3–83
IV	Weil 1998 Maastricht Study years: 1991–1993	Case series: Pre/post	PNE: n= 100 Implanted patients: n=36 male: 9, female: 27 median age: 45 (range 23–67) Indications: urge incontinence: 24 urge frequency: 6 urinary retention: 6 —refractory to other treatment	Implants: n= 36 Treatment: sacral S3 stimulator implant (Itrel® I/Itrel® II pulse generator)	Mean:38 months Range:12–60
IV	Bosch and Groen 1997a Rotterdam Study years?	Case series: pre/post	PNE: n=77 Male: 14, female: 63 Implanted patients: n=38 mean age 45 Indication: urge incontinence—failed conservative treatment	Implants: n=38 Treatment: sacral S3 stimulator implant (Itrel® pulse generator)	Mean:41 months 6 months (n=35) 1 yr (n=33) 2 yrs (n=25 3 yrs (n=19) 4 yrs (n=16) 5 yrs (n=12)
IV	Weil 1997 Maastricht Study years?	Case series: pre/post	PNE subjects: ? Implanted patients:n=12 No demographic details Indication: urge incontinence. No details of other treatments	Implants: n=21 Treatment: sacral S3 stimulator implant (neuromodulation system-Medtronic)	6 months

Level of Evidence	Study	Study design	Patient characteristics	Treatment	Follow-up
IV	Bosch 1995 Rotterdam Study years?	Case series: pre/post	PNE: n=31 male:6; female: 25 Implanted patients: male: 3, female: 15 mean age 46 (range 25–65) Indication: urge incontinence—refractory to drug treatment	Implants: n= 18 Treatment: sacral S3 stimulator implant (pulse generator)	Mean: 29 months 13 patients ≥ 24 months
IV	Elabbady 1994 Montreal Study years: 1989–1993	Case series: pre/post	PNE: 50 Implanted patients: n=17 male: 4, female: 13 mean age 34 (range 20–58) Indication: chronic retention: n =8 Other (urge etc) n=9 —failed pharmacological & surgical treatment	Implants: n= 17 Treatment: sacral S3 nerve stimulator implant, (Itrel® I/Itrel® II pulse generator)	Mean: ? Range: 3–52
IV	Dijkerna 1993 Maastricht Study years: ?	Case series: pre/post	PNE: n = 63 patients urge incontinence (n=39) urge frequency (n=4), retention (n=9), pelvic pain (n=11) Implanted patients: n=23 male: 7, female: 16 mean age 46 (25–67) Indications: urge incontinence (n=16) urge frequency (n=1) retention (n=3), pelvic pain (n=3)—failed conventional treatment	Implants: n=23 Treatment: sacral S3 stimulator implantation (Itrel® I & II pulse generator)	Range: 2–20 months
IV	Groen 1993 Rotterdam Study years: ?	Case series: pre/post	PNE: n= 26 patients Implanted patients: n=13 male: 1, female: 12 mean age 49 Indication: urge incontinence—refractory to pharmacological treatment	Implants: n= 13 Treatment: sacral S3 stimulator (Itrel® pulse generator)	Mean: 13.8 months (range 3–27)
IV	Siegel 1992 Cleveland Study years: 1990–1991	Case series: pre/post	PNE subjects: 49 No demographic details Implanted patients: n=12 No demographic details Indications: pain and voiding dysfunction, urinary retention. No details	Implants: n=12 Treatment: sacral S3 stimulator implant (subcutaneous neurostimulator)	?

Level of Evidence	Study	Study design	Patient characteristics	Treatment	Follow-up
IV	Thon 1991 San Francisco Study years: 1987–1989	Case series: pre/post	PNE: n=?, No demographic details Implanted patients: n=57 No details Indications: urge incontinence:. n=20 voiding dysfunction: n=33 stress incontinence: n=4. —unresponsive to other conservative modes of therapy	Implants: n = 57 Treatment: sacral S3 stimulator implant (no details of generator)	≥1 year
IV	Tanagho & Schmidt 1988 San Francisco Study years: ?	Case series	PNE: ? Implanted patients: n=97 Males:37+ , females: n=39+ Indications: Urge incontinence: n=21 post-prostatic incontinence: n=20 pelvic dysfunction: n=56. previous treatment unknown	Implants = 97 Treatment: sacral S3 stimulator implant Some patients received sacral anterior root stimulator implant (no details of neuro-prosthetic implant)	?

Study design

Included in this review are 19 studies which evaluate the effectiveness of the sacral nerve stimulator implant treatment. Of these, two are reports of a multicentre randomised controlled trial (RCT) funded by the manufacturer, Medtronic: one on urge incontinence patients and the other on patients with urinary retention. The two reports are study investigators' publications in medical journals. Medtronic had earlier submitted this same data to the FDA to support the Pre Marketing Application. To minimise bias, the results considered in this review are based on data reported by Schmidt et al (1999) in a peer-reviewed journal, and by Grünewald et al (1999) in an abstract in a supplement to a peer-reviewed journal. The other 17 studies did not have a control group and were case series which compared the clinical symptoms of patients before and after implantation.

The multicentre, randomised controlled trial recruited patients with urge urinary incontinence and urinary retention. The randomised patients were highly selected patients who had phase I (acute) and phase II (subchronic) testing via percutaneous nerve evaluation (PNE). Schmidt et al (1999) reported the results on urge urinary incontinent patients: 98 (63%) of 155 patients had satisfied response criteria in the 'acute phase' and 'subchronic phase' and completed voiding diaries and were subsequently randomised into the implant arm (n=52) and delayed implant arm (n=46). Patients in the delayed implant arm received implantation at the end of six months. Of the 52 patients who were randomised to have an implant, 46 were actually implanted. No details of the outcomes of these missing six patients are provided. Results, which were not based on intention-to-treat (ITT), are compared between the two groups (n=34 implanted patients, follow-up rate 74%, n=42 control patients, 91% follow-up rate) at six months. Grünewald et al (1999a) reported in an abstract the results of urinary retention patients included in the multicentre RCT. Sixty-eight patients with refractory partial or complete urinary retention were, after phase I and phase II test stimulation, randomly assigned to

either the control group to receive standard medical treatment (n=31), or to have the implant procedure (n=37). The trial became non-randomised in design after six months, when patients in the control group crossed over to the implant group to receive the delayed sacral nerve implant. Results, not based on intention-to-treat, between the two groups (n=29 implanted patients, 78% follow-up rate; n=22 controls, 71% follow-up rate) were compared at six months.

The 17 case–series studies recruited patients with the following indications for neuromodulation: urge incontinence, frequency, urinary dysfunction and non-obstructive retention due to idiopathic or neuropathic causes. All patients underwent PNE before being considered for permanent implants. Follow-up assessments were reported at various times and in many cases no indication was given as to when the follow-up assessment actually occurred. One long-term study by Bosch and Groen (1997a) provided yearly follow-up of patients for up to five years. Four studies (Schmidt et al 1999; Shaker and Hassouna 1998a and 1998b; and Elabbady et al 1994) included quality of life assessments of the patients in their studies.

Expert advice

A supporting committee with expertise in urology and urogynaecology was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for supporting committees, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the supporting committee is provided at Appendix B.

Results of assessment

Is it safe?

Descriptions of complications were provided for a maximum of 401 out of 701 patients receiving a sacral nerve stimulator implant. In the studies that discussed complications, full details were not always provided. Six studies did not discuss complications arising from stimulation implants (Grünewald 1999a; Bosch 1997; Weil 1997; Thon 1991; Siegel 1992; Tanagho 1988). Schmidt et al (1999) report the pooled complications experienced by patients in the urge incontinence and retention groups (n=157). Details of complications reported by individual studies are reported in Table AC1 in Appendix C. A summary of the complication rates is presented in Table 3.

The most commonly reported reasons for revision surgery were pain at the pulse generator or lead implant site, lead migration and infection. The manufacturer claims that changes in surgical techniques and re-design of the device have minimised the potential for pain and lead migration problems occurring in future patients. In particular, changing the preferred site of pulse generator implantation from the lower abdomen to the upper buttock region is claimed to have reduced the incidence of revision surgery for pain at the pulse generator site. Lead redesign to improve lead anchoring is also claimed to have reduced the incidence of post-implant migration of the lead.

The studies reported little information on the site or severity of infections but, according to the manufacturer, the majority are at the pulse generator implant site and are usually treated with temporary removal of the pulse generator and antibiotic therapy.

Table 3 Complication rates in patients who have had sacral nerve stimulator implants

Type of complication event	No. events/ no. patients	Complication rate (95% CI for)	NNH (95% CI)
Reoperations	122/401	30.4% (26.0–35.2)	3 (3–4)
Implants removed	17/189	9.0% (5.3–14.0)	11 (7–19)
Implants replaced	15/126	11.9% (6.8–18.9)	8 (5–15)
Infection	23/233	9.9% (6.4–14.4)	10 (7–16)
Pain[a]	58/270	21.5% (16.7–26.9)	5 (4–6)
Lead problems	41/248	16.5% (12.1–21.8)	6 (5–9)
Stimulator problems	34/79	43.0% (31.9–54.7)	2 (2–3)

[a]Pain at the pulse generator implant site, pain at the lead implant site and new pain.

Is it effective?

Outcome measures

Effectiveness was assessed by subjective or urodynamic measures. In evaluating the effectiveness of sacral nerve stimulation, results have been grouped according to two indications: 1) urge incontinence, frequency and urgency; and 2) chronic urinary retention and voiding dysfunction. Many of the studies included patients with a mix of symptoms, and in most cases the results could be separated according to the above two indications.

Studies with results which could not be separated according to indication were classified as 'mixed' indications and are presented in a separate table.

For patients with urge incontinence, endpoints used were usually:

- mean number of episodes of incontinence (leakages) per 24 hours;
- mean number of pads used per 24 hours;
- proportion of patients with greater than 90 per cent improvement in symptoms; and
- other urodynamic measurements (bladder capacity).

For patients with chronic retention, endpoints were usually:

- mean voided volume;
- mean post-void residual volume;
- bladder capacity;
- mean number of intermittent catheterisations per 24 hours; and
- proportion of patients with more than 90 per cent improvement in symptoms.

Endpoints were obtained from patients' recordings in diaries and from urodynamic tests. Subjective endpoints such as pelvic pain and urinary urge were frequently used in all studies. These may be less reliable than objective clinical endpoints—for example, the mean number of episodes of incontinence or number of pads used per 24 hours—and those measured by urodynamic studies: bladder capacity; amplitude of hyper-reflexic contraction; and percentage residual volume.

Results

The results are arranged according to indication: (a) urge incontinence, frequency, urgency; (b) chronic urinary retention, voiding dysfunction; and (c) mixed. The detailed results of the studies included in this review are in Tables AC2–AC6 (Appendix C).

Results of the multicentre randomised controlled trial

Urge incontinence

Schmidt et al (1999) observed at six months after sacral nerve stimulator implantation, among 34 patients followed up (follow-up rate 74%): significantly reduced leaking episodes, which decreased by an average of seven episodes per day; reduced daily pad consumption, which decreased by an average of five pads per day; and reduced severity of leaking, from moderate to mild. In contrast, patients in the control arm experienced either no improvement or worsening symptoms. Forty-seven per cent (16/34) of treated patients had achieved complete continence, compared to none in the control arm. These results are summarised in Table 4. Additional results are presented in Table AC2 (Appendix C).

Urinary retention

Grünewald et al (1999a) observed that, at six months follow-up, patients with urinary retention who had sacral nerve implants achieved a statistically significant improvement in terms of complete elimination of catheterisation in 20 (69%) patients, decreased number of catheterisations per day by 4.3, and decreased catheter volume per catheterisation by 290ml. Additional results are presented in Table AC3.

A summary of these results is presented in Table 4. The NNT is a calculation based on the study success rate and is used to estimate the number of patients that need to be treated to have one patient with a successful outcome.

Table 4 Clinical trial evaluation of the effectiveness of sacral nerve stimulator implants in patients with 1) urge incontinence 2) urinary retention

Level of evidence	Study	Outcome	Number needed to treat (NNT), 95% CI
II	Schmidt et al 1999	URGE INCONTINENCE	
		Incontinence episodes	
		Implants (n=34) vs Controls (n=42) at 6 months follow-up	
		No incontinence: 47% vs 0	2 (2–3)
		≥50% reduction: 76% vs 5%	1 (1–2)
		Pads replaced per 24 hrs	
		Implants (n=30) vs Controls (n=42) at 6 months follow-up	
		Eliminated pads: 50% vs 2%	2 (2–4)
		≥50% reduction: 87% vs 7%	1 (1–2)
II	Grünewald 1999a	URINARY RETENTION	
		Catheterisations	
		Implants (n=29) vs Controls (n=22) at 6 months follow-up	
		No catheterisation: 69% vs 9%	2 2 (1–3)
		>50% reduction: 83% vs 9%	1 1 (1–2)

Results of case series studies

Urge incontinence, frequency and urgency

Fourteen studies (Table AC4) evaluated the effectiveness of sacral nerve stimulator implants in 267 patients.

Episodes of incontinence per 24 hours

Six of 14 studies report on the change in the average number of incontinence episodes post-implantation compared to baseline (Weil et al 1998; Shaker & Hassouna 1998b; Bosch & Groen 1998; Bosch & Groen 1995; Dijkema et al 1993; Groen et al 1993). This represents only 42.7 per cent of the pool of urge incontinent study patients. The studies reported that the frequency of incontinence or leakage per 24 hours was reduced from 4.1–15.3 to 1.1–9.4 at six months or last follow-up after the implantation (ie, reduced by 3.8 to 5.9 episodes). The significance of this improvement was demonstrated in five studies (all except Dijkema et al 1993) with p values <0.05 ($p<0.01$ in 4 studies).

Pads used per 24 hours

Six of 14 studies presented results of the change in patient pad usage per 24 hours (Bosch & Groen 1998; Hohenfellner et al 1998; Weil et al 1998; Bosch & Groen 1995; Dijkema et al 1993; Groen et al 1993). This represents only 37.8 per cent of the pool of urge incontinent study patients. The mean number of pads used in 24 hours decreased from 4.5–6.6 to 1.0–2.4 (reduced by 2.2 to 4.8 pads). The reduction in pad consumption was statistically significant in four studies (Bosch & Groen 1998; Weil et al 1998; Bosch & Groen 1995; Groen et al 1993) with p values <0.001.

Percentage improvement in symptoms

Twelve of the 13 studies classified patients' success in terms of improvement in symptoms, but various definitions of success were described. Success rates ranged from 0 to 68 per cent and 117 patients of 241 (48.5%) were described as having a clinical benefit from the sacral nerve stimulator implant, although the definition of success varied. Table 5 summarises these results. Calculation of NNT is appropriate in studies with a control group. With no control group, the NNT represents 100 per cent effectiveness and should be interpreted here with caution.

Table 5 Summary of benefit rates in patients with sacral nerve stimulator implants for urge incontinence

Study	Definition	N/sample	Success rate (95% CI)	NNT (95% CI)
Koldewijn 1999	completely dry	18/28	64% (44–81)	2 (1–2)
Grünewald 1999b	clinically cured	7/18	39% (17–64)	3 (2–6)
Weil 1998	clinical benefit	14/24	58% (37–78)	2 (1–3)
Shaker 1998b	completely dry	8/18	44% (22–69)	2 (1–5)
Bosch 1998	completely dry	7/24	29% (36–83)	3 (2–8)
Bosch 1997	complete success*	9/35	26% (13–51)	4 (2–8)
Bosch 1995	>90% dec. incont. episodes	11/18	61% (13–43)	2 (1–3)
Groen 1993	complete success	5/13	38% (14–68)	3 (1–7)
Dijkema 1993	clinical improvement >90%	10/17	59% (33–82)	2 (1–3)
Thon 1991	clinical benefit (75–100%)	15/24	63% (41–81)	2 (1–2)
Hassouna 1991	clinical improvement >90%	0/3	0 (0–71)	infinite
Tanagho 1988	success	13/19	68% (42–55)	1 (1–2)
Total		117/241	48.5% (45)	2 (1–2)

* >90% reduction in both pad use and leakage episodes

Urodynamic studies

Seven of 13 studies compared post-implantation bladder capacity with baseline (Grünewald et al 1999b; Weil et al 1998; Shaker & Hassouna 1998b; Hohenfellner et al 1998; Bosch & Groen 1998; Weil et al 1997; Groen et al 1993). This represents 46.1 per cent of the pool of study patients with urge incontinence. Bladder capacity increased from baseline measures of 130–360 to 260–435 cc by amounts of from 25 to 256 cc. Statistically significant increases were found in three studies (Weil et al 1998; Hohenfellner 1998; Weil et al 1997).

Six of thirteen studies compare post-implantation voided volume with baseline volume of urine (Weil et al 1998; Shaker & Hassouna 1998b; Hohenfellner et al 1998; Bosch & Groen 1998; Grünewald et al 1999b; Dijkema et al 1993). This represents 39.7 per cent of the pool of study patients with urge incontinence. Voided volume increased from 86–

208 to 180–334 for an increase of from 46 to 248 cc. Statistically significant increases were observed in three studies (Grünewald et al 1999b; Hohenfellner et al 1998; Weil et al 1998).

Chronic urinary retention

Nine studies (Table AC5) evaluate the effectiveness of sacral nerve stimulator implants in 106 patients with non-obstructive urinary retention or voiding dysfunction.

Voided volume

Four of nine studies reported post-implantation changes from baseline in voided volume (Grünewald et al 1999b; Hohenfellner et al 1998; Shaker & Hassouna 1998a; Elabbady et al 1994). Sample sizes for these studies are quite small: 21, 5, 18 and 8 respectively. The time interval for this data was inconsistently reported: per 24 hours or not stated. Elabbady reported a significant percentage increase in voided volume from 15 per cent to 71 per cent ($p<0.001$) among seven patients. Both Grünewald and Hohenfellner report significant increases in voided volume: 490 and 334 cc respectively. Shaker & Hassouna 1998a reported a significant increase in voided volume/24 hours of 1250 cc.

Post-void residual volume

Four of nine studies reported measurements of the change from baseline in residual volume after implantation (Grünewald et al 1999b; Hohenfellner et al 1998; Shaker & Hassouna 1998a; Elabbady et al 1994). Statistically significant decreased mean residual volumes of 455 and 334 cc were reported by Grünewald and Hohenfellner respectively. Elabbady reported a significant decrease of 56 per cent in residual volume. The significance level of the 72 per cent decrease reported by Shaker & Hassouna 1998a was not provided.

Catheterisation

Two of nine studies provided data on changes in patients having intermittent catheterisations (Koldewijn et al 1999; Elabbady et al 1994). Among 12 patients in the study by Koldewijn, seven patients were able to stop intermittent catheterisation. Elabbady reported that mean intermittent catheterisations decreased from four to one per day but the decrease was not significant.

Bladder capacity

This was reported in three of nine studies (Hohenfellner et al 1998; Shaker & Hassouna 1998a; Elabbady et al 1994). No significant changes from baseline to post-implantation were reported in any of these studies.

Percentage improvement in symptoms

Five of nine studies classified patient success in terms of improvement in symptoms but definitions of success varied widely. Two studies defined success as a greater than 90 per cent improvement in symptoms (Dijkema et al 1993; Hassouna & Elhilali 1991). Each study reported on only three patients with urinary retention and, in both, two of the three patients experienced a greater than 90 per cent improvement with the neurostimulator implant. Table 6 summarises these results. Because the definition of success varies widely, and because of the fact that NNT assumes 100 per cent effectiveness as there is no control group, these results should be interpreted with caution.

Table 6 Summary of benefit rates in patients with sacral nerve stimulator implants for urinary retention

Study	Definition	n/sample size	Results success rate (95%CI)	NNT (95% CI)
Grünewald 1999b	>50% improvement	18/21	86% (64–97)	1(1–2)
Koldewijn 1999	stopped catheterisation	7/12	58% (28–85)	2 (1–4)
Weil 1998	>50% improvement	3/6	50% (12–88)	2 (1–8)
Dijkema 1993	>90% improvement	2/3	67% (9–99)	2 (1–11)
Hassouna 1991	>90% improvement	2/3	67% (9–99)	2 (1–11)
Thon 1991	75–100% improvement	7/33	52% (34–69)	2 (2–3)
Total		42/78	54% (42–65)	2 (2–2)

Mixed urinary dysfunction

Five studies included 107 patients with a combination of urinary symptoms whose results could not be separated into urge incontinence or urinary retention. The results for these patients with sacral nerve stimulator implants were classified as 'mixed' and are presented in Table AC6.

Long-term effectiveness

Long-term effectiveness of sacral nerve stimulator implants was evaluated in three papers: Siegel (in press), Schmidt et al (1999), and Bosch and Groen (1997a). The Siegel study is an update on the follow-up of patients included in the multicentre trials reported by Schmidt et al (1999) and Grünewald et al (1999a), the results of which were evaluated earlier in this report. Evidence from these three studies is at level IV, as no follow-up data for a control group of patients is provided and it is therefore not possible to delineate the actual effect of the implant from other influences affecting the study patients over time.

Siegel (in press) reports follow-up results at two years (mean: 2.2 years, range: 18 months to 3 years) on 112 (51%) of 219 patients who received permanent sacral nerve stimulator implants. Fifty-two patients (46%) experienced 'complete cures' for their disorders (Table 7). However, this overall treatment benefit rate would be reduced to 39 per cent if the data for 23 patients who had to have their implants removed were included. The follow-up results on other voiding parameters of these patients are presented in Table AC7.

Table 7 Long-term effectiveness of sacral nerve stimulator implants among patients with urge incontinence, urgency–frequency and urinary retention

Indication	N of patients with follow-up	Duration of follow-up	Outcome	%, (95% CI)
Urge incontinence	41	3 years	Completely dry	46% (31–63)
Urgency–frequency	29	2 years	Normal voids per day	32% (15–51)
Urinary retention	42	1.5 years	No catheterisation	58% (41–72)
All indications	112	Average 2.2 years	All above outcomes	46% (37–55)

Schmidt et al (1999) presented data from a study of 21 patients with urge incontinence who had been followed up until 18 months. It appears that the effectiveness of the sacral

nerve stimulator in relieving symptoms and the regaining of bladder control was sustained for at least 18 months, as presented in Table 8.

Table 8 Long-term effectiveness evaluation of sacral nerve stimulator implants in patients with urge incontinence

	% 6 months after implant (n=58)	% 12 months after implant (n=38)	% 18 months after implant (n=21)
Any leaking episode			
Dry	47	45	52
≥50% reduction	28	34	24
Total clinical success	75	79	76
Heavy leaking episodes			
Eliminated	77	70	84
≥50% reduction	13	10	0
Total clinical success	90	80	84
Pads replaced daily			
Eliminated	57	55	57
≥50% reduction	26	21	19
Total clinical success	83	76	76

In another study of 35 patients who had permanent implantation, 12 were followed up to five years (Bosch and Groen 1997a). The follow-up results up to five years post-implantation were reported as: leaking episodes/day, number of pads used/day, number of voids/day, and average volume/void (Table 9).

Table 9 Durability of effects on symptoms and voiding parameters

Follow-up (years)	Patients (n)	Pads/day (n±SEM*)	Leaks/day (n±SEM)	Voids/day (n±SEM)	Average volume/void (ml±SEM)
Pre-implant	35	6.4±0.6	7.5±0.6	14.0±0.9	137±10
½ year	35	1.8±0.3	2.1±0.4	9.6±0.5	188±14
1 year	33	2.0±0.4	2.1±0.4	8.8±0.5	198±15
2 years	25	2.1±0.6	2.6±0.7	9.3±0.5	189±17
3 years	19	1.5±0.4	1.5±0.6	9.3±0.6	188±22
4 years	16	1.6±0.5	2.6±0.8	9.7±0.5	180±27
5 years	12	2.6±0.7	3.2±1.0	9.9±0.8	147±18

*Standard error of the mean

Impact on quality of life

Urge incontinence

Two different instruments have been used to evaluate quality of life in patients undergoing sacral nerve stimulation: Short form-36 (SF-36) and Beck Depression Inventory (BDI).

Short form-36 (SF-36)

Schmidt et al 1999 used this instrument to measure quality of life in 28 stimulation and 32 delayed implantation group patients. Patient scores on the mental and physical component scales only were discussed.

Standardised Mental Component Scale—No significant difference was observed between the treatment groups (mean score 47 vs 45).

Standardised Physical Component Scale—The stimulation group had significantly higher scores for perception of physical health status compared to the delay group (mean score 46 vs 36, p=0.0008).

No significant differences in the scores of any component of the SF-36 (baseline versus 18-month follow-up) were observed in seven patients by Shaker and Hassouna (1998b).

Beck Depression Inventory (BDI)

Shaker and Hassouna (1998b) stated that patients were also assessed with this instrument but no significant differences were observed post-implantation compared to baseline.

Urinary retention

Short form-36 (SF-36)

Shaker and Hassouna (1998a) reported that at six months follow-up patients gave significantly higher scores to general health change in the last year (pre- versus post-mean ± SEM score: 28.6 ± 9 versus 68.3 ± 15, p≤0.5). No significant differences in any other component of the SF-36 were reported.

Beck Depression Inventory (BDI)

The results of 19 patients in the implant group and 21 in the control group at six months were reported. The degree of depression is ranked according to the BDI score (ranged 0–62). Patients in both implant and the control groups manifested similar level of depression (minimal depression, p=0.34).

Overall, at six months after the sacral nerve stimulator implant procedure, patients with urinary retention did not show significant improvement in quality of life measured by SF-36 or BDI.

No significant differences in patients' BDI scores at six months follow-up were reported by Shaker and Hassouna (1998a).

Mixed indications

Medtronic Patient Satisfaction Survey

This survey, conducted on behalf of Medtronic by telephone interview in March 1999, obtained responses from 35 (14%) patients whose names were on a list of 254 people in the United States who had had an implanted continence control device (InterStim®). Responding patients were asked to compare various adverse effects of their urination disorder before and after implant. Patients reported significant improvements after implantation in their ability to perform certain physical activities, their feelings of self-

esteem and their satisfaction with overall health and quality of life. Approximately two-thirds of the responding patients reported being satisfied with the implant.

The low response rate seriously limits the precision of the above estimates of patients' satisfaction with implants and therefore their ability to be used as a basis for generalisation. Only three of the respondents were men and only one patient had treatment for urinary retention, which further limits the relevance of the survey results to these groups of patients. Details of the study design and results are at Appendix D.

Short form-36 (SF-36)

Rosier et al (1997) report results of quality of life based on the SF-36 instrument of 35 patients in the multicentre trial. Scores for the mental and physical components were compared for patients for whom neuromodulation was successful against those for whom it was ineffective in relieving symptoms. Analysis of scores at baseline and at 3, 6, 12 and 18 months are presented. The physical functioning score increased in patients for whom the implantation was successful and decreased over time for those whose implant failed. No statistical analysis was provided.

Quality of life questionnaire

Elabbady et al (1994) assessed quality of life on 18 patients (this number may be an error since the paper reports on 17 implanted patients) using a 'basic quality of life questionnaire' with no details of validation of the instrument. Percentage improvements in activities inside and outside the home were presented but few details provided. Thirty-nine per cent of patients reported a significant benefit, 39 per cent reported a moderate benefit and 22 per cent reported no benefit from the implant.

Interpretation of the results

The best evidence available for evaluating the effectiveness of the sacral nerve stimulator implant in patients with urge incontinence is the RCT of 34 patients reported by Schmidt et al (1999). There are several deficiencies that limit the strength of their results. No details are provided of the randomisation method or of whether concealment of allocation occurred. In addition there is no indication that investigators were blinded to assessment of outcome, which is of particular importance when it is not possible to blind study personnel as to whether or not the patient had an implant. Follow-up results were missing on more than 20 per cent of patients and no details of what happened to these patients are provided.

Similarly, in patients with urinary retention, the best available evidence for the effectiveness of the sacral nerve stimulator implant is that reported by Grünewald et al (1999a). Again the limitations of the results are as for the Schmidt et al study. In addition, the fact that the report is an abstract further reduces the strength of the evidence since it is unlikely to have been peer-reviewed.

Evidence from case series has increased potential for bias in results. Thus, the results from the 17 case series studies in this review have decreased validity, primarily due to the fact that there is no control group and there is increased opportunity for selective reporting of patient results. The sample sizes are generally small, timing of follow-up assessments is rarely standardised, and explicit selection/inclusion criteria are generally omitted. None of the studies provided convincing evidence by itself and pooling the

studies using meta-analysis is inappropriate. One must also consider that the research findings may be overstated since duplication could have occurred inadvertently, when cumulative results of patients receiving the implant are reported over time.

Gender was reported in 364 patients: 58 males (15.9%) and 306 females (84.1%). Although patient demographics were provided on patients undergoing PNE, demographics of patients who proceeded to implant were seldom provided. Results were rarely categorised by gender and the likelihood that neuromodulation may not be effective for men is underlined in a report by Bosch & Groen (1997b). Of six men with urge incontinence who received sacral nerve implants, only two patients had a significant response. They conclude that neuromodulation does not appear to be a recommended treatment for urge incontinence due to bladder instability in men.

A further problem with the research is that most studies do not report using statistical tests for paired samples (Student's t, Mann-Whitney U) to compare differences between pre- and post-implant variables. This may be an issue of reporting.

On the basis of the best available evidence, it appears that the implantable sacral nerve stimulator has provided some benefits to patients with urge incontinence: reducing the incidence of urinary incontinence, reducing pad consumption, and regaining bladder control. Improved clinical symptoms were observed in 43–69 per cent of patients and the effect sustained for at least two years. However, the results of urodynamic studies did not always reflect this effect. Long-term effectiveness to five years has been demonstrated in only 12 (2%) of the patients in the studies in this report.

There is much less evidence available to support the effectiveness of the implant in patients with urinary retention. Possibly, when the final results of the 68 patients in the RCT are reported, additional convincing evidence, as observed in preliminary reports of the trial, will be provided. Recent follow-up data on 42 implanted patients in this trial (Siegel, in press) described a sustained improvement at 18 months in 29 patients.

What are the economic considerations?

No studies of the cost-effectiveness of sacral nerve stimulator implant treatment were found in the literature. A full economic analysis was not done due to a lack of information on the treatment costs of sacral nerve stimulation and those for patients who are unsuitable for the implant or in whom the implant fails. There is also considerable uncertainty with respect to the effect of the intervention on health outcomes such as quality of life and on the personal costs of incontinence. If successful, it is likely to reduce the reliance of patients on incontinence products, reduce personal costs and reduce some demand for more invasive surgery.

An indicative analysis of the likely cost of treatment and the reduction in personal costs for the two indications (urge incontinence and urinary retention) is given in Tables 10–14 below. The analysis is based on the results of the literature review of effectiveness above and in particular on a re-analysis of Schmidt et al (1999). Given the lack of data in a number of key areas, the estimates of costs are subject to considerable uncertainty.

The cost offsets from a reduction in pad use and laundry for urge incontinence and catheterisation for urinary retention were estimated using a range of estimates from the literature. The average reduction in pad use is fairly consistent across studies and the

figure of 3.3 is used from Schmidt et al (1999). The reduction in laundry use depends on the baseline number of leakages and the percentage reduction. The baseline varies considerably between studies and definitions are not always clear. The 9.7 leakages per day per person in Schmidt et al (1999) may be an overestimate, and the cost saving from laundry and pad use may be overestimated. There is also considerable uncertainty regarding surgery revision. The only study to provide details of complication rates is Schmidt et al and the calculated revision rate in that study appears to include patients who were not part of the randomised trial.

Over six months, sacral nerve stimulator implant treatment has an estimated cost per patient initiated to treatment with percutaneous sacral nerve evaluation of approximately $11,000**.** These costs include medical treatment and re-operations arising from complications, for both indications.

It is estimated that the per patient reduction in the cost of incontinence products and laundry is between $277.70 and $574.20 for urge incontinence over six months. It has been suggested that the implant may last for up to five years. Over the long term the total cost saving in incontinence products per patient is likely to increase if the device continues to be effective, but further revision surgery may also be required. No attempt has been made to project costs over a longer period because of a lack of data in current studies.

It is estimated that the per patient reduction in personal costs for urinary retention patients is approximately $245 over six months.

The incremental costs of sacral nerve stimulator implantation per patient are subject to considerable uncertainty associated with the quality of the evidence. Most of the studies have no control group and the one RCT does not use intention-to-treat in reporting outcomes, making it difficult to assess rates of effectiveness, complications, and resource use.

Costs for those who proceed to more invasive surgery have not been calculated but average hospital costs of procedures are available for the relevant Australian National Diagnosis Related Groups (ANDRG) from the National Hospital Cost Data Collection 1997–98 (CDHAC 1999). Procedures such as bladder reconstruction and urinary diversion are covered by DRG LO4A and B. Their average public hospital costs are:

- L04A Kidney, Ureter & Major Bladder Procedures non-neoplasm with catastrophic or severe complications: $9,448.
- LO4B Kidney, Ureter & Major Bladder Procedures non-neoplasm without catastrophic or severe complications: $4,822.

Details of indicative cost analysis

The cost of percutaneous sacral nerve evaluation followed by a permanent implant, for an estimated 50 per cent of all the patients admitted for the percutaneous nerve evaluation, is the same for both urge incontinence and urinary retention. However the potential cost offsets resulting from the reduction in need for disposable products (absorbent pads or intermittent self-catheterisation) differ, so two alternative sets of calculations are provided.

Cost of sacral nerve stimulator implant treatment for urge incontinence

Table 11 and Table 12 show the estimates of the cost of sacral nerve stimulator implant treatment for the two indications. Calculations reported in Table 12 are based on three different estimates of the reduction in the mean number of leakage episodes as shown in Table 10.

Table 10 Mean number of leakage episodes pre- and post-treatment

Pre-treatment	Post-treatment	Reference source
4.1	1.3	Elabbady 1994
7.5	1.9	Bosch & Groen 1995
9.7	5.6	Schmidt et al 1999*

* adjusted for intention-to-treat analysis

The reduction in the mean number of pads used is fairly consistent across the studies. This number from Schmidt et al (1999) is therefore used for all cost calculations.

Table 11 Expected cost per patient of sacral nerve stimulator implant treatment for urge incontinence

Cost components	Cost per percutaneous nerve evaluation patient over 6 months
Equipment (percutaneous nerve evaluation and sacral nerve stimulator implant)	$6,567.00
Surgery and re-surgery costs	$4,464.00
Post-operation medical consultations	$96.00
Incontinence products	$360.00
Laundry cost (depending on the efficacy assumptions)	$171.00 $298.00 $468.00
Total (medical + personal cost)	**$11,658.00** **$11,785.00** **$11,955.00**

Table 12 Cost of comparative treatment per patient for urge incontinence

Cost components	Cost per non-surgical patient over 6 months
Incontinence products	$491.04
Laundry cost	$614.59
Total (Personal cost)	$1105.63

Cost of sacral nerve stimulator implant treatment for urinary retention

Reduction in the mean number of catheterisations per day is taken from an RCT (Medtronic 1997) and adjusted for intention-to-treat analysis. No laundry cost is applicable for this type of indication.

Table 13 Expected cost per patient of sacral nerve stimulator implant (SNSI) treatment for urinary retention

Cost components	Cost per percutaneous nerve evaluation patient over 6 months
Equipment (percutaneous nerve evaluation and sacral nerve stimulator implant)	$6,567.00
Surgery and re-surgery costs	$4,464.00
Post-operation medical consultations	$96.00
Personal cost = catheterisation products	$601.00
Total (SNSI + Personal cost)	$11,728.00

Table 14 Expected cost of comparative treatment for urinary retention

Cost components	Cost per non-surgical patient over 6 months
Personal cost = catheterisation products	$846.45
Total cost = personal cost	**$846.45**

Indicative cost-effectiveness ratio

The expected net cost over six months for a patient initiated to PNE is approximately $10,500. Of 155 patients in Schmidt et al who were tested, 63 per cent were suitable for randomisation and could have benefited from sacral nerve stimulator implantation. Of those randomised to sacral nerve stimulator implantation, 47 per cent were dry at six months. This suggests that about 30 per cent of patients with urge incontinence initiated to PNE and given a sacral nerve stimulator implant would be dry at six months (Schmidt et al 1999). The overall cost per additional person free of incontinence is therefore approximately:

$$\$10,500/0.3 = \$35,000.$$

No confidence intervals for the estimated percentage dry at six months was reported in Schmidt et al (1999). The standard error of the proportion in Schmidt et al has been calculated as:

$$SE\ (p) = \sqrt{\frac{0.3 \times 0.7}{155}} = 0.037$$

and the associated 95% CI (22.60% 33.74%).

The calculated lower estimate of the cost per additional person free of incontinence is about $28,000 and the upper estimate about $46,000, based on the 95% CI for the percentage dry at six months. The incremental cost-effectiveness is obviously sensitive to the success of the device in keeping patients dry.

It is not possible to calculate a similar cost-effectiveness ratio for urinary retention from the data available.

Further analysis of cost-effectiveness

The following areas of uncertainty need to be clarified before a more complete cost-effectiveness analysis could be undertaken:

1. The studies reviewed seem to use different definitions for leakage versus an incontinence episode. The main study by Schmidt et al (1999) uses 'leaking episode' as a measure of outcome, which appears to be different from other efficacy outcomes (voiding frequency, episodes of leakage, incontinence episodes) used in different publications (Groen 1993; Bosch & Groen 1995). The implications for the cost calculation is that while a leakage episode would be likely to involve an extra cost associated with replacing pads and laundry, an incontinence episode may present an inconvenience for the patients, but no other extra cost. To address the problem a range of laundry and incontinence products cost estimates were produced based on the outcomes from three different studies (Elabbady 1994; Bosch & Groen 1995; Schmidt et al 1999).

2. The model uses surgery revision rates taken from Schmidt et al (1999). There is not sufficient information on how the sample of 157 implanted patients was selected, and to what degree the observed surgery revision rates are generalisable. It is not clear what happened to dropouts as the follow-up of the patients is not well documented. It is therefore recommended that these rates be validated over the useful life of the implant.

3. For the purpose of calculating an indicative cost-effectiveness ratio, crude cost estimates are used for two types of surgeries: repositioning of lead and repositioning of pulse generator. These, however, are consistent with an expert's opinion that the cost for these operations is within the $650–$980 range. More accurate cost data are needed with respect to these medical procedures and also some information about the possibility of re-using the originally inserted device (or some parts of it) should the patient require temporary removal and reimplantation. It has been assumed that half of the original devices can be re-implanted.

4. For the purpose of preliminary modelling it is assumed that monthly visits are required during the six months post-surgery period (consistent with an expert's opinion). There is no certainty about how often patients receiving other treatments (eg, a conservative treatment that includes the use of pads and catheters) may see a general or specialist practitioner about their lower urinary tract dysfunction. In the indicative cost-effectiveness model it is assumed that no such visits take place. This may have underestimated the cost of that alternative.

5. Different estimates of the useful life of the device are given in the literature. These vary from three to nine years. More information is needed to clarify the frequency at which the device needs to be replaced.

6. The estimated cost and outcomes are calculated at six months. Available data do not allow extrapolation beyond that period. Clearly, if patients remained dry for a number of years, the cost offsets associated with reduced use of incontinence products would be more significant and the cost-effectiveness ratio would improve. Unfortunately there is no long-term evidence as yet on the duration of the improvement.

7. In a small number of cases, sacral nerve stimulation is offered as an alternative to other more invasive surgical procedures. In this case it would be necessary to evaluate the incremental cost and benefits compared to these procedures. The initial cost of these alternative surgical procedures is likely to be similar to that of sacral nerve stimulation. The cost and rate of revision of these procedures has not been assessed but may be as high as for sacral nerve stimulation. In the absence of available evidence, it has not been possible to calculate the potential incremental cost-effectiveness of the intervention compared to alternative surgical procedures for urinary incontinence or retention. Rather, the indicative cost-effectiveness analysis has been done for a group of refractory incontinent patients who have no alternative treatments available.

Conclusions

Safety

There is a relatively high incidence of adverse events associated with sacral nerve stimulator implants. More than half of the permanent implant patients (51.6%) experienced an adverse event (NNH=2) based on the pooled results of the RCTs of patients with urge incontinence and urinary retention. Among the 10 studies that reported complications, one in three patients required further surgery and in 9 per cent the device had to be removed (NNH=11). The most commonly reported adverse events and reasons for revision surgery were pain at the pulse generator or lead implant site, lead migration and infection.

MSAC noted that the SNSI procedure is complex, and the experience and skill of the service provider have a significant impact on the success of the procedure and the related adverse events. There have been technical refinements to the device and operative procedure which the manufacturers claim are reducing the incidence of the most common adverse effects and causes of re-operation. The risks associated with SNSI also need to be balanced against the fact that it is only indicated for patients who have not responded to, or not tolerated, other available pharmacological and physiological interventions. The available operative alternatives are more invasive, may also require revision and, unlike SNSI, are usually not reversible if unsuccessful.

Effectiveness

The best available evidence is provided by two RCTs, both of which have methodological deficiencies which limit the strength of their results. On the basis of this evidence, sacral nerve stimulation appears to have treatment benefits for female patients with urge incontinence in terms of reducing the incidence of urinary incontinence, reducing pad consumption, and regaining of bladder control. The reported durability of the response is 18 months (Schmidt et al 1999) to at least five years post-implantation (Bosch and Groen 1997a). For patients with urinary retention, observed treatment benefits were eliminating or reducing catheterisation use and improving voiding parameters. The reported durability of the response in these patients is 18 months (Siegel, in press). Evidence from the case series is of lower quality as there is increased potential for bias in the results, but supports the findings of the RCTs.

The impact on the quality of life of patients is uncertain. Many of the quality of life measurements performed did not demonstrate a significant improvement in the quality of life of patients undergoing sacral nerve stimulation, and the results of the Medtronic patient satisfaction survey have limited generalisability due to the low response rate (34 patients of which 24 had implants for urge incontinence or retention). However, the patients surveyed did report significant improvements in their ability to perform certain physical activities, their feelings of self-esteem and their satisfaction with overall health and quality of life. Approximately two-thirds were satisfied with their implant.

Cost-effectiveness

Sacral nerve stimulation has an estimated cost per patient of approximately $11,000 over six months**.** These costs include the device, medical treatment and re-surgery costs arising from complications for both indications.

The costs saving in appliances and laundry per patient is between $277.70 and $574.20 for urge incontinence and approximately $245 for urinary retention, over six months. It is not possible to project costs and cost savings over a longer period because of the lack of available data.

The indicative cost-effectiveness ratio for sacral nerve stimulation treatment for urge incontinence is estimated to be approximately $35,000 per additional patient free of incontinence at six months follow-up. However, there are a number of areas of uncertainty in the data available that need further clarification for a more complete cost-effectiveness analysis to be done.

For the small number of patients who undergo the major alternative procedures (bladder reconstruction or urinary diversion) costs are also high: $4,822 for public hospital treatment in patients without complications and $9,448 for those with catastrophic or severe complications.

Other considerations

MSAC noted that obtaining high level data on this procedure is problematic as it is difficult to randomise these patients to other interventions. Pre/post studies using delayed treatments may be the best option for collecting data. For a quality of life study, a condition-specific measure such as the Urinary Distress Inventory (UDI-6) may be more appropriate than a generic measure to assess or track current symptom distress in incontinent patients (Dugan et al 1998).

Further research is required on the results of recent refinements to the device and procedure, in particular the impact on safety, long-term effectiveness and quality of life.

Recommendations

MSAC found that, on the strength of evidence pertaining to sacral nerve stimulation:

- the intervention is associated with a relatively high rate of adverse events (NNH=2);
- the long-term effectiveness is uncertain; and
- the cost-effectiveness ratios associated with the intervention are unfavourable.

MSAC therefore recommended that public funding for sacral nerve stimulator implantation should not be supported at this time.

Appendix A MSAC terms of reference and membership

The terms of reference of MSAC are to advise the Commonwealth Minister for Health and Aged Care on:

- the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC), and report its findings to AHMAC.

The membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	Expertise
Professor David Weedon (Chair)	pathology
Ms Hilda Bastian	consumer health issues
Dr Ross Blair	vascular surgery (New Zealand)
Mr Stephen Blamey	general surgery
Dr Paul Hemming	general practice
Dr Terri Jackson	health economics
Professor Brendon Kearney	health administration and planning
Mr Alan Keith	Assistant Secretary, Diagnostics and Technology Branch, Commonwealth Department of Health and Aged Care
Dr Richard King	gastroenterology
Dr Michael Kitchener	nuclear medicine
Professor Peter Phelan	paediatrics
Dr David Robinson	plastic surgery
Associate Professor John Simes	clinical epidemiology and clinical trials
Dr Bryant Stokes	neurological surgery, representing the Australian Health Ministers' Advisory Council

Appendix B Supporting committee

Supporting committee for MSAC application 1009
Sacral nerve stimulation for refractory urinary incontinence or retention

Ms Hilda Bastian (Chair) Health consumer advocate Chairperson, Consumers' Health Forum of Australia; Coordinator, Consumer Network of the Cochrane Collaboration	member of MSAC
Dr Peter Dwyer MBBS, FRACOG, CUG, FRCOG UK Director of Urogynaecology, Mercy Hospital for Women and Royal Women's Hospital, Melbourne	nominated by the Royal Australian College of Obstetricians and Gynaecologists
Mr Warren Johnson MBBS, FRACS, FACS USA Director of Urology, Royal Melbourne Hospital	nominated by the Royal Australasian College of Surgeons
Dr John Primrose MBBS (Hons), FRANZCR Senior Medical Adviser, Commonwealth Department of Health and Aged Care	adviser to MSAC
Mr Douglas Travis MBBS, FRACS(Urol) Consultant Urologist	nominated by the Australian and New Zealand Association of Urological Surgeons

Appendix C Detailed results of studies

Table AC1 Complication rates among study patients with sacral nerve stimulator implants

Study	Year	Implants (n)	Re-operations (n)	Number in sample	Explants (n)	Replaced (n)	Infection (n)	Pain (n)	Lead Problem (n)	Stimulator problem (n)
Bosch	1995	18	4	5	0	0		1	3	
Bosch	1997	35								
Bosch[b]	1998	35					5	3		
Dijkema	1993	23	4	11	0			5		1
Elabbady	1994	17	1	1	1			8		
Groen	1993	26				0				
Grünewald (b)	1999	43	13			1	4	4		
Grünewald (a)	1999	29								
Hassouna	1991	7	0	0	0		0			
Hohenfellner	1998	10	4	4	1		5			
Kolderijn	1999	40	20	36	3	8	4			
Schmidt et al	1999	157	51	51			5/83	29/83	6/83	
Siegel	1992	12	1	1						
Shaker (b)	1998	18	2	2	0	2	2	2		
Shaker (a)	1998	20	6	6	0	4	2	2		
Tanagho	1988	97								
Thon	1991	57								
Weil	1998	36	16	56	12			4/36	22/56	33/56
Weil	1997	21								
Total		701	122		17	15	23	58	41	34
Sample of patients (denominator)			401		189	126	233	270	248	79
Rate			30.4%		9.0%	11.9%	9.9%	21.5%	16.5%	43.0%
95% CI:			26.0–35.2		5.3–14.0	6.8–18.9	6.4–14.4	16.7–26.9	12.1–21.8	31.9–54.7

[a]Pain at the pulse generator implant site, pain at the lead implant site and new pain.
[b]complications described in Bosch and Groen (1996)

Table AC2 Urge incontinence—results at 6 months post implantation: Level II evidence from randomised controlled trial (Schmidt et al 1999)

Endpoint	Implant arm (n=34) Baseline ± SD Post-implant ± SD. (change of mean, p value)	Delayed implant arm (n=42) Baseline ± SD Post-implant ± SD (change of mean, p value)
Leaking episodes/day	9.7 ± 6.3 2.6 ± 5.1 (-7.1, p<0.0001)	9.3 ± 4.8 11.3 ± 5.9 (+2, p=0.002)
Number of pads/day	6.2 ± 5.0 1.1 ± 2.0 (-5.1, p<0.0001)	5.0 ± 3.7 6.3 ± 3.6 (+1.3, p<0.003)
% patients with no need of using pads	15/34 (44%)	n/a
Leaking severity ranking*	2.0 ± 0.7 0.8 ± 0.9 (-1.2, p<0.0001)	1.8 ± 0.6 2.0 ± 0.6 (+0.2, p=0.006)
Symptom improvement	(n=32) completely dry:16 (47%) ≥50% improvement:10 (29%) <50% improvement: 5 (15%) no improvement:3 (9%)	 completely dry: 0 50% improvement: 5 (2%) <50% improvement: 9 (21%) no improvement: 31 (47%)
Quality of life – SF-36	Implant patients (n=28) vs controls (n=32) Mental health component, mean score, 47 vs 45 n.s. Physical health component: Perception of physical health status: mean score, 46 vs 36 , p=0.0008	

* rank of 1: (mild) is defined as drops of urine;
rank of 2: (moderate) is defined as 1-2 tablespoons per leaking episode; and
rank of 3: (heavy) is defined as soaking a pad or outer clothing

Table AC3 Urinary retention—results at 6 months post implantation: Level II evidence from randomised controlled trial (Grünewald et al 1999a)

Endpoint	Implant Control n=29 n=22	
Number (%) patients with complete elimination of catheterisation	20 (69)	2 (22)
Number (%) patients with ≥50% reduction in catheterisations	4 (14)	0
Number (%) patients with <50% reduction in catheterisations	4 (14)	12 (55)
Number (%) patients with no reduction in catheterisations	1 (3)	8 (36)
Catherised volume per catheterisation (ml), baseline to 6 months post-implant, mean (sd)	339±176ml to 49±106ml p=0.05	350±152ml to 319±195ml n.s.
Number of catheterisations/day, baseline to 6 mos. post-implant, mean (sd)	5.7± 3.1 to 1.4±2.6 p=0.05	4.0±1.7 to 3.9±2.2 n.s.
Catheterisation volume/day (ml), baseline to 6 months post- implant, mean (sd)	1744±1047 to 237 ±564 p=0.05	1379±845 to 1305±890 n.s.
Maximum catheterisation volume (ml), baseline to 6 months post-implant, mean (sd)	613 ± 461 to 72 ± 145 p=0.05	563± 276 to 484 ± 292 n.s.
Number voids/day, baseline to 6 months post-implant, mean (sd)	4.0 ± 4.9 to 6.5 ± 3.1 p=0.05	3.2 ± 4.1 to 2.9 ± 4.3 n.s.
Volume voids/day, baseline to 6 months post-implant, mean (sd)	722±1036 to 1808 ± 879 p=0.05	560±769 to 488 ±730 p=0.05

Table AC4 Urge, frequency and urge frequency incontinence—Level IV evidence from case series

Study	Outcome	Result Post- vs pre-implantation, change, significance
Grünewald 1999b		N=18, follow-up interval unknown
	Number (%) of patients clinically cured	7/18 (38.9)
	Number (%) of patients with >50% clinical improvement	13/18 (72.2)
	Urodynamics	
	Volume at 1st sensation	109 vs 80, +29, n.s.
	Bladder capacity	306 vs 278, +28, n.s.
	Mean void volume	292 vs 208, +84, p<0.05
Koldewijn 1999		N=28, follow-up interval unknown
	Number (%) patients stopped using pads	18 (64.3)
	Number (%) patients with <50% improvement.	7 (25.0)
Bosch & Groen 1998	[Follow-up rate: (24/30) implants, no details of sex distribution in 24 patients]	N=24 at last follow-up (mean 36.5, range 6–68 months)
	Completely dry, number (%)	7 (29.2)
	Void frequency/24 hrs	10.3 vs 14.1, -3.8, p=0.006
	Void volume	163 vs 142, +19, n.s.
	Leakage episodes/24 hrs	3.3 vs 7.8, -4.4, p=0.0006
	Pads used/24hrs	2.4 vs 6.6, -2.2, p=0.0004
	Urodynamic assessments	N= 24, follow-up at 6 months
	Bladder capacity	380 vs 306, +74, n.s.
	Volume at 1st sensation	291 vs 213, +78, p=0.04
	Volume at 1st contraction	228 vs 182, +46, n.s.
	Post-void residual	47 vs 64, -17, n.s.
Hohenfellner 1998		N=5, follow-up interval unknown
	Frequency/day	7 vs 14, -7, p<0.05
	Frequency/night	1 vs 3, -2, p<0.05
	Pad used/24 hrs	1 vs 5, -4, n.s.
	Voided volume	334 vs 86, +248, p<0.05
	Bladder capacity	386 vs 130, +256, p<0.05
	Volume at 1st sensation	225 vs 76, +149, p<0.05
Shaker 1998b		N=18, follow-up at 1 month
	Mean incontinence episodes/24 hrs	2.0 vs 6.5, -4.5, p<0.05
	Number (%) of patients completely dry	8/18 (44.4)
	Number (%) of patients with mean <1 leakage episode/24hrs	4/18 (22.2)
	Pure Urge	N=10, follow-up at ≥3 mos
	Frequency of voiding/24 hrs	8.8 vs 15.1, -6.3 p<0.05
	Mean volume increase	41%, n.s.
	Max volume void increase	19%, n.s.
	Cystometrograms	no difference post vs pre implant

Table AC4 continued

Study	Outcome	Result Post- vs pre-implantation, change, significance
Weil 1998		N=24, follow-up at 6 months
	Number (%) of patients with no clinical benefit	10 (41.7)
	Frequency (episodes)	8.7 vs 13.7, -5, p = 0.006
	Major leak episodes	1.1 vs 4.9, -3.8, p=0.004
	Pad use/day	2.3 vs 6.6, -4.4, p=0.001
	Urgency (episodes)	3.1 vs 3.1, 0, n.s.
	Volume voided (ml)	228 vs 158, +70, p=0.01
	Bladder capacity	273 vs 187, +86, p=0.01
	Volume at 1st sensation	194 vs 101, +93, p=0.003
	Volume at 1st contraction	179 vs 114, +65, p=0.06
	Post-void residual	66 vs 110, -44, n.s.
		Median duration of group effect >60 months but therapeutic effect reached by 24 months
	Urge + Frequency	N=6, follow-up at 6 months
	Number (%) of patients with clinical benefit	3/6
	Number (%) of patients with no clinical benefit	3/6
Dijkema 1993		N=17, follow-up interval unknown
	Clinical improvement>90%, n (%)	10 (58.8)
	Clinical improvement 50-90%, n (%)	4 (23.5)
	Clinical improvement <50%, nr (%)	3 (17.6)
	Pads used/day	1.8 vs 4.5, -2.7, ?p
	Leaks/day	1.5 vs 7.4, -5.9,?p
	Mean voided volume	207 vs 118, +89, ?p
Bosch & Groen 1997a		N=35, follow-up interval unknown
	Overall success rate, n(%)	20 (57)
	Complete success (>90% reduced pad use + leakage), n (%)	9 (26)
	Partial success (50-90% reduced pad use + leakage), n (%)	11(31)
	Failed (<50% improvement)	15(43)
Weil 1997		N=21, follow-up at 6 months
	Bladder capacity	260 vs 185, +75, p=0.004
	Volume at 1st stimulation	1179 to 115, +1064, p=0.03
	Volume at 1st desire	198 vs 102, +96, p=0.0002
Bosch and Groen 1995		N=18, follow-up at 6 months
	Mean (SEM) voiding episodes/24hrs	9.4±0.6 vs 15.3±1.5, -5.9, p=0.0005
	Number (%) patients achieved >90% decrease	11/18 (61.1)
	Mean (SEM) voided volume (ml)	178±18 vs 127±13, +51, p=0.006
	Number (%) patients achieved >90% decrease	10/18 (55.6)
	Mean incontinence episodes/24hr	1.9±0.7 vs 7.5±0.8, -5.6, p=0.0002
	Mean (SEM) pads/24 hrs	1.6±0.6 vs 6.4±0.8, -4.8, p=0.0003
	Number (%) patients achieved >90% decrease	11/18 (61.1)
Groen 1993		N=13, follow-up intervals unknown (3-27 mos)
	Complete success	38%
	Partial success	54%
	Mean bladder capacity	435 vs 324, +111, n.s.
	Mean leakage episodes/24hr	2.1 vs 7.7, -5.6, p=0.0001
	Mean voiding frequency/24hr	9.6 vs 16.2, -6.6, p=0.003
	Mean pads/24hr	1.9 vs 6.6, -4.7, p<0.001
	Number (%) patients instability not detected	8/13 (61.5)

Table AC4 continued

Study	Outcome	Result Post- vs pre-implantation, change, significance
Hassouna 1991	Symptoms monitored: urge/frequency	N=3, follow-up interval unknown
	Number of patients with >90% improvement	0
	Number of patients with 50-90% improvement	3
	Number of patients with <50% improvement	0
Thon 1991		N=24, follow-up interval unknown
	Clinical benefit 75–100%, number (%)	15 (62.5)
	Clinical benefit 50–75%, number (%)	5 (20.8)
	Failed (<50%)	4 (16.7)
Tanaglo 1988		N=19, follow-up interval unknown
	Number (%) of patients classified as success	13/19 (68.4)
	Number (%) of patients classified as improved	1/19 (5.3)
	Number (%) of patients classified as failed	5/19 (26.3)

Table AC5 Urinary retention and voiding dysfunction—Level IV evidence from case series

Study	Outcome	Result Post- vs pre-implantation, change, significance
Grünewald 1999		N=21, follow-up interval unknown (≥ 2 mos)
	Clinical improvement >50%, number (%)	18 (85.7)
	Voiding without residual, number (%)	13 (61.9)
	Mean voided volume (ml)	523 vs 33, +490, p≤0.05
	Mean residual volume	113 vs 578, -455, p≤0.05
Koldewijn 1999		N=12, follow-up interval unknown (≥ 5 mths)
	Number (%) of patients who stopped intermittent catheterisation	7 (58.3)
Hohenfellner 1998		N=5, follow-up interval unknown
	Mean (SEM) voided volume (cc)	414 ± 47 vs 70 ± 49, +334, p<0.05
	Mean (SEM) bladder capacity (cc)	670 ± 54 vs 636 ± 66, +34, n.s.
	Mean (SEM) residual volume(cc)	106 ± 51 vs 450 ± 102, -334, p<0.05
Shaker 1998a		N=18, follow-up at 6 months
	Mean (SEM) max bladder capacity (ml)	381 ± 53 vs 384 ± 56, -3, ?p
	Post-void residual volume (%)	5.5 vs 78.3, - 72, ?p
		N=13 (approx values as results presented graphically only) at 6 months.
	Voided volume/24 hr	1750 vs 500, +1250, p≤0.05
	Catheterised vol/24 hr	150 vs 1600, -1350, p≤0.05

Table AC5 continued

Study	Outcome	Result Post- vs pre-implantation, change, significance
Weil 1998	 Number of patients classified as success Number of patients classified as failed	N=6, follow-up interval unknown (≥12months) 3/6 3/6
Elabbady 1994	 Mean (SEM) episodes leakages/day Mean (SEM) intermittent catheter/day Mean (SEM) bladder capacity (ml) % voided volume (urodynamic) % residual volume (urodynamic)	N=8, follow-up at 6 months 1.3 vs 4.1, -2.8 , ?p (n=3) 1.3 ±0.8 vs 4.2 ±0.6, -2.9. n.s, (n=7) 595 ± 123 vs 465 ± 92, +130, n.s. 71 ± 7 vs 15 ± 6, +56, p=0.001 (n=7) 29 ±7 vs 85 ± 6, -56, p=0.001
Dijkema 1993	 >90% improvement, number (%) 50-90% improvement, number (%)	N=3, follow-up interval unknown 2 (66.7) 1 (33.3)
Thon 1991	 Clinical improvement 75–100%, number (%) Clinical improvement 50–75%, number (%) Clinical improvement <50%, number (%)	N=33, follow-up at ≥12 mos 17 (51.5) 6 (18.2) 10 (30.3)

Table AC6 Mixed presentations: urgency/frequency/retention/pain—Level IV evidence from case series

Study	Outcome	Result Post- vs pre-implantation, change, significance
Shaker 1998b	Urgency + retention Mean voided volume/24hours, ml Mean catheterised vol/24 hours, ml	N=7, follow-up at 6 months 1500 vs 600, +900, p≤0.05 1700 vs 500, -1200, p≤0.05
Elabbady 1994	Pain/frequency/urge/retention(Group 2) % patients with improved frequency % patients with improved urgency % patients with decreased leaking episodes % patients with decrease pads/day	N=9, follow-up at 6 months 73% 42% 50% 50%
Seigel 1992	Dysfunctional voiding/retention/pain Virtual complete resolution	N=12, follow-up interval unknown 50%
Hassouna 1991	Symptoms monitored: retention, pain >90% improvement, number (%) 50-90% improvement, number (%)	N=3, follow-up interval unknown 2 (66.7) 1 (33.3)
Tanagho 1988	Post-prostatectomy incontinence Success, number (%) Improved, number (%) Failures, number (%) Pelvic dysfunction syndromes Success, number (%) Improved, number (%) Failures, number (%)	N=20, follow-up interval unknown 8 (40) 0 12 (60) N=56, follow-up interval unknown Males (n=17) Females (n=39) 6 (40) 19 (63) 4 (27) 3 (10) 5 (33) 8 (27)

Table AC7 Long-term effectiveness of sacral nerve stimulator implants in voiding parameters of patients with urge incontinence, urgency- frequency and urinary retention

Indication	Patients (n)	Voiding parameter	Baseline mean±SD	At follow-up mean±SD	Significance level
Urge incontinence	41			At 3 years:	
		≥50% reduction in leaks/day	-	59%	-
		Leaks/day (n)	11.6±6.6	5.0±6.1*	p<0.0001
		Heavy episodes/day(n)	3.6±4.0	1.3±3.5*	p<0.0001
		Pads/day (n)	6.7±4.6	3.4±4.9*	p<0.0001
Urgency-frequency	29			At 2 years	
		≥50% reduction in voids/day	-	56%	-
		Voids/day(n)	17.7±8.6	10.6±6.6	p<0.0001
		Volume/void (mL)	132.5±93.6	225±162	p<0.0001
Urinary retention	42			At 1.5 years	
		≥50% reduction in vol/catherisation	-	70%	-
		catheterised volume (ML)	343±167	91.4±154.6	p<0.0001

Appendix D Patient satisfaction survey

Objective of study

The stated objective of the telephone survey was to assess patient satisfaction with sacral nerve stimulator implants (InterStim® Continence Control Therapy) among urinary incontinence and pelvic pain sufferers. The results of the survey were reported to Medtronic on 27 April 1999.

Study design

Details of the study design for the survey are as follows:

Survey design	observational cross-sectional
Number of groups	one
Criteria for selection	patients with implants for bladder control
Number of periods of data collection	one
Reference period for data collection	present, with recall of past
Method of data collection	telephone interview using standardised script
Date of data collection	March 1999

Validity

Randomisation

Random sampling was not used to select patients. A convenience sample was used.

Sample size

The survey's primary objective was to estimate patient satisfaction with implantable stimulators. No details were provided of a priori decisions on confidence levels or range of precision for the estimate of satisfaction used to calculate sample size.

Follow-up rate

Data was collected on 35 (13.8%) patients from a list of 254 names of implanted patients provided by the manufacturer (Medtronic). The remaining patients were lost to follow-up (classified as unreachable, n=62, 24.4%; not at home at time of call, n=157, 61.8%). No details of the existence of patients who refused to participate are reported.

Potential for bias

The potential sources for systematic error or bias in these results derives from whether the survey accurately measures the effects of treatment (for example, validation of instrument with patients' medical records) and the high proportion of selected patients who did not respond. The low response rate also affects the precision of the estimates of patient satisfaction.

Results

Thirty-two women and three men with a mean age of 47 (range 15 to 77) participated in the survey. These patients had the following indications for treatment:

- urge incontinence, urge/frequency: n (%) 23 (65.7%)
- urinary retention: n (%): 1 (2.9%)
- pain, n (%): 11 (31.4%)

The Medtronic report mentions a 10-year coverage of patients with implants. This is misleading as 34 patients had implants in the last four years (since 1996) and only one patient had the implant prior to that, in 1989. Almost one quarter (n=8) of the patients surveyed had their implants for a maximum of 4 months (the survey took place during the period from 2 March to 30 March 1999).

Measures of satisfaction

The survey consisted of closed-ended (eg yes/no; scales from 1 to 10) and open-ended questions. This evaluation evaluates results of a selection of closed-ended questions. Some results were categorised by indication; however, these are not reported here as division of an already small sample size would not add useful information.

Effect of therapy on specific physical activities pre-/post implant

The survey sample (n=35) were asked to rank the importance and then the ability to perform specific physical activities pre- versus post-implantation. Significant improvements for the top five most highly ranked activities were reported for (number of patients pre- versus post-implant): 'sleep all night' (7 vs 18), 'exercise' (13 vs 24), 'leave house' (7 vs 31), 'take short rides in car' (25 vs 32). For the fourth most highly ranked activity 'going out for dinner', improvement did not reach statistical significance.

Effect on feelings of self-esteem pre-/post implant

Patients were asked to recall their feelings of self-esteem pre-implantation versus post-implantation on a 10-point scale where only the extremes were defined (1=very low self-esteem and 10=very high self-esteem). Among 35 patients, there was a significant improvement from pre-implantation ratings to post-implantation ratings: mean (sd) pre- versus post-implant: 3.4 (2.5) versus 7.4 (2.3), $p<0.001$ (unpaired Student t-test). The 95 per cent confidence interval for the difference of 4.0 points is from 2.9 to 5.1 points.

Satisfaction with overall health and quality of life pre-/post-implant

Patients were asked to recall their satisfaction with their health and quality of life pre-/post-implantation on a 10-point scale where only the extremes were defined (1=not at all satisfied and 10=very satisfied). Among 35 patients, there was a significant improvement in satisfaction from pre-implantation to post-implantation: mean (sd) pre- versus post-implant: 3.3 (2.7) vs 7.3 (2.3), $p<0.001$ (unpaired Student t-test). The 95 per cent confidence interval for the 4.0 point difference is from 2.8 to 5.2.

Satisfaction with InterStim® implant therapy

Sixty-five per cent of 34 respondents (n=23) rated their satisfaction with the implant at 8 or higher on a 10-point scale (1=not at all satisfied, 10=very satisfied). Average ranking was 7.3, with a standard deviation of 3.0 and 95 per cent confidence interval of 6.2 to 8.3.

Abbreviations

ANDRG	Australian National Diagnosis Related Groups
BDI	Beck Depression Inventory
CI	confidence interval
FDA	Food and Drug Administration (US)
IPG	implantable pulse generator
ITT	intention-to-treat
MBS	Medicare Benefits Schedule
MCAC	Medicare Coverage Advisory Committee
MS	multiple sclerosis
MSAC	Medicare Service Advisory Committee
NHMRC	National Health and Medical Research Council
NNH	number needed-to-harm
NNT	number needed-to-treat
PNE	percutaneous nerve evaluation
RCT	randomised controlled trial
SEM	standard error of the mean
SF-36	short form 36
SNSI	sacral nerve stimulator implant
UDI-6	Urinary Distress Inventory

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