Horizon scanning in surgery: Application to surgical education and practice

Sacral nerve stimulation for the treatment of refractory constipation

March 2009

AMERICAN COLLEGE OF SURGEONS

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Division of Education

Prepared by the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical for the American College of Surgeons

Disclaimer

This report is not a comprehensive systematic review. Rather, it is an assessment of an emerging surgical procedure or technology in which the methodology has been limited in one or more areas to shorten the timeline for its completion.

Therefore, this report is a limited evidence-based assessment that is based on a search of studies published in the peer-reviewed literature. This report is based on information available at the time of research and cannot be expected to cover any developments arising from subsequent improvements in health technologies. This report is based on a limited literature search and is not a definitive statement on the safety, effectiveness or cost-effectiveness of the health technology covered.

This report is not intended to be used as medical advice or to diagnose, treat, cure or prevent any disease, nor should it be used for therapeutic purposes or as a substitute for a health professional's advice. The Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) does not accept any liability for any injury, loss or damage incurred by use of or reliance on the information.

Objective

This horizon scanning assessment provides a short, rapidly completed, “state of play” report. It provides current information on technologies to alert clinicians, planners and policy makers of the advent and potential impact of a new or emerging procedure or device. This information can assist clinicians, planners and policy makers in controlling and monitoring the introduction of new health technologies, as well as assist in the prioritization and allocation of resources to promote efficient utilization of available resources.

This report is a preliminary summary of the safety, effectiveness and cost-effectiveness of sacral nerve stimulation for constipation.

Introduction

Indications

Constipation is often characterized by abdominal bloating and pain, difficulty in evacuating feces and decreased bowel movement frequency. Chronic constipation can be classified into three main categories: slow-transit constipation, disorders of defecation (rectal evacuation) or both (Holzer et al 2008). Constipation can result from systemic or neurogenic disorders or medications, and the cause is frequently multifactorial. Organic and drug-associated causes typically account for only a small proportion of cases, with the majority of patients experiencing idiopathic functional constipation (Holzer et al 2008).

Burden of disease

Constipation affects between 2% and 27% of the population in Western countries. In the United States this equates to between 4 and 56 million affected adults. From 1988 to 2003 the cumulative incidence of chronic constipation in Minnesota, United States was 17.4% (Choung et al 2007). In the United States, constipation is the reason for more than 2.5 million visits to physicians, 92,000 hospitalizations and $800 million in laxative sales per year (Sonnenberg and Koch 1989, Lembo and Camilleri 2003). Constipation is more prevalent in women, nonwhites, children and the elderly. Severe constipation occurs almost exclusively in women. Constipation is associated with significantly lower quality of life and higher psychological distress. A recent survey found that the estimated average cost of managing constipation was $200 per patient in a large health maintenance organization groups (Singh 2007).

Technology and procedure

Sacral nerve stimulation (SNS) has emerged in recent times as an alternative minimally invasive surgical technique for those who do not respond to conservative treatments. SNS for constipation involves modulating the nerves and muscles of the pelvic floor and hindgut. A low amplitude electrical current is applied to the sacral nerve via an electrode placed through the corresponding sacral foramen (Mowatt et al 2007).

The electrode leads and the stimulation generator typically utilized for SNS were developed by Medtronic, Inc. (Minneapolos, MN, United States) and are marketed as the InterStim® System. The procedure involves an acute/temporary testing phase prior to the implantation of a permanent pulse generator to determine the system's short-term efficacy in selected patients. The acute phase test is performed under local anesthesia with a temporary percutaneous peripheral nerve electrode attached to an external neurostimulator. The electrode is positioned bilaterally into the S2, S3 and S4 foramina. The external neurostimulator is then activated to elicit the best physical response of the pelvic floor. The best foramen for stimulation is then determined via visual judgement and electromyographic measurements. This testing phase is often performed for a 2- to 3-week period after which the temporary electrode is removed (Kenefick et al 2002a).

In patients who are eligible for chronic or permanent SNS, permanent electrodes are implanted and secured (under general anesthesia) in the optimal foramen for stimulation determined during the acute testing phase. The implantable stimulation generator is placed in the ipsilateral buttock or the anterior abdominal wall. SNS can only be utilized for idiopathic constipation because some residual anal sphincter function is necessary for treatment success.

Stage of development

The concept of stimulating the nerve supply to the large bowel to produce a physiological effect was first applied therapeutically by Brindley (1990) for the treatment of bladder and bowel dysfunction in patients with chronic spinal injury. As the technique gained recognition, it was eventually applied successfully to treat detrusor irritability, urinary retention and fecal incontinence (Kenefick et al 2002a). However, the mechanism of action for SNS remains unknown.

Regulatory approval

The InterStim system is widely diffused worldwide and has been used to treat urinary and fecal incontinence. InterStim therapy was released commercially in Europe, Canada and Australia in

April 1994. In 1997 the InterStim system was approved by the United States Food and Drug Administration (FDA) for the treatment of urinary urge incontinence (PMA no: P970004). In 1999 InterStim therapy was approved by the FDA for the treatment of urinary retention and significant symptoms of urgency-frequency (Medtronic 2009a, FDA 1999).

Current clinical trials

A multicentre European study evaluating the efficacy and safety of SNS with InterStim Therapy in patients with fecal incontinence or constipation is currently underway (ClinicalTrials identifier: NCT00200005). This open label case series study is funded by Medtronic and has enrolled 140 patients (ClinicalTrials 2009).

Current treatment and alternatives

Conservative treatment of constipation includes dietary and lifestyle advice, drug therapy (laxatives, enemas, etc.) and biofeedback therapy. These treatments are typically adequate in most patients; however, symptoms may persist in a small group of treatment-resistant individuals. In these patients, surgical treatment may be considered.

The most commonly utilized surgical treatments for constipation are subtotal colectomy and ileocecal anastomosis or stoma formation. However, subtotal colectomy with ileocecal anastamosis has been associated with significant morbidity (Kamm 1988). Approximately 33% of patients who were treated with this technique developed diarrhea, 10% remain constipated and 10% progress to a permanent ileostomy (Kenefick et al 2002a). In addition, stoma formation may not resolve symptoms of abdominal pain and bloating (van der Sijp 1991).

Literature review

Search criteria

Keyword/MeSH terms utilized:

Constipation/therapy*, Electric simulation therapy/methods*, sacral nerve stimulation constipation, neuromodulation constipation

Databases utilized:

PubMed

Inclusion criteria

The inclusion criteria utilized for study selection is listed below (Table 1):

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Randomized controlled trials, non-randomized comparative studies, case series studies
Patient	Adult (≥18 years) male or female patients with constipation refractory to conventional treatment
Intervention	Sacral nerve stimulation
Comparator	Conventional surgery, conservative treatment, placebo/sham
Outcome	Primary outcomes (bowel movement, Wexner score etc.), quality of life (SF-36), secondary outcomes (manometric measurements)
Language	English only

Included studies

Six studies were identified for inclusion in this report (Table 2).

Table 2 Characteristics of included studies

Study/location	Level of evidence	No. of patients	Duration of follow-up
Dinning et al 2006	II	8	3 weeks
Australia	*Randomized trial*		
Kenefick et al 2002a	III-1	2	4 weeks
United Kingdom	*Crossover study*		
Holzer et al 2008	IV	19	12 months
Austria	*Case series study*		
Ganio et al 2001	IV	12	Minimum of 7 days
Italy	*Case series study*		Median: 9.9 days (range: 7-30 days)
Malouf et al 2002	IV	8	3 weeks
United Kingdom	*Case series study*		
Kenefick et al 2002b	IV	4	8 months (range: 1-11 months)
United Kingdom	*Case series study*		

Note: Refer to Appendix B for level of evidence definition

Critical appraisal

One randomized trial and one crossover study were identified and retrieved. The randomized study was conducted by Dinning et al (2006) to evaluate the effect of SNS on colonic pressure patterns and its potential to treat severe constipation. Eight patients were subjected to 14Hz SNS and four sets of parameters were tested (pulse width: 200 or 400 microseconds; S2 or S3 sacral nerve foramina) in random order for 2 days. In the second phase of this study, patients were then discharged and underwent 3 weeks of subchronic, continuous SNS. The data from the second phase will be classified as a case series study for the purposes of this report, as there was no comparator to SNS. SNS methodology, primary outcomes, statistical analysis and follow-up loss were clearly described.

The crossover study by Kenefick et al (2002a) enrolled two patients with the following characteristics: failed maximal conservative treatment, psychologically stable, normal sigmoidoscopy, prolonged whole gut transit time and delayed evacuation. Both patients and investigators were blinded to the treatment (placebo/SNS); it was not clear if outcome assessors were blinded. The study consisted of two 2-week intervals with “on” or “off” subsensory SNS. Patient baseline characteristics were not presented, no statistical tests were conducted and SF-36 quality of life data were not provided despite comments of substantial improvement.

A total of four National Health and Medical Research Council (NHMRC) Level IV studies (Appendix B) were identified for inclusion. These studies were not randomized and did not have a concurrent control group (case series studies). Rationale for patient inclusion was stated clearly in all studies (Table 3).

Table 3 Inclusion criteria and treatment/stimulation parameters of included studies

Study	Inclusion criteria	SNS treatment
Dinning et al 2006	• Constipation for at least 1 year • Failed maximal medical therapy (laxatives and biofeedback) • Met Rome II criteria • Slow transit demonstrated by colonic scintigraphic transit study	Acute testing phase (2 hours) followed by 3 weeks of subchronic, continuous SNS. Pulse width: 300-400 microseconds, frequency: 14Hz
Kenefick et al 2002a	• Severe resistant idiopathic constipation • Failed maximal conservative treatment • Psychologically stable	Temporary 3 weeks SNS stimulation trial, followed by implantation of permanent SNS stimulator. Stimulation parameters not stated.
Ganio et al 2001	• Difficulty (use of finger or squeezing) emptying the rectum or feeling of incomplete evacuation for >50% of bowel movements in previous year • Failure of conventional drugs or biofeedback therapy, structurally intact external and internal anal sphincter • Normal sphincter behaviour	Acute testing phase followed by chronic SNS phase for minimum of 7 days. No permanent implantation. <u>Acute testing phase</u> Unipolar monophase impulse, pulse width: 210 microseconds, frequency: 25 Hz, amplitude: 1-6V <u>Chronic phase (temporary)</u> Unipolar monophase impulse, pulse width: 210 microseconds, frequency: 25 Hz, Amplitude: 2-8V
Holzer et al 2008	• Age 18-85 years • Severe constipation, at least one of the following criteria: a) pathologic colonic transit constipation, b) rectal outlet obstruction	Percutaneous temporary SNS trial followed by implantation of permanent SNS stimulator. Continuous stimulation mode, pulse width: 210 microseconds, frequency:

	• Minimum 1 year symptoms • Failed biofeedback (rectal emptying problems)	16Hz, median stimulation amplitude: 5 volts.
Kenefick et al 2002b	• Severe idiopathic constipation • Failed maximal medical therapy	Temporary stimulation for 21 to 22 days, followed by implantation of permanent SNS stimulator. Stimulation parameters not stated.
Malouf et al 2002	• Constipation defined by Rome criteria and slow gut transit documented on radiopaque marker studies in last 12 months • Failed traditional conservative treatments • Failed full course biofeedback treatment • No surgery for constipation • Psychologically stable	Percutaneous stimulation for 3 weeks. No permanent implantation. Continuous mode, pulse width: 210 microseconds, frequency: 15Hz, amplitude: 3-10V

Two of the Level IV studies utilized short-term/temporary SNS (Malouf et al 2002, Ganio et al 2001) while the remaining two studies performed a short-term testing phase followed by permanent implantation of a stimulator (Kenefick et al 2002b, Holzer et al 2008). All case series studies were conducted prospectively, but consecutive patient recruitment was not clearly stated. Losses to follow-up were described in all studies. Stimulation parameters varied between studies (Table 3) and were generally well described in all but two studies (Kenefick et al 2002a, Kenefick et al 2002b). Of the included studies, one had patients with mixed indications where the overall patient cohort included fecal incontinent patients as well (Ganio et al 2001). There is an overlap of two patients between Kenefick et al 2002b and Malouf et al 2002.

Four of the six studies selected for inclusion were supported by or has an author supported by the manufacturer (Kenefick et al 2002a, Kenefick et al 2002b, Malouf et al 2002, Dinning et al 2006). Three of these studies claimed that Medtronic had no influence on study design, execution, analysis and reporting (Kenefick et al 2002a, Kenefick et al 2002b, Malouf et al 2002).

Given the small sample sizes of all the retrieved studies, short follow-up, lack of comparison of patient outcomes, follow-up losses and inconsistent measures of success, the conclusions that can be elucidated from the available evidence are likely to be limited.

Safety and efficacy

Safety

Dinning and colleagues (2006) noted that one patient (1/8, 12.5%) complained of persistent discomfort around the skin insertion site of the electrodes. Seven days after initial implantation, the electrodes were removed at the request of this patient. Another patient reported that stimulation could no longer be felt (1/8, 12.5%) after 4 days of subchronic testing[1], regardless of voltage applied. As a result, subchronic data are only available for six of the eight patients. None of the patients experienced any abnormal abdominal, bowel or urinary symptoms during the acute

[1] Patients underwent an "acute" SNS testing phase (2 days) to assess the immediate responses to four different combinations of stimulus parameters. After discharge, patients underwent 21 days of continuous subchronic SNS stimulation to assess symptomatic response.

test period (Dinning et al 2006).No safety data were presented in the crossover study (Kenefick et al 2002a).

Kenefick et al (2002b) noted that no major complications occurred during the study. There were no infections of the permanent SNS implants and no implants were removed. Lead dislodgement occurred in one patient (1/4; 25%) due to a major road accident (Kenefick et al 2002b).

Ganio et al (2001) did not report the safety outcomes for patients treated for fecal incontinence or constipation separately. However, there were no complications or infections during the stimulation period or the following weeks (follow-up: median 9.9 days). Holzer et al (2008) observed one loss of stimulation effect (1/19, 5.3%), due to trauma, 4 months after implantation. The patient was scheduled for replacement of the dislodged electrode. The authors did not describe any complications after permanent placement or during follow-up (follow-up: 12 months). Malouf and colleagues (2002) reported no procedural complications and no side effect from continuous stimulation (follow-up: 3 weeks). Similarly, Kenefick et al (2002a) did not notice any complications throughout the study (follow-up: 8 months).

Overall, no severe complications due to SNS were reported in the included studies. Loss of stimulation and lead/electrode dislodgement was the most common complication and was reported in four out of five studies (Kenefick et al 2002b, Ganio et al 2001, Dinning et al 2006, Holzer et al 2008).

Efficacy

A) Primary outcomes

The majority of studies noted marked differences in the frequency of bowel movements or defecation during SNS (Table 4). The crossover study noted that bowel movements per week increased by 150% with SNS (Kenefick et al 2002a). The randomized study noted that patients treated with SNS experienced a significant improvement in bowel movements per week (0.8 ± 1.1 to 7.4 ± 2.7; *P*=0.0003) compared to baseline values (Dinning et al 2006). Three of the four case series studies reported an improvement in bowel movement with SNS compared to baseline values, but these results were not statistically verified (Holzer et al 2008, Kenefick et al 2002b, Malouf et al 2002). In one of these studies, positive results (cessation of symptoms and improved bowel frequency) were only apparent in two of eight patients. The remaining patients did not exhibit any improvement compared to baseline values (Malouf et al 2002). One study noted that the number of voluntary bowel movements per week did not improve with SNS (Ganio et al 2001).

Wexner scores[2] were reported in three of the six studies. All three studies noted improvements in Wexner constipation scores during SNS, but this was not verified statistically (Kenefick et al 2002a, Holzer et al 2008, Kenefick et al 2002b). SF-36 Health Survey scores were utilized to assess patient health-related quality of life in three studies (Kenefick et al 2002a, Kenefick et al 2002b, Holzer et al 2008). The randomized crossover study stated that substantial improvement of SF-36 scores were observed in both patients; however, no data was presented (Kenefick et al 2002a). Similarly, one of the case series studies did not provide SF-36 data despite reporting improvements in patient quality of life (Kenefick et al 2002b). Meanwhile, Holzer et al (2008) reported significant improvements in all SF-36 parameters at 6-months follow-up (Table 4).

[2] Utilized to determine severity of constipation.

Utilising a custom visual analog scale (VAS), Malouf et al (2002) noted that the two of eight patients who experienced improvement in bowel movements reported substantial improvement of their symptoms. VAS scores for the remaining six patients were similar to baseline values. Colonic transit time did not normalize in any patient, including those who achieved symptomatic improvement with SNS (Malouf et al 2002). Although no improvement in bowel frequency was observed, Ganio et al (2001) reported that patients experienced a significant decrease in the perceived difficulty of emptying the rectum (*P*<0.01) and a significant decline in the number of unsuccessful toilet visits (*P*=0.01).

Table 4 Primary efficacy outcomes during SNS for constipation

Study details	Outcomes
Kenefick et al (2002a) Level II intervention evidence No. of patients: 2 Age: 36 years (both patients)	**Patient 1** Bowel frequency: Baseline 1, 1 year 15, Stim. "on" 2, Stim. "off" 10 Time with pain and bloating: Baseline 95, 1 year 0, Stim. "on" 65, Stim. "off" 0 Wexner constipation score (0-30): Baseline 22, 1 year 4, Stim. "on" 15, Stim. "off" 5 Symptom analog score (0-100): Baseline 32, 1 year 94, Stim. "on" 30, Stim. "off" 88 **Patient 2** Bowel frequency: Baseline 6, 1 year 17, Stim. "on" 4, Stim. "off" 8 Time with pain and bloating: Baseline 100, 1 year 0, Stim. "on" 93, Stim. "off" 65 Wexner constipation score (0-30): Baseline 20, 1 year 6, Stim. "on" 13, Stim. "off" 13 Symptom analog score (0-100): Baseline 28, 1 year 84, Stim. "on" 33, Stim. "off" 60 *Stim: SNS stimulation
Dinning et al (2006) Level II intervention evidence No. of patients: 8 Age (mean ± standard deviation): 43 ± 14.6 years	**6/8 patients reported improvement in number of bowel movements per week (*P*=0.0003) [mean ± standard deviation]** Prestimulation: 0.8 ± 1.1 (n=6) During stimulation: 7.4 ± 2.7 (n=6) **Laxative use (days per week) (*P*=0.05)** Prestimulation: 4.7 ± 3.0 days During stimulation: 1.5 ± 1.9 days
Ganio et al (2001) Level IV intervention evidence No. of patients: 12 Age: Not stated	**Number of voluntary bowel movements per week (*P*=0.2) [mean (range)]** Prestimulation: 9.5 (2-28) End of stimulation: 6.4 (range: 2-14) **Number of times experienced difficulty in emptying rectum per week (*P*<0.01)** Prestimulation: 7 (2-21) End of stimulation: 2.1 (0-6) **Number of unsuccessful visits to toilet per week (*P*=0.01)** Prestimulation: 29.2 (7-24) End of stimulation: 6.7 (0-28) **Time necessary to evacuate (*P*=0.4)** Prestimulation: 12.5 (5-20) minutes End of stimulation: 9.3 (5-30) minutes

<table>
<tr><th>Study details</th><th>Outcomes</th></tr>
<tr><td>Holzer et al (2008)

Level IV intervention evidence

No. of patients: 19
Age (median [range]: 64 [21-81]</td><td>8/19 (42%) patients reported improvement according to the following criteria:
• More than 2 bowel movements per week with more than 50% reduction in the weekly amount of laxative intake, and
• Rectal emptying without the need for digital manipulation or a reduction of irrigation procedures by more than 50% during the screening period
Wexner constipation score improved from baseline (median: 23 [18-27]) to 12 months post-implantation (median: 8 [4-13]). No statistical tests were conducted.

SF-36 evaluation (mean ± standard deviation)

<table>
<tr><th></th><th>Pre SNS (n=19)</th><th>6-month follow up (n=7)</th><th>P-value</th></tr>
<tr><td>Physical functioning</td><td>52.82 ± 21.43</td><td>70.29 ± 25.01</td><td><0.001</td></tr>
<tr><td>Role physical</td><td>46.57 ± 29.54</td><td>61.16 ± 27.73</td><td><0.001</td></tr>
<tr><td>Bodily pain</td><td>49.44 ± 21.19</td><td>61.02 ± 23.93</td><td><0.001</td></tr>
<tr><td>General health</td><td>53.34 ± 19.52</td><td>56.37 ± 21.27</td><td><0.033</td></tr>
<tr><td>Vitality</td><td>45.23 ± 27.28</td><td>64.82 ± 29.37</td><td><0.001</td></tr>
<tr><td>Social functioning</td><td>53.43 ± 26.57</td><td>71.06 ± 25.97</td><td><0.001</td></tr>
<tr><td>Role emotional</td><td>65.99 ± 45.2</td><td>74.09 ± 2597</td><td><0.001</td></tr>
<tr><td>Mental health</td><td>57.81 ± 20.63</td><td>68.39 ± 22.0</td><td><0.001</td></tr>
</table>
</td></tr>
<tr><td>Kenefick et al (2002b)

Level IV intervention evidence

No. of patients: 4
Age: 27-36 years</td><td>Bowel frequency (per 3 weeks)
Prestimulation: range 1-6
During stimulation: range 6-28

Evacuation score (0: no difficulty; 4: severe difficulty) [median (range)]
Prestimulation: 4 (0-4)
During stimulation: 1 (0-4)

Wexner score (range from best [0] to worst [30])
Prestimulation: 21 (20-22)
During stimulation: 9 (1-20)

Visual analog score (range from best [100] to worst [0])
Prestimulation: 22 (16-32)
During stimulation: 80 (20-98)</td></tr>
<tr><td>Malouf et al (2002)

Level IV intervention evidence

No. of patients: 8
Age (median [range]): 47 [35-68] years</td><td>Bowel frequency
<table>
<tr><th>Patient</th><th colspan="3"># of bowel actions over 3-week period</th></tr>
<tr><th></th><th>Before stimulation</th><th>During stimulation</th><th>After stimulation</th></tr>
<tr><td>1</td><td>6</td><td>13</td><td>6</td></tr>
<tr><td>2</td><td>1</td><td>9</td><td>1</td></tr>
<tr><td>3</td><td>3</td><td>3</td><td>…</td></tr>
<tr><td>4</td><td>9</td><td>5</td><td>…</td></tr>
<tr><td>5</td><td>6</td><td>4</td><td>…</td></tr>
<tr><td>6</td><td>2</td><td>2</td><td>…</td></tr>
<tr><td>7</td><td>5</td><td>6</td><td>…</td></tr>
<tr><td>8</td><td>4</td><td>6</td><td>…</td></tr>
</table>
Visual analog scale
<table>
<tr><th>Patient</th><th colspan="3">Visual analog score rating for bowel symptoms</th></tr>
<tr><th></th><th>Before stimulation</th><th>During stimulation</th><th>After stimulation</th></tr>
<tr><td>1</td><td>28</td><td>73</td><td>23</td></tr>
<tr><td>2</td><td>32</td><td>88</td><td>15</td></tr>
<tr><td>3</td><td>33</td><td>34</td><td>…</td></tr>
<tr><td>4</td><td>14</td><td>15</td><td>…</td></tr>
</table>
</td></tr>
</table>

Study details	Outcomes			
	5	2	5	…
	6	4	2	…
	7	3	15	…
	8	4	11	…
	Note: …not reported			

B) Secondary outcomes

Colonic propogation sequences are important for normal colonic transit and defecation. These pressure waves are classified into propagating sequences (PS) or high amplitude propagating sequences (HAPSs) based on the amplitude of the component pressure waves. In healthy subjects, defecation is preceded by a substantial increase in the frequency and amplitude of colonic propagating pressure waves throughout the colon (Dinning et al 2006). In an effort to identify the physiological effects of SNS, Dinning et al (2006) conducted a randomized trial to examine the influence of short-term SNS on colonic pressure waves using pan-colonic manometry as an indicator of response. The study demonstrated that SNS increased the frequency of both antegrade (*P* = 0.02) and retrograde PSs (*P* = 0.02) throughout the colon (Table 5). In addition, a significant increase in the frequency of HAPSs (pre SNS: 0.05 ± 0.08 HAPS/hour, during SNS: 0.5 ± 0.4 HAPS/hour; *P* = 0.04) and PSs which propagate more than 30 cm along the bowel (pre SNS: 0.8 ± 0.6 PS/hour, during SNS: 2.7 ± 1.8 PS/hour; *P* = 0.02) was achieved with SNS, a characteristic that is typically associated with luminal propulsion and defecation in healthy individuals. This may explain the improvement in bowel movement and a reduction in laxative requirements experienced by all patients in this study. None of the differences observed in the PS parameters measures could be attributed to pulse width (300 vs 400 μs). Stimulation of the S3 sacral nerve foramen resulted in a significant increase in total antegrade colonic PS frequency (pre SNS: 5.4 ± 4.9 PS/hour, during SNS: 11.3 ± 6.6 PS/hour; *P* = 0.04) and HAPS frequency (pre SNS: 0.06 ± 0.09 HAPS/hour, during SNS: 0.7 ± 0.6 HAPS/hour; *P* = 0.04). Only stimulation of the S2 resulted in an increase of retrograde PS frequency (pre SNS: 2.6 ± 1.8 PS/hour, during SNS: 5.6 ± 4.8 PS/hour; *P* = 0.03). Evaluation of additional frequencies is required to determine the optimal stimulation parameters for the treatment of constipation.

A significant increase in amplitude of maximum squeeze pressure was evident in one study during SNS (*P* = 0.009) as well as a significant reduction in rectal volume for the urge threshold (*P* = 0.004) (Table 5) (Ganio et al 2001). These observations may suggest that SNS has influence on sensory fibers and that the improvement in evacuation difficulties and unsuccessful attempts may be related to a change in rectal sensitivity leading to better coordination between the rectum and sphincter (Ganio et al 2001). In another case series study, the only physiological parameter to change significantly with SNS was the sensory threshold to rectal balloon distension (prestimulation: 47 ml [10-110] vs during stimulation: 25ml [10-30]; *P*=0.02) (Malouf et al 2002).

Kenefick et al (2002b) stated that maximal anal resting pressure increased from 75 (52-99) [median (range)] cmH_2O to 91 (72-114) cmH_2O and maximal incremental squeeze pressure from 42 (32-102) cmH_2O to 63 (40-119) cmH_2O. Rectal sensation, urge sensation and maximum tolerated volume improved with SNS (Table 5). Of the two patients with slow transit time, one patient achieved normal transit time with permanent SNS (Kenefick et al 2002b).

Table 5: Secondary efficacy outcomes during SNS for constipation

Study details	Secondary outcomes
Dinning et al (2006) Level II intervention evidence No. of patients: 8 Age (mean ± standard deviation): 43 ± 14.6 years	**Propagating sequences** **Total colon** **Basal** / **SNS** / ***P*-value** **Antegrade propagating sequences** PS frequency (per hour): 5.4 ± 4.9 / 10.1 ± 6.4 / 0.02 HAPS (per hour): 0.05 ± 0.1 / 0.5 ± 0.4 / 0.04 PS extend >30 cm (per hour): 0.8 ± 0.6 / 2.7 ± 1.8 / 0.02 PS amplitude (mmHg): 28.1 ± 3.6 / 31.7 ± 6.7 / ns PS velocity (cm/s): 1.7 ± 0.6 / 1.7 ± 0.6 / ns **Retrograde propagating sequences** PS frequency (per hour): 2.6 ± 1.8 / 5.1 ± 3.4 / 0.02 HAPS (per hour): 0 PS extend >30 cm (per hour): 0 PS amplitude (mmHg): 25.2 ± 6.9 / 26.7 ± 6.2 / ns PS velocity (cm/s): 1.2 ± 0.5 / 1.5 ± 0.8 / ns **Right colon** **Basal** / **SNS** / ***P*-value** **Antegrade propagating sequences** PS frequency (per hour): 3.5 ± 1.9 / 6.4 ± 3.6 / 0.04 HAPS (per hour): … / … PS extend >30cm (per hour): … / … PS amplitude (mmHg): 26.9 ± 4.2 / 27.8 ± 5.3 / ns PS velocity (cm/s): 1.6 ± 0.7 / 1.4 ± 0.5 / ns **Retrograde propagating sequences** PS frequency (per hour): 1.5 ± 1.6 / 3.0 ± 2.8 / 0.02 HAPS (per hour): … / … PS extend >30 cm (per hour): … / … PS amplitude (mmHg): 23.8 ± 7.8 / 27.5 ± 7.2 / ns PS velocity (cm/s): 1.1 ± 0.4 / 1.3 ± 0.6 / ns **Left colon** **Basal** / **SNS** / ***P*-value** **Antegrade propagating sequences** PS frequency (per hour): 2.2 ± 2.7 / 3.7 ± 3.6 / 0.01 HAPS (per hour): … / … PS extend >30 cm (per hour): … / … PS amplitude (mmHg): 29.5 ± 6.8 / 34.9 ± 9.4 / ns PS velocity (cm/s): 1.8 ± 0.5 / 2.1 ± 1.0 / ns **Retrograde propagating sequences** PS frequency (per hour): 0.7 ± 0.9 / 0.9 ± 0.9 / ns HAPS (per hour): … / … PS extend >30 cm (per hour): … / … PS amplitude (mmHg): 24.8 ± 4.6 / 26.9 ± 6.7 / ns PS velocity (cm/s): 1.4 ± 0.8 / 1.6 ± 1.1 / ns Note: results presented as mean ± standard deviation;… not reported; ns not significant.
Ganio et al (2001) Level IV intervention evidence No. of patients: 12 Age: Not stated	**Manovolumetric results** **Prestimulation** / **End of stimulation** / ***P*-value** Resting pressure (mmHg): 73 ± 27.3 / 80 ± 29.3 / ns Squeeze pressure (mmHg): 120 ± 33.1 / 126 ± 33.8 / ns Max squeeze pressure (mmHg): 63 ± 0 / 78 ± 1 / 0.009 Feeling threshold (cm H2O): 20 ± 9.2 / 18 ± 5.8 / ns Feeling threshold (ml): 106 ± 33.5 / 89 ± 39 / ns

<table>
<tr><th>Study details</th><th>Secondary outcomes</th></tr>
<tr><td></td><td>
<table>
<tr><td>Urge sensation (cm H2O)</td><td>42 ± 23.4</td><td>35 ± 18</td><td>ns</td></tr>
<tr><td>Urge sensation (ml)</td><td>189 ± 52.99</td><td>1389 ± 52.3</td><td>0.004</td></tr>
<tr><td>Rectal compliance (ml/cm H2O)</td><td>3.8 ± 2.1</td><td>4.2 ± 2.4</td><td>ns</td></tr>
</table>
Note: results presented as mean ± standard deviation; ns not significant.
</td></tr>
<tr><td>Kenefick et al (2002b)

Level IV intervention evidence

No. of patients: 4
Age: 27-36 years</td><td>
Manometric results
<table>
<tr><th></th><th>Before stimulation</th><th>During stimulation</th></tr>
<tr><td>Anal resting pressure (cmH_2O)</td><td>75 (52-99)</td><td>91 (72-144)</td></tr>
<tr><td>Max incremental squeeze pressure (cmH_2O)</td><td>42 (32-102)</td><td>63 (40-119)</td></tr>
<tr><td>Volume required to elicit threshold sensation (ml)</td><td>59 (45-71)</td><td>38 (30-45)</td></tr>
<tr><td>Volume required to elicit urge sensation (ml)</td><td>115 (90-185)</td><td>85 (50-90)</td></tr>
<tr><td>Maximum tolerated volume (ml)</td><td>157 (130-245)</td><td>125 (63-130)</td></tr>
</table>
Note: results presented as median (range)
</td></tr>
</table>

C) Placebo effect

The concern that the outcomes of SNS stimulation are influenced by the placebo effect was investigated in the crossover study by Kenefick et al (2002a) where patients underwent two 2-week intervals with subsensory[3] stimulation either "on" or "off". Both patients had experienced a year of successful subsensory SNS for constipation prior to this study and had successfully achieved improvement in clinical symptoms (defined as increased bowel frequency) at 1-year post-implantation. When stimulation was turned off, all clinical benefits were lost and patients reverted to pre-SNS baseline symptoms. When the stimulator was turned on again, the number of evacuations per week increased from 2 to 10 (patient 1) and 4 to 10 (patient 2). The proportion of time with pain and bloating decreased substantially (patient 1: 65% to 0%, patients 2: 93% to 65%) while a marked improvement in the symptom analog score was observed (patient 1: 30 to 88, patient 2: 33 to 60) in both patients (Kenefick et al 2002a). These results suggest that the clinical benefits associated with SNS were not due to the placebo effect in these two patients.

Similar observations were reported by Malouf et al (2002) where two patients who responded to SNS reverted back to pre-SNS symptoms when the stimulating leads were removed. Holzer et al (2008) also reported that after the acute/temporary percutaneous nerve evaluation (PNE) phase, patients reverted to baseline symptoms when SNS was stopped and only improved again after implantation of a permanent SNS system. However, it should be noted that the stimulation utilized in both these studies was not subsensory and that patients were not blinded to the treatment.

Cost impact

No cost-effectiveness studies on the use of SNS for the treatment of constipation were identified at the time of writing. The cost of the InterStim system is approximately $10,000 (for stimulator and lead). The permanent stimulator accounts for most of this cost. The need for clinician training, lead repositioning and recalibration of stimulation parameters should be taken into

[3] SNS was set to levels that the patient could not feel but still achieved symptomatic improvements.

account. One study noted that in the United Kingdom, the total cost for temporary and permanent SNS is approximately £7000 (approximately $10,490), while the total cost for subtotal colectomy is at least £5000 (approximately $7,494).[4] However, the investigators noted that subtotal colectomy is associated with considerable morbidity and is only successful in approximately 50% of cases (Kenefick et al 2002b).

Studies comparing SNS with conservative or surgical treatment for constipation are necessary before cost analysis studies can be conducted.

Clinical practice guidelines and consensus statements

Clinical guidelines or consensus statements with regards to the use of SNS for the treatment of constipation were not identified from our searches on PubMed and the National Guidelines Clearinghouse.

Training and education impact

Issues relating to the training and education surrounding the use of SNS for constipation were not addressed in any of the studies identified. Medtronic offers an InterStim Physician Education Program, an interactive computer program that provides clinicians with the basic principles and practices of InterStim therapy. Medtronic also provides a more comprehensive structured training course which encompasses lectures, online courses, product training with a simulator, observing a SNS chronic lead placement and having an experienced clinician to act as a coach for the first lead implantation (Medtronic 2009b).

Summary

SNS for constipation is still in the investigational stage. Published peer-reviewed evidence to date is mostly supportive of its effectiveness in patients who are unresponsive to conservative treatment. However, current evidence of its effectiveness is limited by small patient cohorts, lack of statistical analysis, short follow-up durations and the absence of comparative data to existing treatments. Nevertheless, the very limited evidence indicates that SNS could potentially alleviate the symptoms of constipation in patients who have failed all conservative treatment. There is some evidence that the application of SNS can improve symptoms for patients with difficulty in rectal emptying/incomplete evacuation as well as those with slow bowel frequency and straining. Several studies also demonstrated that patients who benefited from SNS immediately reverted to baseline symptoms once SNS was halted, suggesting that SNS has a true effect. Additional large prospective comparative studies with long-term outcomes are necessary to determine the safety and efficacy of this technique. Proper patient selection is likely to be important as in some cases SNS did not result in an improvement of voluntary bowel movements despite patient screening with an acute testing phase. Additional research is necessary to determine the optimum

[4] Currency converted utilising historical 2002 exchange rate of £0.6672 per US dollar.

stimulation parameters for the treatment of constipation and to identify patients who are most likely to benefit from this treatment.

Recommendation

From the limited evidence available, SNS for constipation may have future potential for patients who have exhausted all conventional treatment options. The evidence suggests that this technique is not associated with severe adverse events; however, its effectiveness remains unclear as no comparative studies have been conducted to date. Additional research is necessary to determine its effectiveness as an alternative treatment in patients who have failed conventional therapy.

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Holzer B, Rosen HR, Novi G, Ausch C, Hölbling N, Hofmann M, Schiessel R. Sacral nerve stimulation in patients with severe constipation. *Diseases of the Colon and Rectum*. 2008; 51(5): 524-529.

Kamm MA, Hawley PR, Lennard-Jones JE. Outcome of colectomy for severe idiopathic constipation. *Gut* 1988; 29(7): 969-973.

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Appendix A

Studies excluded from this assessment

Humphreys MR, Vandersteen DR, Slezak JM, Hollatz P, Smith CA, Smith JE, Reinberg YE. Preliminary results of sacral neuromodulation in 23 children. *Journal of Urology* 2006; 176(5):2227-2231.	Patient cohort consistent of children.
Indar A, Young-Fadok T, Cornella J. A dual benefit of sacral neuromodulation. *Surgical Innovation* 2008; 15(3): 219-222.	Case report.
Kenefick NJ. Sacral nerve neuromodulation for the treatment of lower bowel motility disorders. *Annals of the Royal College of Surgeons England* 2006; 88(7): 617-623.	Duplicate patients (Kenefick et al 2002a, Kenefick et al 2002b). Same follow-up duration.
Mowatt G, Glazener C, Jarrett M. Sacral nerve stimulation for fecal incontinence and constipation in adults: a short version Cochrane review. *Neurourology and Urodynamics* 2008; 27(3):155-61.	Included one paper on constipation, which has been selected for inclusion in this report (Kenefick et al 2002a).
Roth TJ, Vandersteen DR, Hollatz P, Inman BA, Reinberg YE. Sacral neuromodulation for the dysfunctional elimination syndrome: a single center experience with 20 children. *Journal of Urology* 2008; 180(1): 306-311.	Patient cohort consisted of children.

Appendix B

Designation of levels of evidence according to type of research question

Level	Intervention [§]	Diagnosis [**]	Prognosis	Etiology [†††]	Screening
I [*]	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomized controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, [§§] among consecutive patients with a defined clinical presentation [††]	A prospective cohort study [***]	A prospective cohort study	A randomized controlled trial
III-1	A pseudorandomized controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, [§§] among non-consecutive patients with a defined clinical presentation[††]	All or none [§§§]	All or none [§§§]	A pseudorandomized controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: Non-randomized, experimental trial [†] Cohort study Case-control study Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst untreated control patients in a randomized controlled trial	A retrospective cohort study	A comparative study with concurrent controls: Non-randomized, experimental trial Cohort study Case-control study
III-3	A comparative study without concurrent controls: Historical control study Two or more single arm study [‡] Interrupted time series without a parallel control group	Diagnostic case-control study [††]	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: Historical control study Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard) [‡‡]	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case series

Tablenotes

* A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence.

§ Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b*)*.

† This also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (i.e. utilize A vs. B and B vs. C, to determine A vs. C).

‡ Comparing single arm studies i.e. case series from two studies.

** The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes. See *MSAC (2004) Guidelines for the assessment of diagnostic technologies*. Available at: www.msac.gov.au .

§§ The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study. See Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM, Kleijnen J. The development of QADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Medical Research Methodology* 2003; 3: 25.

†† Well-designed population based case-control studies (e.g. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. These types of studies should be considered as Level II evidence. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias because the spectrum of study participants will not be representative of patients seen in practice.

‡‡ Studies of diagnostic yield provide the yield of diseased patients, as determined by an index test, without confirmation of accuracy by a reference standard. These may be the only alternative when there is no reliable reference standard.

*** At study inception the cohort is either non-diseased or all at the same stage of the disease.

§§§ All or none of the people with the risk factor(s) experience the outcome. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

††† If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the "Intervention" hierarchy of evidence should be utilized. If it is only possible and/or ethical to determine a causal relationship using observational evidence (i.e. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the "Etiology" hierarchy of evidence should be utilized.

Note 1: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomized controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note 2: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question e.g. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence etc.

Hierarchies adapted and modified from: NHMRC 1999; Lijmer et al 1999; Phillips et al 2001; Bandolier editorial 1999