

# Surgery for constipation: systematic review and practice recommendations

## Results V: Sacral Nerve Stimulation

S. A. Pilkington\*, C. Emmett†, C. H. Knowles‡, J. Mason§, Y. Yiannakou†, On behalf of the NIHR CapaCiTY working group¶ and Pelvic floor Society\*\*

\*University Hospital Southampton, Southampton, UK, †County Durham and Darlington NHS Foundation Trust, Durham, UK, ‡National Bowel Research Centre, Blizard Institute, Queen Mary University London, London, UK, §Warwick Medical School, University of Warwick, Coventry, UK, ¶National Institute for Health Research: Chronic Constipation Treatment Pathway, London, UK, and \*\*Affiliate section of the Association of Coloproctology GB and Ireland, London, UK

### Abstract

**Aim** To assess the outcomes of sacral nerve stimulation in adults with chronic constipation.

**Method** Standardised methods and reporting of benefits and harms were used for all CapaCiTY reviews that closely adhered to PRISMA 2016 guidance. Main conclusions were presented as summary evidence statements with a summative Oxford Centre for Evidence-Based Medicine (2009) level.

**Results** Seven articles were identified, providing data on outcomes in 375 patients. Length of procedures and length of stay was not reported. Data on harms were inconsistently reported and heterogeneous, making estimates of harm tentative and imprecise. Morbidity rates ranged between 13 and 34%, with overall device

removal rate between 8 and 23%. Although inconsistently reported, pooled treatment success was typically 57–87% for patients receiving permanent implants, although there was significant variation between studies. Patient selection was inconsistently documented. No conclusions could be drawn regarding particular phenotypes that responded favourably or unfavourably to sacral nerve stimulation.

**Conclusion** Evidence supporting sacral nerve stimulation is derived from poor quality studies. Three methodologically robust trials are have reported since this review and all have all urged greater caution.

**Keywords** Constipation, sacral nerve stimulation, neuromodulation, slow transit constipation

### Introduction

#### Background and procedural variations

Sacral nerve stimulation (SNS) is well established for pelvic urinary indications and for the treatment of faecal incontinence when conservative measures have failed [1,2]. Its role in the management of chronic constipation (CC) has been studied since 2001 [3], based on a century of experimental (multiple species: physiological and anatomical) and clinical data that the sacral innervation has a prokinetic effect on the rectum and colon via ascending colonic nerves [4]. Brindley stimulation has exploited this effect in small numbers of patients since the 1980s [5,6] and mechanistic studies from Adelaide of SNS effects on transit and colonic contractile activity have confirmed potential to

increase anterograde contractile activity, reduce retrograde activity and speed transit [7]. SNS in its current form uses chronic low amplitude stimulation of a chosen sacral nerve root (usually S3) via a percutaneously placed quadripolar electrode and implanted pulse generator. There are procedural variations in terms of testing phase (temporary wire ‘basic’ vs tined lead ‘advanced’ evaluation) however the final assembly of components is uniform reflecting a single current manufacturer (Medtronic Inc Medtronic Limited, Watford, Herts, UK) for this clinical indication.

#### Scope

The purpose of this study was to assess the efficacy and harms of implanted SNS for adult patients whose main presenting complaint is chronic constipation. Procedures beyond the scope of this review include other forms of neurostimulation (e.g. transcutaneous, vaginal,

Correspondence to: Miss Sophie Pilkington, Mailpoint 134, University Hospital Southampton, Tremona Road, Southampton, SO16 6YD, UK.  
E-mail: sophie.pilkington@uhs.nhs.uk

transanal, pudendal) and temporary SNS (i.e. where data are only available during the testing phase).

### Previous reviews

Two systematic Cochrane reviews have focused on SNS for constipation, although faecal incontinence was also included. The first (2007 [8]) concluded that SNS can reduce symptoms in selected patients with constipation, however this was based on a single study which included two patients [9]. The second included two RCTs and concluded that SNS did not improve symptoms in patients with constipation, although it recognised that the evidence was severely limited [10].

### Summary of search results and study quality

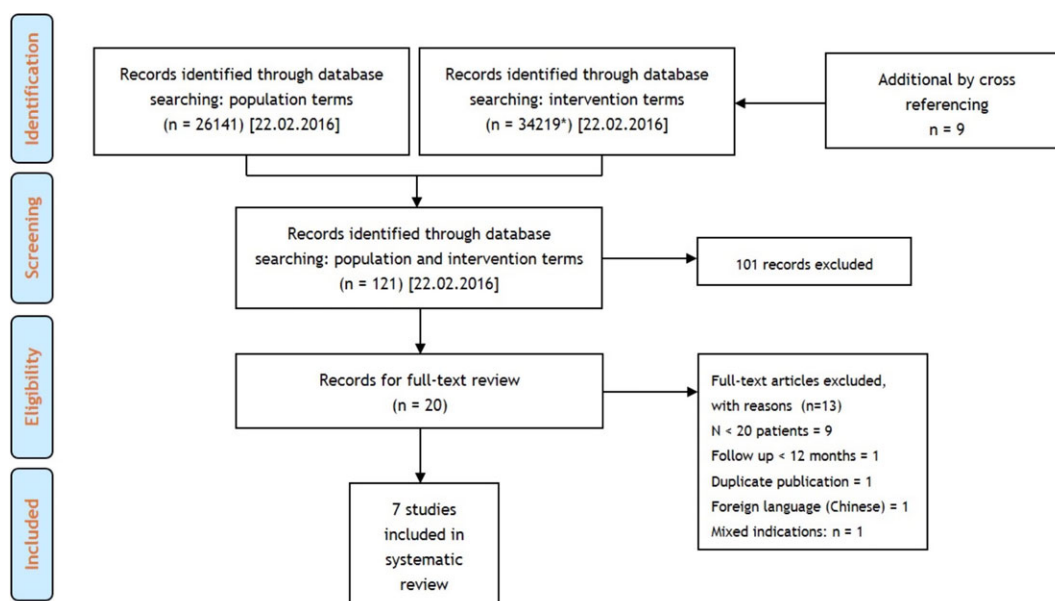
The search yielded a total of 20 citations for full text review from a total of 121 abstracts found by initial search criteria (Fig. 1: PRISMA diagram). From these, only seven articles published between 2001 and 2015 contributed to the systematic review, providing data on outcomes in a total of 375 patients (range 21–117 patients per study) (Table 1. Specific exclusions after full-text review (and after exclusion of non-English language publications:  $n = 1$ ) [11] included nine studies where the population sample was confirmed to be less than 20 patients [3,12–19], one study [20] which was a dual publication reporting a patient cohort that overlapped with another study [21] and one study where

results were combined for mixed indications [22]. Study follow up ranged from 20 to 51 months.

The general quality of studies was poor due to inadequate description of methods. The seven included studies were all observational and all provided uncontrolled LEVEL IV evidence, including one low quality prospective cohort study, two prospective and four retrospective case series. Mean patient follow up ranged from 20 to 51 months (median 27 months). All studies derived from European centres, with three from UK and one each from Spain, The Netherlands, Italy and Sweden.

### Perioperative data

There were few data concerning standard perioperative variables. All studies failed to include data on duration of procedure, number of cases performed as day surgery or duration of inpatient stay. A summary of perioperative data is provided in Table 2. Peculiar to SNS, data were reported on paradigm of test stimulation i.e. there is more than one way to perform test stimulation. The use of a previously described ‘standard procedure’ is stated in the methods section in only three studies [23–25]. The duration of temporary SNS was reported as 2 weeks in two of the studies [25,26] and 3 weeks in five of the studies [21,23,24,27,28]. The use of antibiotics during permanent SNS placement was reported by one study only [23]. Type of anaesthesia for insertion of temporary and permanent leads was reported in two studies [20,27,28] and insertion of temporary wires in the outpatient setting was described in one study [24].



**Figure 1** PRISMA diagram of search results.

**Table 1** All studies included in systematic review.

Author	Year	Centre	Country	Total N	Implanted N	FU*	Number at final follow up N (%) <sup>‡</sup>	Design	Level <sup>†</sup>
Kamm [23]	2010	St Marks	UK	62	45	28	38 (61)	PCH	IV
Sharma [26]	2011	Hull	UK	21	11	34	10 (48)	RCS	IV
Ortiz [24]	2012	Navarra	Spain	48	23	26	14 (29)	RCS	IV
Govaert [21]	2012	Maastricht	Netherlands	117	68	37	61 (52)	RCS	IV
Khan [27]	2014	Durham	UK	22	12	20	12 (55)	PCS	IV
Ratto [25]	2014	Rome	Italy	61	42	51	32 (76)	RCS	IV
Graf [28]	2015	Uppsala	Sweden	44	15	24	11 (25)	PCS	IV

\*Mean follow up in months.

†Oxford 2009 CEBM.

‡Based on intent to treat RCT, Randomised controlled trial; PCH, prospective cohort study; RCS, retrospective case series; PCS, prospective case series; NR, Not recorded.

Most studies used a tined quadripolar lead for permanent stimulation. Five studies used a single lead [21,23,24,28] whilst one study used bilateral stimulation [27] and another used either single or bilateral [25]. Some additional data pertaining to the cohort of patients in the Govaert [21] study were reported in an earlier study by Maeda *et al.* [20].

#### Summary evidence statements: perioperative data

- 1 Standard perioperative data (duration of procedure and length of stay) were not reported by any study (Level IV)
- 2 Where reported, general anaesthesia was used for SNS procedures (Level IV)
- 3 The number of temporary unipolar SNS leads used varied (1 or 2) between studies (Level IV)
- 4 Most studies used a single tined quadripolar lead for permanent stimulation (Level IV)

#### Harms

Surgical morbidity, reported as overall procedural complication rates, vary considerably with individual study rates varying from zero to 39% [24] (Table 3). This heterogeneity may have reflected (for example) differing inclusion, procedural content, context of care, or thresholds or conventions for recording complications. Random effects meta-analysis found the overall complication rate to be 22.7% (95% CI: 12.9% to 34.1%),  $I^2 = 47%$  (Fig. 2). Device removal was similarly heterogeneous: the overall device removal rate was 14.4% (95% CI: 7.8% to 22.5%),  $I^2 = 47%$  (Fig. 3). There were 51 re-operations: 30 for device removal although five were replaced after resolution of pain or infection, 11 to move or replace the implant, 10 lead problems. In addition six operations were carried out for treatment of chronic constipation including three subtotal

colectomies [23,28], two stomas and one appendicectomy [28]. Infection resulting in device removal was reported in three patients. The commonest reason for explantation was lack of effect and this was reported in 19 cases (Table 3). Two explantations were carried out for pain associated with the implant and one for lead migration. There appeared to be no relationship between device explantation rate and length of follow up (Table 1).

Patients with SNS for constipation had high levels of reportable adverse events. Often this was resolved by reprogramming but more than one-third required surgical intervention or discontinued therapy. Such data were specifically reported in the sub-cohort of Govaert *et al.* [21], reported separately by Maeda *et al.* [20] who carried out a retrospective review of 38 patients who had SNS for constipation and found that 22 patients (58%) experienced at least one reportable event. The most common event was lack or loss of efficacy. In 19 events (33%), surgical intervention was required and the most common intervention was electrode replacement (14 events). Three adverse events lead to discontinuation of SNS. The remaining 35 patients were still using SNS but with a variable degree of benefit.

#### Summary evidence statements: harms

- 1 Data on harms were inconsistently reported and heterogeneous (Level IV).
- 2 The overall procedural complication rate resulting in reoperation was typically 13–34% (Level IV).
- 3 Common complications resulting in reoperation included lack of efficacy, infection, lead problems, pain at site of implant, unwanted effects relating to stimulation such as pain (Level IV).
- 4 Infection rates varied from 0 to 7% (Level IV).
- 5 Overall device removal rate was typically 8–23% at mean follow up of 31 months (Level IV)

**Table 2** Perioperative data by procedure.

Author	Total		Implanted	Duration temporary SNS (weeks)	Temporary SNS under GA	Permanent SNS under GA	Type of temporary SNS lead	Number of temporary SNS leads used	Number of Permanent SNS leads used	Permanent SNS using tined quadripolar lead	Antibiotic cover during permanent SNS
	N	N									
Kamm [23]	62	45		3	NR	NR	U	1	1	Y	Y
Sharma [26]	21	11		2	NR	NR	NR	NR	NR	NR	NR
Ortiz [24]	48	23		3	0	NR	14U: 34Q	1	1	Y	NR
Govaert [21]	117	68		3	NR	NR	U	1	1	Y	NR
Khan [27]	22	12		3	Y	Y	U	2	2	Y	NR
Ratto [25]	61	42		2	NR	NR	U	1 OR 2	1 OR 2	NR	NR
Graf [28]	44	15		3	Y	Y	U	≥ 2	1	Y	NR

NR, not reported; U, unipolar lead; Q, quadripolar lead; UT, untined lead; T, tined lead; Y, yes.

## Efficacy

Reported clinical outcomes varied in assessment tools used across the seven studies (Table 4). Most commonly, these consisted of validated summative symptom scores or questionnaires. These included the Cleveland Clinic Constipation score [23,25], the SF-36 questionnaire [23,25], the Wexner Score [21,24], and PAC-SYM and PAC-QOL questionnaire [27]. Additionally, patient bowel diaries were used by several studies, either as the principal outcome measure [26] or alongside other measures [21,24,28]. The definition of treatment success varied between studies. Of the two studies using the Wexner score, one [24] defined success as a 30% improvement in this score. The other [21] defined this as a statistically significant reduction in score from baseline. Kamm *et al.* [23] defined success as either  $\geq 3$  bowel motions per week or  $\geq 50\%$  improvement in straining or  $\geq 50\%$  improvement in incomplete evacuation. Other definitions of sustained treatment success included a statistically significant reduction in Cleveland Clinic Score and SF-36 from baseline [25], patient reported clinical improvement [27,28] and 50% improvement in bowel function (recorded on bowel diaries [26]). The percentage of initial study recruits providing data at final follow up varied between studies, from 25 to 76% (Table 1) denoting significant attrition in prospective studies.

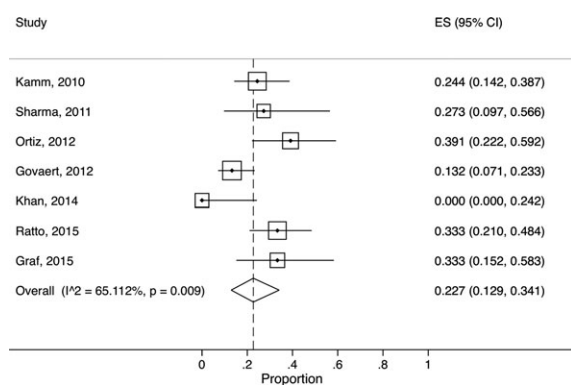
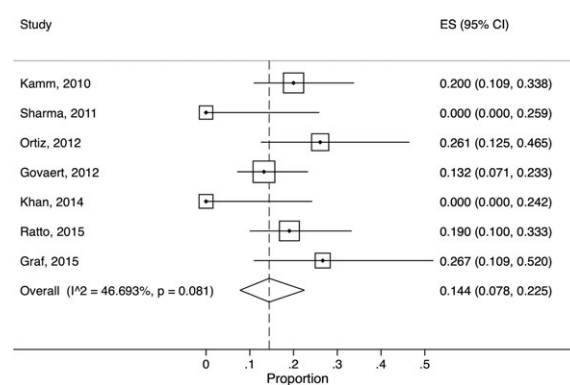
Accepting variation in definitions used, random effects meta-analysis found the overall SNS response rate (i.e. to those beginning treatment but not necessarily implanted) to be 56.9% (95% CI: 46.8% to 66.7%),  $I^2 = 71\%$ . Long term overall treatment success was 40.1% (95% CI: 26.3% to 54.7%),  $I^2 = 87\%$ , considering permanently implanted patients only, treatment success was 73.2% (95% CI: 57.5% to 86.6%),  $I^2 = 80\%$  (Fig. 4).

Overall, success seemed to be dichotomised with four studies [21,23,25,26] demonstrating higher success rates, both in the short and long term, than others. The largest of these, by Govaert *et al.* [21], is a retrospective study at two centres in The Netherlands and Denmark, with follow up at 1, 3, 6 and 12 months (although this is difficult to verify for a retrospective study). It appears that data were collected during routine clinical follow up rather than as part of a planned research study. There was considerable drop-out with Wexner scores available for only 32 (47% of implanted cases) at 6 months. A multi-centre prospective cohort study [23] demonstrated the highest positive response rate to temporary SNS, as well as a high long term success rate (87% of patients with permanent implants); the primary outcome was an improvement in one of three domains; bowel frequency, straining and incomplete evacuation, assessed using questionnaires

**Table 3** Harms.

Author	Total N	Implanted N	Total complications resulting in reoperation	Total adverse events	Infection resulting in device removal	Explantation (permanent device removal)	Additional surgery
Kamm [23]	62	45	11/45 (24%)	101	2/45 (4%)	2/45 (4%) (7/45 exit study)	Subtotal colectomy 1
Sharma [26]	21	11	3/11 (27%)	NR	0	0	NR
Ortiz [24]	48	23	9/23 (39%)	NR	1/23 (4%)	6/23 (27%)	NR
Govaert [21]	117	68	9/68 (13%)	NR	3/68 (4.4%)	9/68 (13%)	NR
Khan [27]	22	12	0	1	0	0	NR
Ratto [25]	61	42	14/42 (33%)	9	0	8/42 (19%)	NR
Graf [28]	44	15	5/15 (33%)	12 PNE 5 PERM	1/15 (7%)	4/15 (27%)	Stoma 2 Colectomy 2 Appendicostomy 1

NR, not reported.

**Figure 2** Forest plot showing rates of total procedural complications (percentage of patients).**Figure 3** Forest plot showing rates of device explantation rate (percentage of patients).

and validated symptom scores. However, treatment success was assessed on last follow up and there was a high drop-out rate (38% drop-out at 24 months). A further retrospective study [26] of 21 patients in a single centre demonstrated a 47% success rate based on patient reported outcomes and laxative use. Ratto *et al.* [25] used a retrospective study design to evaluate outcome based on validated questionnaires. Although 32/42 (76%) of patients still had implant at the end of follow up (and therefore considered to be responders to some degree), only 15 (35%) had a 50% reduction of Cleveland Clinic Score. Three studies [24,27,28] demonstrated relatively poor efficacy of treatment (Table 4). Two of these are retrospective case series while the other [27] studied neurological constipation only.

#### Summary evidence statements: efficacy

**1** Data on efficacy were inconsistently measured with high drop-out rates and heterogeneous findings, making estimates tentative and imprecise [level IV]

**2** Pooled treatment success was typically 57–87% for patients receiving permanent implants, although there was significant variation between studies [level IV]

#### Patient selection

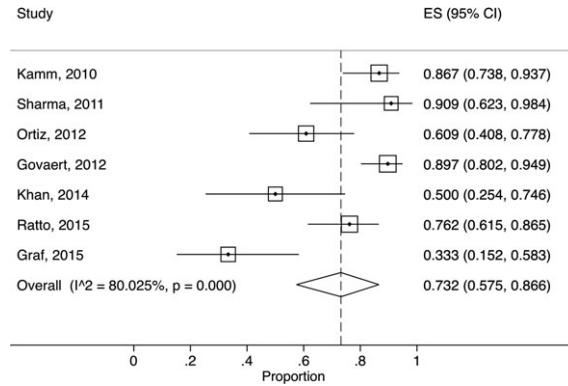
Patient selection was inconsistent between the seven studies. There was no unifying criteria for establishing a diagnosis of chronic constipation (Table 5). Four studies excluded patients with neurological disease and one study only included patients with neurological disease. The proportion of participants with slow transit constipation (STC) was recorded in six of the studies. There was no significant difference in response to SNS when studies were grouped by those with less or more than 50% of patients with STC (Fig. 5). Defaecating proctograms were performed in six of the studies but only used to stratify patients in two studies (Table 5).



**Table 4** Clinical outcomes of SNS.

Author	Year	Total N	Implanted N	Outcome measure used	Definition of long-term success	Median FU (Months)	Response to PNS N (%)	Long term success (Total) N (%)	Long term success (Implanted) N (%)
Kamm [23]	2010	62	45	Cleveland Clinic Constipation Score, Visual Analogue Scale, SF-36	One of: $\geq 3$ bowel movements per week; $> +50\%$ improvement in straining and/or incomplete evacuation	28	45 (73)	39 (63)	39 (87)
Sharma [26]	2011	21	11	Bowel function recorded in patient diaries. Use of laxatives	50% improvement in Bowel function	34	12 (57)	10 (47)	10 (90)
Ortiz [24]	2012	48	23	Wexner score, bowel diaries	30% improvement in Wexner score	26	23 (48)	14 (29)	14 (61)
Govaert [21]	2012	117	68	Wexner score, bowel diaries	Retained implant	37	68 (58)	61 (52)	61 (90)
Khan [27]*	2014	22	12	Patient assessment of symptoms (Likert scale), PAC-SYM, PAC-QOL, EuroQoL	Clinical assessment	20	12 (55)	6 (27)	6 (50)
Ratto [25]	2015	61	42	Cleveland Clinic Constipation Score, SF36	Retained implant	51	42 (69)	32 (52)	32 (76)
Graf [28]	2015	44	15	Bowel diaries, validated symptom questionnaire	Sustained symptom relief (patient reported)	24	15 (34)	5 (11)	5 (33)

\*Neurological constipation. NR, Not Recorded.



**Figure 4** Forest plot showing rates of implant long-term success rate (percentage of patients).

*Summary evidence statements: patient selection*

- 1 All studies included variable phenotypes of chronic constipation making populations heterogeneous (Level IV).
- 2 No conclusions could be drawn regarding particular phenotypes that responded favourably or unfavourably to SNS (Level IV).

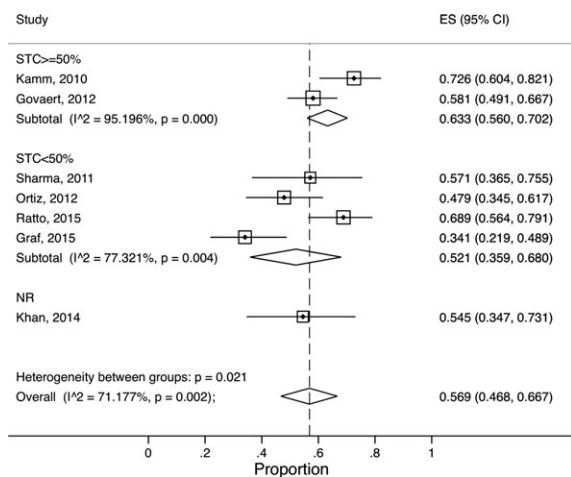
**Discussion**

The possibility of a minimally invasive technique is a very attractive option for the management of patients with chronic constipation, especially as alternative options may involve potentially hazardous major surgery with colectomy and uncertain outcome. This systematic review has identified a number of published series that might suggest benefit of this treatment, with a pooled ‘success rate’ of 73% of those patients undergoing permanent implantation and a device removal rate of around 12%. These findings would certainly merit further study but must be treated with caution as the majority of the studies were retrospective case series. There was evidence of considerable loss to follow up, irregular and imprecise measurement of outcomes, and ill-defined *post-hoc* analysis of the data. The outcomes were, for the most part, reported to the clinicians providing the treatment and there is a well-recognised reporting bias here. In addition there may be a strong publication bias [29].

Several important studies were not included in the review but merit consideration in the discussion. A randomised, double-blind, placebo-controlled, two-phase crossover study by Dinning *et al.* [30] comparing sham, subsensory and suprasensory stimulation in patients with STC was excluded from the review due to inadequate follow up period (< 12 months). The primary outcome measure was the proportion of patients who, on more than 2 days per week for at least 2 of 3 weeks,

**Table 5** Patient baseline phenotypic data.

Authors	N	Inclusion criteria	STC	Neurological disease	Proctogram
Kamm [23]	62	< 2 bowel movements per week and/or straining or incomplete emptying > 25% occasions	50 (81%)	Excluded	Performed not stratified
Sharma [26]	21	2 or fewer bowel movements per week, failed conservative treatment over at least 12 months from GP referral	19 (86%)	Excluded	Performed used to rule out obstructive defaecation but anismus not exclusion criterion
Ortiz [24]	48	Rome III criteria, symptoms at least 1 year, failed conservative treatment with laxatives, suppositories, enemas and behavioural therapy	5 (10%)	Excluded	Performed not stratified
Govaert [21]	117	< 2 bowel movements per week and/or straining or incomplete emptying > 25% occasions. Persistent symptoms 1 year and failed conservative treatment (NB includes 26 patients from Kamm study and 38 patients from Maeda study)	75 (64%)	Not excluded	Performed not stratified
Khan [27]	22	Patients with neurological disease [including multiple sclerosis ( $n = 14$ ) and spinal cord injury ( $n = 5$ )] and severe constipation refractory to conservative treatment	NR	Inclusion criterion	None
Ratto [25]	61	Rome III criteria. Patients identified from GINS: Italian group for sacral nerve neuromodulation (NB may include some patients from Ortiz study although not specifically mentioned)	17 (28%)	Not excluded	Performed and patients with rectocele, intussusception, rectal prolapse and enterocoele excluded
Graf [28]	44	History of 'constipation' for at least 6 months and failure of conservative treatment	21 (48%)	Excluded spinal cord injury	Selective

**Figure 5** Forest plot showing rates of SNS response rate by level of STC patients (percentage of patients). KEY: STC, slow transit constipation.

reported a bowel movement associated with a feeling of complete evacuation. This well-conducted trial showed no clinical effect of sub- or suprasensory stimulation over sham in 55 patients undergoing permanent SNS implantation. The proportion of patients who met the primary outcome measure did not differ between

suprasensory (30%) and sham (21%) stimulations nor between subsensory (25%) and sham (25%) stimulations. In addition there was no significant change in quality of life scores. Long term data from this study have been reported since the systematic review was completed noting that 88% of patients in the original study [30] had undergone device removal at median follow up 5.7 years [31].

A French group have presented data on 20 patients undergoing permanent SNS after a successful 3-week temporary test. A randomised on/off sham controlled sub-sensory stimulation was provided (8 weeks each cycle) with no improvement during active stimulation. At 1 year, only 11 (55%) patients were still responding [32]. The results of a third study have been recently presented (nationally and internationally) from a multi-centre prospective randomised study [ISRCTN44563324]. The main aim of this study was to assess the efficacy of sham controlled timed lead stimulation as a way of identifying true responders. Thirty-nine patients were recruited to the test phase and 27 were implanted with all but one followed up to 6 months. The findings showed, once again, that temporary testing has no value in determining long term response. The response at 6 months was assessed by a reduction of at least 0.5 on

PAC-SYM and this was achieved in 15(55%) of patients.

These more recent prospective studies suggest that the efficacy of SNS in constipation may be very limited, but in particular, that prediction of responders using various temporary testing regimens is poor. In view of the cost and risk of the procedure, the inability to predict responders is likely to hamper the utility of the treatment in the future.

There was a significant difference in the conclusions between the largely retrospective early studies, which supported the use of SNS, and the three recent well-conducted prospective studies, which have all urged greater caution. This is an example of the importance and need for formally planned and robustly executed studies to inform surgical practice and a warning against over-reliance on retrospective cohort studies.

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## Conflict of interest

The authors declare no conflict of interest.

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