Efficacy and outcome of sacral nerve stimulation in slow transit constipation: A randomised, double-blind, placebo-controlled, two phase crossover study.

[1,2]Dinning PG, [2]Hunt L, [2,3]Patton V, [4]Gebski V, [5]Jones M, [6]Stewart P, [2,3]Lubowski DZ, [7]Cook IJ.

[1]Flinders University, Dept of Gastroenterology and Surgery, Flinders Medical Centre. South Australia. [2]St George Clinical School, UNSW Department of Medicine. [3]Anorectal Physiology Dept, St George Hospital. [4]University of Sydney, Clinical Trials Unit. [5]Dept of Psychology, Macquarie University. [6]Department Colorectal Surgery, Concord Hospital. [7]Gastroenterology Department. St George Hospital. New South Wales. Australia.

Australian and New Zealand Clinical Trial Registry: 12611001192976

Background

Sacral nerve stimulation for constipation

G. P. Thomas, T. C. Dudding, G. Rahbour, R. J. Nicholls and C. J. Vaizey

The Sir Alan Parks Physiology Unit, St Mark's Hospital and Academic Institute, Watford Road, Harrow HA1 3UJ, UK
Correspondence to: Miss C. J. Vaizey (e-mail: cvaizey@nhs.net)

Background: For over 10 years sacral nerve stimulation (SNS) has been used for patients with constipation resistant to conservative treatment. A review of the literature is presented.

Methods: PubMed, MEDLINE and Embase databases were searched for studies demonstrating the use of SNS for the treatment of constipation.

Results: Thirteen studies have been published describing the results of SNS for chronic constipation. Of these, three were in children and ten in adults. Test stimulation was successful in 42–100 per cent of patients. In those who proceeded to permanent SNS, up to 87 per cent showed an improvement in symptoms at a median follow-up of 28 months. The success of stimulation varied depending on the outcome measure being used. Symptom improvement correlated with improvement in quality of life and patient satisfaction scores.

Conclusion: SNS appears to be an effective treatment for constipation, but this needs to be confirmed in larger prospective studies with longer follow-up. Improved outcome measures need to be adopted given the multiple symptoms that constipation may be associated with. Comparison with other established surgical therapies also needs consideration.

Paper accepted 17 August 2012
Published online in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.8944

Thomas GP, et al: **Sacral nerve stimulation for constipation**. *Br J Surg* 2013, **100**(2):174-181.

Randomised control trials

(Treatment Efficacy of sacral nerve stimulation in constipation)

Author	Lower bowel disorder	Study Design	Outcome measure
Kenefick, 2002	Constipation	RCT	Stool Frequency

• suggests that SNS can “reduce symptoms in some people with constipation”

Mowatt G, et al, Cochrane Review, 2007

• 14 constipated women with evacuatory dysfunction and rectal hyposensitivity; treatment with temporary sacral nerve stimulation (SNS)

- in comparison to sham, SNS improve rectal sensitivity and percentage of successful defecating episodes.

Knowles CH, et al. *Ann Surg* 2012, **255**(4):643-649.

AIMS

Primary Aim:

To assess, in patients with slow transit constipation, the clinical outcome in response to supra-sensory compared to sham stimulation

Secondary Aim:

To assess, in patients with slow transit constipation, the clinical outcome in response to sub-sensory compared to sham stimulation

Outcome measures

Primary Outcome Measure:

Proportion of patients, who on more than 2 days per week for at least 2 of 3 weeks, report a bowel movement associated with a feeling of complete evacuation during supra-sensory stimulation.

Secondary Outcome Measure:

Proportion of patients, who on more than 2 days per week for at least 2 of 3 weeks, report a bowel movement associated with a feeling of complete evacuation during sub-sensory stimulation.

Tertiary outcome measures:

For both supra and sub sensory stimulation determine the effects of sacral nerve stimulation upon: Abdominal pain score, abdominal bloating score, laxative-free days, quality of life scores.

Patient Eligibility

- Experience a feeling of incomplete evacuation on less than 3 days per week, for at least 2 of 3 weeks of the baseline/surveillance phase.

*Dinning PG, et al. *BMC Gastroenterology* 2011, **11**:121.

- Aged 18 – 75yrs
- Confirmed colonic slow transit
- Normal anorectal manometry
- Unsatisfactory symptomatic response to standard therapies including laxatives, dietary modification, biofeedback

Patient Ineligibility

- Metabolic, neurogenic or endocrine disorder(s) known to cause constipation.
- Drugs which list constipation as a potential side effect deemed to be clinically relevant by the referring physician
- Prior abdominal radiotherapy
- Prior abdominal surgery (except cholecystectomy, appendicectomy, inguinal hernia repair, splenectomy, fundoplication; oophorectomy or hysterectomy)
- Current or planned pregnancy
- Co-morbidity considered by the clinician or the investigators to put the patient at risk from surgical electrode implantation
- Current or prior history of malignancy.

Stool Diary

CODE NO. BL_1

Patient ID:___ ___ ___

Patient initials: ____ ____ ____
first mid last

Baseline diary **Week 1**

Date of the first day of the week
Please complete one row at the end of each day

____/_____/_____ (Investigator to insert start date)
Day Month Year

Day of the week	Actual Bowel Movement: Number of bowel movements (0 = None, 1 = one, 2 = two, 3 = three, >3 = more than three)	Actual Bowel Movement: Feeling of complete evacuation?	Actual Bowel Movement: Straining?	Stool Form Refer to diagram on page 4	Abdominal pain/ discomfort? (0 = None, 1 = Present but tolerable, 2 = present and interfering with but not preventing normal daily activities like work and sleep, 3 = preventing normal daily activities)	Abdominal bloating? (0 = None, 1 = Present but tolerable, 2 = present and interfering with but not preventing normal daily activities like work and sleep, 3 = preventing normal daily activities)	Laxatives: Did you use a laxative today?	Laxatives: Drug name and form*?	Laxatives: Dose?
1	0 1 2 3 >3	yes no	yes no	1 2 3 4 5 6 7	0 1 2 3	0 1 2 3	yes no		
2	0 1 2 3 >3	yes no	yes no	1 2 3 4 5 6 7	0 1 2 3	0 1 2 3	yes no		
3	0 1 2 3 >3	yes no	yes no	1 2 3 4 5 6 7	0 1 2 3	0 1 2 3	yes no		
4	0 1 2 3 >3	yes no	yes no	1 2 3 4 5 6 7	0 1 2 3	0 1 2 3	yes no		
5	0 1 2 3 >3	yes no	yes no	1 2 3 4 5 6 7	0 1 2 3	0 1 2 3	yes no		
6	0 1 2 3 >3	yes no	yes no	1 2 3 4 5 6 7	0 1 2 3	0 1 2 3	yes no		
7	0 1 2 3 >3	yes no	yes no	1 2 3 4 5 6 7	0 1 2 3	0 1 2 3	yes no		

At the end of the week please complete these questions

How satisfied were you with your bowel habits over the past week?

0 = a very great deal satisfied
4 = not at all satisfied

0 1 2 3 4

How bothersome has your constipation been over the past week?

0 = not at all
4 = a very great deal

0 1 2 3 4

* tablets, granules, liquid, suppositories, enema.

Dinning, P. G., L. Hunt, et al. (2011). "The impact of laxative use upon symptoms in patients with proven slow transit constipation." BMC Gastroenterol **11**: 121.

Stratification and randomisation

Patients were stratified on the basis of the following potential correlates to outcome:

a) symptomatic response to PNE (defined as achieving > 2 days per week on which a complete bowel motion is experienced for 2 of 3 weeks);

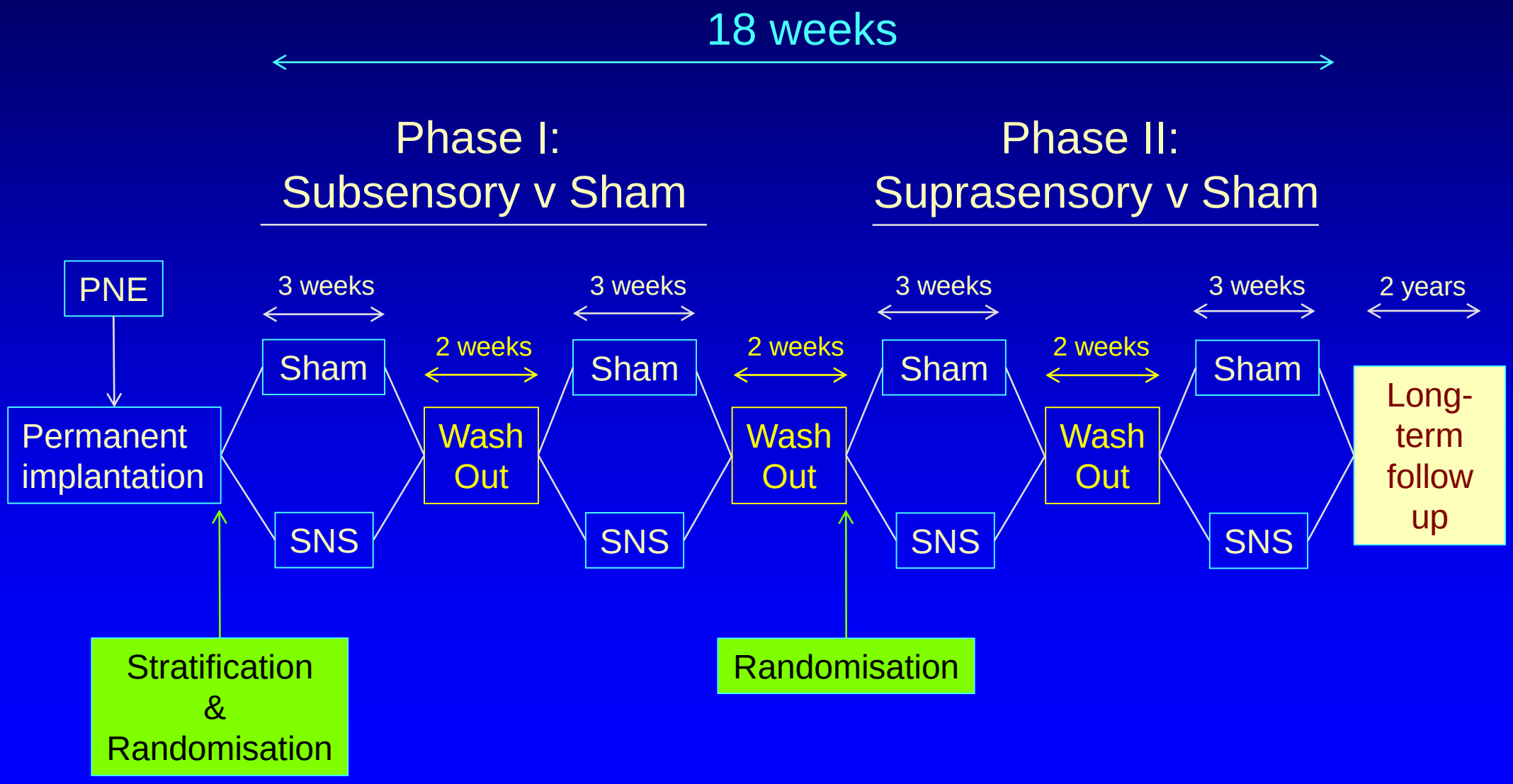
a) duration of constipation (<> 10yrs)

a) prior hysterectomy

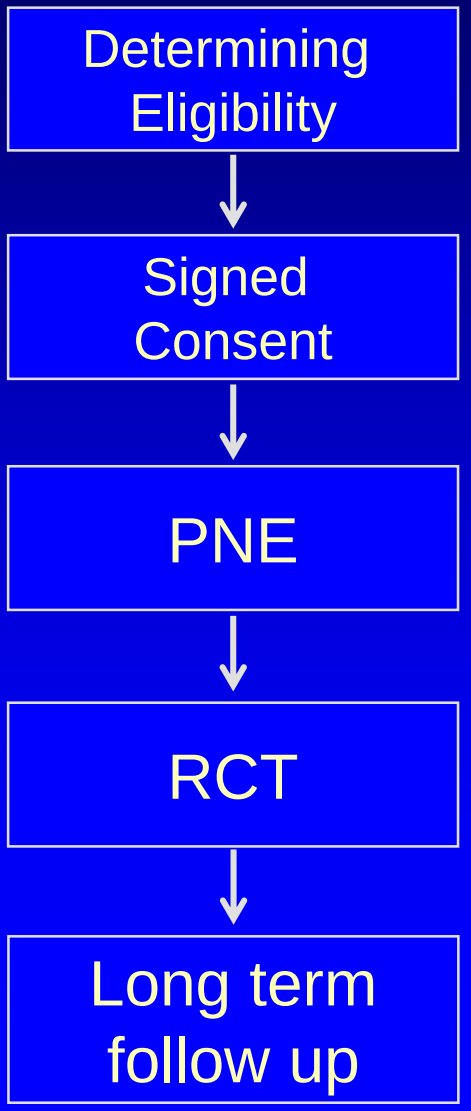
b) study site (St.George Hospital or Concord Hospital; Sydney NSW).

All randomisation was conducted by the NH&MRC clinical trial centre

Study Outline



CONSORT flow diagram



(n = 238; 2007-11)

(n = 59)

(n = 59)

(n = 55)

(n = 53)

Patient Demographics
(RCT; n = 55)

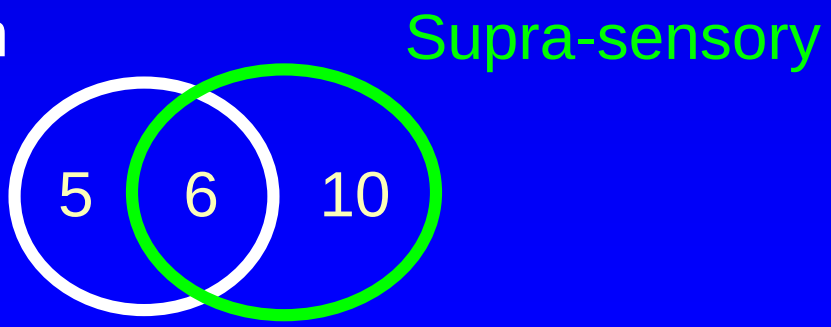
- Age; 44 ± 15 yrs (4 males)
- Duration of symptoms:
  - 1-2 yrs = 9%
  - 2-5 yrs = 7%
  - 5 -10 yrs = 13%
  - >10 yrs = 71%
- Laxative use:
  - 1- 3 d/w = 47%
  - 4 - 7 d/w = 53%
- Response to peripheral nerve evaluation
  - n = 16 (29%)

Primary outcome: supra-sensory phase (n = 53)

Table 1 – Response rate according to treatment arm – supra-sensory phase

Treatment arm for supra-sensory	No. of patients	No. of patients with a successful response	Success rate (%)	95% CI
Sham	53	11	20.8	12.0-33.5
Stimulation	54	16	29.6	19.1-42.8

The response rate was with 20.8% with sham and 29.6% with stimulation. **(p = 0.23)**

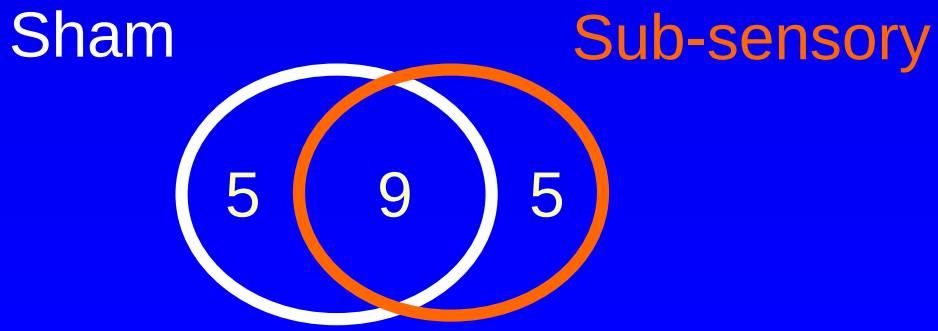


Secondary outcome: sub-sensory phase (n = 55)

Table 4 – Response rate according to treatment arm – sub-sensory phase

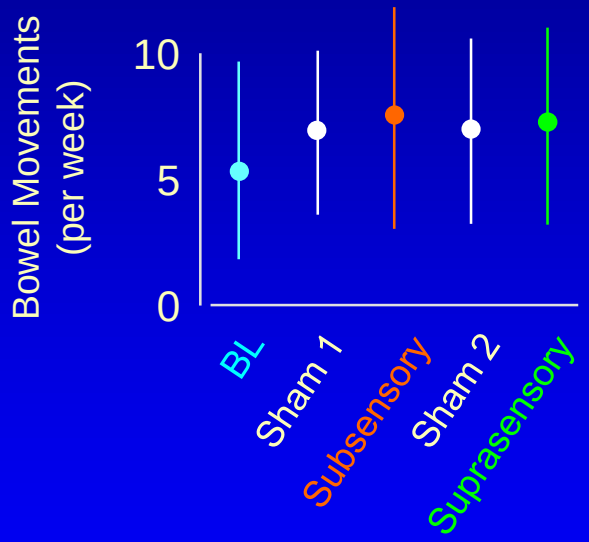
Treatment arm for sub-sensory	No. of patients	No. of patients with a successful response	Success rate (%)	95% CI
Sham	55	14	25.4	15.8-38.3
Stimulation	55	14	25.4	15.8-38.3

The response rate was with 25.4% with both sham and stimulation. **(p = 0.95)**

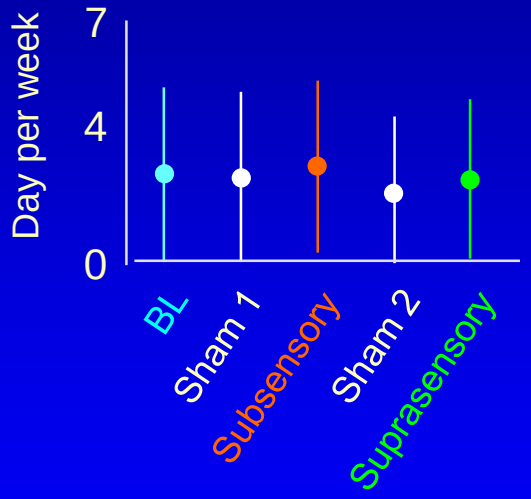


Additional Measures

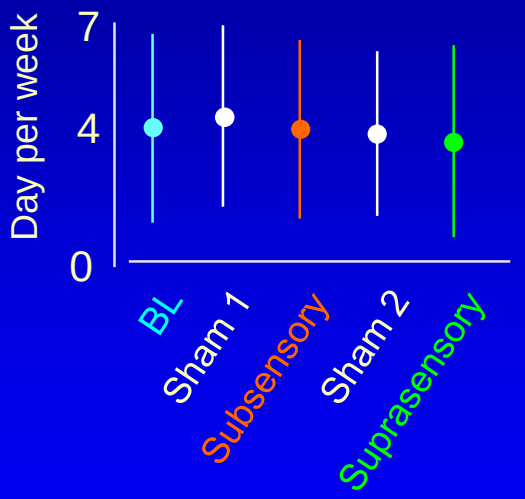
Stool frequency



Straining

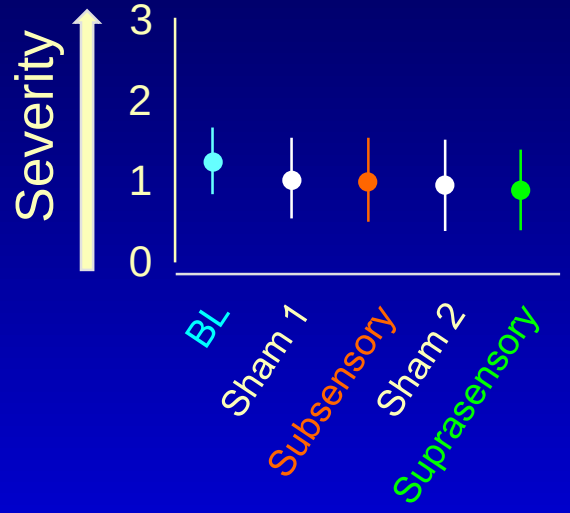


Laxative Use

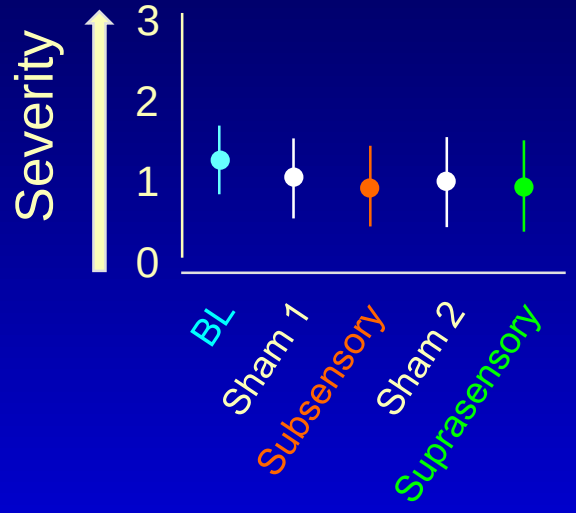


Additional Measures

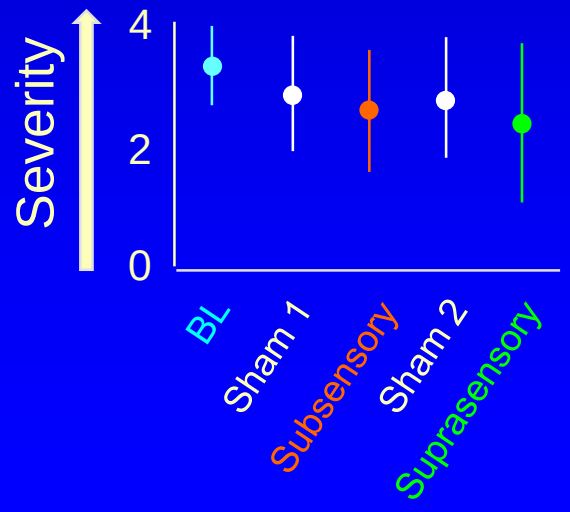
Abdominal Pain



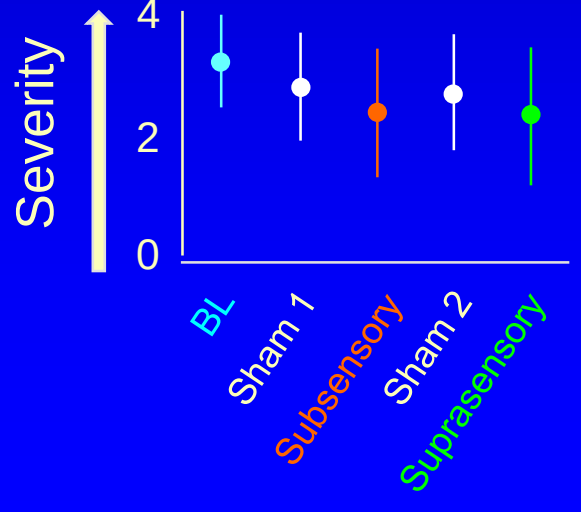
Abdominal Bloating



Satisfaction

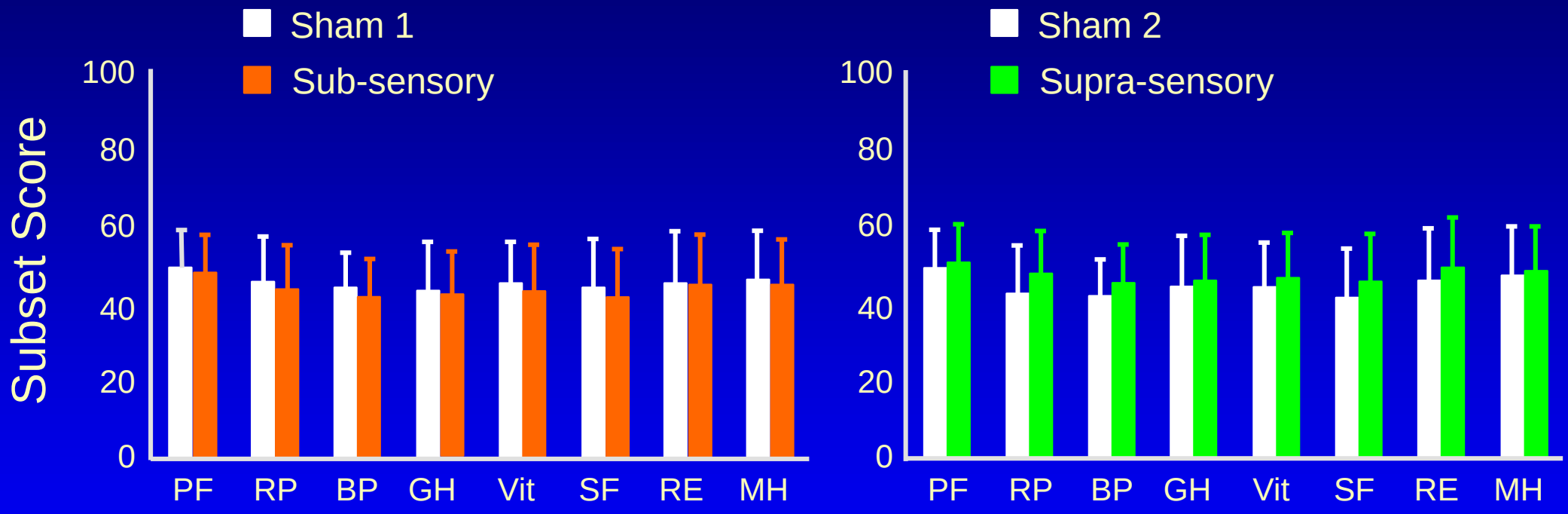


Bothersome



Quality of Life

(SF36)



PF = physical Function
RP = role physical
BP = body pain
GH = general health

Vit = vitality
SF = social functioning
RE = role emotional
MH = mental health

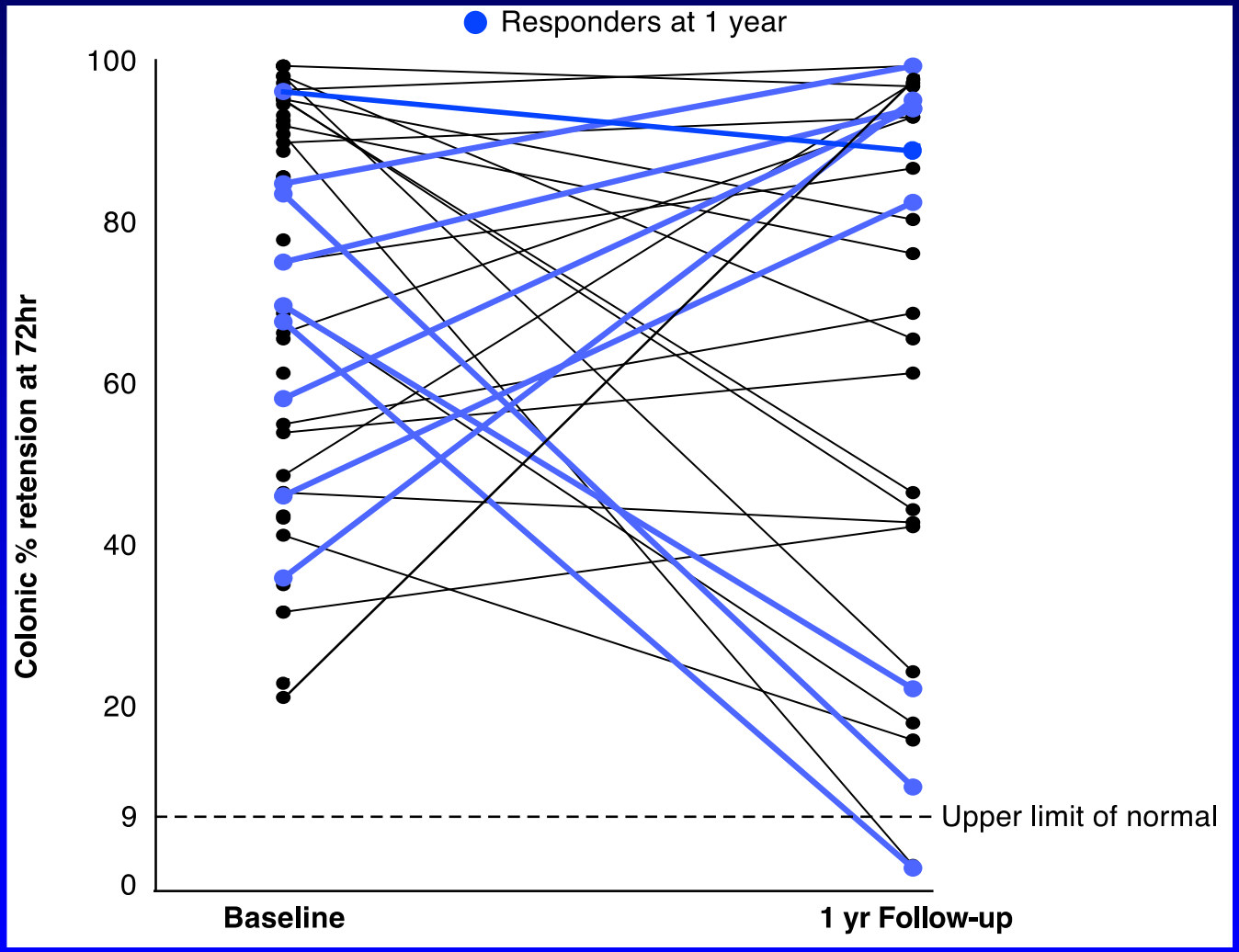
Long-Term Follow-Up
(1 year)

Fifty three patients that entered the long-term follow-up.

- Sixteen patients (30%) had had the sacral nerve stimulator explanted and had dropped out of the study.
- Fourteen patients (26%) still had the stimulating device implanted but the stimulation was turned off.
- Seven patients (13%) were still receiving stimulation but reported that they were not satisfied with the treatment.
- Seventeen (31%) reported some level of satisfaction and requested that the simulation remain on.

- Only nine patients (17%) met our primary endpoint.

Colonic scintigraphy
(Baseline vs 1 year)



Conclusion

• In patients with slow transit constipation, in comparison to sham stimulation, sacral nerve stimulation had **no** significant effects upon

- Frequency of complete bowel movements
- Stool frequency
- Straining
- Quality of life

• These data suggest that sacral nerve stimulation is not an effective treatment for most patients with slow transit constipation

Acknowledgements

Surgical placement

A/Prof David Lubowski

A/Prof Peter Stewart

Statistical analysis

Prof Val Gebski

Prof Mike Jones

Patient Selection & Study Design

Prof Ian Cook

Prof Val Gebski

Trial maintenance

Ms Linda Hunt

Ms Vicki Patton

Supported by

- NHMRC
- Medtronic

Is PNE a predictor of treatment outcome?