

Efficacy of Sacral Nerve Stimulation in Non-constipated Irritable Bowel Syndrome Patients: A Systematic Review

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ABSTRACT

Background & Aims: Irritable bowel syndrome (IBS) is a prevalent disorder with a complex and heterogeneous physiopathology, including a dysregulation of gut-brain axis. Treatment for IBS is targeted to the predominant symptom and requires a multidisciplinary approach. This review aims to evaluate the efficacy and safety of sacral nerve stimulation in non-constipated IBS patients

Methods: A literature search was carried out on MEDLINE, The Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science databases for all relevant articles. Quality of included papers was assessed using standardized guidelines

Results: Of 129 initial citations, 7 articles met our predefined inclusion criteria, including five randomized trials, a pilot study and a descriptive follow-up study. Five of 7 studies reported a positive effect of sacral nerve stimulation on symptoms and quality of life improvement in non-constipated IBS patients. No study reported serious adverse events.

Conclusions: Despite initial promising results of sacral nerve stimulation in non-constipated IBS patients, studies with larger sample sizes and longer follow-up are required.

Key words: irritable bowel syndrome – IBS – functional gastrointestinal diseases – sacral nerve stimulation – gastrointestinal motility – quality of life.

Abbreviations: FGID: functional gastrointestinal disorder; IBS: irritable bowel syndrome; IBS-C: IBS with constipation; IBS-D: IBS with diarrhea; IBS-M; mixed IBS; IBS-U: unsubtyped IBS; QOL: quality of life; SNM: sacral neuromodulation; RCT: randomized controlled trial; SNS: sacral nerve stimulation.

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INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic functional disorder including a variety of chronic or recurrent symptoms such as abdominal pain associated with defecation and changes in bowel movements, defined by the Rome IV criteria. Data from a survey using these criteria estimated that the prevalence of IBS in the general population is 4.1% [1], while due to the great methodological heterogeneity of studies prevalence estimated range can be even broader [2]. Women are nearly twice as likely

as men to be diagnosed with IBS and symptoms usually tend to worsen over the years [3].

Patients with IBS can be classified according to their predominant bowel habit into IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), and patients having mixed IBS (IBS-M) with both characteristics and those which do not include all criteria, included as unsubtyped IBS (IBS-U) [4].

Currently, functional gastrointestinal disorders (FGIDs) have been redefined as disorders of gut-brain interaction, considering the interaction of biological, psychological, and social factors in their pathogenesis [5, 6]. Central nervous system signals are transmitted to the gut by neurotransmitters as serotonin mainly produced in the gut [7, 8]. Features like visceral hypersensitivity, increased intestinal permeability, low-grade inflammation, altered mucosal immune dysregulation and disturbances in the microbiome have been identified as underlying causes [9, 10]. Post-infectious IBS develops in approximately 10% of patients with infectious enteritis,

with a prevalence of IBS after infectious gastroenteritis or enterocolitis reported to be 6–7 times higher than that without prior infectious episode [11, 12].

Irritable bowel syndrome represents a significant economic burden on healthcare systems worldwide, also leading to a negative impact on work productivity [2]. The diagnosis is primarily based on the patient history and commonly examinations reveal no underlying structural abnormality. However, additional investigations should be considered to rule out accompanying pathologies in patients older than 50 years or if alarm symptoms or atypical features are present. Laboratory tests can include lactose intolerance, serological tests for celiac disease, breath test for bacterial overgrowth, thyroid hormone evaluation and stool examination, as biomarkers that enable diagnosis are lacking [13, 14].

The quality of life (QOL) of IBS patients is considered significantly lower than in the general population and comparable to that of depressive patients [15]. Treatment is based on symptom reduction adding consideration to biopsychosocial understanding. Laxatives, antidiarrheals and antispasmodics are the first-line treatment recommended by the guidelines available [16, 17]. Other agents as serotonin receptor modulators (5-HT₃ antagonists and 5-HT₄ agonists) are used for severe IBS but, in addition to his high cost, severe complications such as cardiovascular events and ischemic colitis have been described after long-term administration [18, 19].

The use of gastrointestinal neuromodulation has drawn great interest over the last years. Electrical stimulation has been used as a treatment for morbid obesity and disorders as gastroesophageal reflux disease gastroparesis, nausea, constipation and fecal incontinence [20, 21]. Sacral nerve stimulation (SNS) or sacral neuromodulation (SNM), as current consensus uses, is a minimally invasive procedure introduced in 1995 by Matzel et al. [22]. In the last two decades SNS has become a well-established technique, initially used for urinary incontinence and then for fecal incontinence and constipation. Sacral neuromodulation uses chronic low-voltage stimulation of a sacral root by an electrode lead system connected to a pulse generator subcutaneously implanted.

Currently, fecal incontinence remains the most accepted indication of SNS in use for gastrointestinal disorders, including patients with low anterior resection and neurologic diseases (cerebral, spinal or peripheral) [23, 24]. Irritable bowel syndrome can be a risk factor for fecal incontinence and the coexistence of these prevalent conditions leads to an additive effect on the overall disease burden. Despite its use to treat IBS is still off-label, initial promising results of this therapy deserve further evaluation. This review aims to evaluate the efficacy and safety of SNS on patients with IBS.

METHODS

Protocol and Registration

The study was registered by the international prospective register of systematic reviews (PROSPERO) under CRD42020192192.

Eligibility Criteria

We included people over the age of 18 years diagnosed with IBS of any subtype and all quantitative observational

and interventional designs. Patients considered for enrollment had been diagnosed with diarrhea-predominant (IBS-D) or mixed (IBS-M) IBS according to the Rome III criteria. Studies in which SNM were used predominantly or entirely to treat fecal incontinence were excluded. Other types of electrical modulation for the treatment of IBS patients different from SNS were also excluded.

The main outcome was to investigate the effectiveness of SNS considering gastrointestinal symptoms and QOL. Additional outcomes included adverse events and parameters as small bowel transit, rectal volume tolerability, sensitivity, and rectal biomechanical properties.

Literature Search and Study Selection

A comprehensive search was initially conducted in September 2020 and finally updated in March 21 using online databases: MEDLINE, The Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science for articles that studied the efficacy of sacral neuromodulation treating irritable bowel disease.

The databases were searched using the relevant Medical Subject Headings (MeSH), including all subheadings [irritable bowel syndrome, transcutaneous nerve stimulation] and this was combined with a keyword search that included the terms: sacral nerve stimulation, irritable bowel syndrome, functional gastrointestinal diseases.

Only articles written in the English language involving human adult subjects were included. The search was not limited by publication year. Case reports were excluded, and only single intervention was reviewed. Because of the paucity of evidence, we did not include outcome term in the search term and all intervention comparisons were assessed. Reference lists of eligible studies were reviewed to identify additional suitable publications.

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [25]. Ethical approval was not required for this review article.

Data Extraction and Management

Identified papers were compiled into a Citation Manager and combined to remove duplicates. Data from the selected reports or studies were extracted and filled in the data extraction form by two authors independently (A.M.G.C. and M.L.R.D.). Any disagreements were resolved by consensus or consultation with a third review author.

Information for reference ID, author, year and journal of publication, characteristics of participants, blinding, average duration of follow-up, interventions outcomes and other relevant information was extracted onto an Excel spreadsheet. A data extraction sheet was fulfilled for each paper passing the inclusion/exclusion status.

Quality Assessment

The quality of included articles was assessed using standardized guidelines. Case series studies were assessed using the National Institute for Health and Care Excellence (NICE) 'Quality Assessment for Case Series' system' [26], which assesses characteristics of methodology, outcomes

and interpretation from a possible score of 8. Randomized controlled trials (RCT) were evaluated using the Jadad score [27], which gives points for randomization method, blinding and account of all patients. The score is out of a possible 5 points, with trials scoring 3 or greater considering good quality. The Newcastle-Ottawa quality assessment scale (NOS) assessed cohort studies. NOS contains 8 items within 3 domain and the total maximum score is 9, with studies having less than 5 points being identified as representing at high risk of bias (standard criterion for what constitutes a high-quality study has not yet been universally established) [28].

RESULTS

The PRISMA flow diagram (Fig. 1) summarizes the results of the literature search. A systematic search of the literature resulted in 129 abstracts. After screening the studies by title and abstract, studies that did not focus on the research questions of interest were excluded. The remaining full-text articles were analyzed in more detail to assess whether they met the inclusion criteria, as represented in Fig. 1. Finally, 7 full-text manuscripts were assessed for eligibility and included in the present study.

Data on 7 studies describing 47 patients were retrieved (4 studies shared the same group of patients). The majority of the patients participating in the studies were female (median

percentage of 74.4%). Five RCTs, a pilot study and a descriptive follow-up study were identified. All included studies were single-center series. Table I summarizes the population characteristics of the 7 studies included. Treatment details and tools are shown in Table II.

The median quality score for RCTs was 3.8 (range 3-5), 4 for the pilot study and 6 for the cohort study.

The results reporting the effects of SNS on outcomes in patients with IBS are summarized in Table III. For studies where publications were performed on the same cohort of patients, merely the different outcomes of these cohorts were included. There were not enough data to allow standard meta-analysis.

All studies except one included IBS-D (loose (mushy) or watery stools > 25% and hard or lumpy stools < 25% of bowel movements) or IBS-M (hard or lumpy stools > 25% and loose (mushy) or watery stools >25% of bowel movements); only IBS diarrhoea-predominant patients were considered in the pilot study [29].

Stimulation was turned ON or OFF for the first one month and then to the opposite setting for the next month in studies [34] and [35]. 6-week period of SNM (subsensory or OFF for 2 weeks and then the opposite for another 2 weeks) was performed in one study [30]. Lundby et al [29] completed a 3-week period of SNS.

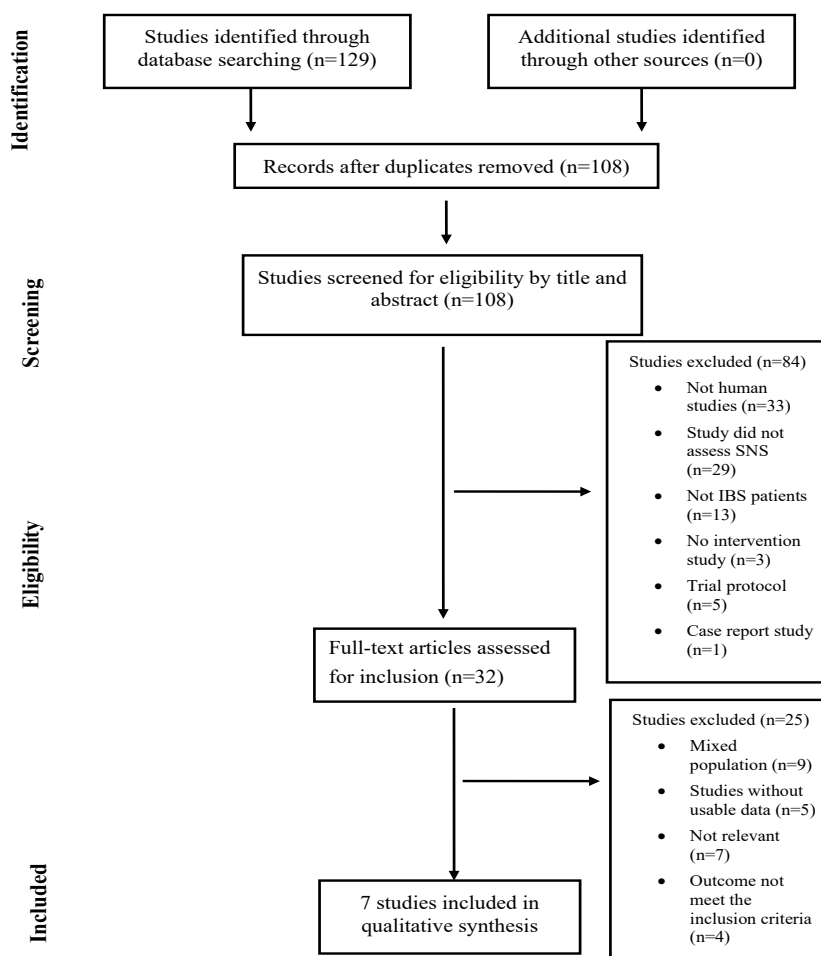


Fig. 1. PRISMA flow-chart

Table I. Characteristics of the included studies

Study	Year	Design Study type	No. of patients	Age (range)	Gender (F/M)	Indication	Quality appraisal
Fassov J et al. [34]	2014	RCT crossover	20	19-48	15/5	IBS (IBS-D or IBS-M)	Jadad 3
Fassov J et al. [30]	2019	RCT Double-blinded, placebo-controlled crossover	21	21-53	15/6	IBS (IBS-D or IBS-M)	Jadad 5
Fassov J et al. [35]	2014	RCT crossover	20	19-48	15/5	IBS (IBS-D or IBS-M)	Jadad 3
Lundby L et al. [29]	2008	Pilot study	6	26-54	5/1	IBS (IBS-D)	NICE 4
Fassov J et al. [31]	2014	RCT blinded crossover	20	19-48	15/5	IBS (IBS-D or IBS-M)	Jadad 3
Fassov J et al. [32]	2016	Descriptive follow-up	20	19-48	15/5	IBS (IBS-D or IBS-M)	NOS 6
Fassov J et al. [33]	2020	Randomized, double-blinded, cross-over study	21	24-53	14/6	IBS diarrhea	Jadad 5

IBS: irritable bowel syndrome; RCT: randomized controlled trial; NICE: National Institute for Health and Care Excellence; NOS: Newcastle-Ottawa Quality Assessment Scale.

Stimulation period of two months was considered for two studies [31, 32] and finally, the protocol established by Fassov et al. [33] in a randomized, double-blinded, cross-over study was a 6-week SNS test period (subsensory stimulation versus no stimulation followed by a 2-week period of suprasensory stimulation). Small bowel transit was evaluated in one study [34] with the Motility Tracking System-1 (MTS-1). No detectable effect on small intestinal transit patterns was found after treatment. Postprandial sensory and motor response was compared before and after treatment with SNS with multimodal

impedance planimetry. Differences on the postprandial response could not be demonstrated and furthermore, no statistically significant differences regarding tension, pressure, or stretch were found between SNM responders and non-responders patients.

Thermal and mechanical stimulation was investigated in a crossover RCT [35], concluding that SNM in these patients relaxed the rectal wall, while making it more sensitive to stretch and less sensitive to cold. Moreover, reduced wall stiffness and increased sensitivity to stretch was associated with improved GSRS-IBS symptom score.

Table II. Treatment methodology and end points

Study	Test phase	Tools used	Treatment details	Primary end point	Secondary end point
Fassov et al. [34]	ND	MTS-1	Turned ON or OFF for the first one month and then to the opposite setting for the next month	Change in the velocity of the magnetic pill within the small intestine (m/h)	ND
Fassov et al. [30]	PNE	■ GSRS-IBS ■ IBS-specific QOL score ■ Bowel habit diary	6-week period of SNM (subsensory or OFF for 2 weeks and then the opposite for another 2 weeks)	Effect in IBS-D or IBS-M	Placebo effect
Fassov et al. [35]	ND	■ Thermal stimulation ■ Mechanical stimulation ■ GSRS-IBS	Turned ON or OFF for the first one month and then to the opposite setting for the next month	Effects of SNS on rectal sensitivity and biomechanical properties in patients with IBS-D and IBS-M	Associations between IBS-specific symptoms and altered biomechanics or sensation
Lundby et al. [29]	PNE	■ GSRS-IBS ■ IBS-specific QOL score	3 weeks period of SNM	Differences between GSRS-IBS and IBS-specific quality of life score before and during stimulation	Differences between the variable domains
Fassov et al. [31]	PS	■ GSRS-IBS ■ IBS-specific QOL score ■ Bowel habit diary	Two months	Effects of permanent SNS on IBS-specific symptoms in patients with severe IBS-D or IBS-M	ND
Fassov et al. [32]	PS	■ GSRS-IBS ■ IBS-specific QOL score ■ Rectal volume tolerability ■ Diary ■ Urgency (episodes per day)	Two months	Medium-term efficacy of SNS for IBS	IBS-specific quality of life score
Fassov et al. [33]	ND	■ Multimodal impedance planimetry ■ GSRS-IBS ■ IBS-specific QOL score	6-week SNS test period. Subsensory stimulation versus no stimulation followed by a 2-week period of suprasensory stimulation	Postprandial sensory and motor response. To evaluate if SNM has an effect on the postprandial response in IBS-D and IBS-M patients	ND

GSRS-IBS: gastrointestinal symptom rating scale- irritable bowel syndrome; IBS: irritable bowel syndrome; IBS-D: diarrhoea predominant IBS; IBS-M: mixed IBS; QOL: quality of life; ND: not described; PNE: peripheral nerve evaluation; PS: permanent stimulator; MTS-1: Motility Tracking System-1; SNS: sacral nerve stimulation.

Table III. Studies reporting the effect of SNS on patients with IBS

Study	Standard deviation (or another spread measure)	p	Outcomes	Adverse events
Fassov et al. [34]	■ Fasting state: (Group ON-OFF: median change 0 m/h (range -1.07, 0.63), Group OFF-ON: median change 0.27 m/h (range -0.59, 1.12)) ■ Postprandial state (Group ON-OFF: median change -0.13 m/h (range -0.46, 0.23), Group OFF-ON: median change 0.015 m/h (range -0.48, 0.59))	0.25 0.14	No detectable effect on small intestinal transit patterns	ND
Fassov et al. [30]	■ GSRS-IBS: (Subsensory-OFF median change -1 (-26, 9), OFF-subsensory median change 8 (-11,36) ■ Pain: Subsensory-OFF, median change -1.5 (-4, 1), OFF-subsensory median change 1 (-4, 3) ■ IBS-specific quality of life score: (Subsensory-OFF median change -4(-8,52), OFF-subsensory median change 13 (-36,53) ■ Daily bowel movements: (Subsensory-OFF median change 0 (-1.8, 0.2), OFF-subsensory median change 0.2 (-0.5, 1.1) ■ Daily bowel movements: (Suprasensory- (1,8 range 0.8;8), OFF(2,15 range 0.5;9,2)	0.0572 0.0188 0.0909 0.0373 0.149	Reduction in IBS specific symptom score, pain and daily bowel movements. Median placebo effect 14% (0, 55) 52% of patients had a placebo response Suprasensory SNS significantly reduces the overall IBS-specific symptom score and improves the IBS-specific quality of life score	Not observed
Fassov et al. [35]	■ Cold stimuli were better tolerated in the ON period (19.9 °C[0.6]) compared to the OFF period (21.8 °C[0.6]) ■ Significantly lower crosssectional areas were needed to elicit sensory responses in the ON period (1545 mm2[95]) compared to the OFF period (1869 mm2[92]) ■ Wall stiffness was significantly lower in the ON period (192 mmHg[10]) compared to the OFF period (234 mmHg[10]) ■ Reduced wall stiffness was significantly associated with improved overall GSRS-IBS symptom score ■ The association between reduced sensory threshold and improvement of constipation was of borderline significance ■ Reduced sensory threshold to stretch was predictor of the GSRS-IBS symptom score ■ Reduced wall stiffness was predictor of the GSRS-IBS symptom score	0.03 0.015 0.004 0.01 0.05 0.02 < 0.001	SNS for diarrhea-predominant and mixed IBS relaxes the rectal wall, while making it more sensitive to stretch and less sensitive to cold. Reduced wall stiffness and increased sensitivity to stretch are associated with improved GSRS-IBS symptom score	ND
Lundby et al. [29]	■ GSRS-IBS : decreased from 48.9 to 28.3 ■ Pain 7.9 to 4.4 ■ Bloating 13.5 to 7.2 ■ Diarrhea 17.3 to 10.6 ■ IBS-specific quality of life score from 99.3 to 59.6 ■ Daily activities 26.9 to 16.9 ■ Emotional distress 22.2 to 13.3 ■ Eating habits 15.2 to 8 ■ Fatigue 23.2 to 14.4 ■ Tendency to a reduction in sleep disturbances ■ Rectal volume tolerability: Median “first sensation,” “desire to defecate,” and “maximal tolerable volume” did not change significantly during stimulation ■ Non significant reduction in the number of bowel movements per day from 3.5 to 2.1 ■ Urgency (episodes per day) decreased from 1.9 to 0.5	0.004 0.02 0.01 0.03 0.009 0.02 0.02 0.02 0.007 0.06 0.07 0.08	Temporary SNS provides a significant reduction in diarrhea-predominant symptoms and improves QOL	No operative morbidity
Fassov et al. [31]	■ GSRS-IBS: median difference in the ON-OFF group was 12 (range, -22 to 44) and in the OFF-ON group -17.5 (range, -48 to -1) ■ Median GSRS-IBS baseline (25; range, 13-65); at 1-year follow-up (62; range, 45-80) ■ IBS-specific quality of life score: median difference in the ON-OFF group was 16 (range, -24 to 69) and in the OFF-ON group -42.5 (range, -77 to 0) ■ Bowel movements per week: [group ON-OFF: median change 2.5 (range, -1 to 5); group OFF-ON: median change -3 (range, -11 to 0)] ■ Number of episodes of urgency per week: [Group ON-OFF: median change 0 (range, 0-2); group OFF-ON: median change -1 (range, -4 to 0)] ■ Time (minutes) spent on the toilet per week: [group ON-OFF: median change 4 (range, -18 to 97); group OFF-ON: median change -22 (range, -76 to 5)]	0.0009 0.0001 0.0003 0.0031 0.0180 0.0184	SNS significantly reduces symptoms and improves QOL of highly selected patients with IBS	Seven patients reported 10 device-related adverse events
Fassov et al. [32]	■ GSRS-IBS: significantly lower at 3-year follow-up (30, range 13-71) than at baseline (62, 45-80) ■ IBS-specific quality of life score: significantly improved at 3-year follow-up (52, 26-significantly improved at 3-year follow-up (52, 26-169) compared with baseline (135, 82-180)	0.0001 0.0002	At medium-term follow-up, SNS continues to be an effective treatment for highly selected patients with IBS-D or IBS-M	First Year: Seven patients reported 10 device-related adverse events.1-3 years: 2 patients

Table III (continued)

Fassov et al. [33]	■ Postprandial increase in wall tension did not reach statistical significance (mean 86.79 [range 28.8 to 204.5] mmHg.mm before the meal, mean 159.71 [range 71.3 to 270.8] mmHg.mm after the meal) ■ No statistically significant difference between the postprandial wall tension at baseline and during SNS ■ No difference between pressure or stretch ratio at baseline and during SNS	p=0.277 p=0.489 p>0.05	No statistical significant difference in the sensory response to heat or cold before and after SNS	No procedure-related adverse effects
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For abbreviations see Table II.

Effect of SNS on Gastrointestinal Symptoms Severity and Quality of Life

Gastrointestinal Symptom Rating Scale-IBS version and IBS-specific QOL score were the questionnaires used in the included studies to assess symptom severity and QOL respectively. A RCT double-blinded, placebo-controlled crossover [30] showed after SNS a reduction in IBS specific symptom score, pain and daily bowel movements with a median placebo effect of 14%. Suprasensory stimulation significantly reduced the overall IBS-specific symptom score and improved the IBS-specific QOL.

Lundby et al. [29] concluded that temporary SNS provided a significant reduction in IBS-D symptoms and improved QOL; remarkably the positive effect disappeared two weeks after cessation of the stimulation.

Bowel movements, number of episodes of urgency and time spent on the toilet per week were significantly reduced after neurostimulation in a 2-month blinded, crossover trial [31] and, at 1-year follow-up, the median IBS-specific symptom score was also significantly lower than baseline. At medium-term follow-up (three years), SNS continued to be an effective treatment for highly selected patients with IBS-D or IBS-M [32].

Adverse Events

No adverse events were observed in three studies [29, 30, 33] and not described in other two [34,35]. Fassov et al. [31] reported seven patients and 10 device-related adverse events in the first year: four were classified as mild (postoperative pain), 1 moderate (recurrent cystitis), and 5 severe (requiring revisional surgery, 3 patients due to persistent postoperative pain at the implantation site of the pacemaker and 2 patients for suspected migration). Two moderate device-related adverse events were reported between the 1- and 3-year follow-up points [32] (a case of recurrent migraine and one case of a tingling sensation under the foot).

DISCUSSION

Irritable bowel syndrome is one of the most common gastrointestinal disorders seen by primary care physicians, with patients experiencing an impaired QOL. Several treatments options are used for symptomatic relief in patients suffering from this condition. In this systematic review the impact of sacral nerve stimulation on severity and QOL scores in patients with IBS was investigated.

Various scoring systems have been developed to quantify the severity of symptoms in patients with IBS. Gastrointestinal Symptom Rating Scale- Irritable Bowel Syndrome Version

(GSRS-IBS) includes 13 items in 5 symptom clusters: abdominal pain, bloating, diarrhea, constipation, and satiety (13 = no symptoms of IBS to 91 = severe symptoms of IBS). The symptom scale is a valid and reliable disease-specific symptom score [36]. The severity of symptoms in IBS patients is also determined in many studies using a Visual Analogue Scale (VAS), based on a numeric scale of 0–10, where 0 indicates no symptoms and 10 the most intense symptoms.

Irritable bowel syndrome-specific QOL score (IBS-QOL) questionnaire is a specific survey assessing the impact of irritable bowel syndrome on patients' QOL and the effects of treatment. Twenty-six items represent five domains: fatigue, impact on daily activities, sleep disturbance, emotional distress, and eating habits [37, 38]. It is also interesting the use of generic survey instruments such as the 36-Item Short Form Health Survey questionnaire (SF-36) as health-related QOL can be compared to patients with other diseases.

Sacral nerve modulation has been used extensively in the management of fecal incontinence over the past 20 years. Several theories are proposed to explain the mechanism of action, including somatic afferent inhibition and effect in the somatosensory cortex by reducing corticoanal excitability, with beneficial effects due to the initiation of action potentials in somatic afferent nerves [39, 40].

To date only the effect of SNS on patients with IBS-D or IBS-M has been investigated and efficacy is assessed using cross-over designs in most of the studies available. In 2008, Lundby et al. [29] were the first to report in a pilot study the outcome of IBS patients after sacral neuromodulation, showing reduced symptoms (pain, bloating, and diarrhea) and improved QOL(daily activities, emotional distress, eating habits and fatigue dimensions).

In bowel dysfunction, a wash-out period of at least three weeks is advised [41]. The same group of researchers carried out a randomized controlled crossover study over 21 patients. Patients were randomized (1:1) to have the stimulator ON or OFF for 1 month and then the opposite for another month. They revealed that SNM significantly alleviated IBS-specific symptoms and improved QOL, reducing the frequency of defecation, episodes of urgency, and time spent on toilet [31].

The placebo effect of neuromodulation is a key concept in the interpretation of results and is known to contribute to the overall treatment response in clinical studies. Tan et al. found in a Systematic Review and Meta-Analysis [42] that sham stimulation is associated with clinical and statistically meaningful improvements in symptoms of fecal incontinence (1.3 episodes per week (95% CI –2.53 to –0.01, $p = 0.05$), fecal urgency by 1.5 episodes per week (CI –3.32 to 0.25, $p = 0.09$), and Cleveland Clinic Severity scores by 2.2 points (CI 1.01 to

3.36, $p = 0.0003$) and constipation (improved stool frequency (1.3 episodes per week, CI 1.16 to 1.42, $p < 0.00001$), Wexner Constipation scores (5.0 points, CI -7.45 to -2.54 $p < 0.0001$)), as well as QOL scores (7.9 points, CI -0.46 to 16.18, $p = 0.06$).

Considering that only 75% of the patients were able to tell whether the neurostimulator was turned ON or not in the previous study, authors designed a double blinded, truly placebo-controlled crossover study [30]. During the first 4 weeks, the patients were randomized 1:1 to have the neurostimulator set subsensory or OFF for 2 weeks and then the opposite for another 2 weeks, with patients and investigators were blinded to settings. In the following 2 weeks, the stimulation was set suprasensory. Pain and number of daily bowel movements were significantly reduced during stimulation and the IBS-specific symptom score was reduced with borderline significance. For the entire cohort, the median placebo effect was 14%.

The role of sacral neuromodulation in relation to gastrointestinal motility and function is unclear. Studies evaluating colonic motility after SNS have observed an increase in retrograde propagating sequences in the left colon and a decrease in antegrade activity in the ascending colon [43-45]. These effects are supposed to be related to therapeutic outcomes in patients with fecal incontinence. Nevertheless, the relationship between function and symptomatic relief has not yet been fully clarified in cases of constipation. Initial reports suggested improvement in slow-transit constipation and obstructed defecation symptoms after sacral neuromodulation. Later publications reported a drop-in success rate from 70 to 30%. Consequently, the use of SNS for functional constipation is progressively being abandoned [46, 47]. As a matter of fact, patients included in the studies were subtyped with IBS-D and IBS-M. The effect of sacral nerve stimulation on constipation-predominant subtype of IBS has not been assessed.

The effect of SNM on intestinal motility has also been evaluated and studies investigating the role of small intestinal dysmotility in IBS patients have shown contrasting results regarding accelerated or delayed small intestinal transit [48, 49]. The lack of effect on small intestinal transit in patients with IBS was supported from Fassov et al. [34]. Gastrointestinal motility was investigated with the Motility Tracking System-1 (MTS-1), showing no differences in the median velocity of the magnetic pill through the small intestine between periods with and without SNS [34].

Most patients with IBS have altered rectal sensibility and increased paracellular permeability. Meurette et al. [50] conducted an experimental study on a porcine model of percutaneous SNM, revealing the ability of neuromodulation to reinforce rectal epithelial barrier, reducing permeability following bilateral stimulation associated with a reduction in mucosal thickness. They further demonstrated that SNM increased epithelial surface mucus amount, enhancing barrier protection on surface epithelium.

Previous studies revealed that SNS acts on anal motor and rectal sensory functions and leads to normalize defecatory desire and maximum tolerable volume in patients with evacuatory dysfunction [51, 52]. Fassov et al. [35] found in a controlled, randomized crossover trial that SNM reduced rectal wall stiffness and sensory thresholds during rectal distension

in IBS-D and IBS-M patients, making it more sensitive to stretch and less sensitive to cold without affecting the sensory response to heat.

Cost-effectiveness of SNS as a treatment option for severe IBS has been evaluated by the same group of researchers from a single center, indicating that the positive effect of SNM for IBS is maintained after at least 3 years estimating to be cost-effective from a 7-year perspective [53].

Based on the modulation effect over autonomic nervous system, the action on the gut-brain axis and the effects on modulation of colonic serotonin receptors, complementary or alternative medicine including acupuncture has been evaluated as a treatment for patients affected by IBS [54]. A Cochrane systematic review including 1,086 patients found significantly greater benefits regarding symptoms severity from acupuncture than from two antispasmodic drugs providing a modest benefit for IBS (RR: 1.28, 95%CI: 1.12-1.45; 5 studies, 449 patients) [55]. In addition to acupuncture, different methods of electrical nerve stimulation have also been tried for treating IBS symptoms, including spinal cord stimulation [56] and interferential current stimulation [57] with promising results.

Sacral nerve stimulation is a minimally invasive technique not exempt from side effects, most of them responding to conservative therapy; however, rates of surgical re-interventions are high. Fassov et al. reported 10 device-related adverse events in the first year [31] and 2 between the 1- and 3-year follow-up points [32]. A systematic literature search extracted data on adverse events requiring an active intervention, reporting reoperations performed to explant (38.2%) or replace (46.5%) the device or a lead, or revise the generator pocket (14.6%) [58].

The limitations of this study include the scarcity of literature related to the management of IBS patients with sacral neuromodulation, with some studies including the same groups of participants as a potential source of bias. Additionally, subgroup analyses for IBS-D and IBS-M patients were not assessed and all of the studies lacked a control group for comparison with other possible treatments. Another limitation of this review is the heterogeneity in stimulation protocols, making it difficult to allow an accurate comparison of results. Larger RCT with long-term follow-up are needed to sustain the use of SNS for the treatment of this gastrointestinal disorder.

CONCLUSIONS

The evidence to support the use of SNS for IBS is limited; however, it is a potential treatment option for symptomatic relief in patients suffering from irritable bowel syndrome. Further studies based in large sample size are encouraged.

Conflicts of interest: None to declare.

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REFERENCES

1. Sperber AD, Bangdiwala SI, Drossman DA, et al. Worldwide Prevalence and Burden of Functional Gastrointestinal Disorders, Results of Rome Foundation Global Study. *Gastroenterology* 2021;160:99-114.e3. doi:10.1053/j.gastro.2020.04.014
2. Sperber AD, Dumitrascu D, Fukudo S, et al. The global prevalence of IBS in adults remains elusive due to the heterogeneity of studies: a Rome Foundation working team literature review. *Gut* 2017;66:1075-1082. doi:10.1136/gutjnl-2015-311240
3. Defrees DN, Bailey J. Irritable Bowel Syndrome: Epidemiology, Pathophysiology, Diagnosis, and Treatment. *Prim Care* 2017;44:655-671. doi:10.1016/j.pop.2017.07.009
4. Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. *JAMA* 2015;313:949-958. doi:10.1001/jama.2015.0954
5. Drossman DA, Hasler WL. Rome IV-Functional GI Disorders: Disorders of Gut-Brain Interaction. *Gastroenterology* 2016;150:1257-1261. doi:10.1053/j.gastro.2016.03.035
6. Ancona A, Petito C, Iavarone I, et al. The gut-brain axis in irritable bowel syndrome and inflammatory bowel disease. *Dig Liver Dis* 2021;53:298-305. doi:10.1016/j.dld.2020.11.026
7. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. *Ann Gastroenterol* 2015;28:203-209.
8. Luo M, Zhuang X, Tian Z, Xiong L. Alterations in short-chain fatty acids and serotonin in irritable bowel syndrome: a systematic review and meta-analysis. *BMC Gastroenterol* 2021;21:14. doi:10.1186/s12876-020-01577-5
9. Burns G, Carroll G, Mathe A, et al. Evidence for Local and Systemic Immune Activation in Functional Dyspepsia and the Irritable Bowel Syndrome: A Systematic Review. *Am J Gastroenterol* 2019;114:429-436. doi:10.1038/s41395-018-0377-0
10. Ceuleers H, Van Spaendonck H, Hanning N, et al. Visceral hypersensitivity in inflammatory bowel diseases and irritable bowel syndrome: The role of proteases. *World J Gastroenterol* 2016;22:10275-10286. doi:10.3748/wjg.v22.i47.10275
11. Barbara G, Grover M, Bercik P, et al. Rome Foundation Working Team Report on Post-Infection Irritable Bowel Syndrome. *Gastroenterology* 2019;156:46-58.e7. doi:10.1053/j.gastro.2018.07.011
12. Thabane M, Kottachchi DT, Marshall JK. Systematic review and meta-analysis: The incidence and prognosis of post-infectious irritable bowel syndrome. *Aliment Pharmacol Ther* 2007;26:535-544. doi:10.1111/j.1365-2036.2007.03399.x
13. Camilleri M. Diagnosis and Treatment of Irritable Bowel Syndrome: A Review. *JAMA* 2021;325:865-877. doi:10.1001/jama.2020.22532
14. Black CJ, Drossman DA, Talley NJ, Ruddy J, Ford AC. Functional gastrointestinal disorders: advances in understanding and management. *Lancet* 2020;396:1664-1674. doi:10.1016/S0140-6736(20)32115-2
15. Ng QX, Soh AYS, Loke W, Venkatanarayanan N, Lim DY, Yeo WS. Systematic review with meta-analysis: The association between post-traumatic stress disorder and irritable bowel syndrome. *J Gastroenterol Hepatol* 2019;34:68-73. doi:10.1111/jgh.14446
16. Fukudo S, Okumura T, Inamori M, et al. Evidence-based clinical practice guidelines for irritable bowel syndrome 2020. *J Gastroenterol* 2021;56:193-217. doi:10.1007/s00535-020-01746-z
17. Lacy BE, Pimentel M, Brenner DM, et al. ACG Clinical Guideline: Management of Irritable Bowel Syndrome. *Am J Gastroenterol* 2021;116:17-44. doi:10.14309/ajg.0000000000001036
18. Lewis JH. The risk of ischaemic colitis in irritable bowel syndrome patients treated with serotonergic therapies. *Drug Saf* 2011;34:545-565. doi:10.2165/11590690-000000000-00000
19. Loughlin J, Quinn S, Rivero E, et al. Tegaserod and the risk of cardiovascular ischemic events: an observational cohort study. *J Cardiovasc Pharmacol Ther* 2010;15:151-157. doi:10.1177/1074248409360357
20. Payne SC, Furness JB, Stebbing MJ. Bioelectric neuromodulation for gastrointestinal disorders: effectiveness and mechanisms. *Nat Rev Gastroenterol Hepatol* 2019;16:89-105. doi:10.1038/s41575-018-0078-6
21. Chen JD, Yin J, Wei W. Electrical therapies for gastrointestinal motility disorders. *Expert Rev Gastroenterol Hepatol* 2017;11:407-418. doi:10.1080/17474124.2017.1298441
22. Matzel KE, Stadelmaier U, Hohenfellner M, Gall FP. Electrical stimulation of sacral spinal nerves for treatment of faecal incontinence. *Lancet* 1995;346:1124-1127. doi:10.1016/S0140-6736(95)91799-3
23. Katuwal B, Bhullar J. Current Position of Sacral Neuromodulation in Treatment of Fecal Incontinence. *Clin Colon Rectal Surg* 2021;34:22-27. doi:10.1055/s-0040-1714247
24. Mirbagheri N, Sivakumaran Y, Nassar N, Gladman MA. Systematic review of the impact of sacral neuromodulation on clinical symptoms and gastrointestinal physiology. *ANZ J Surg* 2016;86:232-236. doi:10.1111/ans.13257
25. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;62:1006-1012. doi:10.1016/j.jclinepi.2009.06.005
26. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. *BMJ Evid Based Med* 2018;23:60-63. doi:10.1136/bmjebm-2017-110853
27. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1-12. doi:10.1016/0197-2456(95)00134-4
28. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25:603-605. doi:10.1007/s10654-010-9491-z
29. Lundby L, Krogh K, Buntzen S, Laurberg S. Temporary sacral nerve stimulation for treatment of irritable bowel syndrome: a pilot study. *Dis Colon Rectum* 2008;51:1074-1078. doi:10.1007/s10350-008-9255-y
30. Fassov J, Lundby L, Laurberg S, Krogh K. Sacral nerve modulation for irritable bowel syndrome: A randomized, double-blinded, placebo-controlled crossover study. *Neurogastroenterol Motil* 2019;31:e13570. doi:10.1111/nmo.13570
31. Fassov JL, Lundby L, Laurberg S, Buntzen S, Krogh K. A randomized, controlled, crossover study of sacral nerve stimulation for irritable bowel syndrome. *Ann Surg* 2014;260:31-36. doi:10.1097/SLA.0000000000000559
32. Fassov J, Lundby L, Laurberg S, Buntzen S, Krogh K. Three-year follow-up of sacral nerve stimulation for patients with diarrhoea-predominant and mixed irritable bowel syndrome. *Colorectal Dis* 2017;19:188-193. doi:10.1111/codi.13428
33. Fassov J, Liao D, Brock C, Lundby L, Laurberg S, Krogh K. Sacral Nerve Modulation Has No Effect on the Postprandial Response in Irritable Bowel Syndrome. *Clin Exp Gastroenterol* 2020;13:235-244. doi:10.2147/CEG.S245209
34. Fassov J, Lundby L, Worsøe J, Buntzen S, Laurberg S, Krogh K. A randomised, controlled study of small intestinal motility in patients treated with sacral nerve stimulation for irritable bowel syndrome. *BMC Gastroenterol* 2014;14:111. doi:10.1186/1471-230X-14-111

35. Fassov J, Brock C, Lundby L, et al. Sacral nerve stimulation changes rectal sensitivity and biomechanical properties in patients with irritable bowel syndrome. *Neurogastroenterol Motil* 2014;26:1597-1604. doi:[10.1111/nmo.12426](https://doi.org/10.1111/nmo.12426)
36. Wiklund IK, Fullerton S, Hawkey CJ, et al. An irritable bowel syndrome-specific symptom questionnaire: development and validation. *Scand J Gastroenterol* 2003;38:947-954. doi:[10.1080/00365520310004209](https://doi.org/10.1080/00365520310004209)
37. Andrae DA, Patrick DL, Drossman DA, Covington P. Evaluation of the Irritable Bowel Syndrome Quality of Life (IBS-QOL) questionnaire in diarrheal-predominant irritable bowel syndrome patients. *Health Qual Life Outcomes* 2013;11:208. doi:[10.1186/1477-7525-11-208](https://doi.org/10.1186/1477-7525-11-208)
38. Longstreth GF, Bolus R, Naliboff B, et al. Impact of irritable bowel syndrome on patients' lives: development and psychometric documentation of a disease-specific measure for use in clinical trials. *Eur J Gastroenterol Hepatol* 2005;17:411-420. doi:[10.1097/00042737-200504000-00004](https://doi.org/10.1097/00042737-200504000-00004)
39. De Wachter S, Vaganee D, Kessler TM. Sacral Neuromodulation: Mechanism of Action. *Eur Urol Focus* 2020;6:823-825. doi:[10.1016/j.euf.2019.11.018](https://doi.org/10.1016/j.euf.2019.11.018)
40. Janssen PTJ, Komen N, Melenhorst J, et al. Sacral Neuromodulation for Fecal Incontinence: A Review of the Central Mechanisms of Action. *J Clin Gastroenterol* 2017;51:669-676. doi:[10.1097/MCG.0000000000000850](https://doi.org/10.1097/MCG.0000000000000850)
41. Assmann R, Douven P, Kleijnen J, et al. Stimulation Parameters for Sacral Neuromodulation on Lower Urinary Tract and Bowel Dysfunction-Related Clinical Outcome: A Systematic Review. *Neuromodulation* 2020;23:1082-1093. doi:[10.1111/ner.13255](https://doi.org/10.1111/ner.13255)
42. Tan K, Wells CI, Dinning P, Bissett IP, O'Grady G. Placebo Response Rates in Electrical Nerve Stimulation Trials for Fecal Incontinence and Constipation: A Systematic Review and Meta-Analysis. *Neuromodulation* 2020;23:1108-1116. doi:[10.1111/ner.13092](https://doi.org/10.1111/ner.13092)
43. Patton V, Wiklendt L, Arkwright JW, Lubowski DZ, Dinning PG. The effect of sacral nerve stimulation on distal colonic motility in patients with faecal incontinence. *Br J Surg* 2013;100:959-968. doi:[10.1002/bjs.9114](https://doi.org/10.1002/bjs.9114)
44. Michelsen HB, Christensen P, Krogh K, et al. Sacral nerve stimulation for faecal incontinence alters colorectal transport. *Br J Surg* 2008;95:779-784. doi:[10.1002/bjs.6083](https://doi.org/10.1002/bjs.6083)
45. Southwell BR. Electro-Neuromodulation for Colonic Disorders-Review of Meta-Analyses, Systematic Reviews, and RCTs. *Neuromodulation* 2020;23:1061-1081. doi:[10.1111/ner.13099](https://doi.org/10.1111/ner.13099)
46. Altomare DF, Picciariello A, Di Ciaula A, Rinaldi M, De Fazio M, Portincasa P. Effects of temporary sacral nerve stimulation on gastrointestinal motility and function in patients with chronic refractory slow-transit constipation. *Tech Coloproctol* 2021;25:291-297. doi:[10.1007/s10151-020-02367-7](https://doi.org/10.1007/s10151-020-02367-7)
47. Patton V, Stewart P, Lubowski DZ, Cook IJ, Dinning PG. Sacral Nerve Stimulation Fails to Offer Long-term Benefit in Patients With Slow-Transit Constipation. *Dis Colon Rectum* 2016;59:878-885. doi:[10.1097/DCR.0000000000000653](https://doi.org/10.1097/DCR.0000000000000653)
48. Cogliandro RF, Antonucci A, De Giorgio R, et al. Patient-reported outcomes and gut dysmotility in functional gastrointestinal disorders. *Neurogastroenterol Motil* 2011;23:1084-1091. doi:[10.1111/j.1365-2982.2011.01783.x](https://doi.org/10.1111/j.1365-2982.2011.01783.x)
49. Evans PR, Bak YT, Shuter B, Hoschl R, Kellow JE. Gastroparesis and small bowel dysmotility in irritable bowel syndrome. *Dig Dis Sci* 1997;42:2087-2093. doi:[10.1023/a:1018874602790](https://doi.org/10.1023/a:1018874602790)
50. Meurette G, Blanchard C, Duchalais-Dassonneville E, et al. Sacral nerve stimulation enhances epithelial barrier of the rectum: results from a porcine model. *Neurogastroenterol Motil* 2012;24:267-273.e110. doi:[10.1111/j.1365-2982.2011.01839.x](https://doi.org/10.1111/j.1365-2982.2011.01839.x)
51. Carrington EV, Knowles CH. The influence of sacral nerve stimulation on anorectal dysfunction. *Colorectal Dis* 2011;13 Suppl 2:5-9. doi:[10.1111/j.1463-1318.2010.02518.x](https://doi.org/10.1111/j.1463-1318.2010.02518.x)
52. Knowles CH, Thin N, Gill K, et al. Prospective randomized double-blind study of temporary sacral nerve stimulation in patients with rectal evacuatory dysfunction and rectal hyposensitivity. *Ann Surg* 2012;255:643-649. doi:[10.1097/SLA.0b013e318247d49f](https://doi.org/10.1097/SLA.0b013e318247d49f)
53. Tipsmark LS, Fassov J, Lundby L, Laurberg S, Ehlers L, Krogh K. Cost-effectiveness analysis of sacral nerve stimulation as treatment for severe irritable bowel syndrome. *Colorectal Dis* 2016;18:O30-O36. doi:[10.1111/codi.13149](https://doi.org/10.1111/codi.13149)
54. Rabitti S, Giovanardi CM, Colussi D. Acupuncture and Related Therapies for the Treatment of Gastrointestinal Diseases. *J Clin Gastroenterol* 2021;55:207-217. doi:[10.1097/MCG.0000000000001455](https://doi.org/10.1097/MCG.0000000000001455)
55. Manheimer E, Cheng K, Wieland LS, et al. Acupuncture for treatment of irritable bowel syndrome. *Cochrane Database Syst Rev* 2012;5:CD005111. doi:[10.1002/14651858.CD005111.pub3](https://doi.org/10.1002/14651858.CD005111.pub3)
56. Rana MV, Knezevic NN. Tripolar spinal cord stimulation for the treatment of abdominal pain associated with irritable bowel syndrome. *Neuromodulation* 2013;16:73-77. doi:[10.1111/j.1525-1403.2012.00451.x](https://doi.org/10.1111/j.1525-1403.2012.00451.x)
57. Coban Ş, Akbal E, Köklü S, et al. Clinical trial: transcutaneous interferential electrical stimulation in individuals with irritable bowel syndrome - a prospective double-blind randomized study. *Digestion* 2012;86:86-93. doi:[10.1159/000338301](https://doi.org/10.1159/000338301)
58. Bielefeldt K. Adverse events of sacral neuromodulation for fecal incontinence reported to the federal drug administration. *World J Gastrointest Pharmacol Ther* 2016;7:294-305. doi:[10.4292/wjgpt.v7.i2.294](https://doi.org/10.4292/wjgpt.v7.i2.294)