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Review Article

Vagus Nerve Stimulation and Sacral Nerve Stimulation for Inflammatory Bowel Disease: A Systematic Review

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Abstract

Background and objectives: In this systematic review, we assessed the efficacy, potential mechanisms, and safety of two neuromodulation therapies in patients with inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis. The first therapy is vagus nerve stimulation (VNS) utilizing implantable or transcutaneous electrodes, and the second is sacral nerve stimulation (SNS) using implantable or percutaneous electrodes.

Methods: We conducted a systematic literature review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The PubMed database was comprehensively searched, and studies were rigorously assessed for inclusion and exclusion criteria.

Results: Our analysis encompassed five clinical studies, three on VNS and two on SNS. Most investigated studies demonstrated significant beneficial effects on IBD symptoms, including disease activity, severity of intestinal lesions, and intestinal pain. When evaluating the impact on key IBD pathophysiologies, both VNS and SNS exhibited trends toward reducing biomarkers of intestinal mucosal inflammation and mitigating sympathetic dominance. Importantly, none of the evaluated neuromodulation methods resulted in long-term adverse effects.

Conclusions: Cumulative evidence from the evaluated studies indicates that VNS and SNS therapies effectively alleviate IBD symptoms and may hold promise in addressing the underlying pathophysiologies of IBD, including intestinal mucosal inflammation and sympathetic dominance. Consequently, they represent valuable options for individualized IBD treatment.

Introduction

The prevalence of IBD is approximately 0.9% of the general population in the US,[1] comprising 0.4% with ulcerative colitis (UC) and 0.5% with Crohn's disease (CD).[2] The direct cost of IBD care in the US amounts to $60 billion ($23K per patient),[3] which is mainly aimed at treating IBD symptoms, such as diarrhea, blood in the stool, weight loss, fever, and abdominal pain. The etiology of IBD is multifactorial, involving genetic predisposition and immunologic disturbances.[4] An exaggerated mucosal immune response to the patient's native microbiota is pivotal in initiating and perpetuating intestinal inflammation.[5] The anti-inflammatory medications include first-line small-molecule drugs like aminosalicylates (e.g., mesalamine), corticosteroids (e.g., budesonide, prednisone), and immunosuppressants (e.g., azathioprine These are followed by second-line anti-inflammatory biologics, such as anti-TNF-α and anti-α4β7 integrin antibodies.[6] However, biological treatments are primarily symptomatic, do not prevent the recurrence of flares, and are associated with significant side effects. Furthermore, approximately 50% of UC[7] and CD patients[8] do not initially respond favorably to these treatments. Additionally, within the first year of drug use, 30–35% of initial responders experience a secondary loss of clinical response.[9–11] For patients with CD and UC who are refractory to

Keywords: Vagus nerve stimulation; Sacral nerve stimulation; Neuromodulation; Inflammatory bowel disease; Crohn's disease; Ulcerative colitis.

Abbreviations: CD, Crohn's disease; CDAI, Crohn's Disease activity index; pCDAI, pediatric CDAI; CDEIS, Crohn's Disease endoscopic index of severity; CRP, C-reactive protein; FC, fecal calprotectin; FDA, Food and Drug Administration; GI, gastrointestinal; HRV, heart rate variability; IBD, inflammatory bowel disease; IPG, implantable pulse generator; iSNS, implantable SNS; iVNS, implantable VNS; LF/HF, low-frequency to high-frequency ratio; pSNS, percutaneous SNS using electroacupuncture needles; RCT, randomized controlled trial; SES-CD, simple endoscopic score for Crohn's Disease; SNS, sacral nerve stimulation; taVNS, transcutaneous auricular VNS; TNF-α, Tumor Necrosis Factor-α; UC, ulcerative colitis; UCDAI, ulcerative colitis disease activity index; pUCDAI, pediatric UCDAI; VAS, Visual Analogue Scale; VNS, vagus nerve stimulation.

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Table 1. Search keywords for PubMed for two evaluated therapies

Therapy	Search keywords for PubMed
VNS	("vagus nerve stimulation" [Title/Abstract] OR "vagal nerve stimulation" [Title/Abstract] OR (auricular[Title/Abstract] AND "nerve stimulation" [Title/Abstract])) AND ("Inflammatory Bowel Disease*" [Title/Abstract] OR "Crohn*" [Title/Abstract] OR colitis[Title/Abstract])
SNS	("sacral nerve stimulation" [Title/Abstract] OR "sacral neuromodulation" [Title/Abstract]) AND ("Inflammatory Bowel Disease*" [Title/Abstract] OR "Crohn*" [Title/Abstract] OR colitis[Title/Abstract])

SNS, sacral nerve stimulation; VNS, vagus nerve stimulation.

biologic medications, irreversible surgical procedures may be necessary to remove inflamed portions of the intestine.[12] Removal of the colon (colectomy) is associated with an 81% risk of postoperative complications (e.g., depression, work productivity, diet restrictions, body image, sexual function)[13] and a high cost of $140K.[14] Low adherence to drug self-administration is an unsolved need in IBD patients.[15] Given the shortcomings of existing therapies, there is a clear need for more effective, patient-adherent, and less expensive strategies for IBD treatment.

Recently, the vagus nerve stimulation (VNS) and sacral nerve stimulation (SNS) methods have been evaluated in the animal models of IBD. Both methods reduced the levels of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-18). They increased the levels of anti-inflammatory cytokines (IL-10, TGF-β) in the blood plasma, indicating healing of intestinal mucosal inflammation.[16–24] The effectiveness of the VNS and SNS in IBD could be explained by normalizing the sympathetic and parasympathetic signaling, as the autonomic balance is shifted toward sympathetic dominance during the flares.[25–29] In the rodent models of IBD, the VNS and SNS therapies effectively reduced sympathetic dominance in the autonomic balance.[16–18,30] The SNS effects on the autonomic balance are likely mediated via two neural pathways: direct efferent sacral pathway to the colon and indirect spinal afferent-vagal efferent pathway to the colon.[31] The VNS and SNS are typically applied using a minimally invasive procedure by implanting the VNS electrodes on the cervical vagus[32,33] or SNS electrodes in the sacral foramen.[34] Both VNS and SNS neuromodulation procedures have received FDA approval for various indications, demonstrating a well-established safety profile comparable to that of other neuromodulation implants during long-term implantation and use.[35–38] In addition to the implantable VNS and SNS methods, two non-implantable approaches have also shown a safe track record during intermittent daily use: transcutaneous auricular vagus nerve stimulation[39] and percutaneous sacral nerve stimulation based on electroacupuncture.[40]

In summary, despite the availability of various symptomatic treatments for IBD, there remains a gap in therapies that specifically target the underlying pathophysiologies of the disease. Two neuromodulation therapies, VNS and SNS, have been investigated as potential treatments for IBD. These therapies encompass both implantable and transcutaneous VNS, as well as implantable and percutaneous SNS. In this systematic review, we have assessed the effectiveness of these neuromodulation approaches in addressing IBD symptoms and key pathophysiologies, including intestinal mucosal inflammation and sympathetic dominance.

Materials and methods

The systematic review was performed per the 2020 version of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement.[41]

Data sources and searches

On December 25, 2023, the PubMed database was searched for scientific papers. The search keywords are provided in Table 1.

Data collection and evaluation

All identified records were imported into the EPPI Reviewer Software for review. Abstracts were initially screened, followed by full text reviewed per the inclusion and exclusion criteria.

Study selection

Both sham-controlled RCTs and open-label single-arm non-RCTs were considered for inclusion in our review. Due to the invasive nature of implantable VNS and SNS therapies, the inclusion of a sham group was deemed unethical. The criteria for inclusion were as follows: (1) papers published in English, (2) papers with full-text availability, and (3) presentation of statistical results. Animal studies, non-English papers, reviews, abstracts, and case studies were excluded from consideration.

Results

Search outcomes

For the VNS and SNS searches, we initially identified 69 and 27 records, respectively, from the PubMed database, which were then imported into the EPPI Reviewer software.[42] Upon screening, all records were successfully retrieved and assessed for eligibility. Among the 89 records excluded, 64 were related to VNS, and 25 were related to SNS. The exclusions comprised 51 reviews (39 VNS and 12 SNS), 27 animal studies (19 VNS and 8 SNS), 7 records without an assessment of IBD symptoms (2 VNS and 5 SNS), 1 case study (VNS), 1 abstract (VNS), 1 study protocol (VNS), and 1 record unrelated to VNS therapy.

Subsequently, we included 7 records in the analysis: 5 for VNS and 2 for SNS. A visual representation of the record selection process is depicted in Figure 1 using the PRISMA flow diagram. The results of the VNS and SNS studies are summarized in Tables 2 and 3,[43–49] respectively. These tables present the IBD symptom outcomes as the mean ± standard deviation of the difference between post-therapy data and pre-therapy data.

VNS studies

We identified three VNS studies, including two open-label single-arm iVNS studies (with VNS electrodes implanted on the cervical vagus) and one RCT taVNS study (with transcutaneous auricular VNS electrodes).

In two iVNS studies, NCT01569503 and NCT02311660,[43–46] bipolar electrical stimulation was delivered via the helical cuff electrode (Model 302 or 304, Cyberonics) implanted on the left cervical vagus nerve and tunneled to an IPG (Model 102 or 103,

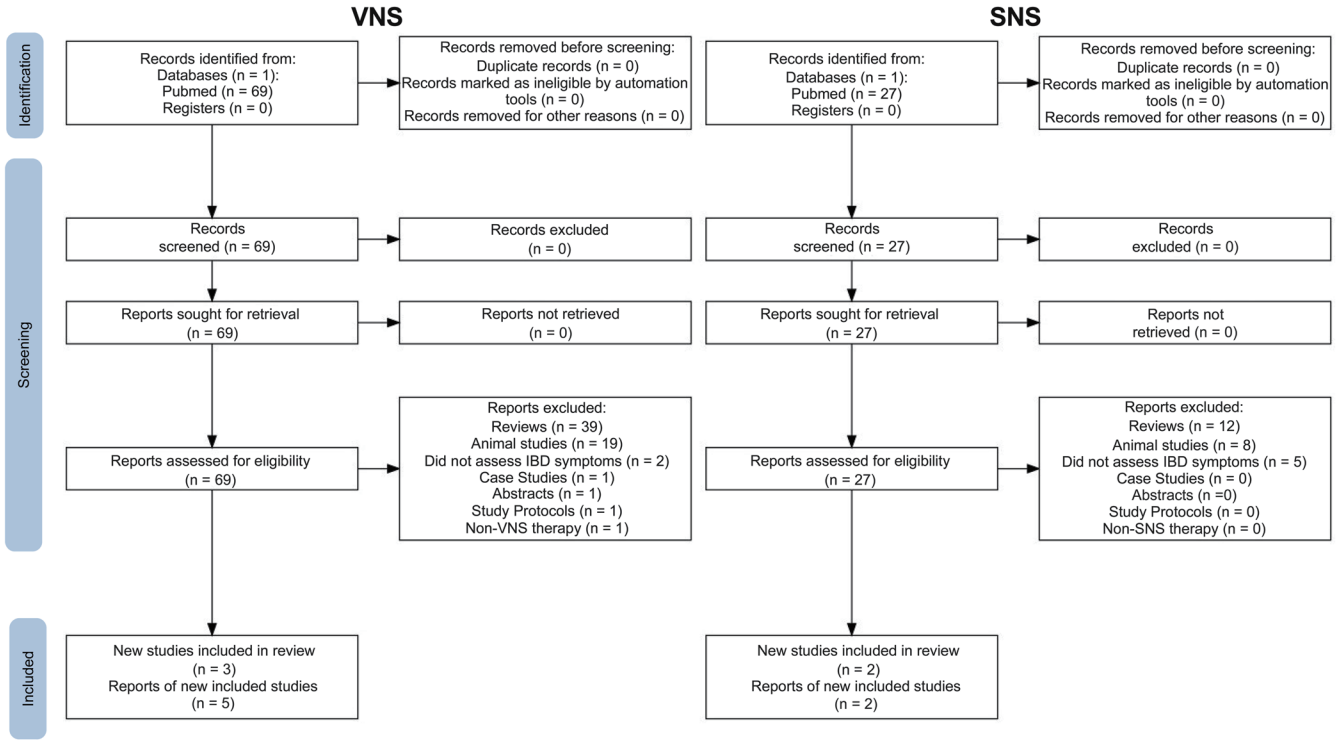

Fig. 1. PRISMA flow diagram of record selection. IBD, inflammatory bowel disease; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SNS, sacral nerve stimulation; VNS, vagus nerve stimulation.

Cyberonics), which was placed in the subcutaneous pocket on the left chest wall. The first iVNS study (NCT01569503) was performed in Grenoble, France, where 7 adult patients with moderate CD (220 ≤ CDAI ≤ 450) diagnosed for at least 3 months before enrollment and naive of biologic treatment were subjected to iVNS with the following parameters: frequency of 10 Hz, current amplitude of 0.5–1.25 mA, pulse width of 500 μs, duty cycle of 9% (0.5 min every 5.5 min), delivered continuously for 12 months.[43–45] The second iVNS study (NCT02311660) was performed at four European locations (Zagreb, Croatia; Milano, Italy; Amsterdam, Netherlands; and Stockholm, Sweden), where adult patients with moderate CD (220 ≤ CDAI ≤ 450, SES-CD ≥ 2 in at least one segment, and FC ≥ 200 ug/g) diagnosed for at least 4 months before enrollment and refractory or intolerant to at least one biologic treatment (infliximab, adalimumab, or vedolizumab) were subjected to iVNS with the following parameters: frequency of 10 Hz, current amplitude of 0.25–2.0 mA, pulse width of 250 μs, duty cycle of 100%, delivered for 5 minutes four times per day for 4 months.[46]

In the taVNS study NCT03863704,[47] active bipolar electrical stimulation was delivered via the hand-held skin probe with two electrodes (Blue Moon Health) placed on the cymba concha area inside the left ear, while sham electrical stimulation was delivered in

Table 2. Summary of three clinical studies evaluating the effects of VNS therapy on CD and UC

NCT number, duration	N per arm	Daily therapy dose	CDAI, pCDAI, pUCDAI	CDEIS	GI-related VAS	CRP (mg/l)	FC (μg/g)	LF/HF	Ref.
NCT01569503, 6 months	5 CD	2.2 h (24 h * 9%)	Δ −166 ± 58, p < 0.01	Δ −6.8 ± 1.5, p < 0.001	Δ −2.1 ± 1.4, p < 0.05	Δ −3.6 ± 5.7, p > 0.05	Δ −1,070 ± 1,301, p > 0.05	Δ −2.4 ± 2.3, p > 0.05	43, 44
NCT01569503, 12 months	7 CD	2.2 h (24 h 9%)	Δ −156 ± 62, p < 0.001	Δ −4.2 ± 4.1, p < 0.05	Δ −1.9 ± 1.9, p < 0.05	Δ −7.9 ± 9.3, p > 0.05	Δ −1,168 ± 912, p > 0.05	Δ −1.7 ± 2, p > 0.05	45
NCT02311660, 4 months	12 CD	20 min (5 min * 4x)	Δ −115 ± 24, p < 0.001	ND	ND	Δ −0.9 ± 0.9, p > 0.05	Δ −3,209 ± 937, p < 0.01	ND	46
NCT03863704, 3.5 months	10 CD	10 min (5 min * 2x)	Δ −15 ± 17, p < 0.05	ND	ND	ND	Δ −357 ± 800, p > 0.05	ND	47
NCT03863704, 3.5 months	12 UC	10 min (5 min * 2x)	Δ −8 ± 15, p > 0.05	ND	ND	ND	Δ −833 ± 250, p < 0.05	ND	47

ND, no data; Δ = difference of post-VNS data minus pre-VNS data. CD, Crohn's disease; CDAI, Crohn's Disease activity index; CDEIS, Crohn's Disease endoscopic index of severity; CRP, C-reactive protein; FC, fecal calprotectin; GI, gastrointestinal; LF/HF, low-frequency to high-frequency ratio; pCDAI, pediatric CDAI; pUCDAI, pediatric UCDAI; SNS, sacral nerve stimulation; UC, ulcerative colitis; VAS, Visual Analogue Scale; VNS, vagus nerve stimulation.

Table 3. Summary of two clinical studies evaluating the effects of SNS and sham therapies

NCT number, duration	N per arm	Daily therapy dose	UCDAI	Mayo score	TNF-α (pg/ml)	CRP (mg/l)	FC (μg/g)	LF/HF	Ref.
NCT02748590, 4 months	8 UC + SNS	24 h	Δ −1.5 ± 2.8, p > 0.05	ND	ND	ND	Δ −234 ± ND	ND	48
N/A, 2 weeks	15 UC + SNS	6 min (60 min *10%)	ND	Δ −2.1 ± 1.8, p < 0.01	Δ −9.5 ± 8.9, p < 0.001	Δ −6.6 ± 9.9, p < 0.05	ND	Δ −0.68 ± 1.78, p > 0.05	49
N/A, 2 weeks	11 UC + sham	6 min (60 min *10%)	ND	Δ −0.6 ± 1.3, p > 0.05	Δ −5.4 ± 14.1, p > 0.05	Δ −1.0 ± 6.7, p > 0.05	ND	Δ 0.96 ± 1.13, p < 0.05	49

N/A, not available; ND, no data; Δ = difference of post-therapy (SNS or sham) data minus pre-therapy data. CRP, C-reactive protein; FC, fecal calprotectin; LF/HF, low-frequency to high-frequency ratio; SNS, sacral nerve stimulation; TNF-α, Tumor Necrosis Factor-α; UC, ulcerative colitis; UCDAI, ulcerative colitis disease activity index.

the middle of the left calf, with the cross-over design, where patients served as their controls. The study was performed in New York, USA, where pediatric and young adult patients (10–21 years) with mild and moderate CD and UC (FC≥200 ug/g) diagnosed for at least 3 months prior to enrollment and irrespective of biologic treatment (only those on infliximab were excluded) were subjected to taVNS with the following parameters: frequency of 20 Hz, current amplitude just below the pain threshold, pulse width of 300 μs, duty cycle of 100%, delivered for 5 minutes two times per day for 3.5 months.[47]

The results of three VNS studies are summarized in Table 2.

The clinical studies examined the long-term effects of iVNS and taVNS on IBD symptoms, with a follow-up period of up to 12 months for iVNS and 3.5 months for taVNS.

In all iVNS and taVNS studies, a significant reduction in IBD disease activity was observed in CD patients. This reduction was assessed using the CDAI and GI-related VAS in adults and the pCDAI in adolescents. However, this reduction was not observed in adolescent patients with UC who were treated with taVNS, as assessed by the pUCDAI.

One of the iVNS studies (NCT01569503) also demonstrated a significant long-term improvement, both at 6 and 12 months, in the severity of intestinal lesions, assessed endoscopically as the CDEIS, as well as in intestinal pain, assessed using the GI-related VAS.

Two iVNS studies (NCT01569503, NCT02311660) additionally assessed blood biomarkers, including CRP, and fecal biomarkers, including FC, for intestinal mucosal inflammation. In both iVNS studies, CRP was not significantly reduced in CD patients. However, FC was significantly reduced in only one of the two studies (NCT02311660).

Regarding the taVNS study, FC was assessed, but the results were inconclusive. FC was significantly reduced in UC patients but not in CD patients.

One of two iVNS studies (NCT01569503) evaluated a possible mechanism of action for the VNS therapy, the recovery of the autonomic balance (assessed as the LF/HF ratio of the power spectrum of the HRV derived from the electrocardiogram) and, while there was a trend toward a decreased sympathetic dominance at both 6 and 12 months, it was not statistically significant.

The iVNS therapy is associated with the risk of surgical and post-surgical complications. Among 16 implanted subjects in the NCT02311660 study, one experienced transient postoperative skin infection requiring device explantation. No complications were reported in the NCT01569503 study. In both iVNS studies, the VNS-related adverse effects included only discomfort due to voice hoarseness, a typical iVNS side effect. In the taVNS study (NCT03863704), one subject developed a transient skin redness and a minor break in the skin because of excessive pressure applied to the ear with the taVNS probe during the first week of stimulation, which was resolved by further educating the subject on the taVNS technique.

SNS studies

We identified two studies related to SNS: one open-label single-arm study involving implantable SNS electrodes (iSNS) and one RCT focusing on percutaneous SNS electrodes (pSNS).

In the iSNS study, registered as NCT02748590,[48] bipolar electrical stimulation was administered through a 4-electrode SNS lead (Model 3889, Medtronic) implanted within the S3 foramen. The lead was then tunneled to connect with an IPG, specifically the InterStim II (Model 3058, Medtronic), placed in a subcutaneous pocket on the left chest wall. This study was conducted in Nantes, France. It involved eight adult patients diagnosed with moderate ulcerative UC who exhibited a UCDAI ranging from 6 to 9 and an endoscopic UCDAI score of at least 2. These patients had been diagnosed with UC for at least 2 years before enrollment and were resistant to immunosuppressive or biologic anti-TNF treatments. During the iSNS intervention, the following stimulation parameters were employed: a frequency of 14 Hz, a current amplitude of 1.1 V, a pulse width of 210 μs, a duty cycle of 100%, and continuous stimulation for a duration of 4 months.[48]

In the pSNS study,[49] bipolar electrical stimulation was delivered via four stainless steel acupuncture needles (diameter 0.45 mm, length 100–125 mm) inserted bilaterally inside the S3 and S4 foramens and attached to an external stimulator (Transcutaneous Electrical Applicator, Model SNM-FDC01, MedKinetic Medical Device Co. Ltd, Ningbo, China), while the sham electrical stimulation was delivered using the same needles placed 20 mm downward and 8–10 cm lateral from these sacral foramina. The study was performed in Nanjing, China, where 26 adult patients with mild and moderate UC (3 ≤ Mayo score ≤ 10) diagnosed for at least 3 months prior to enrollment were subjected to pSNS with the following parameters: frequency of 5 Hz, current amplitude of 2–10 mA, pulse width of 500 μs, duty cycle of 10% (10 sec every 100 sec), delivered for 1 hour per day for 2 weeks.[49]

The results of two SNS studies are summarized in Table 3.

The clinical studies evaluated the medium-term effect of iSNS and pSNS on IBD symptoms with a follow-up period of 4 months for iSNS and 2 weeks for pSNS. Only the UC patients were evaluated in both studies: in the iSNS study, the UC disease activity assessed as the UCDAI was insignificantly reduced, while in the pSNS study, it was assessed as the Mayo score and was significantly reduced in the SNS arm but not in the sham arm. The pSNS study also assessed the blood biomarkers of intestinal mucosal inflammation (TNF-α and CRP), with both biomarkers significantly reduced in the SNS arm but not in the sham arm. In contrast, the iSNS study assessed the fecal biomarker FC, and while the FC level was reduced post-SNS, no statistical significance calculation

Table 4. Summary of advantages and disadvantages of VNS and SNS for IBD treatment

Neuromodulation method	Advantages	Disadvantages
iVNS and iSNS	Confirmed efficacy for treating CD (iVNS); "Implant it and forget it" approach of achieving high patient adherence for timely therapy use	High cost and extensive clinical resources involved in the implantation procedure; Risks associated with the surgery and long-term implantation; Not FDA approved for treating IBD
taVNS and pSNS	Confirmed efficacy for treating CD (taVNS) and UC (pSNS); Non-invasive; Inexpensive; Can be used at home	Requires the patient to learn the location of cymba concha area inside the ear (taVNS); Requires visits to an acupuncturist (pSNS); Not FDA approved for treating IBD

CD, Crohn's disease; FDA, Food and Drug Administration; IBD, inflammatory bowel disease; iSNS, implantable SNS; iVNS, implantable VNS; pSNS, percutaneous SNS using electroacupuncture needles; SNS, sacral nerve stimulation; taVNS. transcutaneous auricular VNS; UC, ulcerative colitis; VNS, vagus nerve stimulation.

was provided for that effect.

The pSNS study also evaluated a possible mechanism of action for the SNS therapy, the recovery of the autonomic balance (assessed as the LF/HF ratio). While there was a statistically insignificant trend toward a decreased sympathetic dominance in the SNS arm, the sympathetic dominance significantly worsened in the sham arm.

The iSNS therapy is associated with the risk of surgical and post-surgical complications. Among 8 implanted subjects in the NCT02748590 study, one lead disconnection occurred during the test phase, while the implanted lead was percutaneously connected to the external stimulator. There were no SNS-related adverse effects in both the iSNS and pSNS studies.

Discussion

This systematic review assessed the efficacy, mechanisms, and safety of two parasympathetic neuromodulation methods (VNS and SNS) in patients with IBD. Notably, all VNS treatment arms involving patients with CD and the pSNS treatment arm involving patients with UC demonstrated significant and beneficial neuromodulatory effects on IBD symptoms. These effects encompassed improvements in disease activity, the severity of intestinal lesions, and alleviation of intestinal pain.

However, a contrast was observed in the case of iSNS, involving eight UC patients, and pSNS in eleven CD patients. These treatments showed insignificant trends in improving IBD symptoms, which could be attributed to the relatively small number of patients and/or the rather short follow-up duration, with the pSNS study spanning only 2 weeks.

Furthermore, evaluating blood and fecal biomarkers related to intestinal mucosal inflammation in the VNS and SNS studies yielded inconclusive results. In the VNS studies, these biomarker changes did not demonstrate clear trends, while in the pSNS study, blood biomarkers such as TNF-α and CRP significantly reduced in the pSNS treatment arm, contrasting with a lack of effect observed in the sham pSNS arm.

The potential mechanism of action involving the recovery of autonomic balance was explored in one iVNS study (NCT01569503) and the pSNS study. These investigations showed a statistically insignificant trend toward a reduction in sympathetic dominance in both studies.

Neither of the evaluated neuromodulation methods was associated with long-term adverse effects. Both iVNS and iSNS can be considered safe for long-term use, while taVNS and pSNS provide even safer options for short-term treatment. The selection of an implanted vs. transcutaneous vs. percutaneous option would, therefore, depend on the patient's risk acceptance and desired convenience, as transcutaneous vs. percutaneous options require daily placement of the stimulation electrodes.

Comparing and contrasting these neuromodulation methods for IBD treatment, several advantages and disadvantages are associated with each method, outlined in Table 4.

Additional clinical studies must be conducted to further evaluate the efficacy of the VNS and SNS methods. Based on the evaluated studies, both methods improve IBD symptoms and intestinal mucosal inflammation biomarkers. In addition, there is a trend toward decreased sympathetic dominance in both methods. In contrast, existing medications aim only for symptom alleviation without beneficial effects on sympathetic dominance.

The availability of VNS and SNS therapies provides clinicians with valuable options for optimizing the treatment of IBD patients. For example, the taVNS and/or pSNS may be prescribed as adjunct therapies to the anti-inflammatory medications, as their combined use may lead to longer-lasting and more sustainable results with fewer side effects. As the IBD severity worsens over time, the use of reversible and minimally-invasive iVNS and/or iSNS can also replace or delay the need for irreversible surgical procedures to resect an inflamed portion of the intestine, such as colectomy.

The study limitation is excluding studies published in other languages, while all relevant studies published in English have been included.

Conclusions

While the current clinical evidence does not yet firmly establish the role of the examined VNS and SNS therapies in directly targeting the IBD pathophysiologies, both therapies effectively alleviate IBD symptoms and impact biomarkers associated with intestinal mucosal inflammation. Consequently, they represent valuable options for personalized IBD treatment.

Given the relatively small sample sizes of the studies we have reviewed, larger-scale investigations in the future will be essential to arrive at definitive conclusions regarding the efficacy and mechanisms of action of VNS and SNS therapies in the context of IBD.

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Conflict of interest

Victor Pikov is the Founder and CEO of Medipace Inc.

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