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

Short title: Pikov V.: VNS and SNS for IBD

Victor Pikov

1Medipace Inc, Pasadena, California, USA

*Correspondence to: Victor Pikov, Medipace Inc, Pasadena, 91101, California, USA. ORCID: https://orcid.org/0000-0003-0124-0877. Tel: +16264979441, E-mail: pikov@hotmail.com

Author contributions: Conceptualization (VP), methodology (VP), writing and original draft preparation (VP), draft review and editing (VP), data analysis (VP), resources (VP), supervision and funding acquisition (VP). The author agreed to the published version of the manuscript.

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

Received: December 13, 2023; Revised: TBD; Accepted: TBD
Abstract

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

**Methods:** A systematic review of literature according to the PRISMA guidelines was performed. The PubMed database was searched. Studies were assessed for inclusion and exclusion criteria.

**Results:** Analysis included five clinical studies, including three for VNS and two for SNS. Most of the evaluated studies demonstrated significant beneficial effects on IBD symptoms, including the disease activity, severity of intestinal lesions, and intestinal pain. In evaluating the effect on key IBD pathophysiologies, both VNS and SNS showed the trends toward reducing the biomarkers of intestinal mucosal inflammation and decreasing the sympathetic dominance. None of the evaluated neuromodulation methods produced long-term adverse effects.

**Conclusions:** Cumulative evidence from the evaluated studies indicates that VNS and SNS therapies are effective in treating the IBD symptoms and might be effective in targeting the underlying IBD pathophysiologies, intestinal mucosal inflammation and sympathetic dominance. They are thus valuable options for individualized IBD treatment.

**Keywords:** vagus nerve stimulation; sacral nerve stimulation; neuromodulation; inflammatory bowel disease, Crohn’s disease, ulcerative colitis
Introduction

Prevalence of IBD is around 0.9% of general population in the US [1], including 0.4% with UC and 0.5% with CD [2]. The direct cost of IBD care in the US is $60 billion ($23K per patient) [3], which is mainly aimed on treating IBD symptoms, such as diarrhea, blood in the stool, weight loss, fever, and abdominal pain. The etiology of IBD is multi-factorial, including genetic predisposition and immunologic disturbances [4]. An excessive mucosal immune response toward patient’s native microbiota plays a critical role in both initiation and perpetuation of intestinal inflammation [5]. The anti-inflammatory medications include first-line small-molecule drugs including aminosalicylates (e.g. mesalamine), corticosteroids (e.g. budesonide, prednisone), immunosuppressants (e.g. azathioprine), followed by the second-line anti-inflammatory biologics, such as anti-TNF-α and anti-α4β7 integrin antibodies [6]. The biologic treatments are symptomatic, do not prevent recurrence of flares, and display significant side effects and primary lack of clinical response in about 50% of UC [7] and CD patients [8], with further 30-35% of initial responders developing a secondary loss of clinical response after 1 year of the drug use [9-11]. Patients with CD and UC who are refractory to biologic medications may require an irreversible surgical procedure to remove an inflamed portion of the intestine [12]. Removal of the colon (colectomy) is associated with 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 VNS and SNS methods have been evaluated in the animal models of IBD, and both methods reduced the levels of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-18) and increased the levels of anti-inflammatory cytokines (IL-10, TGF-β) in the blood plasma, indicating healing of intestinal mucosal inflammation [16-24]. 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 were shown to be effective in reducing 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 the VNS and SNS neuromodulation procedures are FDA-approved for other indications, with a demonstrated safety profile during long-term implantation and use [35-38]. In addition to implantable VNS and SNS methods, there are two non-implantable methods with a demonstrated safety profile during intermittent daily use: taVNS [39] and electroacupuncture-based pSNS [40].
In summary, although various symptomatic treatments for IBD are available, a therapy that targets IBD pathophysiologies is lacking. Two neuromodulation therapies, VNS and SNS, have been trialed in the treatment of IBD. These include implantable and transcutaneous VNS and implantable and percutaneous SNS. In this systematic review, we evaluated the effectiveness of these neuromodulation therapies for IBD symptoms and key IBD pathophysiologies, including intestinal mucosal inflammation and sympathetic dominance.

**Materials and Methods**

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

*Data sources and searches*

On December 9, 2023, the PubMed database was searched for scientific papers. The search keywords are provided in Table 1.

*(Table 1. Search keywords table.)*

*Data collection and evaluation*

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

*Study selection*

Both the sham-controlled RCTs and open-label single-arm non-RCTs were included. The invasive nature of the implantable VNS and SNS therapies makes the inclusion of a sham group unethical. The criteria for inclusion were: (1) papers published in English; (2) papers with full text available; and (3) statistical evaluation of the results is presented. The animal studies, non-English papers, reviews, abstracts, and case studies were excluded.

**Results**

*Search outcomes*

For the VNS and SNS searches, 20 and 6 records, respectively, were imported from the PubMed database into the EPPI Reviewer [42]. Upon screening, all recorded were successfully retrieved and assessed for eligibility. Among 19 excluded records, there were 15 VNS and 4 SNS records: 6 reviews (all VNS), 9 animal studies (6 VNS and 3 SNS), 1 case study (VNS), 1 abstract (VNS), and 2 without assessment of
IBD symptoms (1 VNS and 1 SNS). The 7 records were included in the analysis: 5 for VNS and 2 for SNS. The PRISMA flow diagram of the record selection is shown in Figure 1.

**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, 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 prior to 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 µg/g) diagnosed for at least 4 months prior to 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 handheld 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 the middle of the left calf, with the cross-over design, where patients served as their own 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 µg/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 evaluated the long-term effect 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, the IBD disease activity was significantly reduced in the CD patients (assessed as CDAI and GI-related VAS in adults and as pCDAI in adolescents), but not in the UC adolescent patients treated with taVNS (assessed as pUCDAI). One of the iVNS studies (NCT01569503) also demonstrated a significant long-term improvement (at 6 and 12 months) in the severity of intestinal lesions (assessed endoscopically as CDEIS) and intestinal pain (assessed as GI-related VAS). Two iVNS studies (NCT01569503, NCT02311660) also assessed the blood (CRP) and fecal (FC) biomarkers of intestinal mucosal inflammation, with the CRP not significantly reduced in the CD patients in both iVNS studies, while the FC was significantly reduced only in one of two studies (NCT02311660). The FC was assessed in the taVNS study and the results were similarly inconclusive, with the FC significantly reduced in the UC patients, but not the 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 the device explantation. while no complications were reported in the NCT01569503 study. In both iVNS studies, the VNS-related adverse effects included only a discomfort due to voice's 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 as result 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 SNS studies, including one open-label single-arm iSNS study (with implanted SNS electrodes) and one RCT pSNS study (with percutaneous SNS electrodes).

In the iSNS study NCT02748590 [48], bipolar electrical stimulation was delivered via the 4-electrode SNS lead (Model 3889, Medtronic) implanted inside the S3 foramen and tunneled to an IPG (InterStim II, Model 3058, Medtronic), which was placed in the subcutaneous pocket on the left chest wall. The study was performed in Nantes, France, where 8 adult patients with moderate UC (6 ≤ UCDAI ≤ 9, endoscopic UCDAI score ≥ 2) diagnosed for at least 2 years prior to enrollment and resistant to immunosuppressive or
biologic anti-TNF treatment were subjected to iSNS with the following parameters: frequency of 14 Hz, current amplitude of 1.1 V, pulse width of 210 µs, duty cycle of 100%, delivered continuously for 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.

(Table 3. SNS.)

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 reduced but not significantly, 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 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) and, 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. In both the iSNS and pSNS studies, there were no SNS-related adverse effects.

Discussion
This systematic review evaluated the efficacy, mechanisms, and safety of two parasympathetic neuromodulation methods (VNS and SNS) in patients with IBD. All VNS treatment arms in CD patients and the pSNS treatment arm in UC patients demonstrated significant beneficial neuromodulation effects on IBD symptoms, including the disease activity, severity of intestinal lesions, and intestinal pain. In contrast, iSNS in 8 UC patients and pSNS in 11 CD patients showed insignificant trends in improving IBD symptoms, potentially due to a small patient number and/or rather short follow-up duration (only 2 weeks in the pSNS study).

The blood and fecal biomarkers of intestinal mucosal inflammation were evaluated in the VNS and SNS studies, and the observed changes were inconclusive in the VNS studies, while the blood biomarkers TNF-α and CRP significantly reduced in the pSNS arm in contrast to a lack of effect in the sham pSNS arm. The recovery of the autonomic balance was evaluated as a possible mechanism of action in one iVNS study (NCT01569503) and in the pSNS study, demonstrating a statistically insignificant trend toward a decreased 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 options would therefore depend on the patient’s individual 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, there are several advantages and advantages associated with each method, which are outlined in Table 4.

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

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

Availability of VNS and SNS therapies provide clinicians with valuable options for optimizing the treatment for 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 the exclusion of studies published in other languages, while all relevant studies published in English have been included.

Conclusions
In conclusion, while there is still insufficient clinical evidence implicating the examined VNS and SNS therapies in targeting the IBD pathophysiologies, both therapies appear to be effective in treating the IBD symptoms and biomarkers of intestinal mucosal inflammation, thus providing valuable options for individualized IBD treatment. As the sample sizes of evaluated studies are rather small, larger studies are needed in the future to draw definitive conclusion regarding the efficacy and mechanisms of action of the VNS and SNS therapies for IBD.

Acknowledgments
None.

Funding statement: Victor Pikov’s effort in preparation of the manuscript was partially supported by a grant from the National Institutes of Health (U41NS129514).

Conflicts-of-Interest statement: Victor Pikov is the Founder and CEO of Medipace Inc.
Table 1. Search keywords for PubMed.

VNS: (“vagus nerve stimulation”[Title] OR “vagal nerve stimulation”[Title] OR (auricular[Title] AND “nerve stimulation”[Title])) AND (“Inflammatory Bowel Disease*”[Title] OR “Crohn*”[Title] OR colitis[Title])

SNS: (“sacral nerve stimulation”[Title] OR “sacral neuromodulation”[Title]) AND (“Inflammatory Bowel Disease*”[Title] OR “Crohn*”[Title] OR colitis[Title])
Table 2. Summary of three clinical studies evaluating the effects of VNS therapy on CD and UC.

<table>
<thead>
<tr>
<th>NCT number, duration</th>
<th>N per arm</th>
<th>Daily therapy dose</th>
<th>CDAI, pCDAI, pUCDAI</th>
<th>CDEIS</th>
<th>GI-related VAS</th>
<th>CRP (mg/l)</th>
<th>FC (μg/g)</th>
<th>LF/HF</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT 01569503, 6 months</td>
<td>5 CD</td>
<td>2.2 h (24 h * 9%)</td>
<td>Δ -166 ± 58 p &lt; 0.01</td>
<td>Δ -6.8±1.5 p&lt;0.001</td>
<td>Δ-2.1±1.4 p &lt; 0.05</td>
<td>Δ -3.6±5.7 p &gt; 0.05</td>
<td>Δ -1070±1301 p &gt; 0.05</td>
<td>Δ -2.4 ± 2.3 p&gt;0.05</td>
<td>[43, 44]</td>
</tr>
<tr>
<td>NCT 01569503, 12 months</td>
<td>7 CD</td>
<td>2.2 h (24 h 9%)</td>
<td>Δ -156 ± 62 p &lt; 0.001</td>
<td>Δ -4.2±4.1 p &lt; 0.05</td>
<td>Δ -1.9±1.9 p &lt; 0.05</td>
<td>Δ -7.9±9.3 p &gt; 0.05</td>
<td>Δ -1168 ± 912 p &gt; 0.05</td>
<td>Δ -1.7 ± 2 p&gt;0.05</td>
<td>[45]</td>
</tr>
<tr>
<td>NCT 02311660, 4 months</td>
<td>12 CD</td>
<td>20 min (5 min * 4x)</td>
<td>Δ -115 ± 24 p &lt; 0.001</td>
<td>ND</td>
<td>ND</td>
<td>Δ -0.9±0.9 p &gt; 0.05</td>
<td>Δ -3209 ± 937 p &lt; 0.01</td>
<td>ND</td>
<td>[46]</td>
</tr>
<tr>
<td>NCT 03863704, 3.5 months</td>
<td>10 CD</td>
<td>10 min (5 min * 2x)</td>
<td>Δ -15 ± 17 p &lt; 0.05</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Δ -357 ± 800 p &gt; 0.05</td>
<td>ND</td>
<td>[47]</td>
</tr>
<tr>
<td>NCT 03863704, 3.5 months</td>
<td>12 UC</td>
<td>10 min (5 min * 2x)</td>
<td>Δ -8 ± 15 p &gt; 0.05</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Δ -833 ± 250 p &lt; 0.05</td>
<td>ND</td>
<td>[47]</td>
</tr>
</tbody>
</table>

ND, no data; Δ = difference of post-VNS data minus pre-VNS data.
Table 3. Summary of two clinical studies evaluating the effects of SNS and sham therapies.

<table>
<thead>
<tr>
<th>NCT number, duration</th>
<th>N per arm</th>
<th>Daily therapy dose</th>
<th>UCDAI Mayo score</th>
<th>TNF-α (pg/ml)</th>
<th>CRP (mg/l)</th>
<th>FC (μg/g)</th>
<th>LF/HF</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT 02748590, 4 months</td>
<td>8 UC + SNS</td>
<td>24 h</td>
<td>Δ -1.5 ± 2.8 p &gt; 0.05</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Δ -234 ± ND</td>
<td>ND</td>
</tr>
<tr>
<td>N/A, 2 weeks</td>
<td>15 UC + SNS</td>
<td>6 min (60 min *10%)</td>
<td>ND</td>
<td>Δ -2.1±1.8 p &lt; 0.01</td>
<td>Δ -9.5±8.9 p &lt; 0.001</td>
<td>Δ -6.6±9.9 p &lt; 0.05</td>
<td>ND</td>
<td>Δ -0.68 ± 1.78 p &gt; 0.05</td>
</tr>
<tr>
<td>N/A, 2 weeks</td>
<td>11 UC + sham</td>
<td>6 min (60 min *10%)</td>
<td>ND</td>
<td>Δ -0.6±1.3 p &gt; 0.05</td>
<td>Δ -5.4±14.1 p &gt; 0.05</td>
<td>Δ -1.0±6.7 p &gt; 0.05</td>
<td>ND</td>
<td>Δ 0.96 ± 1.13 p &lt; 0.05</td>
</tr>
</tbody>
</table>

N/A, not available; ND, no data; Δ = difference of post-therapy (SNS or sham) data minus pre-therapy data.
Table 4. Summary of advantages and advantages of VNS and SNS for IBD treatment

<table>
<thead>
<tr>
<th>Neuromodulation method</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| 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 |
Fig. 1. PRISMA flow diagram of record selection.
References.


