Short Communication

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Transcutaneous auricular vagus nerve stimulation for the treatment of irritable bowel syndrome: a pilot, open-label study

François Mion*[,1,2,3], Sonia Pellissier[4], Aurélien Garros[1], Henri Damon[1], Sabine Roman[1,2,3] & Bruno Bonaz[5,6,7]

[1]Department of Digestive Physiology, Hospices Civils de Lyon, Lyon, France
[2]Department of Physiology, Université de Lyon, Lyon, France
[3]Inserm U1032, LabTau, Lyon, France
[4]Université Savoie Mont Blanc, Université Grenoble Alpes, LIP/PC2S, 73000, Chambéry
[5]Division of Hepato-Gastroenterology, CHU Grenoble Alpes, 38000 Grenoble, France
[6]Hepatogastroenterology, Université Grenoble Alpes, Grenoble
[7]INSERM U1216, Grenoble Institute Neurosciences, Grenoble
*Author for correspondence: francois.mion@chu-lyon.fr

Aim: Irritable bowel syndrome (IBS) is a frequent disease, associating chronic abdominal pain and abnormal bowel habits. The sympatho-vagal balance may be altered in IBS. We tested the effect of transcutaneous auricular stimulation of the left vagus nerve (taVNS) on symptoms and physiological and biological variables. **Patients & methods:** Twelve IBS women agreed to apply taVNS for 6 months. Evaluation was based on feasibility, symptoms, psychological questionnaires, fecal caprotectin, blood cytokines and bowel transit times. **Results:** Nine patients completed the trial: there was a significant improvement of symptoms at 3 and 6 months although none of the measured variables were modified by taVNS. **Conclusion:** The results suggest taVNS is feasible and may improve IBS symptoms. Randomized controlled studies are needed to confirm these preliminary results. ClinicalTrials.gov: NCT02420158.

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Irritable bowel syndrome (IBS) is a highly prevalent functional digestive disorder, characterized by the association of chronic abdominal pain and altered bowel habits, in the absence of biological or structural abnormalities [1]. Efficient drug therapies are very limited in the IBS field, and patients are looking eagerly for alternative solutions, including probiotics, hypnotherapy, osteopathy, diet modifications and fecal microbiota transplantation [2–5]. Bioelectric modulation should also be of interest for IBS patients, often suspicious toward conventional drug therapies and prone to develop side effects. Vagus nerve stimulation (VNS) may be an option to improve IBS symptoms, for several reasons. Chronic stress is frequently associated to the pathogenesis of IBS [6–8], and the possible role of an imbalance between the sympathetic and parasympathetic branches of the autonomic nervous system has been reported, revealing a blunted parasympathetic vagal regulation [6,9,10]. Indeed, the interactions between the digestive tract and psychological disturbances appear as one of the link of the brain–gut axis, modulated mainly by the autonomic nervous system. The anti-inflammatory effects of the VNS have already been demonstrated, and mucosal low grade inflammation can be present in IBS [11,12]. The vagus nerve is also at the interface of the microbiota and mucosal gut interactions, and dysbiosis may be present in IBS [13,14]. Furthermore, the afferent vagus nerve is also implicated in the mediation of visceral pain that may count for the decrease in the parasympathetic vagal tone, and chronic abdominal pain is the main symptom of IBS [15].

Invasive VNS, with surgical implantation of an electrode around the left vagus nerve at the cervical level and the neurostimulation device subcutaneously, has been initially developed for the treatment of drug-refractory epilepsy [16], and had been authorized by the US FDA for the treatment of depression [17]. Several animal experiments and one pilot study evaluated the potential therapeutic effect of invasive VNS on intestinal models

Future Medicine

of inflammation, and in Crohn's disease, because of its potential anti-inflammatory effect [18–21]. In a less invasive manner, transcutaneous auricular VNS (taVNS) of the concha of the left ear (innervated by the auricular branch of the vagus nerve) has been tested for the treatment of drug-refractory epilepsy [22], chronic pain [23] and acute inflammation in an animal model of endotoxemia [24].

The objective of this pilot study was to evaluate the potential interest of this noninvasive approach of taVNS in female IBS patients, based on the evolution of the severity of gastrointestinal symptoms, psychological state and global quality of life, digestive motility and systemic and gut inflammation.

Patients & methods

This prospective open-label uncontrolled study was approved by the Agence Nationale de Sécurité du Médicament (ANSM), and an independent ethics committee (CPP Sud-Est III), as requested by the French law on biomedical research (Jardé law, 2016). Patients gave their written informed consent before any procedure requested by the protocol.

Patients could be included if they were women between 18 and 70 year-old, presenting clinical symptoms of IBS in accordance with Rome IV criteria, with a moderate to severe intensity of symptoms (IBS symptom severity scale >150) [25]. Women were selected because of the female predominance of this disease [26], and to limit confounding variables in this small pilot study. Exclusion criteria were clinical or biological signs of celiac disease, inflammatory bowel disease, past history of abdominal surgery (except appendectomy and cholecystectomy). Associated severe chronic diseases (diabetes, cancer, cardiac or respiratory insufficiency) were also exclusion criteria, as well a chronic consumption of alcohol, cannabis or other recreational drugs. Any other disease that could affect the vagus nerve activity was excluded. Chronic treatment with antalgics such as tramadol, opiates, pregabaline, gabapentine and amitryptiline were not allowed during the study. Antispasmodics, laxative or antidiarrheal drugs were allowed, provided these therapies were taken on a regular basis for >3 months before the inclusion in the study.

Before the start of taVNS, patients had to fill in questionnaires for evaluation of the severity of IBS (IBS-Severity Scoring System [IBS-SSS] [25] and UCLA-scale [27]), quality of life (SF-12 [28]), and several psychological questionnaires (Positive and Negative Affects Scale [PANAS] [29], State-Trait Anxiety Inventory [STAI] [30], Center for Epidemiologic Studies-Depression Scale [CES-DS] [31], Perceived Stress Scale [PSS] [32], Ways of Coping Checklist [WCC] [33], Visceral Sensitivity Index [34]): most of these questionnaires have been validated for the French language.

At the same time, blood sample was obtained to measure high-sensitivity CRP and several cytokines (IL-6, IL-8, IL-10, IL-17 and TNF). A stool sample was obtained for the measurement of fecal calprotectin, a well-known marker of intestinal inflammation [35]. Bowel transit times were measured with the the Smartpill® Motility Testing System (Medtronic, MN, USA) capsule: after the capsule has been activated and then swallowed by the subject, this device detects and transmits to a belt recorder measurements of temperature, pH and pressure during its transit along the gut, up to the anal exit of the capsule, or a maximum of 7 days [36].

Patients were asked to apply taVNS (Urostim 2® stimulator and ear plug; Schwa Medico, Rouffach, France) to the concha of the left ear at least 3 h per day (preferably before bed time), 5 days a week, for a total of 6 months. The ear plug was applied after spraying with a conductive liquid, and held in place, if necessary with adhesive tape (Figure 1). The stimulation was applied continuously with a pulse width of 250 μs, and a frequency of 30 Hz, as high frequency stimulation has been shown to modulate pain sensitivity [23,37]. The intensity was set by the patient at an infra-sensitive level between 0.5 and 20 mA.

The same questionnaires and tests were applied at 3 and 6 months after the beginning of taVNS, except for the Smartpill capsule that was performed only at baseline and after 6 months of stimulation. Additionally, patients answered the IBS-SSS questionnaire at 1, 2 and 5 months after the beginning of the stimulation.

Statistical analyses

Due to the exploratory nature of this pilot study, no calculation of the number of patients to be included was performed: the budget of the study allowed us to include 12 patients. The primary outcome measure was a significant clinical response based on a decrease of more than 30% of the IBS-SSS score at 3 months. Secondary outcome measures were the feasibility and tolerance of the stimulation, and the evolution of physiological measurements in relation with symptoms.

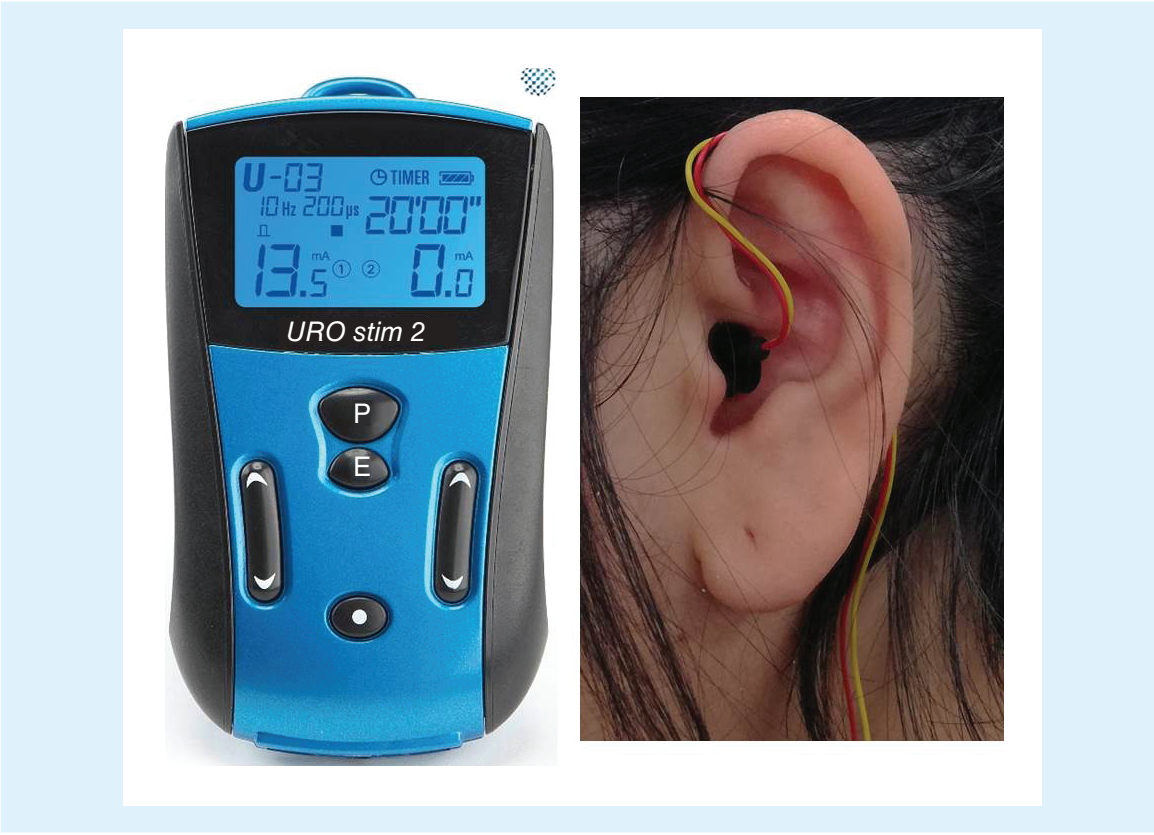

Figure 1. Pictures of the Urostim 2® stimulator used in the study, and the ear plug positioned in the left ear (adhesive tape was needed in some cases to hold the tape in place). Reproduced with permission from Schwa-Medico France.

Data were expressed as mean (standard deviation) unless otherwise indicated. Comparisons of scores and biological variables before and after taVNS were performed using nonparametric Kruskal–Wallis analysis, and *post hoc* comparisons with the Wilcoxon test. A p value < 0.05 was considered as significant.

Results

Twelve women were included in the study (mean age 49, range: 28–70). Three patients withdrew from the study before 3 months of stimulation, two because they did not find the motivation to carry on the stimulation, and one because she could not fit adequately the ear plug. The evaluation was thus made on nine patients, four IBS-diarrhea and five IBS-constipation. They complained of IBS symptoms for a mean of 5.3 years (range: 3–18 years). Their mean BMI was 23 kg/m^2 (range: 18–27). Five patients were taking laxative drugs on a regular basis (macrogol: 4 patients, psyllium: 1 patient), 2 patients were taking loperamide (anti-diarrheic drug), and 6 were taking antispasmodic drugs (pholoroglucinol: 3 patients, trimebutine: 3 patients). Only one patient was not taking any digestive medication at the start of the study.

None of the 12 patients complained of pain or cutaneous lesions at the site of the electrical stimulation. Among the nine patients that completed the study, all acknowledged to be compliant to the protocol.

With regards to the primary outcome, there was a significant decrease of the IBS-SSS at 3 and 6 months compared with baseline (336 [26] at baseline versus 231 [26] at 3 months [p = 0.0084] and 246 [26] at 6 months [p = 0.0209]), without significant difference between 3 and 6 months. Clinical significant response as defined by a decrease of at least 30% of the IBS-SSS was present in five patients at 3 months (two IBS-D and three IBS-C), and four at 6 months (two IBS-D and two IBS-C).

As for the secondary outcomes, the severity and frequency of abdominal pain (according to the first two questions of the IBS-SSS), were significantly decreased after 1 month of taVNS, and the difference compared with baseline values remained significant until the end of the study, as shown in Figure 2. Asked if digestive symptoms improved

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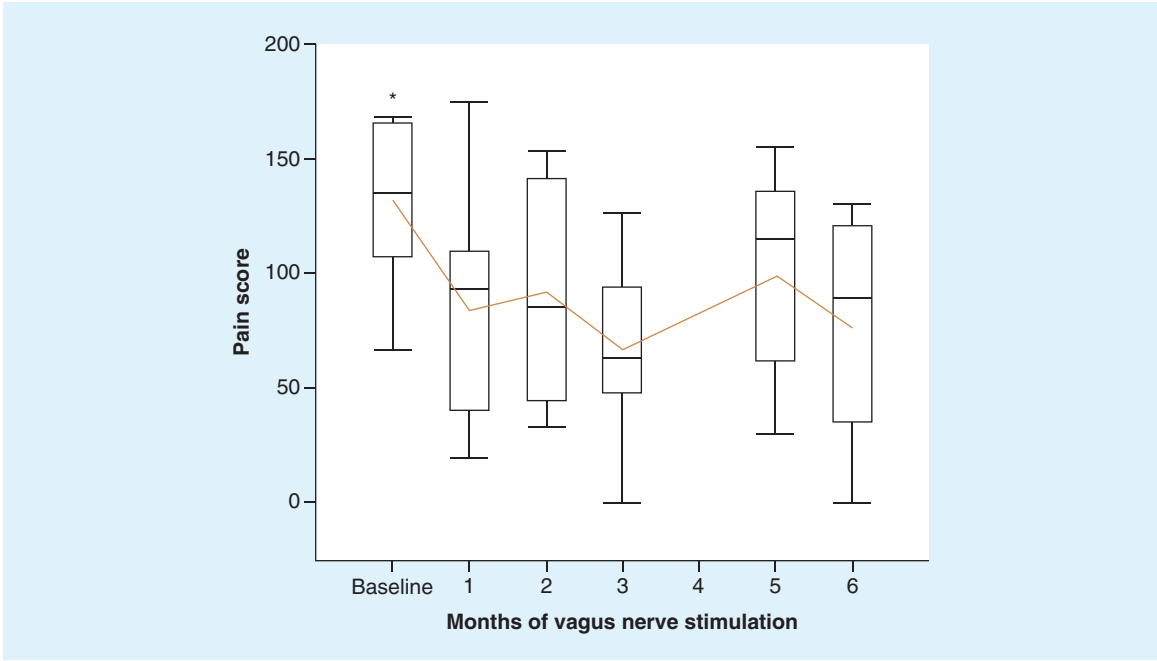

Figure 2. Evolution of abdominal pain score (severity and frequency of abdominal pain of the irritable bowel syndrome severity scoring system), at baseline and during 6 months of transcutanous auricular vagus nerve stimulation (whisker plots representing minimal and maximal scores, interquartile and median values). Baseline values were significantly higher than all the scores obtained during vagus nerve stimulation period (*$p < 0.03$).

Table 1. Results of fecal calprotectin, serum ultrasensitive CRP, interleukines and TNF-α at baseline, and after 3 and 6 months of transcutaneous auricular vagus nerve stimulation, in nine patients.

Biological values	Baseline	3 months	6 months
Fecal calprotectin (μg/g feces)	45 (13)	48 (16)	44 (15)
usCRP (mg/l)	1.00 (0.91)	0.09 (0.11)	0.05 (0.09)
IL-6 (pg/ml)	1.24 (0.27)	1.33 (0.58)	1.10 (0.27)
IL-8 (pg/ml)	4.43 (1.51)	4.46 (1.46)	4.40 (1.25)
IL-10 (pg/ml)	2.1 (0.5)	2.2 (0.8)	2.3 (0.9)
IL-17 (pg/ml)	0.10 (0.12)	0.09 (0.11)	0.05 (0.09)
TNF-α (pg/ml)	1.05 (0.39)	1.06 (0.30)	1.11 (0.40)

Results are expressed as mean (standard deviation).
us CRP: Ultrasensitive CRP.

with taVNS, six responded yes at 3 months, and five at 6 months. Laxative drugs were decreased in three cases out of five (stopped in one case), loperamide therapy in one case out of two, and antispasmodics in three cases out of six (stopped in one case). Three patients requested to carry on taVNS at the end of the study.

Fecal calprotectine levels were similar at baseline (45 [13] μg/g stool), 3 months (48 [16]; μg/g) and 6 months (44 [15]; μg/g). Similarly, blood levels of ultrasensitive CRP, as well as IL-6, IL-8, IL-10, IL-17 and TNF, were not significantly different at baseline, and after 3 and 6 months of taVNS (Table 1).

Gut transit times as measured by the Smartpill capsule (gastric emptying, small bowel transit and colonic transit time, as well as whole gut transit time) were not statistically changed after 6 months of taVNS, compared with baseline (Table 2). However, a decrease in the colonic transit time was observed in all patients but two after 6 months of vagal stimulation.

Quality of life and psychological questionnaires were not significantly different after 3 and 6 months of vagal stimulation, compared with baseline (Table 3). There was a nonsignificant trend toward improvement of sensitivity to visceral pain.

Table 2. Bowel transit times as measured by the Smartpill® capsule, before and after 6 months of transcutaneous auricular vagus nerve stimulation, in nine patients.

Bowel transit times	Baseline	6 months	p-value
Gastric emptying time: mean value (SD) in minutes	285 (82)	176 (31)	0.22
Small bowel transit time: mean value (SD) in minutes	268 (23)	338 (35)	0.31
Colonic transit time: mean value (SD) in minutes	2599 (645)	1725 (732)	0.37

SD: Standard deviation.

Table 3. Descriptive variables (mean [standard deviation], nine patients) representative of anxiety, positive or negative mood, depression, perceived stress and visceral pain sensitivity at baseline, and after 3 and 6 months of transcutaneous auricular vagus nerve stimulation.

Psychological questionnaires	Baseline	3 months	6 months
PANAS:			
– Positive effect	33 (5)	32 (9)	37 (6)
– Negative effect	23 (5)	17 (6)	18 (7)
STAI-trait (anxiety)	44 (12)	42 (10)	37 (11)
CES-D (depression)	21 (4)	19 (5)	19 (4)
PSS (stress)	25 (7)	21 (9)	19 (6)
WCC (coping):			
– Problem	32 (4)	33 (4)	32 (6)
– Emotion	23 (4)	20 (5)	20 (5)
– Social	23 (6)	22 (6)	25 (6)
Visceral pain index	41 (8)	47 (16)	50 (16)
SF-12 (quality of life)	42 (4)	43 (2)	41 (2)

Results are expressed as mean (standard deviation).
CES-D: Center for Epidemiologic Studies-depression scale; PANAS: Positive and negative affects scale; PSS: Perceived stress scale; STAI: State-trait anxiety inventory; WCC: Ways of coping checklist.

Discussion

The results of this pilot study assessing the effect of taVNS indicate, first, the feasibility of this noninvasive approach of VNS, and show a significant improvement of IBS severity symptoms in women completing the study, after 3 and 6 months of stimulation. However, none of the physiological and biological parameters, measured to evaluate the impact of VNS on digestive motility and inflammation, were significantly modified. The results are different from acute experiments showing a positive effect, on digestive motility and visceral pain, of direct or transcutaneous stimulation of the vagus nerve [37,38]. However, it should be noted that colonic transit time was decreased in seven out of the nine cases after 6 months of taVNS: future studies may try to include IBS patients with constipation, to see if the beneficial effect would be increased.

With regards to systemic and gut inflammation, the absence of detectable effect of taVNS may be due to the low levels of serum interleukins, CRP and TNF detected in our patients at baseline, as well as the normal values of fecal calprotectin. Psychological emotional state was not significantly modified after 3 and 6 months of stimulation. In comparison with previous results, the patients included in the study had a rather low level of perceived stress, anxiety, depression and visceral pain sensitivity, with equilibrate coping strategies [6]. This may indicate that the rather stable emotional status of these patients allowed them to participate actively to the study along the 6 months.

It is of interest to note that IBS patients are frequently disappointed by the standard of care applied to them, as well as the relative poor efficiency of drug therapies available [39]. A recent survey performed in France among IBS patients affiliated to a patient association (APSSII) showed that nondrug therapies are frequently used, leading to high medical expenses for IBS patients, as these therapies are not yet reimbursed in France [40]. Although it was not an objective of the study, we noted that IBS patients were quite motivated by the taVNS therapeutic approach.

This open-label uncontrolled pilot study had some weaknesses: the positive effect of the stimulation on the severity of IBS symptoms (global improvement and decrease of abdominal pain) could of course be related to

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a placebo effect. Indeed, patients included in the study were motivated to accept the rather lengthy protocol of stimulation, as well as the different tests that were performed.

The duration of the stimulation (at least 3 h per day, 5 days a week for 3 and 6 months) was chosen in order to obtain a significant increase of vagal tone, and potentially a clinically meaningful improvement of the symptoms of IBS. However, the stimulation system used in the present study did not allow monitoring the actual duration of stimulation performed by the patients. The evaluation of compliance was thus based only on patients' declarations. It may be possible that shorter periods of stimulation will be more acceptable to patients. Furthermore, we did not measure the effect of stimulation on sympatho-vagal balance (e.g., by measuring heart rate variability), a parameter that could have given us an indirect monitoring of patients' compliance to therapy.

It is also clear that technical improvements need to be made, especially for the ear plug to adapt more easily to all ears: out of the 12 patients included in the study, one could not fit the plug appropriately, and two did not want to carry on stimulation after 1 and 2 months because of the cumbersome procedure to hold the ear plug in place.

Conclusion

In conclusion, this small pilot study showed that taVNS is feasible, that IBS patients are potentially interested by this nondrug therapy, and that it may decrease the severity of IBS symptoms in some cases. However, the positive effect on symptoms was not associated with modification of bowel transit time or detectable anti-inflammatory responses. Additional controlled studies are needed to optimize technical design, stimulation parameters, and to confirm the potential efficacy of this noninvasive approach.

Summary points

- Irritable bowel syndrome (IBS) is a frequent chronic disease associating abdominal pain and perturbations of gut transit, most frequent in women.
- Currently available drug therapies are inefficient, especially for the most severe cases.
- Thus, research on IBS treatment is focusing on alternate therapies.
- Electrical vagus nerve stimulation (VNS) may be attractive, as the sympatho-vagal balance is often altered in IBS patients.
- Noninvasive transcutaneous auricular VNS (taVNS) was tested for 6 months in 12 IBS women, in a pilot study.
- taVNS protocol was completed in nine patients, and was associated with a significant decrease of the severity of IBS symptoms, 3 and 6 months after the start of stimulation.
- taVNS did not modify significantly gut transit times, digestive and systemic inflammation parameters and psychological status.
- These preliminary results should prompt additional controlled studies.

Author contributions

F Mion was responsible for study conception and design, acquisition of data, data analysis and drafting and revision of the manuscript. S Pellissier and B Bonaz were responsible for data analysis, drafting and revision of the manuscript. H Damon, A Garros and S Roman were responsible acquisition of data, and data analysis.

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that the research described was approved by the Agence Nationale de Sécurité du Médicament (ANSM), and an independent ethics committee (CPP Sud-Est III), as requested by the French law on biomedical research (Jardé law, 2016). Patients gave their written informed consent before any procedure requested by the protocol.

Data sharing statement

The authors certify that this manuscript reports original clinical trial data, NCT 02420158. All individual participant data that underlies the results reported in the article, after de-identification will be available along with the study protocol. The data will be available for any purpose immediately following article publication with no end date. Proposals to access data should be directed to the corresponding author.

References

1. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology* 130(5), 1480–1491 (2006).
2. Wang Y, Zheng F, Liu S, Luo H. Research progress in fecal microbiota transplantation as treatment for irritable bowel syndrome. *Gastroenterol. Res. Pract.* 2019, 9759138 (2019).
3. Shah K, Ramos-Garcia M, Bhavsar J, Lehrer P. Mind-body treatments of irritable bowel syndrome symptoms: an updated meta-analysis. *Behav. Res. Ther.* 128, 103462 (2019).
4. Muller A, Franke H, Resch KL, Fryer G. Effectiveness of osteopathic manipulative therapy for managing symptoms of irritable bowel syndrome: a systematic review. *J. Am. Osteopath. Assoc.* 114(6), 470–479 (2014).
5. Ford AC, Harris LA, Lacy BE, Quigley EMM, Moayyedi P. Systematic review with meta-analysis: the efficacy of prebiotics, probiotics, synbiotics and antibiotics in irritable bowel syndrome. *Aliment. Pharmacol. Ther.* 48(10), 1044–1060 (2018).
6. Pellissier S, Dantzer C, Canini F, Mathieu N, Bonaz B. Psychological adjustment and autonomic disturbances in inflammatory bowel diseases and irritable bowel syndrome. *Psychoneuroendocrinology* 35(5), 653–662 (2010).
7. Pellissier S, Bonaz B. The place of stress and emotions in the irritable bowel syndrome. *Vitam. Horm.* 103, 327–354 (2017).
8. Chang L. The role of stress on physiologic responses and clinical symptoms in irritable bowel syndrome. *Gastroenterology* 140(3), 761–765 (2011).
9. Mazur M, Furgala A, Jablonski K, Mach T, Thor P. Autonomic nervous system activity in constipation-predominant irritable bowel syndrome patients. *Med. Sci. Monit.* 18(8), CR493–CR499 (2012).
10. Spetalen S, Sandvik L, Blomhoff S, Jacobsen MB. Autonomic function at rest and in response to emotional and rectal stimuli in women with irritable bowel syndrome. *Dig. Dis. Sci.* 53(6), 1652–1659 (2008).
11. Bonaz B, Picq C, Sinniger V, Mayol JF, Clarencon D. Vagus nerve stimulation: from epilepsy to the cholinergic anti-inflammatory pathway. *Neurogastroenterol. Motil.* 25(3), 208–221 (2013).
12. Borovikova LV, Ivanova S, Zhang M *et al.* Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature* 405(6785), 458–462 (2000).
13. Bonaz B, Bazin T, Pellissier S. The vagus nerve at the interface of the microbiota–gut–brain axis. *Front. Neurosci.* 12, 49 (2018).
14. Foster JA, Rinaman L, Cryan JF. Stress & the gut–brain axis: regulation by the microbiome. *Neurobiol. Stress* 7, 124–136 (2017).
15. Furuta S, Shimizu T, Narita M *et al.* Subdiaphragmatic vagotomy promotes nociceptive sensitivity of deep tissue in rats. *Neuroscience* 164(3), 1252–1262 (2009).
16. Handforth A, DeGiorgio CM, Schachter SC *et al.* Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. *Neurology* 51(1), 48–55 (1998).
17. Rong PJ, Fang JL, Wang LP *et al.* Transcutaneous vagus nerve stimulation for the treatment of depression: a study protocol for a double blinded randomized clinical trial. *BMC Complement. Altern. Med.* 12, 255 (2012).
18. Bonaz B, Sinniger V, Hoffmann D *et al.* Chronic vagus nerve stimulation in Crohn's disease: a 6-month follow-up pilot study. *Neurogastroenterol. Motil.* 28(6), 948–953 (2016).
19. Jin H, Guo J, Liu J *et al.* Anti-inflammatory effects and mechanisms of vagal nerve stimulation combined with electroacupuncture in a rodent model of TNBS-induced colitis. *Am. J. Physiol. Gastrointest. Liver Physiol.* 313(3), G192–G202 (2017).
20. Payne SC, Furness JB, Burns O *et al.* Anti-inflammatory effects of abdominal vagus nerve stimulation on experimental intestinal inflammation. *Front. Neurosci.* 13, 418 (2019).
21. Meroni E, Stakenborg N, Gomez-Pinilla PJ *et al.* Functional characterization of oxazolone-induced colitis and survival improvement by vagus nerve stimulation. *PLoS ONE* 13(5), e0197487 (2018).
22. Stefan H, Kreiselmeyer G, Kerling F *et al.* Transcutaneous vagus nerve stimulation (t-VNS) in pharmacoresistant epilepsies: a proof of concept trial. *Epilepsia* 53(7), e115–e118 (2012).
23. Busch V, Zeman F, Heckel A, Menne F, Ellrich J, Eichhammer P. The effect of transcutaneous vagus nerve stimulation on pain perception: an experimental study. *Brain Stimul.* 6(2), 202–209 (2013).
24. Zhao YX, He W, Jing XH *et al.* Transcutaneous auricular vagus nerve stimulation protects endotoxemic rat from lipopolysaccharide-induced inflammation. *Evid. Based Complement. Alternat. Med.* 2012, 627023 (2012).

25. Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. *Aliment. Pharmacol. Ther.* 11(2), 395–402 (1997).
26. Saito YA, Schoenfeld P, Locke GR 3rd. The epidemiology of irritable bowel syndrome in North America: a systematic review. *Am. J. Gastroenterol.* 97(8), 1910–1915 (2002).
27. Spiegel B, Strickland A, Naliboff BD, Mayer EA, Chang L. Predictors of patient-assessed illness severity in irritable bowel syndrome. *Am. J. Gastroenterol.* 103(10), 2536–2543 (2008).
28. Gandek B, Ware JE, Aaronson NK *et al.* Cross-validation of item selection and scoring for the SF-12 health survey in nine countries: results from the IQOLA project. International quality of life assessment. *J. Clin. Epidemiol.* 51(11), 1171–1178 (1998).
29. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J. Pers. Soc. Psychol.* 54(6), 1063–1070 (1988).
30. Spielberger CD, Bruchon-Schweitzer M, Paulhan I. *Adaptation Française de L'invetaire D'anxiété État-trait Forme Y (STAI-Y)*. Les Editions du Centre de Psychologie Appliquée, Paris, France (1993).
31. Fuhrer R, Rouillon F. La version française de l'échelle Center for Epidemiologic Studies-Depression Scale. *Psych. Psychobiol.* 4, 163–166 (1989).
32. Cohen S, Williamson G. Perceived stress in a probability sample of the United States. In: *The Social Psychology of Health: Claremont Symposium on Applied Social Psychology.* Spacacan S, Oskamp S (Eds). SAGE, LA, USA (1989).
33. Cousson F, Bruchon-Schweitzer M, Quintard B. Analyse multidimensionnelle d'une échelle de coping: validation française de la (ways of coping checklist). *Psychol. Française* 41, 155–164 (1996).
34. Labus JS, Bolus R, Chang L *et al.* The visceral sensitivity index: development and validation of a gastrointestinal symptom-specific anxiety scale. *Aliment. Pharmacol. Ther.* 20(1), 89–97 (2004).
35. Konikoff MR, Denson LA. Role of fecal calprotectin as a biomarker of intestinal inflammation in inflammatory bowel disease. *Inflamm. Bowel Dis.* 12(6), 524–534 (2006).
36. Tran K, Brun R, Kuo B. Evaluation of regional and whole gut motility using the wireless motility capsule: relevance in clinical practice. *Therap. Adv. Gastroenterol.* 5(4), 249–260 (2012).
37. Frokjaer JB, Bergmann S, Brock C *et al.* Modulation of vagal tone enhances gastroduodenal motility and reduces somatic pain sensitivity. *Neurogastroenterol. Motil.* 28(4), 592–598 (2016).
38. Gidda JS, Goyal RK. Influence of vagus nerves on electrical activity of opossum small intestine. *Am. J. Physiol.* 239(5), G406–G410 (1980).
39. Halpert A, Dalton CB, Palsson O *et al.* Irritable bowel syndrome patients' ideal expectations and recent experiences with healthcare providers: a national survey. *Dig. Dis. Sci.* 55(2), 375–383 (2010).
40. Sabate JM, Ducrotte P, Piche T *et al.* Expectations of IBS patients concerning disease and healthcare providers: results of a prospective survey among members of a French patients'association. *Clin. Res. Hepatol. Gastroenterol.* doi.org/10.1016/ (2020) (Epub ahead of print).