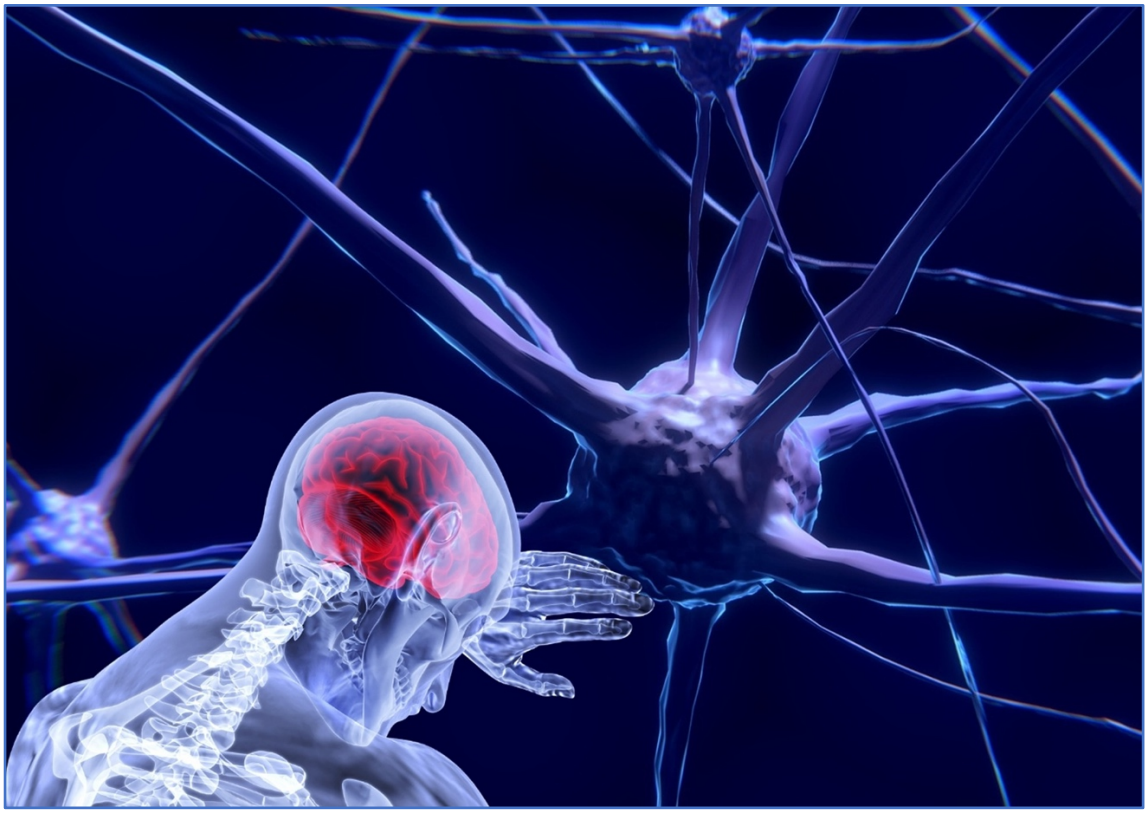
Master of Pain Science and Multidisciplinary Pain Management

MASTER´S THESIS



SCOPING REVIEW:

POTENTIAL EFFECTS OF VAGUS NERVE STIMULATION ON VISCERAL PAIN IN ADULT PATIENTS WITH IRRITABLE BOWEL SYNDROME

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Synopsis:

Background: Visceral pain is a crucial symptom in irritable bowel syndrome (IBS) and has been linked to alterations of the autonomic nervous system (ANS) and its anti-nociceptive function. Modulation of the ANS using "Vagus Nerve Stimulation" (VNS) may be a promising treatment option in IBS and especially IBS-related visceral pain. However, the body of evidence whether VNS has beneficial effects on visceral pain in adults with IBS is undetermined. **Objectives:** This scoping review aims to summarize knowledge on ANS role in IBS (part 1) and to systematically identify literature and available evidence on VNS effects in IBS and IBS-related pain (part 2). **Methods:** The review process followed the PRISMA Statement ("Transparent Reporting of Systematic Reviews and Meta-Analyses") supplemented by PRISMA-ScR ("PRISMA extensions for scoping reviews"). **Results:** At all, 7 relevant studies were identified: 6 studies on VNS effects on somatic pain could be identified, 3 of these documented pain-reducing effects, 2 demonstrated pro-nociceptive effects. Further, 1 study investigating VNS in a model of visceral pain could be identified: VNS significantly reduced reactive esophageal hyperalgesia. No studies on VNS effects on either IBS or IBS-related pain could be identified. **Conclusion:** VNS is involved in both visceral and somatic pain modulation and exerts significant anti-nociceptive effects. This scoping review hopefully inspirers future research to start investigation of VNS conceivable potential in IBS and IBS-related pain.

FOREWORD AND ACKNOWLEDGEMENT

Irregular bowel habits and abdominal pain is a common reason for patients to seek medical care. Some of these patients report, that they suffered of these partially disabling symptoms a tremendous part of their lives, others developed symptoms over only a short period of time. Many are afraid of being seriously ill or even to have cancer. It is common for most of them, that the experienced symptoms have crucial impact on their quality of life.

As a surgeon in a clinical department I meet many people in this patient category. After assuring, that no serious disease is causing the named symptoms, what is very rarely the case, patients are most often send home with the message “There is nothing wrong, it is just irritable colon!” Options of beneficial treatment are rare and most often with very limited effect. Furthermore, knowledge on the disorder itself seems to be very limited among surgeons, even abdominal surgeons: Irritable colon is often seen as a pure functional disease with an essential psychological component, many patients state the feeling of not being taken serious in their suffering.

I have always had a special interest for patients suffering irritable bowel syndrome and/ or patients with abdominal pain without obvious organic disease. The attempt to get a better insight in the mechanisms behind chronic abdominal pain and especially to get better educated in treatment of chronic pain has driven me to invest time (and money) in this master course “Master of Pain Science and Multidisciplinary Pain Management”. This master´s thesis condenses my interests and motivation to discover better treatment possibilities for patients with idiopathic abdominal pain and hopefully forms the basis for future research projects.

Ken Steffen Frahm did not only supervise the working process on this master´s thesis, but also two previous study projects. Thanks for always constructive sparring, helpful comments and competent supervision.

Thanks also to family and friends, who have supported me over the past turbulent weeks. Special thanks to my “little co-author” Linnéa: “Es war (k)eine schwere Geburt!” ☺

RESUMÉ PÅ DANSK

Titel	Scoping Review: Effekter af Vagus Nerve Stimulation på viscerale smerter ved colon irritabile.
Forfatter	Katrin Schättiger
Vejleder	Ken Steffen Frahm
Baggrund og formål	Irritabel tarmsyndrom (IBS) er en hyppig forekommende kronisk mave-tarmlidelse, som er kendetegnet ved forstyrret afføringsmønster og viscerale smerter. Smerterne beskrives ofte som diffuse og skiftende i karakter, lokalisering samt intensitet over tid. Især hyppigheden og sværhedsgraden af smerterne ved IBS har en stor betydning for patienternes livskvalitet. Smerterne ved IBS er formentlig, blandt andet, begrundet i en dysregulering af det autonome nervesystem (ANS) og dets anti-nociceptive funktion. Modulering af ANS-balancen ved hjælp af Vagus Nerve Stimulation (VNS) kan tænkes som en mulig behandling af IBS og især IBS-relaterede viscerale smerter. Hvorvidt og hvor meget forskning der på dette område eksisterer, er midlertidig uklart, men ANS og VNS synes ikke at være i fokus i IBS-forskningen. Formålet ved denne rapport er derfor, at kortlægge eksisterende viden om ANS rolle i IBS (del 1) samt systematisk at kortlægge relevant litteratur samt identificere den tilgængelige evidens om VNS eventuelle potentiale i behandlingen af IBS og især IBS-relaterede smerter (del 2).
Metode	På grund af ukendt evidens og formodet mindre fokus på ANS, IBS og behandlingen af IBS relaterede smerter ved hjælp af VNS i hidtidige studier blev rapportering i form af en scoping review valgt. Arbejdsprocessen blev struktureret svarende til en på forhånd udarbejdet protokol og fulgte anbefalinger af PRISMA-P ("Preferred Reporting Items for Systematic reviews and Meta-Analyses"). Strukturering af resultaterne i form af den foreliggende rapport orienterede sig tilsvarende efter "PRISMA extensions for scoping reviews" (PRISMA-ScR).
Resultater og diskussion	I alt kunne 7 studier om VNS-effekter på eksperimentelle smerter identificeres. 6 af de 7 studier konkluderer smertemodulerende effekter af VNS. 6 af de 7 studier undersøger effekter af VNS på somatiske smerter. 3 af disse studier finder en anti-nociceptiv effekt af VNS og 2 viste pro-nociceptive effekter. Der blev alene identificeret 1 studie som undersøger effekter af VNS i en model af viscerale smerter: VNS reducerer signifikant reaktiv esofageal hyperalgesi. Ingen studier om VNS-effekter på hverken IBS eller IBS-relaterede smerter kunne identificeres.
Konklusion	ANS mulige rolle i patofysiologien af IBS er bredt beskrevet i litteraturen og er alment anerkendt i især den nyere litteratur. Behandlingen af IBS og IBS-relaterede smerter ved hjælp af VNS er til gengæld ikke undersøgt. Til trods for et formodet stort og gavnligt potentiale for VNS som non-farmakologisk behandlingsmulighed af IBS og IBS-relaterede smerter, er forskningen om elektronisk ANS-modulation til behandlingen af viscerale smerter ikke prioriteret. Dette scoping review kan forhåbentlig inspirere til fremtidige forskningsprojekter om VNS i IBS, da VNS anses som lovende non-farmakologisk interventionsmulighed i en udbredt sygdom med ellers manglende effektive og tilfredsstillende behandlingsmuligheder.
Nøgleord	Autonome nervesystem, ANS, "Vagus Nerve Stimulation", VNS, iVNS, t-VNS, ta-VNS, colon irritabile, irritabel tyktarm, IBS, viscerale smerter, abdominale smerter

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INTRODUCTION

IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) is a gastrointestinal chronic disorder characterized by visceral pain and altered bowel movements.[1] IBS presents one of the most common disorders of the gastrointestinal tract with a prevalence of approximately 11.2%[2] of the world´s population and an incidence of 1.35% to 1.5%.[3] It is more prevalent in patients under the age of 50 as well as in females (female-male-ratio: 2-3:1).[4,5] As organic abnormalities or reliable diagnostic biomarkers cannot be identified,[6-8] patients are diagnosed according to symptom-based criteria.[5,9-11] IBS is accordingly further divided into subcategories as diarrhea predominant (IBS-D), constipation predominant (IBS-C), alternating (IBS-A), or unspecified (IBS-U).[1,2,5] Although patients with IBS do not face an enhanced risk of gastrointestinal malignancies[12] or mortality,[13] IBS and IBS-related pain challenges both the individual and the society by causing loss of productivity as well as substantial costs to healthcare services.[14]

PATHOPHYSIOLOGY OF IRRITABLE BOWEL SYNDROME

Pathophysiological mechanisms of IBS are still debated and presumably varying:[2,5,15,16] Dysfunctional gastrointestinal motility,[17] subclinical inflammation of the gastrointestinal tract[18,19] as well as visceral hypersensitivity[20] is thought to be substantial. Further etiological concepts enclose an altered intestinal milieu,[21-24] enhanced gut permeability as well as altered mucosal and immune function.[25-27]

Additionally, genetical, psychological and environmental factors are presumed to be contributing to patients partially disabling symptoms.[23,25,28-30]

BACKGROUND (PART 1)

THE AUTONOMIC NERVOUS SYSTEM IN IRRITABLE BOWEL SYNDROME

Already in 1928, Bockus et al.[31] suggested an imbalance within the ANS as a contributing factor in IBS-pathology, but first again in the 1990s a role of the ANS was increasingly reconsidered.[32,33] Today, accumulating evidence suggests altered ANS function in IBS, resulting in a dysregulation of the sympathetic and/ or parasympathetic systems.[19,34] Especially the parasympathic nervous system (PNS) executes a substantial anti-nociceptive function[35-37] and plays an important role in the sensorimotor gut-function.[17,20,38] Furthermore, PNS is essentially involved in the neuroimmune-axis, the hypothalamic-pituitary-adrenal axis as well as the cholinergic anti-inflammatory pathway (CAP).[19,34]

An underlying dysfunction of ANS is assumed to be a key element in pathophysiology of IBS: [18,19,34] In 26–52% of patients with IBS an imbalance of the ANS can be demonstrated,[32,39-41] indicating changed sympathetic activity,[42-44] and/or parasympathetic activity,[41,45-50] but the results diverge and are probably at least partially depending on IBS-subgroups.[33,41,51-53]

THE ROLE OF THE VAGUS NERVE IN THE AUTONOMIC NERVOUS SYSTEM

The vagus nerve (VN) represents the largest and main nerve of the PNS, transmitting visceral, somatic, and taste sensations. The vagus nerve also contains myelinated A- and B-fibers, mainly parasympathetic efferents, which innervate heart, lungs, and gastrointestinal tract.[54-56] The VN regulates the activity of almost all internal organs and is assumed to be involved inter alia in the modulation of gastrointestinal motility,[17] inflammatory responsiveness[18,19,34] as well as visceral nociception.[54,57-60]

VAGUS NERVE STIMULATION

In the 1990s VNS was introduced as a therapeutic option in the treatment of refractory epilepsy,[61] later it was also approved for the treatment of refractory depression.[58,62,63] VNS is discussed as a potential regulator of inflammation, thereby of interest in disorders like rheumatoid arthritis and inflammatory bowel disease.[64,65] A positive effect in patients

suffering after stroke and traumatic brain injury by modulation of neuroprotective processes and neurogenesis is furthermore conceivable.[58,66-68]

Today, VNS is under investigation as a treatment option in asthma, bipolar disorder, dementia (Alzheimer's disease), obesity, impaired glucose tolerance, gastroparesis, as well as different chronical pain disorders.[54,58,59,66,67,69-74]

VAGUS NERVE STIMULATION AND PAIN

Abdominal pain is a dominant symptom in IBS: The severity and frequency of abdominal pain significantly reduces quality of life.[75-77] Visceral pain in IBS has been linked to dysfunctional peripheral and central pain processing as IBS patients tend to both peripheral and central hyperalgesia.[78-81] Furthermore, alterations of the microbiota-gut-brain axis are considered as likely.[9,19,34,78,82] This axis is additionally modulated by the ANS in particular the parasympathetic VN.[17,34] Dysbalance of the vagal tone is suspected to interfere with the anti-nociceptive function of the ANS and VN.[17,19,20,34,38,78,83,84]

A growing body of literature supports the potential of VNS in multiple pain diseases as vagal afferent stimulation was demonstrated to have pain relieving potential.[55,85-87] The analgesic potential of VNS in humans was incidentally observed in patients treated with VNS for either epilepsy or depression and a comorbidity with migraine or cluster headache,[85,88-93] suggesting that VNS could decrease both frequency and severity of disorder related painful attacks or even lead to a complete relief.[60] The antinociceptive effect of VNS is presumably caused by exerting a modifying or controlling influence on multiple pain-associated structures in the brain as well as on the spinal cord. Thereby VNS probably affects peripheral and central nociception as well as the secondary opioid response and the general autonomic activity.[54,58-60]

Over the last two decades, VNS use for multiple pain indications as chronic pelvic pain, fibromyalgia, trigeminal allodynia, and chronic headaches including migraines has been increasingly recognized.[55,58,69,74,87,89,94-101]

Several electrical stimulating devices for VNS exist: In addition to implantable vagus nerve stimulators (iVNS), two non-invasive transcutaneous systems have been developed, which

stimulate auricular VN (taVNS) or carotid VN (tVNS).[54,58,59] While iVNS poses a risk for both implantation-related intraoperative complications as well as adverse events including all from infections to potential cardiac events, noninvasive stimulators provide a better balance between safety, efficacy and tolerability.[55,58,62,102-106] Non-invasive VNS is supposed to exhibit equivalent therapeutic effects on drug-resistant epilepsy and treatment-resistant depression as demonstrated with iVNS including antinociceptive effects.[107-112] The recent development of transcutaneous and thereby non-invasive methods has made it feasible to test vagal stimulation in not only patients, but healthy participants as well.[60]

RATIONALE: WHY A SCOPING REVIEW ON EFFECTS OF VNS ON PAIN IN IBS?

Pathophysiology of IBS is controversial, altered gastrointestinal motility[17] subclinical inflammation of the gastrointestinal tract[19] as well increased visceral sensitivity[20] are believed to be crucial. Effective treatments, both pharmacological and non-pharmacological interventions, are rare and mostly very limited in their beneficial effects.[15,113,114] Concurrently, ANS and especially the parasympathic VN is important in the regulation of inflammatory processes,[18] gastrointestinal motility and nociception.[18,20,34,38,54,58,59] Electrical modulation of the ANS using Vagus Nerve Stimulation (VNS) may present a promising treatment option of IBS and especially IBS-related visceral pain.[17,19,34,64] However, ANS and VNS seem predominantly not to be in focus in studies on IBS and IBS-related pain. Whether and if, to what extent this topic is investigated in literature is not clear, though. Hence, a scoping review[115] was conducted to systematically cover the research carried out in this area of interest, as well as to discover possibly existing gaps in knowledge.

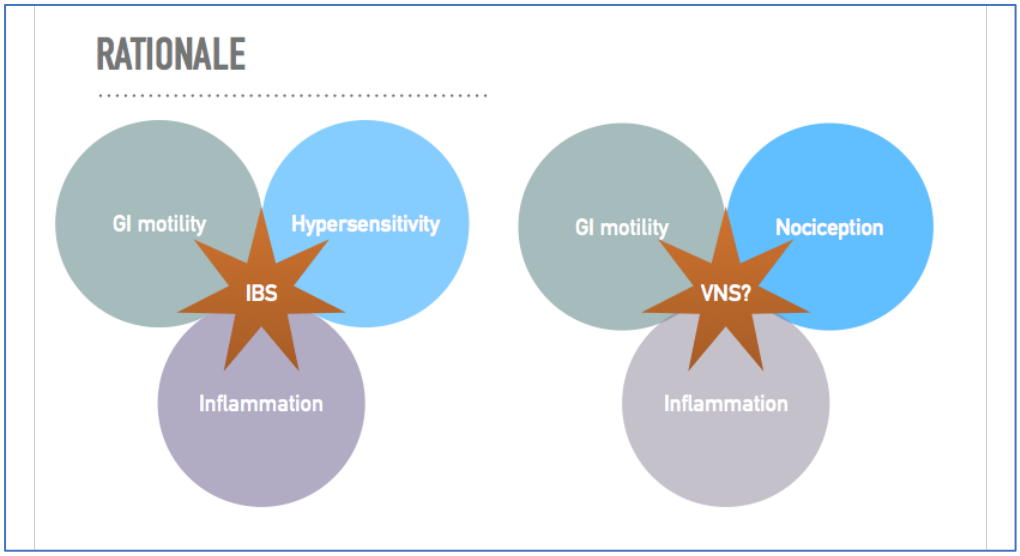

Figure A: Left side presents the three main reasons suspected to cause IBS; right side presents normalizing effects conceivably induced by VNS

This scoping review was organized in 2 parts: In the 1st part (Background), ANS-role in pathophysiology of IBS and IBS-related pain is explicated in order to give a general summary on the chosen topic. In the 2nd part, the systematically identified literature and available evidence on VNS effects in IBS and IBS-related pain is presented (Results) and analyzed (Discussion).

METHODS

PROTOCOL AND REGISTRATION

This scoping review was conducted using a detailed protocol (see appendix 1), elaborated and tested beforehand according to the "guidelines for systematic reviews and meta analyses of studies evaluating health care interventions" published as the "Preferred Reporting Items for Systematic reviews and Meta-Analyses", so-called PRISMA-P.[116,117]

CHOICE OF REVIEW METHOD: SCOPING REVIEW

In preparation of this thesis, a preliminary literature search according to the settings of the protocol was carried out and revealed a presumably limited number of records on the chosen topics. As the body of literature on especially VNS-effects on IBS and IBS related pain was indefinite, it was decided to conduct a scoping review instead of an originally planned systematic review (Modul 7, "Protocol for a systematic review"). According to PRISMA scoping reviews

> "*can be conducted to meet various objectives. They may examine the extent (that is, size), range (variety), and nature (characteristics) of the evidence on a topic or question; determine the value of undertaking a systematic review; summarize findings from a body of knowledge that is heterogeneous in methods or discipline; or identify gaps in the literature to aid the planning and commissioning of future research.*"[115]

"PRISMA extensions for scoping reviews" (PRISMA-ScR)[115] was used to structure the working process. The sections used in this rapport are structured likewise according to recommendations of PRISMA and Prisma-ScR (see appendix 2)[115-117] with adjustments where appropriate.

ELIGIBILITY CRITERIA

The 1st part of this scoping review (Background) presents a summary of the existing literature on the impact of ANS in IBS. Its focus is especially directed on the potential role of the ANS and VN in pathophysiology of IBS and IBS-related abdominal pain.

The 2nd part (Results) investigates existing evidence of effects induced by VNS on IBS of any subtype and IBS-related abdominal pain. To uncover all relevant VNS-research and any linking experiments, the focus was further extended: Studies on VNS-effects on pain, especially visceral pain, on the microbiota-gut-brain-axis as well as on the gastrointestinal tract in human subjects aged ≥ 18 years of any sex, and any BMI were considered. Furthermore, studies investigating VNS-effects on pain in healthy subjects as well as in patients treated with VNS due to other diseases than IBS were included. Though, studies on VNS-effects on other diseases as well as on other chronic pain disorders than IBS were not included.

VNS in this review was defined as invasive Vagus Nerve Stimulation (iVNS), noninvasive transcutaneous Vagus Nerve Stimulation (t-VNS) as well as noninvasive transcutaneous auricular Vagus Nerve Stimulation (ta-VNS) in all frequencies, intensities and any duration.

Quantitative studies as well as qualitative studies meeting the eligibility criteria defined in the protocol (see appendix 1) were included. Case studies meat the criteria of inclusion, if they describe effects of VNS on IBS and/ or IBS-related abdominal pain, on the microbiota-gut-brain axis and/ or on the gastrointestinal tract.

INFORMATION SOURCES

A 3-step-search-strategy was chosen to identify any relevant literature:

1. Pubmed (1996 – Januar 2019) was searched broad to identify key words and relevant MeSH-terms.
2. Pubmed (1996 – Januar 2019), EMBASE (1974 – Januar 2019), and PsycINFO (1806 – Januar 2019) was searched according to a detailed search protocol developed beforehand with the assistance of a librarian.
3. Reference lists from reviewed articles were perused to secure inclusion of any further relevant literature.

RefWorks was used to manage literature throughout this reviewing process.

SEARCH

To cover all relevant literature a broad search strategy was applied. The search was conducted according to subthemes using the beforehand elaborated and tested search strategy protocol. Only literature in English, German and Danish were included. As example of the used search strategy, session results of Embase are chosen (PubMed: see appendix 3; PsycInfo: see appendix 4).

Embase Session Results

No.	Query	Results
#28	#23 OR #24 OR #25 OR #26 OR #27	1,129
#27	#4 AND #8	72
#26	#1 AND #8	35
#25	#8 AND #9	62
#24	#5 AND #8	1,047
#23	#8 AND #12	25
#22	#20 OR #21	2,590
#21	#18 OR #19	1,960
#20	#15 OR #16 OR #17	909
#19	#4 AND #14	1,960
#18	#4 AND #13	1,892
#17	#1 AND #4 AND #14	279
#16	#1 AND #14	909
#15	#1 AND #13	806
#14	#12 OR #13	276,835
#13	'autonomic nervous system'/exp OR 'autonomic nervous system'	275,699
#12	#10 OR #11	1,320
#11	'microbiota gut brain axis'/exp	18
#10	'gut brain axis'/exp OR 'gut brain axis'	1,320
#9	'gastrointestinal tract'/exp	56,435
#8	#6 OR #7	9,852
#7	'transcutaneous vagus nerve stimulation'/exp OR 'transcutaneous vagus nerve stimulation'	130
#6	'vagus nerve stimulation'/exp OR 'vagus nerve stimulation'	9,852
#5	'pain'/exp OR pain	1,502,787
#4	#2 OR #3	207,730
#3	'visceral pain'/exp OR 'visceral pain'	43,892
#2	'abdominal pain'/exp OR 'abdominal pain'	171,481
#1	'irritable colon'/exp OR 'irritable colon'	23,938

Figure B: Protocol of literature search using Embase

SELECTION OF SOURCES OF EVIDENCE

One reviewer was responsible to collect relevant data from the selected articles applying the screening-, eligibility- and inclusion-criteria defined beforehand in the protocol (see appendix 1). In a 1st step, possibly eligible literature was selected by title:

PUBMED

Subthemes, 1st part:	No. of articles		# OR #	# OR #	No animals No kids Relevance	Screening
Role of ANS in IBS	#46+#47	413	Tema 1(IBS): 660	1st part: 1235	172	68
Role of ANS and microbiota gut brain axis in IBS	#46+#54	660				
Role of ANS and microbiota gut brain axis in abd. pain + IBS	#46+#54+#49	187				
Role of ANS in abdominal pain	#47+#49	672	Tema 2(ANS): 672			
Role of ANS and microbiota gut brain axis in abd. pain	#47+#48+#49	70				
Subthemes, 2nd part:					No animals No kids Relevance	Screening
Effects of VNS/ tVNS on microbiota gut brain axis	Ny#21+#52	11	470	2nd part: 470	81	13
Effects of VNS/ tVNS on pain	Ny#17+#52	301				
Effects of VNS/ tVNS on GI-tract	Ny#16+#52	170				
Effects of VNS/ tVNS on IBS	#46+#52	10				
Effects of VNS/ tVNS on abd. pain	#49+#52	8				

EMBASE

Subthemes, 1st part:	No. of articles		# OR #	# OR #	No animals No kids Relevance	Screening
Role of ANS in IBS	#1+#13	806	Tema 1(IBS): 909	1st part: 2590	77	52
Role of ANS and microbiota gut brain axis in IBS	#1+#14	909				
Role of ANS and microbiota gut brain axis in abd. pain + IBS	#1+#14+#4	279				
Role of ANS in abdominal pain	#13+#4	1892	Tema 2(PAIN): 1960			
Role of ANS and microbiota gut brain axis in abd. pain	#14+#4	1960				
Subthemes, 2nd part:					No animals No kids Relevance	Screening
Effects of VNS/ tVNS on microbiota gut brain axis	#8+#12	25	1129	2nd part: 1129	109	22
Effects of VNS/ tVNS on pain	#8+#5	1047				
Effects of VNS/ tVNS on GI-tract	#8+#9	62				
Effects of VNS/ tVNS on IBS	#8+#1	35				
Effects of VNS/ tVNS on abd. pain	#8+#4	72				

PSYCINFO

Subthemes, 1st part:	No. of articles		# OR #	# OR #	No animals No kids Relevance	Screening
Role of ANS in IBS		37	Tema 1(IBS): 85	1st part: 125	38	14
Role of ANS and microbiota gut brain axis in IBS		85				
Role of ANS and microbiota gut brain axis in abd. pain + IBS		17				
Role of ANS in abdominal pain		40	Tema 2(PAIN): 57			
Role of ANS and microbiota gut brain axis in abd. pain		57				
Subthemes, 2nd part:					No animals No kids Relevance	Screening
Effects of VNS/ tVNS on microbiota gut brain axis		2	94	2nd part: 94	42	12
Effects of VNS/ tVNS on pain		89				
Effects of VNS/ tVNS on GI-tract		4				
Effects of VNS/ tVNS on IBS		2				
Effects of VNS/ tVNS on abd. pain		4				

The hereby identified records were hereafter in a 2nd step screened by title and abstract. Duplicates were removed. In a third and final step, full text screening of the remaining articles was conducted. Articles meeting all criteria of inclusion as prior defined in the protocol, were included. As the 1st part of this review was meant as a general introduction to the topic, exclusion criteria were less restrictive than the ones applied for the 2nd part of this scoping review (see protocol, appendix 1). Hence, reasons for exclusion were only documented for literature sources screened for the 2nd part (see flow-chart[116,117]).

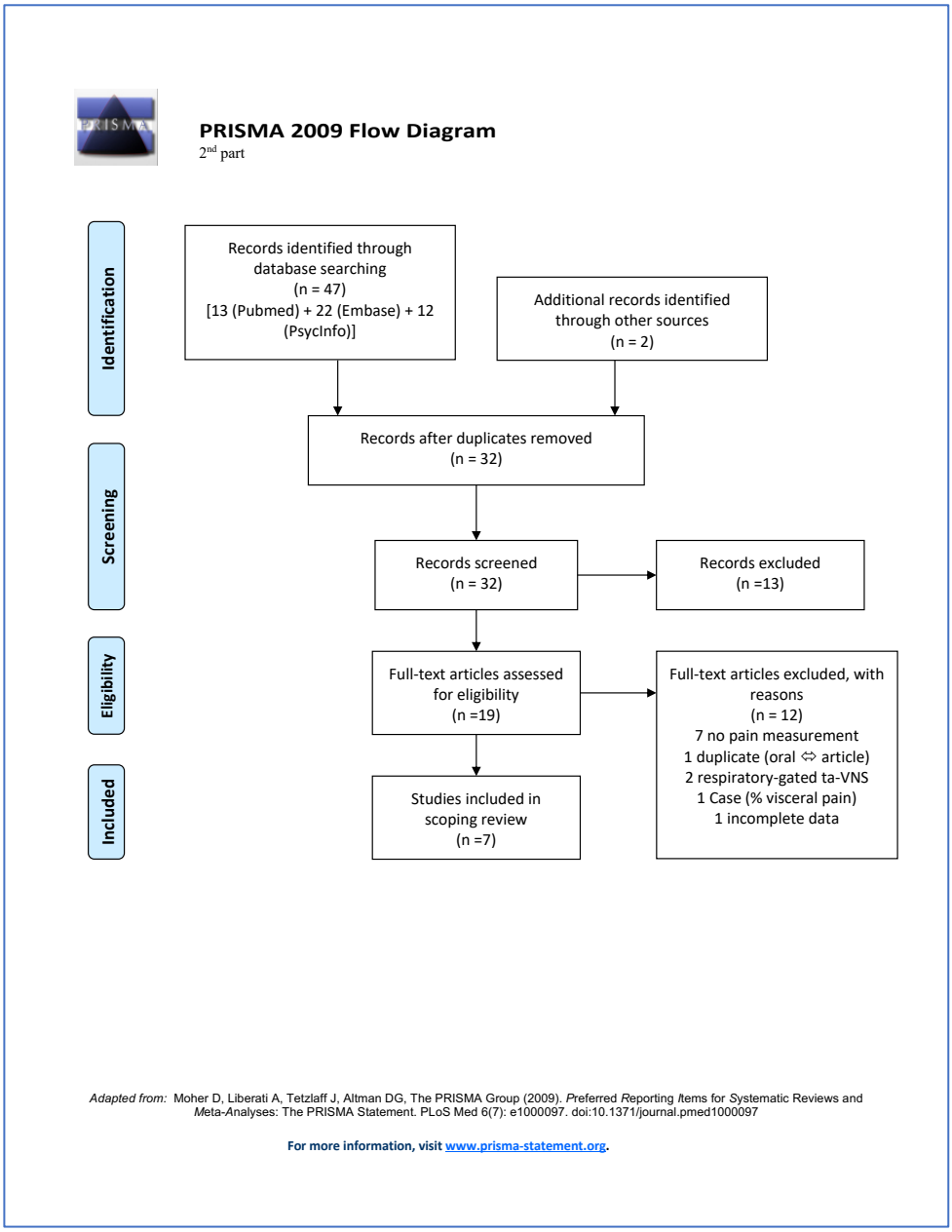

Figure C: Flow diagram according to Prisma[116,117] , screening results part 2.

RESULTS (PART 2)

EFFECTS OF VAGAL NERVE STIMULATION ON PAIN IN IBS

SYNTHESIS OF RESULTS

In total, 7 articles which meet the inclusion-criteria could be identified.[118-124] All identified studies are experimental studies, investigating effects of VNS on experimental pain. Only 1 of these 7 studies investigated effects of VNS on the gastrointestinal tract (esophagus) in a model of visceral pain,[118] the other 6 investigate effects of VNS on somatic pain. No quantitative, qualitative studies or case-reports investigating a potential effect of VNS on IBS, IBS-related pain or microbiota-gut-brain-axis could be detected.

METHODS OF IDENTIFIED STUDIES:

The number of participants in the different studies varied from 8 to 47. 5 of the 7 studies were structured as prospective, randomized, placebo controlled, subject blinded trials.[119-123] One study was furthermore conducted in a cross-over design.[118] Only one study was designed as a prospective, randomized, placebo controlled, double-blinded trial.[124]

As interventions 4 of the 7 studies did use iVNS[119-122] and 3 studies investigated ta-VNS.[118,123,124] No studies investigating the effect of t-VNS could be identified.

4 studies investigated solely 1 single experimental pain setting (heat pain thresholds or tonic pressure pain or heat tolerance time).[118,120-122] 1 study explored 4 different experimental pain settings (mechanical pain threshold, tonic pressure pain, temporal summation and heat pain thresholds),[119] only 1 study investigated VNS effect on experimental pain using quantitative sensory testing (QST).[124]

RESULTS OF IDENTIFIED STUDIES

6 of the 7 identified studies could document a significant effect of VNS on pain-perception,[118-122,124] 4 of these could demonstrate a significant anti-nociceptive effect.[118-120,124] 2 demonstrated pro-nociceptive effects.[121,122] 1 study could not identify significant effects on pain perception.[123]

Author	Farmer et al.[118]	Kirchner et al.[119]	Ness et al.[122]	Kirchner et al.[120]	Borckardt et al.[121]	Busch et al.[124]	Usichenko et al.[123]
Year	2016	2000	2000	2006	2005	2013	2017
Participants	Healthy	Epilepsy	Epilepsy	Epilepsy	Depression	Healthy	Healthy
VNS-type	ta-VNS	iVNS	iVNS	iVNS	iVNS	ta-VNS	ta-VNS
Number of participants	15 (11m, mean age 30 years)	10 (8m, mean age 32±4.4 years)	8 (7m, aged 18-43)	9 (2m, mean age 32±8 years)	8 (2m, mean age 48.6)	48	20 (11m, mean age 28 (24-44) years)
Control?	-	12 (4m, mean age 34±7.3 years) Healthy; NO VNS	-	9 (2m, mean age 30±9 years) Healthy; NO VNS	-	-	-
Sham-VNS?	Yes	No	Yes	No	Yes	Yes	Yes
Effect of VNS on pain perception?	Yes	Yes	Yes	Yes	Yes	Yes	No
Esophageal hyperalgesia*	No** (p=0.001)	-	-	-	-	-	-
Mechanical pain threshold	-	n.s.	-	-	-	Increased ipsi-lateral (p<0.008)	-
Mechanical pain sensitivity	-	-	-	-	-	Reduced ipsi-lateral (p<0.014)	-
Pressure pain thresholds	-	-	-	-	-	Increased ipsi-lateral (p<0.037)	-
Tonic pressure pain		Reduced (p<0.03)	-	Reduced (p<0.05)	-	-	-
Temporal summation	-	Reduced (p<0.001)	-	-	-	n.s.	-
Heat pain thresholds	-	n.s.	Reduced (p<0.03)	-	-	n.s.	n.s.
Heat tolerance time	-	-	-	-	Reduced (p<0.05)	-	-
Tonic heat pain	-	-	-	-	-	Reduced (p<0.001)	-

* Pain thresholds to electrical stimulation in the proximal esophagus prior and after infusion of hydrochloric acid to the distal esophagus

** Pain thresholds stay unaffected of acid-infusion under ta-VNS

\- Not investigated

n.s. Not significant

Pro-nociceptive effect

Anti-nociceptive effect

Visceral pain

However, the effect of VNS on visceral pain was described in only one literature source (ta-VNS): Farmer et al.[118] conducted a prospective, randomized, placebo controlled, subject blinded crossover trial in healthy subjects to investigate, whether ta-VNS has an impact on the

development of hypersensitivity in visceral pain: Using a model of acid induced esophageal hyoeralgesia, pain thresholds to electrical esophageal stimulation in 15 healthy subjects were investigated. In subjects treated with ta-VNS, no development of acid-induced esophageal hypersensitivity occurred ($p < 0.001$).

Somatic pain under the influence of VNS were investigated in the remaining 6 identified studies: 3 of them were conducted in patients treated with iVNS due to pharmacologically refractory epilepsy,[119,120,122] 1 of them was conducted in patients treated with iVNS due to depression.[121] 2 studies investigated effects of ta-VNS in healthy subjects.[123,124]

Kirchner et al.[119] investigated experimental pain in 10 patients with pharmacologically refractory epilepsy treated with iVNS (pre- and postdevice implantation) and 12 age-matched healthy volunteers (no device implantation): iVNS reduced temporal summation ("wind-up"; $p<0.001$) as well as tonic pressure pain ($p<0.03$). No effect could be demonstrated for pain associated with single-impact stimuli or heat pain thresholds. In a 2nd study, Kirchner et al.[120] could reproduce effects of iVNS on tonic pressure pain: 11 patients treated with iVNS due to pharmacologically refractory epilepsy showed significantly reduced ($p<0.05$) tonic pressure pain in comparison to 9 age- and gender-matched healthy controls.

Ness et al.[122] demonstrated, that iVNS in variating intensities significantly decreased thermal pain thresholds ($p<0.03$) in 8 patients treated with iVNS due to pharmacologically refractory epilepsy.

Borckardt et al.[121] conducted a study in patients treated with iVNS due to depression and showed significant effects on heat tolerance time: the duration participants could tolerate heat pain was reduced under iVNS activation ($p<0.05$).

Busch et al.[124] investigated ta-VNS in 48 healthy volunteers using quantitative sensory testing (QST). They could demonstrate increased mechanical and pressure pain thresholds. Sensitivity to mechanical pain as well as tonic heat pain was reduced. No significant effect of ta-VNS on temporal summation or heat pain thresholds could be detected. Similar findings were made of Usichenko et al.,[123] who investigated pain thresholds to experimental heat pain stimulation in 20 healthy volunteers: A significant effect on pain thresholds could not be demonstrated.

CONCLUSIONS OF IDENTIFIED STUDIES

Kirchner et al. [119,120] concluded, that iVNS has the potential to reduce pain in humans and assume central mechanisms to be crucial in VNS-mediated analgesia.

Ness et al.[122] as well as Borckardt et al.[121] interpret their findings (decreased thermal pain thresholds/ decreased heat tolerance time) as pro-nociceptive effects of VNS and as a proof of its modulating effect on pain perception in humans.

Busch et al.[124] concluded a decisively anti-nociceptive effect of t-VNS regarding mechanical and tonic heat pain stimuli, while non-noxious somatosensory perception was described as unaffected. Thus, they emphasize especially the potential of ta-VNS in clinical use as they assume VNS to be a promising treatment option in patients with chronic pain.

Usichenko et al.[123] could not demonstrate an effect on pain thresholds. They presume, though, that their choice of experimental pain testing potentially be inadequate for the chosen experimental setting.

Only Farmer et al.[118] conducted a VNS-study using a model of visceral pain. As the development of esophageal hyperalgesia was inhibited by the use of ta-VNS, they postulate evidence for the anti-nociceptive role of the parasympathetic nervous system within the esophagus. Furthermore, they conclude big potential of VNS-treatment in esophageal diseases.

DOCUMENTED SIDE EFFECTS OF VNS

Patients included in the study of Ness et al.[122] (chronic iVNS due to pharmacologically refractory epilepsy) reported side effects in form of dysphonia during VNS activation (6 of 8 subjects) as well as Nausea (2 of 8 subjects).

Busch et al.[124] reported, that no clinical relevant side effects were observed during ta-VNS-activation. Kirchner et al. (iVNS), [119,120] Borckardt et al. (iVNS)[121] and Farmer et al. (ta-VNS)[118] as well as Usichenko et al.(ta-VNS)[123] did not report, whether any side effects were observed during the studies.

LIMITATIONS OF IDENTIFIED STUDIES

The major limitation of the identified studies is the limited number of participants as well as the limited number of experimental pain settings in 6 of the 7 identified studies. Only one study used QST as a structured, well defined experimental pain setting. Furthermore, most studies tested different pain settings, which makes comparison across the different studies very difficult. Only 2 studies used healthy volunteers as subjects, the remaining studies involved patients, who had implanted VNS-devices due to either epilepsy or depression. Both the taken numerous medications as well as the disorders themselves affect CNS processing and could be presumed to influence the potential outcome of VNS-treatment. Furthermore, the duration of VNS-treatment was not congruent: While the involved patients were due to their diseases treated with chronic VNS, VNS use in healthy subjects was of limited time. But not only duration of VNS-intervention (long term vs. short term) was differing between studies and even between subjects included in the different studies, but also VNS-settings (stimulation frequency, amplitude and pulse width) with unknown consequences for VNS-effectiveness.

DISCUSSION

SUMMARY OF EVIDENCE

In total, 7 studies could be identified investigating effects of VNS on experimental pain. [118-124] 6 of these 7 identified studies concluded, that VNS had an altering effect on experimental pain, [118-122,124] 4 demonstrated a significant anti-nociceptive effect.[118-120,124] The anti-nociceptive potential of VNS-treatment is further emphasized of several case reports: Kirchner et al.[119] report one case of a man suffering from chronic tension-type headaches 4 days a week, 12 hours per attack over more than 10 years. After implantation of the iVNS-device due to pharmacologically refractory epilepsy, the patient experienced a lasting reduction of headache by 80%. Borckardt et al.[121] report 2 cases of reduced chronic pain after implantation of iVNS-device due to depression: 1 man suffering of debilitating low back pain and daily tension-type headaches experienced reduction of headaches to once per month, while back-pain was reported to no longer "be bothering". 1 woman experienced less back pain after device implantation. Although these case reports are very positive, it is important to remember, that case reports present anecdotal reports with very low level of evidence. This is further noticeable as Borckardt et al.[121] noted 6 other patient suffering of chronic pain diseases including headache, low back pain and neck pain, who did not experience any pain reduction under iVNS-therapy due to depression. This phenomenon of responders and non-responders is also described in VNS-therapy of both epilepsy[125-127] and depression[128,129], underlying mechanisms are not fully understood, though, but VNS-induced processes of neuromodulation are suspected.[58,130]

In 2 studies, pro-nociceptive phenomena were observed: Ness et al.[122] reported reduced heat pain thresholds ($p<0.03$) in 8 patients treated with iVNS-treatment due to epilepsy. Borckardt et al.[121] reported reduced heat tolerance time ($p<0.05$) in 8 patients with iVNS-treatment due to depression. Both studies display several limitations: Sample size is very small and samples are not representative. The included subjects suffer of "brain diseases" and are medicated for these. Changed pain perception due to the underlying disease, due to the numerous medications or the combination of both cannot be excluded. Therefore, the results of both

studies should be reflected with caution.[121] Anyway, similar findings are stated in animal studies, where VNS could be demonstrated to have contrasting effects on pain behavior: While VNS in high frequencies (>50µA) had inhibitory, anti-nociceptive effects, induced low frequency VNS (20-50µA) facilitatory, pro-nociceptive effects.[131,132] Ness et al.[122] emphasize, that their findings of reduced thermal pain thresholds as a pro-nociceptive effect was demonstrated under low intensity VNS, therewith consistent to findings in animal studies. The underlying neurophysiological mechanisms of VNS in humans are not elucidated, yet.[58] Busch et al.[124] conclude, though, that effects of VNS on pain perception may depend on both pain modalities, which are investigated as well as mood states of the investigated subjects during VNS stimulation and thereby be depending on central processing. Kirchner et al.[119,120] point out, that VNS in their experimental settings demonstrated anti-nociceptive effects, when central processing was involved.

Only 1 study investigated effects of VNS on the gastrointestinal tract: Farmer et al.[118] could demonstrate, that reactive esophageal hyperalgesia is significantly reduced by ta-VNS. Similar findings were demonstrated in 2 other studies, investigating the effect of **respiratory gated** ta-VNS (RAVANS):[17,86] As RAVANS is seen as a combined electrical and physiological modulation of vagal tone with reported synergistic antinociceptive effect,[87] both studies did not meet the criteria of inclusion defined in the protocol (see appendix 1) and were accordingly excluded of the review. Never the less, findings are pointing at the importance of the vagal tone and the huge potential of ANS-modulation as anti-nociceptive intervention: Frøkjær et al.[17] demonstrated that modulation of vagal tone by RAVANS did not only reduce somatic pain sensitivity, but also enhanced gastroduodenal motility. Napadow et al.[86] investigated the effect of RAVANS in patients with chronic pelvic pain: RAVANS tended to diminish evoked pain intensity and temporal summation of mechanical pain. Reduction of clinical pain could not be proven, though. Considering, that clinical pain was assessed before and after only one single RAVANS treatment in a patient group suffering from chronical pelvic pain, this is not really surprising: Most authors of the here reviewed studies point on a potential role of VNS in clinical use, especially as a long-term treatment option in chronic pain disorders. As most plausible mechanisms of VNS anti-nociceptive action the majority of the

authors indicate influences and alterations of VNS on central pain processing. This assumption is congruent to the observation, that clinical efficacy of VNS increases over time, suggesting an underlying disease-modifying neuromodulation. Or, as postulated of Yuan et al.:[58]

> "Instead of picturing VNS as stimulating a nerve fiber to get a simple, short-term, localized electrochemical action potential, VNS may actually produce long-term neuromodulatory effects."

LIMITATIONS

Only one person was responsible for both the concept and the execution of this review, comprehending all the subsequent limitations. Majority of these could be diminished by the supervisor, though.

Further limitations reason in the protocol (see appendix 1): Although the focus of the review was extended from solely including VNS-effects on IBS and IBS-related abdominal pain to also include VNS-effects on pain, especially visceral pain, on the microbiota-gut-brain-axis as well as on the gastrointestinal tract, the number of identified studies was very small. To provide a broader picture of VNS-effects and underlying mechanisms, the focus could have been extended to also include neurophysiological and brain imaging studies. The review was further limited as studies investigating effects of VNS on other diseases than IBS were excluded. Due to these beforehand defined criteria of exclusion, case reports as well as studies investigating VNS effects on other chronic pain disorders as headache, migraine and fibromyalgia, were not systematically included in this review. Hence, clinical aspects of VNS-treatment are possibly underestimated.

CONCLUSIONS

ANS assumed role in pathophysiology of IBS is found to be well documented. Its modulating potential is increasingly recognized in particular in recent literature. However, effects of VNS in IBS and IBS-related pain have not been investigated yet. Despite a presumed tremendous potential of VNS as a non-pharmacological treatment option for IBS and IBS-related pain, research focusing on electronic ANS modulation to ease visceral pain is not prioritized. This gap in research could be well documented in the conducted scoping review and can hereby hopefully inspire future research projects: VNS is considered to be a promising non-pharmacological intervention option in a widespread disease with otherwise lacking possibilities of effective treatment. Despite the small number of identified studies and their limitations (e.g. small number of included participants, different used VNS-settings/ frequencies, inconsistent experimental pain modalities), an effect of VNS on experimental pain and pain processing can be considered as likely: The reviewed studies could prove significant anti-nociceptive effects in both somatic and visceral pain. A potential role of VNS in treatment of chronical pain disorders as IBS is conceivable, why research especially in clinical use of VNS in diseases as IBS is highly desirable. Research investigating potential beneficial treatment effects of VNS should not only consider evaluations of clinical pain, but also include experimental pain ratings as well as ANS-measurements. Furthermore, use of QST as defined and standardized experimental pain modality is emphasized to enable comparison of findings across different studies. Both acute and long-term effects of VNS on pain perception should be investigated and the possible interference of VNS-settings (frequencies) on pain perception should be taken into account in study-setup.

APPENDIX 1, PROTOCOL

1.1 ADMINISTRATIVE INFORMATION

1.1.1 TITLE

Scoping review: The role of the vagus nerve in visceral pain in irritable bowel syndrome and potential effects on visceral pain by electrical modulation of the vagal tone in adult patients with IBS.

1.1.2 REGISTRATION

PROSPERO does not accept registrations for scoping reviews, why a registration number is not provided.

1.1.3 AUTHORS

Katrin Schättiger

1.1.3.1 CONTACT

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1.1.3.2 CONTRIBUTIONS

Steffen Frahm, MSc BME, PhD; Department of Health Science & Technology, Aalborg University; Fredrik Bajersvej 7, 9220 Aalborg, DK

1.1.4 AMENDMENTS

If protocol amendments are needed, the date of each amendment will be given and changes and their rationale will be described.

1.1.5 SUPPORT

1.1.5.1 SOURCES

No sources of financial or other support have been received for this study.

1.1.5.2 SPONSOR

No funder and/or sponsor is involved in this study.

1.2 INTRODUCTION

1.2.1 RATIONALE

Irritable bowel syndrome (IBS) is a frequent disease with a worldwide prevalence of approximately 12%. IBS considerably diminishes patients' quality of life and implies a substantial economic burden to the society.[7] As apparent structural alterations of the gastrointestinal tract cannot be clinically proven, diagnosis of IBS is symptom based on the Rome IV criteria: IBS is categorized into constipation predominant (IBS-C), diarrhea predominant (IBS-D), mixed constipation and diarrhea (IBS-M), and unsubtyped (IBS-U) subgroups.[6,7] Etiologic mechanisms of IBS are still uncertain. Increased gut permeability, abnormality of intestinal microbiota as well as altered mucosal and immune function are suspected as causal components of IBS.[6,15] Furthermore, genetic predisposition, psychological disorders including negative life experiences, and environmental contributions are considered to be crucial factors in what is probably a multifactorial pathophysiology.[15,16,22]

Visceral pain is a fundamental symptom in IBS. As IBS patients demonstrate both peripheral and central hyperalgesia, visceral pain in IBS has been linked to alterations of the gut-brain axis,[93] lately enlarged to the microbiota-gut-brain axis: The microbiota, the gut, and the brain interact bidirectionally additionally modulated by the autonomic nervous system (ANS), in particular the parasympathetic vagus nerve (VN). The ANS is capable of not only sensing the microbiota in the gut, but also to transmit this information to the central nervous system (CNS), where it is integrated resulting in a specific response including anti-inflammatory effects.[83] An imbalance of ANS has been identified as a pathophysiological feature in IBS.[84,88,90]

1.2.2 OBJECTIVES

Evidence on the impact of the ANS in pathophysiology of IBS is increasing.[38,39,83,87,88,90] Targeting the ANS is seen as a promising approach to normalize several elements of the pathophysiological mechanisms underlying symptoms in IBS, including visceral pain.[83,86] Tough, only few IBS-studies focus on potentially mechanisms of interventions mediated by the ANS. Randomized clinical trials on this topic are rare. Reviews reflecting treatment options of pain in IBS with help of electrical ANS-modulation by targeting the vagal tone through vagal nerve stimulation in form of VNS or t-VNS or ta-VNS do not exist according to authors knowledge at this timepoint.[83]

Hence, this review aims to give a general overview over current knowledge of ANS´s role in pathophysiology of IBS in adult patients, especially focusing on IBS-related abdominal pain. (1st part).

Furthermore, this review will focus on the present knowledge of therapeutic possibilities of electrical ANS-modulation by targeting the vagal tone through vagal nerve stimulation to diminish visceral pain in IBS (2nd part). Due to this purpose, research investigating effects of electrical vagal nerve stimulation on pain, especially abdominal pain, on the microbiota-gut-brain-axis, on the gastrointestinal tract, and/ or IBS will be investigated. Effects on visceral pain in IBS by direct electrical modification of vagal tone by invasive vagus nerve stimulation (VNS) as well as noninvasive transcutaneous VNS (t-VNS/ ta-VNS) will be covered.

1.3 METHODS

1.3.1 ELIGIBILITY CRITERIA

PART 1: The 1st part of this review will be of general character and will aim to give an overview over the role of the ANS and especially the vagus nerve in pathophysiology of IBS and IBS-related abdominal pain.

PART 2: The 2nd part will focus on effects of electrical modification of vagal tone on pain, especially abdominal pain, on the microbiota-gut-brain-axis, on the gastrointestinal tract, and/ or IBS and IBS-related abdominal pain.

Study design: Both quantitative and qualitative studies of any study design will be included.

Participants: Human subjects aged ≥ 18 years of any sex, and any BMI will be included. Both healthy subjects as well as patients with any IBS subtype as diagnosed by a medical doctor according to Manning criteria, Asian criteria or Rome I, II, III or IV will be included. Studies in which participants with IBS were not diagnosed by a physician must meet Rome IV criteria as assessed by the study investigator. In patients with IBS, common comorbidities as intestinal disorders (gastroesophageal reflux dysphagia, esophageal spasms and functional dyspepsia) and/or extra-intestinal disorders (low back pain, fibromyalgia, chronic fatigue, dysmenorrhea and cystitis) alongside IBS will not be a reason of exclusion, while persons with accompanied inflammatory bowel diseases, gastrointestinal tumor, and/ or hemafecia will be excluded. Studies on effects of electrical modulation of the vagal tone on other diseases as epilepsy, depression, migraine, inflammatory bowel disease (IBD) etc. will not be included. Studies investigating effects on pain and pain related mechanisms in patients treated with VNS due to other diseases than IBS will be included, though.

Context: The context elements of the 2nd part of this review are any settings, where the effects of direct electrical modification of vagal tone on pain, especially abdominal pain, on the microbiota-gut-brain-axis, on the gastrointestinal tract, and/ or IBS is investigated.

Electrical modifications of vagal tone in this review is defined as invasive vagus nerve stimulation (iVNS), noninvasive transcutaneous VNS (t-VNS) as well as noninvasive transcutaneous auricular VNS (ta-VNS) of vagal afferents and efferents in all frequencies and any time frame.

1.3.2 INFORMATION SOURCES

Literature will be identified by application of 3-step-search-strategy: In the 1st step, Pubmed (1996 – Januar 2019) will be searched broad, identifying key words and relevant MeSH-terms. In the 2nd step, Pubmed (1996 – Januar 2019), EMBASE (1974 – Januar 2019), and PsycINFO (1806 – Januar 2019) will be searched according to search protocols elaborated with assistance of a librarian. In the 3rd step, reference lists from reviewed articles will be searched to identify further relevant articles and reviews.

1.3.3 SEARCH STRATEGY

Search strategy is applied according to subthemes. Starting with search in Pubmed, medical subject headings (MeSH) as well as text words will be applied according to the medline search strategy protocol (see appendix). Pubmed-search strategy will hereafter be adapted according to the requirements of the other data sources. Search strategy is broad to cover relevant literature for a scoping review. Language will be restricted to English, German and Danish. Embase and PsycInfo will be covered accordingly.

1.3.4 STUDY RECORDS

1.3.4.1 DATA MANAGEMENT

Mendeley will be used to manage literature throughout the review.

1.3.4.2 SELECTION AND DATA COLLECTION (PART 2)

One reviewer will collect data from the selected articles according to screening-, eligibility- and inclusion-criteria defined in this protocol in a 3-step-process: First, potentially eligible records will be identified by title, the different data sources will be combined. Second, remaining literature will be screened by title and abstract, hereafter will duplications be removed. Third, final decision on inclusion will be based on full text screening, reasons for excluding studies will be documented. If necessary, the supervisor becomes involved to make a final decision. No additional information from study authors will be obtained.

main outcome (pain)/ findings, author´s conclusion. Potential conflicts of interest will be documented.

The primary outcome measure is pain and pain-intensity. A reduction of 30% will be evaluated as relevant. Side effects will be documented.

Qualitative studies: Authors, year, country, participants number and setting, methodology, aim of the study, main findings (pain), author´s conclusion. Potential conflicts of interest will be documented.

1.3.6 DATA SYNTHESIS

Information will be presented in a systematic narrative synthesis using text and tables. Outcomes of the different interventions will be categorized according to the suggested subthemes (pain, especially abdominal pain, on the microbiota-gut-brain-axis, on the gastrointestinal tract, and/ or IBS and IBS-related abdominal pain) and/ or IBS-subgroups, when appropriate. Potential relationships and findings within and between the included studies will be covered.

APPENDIX 2, PRISMA-SCR

Table. PRISMA-ScR Checklist

Section	Item	PRISMA-ScR Checklist Item
Title	1	Identify the report as a scoping review.
Abstract		
Structured summary	2	Provide a structured summary that includes (as applicable) background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.
Introduction		
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.
Methods		
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).
Summary measures	13	Not applicable for scoping reviews.
Synthesis of results	14	Describe the methods of handling and summarizing the data that were charted.
Risk of bias across studies	15	Not applicable for scoping reviews.
Additional analyses	16	Not applicable for scoping reviews.
Results		
Selection of sources of evidence	17	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.
Characteristics of sources of evidence	18	For each source of evidence, present characteristics for which data were charted and provide the citations.
Critical appraisal within sources of evidence	19	If done, present data on critical appraisal of included sources of evidence (see item 12).
Results of individual sources of evidence	20	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.
Synthesis of results	21	Summarize and/or present the charting results as they relate to the review questions and objectives.
Risk of bias across studies	22	Not applicable for scoping reviews.
Additional analyses	23	Not applicable for scoping reviews.
Discussion		
Summary of evidence	24	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.
Limitations	25	Discuss the limitations of the scoping review process.
Conclusions	26	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.
Funding	27	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.
* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.
† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).
‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.
§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy documents).

APPENDIX 3, SEARCH PROTOCOL PUBMED

History

Download history Clear history

Search	Add to builder	Query	Items found
#24	Add	Search **((((((((((visceral pain[MeSH Terms]) OR "visceral pain") OR "abdominal pain"[MeSH Terms]) OR "abdominal pain"))) AND ((((((((((((((vagus nerve stimulation[MeSH Terms]) OR "vagus nerve stimulation") OR "vagal nerve stimulation") OR "VNS") OR "transcutaneous vagus nerve stimulation") OR "transcutaneous vagal nerve stimulation") OR "transcutaneous vagal stimulation") OR "transcutaneous vagus stimulation") OR "tVNS") OR "transcutaneous auricular vagus nerve stimulation") OR "transcutaneous auricular vagal nerve stimulation") OR "transcutaneous auricular vagus stimulation") OR "transcutaneous auricular vagal stimulation") OR "taVNS")))) OR ((((((((((((((((vagus nerve stimulation[MeSH Terms]) OR "vagus nerve stimulation") OR "vagal nerve stimulation") OR "VNS") OR "transcutaneous vagus nerve stimulation") OR "transcutaneous vagal nerve stimulation") OR "transcutaneous vagal stimulation") OR "transcutaneous vagus stimulation") OR "tVNS") OR "transcutaneous auricular vagus nerve stimulation") OR "transcutaneous auricular vagal nerve stimulation") OR "transcutaneous auricular vagus stimulation") OR "transcutaneous auricular vagal stimulation") OR "taVNS"))) AND ((((irritable bowel syndrome[MeSH Terms]) OR "irritable bowel syndrome") OR "IBS")))) OR ((((("Pain"[Mesh]) OR "pain")) AND ((((((((((((((vagus nerve stimulation[MeSH Terms]) OR "vagus nerve stimulation") OR "vagal nerve stimulation") OR "VNS") OR "transcutaneous vagus nerve stimulation") OR "transcutaneous vagal nerve stimulation") OR "transcutaneous vagal stimulation") OR "transcutaneous vagus stimulation") OR "tVNS") OR "transcutaneous auricular vagus nerve stimulation") OR "transcutaneous auricular	470

		vagal nerve stimulation") OR "transcutaneous auricular vagus stimulation") OR "transcutaneous auricular vagal stimulation") OR "taVNS")))) OR (((((((("gut brain axis") OR "brain gut axis") OR "microbiome gut brain axis") OR "microbiota gut brain axis")))) AND ((((((((((((((vagus nerve stimulation[MeSH Terms]) OR "vagus nerve stimulation") OR "vagal nerve stimulation") OR "VNS") OR "transcutaneous vagus nerve stimulation") OR "transcutaneous vagal nerve stimulation") OR "transcutaneous vagal stimulation") OR "transcutaneous vagus stimulation") OR "tVNS") OR "transcutaneous auricular vagus nerve stimulation") OR "transcutaneous auricular vagal nerve stimulation") OR "transcutaneous auricular vagus stimulation") OR "transcutaneous auricular vagal stimulation") OR "taVNS")))) OR ((((("gastrointestinal tract") OR "Gastrointestinal Tract"[Mesh])) AND ((((((((((((((vagus nerve stimulation[MeSH Terms]) OR "vagus nerve stimulation") OR "vagal nerve stimulation") OR "VNS") OR "transcutaneous vagus nerve stimulation") OR "transcutaneous vagal nerve stimulation") OR "transcutaneous vagal stimulation") OR "transcutaneous vagus stimulation") OR "tVNS") OR "transcutaneous auricular vagus nerve stimulation") OR "transcutaneous auricular vagal nerve stimulation") OR "transcutaneous auricular vagus stimulation") OR "transcutaneous auricular vagal stimulation") OR "taVNS")))	
#23	Add	Search **(((("gastrointestinal tract") OR "Gastrointestinal Tract"[Mesh])) AND ((((((((((((((vagus nerve stimulation[MeSH Terms]) OR "vagus nerve stimulation") OR "vagal nerve stimulation") OR "VNS") OR "transcutaneous vagus nerve stimulation") OR "transcutaneous vagal nerve stimulation") OR "transcutaneous vagal stimulation") OR "transcutaneous vagus stimulation") OR "tVNS") OR "transcutaneous auricular vagus nerve stimulation") OR "transcutaneous auricular vagal nerve stimulation") OR "transcutaneous auricular vagus stimulation") OR "transcutaneous auricular vagal stimulation") OR "taVNS"))**	170
#22	Add	Search **(((((((("gut brain axis") OR "brain gut axis") OR "microbiome gut brain axis") OR "microbiota gut brain axis")))) AND ((((((((((((((vagus nerve stimulation[MeSH Terms]) OR "vagus nerve stimulation") OR "vagal nerve stimulation") OR "VNS") OR "transcutaneous vagus nerve stimulation") OR "transcutaneous vagal nerve stimulation") OR "transcutaneous vagal stimulation") OR "transcutaneous vagus stimulation") OR "tVNS") OR "transcutaneous auricular vagus nerve stimulation") OR "transcutaneous auricular vagal nerve stimulation") OR "transcutaneous auricular vagus stimulation") OR "transcutaneous auricular vagal stimulation") OR "taVNS"))**	11
#21	Add	Search **(((((("gut brain axis") OR "brain gut axis") OR "microbiome gut brain axis") OR "microbiota gut brain axis"))**	1483
#20	Add	Search **((((((((((((((((vagus nerve stimulation[MeSH Terms]) OR "vagus nerve stimulation") OR "vagal nerve stimulation") OR "VNS") OR "transcutaneous vagus nerve stimulation") OR "transcutaneous vagal nerve stimulation") OR "transcutaneous vagal stimulation") OR "transcutaneous vagus stimulation") OR "tVNS") OR "transcutaneous auricular vagus nerve stimulation") OR "transcutaneous auricular**	11

		vagal nerve stimulation") OR "transcutaneous auricular vagus stimulation") OR "transcutaneous auricular vagal stimulation") OR "taVNS"))) AND (((((("gut brain axis") OR "brain gut axis") OR "microbiome gut brain axis") OR "microbiota gut brain axis"))	
#19	Add	Search **((((((((((((((((vagus nerve stimulation[MeSH Terms]) OR "vagus nerve stimulation") OR "vagal nerve stimulation") OR "VNS") OR "transcutaneous vagus nerve stimulation") OR "transcutaneous vagal nerve stimulation") OR "transcutaneous vagal stimulation") OR "transcutaneous vagus stimulation") OR "tVNS") OR "transcutaneous auricular vagus nerve stimulation") OR "transcutaneous auricular vagal nerve stimulation") OR "transcutaneous auricular vagus stimulation") OR "transcutaneous auricular vagal stimulation") OR "taVNS"))) AND (((((("gut brain axis") OR "brain gut axis") OR "microbiome gut brain axis") OR "microbiota gut brain axis") OR "vagus nerve") OR "nervus vagus"))**	3020
#18	Add	Search **(((("Pain"[Mesh]) OR "pain")) AND ((((((((((((((((vagus nerve stimulation[MeSH Terms]) OR "vagus nerve stimulation") OR "vagal nerve stimulation") OR "VNS") OR "transcutaneous vagus nerve stimulation") OR "transcutaneous vagal nerve stimulation") OR "transcutaneous vagal stimulation") OR "transcutaneous vagus stimulation") OR "tVNS") OR "transcutaneous auricular vagus nerve stimulation") OR "transcutaneous auricular vagal nerve stimulation") OR "transcutaneous auricular vagus stimulation") OR "transcutaneous auricular vagal stimulation") OR "taVNS"))**	301
#17	Add	Search **("Pain"[Mesh]) OR "pain"**	762943
#16	Add	Search **("gastrointestinal tract") OR "Gastrointestinal Tract"[Mesh]**	657298
#15	Add	Search **"gastrointestinal tract"**	74217
#13	Add	Search **"Gastrointestinal Tract"[Mesh]**	619584
#10	Add	Search **((((((("gut brain axis") OR "brain gut axis") OR "microbiome gut brain axis") OR "microbiota gut brain axis") OR "vagus nerve") OR "nervus vagus")**	27072
#9	Add	Search **"pain"**	686903
#8	Add	Search **"Pain"[Mesh]**	368949
#5	Add	Search **((((((((((((((((vagus nerve stimulation[MeSH Terms]) OR "vagus nerve stimulation") OR "vagal nerve stimulation") OR "VNS") OR "transcutaneous vagus nerve stimulation") OR "transcutaneous vagal nerve stimulation") OR "transcutaneous vagal stimulation") OR "transcutaneous vagus stimulation") OR "tVNS") OR "transcutaneous auricular vagus nerve stimulation") OR "transcutaneous auricular vagal nerve stimulation") OR "transcutaneous auricular vagus stimulation") OR "transcutaneous auricular vagal stimulation") OR "taVNS"))) AND ((((irritable bowel syndrome[MeSH Terms]) OR "irritable bowel syndrome") OR "IBS"))**	10
#4	Add	Search **(((irritable bowel syndrome[MeSH Terms]) OR "irritable bowel syndrome") OR "IBS")**	17686
#3	Add	Search **((((((visceral pain[MeSH Terms]) OR "visceral pain") OR "abdominal pain"[MeSH Terms]) OR "abdominal pain"))) AND**	8

		((((((((((((((vagus nerve stimulation[MeSH Terms]) OR "vagus nerve stimulation") OR "vagal nerve stimulation") OR "VNS") OR "transcutaneous vagus nerve stimulation") OR "transcutaneous vagal nerve stimulation") OR "transcutaneous vagal stimulation") OR "transcutaneous vagus stimulation") OR "tVNS") OR "transcutaneous auricular vagus nerve stimulation") OR "transcutaneous auricular vagal nerve stimulation") OR "transcutaneous auricular vagus stimulation") OR "transcutaneous auricular vagal stimulation") OR "taVNS"))	
#2	Add	Search **((((visceral pain[MeSH Terms]) OR "visceral pain") OR "abdominal pain"[MeSH Terms]) OR "abdominal pain")**	68965
#1	Add	Search **((((((((((((((vagus nerve stimulation[MeSH Terms]) OR "vagus nerve stimulation") OR "vagal nerve stimulation") OR "VNS") OR "transcutaneous vagus nerve stimulation") OR "transcutaneous vagal nerve stimulation") OR "transcutaneous vagal stimulation") OR "transcutaneous vagus stimulation") OR "tVNS") OR "transcutaneous auricular vagus nerve stimulation") OR "transcutaneous auricular vagal nerve stimulation") OR "transcutaneous auricular vagus stimulation") OR "transcutaneous auricular vagal stimulation") OR "taVNS")**	3736

APPENDIX 4, SEARCH PROTOCOL PSYCINFO

Subthemes, 1st part:	# OR #
Role of ANS in IBS	**Tema 1(IBS):** https://psycnet-apa-org.zorac.aub.aau.dk/permalink/b34d4618-9cff-aa01-b917-f79cc20f061c
Role of ANS and microbiota gut brain axis in IBS	
Role of ANS and microbiota gut brain axis in abd. pain + IBS	
Role of ANS in abdominal pain	**Tema 2(PAIN):** https://psycnet-apa-org.zorac.aub.aau.dk/permalink/d7cbc160-d174-4546-0b8e-d1b492d08212
Role of ANS and microbiota gut brain axis in abd. pain	
Subthemes, 2nd part:	
Effects of VNS/ tVNS on microbiota gut brain axis	https://psycnet-apa-org.zorac.aub.aau.dk/permalink/7d10468b-1419-4155-2ce3-fa88b0eb0dc8
Effects of VNS/ tVNS on pain	
Effects of VNS/ tVNS on GI-tract	
Effects of VNS/ tVNS on IBS	
Effects of VNS/ tVNS on abd. pain	

REFERENCES

1. Lacy BE, Patel NK. Rome criteria and a diagnostic approach to irritable bowel syndrome. *Journal of clinical medicine*. 2017;6(11):99. https://www.ncbi.nlm.nih.gov/pubmed/29072609. doi: 10.3390/jcm6110099.

2. Lacy BE, Mearin F, Chang L, et al. Bowel disorders. *Gastroenterology*. 2016;150(6):1407.e5. https://www.clinicalkey.es/playcontent/1-s2.0-S0016508516002225. doi: 10.1053/j.gastro.2016.02.031.

3. Ford AC, Forman D, Bailey AG, Axon ATR, Moayyedi P. Irritable bowel syndrome: A 10-yr natural history of symptoms and factors that influence consultation behavior. *The American Journal of Gastroenterology*. 2008;103(5):1229-1239. http://www.ingentaconnect.com/content/bsc/ajg/2008/00000103/00000005/art00025. doi: 10.1111/j.1572-0241.2007.01740.x.

4. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: A meta-analysis. *Clinical gastroenterology and hepatology*. 2012;10(7):721.e4.

5. Drossman DA. Functional gastrointestinal disorders: History, pathophysiology, clinical features and rome IV. *Gastroenterology (New York, N.Y.1943)*. 2016.

6. Clarke G, Quigley EMM, Cryan JF, Dinan TG. Irritable bowel syndrome: Towards biomarker identification. *Trends Mol Med*. 2009;15(10):489.

7. Drossman DA, Camilleri M, Mayer EA, Whitehead WE. AGA technical review on irritable bowel syndrome. *Gastroenterology (New York, N.Y.1943)*. 2002;123(6):2131.

8. Kennedy PJ, Clarke G, Quigley EMM, Groeger JA, Dinan TG, Cryan JF. Gut memories: Towards a cognitive neurobiology of irritable bowel syndrome. *Neuroscience and Biobehavioral Reviews*. 2012;36(1):310-340. https://www.sciencedirect.com/science/article/pii/S0149763411001369. doi: 10.1016/j.neubiorev.2011.07.001.

9. Mulak A, Bonaz B. Irritable bowel syndrome: A model of the brain-gut interactions. *Medical science monitor : international medical journal of experimental and clinical research*. 2004;10(4):RA55. https://www.ncbi.nlm.nih.gov/pubmed/15260348.

10. Maneerattanaporn M, Chang L, Chey WD. Emerging pharmacological therapies for the irritable bowel syndrome. *Gastroenterol Clin North Am*. 2011;40(1):243.

11. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology (New York, N.Y.1943)*. 2006;130(5):1491.

12. M Nørgaard, D K Farkas, L Pedersen, et al. Irritable bowel syndrome and risk of colorectal cancer: A danish nationwide cohort study. *British Journal of Cancer*. 2011;104(7):1202-1206. http://dx.doi.org/10.1038/bjc.2011.65. doi: 10.1038/bjc.2011.65.

13. Chang JY, Locke 3, G Richard, McNally MA, et al. Impact of functional gastrointestinal disorders on survival in the community. *The American Journal of Gastroenterology*. 2010;105(4):822-832. http://dx.doi.org/10.1038/ajg.2010.40. doi: 10.1038/ajg.2010.40.

14. Paré P, Gray J, Lam S, et al. Health-related quality of life, work productivity, and health care resource utilization of subjects with irritable bowel syndrome: Baseline results from logic (longitudinal outcomes study of gastrointestinal symptoms in canada), a naturalistic study. *Clinical Therapeutics*. 2006;28(10):1726-1735. https://www.sciencedirect.com/science/article/pii/S0149291806002505. doi: 10.1016/j.clinthera.2006.10.010.

15. Ford AC, Lacy BE, Talley NJ. Irritable bowel syndrome. *The New England Journal of Medicine*. 2017;376(26):2566-2578. http://dx.doi.org/10.1056/NEJMra1607547. doi: 10.1056/NEJMra1607547.

16. Oświęcimska J, Szymlak A, Roczniak W, Girczys-Połedniok K, Kwiecień J. New insights into the pathogenesis and treatment of irritable bowel syndrome. *Advances in Medical Sciences*. 2017;62(1):17-30. https://www.sciencedirect.com/science/article/pii/S1896112616300372. doi: 10.1016/j.advms.2016.11.001.

17. Frøkjær JB, Bergmann S, Brock C, et al. Modulation of vagal tone enhances gastroduodenal motility and reduces somatic pain sensitivity. *Neurogastroenterology & Motility*. 2016;28(4):592-598. https://onlinelibrary.wiley.com/doi/abs/10.1111/nmo.12760. doi: 10.1111/nmo.12760.

18. Bonaz B, Sinniger V, Pellissier S. Anti-inflammatory properties of the vagus nerve: Potential therapeutic implications of vagus nerve stimulation. *J Physiol (Lond)*. 2016;594(20):5790.

19. Bonaz B, Sinniger V, Pellissier S. The vagus nerve in the neuro-immune axis: Implications in the pathology of the gastrointestinal tract. *Frontiers in immunology*. 2017;8:1452.

20. Spaziani R, Bayati A, Redmond K, et al. Vagal dysfunction in irritable bowel syndrome assessed by rectal distension and baroreceptor sensitivity. *Neurogastroenterology & Motility*. 2008;20(4):336-342. https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1365-2982.2007.01042.x. doi: 10.1111/j.1365-2982.2007.01042.x.

21. Schwille-Kiuntke J, Mazurak N, Enck P. Systematic review with meta-analysis: Post-infectious irritable bowel syndrome after travellers' diarrhoea. *Alimentary Pharmacology & Therapeutics*. 2015;41(11):1029-1037. https://onlinelibrary.wiley.com/doi/abs/10.1111/apt.13199. doi: 10.1111/apt.13199.

22. Chey WY, Jin HO, Lee KY, Lee MH, Sun SW. Colonic motility abnormality in patients with irritable bowel syndrome exhibiting abdominal pain and diarrhea. *The American Journal of Gastroenterology*. 2001;96(5):1499-1506. https://www.sciencedirect.com/science/article/pii/S000292700102367X. doi: 10.1016/S0002-9270(01)02367-X.

23. Camilleri M, Heading RC, Thompson WG. Clinical perspectives, mechanisms, diagnosis and management of irritable bowel syndrome. *Aliment Pharmacol Ther*. 2002;16(8):1430.

24. Dinan T. How the gut influences the brain: The intestinal microbiome as a new dimension for understanding mental health. *European Neuropsychopharmacology*. 2016;26:S24. https://www.clinicalkey.es/playcontent/1-s2.0-S0924977X16700265. doi: 10.1016/S0924-977X(16)70026-5.

25. Camilleri M, Lasch K, Zhou W. Irritable bowel syndrome: Methods, mechanisms, and pathophysiology. the confluence of increased permeability, inflammation, and pain in irritable bowel syndrome. *AJP-Gastrointestinal and Liver Physiology*. 2012;303(7):G785.

26. Camilleri M. Peripheral mechanisms in irritable bowel syndrome. *N Engl J Med*. 2012;367(17):1635.

27. Barbara G, Stanghellini V, De Giorgio R, et al. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. *Gastroenterology (New York, N.Y.1943)*. 2004;126(3):702.

28. Chang L. The role of stress on physiological responses and clinical symptoms in irritable bowel syndrome. *Gastroenterology*. 2011;140(3):761-765.

29. Suarez K, Mayer C, Ehlert U, Nater UM. Psychological stress and self-reported functional gastrointestinal disorders. *Journal of Nervous & Mental Disease*. 2010;198(3):229.

30. Whitehead WE, Palsson OS, Levy RR, Feld AD, Turner M, Von Korff M. Comorbidity in irritable bowel syndrome. *Am J Gastroenterol*. 2007;102(12):2776.

31. Bockus HL, Bank J, Wilkinson SA. Neurogenic mucous colitis *The American Journal of the Medical Sciences*. 1928;176(6):813-829. doi: 10.1097/00000441-192812000-00006.

32. Bharucha AE, Camilleri M, Low PA, Zinsmeister AR. Autonomic dysfunction in gastrointestinal motility disorders. *Gut*. 1993;34(3):397-401. https://www.ncbi.nlm.nih.gov/pubmed/8472990. doi: 10.1136/gut.34.3.397.

33. Aggarwal A, Cutts TF, Abell TL, et al. Predominant symptoms in irritable bowel syndrome correlate with specific autonomic nervous system abnormalities. *Gastroenterology*. 1994;106(4):945-950. https://www.sciencedirect.com/science/article/pii/0016508594907536. doi: 10.1016/0016-5085(94)90753-6.

34. Bonaz B, Bazin T, Pellissier S. The vagus nerve at the interface of the microbiota-gut-brain axis. *Frontiers in neuroscience*. 2018;12:49.

35. Ruffle JK, Coen SJ, Giampietro V, et al. Morphology of subcortical brain nuclei is associated with autonomic function in healthy humans. *Human Brain Mapping*. 2018;39(1):381-392. https://onlinelibrary.wiley.com/doi/abs/10.1002/hbm.23850. doi: 10.1002/hbm.23850.

36. Farmer AD, Coen SJ, Kano M, et al. Normal values and reproducibility of the real-time index of vagal tone in healthy humans: A multi-center study. *Annals of gastroenterology*. 2014;27(4):368.

37. Schlereth T, Birklein F. The sympathetic nervous system and pain. *NeuroMolecular Medicine*. 2008;10(3):147.

38. Tak LM, Riese H, de Bock GH, Manoharan A, Kok IC, Rosmalen JGM. As good as it gets?A meta-analysis and systematic review of methodologicalquality of heart rate variability studies in functional somatic disorders. *Biological Psychology*. 2011;88(2):284-285. https://www.sciencedirect.com/science/article/pii/S0301051111002328. doi: 10.1016/S0301-0511(11)00232-8.

39. Salvioli B, Pellegatta G, Malacarne M, et al. Autonomic nervous system dysregulation in irritable bowel syndrome. *Neurogastroenterology & Motility*. 2015;27(3):423-430. https://onlinelibrary.wiley.com/doi/abs/10.1111/nmo.12512. doi: 10.1111/nmo.12512.

40. Spetalen S, Sandvik L, Blomhoff S, Jacobsen M. Autonomic function at rest and in response to emotional and rectal stimuli in women with irritable bowel syndrome. *Dig Dis Sci*. 2008;53(6):1652-1659. https://www.ncbi.nlm.nih.gov/pubmed/17990112. doi: 10.1007/s10620-007-0066-0.

41. Heitkemper M, Burr R, Jarrett M, Hertig V, Lustyk M, Bond E. Evidence for autonomic nervous system imbalance in women with irritable bowel syndrome. *Dig Dis Sci*. 1998;43(9):2093-2098. https://www.ncbi.nlm.nih.gov/pubmed/9753278. doi: 1018871617483.

42. Orr WC, Elsenbruch S, Harnish MJ. Autonomic regulation of cardiac function during sleep in patients with irritable bowel syndrome. *The American Journal of Gastroenterology*. 2000;95(10):2865-2871. https://www.sciencedirect.com/science/article/pii/S0002927000011102. doi: 10.1016/S0002-9270(00)01110-2.

43. Karling P, Nyhlin H, Wiklund U, Sjöberg M, Olofsson BO, Bjerle P. Spectral analysis of heart rate variability in patients with irritable bowel syndrome. *Scandinavian Journal of Gastroenterology*. 1998;33(6):572-576.

44. Heitkemper M, Jarrett M, Cain K, et al. Increased urine catecholamines and cortisol in women with irritable bowel syndrome. *Am J Gastroenterol*. 1996;91(5):913.

45. Tousignant-Laflamme Y, Goffaux P, Bourgault P, Marchand S. Different autonomic responses to experimental pain in IBS patients and healthy controls. *Journal of Clinical Gastroenterology*. 2006;40(9):814-820. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=n&CSC=Y&PAGE=fulltext&D=ovft&AN=00004836-200610000-00010. doi: 10.1097/01.mcg.0000225607.56352.ce.

46. Adeyemi EOA, Desai KD, Towsey M, Ghista D. Characterization of autonomic dysfunction in patients with irritable bowel syndrome by means of heart rate variability studies. *The American Journal of Gastroenterology*. 1999;94(3):816-823. https://www.sciencedirect.com/science/article/pii/S0002927098007424. doi: 10.1016/S0002-9270(98)00742-4.

47. van Orshoven NP, Aniesse GI, van Schelven LJ, Smout AJ, Akkermans LMA, Oey PL. Subtle involvement of the parasympathetic nervous system in patients with irritable bowel syndrome. *Clin Auton Res*. 2006;16(1):33-39. https://www.narcis.nl/publication/RecordID/oai:pure.amc.nl:publications%2F192b8070-8243-4989-80fc-1ced2de3f3f0. doi: 10.1007/s10286-006-0307-x.

48. Waring W, Chui M, Japp A, Nicol E, Ford M. Autonomic cardiovascular responses are impaired in women with irritable bowel syndrome. *Journal of Clinical Gastroenterology*. 2004;38(8):658-663. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=n&CSC=Y&PAGE=fulltext&D=ovft&AN=00004836-200409000-00007. doi: 10.1097/01.mcg.0000135362.35665.49.

49. Punyabati O, Deepak KK, Sharma MP, Dwivedi SN. Autonomic nervous system reactivity in irritable bowel syndrome. *Indian journal of gastroenterology : official journal of the Indian Society of Gastroenterology*. 2000;19(3):122. https://www.ncbi.nlm.nih.gov/pubmed/10918719.

50. Tillisch K, Mayer EA, Labus JS, Stains J, Chang L, Naliboff BD. Sex specific alterations in autonomic function among patients with irritable bowel syndrome. *Gut*. 2005;54(10):1401.

51. Lee C, Chuang T, Lu C, Chen C, Chang F, Lee S. Abnormal vagal cholinergic function and psychological behaviors in irritable bowel syndrome patients A hospital-based oriental study. *Dig Dis Sci*. 1998;43(8):1794-1799. https://www.ncbi.nlm.nih.gov/pubmed/9724171. doi: 1018848122993.

52. Elsenbruch S, Orr WC. Diarrhea- and constipation-predominant IBS patients differ in postprandial autonomic and cortisol responses. *Am J Gastroenterol*. 2001;96(2):466.

53. Robert J, Elsenbruch S, C. Orr W. Sleep-related autonomic disturbances in symptom subgroups of women with irritable bowel syndrome. *Dig Dis Sci*. 2006;51(12):2121-2127. https://www.ncbi.nlm.nih.gov/pubmed/17080247. doi: 10.1007/s10620-006-9305-z.

54. Yuan H, Silberstein SD. Vagus nerve and vagus nerve stimulation, a comprehensive review: Part I. *Headache: The Journal of Head and Face Pain*. 2016;56(1):71-78. https://onlinelibrary.wiley.com/doi/abs/10.1111/head.12647. doi: 10.1111/head.12647.

55. Chakravarthy K, Chaudhry H, Williams K, Christo P. Review of the uses of vagal nerve stimulation in chronic pain management. *Curr Pain Headache Rep*. 2015;19(12):1-9. https://www.ncbi.nlm.nih.gov/pubmed/26493698. doi: 10.1007/s11916-015-0528-6.

56. Berthoud HR, Neuhuber WL. Functional and chemical anatomy of the afferent vagal system. *Autonomic neuroscience*. 2000;85(1-3):17.

57. Botha C, Farmer AD, Nilsson M, et al. Preliminary report: Modulation of parasympathetic nervous system tone influences oesophageal pain hypersensitivity. *Gut*. 2015;64(4):617.

58. Yuan H, Silberstein SD. Vagus nerve and vagus nerve stimulation, a comprehensive review: Part III. *Headache: The Journal of Head and Face Pain*. 2016;56(3):479-490. https://onlinelibrary.wiley.com/doi/abs/10.1111/head.12649. doi: 10.1111/head.12649.

59. Yuan H, Silberstein SD. Vagus nerve and vagus nerve stimulation, a comprehensive review: Part II. *Headache: The Journal of Head and Face Pain*. 2016;56(2):259-266. https://onlinelibrary.wiley.com/doi/abs/10.1111/head.12650. doi: 10.1111/head.12650.

60. Frangos E, Richards EA, Bushnell MC. Do the psychological effects of vagus nerve stimulation partially mediate vagal pain modulation? *Neurobiology of Pain*. 2017;1:45.

61. Rutecki P. Anatomical, physiological, and theoretical basis for the antiepileptic effect of vagus nerve stimulation. *Epilepsia*. 1990;31 Suppl 2(s2):S6. https://www.ncbi.nlm.nih.gov/pubmed/2226360. doi: 10.1111/j.1528-1157.1990.tb05843.x.

62. Krahl SE. Vagus nerve stimulation for epilepsy: A review of the peripheral mechanisms. *Surgical Neurology International*. 2012;3(Suppl 1):S52.

63. YAMAMOTO T. Vagus nerve stimulation therapy: Indications, programing, and outcomes. *Neurologia medico-chirurgica*. 2015;55(5):407-415. https://jlc.jst.go.jp/DN/JLC/20010482306?from=SUMMON. doi: 10.2176/nmc.ra.2014-0405.

64. Bonaz B, Sinniger V, Hoffmann D, et al. Chronic vagus nerve stimulation in crohn's disease: A 6-month follow-up pilot study. *Neurogastroenterology & Motility*. 2016;28(6):948-953. https://onlinelibrary.wiley.com/doi/abs/10.1111/nmo.12792. doi: 10.1111/nmo.12792.

65. Levine YA, Koopman F, Faltys M, Zitnik R, Tak P. Neurostimulation of the cholinergic antiinflammatory pathway in rheumatoid arthritis and inflammatory bowel disease. *Bioelectronic Medicine*. 2014;1(1):34-43. doi: 10.15424/bioelectronmed.2014.00008.

66. Howland RH. Vagus nerve stimulation. *Current Behavioral Neuroscience Reports*. 2014;1(2):73.

67. Beekwilder JP, Beems T. Overview of the clinical applications of vagus nerve stimulation. *Journal of clinical neurophysiology*. 2010;27(2):138.

68. Kumaria A, Tolias CM. Is there a role for vagus nerve stimulation therapy as a treatment of traumatic brain injury? *Br J Neurosurg*. 2012;26(3):320.

69. Lange G, Janal MN, Maniker A, et al. Safety and efficacy of vagus nerve stimulation in fibromyalgia: A phase I/II proof of concept trial. *Pain Medicine*. 2011;12(9):1406-1413. https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1526-4637.2011.01203.x. doi: 10.1111/j.1526-4637.2011.01203.x.

70. Paulon E, Nastou D, Jaboli F, Marin J, Liebler E, Epstein O. Proof of concept: Short-term non-invasive cervical vagus nerve stimulation in patients with drug-refractory gastroparesis. *Frontline Gastroenterology*. 2017;8(4):330.

71. Kamath MV, Thomson MS, Gaitonde S, Upton A. Longer-term effects of implanted vagal nerve stimulation. *J Long Term Eff Med*. 2010;20(3):267.

72. Huang F, Dong J, Kong J, et al. Effect of transcutaneous auricular vagus nerve stimulation on impaired glucose tolerance: A pilot randomized study. *BMC Complementary and Alternative Medicine*. 2014;14:203.

73. Miner JR, Lewis LM, Mosnaim GS, Varon J, Theodoro D, Hoffmann TJ. Feasibility of percutaneous vagus nerve stimulation for the treatment of acute asthma exacerbations. *Acad Emerg Med*. 2012;19(4):429.

74. Yuan H, Silberstein SD. Vagus nerve stimulation and headache. *Headache: The Journal of Head and Face Pain*. 2017;57(S1):29-33. https://onlinelibrary.wiley.com/doi/abs/10.1111/head.12721. doi: 10.1111/head.12721.

75. Wilson A, Longstreth GF, Knight K, et al. Quality of life in managed care patients with irritable bowel syndrome. *Manag Care Interface*. 2004;17(2):28+34.

76. Spiegel BMR, Gralnek IM, Bolus R, et al. Clinical determinants of health-related quality of life in patients with irritable bowel syndrome. *Archives of Internal Medicine (1960)*. 2004;164(16):1780.

77. El-Salhy M, Gundersen D, Gilja OH, Hatlebakk JG, Hausken T. Is irritable bowel syndrome an organic disorder? *World J Gastroenterol.* 2014;20(2):384-400. http://lib.cqvip.com/qk/84123X/201402/90888889504849524850484853.html. doi: 10.3748/wjg.v20.i2.384.

78. Pellissier S, Bonaz B. The place of stress and emotions in the irritable bowel syndrome. *Vitamins and hormones*. 2017;103:327-354. https://www.ncbi.nlm.nih.gov/pubmed/28061975. doi: 10.1016/bs.vh.2016.09.005.

79. Yunus MB. Role of central sensitization in symptoms beyond muscle pain, and the evaluation of a patient with widespread pain. *Baillière's best practice & research.Clinical rheumatology*. 2007;21(3):497.

80. Bonaz B. Abnormal brain microstructure in patients with chronic pancreatitis. *Gut*. 2011;60(11):1446.

81. Chang F. Irritable bowel syndrome:The evolution of multi-dimensional looking and multidisciplinary treatments. *World J Gastroenterol.* 2014;20(10):2499-2514. http://lib.cqvip.com/qk/84123X/201410/90888889504849524948484857.html. doi: 10.3748/wjg.v20.i10.2499.

82. Weltens N, Iven J, Van Oudenhove L, Kano M. The gut-brain axis in health neuroscience: Implications for functional gastrointestinal disorders and appetite regulation. *Ann N Y Acad Sci*. 2018;1428(1):150.

83. Mayer EA, Tillisch K. The brain-gut axis in abdominal pain syndromes. *Annual Review of Medicine*. 2011;62(1):381-396. https://www.ncbi.nlm.nih.gov/pubmed/21090962. doi: 10.1146/annurev-med-012309-103958.

84. Pellissier S, Dantzer C, Canini F, Mathieu N, Bonaz B. Psychological adjustment and autonomic disturbances in inflammatory bowel diseases and irritable bowel syndrome. *Psychoneuroendocrinology*. 2010;35(5):653-62. http://www.hal.inserm.fr/inserm-00528271. doi: 10.1016/j.psyneuen.2009.10.004.

85. Kirchner A, Birklein F, Stefan H, Handwerker HO. Vagusstimulation - eine behandlungsoption für chronische schmerzen? *Der Schmerz*. 2001;15(4):272-277. doi: 10.1007/s004820100067.

86. Napadow V, Edwards RR, Cahalan CM, et al. Evoked pain analgesia in chronic pelvic pain patients using Respiratory-Gated auricular vagal afferent nerve stimulation. *Pain Medicine*. 2012;13(6):777-789. https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1526-4637.2012.01385.x. doi: 10.1111/j.1526-4637.2012.01385.x.

87. Randich A, Gebhart GF. Vagal afferent modulation of nociception. *Brain Res Rev*. 1992;17(2):99.

88. Sadler RM, Purdy RA, Rahey S. Vagal nerve stimulation aborts migraine in patient with intractable epilepsy. *Cephalalgia*. 2002;22(6):482-484. http://www.ingentaconnect.com/content/bsc/cha/2002/00000022/00000006/art00011. doi: 10.1046/j.1468-2982.2002.00387.x.

89. Hord ED, Evans MS, Mueed S, Adamolekun B, Naritoku DK. The effect of vagus nerve stimulation on migraines. *Journal of Pain*. 2003;4(9):530-534. https://www.sciencedirect.com/science/article/pii/S1526590003008095. doi: 10.1016/j.jpain.2003.08.001.

90. Borckardt JJ, Anderson B, Andrew Kozel F, et al. Acute and long-term VNS effects on pain perception in a case of treatment-resistant depression. *Neurocase*. 2006;12(4):216-220. http://www.tandfonline.com/doi/abs/10.1080/13554790600788094. doi: 10.1080/13554790600788094.

91. Lenaerts ME, Oommen KJ, Couch JR, Skaggs V. Can vagus nerve stimulation help migraine? *Cephalalgia*. 2008;28(4):392-395. http://www.ingentaconnect.com/content/bsc/cha/2008/00000028/00000004/art00012. doi: 10.1111/j.1468-2982.2008.01538.x.

92. Franzini A, Messina G, Leone M, Cecchini A, Broggi G, Bussone G. Feasibility of simultaneous vagal nerve and deep brain stimulation in chronic cluster headache: Case report and considerations. *Neurol Sci*. 2009;30(S1):137-139. https://www.ncbi.nlm.nih.gov/pubmed/19415445. doi: 10.1007/s10072-009-0076-0.

93. Proietti Cecchini A, Mea E, Tullo V, et al. Vagus nerve stimulation in drug-resistant daily chronic migraine with depression: Preliminary data. *Neurol Sci*. 2009;30(S1):101-104. https://www.ncbi.nlm.nih.gov/pubmed/19415436. doi: 10.1007/s10072-009-0073-3.

94. Chalaye P, Goffaux P, Bourgault P, et al. Comparing pain modulation and autonomic responses in fibromyalgia and irritable bowel syndrome patients. *The Clinical Journal oF Pain*. 2012;28(6):519-526. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=n&CSC=Y&PAGE=fulltext&D=ovft&AN=00002508-201207000-00009. doi: 10.1097/AJP.0b013e31823ae69e.

95. Gaul C, Magis D, Liebler E, Straube A. Effects of non-invasive vagus nerve stimulation on attack frequency over time and expanded response rates in patients with chronic cluster headache: A post hoc analysis of the randomised, controlled PREVA study. *J Headache Pain*. 2017;18(1):1-7. https://www.ncbi.nlm.nih.gov/pubmed/28197844. doi: 10.1186/s10194-017-0731-4.

96. Trimboli M, Al-Kaisy A, Andreou AP, Murphy M, Lambru G. Non-invasive vagus nerve stimulation for the management of refractory primary chronic headaches: A real-world experience. *Cephalalgia : an international journal of headache*. 2018;38(7):1276-1285. https://www.ncbi.nlm.nih.gov/pubmed/28899205. doi: 10.1177/0333102417731349.

97. Schenker E. Trigeminal and occipital neuromodulation for rapid pain reduction in occipital migraines. *Brain Stimulation*. 2019;12(2):e66. https://www.sciencedirect.com/science/article/pii/S1935861X18305941. doi: 10.1016/j.brs.2018.12.176.

98. Juel J, Brock C, Olesen SS, et al. Acute physiological and electrical accentuation of vagal tone has no effect on pain or gastrointestinal motility in chronic pancreatitis. *Journal of pain research*. 2017;10:1347-1355. https://www.ncbi.nlm.nih.gov/pubmed/28615966. doi: 10.2147/JPR.S133438.

99. Silberstein S, Calhoun A, Lipton R, et al. Chronic migraine headache prevention with noninvasive vagus nerve stimulation: The EVENT study. *Neurology*. 2016;87(5):529-538. https://www.ncbi.nlm.nih.gov/pubmed/27412146. doi: 10.1212/WNL.0000000000002918.

100. Silberstein S, Da Silva AN, Calhoun AH, et al. Non-invasive vagus nerve stimulation for chronic migraine prevention in a prospective, randomized, sham-controlled pilot study (the event study): Report from the doubleblind phase. *Headache*. 2014;54(8):1426.

101. De Coo IF, Marin J, Silberstein SD, et al. Non-invasive vagus nerve stimulation for acute treatment of episodic and chronic cluster headache: Pooled analysis of data from two randomised, double-blind, sham-controlled clinical trials. *Cephalalgia*. 2017;37(1):175-176.

102. Révész D, Rydenhag B, Ben-Menachem E. Complications and safety of vagus nerve stimulation: 25 years of experience at a single center. *Journal of neurosurgery. Pediatrics*. 2016;18(1):97-104. https://www.ncbi.nlm.nih.gov/pubmed/27015521. doi: 10.3171/2016.1.PEDS15534.

103. Ben-Menachem E, Revesz D, Simon BJ, Silberstein S. Surgically implanted and non-invasive vagus nerve stimulation: A review of efficacy, safety and tolerability. *European Journal of Neurology*. 2015;22(9):1268.

104. Johnson RL, Wilson CG. A review of vagus nerve stimulation as a therapeutic intervention. *Journal of Inflammation Research*. 2018;11:213.

105. Asconapé JJ, Moore DD, Zipes DP, Hartman LM, Duffell WH. Bradycardia and asystole with the use of vagus nerve stimulation for the treatment of epilepsy: A rare complication of intraoperative device testing. *Epilepsia*. 1999;40(10):1454.

106. Iriarte J, Urrestarazu E, Alegre M, et al. Late-onset periodic asystolia during vagus nerve stimulation. *Epilepsia*. 2009;50(4):932.

107. Rong P, Liu J, Wang L, et al. Effect of transcutaneous auricular vagus nerve stimulation on major depressive disorder: A nonrandomized controlled pilot study. *J Affect Disord*. 2016;195:179.

108. Liu J, Fang J, Wang Z, et al. Transcutaneous vagus nerve stimulation modulates amygdala functional connectivity in patients with depression. *J Affect Disord*. 2016;205:326.

109. Bauer S, Baier H, Baumgartner C, et al. Transcutaneous vagus nerve stimulation (tVNS) for treatment of drug-resistant epilepsy: A randomized, double-blind clinical trial (cMPsE02). *Brain Stimulation*. 2016;9(3):363.

110. Aihua L, Lu S, Liping L, Xiuru W, Hua L, Yuping W. A controlled trial of transcutaneous vagus nerve stimulation for the treatment of pharmacoresistant epilepsy. *Epilepsy & behavior*. 2014;39:110.

111. Hein E, Nowak M, Kiess O, et al. Auricular transcutaneous electrical nerve stimulation in depressed patients: A randomized controlled pilot study. *J Neural Transm*. 2013;120(5):827.

112. Stefan H, Kreiselmeyer G, Kerling F, et al. Transcutaneous vagus nerve stimulation (t-VNS) in pharmacoresistant epilepsies: A proof of concept trial. *Epilepsia*. 2012;53(7):e118.

113. Camilleri M, Ford AC. Irritable bowel syndrome: Pathophysiology and current therapeutic approaches. *Handbook of experimental pharmacology*. 2017;239:75. https://www.ncbi.nlm.nih.gov/pubmed/27995391.

114. Törnblom H, Drossman DA. Centrally targeted pharmacotherapy for chronic abdominal pain: Understanding and management. *Handbook of experimental pharmacology*. 2017;239:417. https://www.ncbi.nlm.nih.gov/pubmed/28204956. doi: 10.1007/164_2016_106.

115. Tricco AC, Lillie E, Zarin W, et al. PRISMA extension for scoping reviews (PRISMA-ScR): Checklist and explanation. *Annals of internal medicine*. 2018;169(7):467. https://www.ncbi.nlm.nih.gov/pubmed/30178033. doi: 10.7326/M18-0850.

116. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: Elaboration and explanation. *BMJ : British Medical Journal*. 2015;349(jan02 1):g7647. http://dx.doi.org/10.1136/bmj.g7647. doi: 10.1136/bmj.g7647.

117. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic reviews*. 2015;4(1):1. https://www.ncbi.nlm.nih.gov/pubmed/25554246. doi: 10.1186/2046-4053-4-1.

118. Farmer AD, Amersinghe G, Brock C, Drewes C, Drewes AM, Aziz Q. Electrical vagal nerve stimulation prevents the development of acid induced esophageal hyperalgesia. *Neurogastroenterology and Motility*. 2016;28:48.

119. Kirchner A, Birklein F, Stefan H, Handwerker HO. Left vagus nerve stimulation suppresses experimentally induced pain. *Neurology*. 2000;55(8):1167-1171. https://www.ncbi.nlm.nih.gov/pubmed/11071495. doi: 10.1212/WNL.55.8.1167.

120. Kirchner A, Stefan H, Bastian K, Birklein F. Vagus nerve stimulation suppresses pain but has limited effects on neurogenic inflammation in humans. *European Journal of Pain*. 2006;10(5):449-455. https://www.sciencedirect.com/science/article/pii/S1090380105000819. doi: 10.1016/j.ejpain.2005.06.005.

121. Jeffrey J Borckardt, F Andrew Kozel, Berry Anderson, Angela Walker, Mark S George. Vagus nerve stimulation affects pain perception in depressed adults. *Pain research & management*. 2005;10(1):9-14. http://dx.doi.org/10.1155/2005/256472. doi: 10.1155/2005/256472.

122. Ness TJ, Fillingim RB, Randich A, Backensto EM, Faught E. Low intensity vagal nerve stimulation lowers human thermal pain thresholds. *Pain*. 2000;86(1):81-85. https://www.sciencedirect.com/science/article/pii/S0304395900002372. doi: 10.1016/S0304-3959(00)00237-2.

123. Usichenko T, Laqua R, Leutzow B, Lotze M. Preliminary findings of cerebral responses on transcutaneous vagal nerve stimulation on experimental heat pain. *Brain imaging and behavior*. 2017;11(1):30-37. https://www.ncbi.nlm.nih.gov/pubmed/26781484. doi: 10.1007/s11682-015-9502-5.

124. Busch V, Zeman F, Heckel A, Menne F, Ullrich F, Eichhammer P. The effect of transcutaneous vagus nerve stimulation on pain perception – an experimental study. *Brain Stimulation*. 2013;6(2):202-209. https://www.clinicalkey.es/playcontent/1-s2.0-S1935861X12000708. doi: 10.1016/j.brs.2012.04.006.

125. Englot D, Rolston J, Wright C, Hassnain K, Chang E. Rates and predictors of seizure freedom with vagus nerve stimulation for intractable epilepsy. *Neurosurgery*. 2016;79(3):345-353. https://www.ncbi.nlm.nih.gov/pubmed/26645965. doi: 10.1227/NEU.0000000000001165.

126. Panebianco M, Rigby A, Weston J, Marson AG. Vagus nerve stimulation for partial seizures. *The Cochrane database of systematic reviews*. 2015(4):CD002896. https://www.ncbi.nlm.nih.gov/pubmed/25835947. doi: 10.1002/14651858.CD002896.pub2.

127. Kawai K, Tanaka T, Baba H, et al. Outcome of vagus nerve stimulation for drug-resistant epilepsy: The first three years of a prospective japanese registry. *Epileptic Disorders*. 2017;19(3):327-338. https://onlinelibrary.wiley.com/doi/abs/10.1684/epd.2017.0929. doi: 10.1684/epd.2017.0929.

128. Carreno F, Frazer A. Vagal nerve stimulation for treatment-resistant depression. *Neurotherapeutics*. 2017;14(3):716-727. https://www.ncbi.nlm.nih.gov/pubmed/28585221. doi: 10.1007/s13311-017-0537-8.

129. Aaronson ST, Conway CR. Vagus nerve stimulation: Changing the paradigm for chronic severe depression? *The Psychiatric clinics of North America*. 2018;41(3):409. https://www.ncbi.nlm.nih.gov/pubmed/30098654.

130. Conway C, Xiong W. The mechanism of action of vagus nerve stimulation in treatment-resistant depression. *Psychiatric Clinics of North America*. 2018;41(3):395-407. https://www.clinicalkey.es/playcontent/1-s2.0-S0193953X18311018. doi: 10.1016/j.psc.2018.04.005.

131. Ren K, Randich A, Gebhart GF. Spinal serotonergic and kappa opioid receptors mediate facilitation of the tail flick reflex produced by vagal afferent stimulation. *Pain*. 1991;45(3):321-329. https://www.sciencedirect.com/science/article/pii/0304395991900575. doi: 10.1016/0304-3959(91)90057-5.

132. Ren K, Randich A, Gebhart GF. Vagal afferent modulation of a nociceptive reflex in rats: Involvement of spinal opioid and monoamine receptors. *Brain Research*. 1988;446(2):285-294. https://www.sciencedirect.com/science/article/pii/0006899388908876. doi: 10.1016/0006-8993(88)90887-6.

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