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ORIGINAL ARTICLE

The effectiveness of vagus nerve stimulation in rheumatoid arthritis: a systematic review

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Abstract

Objective: *This review aims to assess the effectiveness of vagus nerve stimulation (VNS) in relieving RA symptoms.* **Methods***: A systematic review was performed in seven databases to identify randomized clinical trials that investigated the use of VNS on the symptom improvement of adults with RA. The review adhered to PRISMA guidelines and assessed bias risk using the RoB 2.0 Tool.* **Results***: A total of 1131 documents were identified, but only four were included. It was found no significant difference between active and sham stimulation in ACR20 response rates at week 12 (25.0% vs. 26.9%, p = 0.823), with similar results for Disease Activity Score 28 with C-reactive protein (DAS28-CRP) and HAQ-DI. However, high-disease activity participants showed significant reductions in DAS28-CRP, CRP levels, and interferon-y with non-invasive VNS (n-VNS), whereas low-disease activity participants did not benefit and experienced a decrease in cardiac vagal tone and interleukin-10 levels. Overall, n-VNS was well tolerated. VNS with a small neurostimulator was safe and effective in alleviating RA symptoms in drug-resistant patients. Two patients experienced significant improvements in various measures between the screening visit and day 42, but after device deactivation, they experienced worsened DAS28 and VAS pain scores.* **Conclusions:** *VNS was well-tolerated and yielded favorable results, indicating its potential as a viable treatment option. Its efficacy in treatment-resistant RA patients offers promising prospects.*

Keywords: *Rheumatoid arthritis. Vagus nerve stimulation. Treatment outcome.*

La eficacia de la estimulación del nervio vago en artritis reumatoide: una revisión sistemática

Resumen

Objetivo: *Esta revisión tiene como objetivo evaluar la eficacia de la estimulación del nervio vago (ENV) para aliviar los síntomas de la AR.* **Métodos:** *Se realizó una revisión sistemática en siete bases de datos para identificar ensayos clínicos aleatorizados. que investigaran el uso de la ENV en la mejora de los síntomas de los adultos con AR. La revisión se adhirió a las pautas PRISMA y evaluó el riesgo de sesgo utilizando la herramienta RoB 2.0.* **Resultados:** *Se identificaron un total de 1131 documentos, pero solo se incluyeron 4. No se encontró ninguna diferencia significativa entre la estimulación activa y simulada en las tasas de respuesta ACR20 en la semana 12 (25,0% frente a 26,9%, p = 0,823), con resultados similares para DAS28-CRP y HAQ-DI. Sin embargo, los participantes con alta actividad de la enfermedad mostraron reducciones significativas en DAS28-CRP, niveles de CRP e interferón-y con estimulación no invasiva del nervio vago (n-VNS), mientras*

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que los participantes con baja actividad de la enfermedad no se beneficiaron y experimentaron una disminución en el tono vagal cardíaco y los niveles de interleucina-10. En general, la n-VNS fue bien tolerada. La VNS con un pequeño neuroestimulador fue segura y efectiva para aliviar los síntomas de AR en pacientes resistentes a los medicamentos. Dos pacientes experimentaron mejoras significativas en varias medidas entre la visita de selección y el día 42, pero después de la desactivación del dispositivo, experimentaron un empeoramiento de las puntuaciones de dolor DAS28 y VAS. **Conclusiones:** *La VNS fue bien tolerada y arrojó resultados favorables, lo que indica su potencial como una opción de tratamiento viable. Su eficacia en pacientes con AR resistente al tratamiento ofrece perspectivas prometedoras.*

Palabras clave: *Artritis reumatoide. Estimulación del nervio vago. Resultado del tratamiento.*

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease that causes joint inflammation, pain, stiffness, and deformities. RA involves chronic synovial inflammation, joint erosion, and physical abnormalities[1]. While current treatments have improved RA management, there is a need for more effective therapies. Despite progress in current treatments, some patients face challenges in treatment response, and disease progression can occur[2,3].

Research on the autonomic nervous system, specifically on the autonomic portion of the vagus nerve, shows promise for innovative treatments. The vagus nerve regulates immune and inflammatory responses. Studies using advanced neuroimaging confirm its potential in modulating these responses, especially in autoimmune diseases such as RA[4-6]. The "vagus nerve-brain-immunity axis" plays a vital role in immune regulation. Experimental studies demonstrate that vagus nerve stimulation (VNS) can reduce pro-inflammatory cytokines while increasing anti-inflammatory ones[7,8].

Recent research suggests a potential link between vagus nerve dysfunction and RA development[9]. Insufficient activation of the vagus nerve may lead to imbalanced immune responses, perpetuating chronic joint inflammation. Pre-clinical studies on animal models of RA have shown that VNS can reduce synovial inflammation and limit joint damage, providing encouraging evidence of its effectiveness[4]. This review aims to consolidate scientific evidence on the effectiveness of VNS in the treatment of people with RA.

Materials and methods

Protocol and registration

This systematic review strictly followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered on the International Prospective Register of Systematic Reviews (PROSPERO) database under registration number CRD42023452467.

Eligibility criteria

The study employed the PICOTS strategy: population (adults older than 18 years old diagnosed with RA according to the American College of Rheumatology and/or European League Against Rheumatism [EULAR]), intervention (electrical stimulation of the vagus nerve), comparison (other interventions), outcome (improvement in clinical symptoms), publication period (no specific limitation), and study design (randomized clinical trials).

Studies exclusively involving human subjects were included, without restrictions on publication date, country of publication, or language. Duplicates were removed, and the authenticity of the information was verified.

Studies with missing or incomplete data, scientific papers presented at conferences, letters, conference abstracts, expert opinions, case reports, studies involving patients with other forms of arthritis (e.g., psoriatic arthritis and juvenile idiopathic arthritis), stimulation of the vagus nerve associated with another intervention studies involving animals and studies that stimulate the vagus nerve in a non-electrical way were excluded.

Search strategy and selection process

An extensive exploration was undertaken across various databases, including PubMed, Scopus, Cochrane Central, SciELO, Web of Science, Science Direct, and Google Scholar (see Table S1 in supplementary material). Key terms included: Rheumatoid Arthritis and Vagus Nerve Stimulation. The search covered data until July 2023, with PubMed encompassing records from 1947, Scopus from 1960, Cochrane Central from 1992, SciELO from 1998, Science Direct from 1997, and Google Scholar from 2004.

After the removal of duplicates, these articles were rigorously screened on the Rayyan platform by two independent evaluators (DD and VB) based on titles and abstracts. A third researcher (JF) resolved any conflicts. Population characteristics, eligibility criteria, intervention protocol, and results of individual studies were extracted by a single reviewer (DD) and cross-checked with the assistance of two additional reviewers (VB and JF). All data were recorded in a table adapted from the Cochrane Consumers and Communication Review Group data collection handbook[10].

Risk of bias assessment

The risk of bias was assessed using the Cochrane Risk of Bias (RoB 2) tool for randomized clinical trials, categorizing the risk into five domains of bias as high, uncertain, or low. Two investigators (DD and VM) independently evaluated the risk of bias in each trial included with the updated RoB tool version 2. Any discrepancies were resolved by discussion and intervention of a third reviewer (JF) whenever necessary. Following the methodological quality appraisal of each study, the Kappa coefficient of inter-rater reliability was calculated (IBM SPSS Statistics) (IBM, 2021). Values range from near perfect, 0.81-1.00, substantial, 0.61-0.80, moderate, 0.41-0.60, fair, 0.21-0.40, and slight 0.0-0.2[11].

Ethical approval

As a secondary study of systematic reviews, formal ethics committee approval, and informed consent were unnecessary.

Data synthesis and analysis

The data were meticulously organized in a Google spreadsheet. Study comparisons between intervention and control groups utilizing mean differences and standard deviation were grouped according to outcomes. A meta-analysis was not attempted due to the heterogeneity of the study protocols.

Certainty of evidence

The certainty of evidence for individual results was assessed through the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) approach[12]. Certainty of evidence ratings was conducted independently by two authors (DD and VB), with disagreements resolved through discussion with a third author (JF). Certainty of evidence across results was graded high, medium, low, or very low certainty Grading of Recommendation Assessment, Development, and Evaluation (GRADE) approach[12]. Due to all included studies being randomized controlled trials, each outcome began with a high certainty rating. Studies were downgraded for the following reasons: (1) risk of bias or limitations in the detailed design and implementation, (2) unexplained heterogeneity or inconsistency of results, (3) indirectness of evidence, (4) imprecision of results, (5) high probability of publication bias.

Results

Study selection

Initially, 1,131 documents were identified in our database searches and after removing duplicates, 950 articles remained. After analyzing the title and summary of these records, 20 documents were searched for retrieval and subsequently screened by reading and studying the full text. Conflicts between the two reviewers (DD and VB) were resolved by consensus with a third reviewer (JF), and four articles met the inclusion criteria for qualitative synthesis[8,13-16]. The exclusions that occurred in the full-text screening were justified in a PRISMA flowchart together with the complete screening and selection process (Fig. 1).

Study characteristics (Table 1 and Table S2)

The included articles, dated from 2016 to 2023, were conducted in Denmark, Croatia, and the United States, involving 165 participants, 136 women, and 29 men. The average age ranged between 49.3 and 56.22; however, the Danish study did not specify the age of the patients included in the study[14] (Table 1). Among the four articles included, two did not have a control group. Once the intervention was carried out on all research participants, the evaluation of the effectiveness of the intervention was carried out by comparing parameters before and after stimulation of the vagus nerve. All participants in the included studies[8,13,14,15] were adults and diagnosed with RA. The full outlined eligibility criteria for studies are reported in table S2 (see Table S2 in supplementary material). Various types of vagal stimulation were used, including auricular transcutaneous stimulation[13], miniaturized cervical devices[8,15], and subcutaneous pulse generators[14]. These interventions were applied over periods ranging from 5 days to 12 weeks.

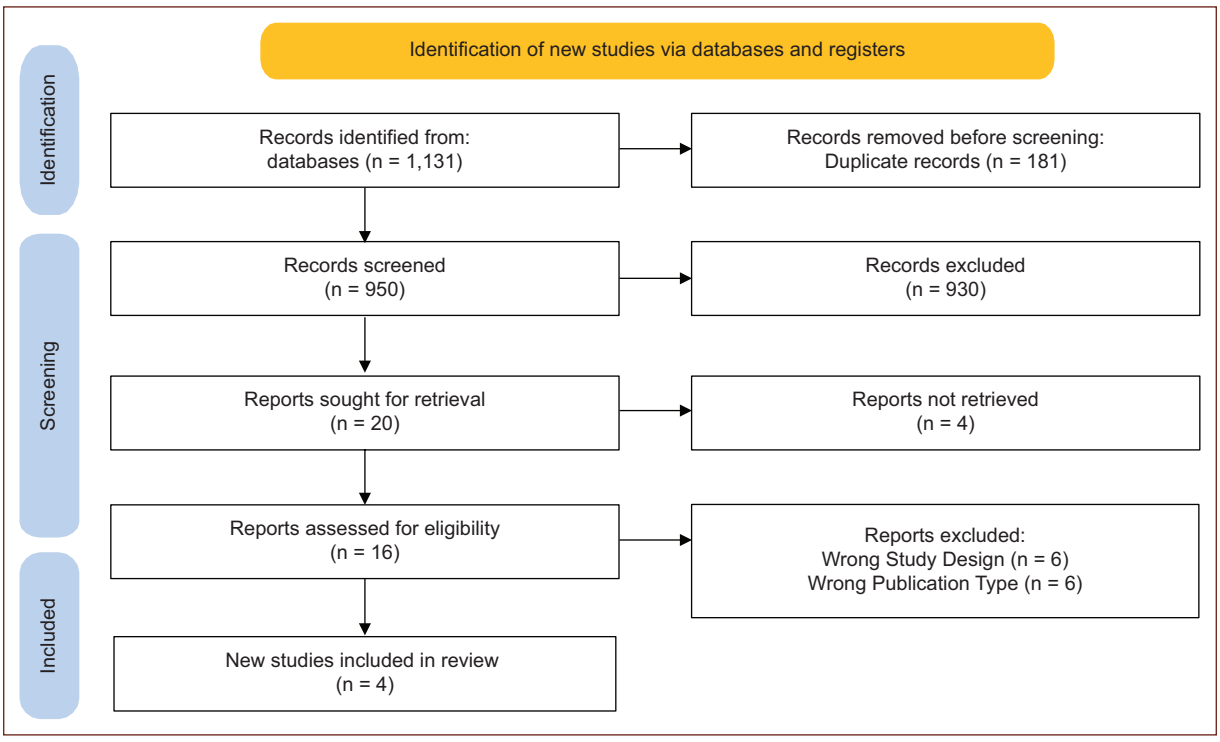

Figure 1. Prisma flow chart of the search, screening, and selection process.

Table 1. Baseline study and participant characteristics of included studies

Author, year, country	Title	Control			Experimental		
		No. of participants	Sex (M/F)	Mean age years (SD)	No. of participants	Sex (M/F)	Mean age years (SD)
Baker et al., 2023, USA	A randomized, double-blind, sham-controlled, clinical trial of auricular vagus nerve stimulation for the treatment of active RA	52	10/42	53.8	61	10/51	54.9
Drewes et al., 2020, Denmark†	Short-term transcutaneous non-invasive vagus nerve stimulation may reduce disease activity and pro-inflammatory cytokines in RA: results of a pilot study	-	-	-	36	5/31	56.22
Genovese et al., 2020, USA	Safety and efficacy of neurostimulation with a miniaturized vagus nerve stimulation device in patients with multidrug-refractory RA: a two-stage multicentre, randomized pilot study	4	2/2	55.0	10	1/9	49.3
Doko et al., 2016, Croatia†	Elektrostimulacija vagalnog živca u liječenju bolesnika s reumatoidnim artritisom - rezultati hrvatskog centra do 84. dana u sklopu međunarodnog pilot-istraživanja	-	-	-	2	1/1	Not reported

†The intervention was carried out on all study participants and, therefore, there is no control group.

Risk of bias assessment (Fig. 2)

Three studies raised some concerns[8,13,14], whereas one had a low risk of bias[15], as detailed in figure 2, outlining the assessed domains and overall risk of bias. The agreement between individual scores produced a Cohen's Kappa result of 0.744, demonstrating substantial agreement between the reviewers (see Table S3 in supplementary material). The level of evidence[16] for each outcome has been presented in figure 2.

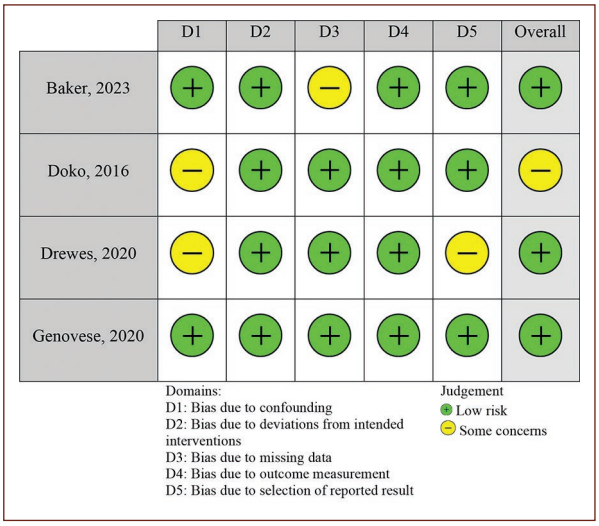

Figure 2. Risk of bias according to RoB 2.0 tool.

Study interventions and outcomes (Table 2)

Baker et al. instructed patients to use the device for 15 min daily[13]. The device emitted 20 kHz stimulation pulses with non-sensible amplitudes tailored to patient tolerance (median 2.6 mA, range 1.0-2.6, IQR 2.6-2.6). A total of 113 patients (mean age 54 years, 82% female) were enrolled, and 101 patients (89.4%) completed week 12. The American College of Rheumatology criteria 20 (ACR20) response at week 12 was 25.0% for active stimulation versus 26.9% for placebo (difference vs. placebo [95% CI]: –1.9 [–18.8-14[9], p = 0.823). The change in mean least squares in Disease Activity Score 28 with C-reactive protein (DAS28-CRP) was –0.95 ± 0.16 for active stimulation versus –0.66 ± 0.16 for placebo (p = 0.201); in the Health Assessment Questionnaire Disability Index (HAQ-DI), it was -0.19 ± 0.06 for active stimulation versus –0.02 ± 0.06 for placebo (p = 0.044). Adverse events occurred in 17 patients (15%), all mild or moderate. Auricular VNS did not significantly improve RA activity.

Doko et al. used stimulation for 60 s at 10 Hz, with a pulse duration of 250 μs and output currents from 0.25 to 2.0 mA[14]. Follow-ups were on the 1st and 4th days to assess blood biomarkers, and on the 7th day, patients received another 60-s stimulation and were instructed to use a magnet for daily at-home electrostimulation. VNS showed positive effects in both patients: DAS28 (7.00 and 6.22 vs. 4.03 and 2.13), Patient Global Assessment (PGA) (70 and 53 vs. 27 and 16), PtGA (48 and 43 vs. 15 and 14), tender joints (26 and 28 vs. 4 and 0), swollen joints (24 and 14 vs. 8 and 2), pain intensity (72 and 87 vs. 21 and 7), HAQ (2.25 and 2.25 vs. 1.5 and 1.375), and CRP (23.8 and 5.58 vs. 13 and 4.61). Fourteen days post-deactivation (day 56), CRP levels increased (13-16.3; 4.61-5.33), DAS28 (4.03-5.04; 2.13-2.18), and pain Visual Analog Scale (VAS) (21-73; 7-19). On day 84, subject 2's DAS28 (5.04-4.58) and VAS pain (73-28) decreased, whereas subject 1's DAS28 (2.18-3.19), and VAS pain (19-29) increased. The study concluded that VNS is effective in reducing clinical symptoms and inflammation in RA patients unresponsive to methotrexate therapy.

Drewes et al. used a device that administered 120 seconds of non-invasive transcutaneous VNS (n-VNS)[8]. Participants self-stimulated the left and right cervical vagus nerves three times daily (morning, afternoon, and evening) over 4 days. The device delivered approximate sinusoidal wave electrical pulses (1 ms [five waves, each 200 μs]), at 25 Hz with a maximum current of 60 mA, and voltage capped at 24 V. In participants with high RA disease activity, n-VNS did not change cardiac vagal tone (CVT), heart rate (HR), or diastolic blood pressure (BP), but reduced systolic BP by 12 mmHg (p = 0.003); DAS28-CRP decreased on days 2 and 5 (p = 0.02), as did interferon-gamma (p = 0.02), without changes in other cytokines. In those with low RA activity, n-VNS decreased CVT (p = 0.03) without changing HR or BP, and DAS28-CRP remained unchanged, though interleukin 10 decreased (p = 0.02). Participants with high RA activity had lower baseline CVT than those with low activity (3.6 ± 2 vs. 4.9 ± 3, p = 0.03).

Genovese et al. found the intervention safe and well-tolerated, reducing RA symptoms in patients resistant to multiple drug therapies[15]. They assessed outcomes using DAS28, PCR response, 20% improvement in ACR 20, ACR50, ACR70 responses, and EULAR response criteria.

Grading the evidence

The GRADE certainty of evidence rating and rationale used for each outcome measure are reported in full in

Table 2. Study methodology and summarized results of individual studies

Author, year	Intervention and its parameters	Intervention duration, N° of sessions, session duration	Usual care (control group)	Functional outcome measures	Measurement tool	Assessment timing (weeks)
Baker et al., 2023	VNS auricular nerves of the external ear, through customized auricular devices. – Pulse shape: biphasic square waves, current-controlled, and charge-balanced. – Stimulation frequency: 20 kHz. – Current amplitude: individually adjusted to imperceptible levels, with a median of 2.6 mA (range: 1.0 to 2.6 mA, interquartile range: 2.6-2.6 mA). – Session duration: 15 minutes, once daily.	12 weeks 84 sessions 15 min	Usual medications for RA	RA activity	ACR20; DAS28-CRP; HAQ-DI	0 (start of the study) 6th week 12th week
Drewes et al., 2020	VNS Cervical part of the vagus nerve (left and right sides) – Pulse frequency: 25 Hz (every 40 ms). – Maximum output current: 60 mA. – Adjustable voltage: Up to 24 V, depending on patient tolerance.	4 days 12 sessions 2 min	-	Vital signs RA activity	CVT HR BP DAS28-CRP IFN-γ	1st day (start of the study) 2nd day 5nd day
Genovese et al., 2020	VNS Left vagus nerve in the cervical region – Pulse frequency: 10 Hz. – Pulse duration: 250 μs. – Current intensity: Increased by 0.1 mA weekly until reaching the maximum tolerated level, with a limit of 2.5 mA.	12 weeks 84 or 252 sessions 1 min	Usual medications for RA	RA activity	DAS28-CRP ACR 20 ACR50 ACR70 EULAR	6 weeks before the study start 0 (start of the study) 1th week 2th week 3th week 4th week 5th week 6th week 8th week 12th week
Doko et al., 2016	VNS Left vagus nerve in the cervical region – Stimulation frequency: 10 Hz. – Pulse duration: 250 μs. – Current intensity: individually adjusted to the maximum tolerable level: range between 0.25 mA and 2.0 mA. The initial intensity was set at 0.75 mA for one participant and 1.0 mA for the other.	12 weeks (There was a break in intervention from week 6 to 8) 70 sessions 1 min	-	RA activity	DAS28; PGA PtGA HAQ PCR VSA pain	Day 1 Day 4 Day 7 2th week 3th week 4th week 6th week 8 th week 12 th week

RA: rheumatoid arthritis; ACR: American College of Rheumatology criteria; DAS28-CRP: disease activity score 28 with C-reactive protein; HAQ-DI: health assessment questionnaire disability index; CVT: cardiac vagal tone; HR: heart rate; BP: diastolic blood pressure; IFN-γ: interferon-gamma activity; EULAR: European League Against Rheumatism response criteria; PGA/PtGA: patient global assessment; VSA: Visual Analog Scale.

table S4 (see Table S4 in supplementary material). We found only one low-quality evidence (downgraded by one point due to some concerns regarding the risk of bias; inconsistency and imprecision, respectively) for the Disease Activity Score in 28 joints (DAS-28-CRP), as the articles present methodologies considerably heterogeneous, small samples and some concerns about the risk of bias, especially in Doko et al. in this aspect[14].

Discussion

The systematic review in this study presented a spectrum of VNS modalities administered over varying durations as a potential therapeutic intervention for RA. Some contrasts across the studies need careful analysis of stimulation techniques and possibly the demographic compositions of the studied populations. Such disparities underscore the critical need for discernment when considering the application of VNS in the context of RA treatment, particularly given that the studies were conducted in different countries and formulated different methodologies for intervention and participant inclusion.

The convergence in some studies results with broader literature validates the potential of VNS as a mechanism-based neuromodulating therapy for RA. The multifaceted anti-inflammatory effects of VNS, mediated through the cholinergic anti-inflammatory pathway and α7 nicotinic acetylcholine receptor subunit (α7nAChR), coalesce seamlessly with the theoretical framework underpinning VNS's role in autoimmune diseases. Acetylcholine acts as the cognate or "natural" ligand for α7 nicotinic acetylcholine receptors (α7nAChR) expressed on monocytes, macrophages, and cytokine-producing stromal cells, inhibiting inflammasome activation in macrophages exposed to lipopolysaccharide and other pro-inflammatory stimuli. This receptor serves as a central axis in the inhibition of pro-inflammatory cytokine release, thereby acting as a key mediator in the anti-inflammatory cascade. Acetylcholine's instrumental role in inhibiting inflammation through the α7 nicotinic acetylcholine receptor subunit dovetails with the tangible reductions in inflammation indicators and clinical symptoms evidenced in the reviewed studies[4,17,18].

The efficacy of VNS in RA treatment originates in the intricate interplay between the autonomic nervous system and the innate and adaptive immune responses[5]. The vagus nerve, as the principal parasympathetic nerve, plays a pivotal role in modulating inflammation. Recent research has unraveled the anti-inflammatory potential of the vagus nerve through various pathways[7]. This includes, first, the anti-inflammatory hypothalamic-pituitary-adrenal axis, cortisol release reduces pro-inflammatory cytokines, but its dysfunction in RA may impair the anti-inflammatory effect, second, the cholinergic anti-inflammatory pathway, which involves the interaction of acetylcholine with nicotinic receptors (α7nAChR) on macrophages, as previously mentioned and, finally, the splenic sympathetic anti-inflammatory pathway, which uses norepinephrine released by splenic nerves to inhibit the release of TNF-α, is also dysregulated in chronic inflammatory states[4,19,20]. One of the circuits widely described in the literature and worthy of note is the so-called "inflammatory reflex." This signaling mechanism, enhanced by vagal stimulation, has been shown to reduce the production of pro-inflammatory cytokines, thereby mitigating the severity of RA in experimental models[4]. These mechanisms collectively contribute to the suppression of pro-inflammatory cytokines, thereby dampening the immune response.

Looking ahead, the future of VNS in RA treatment appears promising. A pioneering study shed light on the critical involvement of the α7nAChR in the cholinergic anti-inflammatory pathway[19]. This revelation laid the foundation for exploring VNS as a potential therapeutic avenue for RA. Further studies have advanced our understanding of VNS techniques, ranging from invasive implantation to non-invasive transcutaneous stimulation, and their impact on musculoskeletal diseases[6,18,21-23].

Current research endeavors are steering toward refining VNS protocols, optimizing stimulation parameters, and delving into personalized approaches tailored to individual patient profiles. With the advent of novel device technologies, such as the AspireSR® and SenTiva™ VNS therapy systems, the landscape of VNS is undergoing rapid evolution, providing an increasingly precise and personalized treatment based on the best therapeutic approach for the patient, and consequently, making it safer and more effective overall[4,23-25]. Although the self-stimulant provides greater convenience for the patient and offers the described anti-inflammatory benefits, we have not yet found evidence in the literature suggesting an immediate response, as seen in the preventive treatment of epileptic seizures. These new technologies herald a new era in the application of VNS for not only epilepsy and depression but also for chronic inflammatory conditions such as RA[8,26,27].

Moreover, ongoing clinical trials are exploring the expansive potential of VNS in diverse domains. The investigation of VNS in stroke rehabilitation, chronic

heart failure, and inflammatory bowel disease represents a paradigm shift in our approach to utilizing this therapy[17]. In addition, studies investigating the effects of VNS on depression and cluster headaches hint at the far-reaching impact of this modality[28].

The exploration of VNS in the context of RA unveils a multifaceted approach to modulating inflammation. Understanding the relationship between the vagus nerve and RA could lead to innovative therapies, offering hope for an improved quality of life for RA patients. As we stand at the cusp of a new era in medical technology, the future of VNS in RA treatment holds great promise. With ongoing research endeavors and the advent of innovative device technologies, we are poised to unlock new dimensions in the therapeutic potential of VNS, not only in RA but across a spectrum of chronic inflammatory conditions.

This review highlights VNS as a promising frontier in innovative RA therapies, supported by its validation in the literature as a neuromodulatory therapy with anti-inflammatory mechanisms. Divergences among studies indicate the need for further exploration of confounding variables. Limitations include the lack of standardization in VNS characteristics, a limited number of studies, and research conducted in a few countries, necessitating testing in diverse populations and contexts. Ongoing research, exploring varied VNS protocols and advanced devices, promises new therapeutic perspectives, suggesting a shift in RA treatment. More studies are required to validate these findings and address the identified limitations.

Conclusion

From this perspective, the evidence supporting the use of VNS in RA appears to offer promising prospects, particularly for patients resistant to conventional pharmacological treatment. VNS was well tolerated and demonstrated relative safety in the studies reviewed, as most adverse events were mild and/or moderate, indicating its potential as a viable treatment option. Patients with high disease activity exhibited more notable reductions in inflammatory markers–C-reactive protein (CRP) and interferon-γ–and in the attenuation of clinical symptoms, compared to milder outcomes in patients with low disease activity. Thus, the integration of VNS as part of a multidisciplinary treatment approach seems to foster a new perspective in the management of RA, promoting significant improvements in patient's quality of life by alleviating symptoms and the functional impact of the disease. However, the limitations of this review may affect the quality of the presented results. Future research with greater methodological rigor in clinical trials, larger sample sizes, and longer intervention periods is essential to better evaluate clinical outcomes, the most benefited populations, and the long-term adverse events of the therapy.

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The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

Supplementary data

Supplementary data are available at DOI: 10.24875/RMN.24000037. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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