# Efficacy and safety of transcutaneous auricular vagus nerve stimulation plus pregabalin for radiotherapy-related neuropathic pain in patients with head and neck cancer (RELAX): a phase 2 randomised trial

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## Summary

**Background** Rapid relief of radiotherapy-related neuropathic pain (RRNP) in head and neck cancer (HNC) survivors is challenging when relying solely on pharmacologic treatments, especially in the early stages of medication. Whether transcutaneous auricular vagus nerve stimulation (taVNS) can effectively and rapidly control the RRNP in HNC survivors remains uncertain.

**Methods** The RELAX trial was a randomised, parallel, sham-controlled trial conducted at four centres in China. We randomly assigned (1:1) HNC survivors with moderate-to-severe RRNP (as defined by Numeric Rating Scale [NRS] score of ≥4) to receive taVNS or sham stimulation (concha of the left ear) for 30 min twice daily over 7 days. Participants, outcome assessors, and statisticians were blinded to assignment and intervention. All patients also received a basal dose of pregabalin (75 mg twice daily). The primary outcome was pain intensity reduction, as measured by the change of NRS scores from baseline to day 7. This trial is registered at ClinicalTrials.gov, NCT05543239.

**Findings** Between September 16, 2022, and December 1, 2023, 116 eligible patients (mean age, 50.8 [standard deviation (SD), 8.8] years; 40 [34.5%] were women) were randomly assigned into groups. All patients completed NRS score at baseline and day 7, and 112 (96.6%) completed 80% or more of the intervention course. The pain intensity at baseline was 5.79 (SD, 1.59) in the taVNS group and 5.66 (SD, 1.54) in the control group. At day 7, pain intensity decreased by 2.43 (SD, 2.19) in the taVNS group and 1.12 (SD, 1.64) in the Control group; between-group difference, 1.31 points (95% confidence interval [CI], 0.60–2.02; P = 0.00042). The most common adverse event (AE) related to taVNS was mild, transient local skin irritations at the electrode site (8.6% versus 1.7%, P = 0.21), and no serious AE were associated with the device.

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**Interpretation** In this trial, taVNS for 7 days at the initial stage of pregabalin treatment resulted in significantly better pain relief in HNC survivors with moderate-to-severe RRNP with no serious AE. Further prospective investigations to observe the longer term effects of taVNS on RRNP are warranted.

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**Keywords:** Radiotherapy; Radiotherapy-related neuropathic pain; Head and neck cancer; Transcutaneous auricular vagus nerve stimulation; Pregabalin; Randomised clinical trial

### Research in context

#### Evidence before this study

We searched PubMed from database inception to Dec 31, 2023 using the search terms: ("Head and Neck Neoplasms" [Mesh] OR "Head and Neck Cancer" [Title/Abstract]) AND ("Radiotherapy" [Mesh] OR "Radiotherapy" [Title/Abstract])) AND (pain [Title/Abstract]); ("Vagus Nerve Stimulation" [Mesh]) AND ("Pain Management" [Mesh] OR "Neuralgia" [Mesh] OR "Headache" [Mesh] OR "Pain" [Mesh]). Generally, rapid relief of radiotherapy-related neuropathic pain (RRNP) in head and neck cancer (HNC) survivors is challenging when relying solely on pharmacologic treatments, especially in the early stages of medication. Previous studies have shown that transcutaneous auricular vagus nerve stimulation (taVNS) can increase the pain threshold in healthy individuals, relieve the symptoms of migraine. Whether taVNS can effectively and rapidly control the RRNP in HNC survivors remains uncertain.

#### Added value of this study

We conducted the Efficacy of TaVNS plus pregabalin on RRNP in Patients with Head and Neck Cancers (RELAX) trial to evaluate the efficacy and safety of initiating taVNS with basal pregabalin therapy in pain relief among HNC survivors with RRNP. Our study is the first to show that taVNS for 7 days at the initial stage of pregabalin treatment provides significant analgesic benefits for the patients with RRNP and has good safety and tolerability. Additionally, patients treated with taVNS showed significant reduction in fatigue and improvement in quality of life. Longer term outcomes were assessed as secondary outcomes, including (1) quality of life (QoL) in various ways (including mood and fatigue, via WHO-QoL-BREF, BFI-SF, FACIT-F, POMS-SF]) at day 7 and week 16; (2) clinically meaningful (≥30%) and highly meaningful (≥50%) change in pain intensity at day 7 and weeks 2/4/8/12/16; and (3) treatment success (via PGIC scale and CGIC scale) at day 7. During the follow-up period, no significant difference in pain relief was observed between groups. At week 16, there were no significant differences in the scores of the secondary outcomes between groups.

#### Implications of all the available evidence

This study supports taVNS as an effective therapy for RRNP, providing significant analgesic benefits with a favourable safety profile. Future studies are warranted to observe the long-term effects of taVNS on alleviating RRNP.

## Introduction

Radiotherapy-related neuropathic pain (RRNP) is a late complication affecting more than 30% of head and neck cancer (HNC) survivors after radiation therapy.[1–3] As one of the limited high-quality clinical trials targeting this condition, the benefit of pregabalin for HNC survivors with RRNP has been verified in our previous clinical trial.[4] However, pregabalin provides limited pain relief in the first week of dosage adjustment, the decrease in pain intensity was only a quarter of that at the end of the trial (16 weeks), resulting in insufficient pain control in the early stage of treatment, while rapid dose increase of pregabalin can lead to more side effects.[4] Similarly, many common pharmacologic pain treatments do not always manage neuropathic pain effectively, and their use may increase the risk of drug-related adverse outcomes such as addiction (e.g., opioid addiction) and polypharmacy.[5]

Vagus nerve stimulation (VNS) has been proven to attenuate systemic inflammatory response, which is involved in the pathological processes of neuropathic pain, through a unique "parasympathetic anti-inflammatory pathway".[6] The transcutaneous auricular vagus nerve stimulation (taVNS), which works by transcutaneous electrical stimulation of the auricular branch of the vagus nerve,[7] has shown promising efficacy in pain relief (such as increased the pain threshold in healthy individuals and relieved the symptoms of migraine) with few adverse events.[8–10] Combination therapy of vagus nerve stimulation and pregabalin has been implemented in patients with epilepsy, supported by evidence demonstrating its feasibility and safety.[11]

Nevertheless, the efficacy of combining taVNS during the early phase of inadequate pain control in pregabalin dose adjustment for treating RRNP remains uncertain, as high-quality randomised controlled trial data are currently lacking in this specific therapeutic context.

We conducted the Efficacy of TaVNS plus pregabalin on RRNP in Patients with Head and Neck Cancers (RELAX) trial to evaluate the efficacy and safety of initiating taVNS with basal pregabalin therapy in pain relief among HNC survivors with RRNP.

## Methods

### Study design and ethics

We conducted this phase 2, multicentre, prospective, randomised, sham-control trial at four centres in China. Participants, outcome assessors, and statisticians were blinded. Details of the rationale, design, and data analysis plan are provided in the protocol, published previously[12] and available in the Supplementary Appendix 2.

The investigators were responsible for data collection and the conduct of the trial. The Clinical Research Centre of Sun Yat-sen Memorial Hospital, an independent research organisation, was responsible for the data management and statistical analysis. All the authors made the decision to submit the manuscript for publication and vouch for the completeness and accuracy of the reported data and for the fidelity of the trial to the protocol.

The ethics committee of each participating centre approved the study protocol (the name of the authority and reference numbers are provided in Table S1 of Supplementary Appendix 1), and all patients provided written informed consent. The trial conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines. This trial is registered at ClinicalTrials.gov, NCT05543239.

### Participants

Patients were eligible if they were aged 18 or older with an estimated survival of at least five months; had undergone radiotherapy for histologically confirmed HNC at least six months before study recruitment; had experienced pain for at least four weeks with a baseline pain intensity of ≥4 on the 11-point Numeric Rating Scale (NRS) and pain locations consistent with irradiated areas (the baseline pain intensity was assessed using the mean value of two NRS scores over two consecutive days before enrolled). Eligible patients also had to be diagnosed with neuropathic pain based on clinical history, symptoms, physical signs, and a score of 12 or higher on the Chinese version of the Leeds Assessment of Neuropathic Symptoms and Signs questionnaire (LANSS).[13] Exclusion criteria included current tumour recurrence or metastasis and evidence of tumour-associated pain. Detailed inclusion and exclusion criteria are described in the trial protocol (see Supplementary Appendix 2).

### Randomisation and masking

After confirmation of eligibility, patients were randomised in a 1:1 ratio to receive either taVNS or sham stimulation using a computer-generated schedule with a variable block length with 4 or 6. The allocation sequence was kept in non-transparent envelopes stored by an independent study coordinator. After screening procedures were completed, the independent physiotherapist administering the intervention received treatment assignments from the study coordinator by telephone. Patients, physicians, investigators, data collectors and outcome assessors were blinded to the group assignments. During the data analysis, statisticians and authors were also unaware of the assignments. The physiotherapist and the study coordinator were aware of the assignments but were not involved in the data collection or data analysis.

The sham stimulation strategy employed "transient sham stimulation," which allows for effective blinding while delivering a placebo treatment.[14] All participants were informed that the treatment's intensity might not be felt, and the device was placed in an opaque airtight pouch to maintain blinding. Participants were reminded not to discuss stimulation procedures with assessors, and Case Report Forms (CRFs) related to stimulation were kept separately. Blinding was tested by asking patients whether they thought the taVNS device functioned properly after the treatment period.

### Intervention

For all patients, after skin cleaning with an alcohol pad, electrodes were placed on the concha of the left ear. Stimulation pulses (frequency 30 Hz, pulse width 300 μs) were generated by a commercial transcutaneous ear vagus nerve stimulation device (taVNS 501, Jiangsu, China; Fig. S1 in the Supplementary Appendix 1). For the taVNS group, the amplitude was increased within 30 s to a tingling sensation and then decreased within 15 s to the maximum tolerable level without pain. For the Control (sham-stimulation) group, the amplitude was similarly increased to a tingling sensation but then ramped down to zero over 15 s. All participants received 30-min interventions twice daily (conducted between 9:00–10:00 and 15:00–16:00) for 7 days consecutively.

All patients received and maintained a dose of 75 mg pregabalin twice daily for analgesia during the treatment period (7 days), and then patients stopped stimulation and entered a 16-week follow-up period. During the follow-up period, patients performed dosage adjustments of pregabalin on the basis of their pain relief and tolerability with the maximum dosage of 300 mg twice daily. Rescue medications (e.g., Nonsteroidal anti-inflammatory drugs [NSAIDs], cyclo-oxygenase-2 [COX-

2] inhibitors, acetaminophen, and opioids) were permitted for breakthrough pain, and participants were instructed to record their use of these medications.

### Outcomes

The primary outcome was the change in pain intensity (average intensity in the last 24 h) from baseline at day 7, assessed using NRS of 0–10 (0 = no pain, 10 = worst pain imaginable).[14]

Secondary outcomes included responder status defined as clinically meaningful (≥30%) and highly meaningful (≥50%) pain reduction at day 7 (in keeping with the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials [IMMPACT] guidelines),[15] the change in pain intensity at week 2, week 4, week 8, week 12, and week 16, the change of the scores of the Chinese version of Brief Pain Inventory-Short Form (BPI-SF),[16] Profile of Mood States (POMS-SF),[17] Brief Version of the World Health Organization Quality of Life (WHOQOL-BREF),[18] and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)[19] at day 7 and week 16. Treatment effectiveness was evaluated using the Patient Global Impression of Change (PGIC)[20] and Clinical Global Impression of Change (CGIC),[21] with treatment success defined as "much" or "very much" improved at day 7. The percentage-based pain relief was used as an additional supplementary outcome (post-hoc analysis). The proportion of participants with perfect (100%) compliance was reported to describe the adherence with the assigned treatment (post-hoc analysis).

Safety endpoints included adverse effects classified according to the Common Terminology Criteria for Adverse Events: Version 4 and AE of special interest. Participants' use of concomitant and rescue medications during the trial was also reported. Exploratory outcomes assessed changes in serum levels of tumour necrosis factor-α (TNF-α), interleukin-1beta (IL-1β), interleukin-6 (IL-6) and interleukin-10 (IL-10) from baseline to day 7, to evaluate the potential inflammatory response mechanism of taVNS.

### Statistical analysis

We calculated that a sample size of 116 patients (taVNS group = Control group = 58 patients) would provide 90% power to detect a significant difference of 0.9 points and a standard deviation of 1.4 in the change of NRS from baseline to day 7 between the taVNS and Control groups with a 1-sided type I error rate of 2.5%, allowing for a 10% drop-out rate. The proposed group difference and the standard deviation of pain intensity reduction were determined on the basis of our previous trial and preliminary data.[4]

Continuous variables were described as median and interquartile range (IQR) due to its skewed distribution and those taking positive values with mean/standard deviation (SD) < 2, while mean and SD for other continuous variables.[22] For categorical variables, counts and percentages were presented. For continuous variables, Student's T test when assumptions of normality and variance homogeneity were met and Mann–Whitney U test otherwise, while $\chi^2$ test was used when all expected frequencies ≥5; otherwise, Fisher's exact test was applied for classification variables to compare the difference between two groups.

Primary analysis for the efficacy outcomes was performed according to the intention-to-treat (ITT) principle, including all randomised patients. The data for the main efficacy analyses were complete; therefore, no imputation for missing data was needed. Student's T test was used to compare primary outcome differences between groups. A post-hoc analysis for the primary outcome was performed using analysis of covariance (ANCOVA), adjusting for baseline NRS score, age and centres. Per-protocol (PP) analysis also served as a sensitivity analysis, including ITT patients who completed at least 80% of the intervention without significant protocol violations. The proportion of participants with complete (100%) compliance has been reported to describe compliance with specified treatments.

For secondary outcomes, the absolute proportion differences with 95% CI were calculated for responder status (≥30% and ≥50% pain relief) and treatment success proportions for PGIC and CGIC using the Newcombe-Wilson score method,[23] and comparison between groups was performed with the Cochran–Mantel–Haenszel (CMH) test (stratified by study centre). Continuous secondary endpoints were compared using Student's T test or Mann–Whitney U test in both ITT and PP sets. The safety set (SS) included all patients who received at least one electrical stimulation and was used for safety comparisons. The difference between two groups in the incidence of AE or serious AE, or the use of concomitant drug or rescue medications were compared using $\chi^2$ or Fisher's exact tests. Prespecified subgroups were defined according to age (≤60 years versus >60 years), sex, cancer type (nasopharynx versus other), clinical tumour node metastasis (TNM) stage grouping (II versus III versus IV), radiation approach (conventional versus intensity-modulated radiation therapy), chemotherapy (without versus with), symptom sites (one site versus >1 site), corticosteroids (without versus with) to evaluate whether the efficacy outcomes differed in association with variables of interest.

A two-tailed P value of less than 0.05 was considered to be statistically significant. All statistical analyses were performed with the use of R software, version 4.2 (R Foundation for Statistical Computing). Details for the statistical analysis plan are provided in the Supplementary Appendix 2.

### Role of the funding source

The funder had no role in the design and conduct of the study; collection, management, analysis, and

interpretation of the data; preparation, review, or approval of the manuscript; nor the decision to submit the manuscript for publication.

## Results

Between September 16, 2022, and December 1, 2023, 169 patients were screened and 116 eligible patients were randomly assigned into groups (Fig. 1). All patients received the designated treatments as per their randomisation. Consequently, 116 participants from four centres (Table S1b in the Supplementary Appendix 1) were included in the ITT analysis (58 in each group). Baseline characteristics were similar between groups (Table 1). There were 4 patients (2 in each group) who were discharged early for personal reasons and did not complete the stimulation course being excluded from the PP analysis (56 in each group). The adherence with the assigned treatment was shown in Supplementary Table S11, there were 85.34% (99/116) of participants had "100% adherence".

The mean (±SD) pain intensity at baseline was 5.79 ± 1.59 in the taVNS group and 5.66 ± 1.54 in the Control group. At day 7, pain intensity decreased by 2.43 ± 2.19 in the taVNS group and 1.12 ± 1.64 in the Control group, with a between-group difference of 1.31 points (95% confidence interval [CI], 0.60 to 2.02; P = 0.00042; Table 2 and Fig. 2A).

At day 7, the percentage relief of pain in the taVNS group was further reduced by 20.45 (7.60–33.29) compared to the control group (P = 0.0021; Table S2a in the Supplementary Appendix 1). The number of patients who achieved pain relief of 50% or greater according to the NRS on day 7 was 28 of 58 (48.3%) in the taVNS group versus 14 of 58 (24.1%) in the Control

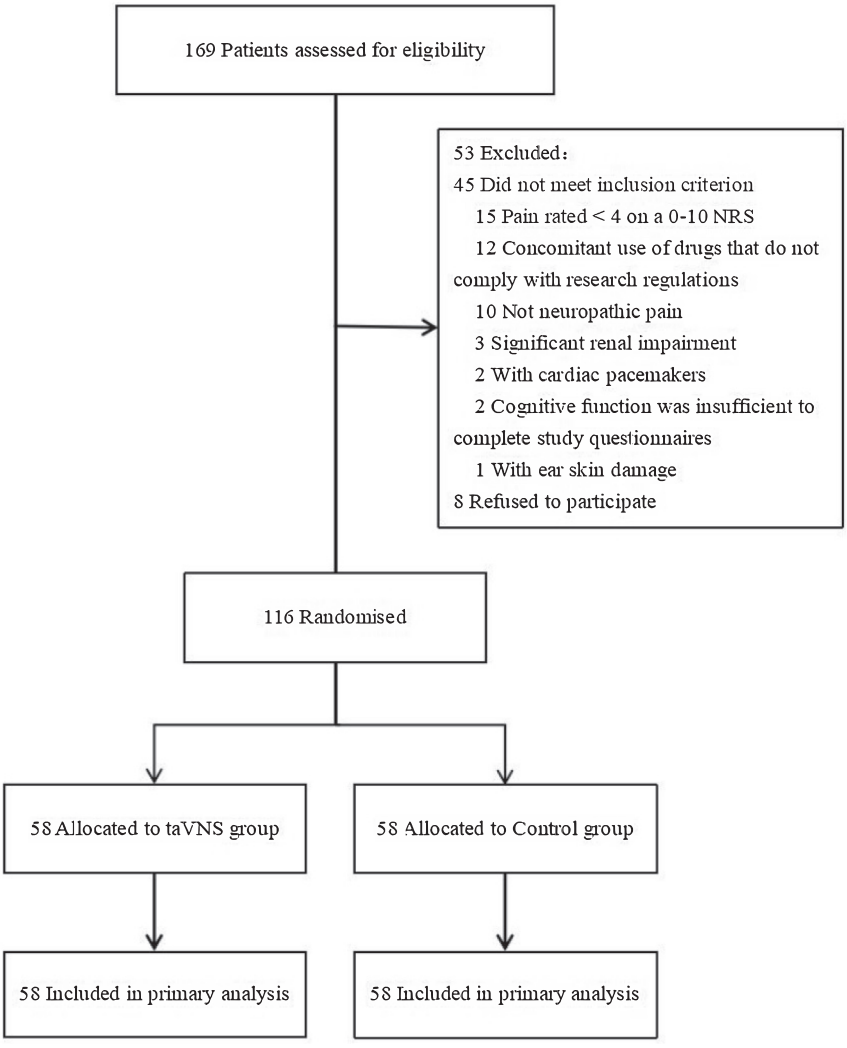


*Fig. 1:* **Participant flow diagram.**

| Characteristics | taVNS group (N = 58) | Control group (N = 58) |
|---|---|---|
| Age, mean (SD), yr | 49.5 (8.9) | 52.2 (8.8) |
| Female sex | 22 (37.9) | 18 (31.0) |
| Body-mass index, mean (SD)[a] | 21.6 (3.8) | 21.1 (3.7) |
| Smoking | 6 (10.3) | 8 (13.8) |
| Drinking | 4 (6.9) | 3 (5.2) |
| Hypertension | 9 (15.5) | 10 (17.2) |
| Diabetes | 3 (5.2) | 3 (5.2) |
| Cardio-cerebrovascular disease | 5 (8.6) | 6 (10.3) |
| Brain necrosis after radiotherapy | 38 (65.5) | 40 (69.0) |
| Primary tumour site | | |
| Nasopharynx | 55 (94.8) | 55 (94.8) |
| Other | 3 (5.2) | 3 (5.2) |
| TNM stage of primary tumour[b] | | |
| Stage 2 | 3 (5.2) | 9 (15.5) |
| Stage 3 | 34 (58.6) | 19 (32.8) |
| Stage 4 | 19 (32.8) | 26 (44.8) |
| Radiation approach | | |
| Intensity-modulated radiation therapy | 44 (75.9) | 47 (81.0) |
| Conventional radiation therapy | 14 (24.1) | 11 (19.0) |
| Radiotherapy dose for primary tumour site, median (IQR), Gy | 70 (70–70) | 70 (70–70) |
| Times of radiation for primary tumour site, median (IQR) | 33 (31–33) | 32 (32–33) |
| Radiotherapy dose for neck lymph node site, median (IQR), Gy | 70 (60–70) | 68 (60–70) |
| Times of radiation for neck lymph node site, median (IQR) | 32 (30–33) | 32 (30–33) |
| With chemotherapy | 54 (93.1) | 54 (93.1) |
| Prior surgery for head and neck cancer | 9 (15.5) | 7 (12.1) |
| Score for intensity of pain, mean (SD)[c] | 5.8 (1.6) | 5.7 (1.5) |
| Latency since the time of completion of radiotherapy to the first symptom, median (IQR), yr | 5.2 (3.1–10.0) | 5.2 (2.2–9.9) |
| Symptom onset site >1 | 9 (15.5) | 11 (18.9) |
| Baseline serum inflammatory factors, median (IQR), pg/ml | | |
| Tumour necrosis factor -α | 2.5 (0.5–5.2) | 2.5 (1.1–2.5) |
| Interleukin -1β | 2.5 (0.7–2.5) | 2.5 (0.7–2.5) |
| Interleukin –6 | 8.6 (3.6–21.4) | 7.5 (2.5–19.9) |
| Interleukin –10 | 2.3 (0.6–2.5) | 2.4 (0.9–2.5) |

Data are presented as No. (%) unless indicated otherwise. For continuous variables, mean (SD) was used for approximately normal distributions and median (IQR) for skewed data. Abbreviations: SD, standard deviation; IQR, interquartile range. [a]The body-mass index is the weight in kilograms divided by the square of the height in meters. [b]Six patients had missing values (2 in the taVNS group and 4 in the control group). [c]Pain was measured on a scale from 0 to 10, with 0 indicating no pain and 10 "the worst pain imaginable.

*Table 1:* **Baseline demographics and clinical characteristics by group.**

group (P = 0.007; Fig. 2B, and Table S2b in the Supplementary Appendix 1). The proportion of patients who experienced a reduction in pain intensity of 30% or greater at day 7 was also higher in the taVNS group compared with the Control group (65.5% [38 of 58] versus 36.2% [21 of 58]; P = 0.002; Fig. 2B, and Table S2b in the Supplementary Appendix 1). After adjusting for baseline NRS scores, age and centres, the taVNS group also demonstrated a greater reduction in pain intensity compared to the control group at day 7, with an adjusted between-group difference of 1.28 points (95% CI, 0.57 to 1.99; P = 0.00051; Table S3a). The overall direction results for the primary outcome remained unchanged in PP set (Table S3b in the Supplementary Appendix 1).

The taVNS group achieved a significant decrease in BPI-SF pain severity (the mean of the four pain items, including pain at its worst, least, average, and current pain) compared with the Control group at day 7 (net between-group difference, –1.00; 95% CI, –1.60 to –0.42; P = 0.001; Table 2). POMS-SF scores for fatigue/inertia (net between-group difference, –1.42; 95% CI, –2.63 to –0.29; P = 0.021) and FACIT-F fatigue scores (net between-group difference, 4.29; 95% CI, 1.63–6.93; P = 0.002) also improved significantly with taVNS versus Control (Table 2). Likewise, there were significant improvements in the physiology and psychology domains of WHOQOL-BREF scores for taVNS versus Control (P = 0.046 and 0.041, respectively; Table 2).

Treatment success was reported by 29 patients (50.0%) in the taVNS group according to the PGIC scale, compared with 18 patients (31.1%) in the Control group (P = 0.011; Fig. 2C, and Table S4 in the Supplementary Appendix 1). Similarly, 33 patients (56.9%) in the taVNS group reported treatment success by the CGIC scale, compared with 16 patients (27.6%) in the Control group (P = 0.001; Fig. 2D, and Table S4 in the Supplementary Appendix 1).

There were no significant differences among the groups in the overall frequency of AEs (Table 3, and Table S5 in the Supplementary Appendix 1). Twenty-eight patients (48.3%) in the taVNS group and 26 patients (44.8%) in the Control group experienced at least one AE (P = 0.36). The only AE related to the device was local skin irritation (redness and stinging) from electrode placement (taVNS group [n = 5; 8.6%] versus control group [n = 1; 1.7%]; P = 0.21), but the irritation was mild and resolved within 1–2 days. No serious AE related to the device. Six patients died during the follow-up period, with five deaths attributed to pneumonia during the COVID-19 pandemic in China (2 in the taVNS group, 3 in the Control group) and one death from massive nasopharyngeal haemorrhage (in the taVNS group). None of these deaths were attributed to be caused by the device. Four patients (2 in each group) discontinued the trial early for personal reasons.

Participants' use of concomitant and rescue medications during the trial is reported in Table S6 in the Supplementary Appendix 1. Seven patients (12.1%) in the taVNS group and 12 patients (20.7%) in the Control group took rescue medications during the treatment period (P = 0.21). No significant difference was found in the use of concomitant medications between groups (P = 0.559). Compliance was similar between groups, with 96.6% (112 of 116) of patients completing 80% or more of the intervention course.

During the follow-up period, no significant difference in pain relief was observed between groups (Table S7 and Fig.S2 in the Supplementary Appendix 1). At week 16, there were no significant differences in the scores of the secondary outcomes between groups (Table S8 in the

| Outcome | taVNS group (N = 58) | | | Control group (N = 58) | | | Net between-groups difference (95% CI[a]) | P value[c] |
|---|---|---|---|---|---|---|---|---|
| | Baseline | Day 7 | Change from baseline | Baseline | Day 7 | Change from baseline | | |
| **Primary outcome** | | | | | | | | |
| NRS[e] | 5.5 (4.5–7) | 3 (2–5) | −2.5 (−4 to 1) | 5 (4.5–6.7) | 5 (3–6) | −1 (−2.13 to 0) | −1.31 (−2.02 to −0.60)[b] | 0.00042[d] |
| **Secondary outcome** | | | | | | | | |
| BPI severity[f] | 3.75 (2.5–5.25) | 2 (0.75–3.5625) | −1.5 (−3.06 to 0.69) | 3.5 (2.75–5) | 3 (1.94–4.56) | −0.75 (−1.56 to 0.25) | −1.00 (−1.60 to −0.42)[b] | 0.001[d] |
| BPI-SF Interference subscale[f] | | | | | | | | |
| General activity | 4 (1.75–5) | 2 (0–4.25) | 0 (−2 to 0) | 5 (2.75–6) | 3 (2–5.25) | 0 (−1 to 0) | −0.57 (−1.43 to 0.21) | 0.20 |
| Mood | 3 (1–5) | 2 (0–3) | −1 (−3 to 0) | 3.5 (2–6) | 3 (1–6) | 0 (−1 to 1) | −0.97 (−2.14 to 0.23) | 0.07 |
| Walking ability | 0 (0–2) | 0 (0–2) | 0 (0–0) | 1 (0–4.25) | 0 (0–3.25) | 0 (0–0) | −0.013 (−0.79 to 0.73) | 0.96 |
| Work | 2 (0–5) | 1.5 (0–3.25) | 0 (−2 to 0) | 3.5 (1–7) | 3 (0–6) | 0 (0–0) | −0.20 (−1.04 to 0.69) | 0.38 |
| Social relations | 1 (0–3.25) | 0 (0–3) | 0 (0–0) | 0 (0–3.5) | 0.5 (0–3.25) | 0 (0–0) | −0.33 (−1.12 to 0.42) | 0.36 |
| Sleep | 3.5 (1.75–6) | 2 (0.75–4.25) | −1 (−3 to 0) | 5 (3–8) | 5 (2–7.25) | 0 (−1 to 0.25) | −0.68 (−1.59 to 0.30) | 0.06 |
| Life enjoyment | 2 (0–5) | 1 (0–3) | 0 (−2 to 0) | 3.5 (0–7) | 3 (0–6) | 0 (−1 to 0) | −0.38 (−1.31 to 0.51) | 0.13 |
| POMS-SF subscale[g] | | | | | | | | |
| Tension/anxiety | 4 (1–7.25) | 3 (1–6) | −1 (−2.25 to 0) | 5 (1.75–7.25) | 5 (2–7) | 0 (−1.25 to 1) | −0.35 (−1.47 to 0.68) | 0.31 |
| Depression/dejection | 3.5 (1–6) | 2 (1–5) | 0 (−2 to 0.25) | 4 (1–8.25) | 5 (1–6.5) | 0 (−1.25 to 1) | −0.25 (−1.42 to 0.95) | 0.49 |
| Anger/hostility | 3.5 (1–7) | 2 (1–5) | 0 (−2 to 0) | 4.5 (1–6.25) | 4 (1–6) | 0 (−2 to 1) | −0.21 (−1.44 to 1.07) | 0.59 |
| Vigor/activity | 6 (3–10) | 7 (3.5–10) | 0 (−1 to 1.25) | 5 (1–9.25) | 5 (0–9) | 0 (−1 to 1.25) | 0.39 (−0.74 to 1.50) | 0.67 |
| Fatigue/inertia | 6 (3–11) | 4 (1–8) | −2 (−4 to 0) | 7.5 (4–10) | 7 (4.5–9) | 0 (−2.5 to 0.5) | −0.92 (−2.2 to 0.27) | 0.021 |
| Confusion/bewilderment | 5 (3–8.25) | 5 (3–7) | 0 (−2 to 1) | 6 (4–9.25) | 5 (3.5–9) | 0 (−2 to 0) | 0.53 (−0.58 to 1.53) | 0.47 |
| WHOQOL-BREF domain[h] | | | | | | | | |
| Physiology | 12 (10.15–13.28) | 12.57 (10.86–14) | 0 (−0.57 to 2.29) | 11.45 (8.57–13.71) | 11.43 (8.57–13.71) | 0 (−1.14 to 0.58) | 0.66 (−0.23 to 1.46) | 0.046 |
| Psychology | 12 (9.83–14) | 12.67 (12–14) | 0 (0–1.34) | 12 (9.33–14.34) | 12 (9.33–14) | 0 (−0.67 to 0.67) | 1.11 (0.07–2.08) | 0.041 |
| Social relationship | 12.67 (12–14.67) | 13.33 (12–14.67) | 0 (−1.33 to 0) | 13.33 (12–16) | 12 (12–14.67) | 0 (0–0) | 0.56 (−0.57 to 1.59) | 0.36 |
| Environment | 12.5 (12–14.625) | 13 (12–14.5) | 0 (−1 to 1) | 13 (11.5–14) | 12 (11.5–14) | 0 (−0.5 to 0) | 0.30 (−0.59 to 1.10) | 0.48 |
| FACIT-F subscale[i] | 36 (28.75–41) | 41 (35–45) | 4 (0–10) | 33 (26–41) | 33 (26.5–43) | 0.5 (−1.25 to 2.25) | 4.69 (1.78–7.53) | 0.002 |

Median (IQR) was used for description of variables with skewed distribution including those taking positive values with mean/SD < 2. Net between-group difference was calculated as change in taVNS group minus change in Control group. Abbreviations: BPI-SF, Brief Pain Inventory-Short Form; CI, confidence interval; NRS, numeric rating scale; POMS-SF, Profile of Mood States-Short Form; SD, standard deviation; WHOQOL-BREF, World Health Organization Quality of Life-BREF; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue. [a]CIs were computed using Bootstrap method unless otherwise specified. [b]CI was computed using Normal approximate method. [c]P values are from Non-parametric Mann–Whitney U Test for two group different unless otherwise specified. [d]Analysis from Student's t-test. [e]Score range: 0–10. Higher scores indicate greater pain. The primary outcomes came from the ITT population. [f]Score ranges on BPI-SF subscales: Severity, 0–10; Interference, 0–10. The pain severity score was assessed as the mean of the four pain items (ie, pain at its worst, least, average, and current pain). Higher scores represent increased pain and pain interference. [g]The POMS-SF subscale, 30 items with five-point response options from 0 to 4; Higher scores represented worse function or balance in the POMS total score and items except Vigor-Activity. [h]Score ranges: 0–100. Higher scores represent better quality of life. [i]Score ranges: 0–52. Higher scores represented less fatigue.

***Table 2:*** **Primary outcome and secondary outcomes at day 7 (full analysis set).**

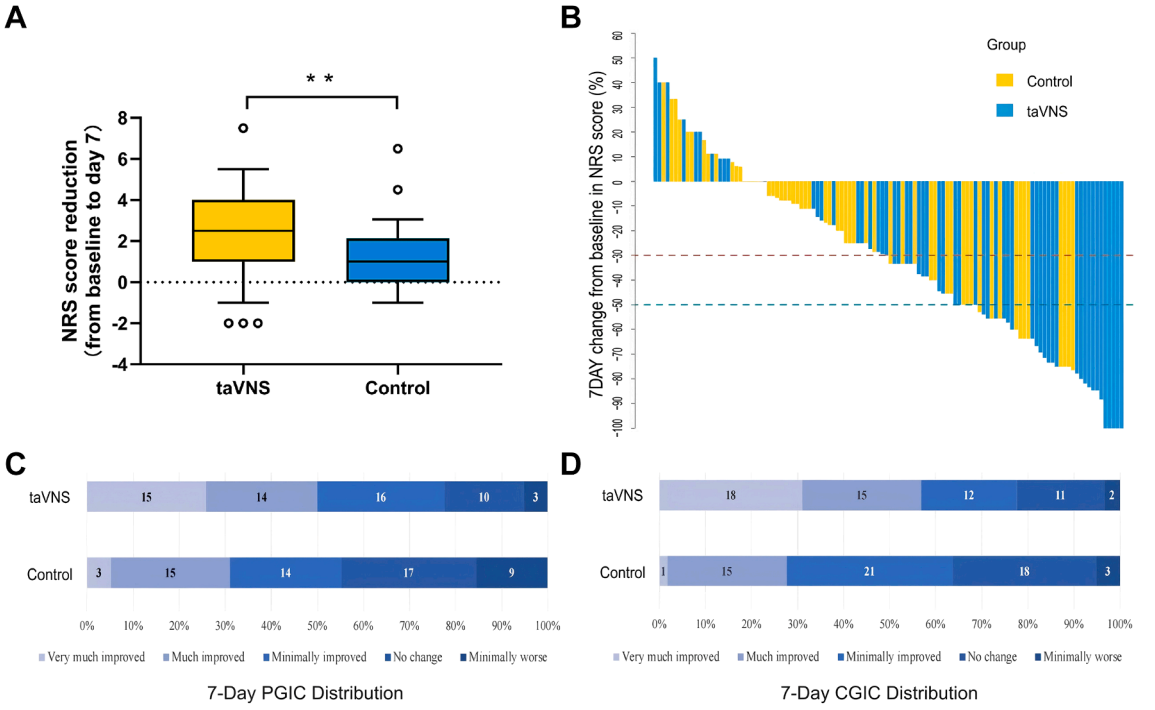


***Fig. 2:* Effects of taVNS on Pain Intensity**. Panels A show the NRS score changes (primary outcome). ** indicates that there is significant difference in the NRS score changes between groups (P < 0.00042). Outliers (○) defined as values beyond Mean-2 × SD or Mean + 2 × SD. Panels B show the percentage change in pain intensity (based on NRS score) from baseline to Day 7. The red and green dashed lines indicate a reduction in pain intensity of 30% and 50%, respectively. Panels C and D show the outcome of Patient Global Impression of Change (PGIC) and Clinical Global Impression of Change (CGIC) at Day 7 by Treatment Group. NRS denotes numeric rating scale (range from 0 to 10, higher scores indicating greater pain). NOTE: N = 116 samples (taVNS: Control = 1:1).

Supplementary Appendix 1). No significant changes in inflammatory cytokines were detected between groups from baseline to day 7 (Table S9 in the Supplementary Appendix 1). The post-treatment survey showed no difference in the proportion of participants accurately inferring their treatment allocation between groups (Table S10a and S10b in the Supplementary Appendix 1). A subgroup analysis of pain intensity data based on clinical factors that might influence the outcome is provided in Fig.S3 in the Supplementary Appendix 1. Post-hoc analyses of the primary outcome measures using ANCOVA models (Table S3a) further supported the main findings.

## Discussion

The results of this randomised, multicentre, parallel, sham-controlled trial demonstrate that taVNS provides significant analgesic benefits for HNC patients with RRNP and has good safety and tolerability. Additionally, patients treated with taVNS showed significant reduction in fatigue and improvement in quality of life.

The clinical analgesic application of auricular stimulation has a long history in many cultures, such as the ancient Chinese, Persia, and Italian societies.[24,25] The auricular branch is the only superficial branch of the vagus nerve, projecting to the nucleus tractus solitarius.[26] Electrical stimulation of the cymba concha, which is exclusively supplied by the auricular vagus nerve, effectively activates central vagal projections.[27,28] Modern studies have shown that taVNS increases pain thresholds,[8] alleviates migraine symptoms[8] and reduces musculoskeletal pain in systemic lupus erythematosus.[29]

In this trial, after seven days of intervention, the 1.31-point difference in pain reduction between the taVNS and Control groups met the minimum clinically important difference in the pain rating scale of 1 point on a scale of 0–10,[30] and it aligned with previous studies on transcutaneous electrical nerve stimulation for chronic pain.[31] Meanwhile, the relief of pain in the taVNS group was further reduced by 20.45% compared to the control group, and the responder status, defined a priori as 50% and 30% pain relief, was significantly higher in the taVNS group, further revealing the clinical benefit of taVNS in the treatment of RRNP.

Vagus nerve stimulation plays a therapeutic role through multi-level neuromodulatory and immunoregulatory pathways, including reducing sympathetic nerve activity, enhancing GABAergic inhibition,

| Event | taVNS group (N = 58) | Control group (N = 58) | P value |
|---|---|---|---|
| Total Number of AE | 32 | 33 | – |
| Patients with any AE | 28 (48.3) | 26 (44.8) | – |
| Number of deaths | 3 (5.2) | 3 (5.2) | – |
| Number of deaths during 7 days treatment period | 0 | 0 | |
| Number of deaths during 2–16 week of follow-up period[c] | 3 (5.2) | 3 (5.2) | |
| Number of deaths related to device | 0 | 0 | |
| Number of serious AE | 3 | 3 | – |
| Number of participants with serious AE | 3 (5.2) | 3 (5.2) | – |
| Number of serious adverse device events | 0 | 0 | |
| Number of participants with serious adverse device events | 0 | 0 | |
| Number of NS–AE | 29 | 30 | – |
| Number of NS adverse device events | 5 | 1 | 0.21[a] |
| Possibly related | 1 | 1 | |
| Probably related | 4 | 0 | |
| Definitely related | 0 | 0 | |
| Number of participants with NS–AE | 25 (43.1) | 23 (39.7) | 0.71[b] |
| Number of participants with a NS adverse device event | 5 (8.6) | 1 (1.7) | 0.21[a] |
| Possibly related | 1 (1.7) | 1 (1.7) | |
| Probably related | 4 (6.9) | 0 | |
| Definitely related | 0 | 0 | |

Data are presented as No. (%) unless indicated otherwise. Abbreviations: AE, adverse event; NS, non-serious. [a]P values are from Fisher's exact test. [b]P values are from $\chi^2$ test. [c]Six patients died during the 16-week follow-up period, 5 of whom (2 in taVNS group and 3 in Control group) died of pneumonia during the COVID-19 pandemic in China, and 1 patient (taVNS group) died of massive nasopharyngeal hemorrhage.

***Table 3:*** **Summary of serious and non-serious (NS) adverse events for all participants.**

cholinergic anti-inflammatory mechanisms and counteracting central sensitisation.[32–34] The sympathetic nervous system's role in neuropathic pain development has been confirmed, and a combination of sympathetic and sensory blocks is more effective in controlling neuropathic pain than sensory block alone.[35,36] Pregabalin, a structural derivative of gamma-aminobutyric acid (GABA), reduces the influx of $Ca^{2+}$ and subsequent excitatory neurotransmitters release by binding to the α2-δ subunit of synaptic voltage-gated calcium channels (VGCC) in the central nervous system, thereby alleviating neuropathic pain.[37,38] The combination of taVNS and pregabalin is more effective than pregabalin alone in treating RRNP, indicating potential synergy between their mechanisms. VNS enhances inhibitory functions of the central GABAergic system. Although pregabalin not directly targeting GABA receptors, pregabalin reduces neuronal hyperexcitability by inhibiting presynaptic calcium channels to suppress glutamate release.[39] Their combined actions may generate additive effects in blocking pathological neuronal discharges. Additionally, VNS suppresses pro-inflammatory cytokine release e.g., TNF–α, IL–6 via the cholinergic anti-inflammatory pathway,[32] while pregabalin mitigates neuroinflammation by modulating NF-κB signaling.[40] Such dual anti-inflammatory actions are particularly critical for neuroinflammation-driven neuropathic pain like RRNP. Although no significant changes in circulating inflammatory cytokines were detected at day 7, longer stimulation periods may be needed to observe such effects.[41,42] Further studies are needed to investigate the potential mechanisms in combination of pregabalin and VNS.

Fatigue, a significant issue for cancer patients, lacks specific drug treatments.[43] This study found significant fatigue relief with taVNS, consistent with previous findings in healthy volunteers, patients with primary Sjögren's syndrome, and patients with systemic lupus erythematosus.[29,44,45] Activation of the locus coeruleus noradrenergic system, which enhances wakefulness and can be stimulated by taVNS, may explain this effect.[26,46,47] We have also found the improvement in quality of life for taVNS versus Control. The taVNS device has received European certification as a treatment for depression and anxiety,[48] these effects combined with the relief of pain and fatigue, might account for the improvement of the global life status in patients who were treated with taVNS.

Adverse events related to taVNS were mild and limited to local skin irritation. No serious AE were related to the device. Six deaths during the follow-up period were unrelated to taVNS. The study's robust design, including rigorous blinding and outcome measures consistent with IMMPACT recommendations,[15] ensures comprehensive evaluation. Low numbers of missing data and high compliance rates further support the study's validity. However, during the follow-up period, we did not find a significant

difference in pain relief between the two groups. This is consistent with previous studies that have shown that the effect of transcutaneous electrical nerve stimulation for pain relief is shorter in duration after stimulation.[31] On the other hand, this may be related to the adjustment of analgesic drugs based on the pain condition after the treatment period.

The study has several limitations. The predominance of nasopharyngeal carcinoma in the patient population may limit generalisability to other HNC types. The optimal parameters for taVNS remain unclear,[48] with our study referring to the recommendations from International Consensus Based Review and Recommendations for Minimum Reporting Standards in Research on Transcutaneous Vagus Nerve Stimulation (Version 2020)[48] and a previous related trial.[29] Due to the nature of taVNS manipulation, physiotherapists in this trial could not be blinded. To reduce the impact, we provided detailed training to physiotherapists, including standardised communication with patients and operational segregation. The intervention duration in this study was relatively short, and further prospective investments to observe the long-term effects of taVNS on RRNP are warranted in the future. Finally, while intention-to-treat analysis carries inherent measurement bias risks and per-protocol analysis may introduce selection bias, the concordant directionality of treatment effects across both analytical approaches substantiates the robustness of our principal finding.

In conclusion, among HNC survivors with RRNP, the taVNS for 7 days plus pregabalin resulted in better pain relief than pregabalin alone. The adverse events were transient and tolerable. This study supports taVNS as an effective therapy for RRNP, providing significant analgesic benefits with a favourable safety profile.

#### Contributors

YT and XZ accessed and verified the underlying data. YT, XZ, YZ, DP, XR, HL and JJ conceived and designed the study. All authors acquired, analysed, and interpretated the data. YZ, PC implemented statistical analysis. XZ, YX, SL, JJ and JW drafted the manuscript. CBS, JL, DZ, KL, HM and MC critically revised of the manuscript for important intellectual content. YL, QS, SX and YT provided administrative, technical, or material support. YT, XZ and YX supervised the study. All authors approved the decision to submit.

#### Data sharing statement

Data supporting the findings of the study are available on reasonable request after approval of a proposal from the corresponding author (YT; tangym@mail.sysu.edu.cn).

#### Declaration of interests

We declare no competing interests.

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#### Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103345.

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