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Review

Non-invasive vagus nerve stimulation for substance use disorder: A narrative review

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ABSTRACT

Background: Recent technological advances have led to increased experimentation in non-invasively modulating the brain to reduce craving and drug use in substance use disorder (SUD). However, many forms of neuromodulation remain costly and require administration in a medical setting, limiting scalability. Vagus nerve stimulation (VNS) circumvents these limitations. A substantial body of neurobiological and clinical evidence suggests that VNS may be well-suited to target core mechanisms underlying substance use, including craving, mood, and stress dysregulation.

Methods: Fifty-two searches with terms related to VNS and SUD were used to find papers reporting results on the use of non-invasive VNS in SUD. Data were extracted to tables and collated for a narrative review.

Results: Eleven publications were found (eight unique trials) in individuals with opioid or alcohol use disorder. No investigations into other substances were identified. Outcomes range from acute withdrawal to longer-term reduction of craving and depression. Studies differ in outcomes, stimulation location (auricular or cervical), parameters, laterality, and number and length of sessions. Despite methodological variation, studies provide preliminary evidence that non-invasive VNS may be feasible, safe, and capable of modulating withdrawal-related, affective, and autonomic outcomes, though current evidence for craving reduction is limited and inconsistent.

Conclusions: Increasing sample sizes, reporting on sex-differences, and including randomized-sham controlled designs in a wider range of SUDs is critical to conclusively determine the utility of VNS for SUD. As with other neuromodulation techniques, maintaining consistency with device parameters and reporting is needed to enhance standard of care.

1. Introduction

Substance use disorder (SUD) is a major health crisis, and in 2024 there were 48.4 million people with an SUD diagnosis (Substance Abuse and Mental Health Services Administration, 2025). While overdose rates have marginally improved in the US in the last year (American Medical Association, 2025), largely as a result of the increased accessibility of opioid overdose-reversal medications (i.e., Naloxone), the number of deaths remain elevated (~73,000 in 2025) (Centers for Disease Control and Prevention, 2024). The current standard of care includes medication for opioid- (OUD) or alcohol use disorder (AUD), and behavioral treatment, either alone or in combination. Despite advances in treatment, drug use recurrence (DUR; previously known as relapse) rates are prevalent, with many individuals using substances within the first 90 days of leaving a treatment setting, and an estimated ~70–85% within one year (Yazıcı and Bardakçı, 2023; Sinha, 2011). In addition, for many substances, such as cocaine and methamphetamine, there are no medications available, further impeding successful outcomes for those seeking abstinence.

Recent medical and technological advances have led to a wave of experimentation in non-invasively modulating the brain to try to reduce craving and drug use. Examples of neuromodulation techniques include transcranial magnetic stimulation or direct current stimulation which target mainly cortical regions. Transcranial magnetic stimulation is FDA approved for nicotine use and a recent meta-analysis also demonstrates its utility in reducing craving in AUD (Sorkhou et al., 2022). More

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recently the field has seen the emergence of focused ultrasound, which can target subcortical regions (for review see Thurn et al., 2025; Mahoney et al., 2026). Despite a scarcity in the literature, publications using focused ultrasound as an adjunctive treatment for SUD are extremely encouraging (Mahoney et al., 2025, 2023; Rezai et al., 2025). However, to date, these publications have all used a device requiring MR imaging, a full head shave and extensive patient monitoring. In addition, the requisite of a stereotactic frame necessitates sedation, anesthesiologists, and a surgical team. Moreover, this device has not yet been proven suitable for use in cases of milder addiction severity at low-intensity thresholds (Aubry et al., 2025; Klein-Flugge et al., 2026). Newer, less cumbersome, and even portable neuromodulation devices are being trialed for SUD. However, these remain costly and often need to be administered in a hospital or research setting; both of which are prohibitive for individuals with SUD.

Vagus nerve stimulation (VNS) is a form of neuromodulation that may circumvent these limitations while reducing negative symptoms of SUD associated with continued drug use and therefore aiding abstinence attempts. The vagus nerve (VN) is the Xth cranial nerve of the brain. It is the main parasympathetic nerve in the body, with 80% of its fibers relaying information *from* the body to the brain (Ma et al., 2025; Butt et al., 2020). Composed of three different fibers (A, B, and C fibers) with distinct myelination properties and physiological roles, it diverges into multiple different branches throughout the body (Yuan and Silberstein, 2016). Through this widespread network of nerve fibers, it connects the brain to all internal organs, relaying information related to respiration, heart rate, pain, temperature, and many other somatic, sensory and visceral signals. As a result, the brain can interpret and regulate physiological states, arousal, stress, and inflammation (for review see Yuan and Silberstein, 2016; Ma et al., 2025).

The afferent nerve fibers of the VN projecting from the body to the brain terminate in the nucleus tractus solitarius of the medulla oblongata, where ascending projections reach the locus coeruleus and dorsal raphe nucleus. This results in increased release of norepinephrine (locus coeruleus) or serotonin (raphe nucleus). These neurotransmitter systems exert widespread modulatory effects on limbic and prefrontal circuitry implicated in mood regulation, stress responsivity, reward processing, and emotional control (Hachem et al., 2018; Kovner et al., 2019). Through projections to higher-order cortical and subcortical regions, including the nucleus accumbens, insula, anterior cingulate cortex, and prefrontal cortex, norepinephrine and serotonin regulate neural activity via interacting effects on gamma-aminobutyric acid (GABA) and dopamine pathways (Ciranna, 2006). GABA, the primary inhibitory neurotransmitter in the central nervous system, reduces neuronal hyperexcitability within stress-related limbic circuits, particularly the amygdala, whereas dopaminergic modulation within mesolimbic regions influences reward processing, motivation, and affective state. In addition to these neurotransmitter effects, VNS has been associated with reductions in pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin−6 (IL−6) (Hachem et al., 2018), both of which are implicated in the pathophysiology of depression, chronic stress, and substance use disorders (Hassamal, 2023; Martinez et al., 2018). VNS has also been shown to modulate the expression of brain-derived neurotrophic factor (BDNF), a neurotrophin involved in synaptic plasticity, neuronal survival, and antidepressant response (Amagase et al., 2023). Collectively, these neurochemical, inflammatory, and neuroplastic effects suggest that vagal afferent signaling is a major contributor to the regulation of limbic-prefrontal circuits central to emotional regulation, stress responsivity, craving, and affective symptomology.

Modulation of the VN as a medical treatment has been around since the late 1880s (Lanska, 2002), and an implantable device, placed at the left cervical branch of the VN, was approved for medication-resistant epilepsy in 1997 (Morris and Mueller, 1999). Through observational improvements in patients' mood after implantation, further work was carried out, and implantable VNS was approved by the FDA for treatment-resistant depression in 2005 (Austelle et al., 2022). While implantable VNS offers hope to individuals who do not respond to medications, it is not without caveats; the highly invasive nature of the treatment and subsequent surgeries needed for battery changes, are costly, and prohibitive for many individuals. Additionally, efficacy of the surgery may take between six to 12 months, and not all individuals will experience symptom reductions (Elliott et al., 2011; Aaronson et al., 2017).

1.1. Non-invasive vagus nerve stimulation

To circumvent these limitations, two non-invasive forms of VNS modulation have been explored for various medical indications. These deliver electrical stimulation targeting either the cervical or the auricular branch of the VN without implantation, and can be administered remotely by the patient.

Transcervical VNS (tcVNS) uses a handheld device with two electrodes, to modulate the cervical branch of the VN through the skin on the neck (Yap et al., 2020). Research has led to the FDA approval of tcVNS (e.g., gammaCore) for indications including episodic cluster headache and migraine (Goadsby et al., 2018; Mwamburi et al., 2018), with additional clinical investigation in chronic pain (Costa et al., 2024). The mechanistic rationale for the location of device placement is its proximity to the main vagus trunk targeted in implantable VNS, and therefore stimulation may engage many fibers, both afferent and efferent of the VN. However, there exists some uncertainty regarding exactly which or how many fibers are engaged, especially when self-delivered by the patient in an unmonitored setting.

Transauricular VNS (taVNS) involves stimulating the VN via dense fibers that run through sections of the ear; specifically, the cymba concha, and the tragus. While tcVNS can be noted for its depth of research in specific disorders, taVNS has been investigated across a wider range of neuropsychiatric and medical conditions, including mood disorders, autonomic regulation, and pain (Bremner et al., 2020; Hein et al., 2013; Austelle et al., 2024), but it has not yet received FDA approval for any therapeutic indications. The auricular branch of the VN does not innervate all regions of the ear; for example, the ear lobule is typically devoid of vagal innervation and is therefore often used as a sham stimulation site (Butt et al., 2020; de Gurtubay et al., 2021). As with tcVNS, this partial and variable innervation introduces uncertainty regarding which nerve fibers are engaged by different taVNS devices. This uncertainty is further compounded by interindividual variability in ear anatomy and vagal nerve fiber density (Butt et al., 2020; Peuker and Filler, 2002). Notwithstanding these limitations, both cervical and auricular VNS show great promise for improving symptoms of several conditions; they are portable, comparatively affordable, have minimal side-effects with no recovery time required, and can be self-administered by the patient.

There is a substantial body of neurobiological and clinical evidence suggesting that non-invasive VNS may be well-suited to target core mechanisms underlying substance use, including pain, mood dysregulation, and stress responsivity (Shao et al., 2023; Bremner et al., 2020; Ferstl et al., 2022). Non-invasive VNS has demonstrated efficacy in reducing pain and anxiety symptoms (Shao et al., 2023; Austelle et al., 2025), highly prevalent in individuals with SUD and known to contribute to DUR (Sinha, 2024). Mood disturbances, particularly depression, represent a major contributor to suboptimal SUD treatment outcomes, and are associated with increased substance use and DUR vulnerability (Nunes and Levin, 2004; Hasin et al., 2002). Individuals with SUD show higher rates of depressive symptoms, lifetime stress exposure, and traumatic experiences compared with healthy controls (Mahoney et al., 2015; Dunn et al., 2022). Additionally, the same underlying corticostriatal circuit dysregulation has been demonstrated in both individuals with depression and SUD (Siemsen et al., 2025). Invasive VNS has demonstrated robust and sustained antidepressant effects, including long-term symptom improvement in a five-year

prospective study (Aaronson et al., 2017) and supportive evidence from meta-analyses (Berry et al., 2013). Collectively, these findings suggest that non-invasive VNS may beneficially modulate affective and stress-related processes that play a central role in the initiation and perseverance of addictive behaviors.

From a mechanistic perspective, VNS engages brain regions and neurobiological systems implicated in SUD withdrawal, stress regulation, and negative reinforcement processes, including pathways involving the hypothalamic-pituitary-adrenal axis (Sinha, 2008). Dysregulation of stress systems has been associated with impaired distress tolerance and maladaptive responses to negative affect, which are key drivers of continued substance use (Daughters et al., 2009). A focused review of VNS in the context of opioid withdrawal highlights its potential to modulate withdrawal-related neurocircuitry and alleviate acute symptoms (Bremner et al., 2023). However, the therapeutic effects of VNS may extend beyond acute detoxification. Protracted withdrawal symptoms, such as persistent anxiety, dysphoria, sleep disturbance, heightened stress sensitivity, and craving, remain significant barriers to sustained recovery and are insufficiently addressed by existing treatments (Volkow et al., 2019; Sinha, 2024). Accordingly, this review examines the application of VNS across multiple substance classes, including alcohol, stimulants, and opioids, both within the context of withdrawal and expanding to outcomes known to impede successful outcomes (e.g., abstinence). By integrating evidence across these domains, this review aims to assess the validity of VNS as a feasible and clinically useful adjunctive intervention for SUD that targets neurobiological vulnerabilities both during and beyond the acute withdrawal period.

2. Methods

2.1. Eligibility criteria

A manual (i.e., Artificial Intelligence tools were not utilized) electronic literature search was conducted between October 2025 and May 2026 using PubMed, Web of Science, and Scopus. PubMed was selected as the primary database due to its inclusion of ahead-of-print and non-indexed records, and searches were replicated in Web of Science and Scopus to ensure comprehensive coverage. No additional records were identified using reference lists of publications. Device-specific terminology was not included in the search strategy to avoid inadvertently excluding studies that used non-commercial or variably labeled stimulation devices. Initial abstract screening was performed independently by two reviewers (GS and LJ). In cases of discrepancies, full texts were retrieved and reviewed. A third reviewer (DTL) adjudicated and made final inclusion decisions. Data extraction and eligibility determinations were based on predefined inclusion and exclusion criteria. The search used the following words to search all fields:

1. Terms referring to stimulation: *vagus, auricular, VNS, cervical*
2. Terms referring to substance use: *substance, opioid, cocaine, methamphetamine, methadone, heroin, stimulant, alcohol, cannabis, mari*, benzo*, sedative, nicotine*

Every term used for stimulation (term 1) was combined using the 'and' operator with every term used for substance use (term 2) for a total of 52 searches. Papers were searched using '[All fields]' for each term combination with the exception of 'cervical and alcohol' and 'cervical and mari*', which were limited to a title/abstract due to the number of results.

Studies were selected if they reported results on one or more outcome measures using a method of non-invasive VNS in a human population with a diagnosis of SUD. Articles were excluded if they included invasive stimulation, acupuncture, acupressure, or preclinical studies of VNS. Only studies in English or translated to English, where the full article could be accessed, were selected.

2.2. Published studies selection

A total of 52,716 studies were identified. After full screening and removing of duplicates, 11 studies fulfilled eligibility criteria and were selected for review. Of these, three report additional and secondary analyses on data from another published trial. These will be discussed briefly within the context of the original studies. Thus, a total of 11 studies met criteria for study selection, but only eight unique trials/cohorts were identified (Fig. 1).

2.3. Clinical trials search and study selection

A second search for ongoing or planned studies using clinicaltrials.gov was conducted between November 2025 and February 2026. The search terms above were entered in the 'other terms' category. Additionally, two searches were conducted by entering 'auricular neuromodulation therapy' and 'cervical neuromodulation therapy' into the 'Intervention/treatment' category.

A total of 1990 studies were identified using clinicaltrials.gov. By screening titles and study summaries, 21 studies were selected.

2.4. Data collection

Data extraction was performed using standardized tables. Categories include; author and year of publication, substance, study design, sample size, participant age, and outcome measures (Table 1). Information regarding the device, length and number of sessions, and device parameters can be found for each study in Table 2. Clinical Trial information was extracted using the same categories as Table 1, with trial number and study location in place of author (Table 3). The current stage of the clinical trial and outcome measures are reported in Table 4.

2.5. Data analysis

A narrative synthesis was conducted. Studies were assessed for methodological quality and risk of bias by two independent reviewers (GS and LJ) using an updated 28-item of the Downs and Black checklist (Downs and Black, 1998), including the 0–5 power scoring and an additional item on funding reporting, consistent with recent review articles. As no cut-offs for the scale exist, scores were interpreted descriptively using percentage-based ranges from the maximum score for contextual interpretation ($\geq$80% excellent; 60–79% good; 40–59% fair; $<$40% poor). Discrepancies in scoring were assessed by a third reviewer (DTL). Challenges in synthesis, including difference in stimulation devices, session length, outcome measures, and study populations, are addressed by presenting results in thematic subgroups rather than attempting quantitative pooling. Narrative summaries are grouped by substance in chronological order.

3. Results

Eleven publications met review criteria. Eight unique trials were found. Of these, four are randomized, sham-controlled studies, three are open-label studies, and one study combines these designs. Three studies focused on alcohol as the primary substance (two using taVNS and one with tcVNS) and five on opioids (three using taVNS and two with tcVNS). No studies were identified for any other substances. Details for each published report are presented in Table 1 and Table 2. Methodological reporting quality for all studies was rated as 'good' or 'excellent' (See Table 5). However, it is important to note that the ratings assigned using the Downs and Black bias checklist reflect methodological quality and reporting transparency and should not be interpreted as indicators of evidentiary strength or clinical efficacy. A high score does not preclude important limitations, which will be discussed for each study.

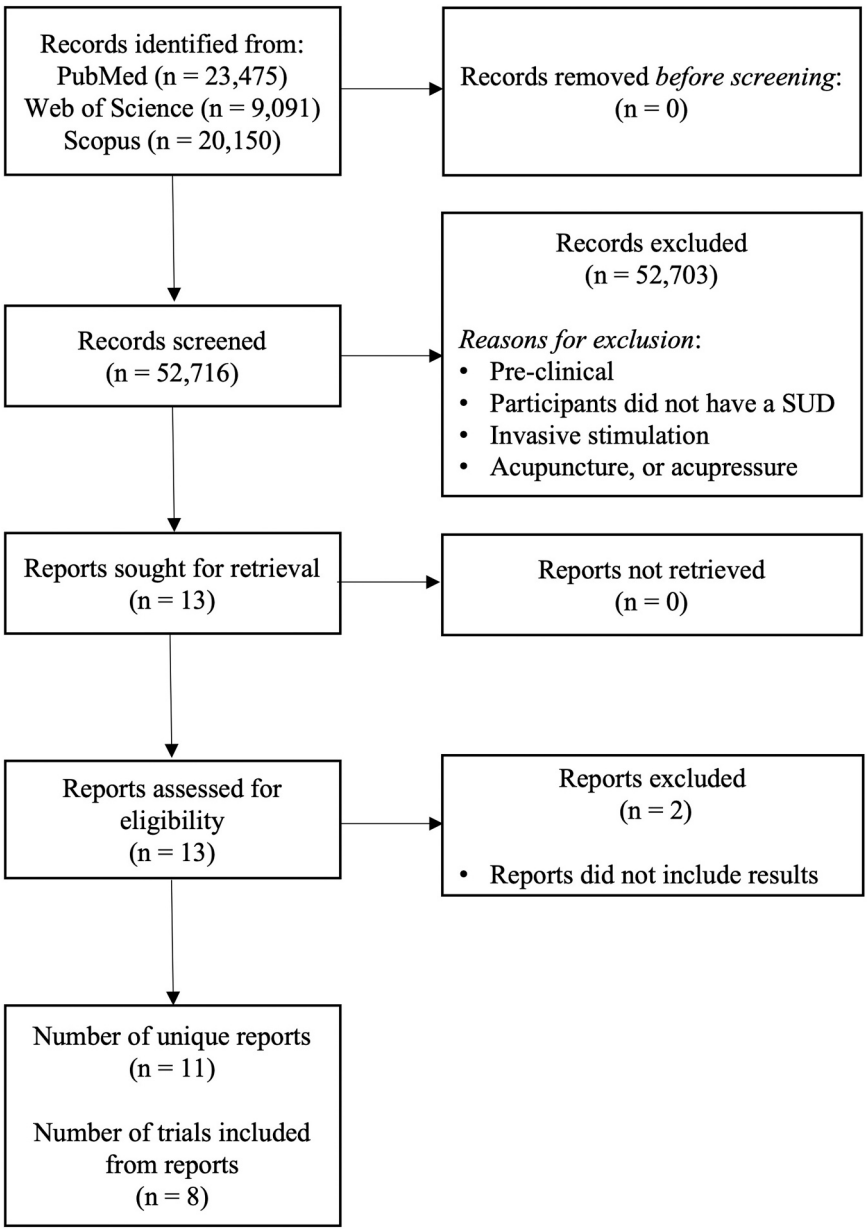


Fig. 1 PRISMA flow diagram of study selection.

3.1. Opioids

The earliest non-invasive VNS study (Miranda and Taca, 2018), was an open-label retrospective design retrieving records from 73 patients during opioid withdrawal treatment. Participants wore a BRIDGE (Innovative Health Solutions, Versailles, IN, USA) percutaneous VNS placed behind the ear (laterality unspecified) which connected to electrodes placed on the ear and delivered electrical stimulation for up to five days. The study assessed if this reduced acute symptoms of opioid withdrawal and increased transition to medication for OUD. The device was safe and well tolerated, with no adverse events (AEs) recorded. Authors report a substantial decrease in Clinical Opiate Withdrawal Scale (COWS) by at least 36.4% following 60 minutes of stimulation, and this remained reduced for the following five days. A majority of patients (88.8%) successfully transitioned to medication-assisted treatment. The finding from this multisite study led to FDA approval of the BRIDGE device for use in opioid withdrawal in 2017. There have been some criticisms of the regulatory reliance on a single study, which was retrospective and with no sham control. This study was groundbreaking in that it opened the possibility for VNS as an adjunctive treatment to opioid withdrawal, however, other non-invasive VNS devices for other SUD indications are yet to receive FDA approval in SUD.

The next OUD study addressed taVNS as an adjunctive to accelerated morphine-assisted treatment for Neonatal Opioid Withdrawal Syndrome (Jenkins et al., 2021). In this open-label trial, eight infants received taVNS via a wearable earpiece (Roo™ Therapy System, Spark Biomedical, Dallas, TX, USA) on their left ear, targeting both the auricular branch of the VN and auriculotemporal nerve for 30 minutes, one hour before receiving a morphine dose, up to four times daily for a maximum of 12 days. There was a large range in the number of sessions administered (median: 30; range: 13–43). Consistent with the previous study, no unexpected AEs occurred. During taVNS therapy, all infants achieved average clinician scored withdrawal results showing an overall reduction of symptoms and all but one infant were weaned off morphine during taVNS. The median length of time for weaning from morphine, from both the start of administering oral morphine and after taVNS initiation, were both significantly lower than previously published data without a VNS device (Patrick et al., 2015). This suggests that VNS could

Table 1
Study design and outcome measures of published VNS reports in SUD.

Author (Year)	Substance	Study Design	Sample Size	Age Range	Length of Substance Use (Years)	Outcome Measures	SUD Treatment Status
Miranda et al. (2018)	Opioids	Retrospective, open-label, single arm	25F/48M	23–42 (Years)	1–10	COWS Successful transition to MAT	Outpatient, receiving opioid withdrawal treatment
Jenkins et al. (2021)	Opioids	Prospective, open-label, single arm	3F/5M	35–44 (Weeks)	N/A	FNAST HR NIPS LOT of oral morphine in days Oral morphine LOT after tAN initiation Length of hospital stay in days	Inpatient, acute withdrawal morphine-assisted treatment
Tirado et al. (2022)	Opioids	30 min double-blind, randomized, sham-controlled followed by 5 day open-label period	11F/20M	25–41 (Years)	0.5–27	COWS HRV PHQ−9 PCL−5 WHOQOL−5	Inpatient, acute withdrawal
Gazi et al. (2022) *	Opioids	Double-blind, randomized, sham-controlled	6F/15M	24–46 (Years)		VAS-withdrawal COWS VAS-craving VAS-anxiety NRS for pain SUDS HR	Outpatient, induced acute withdrawal
Rahman et al. (2025) **	Opioids	Double-blind, randomized, sham-controlled	7F/4M	29–57 (Years)		Brain blood flow in anterior cingulate (PET) COWS VAS	Outpatient, completed acute detoxification and clinically stable
Wang et al. (2021)	Alcohol	Randomized, sham-controlled	114M	39–42 (Years)	14–18	PACS SDS SAS PSQI Plasma BDNF, IL−6, TNF-a, and leptin levels	Inpatient, completed acute detoxification and clinically stable
Treiber et al. (2024)	Alcohol	Open-label, single arm	12F/18M	40–60 (Years)		Quantitative pupillometry VAS-craving	Inpatient, acute withdrawal and receiving standard withdrawal pharmacotherapies
Klaming et al. (2025)	Alcohol	Double-blind, randomized, sham-controlled	19M	31–47 (Years)		Treatment adherence and acceptability ratings PHQ−8 STAI-S BAI DrInC−2R BIPF	Outpatient, not in withdrawal and could drink ad libitum

Abbreviations: BAI, Beck Anxiety Inventory; BDNF, brain-derived neurotrophic factor; BIPF, Brief Inventory of Psychosocial Functioning; COWS, Clinical Opiate Withdrawal Scale; DrInC−2R, Drinker Inventory of Consequences; ECG, electrocardiogram; EEG, electroencephalogram; fMRI, functional magnetic resonance imaging; FNAST, Finnegan Neonatal Abstinence Scoring Tool; GAD−7, Generalized Anxiety Disorder Scale−7; HDT, heartbeat discrimination task; HR, heart rate; HRV, heart rate variability; IL−6, interleukin−6; IQR, interquartile range; LOT, length of treatment; MAT, medication assisted therapy; NIPS, Neonatal Infant Pain Scale; NRS, Numerical Rating Scale; PACS, Pennsylvania Alcohol Craving Scale; PCL−5, Post-traumatic Stress Disorder Checklist for DSM−5; PEP, pre-ejection period; PET, positron emission tomography; PHQ−8, Patient Health Questionnaire−8; PHQ−9, Patient Health Questionnaire−9; PPG, photoplethysmography; PROMIS, Patient-Reported Outcomes Measurement Information System; PSQI, Pittsburgh Sleep Quality Index; RPV, respiration pattern variability; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale; SGNG, Simon Go/NoGo; SOWS, Subjective Opiate Withdrawal Scale; STAI-S, State-Trait Anxiety Inventory-State; SUDS, Subjective Units of Distress Scale; tAN, transcutaneous auricular neurostimulation; TNF-a, tumor necrosis factor-alpha; VAS, Visual Analog Scale; WHOQOL-BREF, World Health Organization Quality of Life Assessment
*Two additional papers published from the same cohort
** One additional paper published from the same cohort

Table 2
Device and stimulation parameters of published VNS reports in SUD.

Author (Year)	Device	Number of Sessions	Length of Sessions	VNS Treatment Period	Parameters
Miranda et al. (2018)	BRIDGE® percutaneous auricular electrical nerve field stimulator	1	Up to 5 days	5 days	3.2 V with alternating frequencies of stimulation
Jenkins et al. (2021)	Roo™ Therapy System transcutaneous auricular nerve stimulator	13–43	30 min	12 days	Frequency: 5 Hz at cymba concha and 100 Hz at temporomandibular joint Intensity: set 0.1 mA below perception intensity
Tirado et al. (2022)	Sparrow Therapy System™ auricular vagus nerve stimulator	5	Up to 24 h	5 days	Frequency: 5 Hz at cymba concha and 100 Hz adjacently anterior to tragus Intensity: average of 1.0 mA for cymba concha and 1.4 mA for trigeminal area
Gazi et al. (2022) *	gammaCore™ transcutaneous cervical vagus nerve stimulator	6	2 min	1 day	Alternating current: 5 periods of 5 kHz sinusoid repeating every 40 ms Output voltage: 0 – 26 V; sham devices delivered a biphasic AC square waveform at 0.1 Hz, with peak-to-peak amplitude ranging from 0 to 4 V
Rahman et al. (2025) *	gammaCore™ transcutaneous cervical vagus nerve stimulator	6	2 min	1 day	Alternating current: 5 periods of 5 kHz sinusoid repeating every 40 ms Output voltage: 0 – 52 V; sham devices delivered a biphasic AC square waveform at 0.2 Hz, with peak-to-peak amplitude ranging from 0 to 7 V
Wang et al. (2021)	Transcutaneous auricular vagus nerve stimulator	84	30 min	4 weeks	Frequency: 20 Hz Intensity: 0.4 – 1.0 mA
Treiber et al. (2024)	AuriStim percutaneous auricular vagus nerve stimulator	1	72 h	3 days	Frequency: 1 Hz Monophasic volt impulse: 1 ms Amplitude: 4 mV
Klaming et al. (2025)	gammaCore™ transcutaneous cervical vagus nerve stimulator	14	2 min	7 days	Alternating current low-voltage electrical signal at 5 kHz sinusoid wave series occurring for 1 ms with a repetition rate of 25 Hz; sham devices produced a varying direct current signal of 0.1 Hz

Abbreviations: Hz, hertz; kHz, kilohertz; mA, milliampere; ms, millisecond; mV, millivolt; V, volt
*Additional papers were published from the same cohort

lead to a substantially reduced time on morphine and in the NICU for infants in withdrawal.

The next published study addressed withdrawal in OUD using transcutaneous (i.e., surface electrodes) auricular VNS in adults (Tirado et al., 2022). In this double-blind, sham-controlled study, participants physically dependent on opioids were randomized to receive active or sham taVNS (Sparrow device, Spark Biomedical Inc., Dallas, TX) for 30 minutes and withdrawal symptoms were assessed for up to 120 minutes. This was followed by a five-day open-label period of active stimulation (both groups) for up to 24 hours per session. The safety profile of the device was positive. Active taVNS group demonstrated a significantly greater reduction in COWS score and heart rate after 30 minutes compared to sham group. Sixty minutes after both groups received active VNS, a significant and clinically relevant reduction in COWS score (45.9%) was observed across all participants. At day five, there was a significant reduction in depression and post-traumatic stress symptoms but no change in quality-of-life score. While the sample size is small, the power calculation prior to enrollment was conservative, and an interim analysis revealed the study was powered to demonstrate effects. This study is important as the first blinded and sham-controlled study for the use of VNS in OUD withdrawal. A limitation, noted by the authors, is that the blinded comparison was conducted after only 30 minutes of VNS, and a longer duration of assessment is needed in order to truly assess the effects. Throughout the open-label follow-up trial ~50% of the participants dropped out of the trial, for reasons stated as either related to the device, switching to an opioid treatment, or leaving the treatment facility. While treatment dropout is expected in such a trial and population, commentary on the large number of participants dropping out while on active VNS is omitted from the paper. While this open-label period does not affect the initial double-blind, sham-controlled results of the study, which focus on acute withdrawal, it has possible implications for longer term tolerability and efficacy. The trial was noted as 'excellent' for methodological quality in the Downs and Black Bias Checklist; however, the checklist does not account for potential funding bias. In this instance, the trial was funded by the device manufacturer who also contributed to the design, data interpretation and the manuscript, which should be considered when interpreting the trial results.

Gazi et al., 2022a conducted a double-blind, randomized, sham-controlled pilot study examining the effects of tcVNS on acute withdrawal in participants with OUD prior to initiation of medication-assisted treatment. Primary outcomes were drug craving and heart rate. Twenty-one participants were randomized to receive either active tcVNS (n=10) or sham stimulation (n=11) using a handheld gammaCore (electroCore, Basking Ridge, New Jersey) applied to the right cervical VN. In order to induce withdrawal, participants were required to abstain from opioids for a minimum of eight hours prior to testing. During a two-hour laboratory session, participants viewed drug-related and neutral videos while receiving 120-seconds of stimulation across six different conditions (e.g., drug/neutral, audio/visual), and withdrawal-related outcomes were repeatedly assessed. Subjective measures included visual analog scales (VAS) for withdrawal severity, pain, anxiety, craving, and subjective distress and heart rate was continuously recorded using Biopac (Goleta, CA) instrumentation. Outcome variables were analyzed as changes from baseline.

Relative to sham, active tcVNS significantly reduced heart rate and produced significant reductions in subjective withdrawal severity, including VAS-rated withdrawal symptoms, pain, and distress; these remained significant after adjusting for history of depression. However, while craving was numerically lower in the active tcVNS group, this did not reach statistical significance, a finding the authors suggest may reflect distinct neural substrates underlying craving versus withdrawal-related distress and autonomic arousal. No serious AEs were reported in these studies, further demonstrating the safety of VNS. Although craving was not significantly reduced, the reduction of other subjective measures and heart rate support the adjunctive utility of tcVNS during acute

Table 3
Study characteristics of registered clinical studies for VNS in SUD.

NCT	Location	Substance	Study Design	Sample Size	Age	Withdrawal Focus (Y/N)
03762798	Cleveland, OH, US	Opioids	Open-label, non-randomized	0 (actual)	18–99 (Years)	N
04075214	Austin, TX, US	Opioids	Double-blind, randomized, sham-controlled	35 (actual)	18–65 (Years)	Y
04106739	Karnataka, India	Alcohol	Double-blind, randomized, sham-controlled	44 (actual)	18–50 (Years)	N
04159909	Manhasset, NY, US	Alcohol	Single-blind, randomized, sham-controlled	0 (actual)	18–65 (Years)	Y
04556552	Atlanta, GA, US	Opioids	Double-blind, randomized, sham-controlled	12 F/8 M (actual)	28–59 (Years)	N
04588519	Charleston, SC, US	Opioids	Open-label, non-randomized	3 F/5 M (actual)	35.1–43.9 (Weeks)	Y
04731935	Austin, TX, US	Opioids	Open-label, non-randomized	6 (actual)	18–65 (Years)	Y
05053503 Phase I	Rancho Mirage, CA, US Crownsville, MD, US Center City, MN, US Plymouth, MN, US	Opioids	Double-blind, randomized, sham-controlled	108 (actual)	18–65 (Years)	Y
05053503 Phase II	Rancho Mirage, CA, US Crownsville, MD, US Center City, MN, US Plymouth, MN, US	Opioids	Double-blind, randomized, sham-controlled	108 (actual)	18–65 (Years)	Y
05129020	Charleston, SC, US Dallas, TX, US San Antonio, TX, US	Opioids	Double-blind, randomized, sham-controlled	52 (actual)	33–52 (Weeks)	Y
05131334	Vienna, Austria	Alcohol	Open-label, non-randomized	30 (actual)	20–65 (Years)	Y
05226130	San Diego, CA, US	Alcohol	Double-blind, randomized, sham-controlled	19 M (actual)	30–46 (Years)	N
05591703 (Phase III of 05053503)	Rancho Mirage, CA, US Center City, MN, US Plymouth, MN, US	Opioids	Prospective, longitudinal, observational	32 (actual)	18–65 (Years)	N
05834478	Atlanta, GA, US	Opioids	Double-blind, randomized, sham-controlled	103 (estimated)	18–75 (Years)	Y
06130501	Cape Girardeau, MO, US	Opioids	Double-blind, randomized, sham-controlled	20 (estimated)	18–65 (Years)	N
06308484	Berlin, Germany	Alcohol	Single-blind, randomized, sham-controlled	140 (estimated)	18–70 (Years)	N
06399653	San Diego, CA, US	Alcohol	Double-blind, randomized, sham-controlled	80 (estimated)	21–65 (Years)	Y
06771037	Wernersville, PA, US	Alcohol	Double-blind, randomized, sham-controlled	60 (estimated)	18–65 (Years)	Y
07036055	Yunnan, China	Alcohol	Single-blind, randomized, sham-controlled	60 (actual)	18–55 (Years)	N
07079215	Daegu, South Korea	Opioids	Double-blind, randomized, sham-controlled	24 (estimated)	19–80 (Years)	Y
07079826	Pittsburgh, PA, US	Opioids	Double-blind, randomized, sham-controlled	50 (estimated)	18 + (Years)	Y
072818261	Houston, TX, US	Alcohol	Single-blind randomized, sham-controlled	20 (estimated)	18–64 (Years)	Y

Table 4
Device and stimulation parameters of registered clinical trials for VNS in SUD.

NCT	Location	Device Used	Number of Sessions	Length of Sessions	Stage	Outcome Measures
03762798	Cleveland, OH, US	NSS−2 BRIDGE percutaneous auricular field stimulator			Withdrawn	Number of patients who complete three follow-up visits while taking naltrexone and produce entirely negative urine opiate screens during that period
04075214	Austin, TX, US	Transcutaneous auricular vagus nerve stimulator	5	30 min	Completed	COWS HRV CRP levels Cortisol levels Cytokine levels PHQ−9 PCL−5 WHOQOL-BREF
04106739	Karnataka, India	Transcutaneous auricular vagus nerve stimulator			Completed	Craving scores Cue-induced craving resting state fMRI
04159909	Manhasset, NY, US	Transcutaneous auricular vagus nerve stimulator	8	5 min	Withdrawn	CIWA-Ar Change in neuroinflammatory reflex by blood cytokine levels
04556552	Atlanta, GA, US	electroCore gammaCore™-S transcutaneous cervical vagus nerve stimulator	2	2 min	Completed	VAS-craving HR PEP PPG amplitude Brain blood flow in anterior cingulate (PET) Levels of IL−6
04588519	Charleston, SC, US	Roo™ Therapy System transcutaneous auricular nerve stimulator	48	30 min	Completed	Number of participants with no adverse events related to bradycardia (HR < 80 bpm), worsening of swallowing or feeding, skin irritation, or elevation of NIPS Mean FNASS during days of tAN sessions Length of morphine weaning Length of hospital stay
04731935	Austin, TX, US	Sparrow® Therapy System transcutaneous auricular vagus nerve stimulator	1	120 h	Completed	COWS HRV PHQ−9 PCL−5 WHOQOL-BREF
05053503 Phase I	Rancho Mirage, CA, US Crownsville, MD, US Center City, MN, US Plymouth, MN, US	Sparrow® Ascent Therapy transcutaneous auricular vagus nerve stimulator	1	168 h	Completed	COWS SOWS-Gossop OCS PHQ−9 PCL−5 GAD−7 WHOQOL-BREF BARC−10 Xylazine test strip screen 14-panel urine drug screen
05053503 Phase II	Rancho Mirage, CA, US Crownsville, MD, US Center City, MN, US Plymouth, MN, US	Sparrow® Ascent Therapy transcutaneous auricular vagus nerve stimulator	36	2 h	Completed	14-panel urine drug screen Self-report of drug use OCS SOWS-Gossop Proportion of patients who receive and tolerate an XR-NTX injection post-acute detox treatment PHQ−9 PCL−5 GAD−7 WHOQOL-BREF BARC−10 Xylazine test strip screen

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Table 4 (*continued*)

NCT	Location	Device Used	Number of Sessions	Length of Sessions	Stage	Outcome Measures
05129020	Charleston, SC, US Dallas, TX, US San Antonio, TX, US	Sparrow Fledging™ transcutaneous auricular vagus nerve stimulator	8	30 min	Active, not recruiting	Median days of oral morphine medication after treatment start FNASS Median length of hospital stay due to NOWS and secondary NNNS-II Mean days of oral morphine medication Mean days from birth to medical readiness for discharge Median length of time to reach oral morphine control dose Mean total oral morphine delivered Proportion of infants with episodes of bradycardia, apnea, and/or laryngospasm due to tAN NIPS Number of infants with ASQ−3 score greater than 2 standard deviations below the mean for any domain Number of infants who have scores outside of "typical performance", as calculated by a score greater than 1 standard deviation away from the mean on SP−2 Proportion of participants who do not meet criteria for normal neurodevelopment as measured by BSID-III
05131334	Vienna, Austria	AuriStim percutaneous auricular vagus nerve stimulation	1	72 h	Completed	Mean pupillary diameter Resting pupillary diameter Latency Amplitude of constriction Constrictive ratio Duration of constriction Pupillary oscillations
05226130	San Diego, CA, US	Transcutaneous cervical vagus nerve stimulator	14	120 min	Completed	TAQ Feasibility SURE WHOQOL-BREF BAI PROMIS Pain Interference AUQ Neural response to heat pain fMRI
05591703 (Phase III of 05053503)	Rancho Mirage, CA, US Center City, MN, US Plymouth, MN, US	Sparrow® Ascent Therapy transcutaneous auricular vagus nerve stimulator			Completed	Proportion of participants in either Phase I or Phase II with a relapse event Mean change in BARC−10 Mean change in OCS Mean change in SOWS-Gossop Mean change in PHQ−9 Mean change in GAD−7 Mean change in PCL−5 Mean change in WHOQOL-BREF Mean change in CSS−5 LEC−5 Self-report of peer recovery support engagement Self-report of MOUD prevalence and adherence
05834478	Atlanta, GA, US	gammaCore® transcutaneous cervical vagus nerve stimulator	28	4 min	Recruiting	Proportion of participants who qualify for a change in ICD−10 code SOWS Safety of tcVNS Study retention Treatment adherence Brain dopamine D1 and D2/3 receptor regional binding potentials HR Inflammatory biomarkers Catecholamine concentration Time to rescue medication

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Table 4 (*continued*)

NCT	Location	Device Used	Number of Sessions	Length of Sessions	Stage	Outcome Measures
06130501	Cape Girardeau, MO, US	Sparrow® Ascent Therapy transcutaneous auricular vagus nerve stimulator			Recruiting	COWS Transition to MOUD or behavioral treatment BDNF levels S100B levels Device acceptability Device tolerability Device feasibility 3-month BUP retention Device adherence BUP medication compliance Substance use PCL−5 CAPS−5 PTSD remission status via CAPS−5 SOWS-Gossop COWS PCS WHOQOL-BREF BARC−10 PHQ−9 GAD−7
06308484	Berlin, Germany	Transcutaneous auricular vagus nerve stimulator	6–8	30 min	Recruiting	Blinding to condition Cognitive control Interoception Cue-reactivity HR HRV Mindfulness
06399653	San Diego, CA, US	Transcutaneous cervical vagus nerve stimulator	14	2 min	Recruiting	Alcohol consumption Dependence severity HAM-A CIWA-Ar AUQ WHOQOL-BREF Neural and physiological response to heat pain fMRI DrInC SURE
06771037	Wernersville, PA, US	Sparrow® Link transcutaneous auricular vagus nerve stimulator			Recruiting	CIWA-Ar Amount of comfort medications utilized VAS-craving Change in objective and subjective sleep Change in mood
07036055	Yunnan, China	Transcutaneous auricular vagus nerve stimulator	10	30 min	Completed	Emotional inhibitory control in emotional GNG Drift rate Brain-heart coupling strength (HRV-EEG coupling) DERS Score VAS-craving GAD−7 PHQ−9
07079215	Daegu, South Korea	ADTPM1 auricular nerve stimulator	28	60 min	Recruiting	TEAEs COWS SOWS VAS-craving HR NRS

(*continued on next page*)

Table 4 (*continued*)

NCT	Location	Device Used	Number of Sessions	Length of Sessions	Stage	Outcome Measures
						MADRS GAD−7 ISI-K PHQ−15 Change in DSM−5 criteria for opioid use disorder OCS−3
07079826	Pittsburgh, PA, US	Sparrow® Link transcutaneous auricular vagus nerve stimulator			Not yet recruiting	Device usage consistency Early device discontinuation COWS Early device refusal rate Device discomfort reported Referral to follow-up care rate Intent to engage in care rate Post discharge engagement Desire to continue device use SOWS NPRS OCS−3 STAI-S MADRS HRV Mean MME per 24-hour period
072818261	Houston, TX, US	Sparrow® Ascent Therapy transcutaneous auricular vagus nerve stimulator	5	4 h	Not yet recruiting	CIWA-Ar Average benzodiazepine use PACS MADRS SBQ-R PAWSS

Abbreviations: ASQ−3, Ages and Stages Questionnaire−3; AUDIT, Alcohol Use Disorder Identification Test; AUQ, Alcohol Urge Questionnaire; BAI, Beck Anxiety Inventory; BARC−10, Brief Assessment of Recovery Capital−10; BDI, Beck Depression Inventory; BDNF, brain-derived neurotrophic factor; BIS, Barratt Impulsiveness Scale; bpm, beats per minute; BSID-III, Bayley Scale of Infant and Toddler Development III; BUP, buprenorphine; CAPS−5, Clinician Administered PTSD Scale for DSM−5; CAT, Credit Assignment Task; CIWA-Ar, Clinical Institute Withdrawal Assessment for Alcohol-Revised; COWS, Clinical Opiate Withdrawal Scale; CRAT, Choice Under Risk and Ambiguity Task; CRP, C-reactive protein; CSS−5, Commitment to Sobriety Scale−5; D1 and D2/3, brain dopamine receptors; DDT, Delay Discounting Task; DERS, Difficulties in Emotion Regulation Scale; DMQ-R, Drinking Motives Questionnaire-Revised; DrInC, Drinker Inventory of Consequences; EEG, electroencephalogram; fMRI, functional magnetic resonance imaging; FNASS, Finnegan Neonatal Abstinence Scoring System; GAD−7, Generalized Anxiety Disorder−7; HAM-A, Hamilton Anxiety Rating Scale; HR, heart rate; HRV, heart rate variability; ICD−10, International Classification of Disease−10; IL−6, interleukin−6; ISI-K, Insomnia Severity Index-Korean; LAT, Loss Aversion Task; LEC−5, Life Events Checklist for DSM−5; MADRS, Montgomery-Asberg Depression Rating Scale; MAIA, Multidimensional Assessment of Interoceptive Awareness; MCQ, Meta Cognitions Questionnaire; MME, morphine milligram equivalents; MOUD, medication for opioid use disorder; NIPS, Neonatal Infant Pain Scale; NNNS-II, Neonatal Neurobehavioral Scale-II; NOWS, Neonatal Opioid Withdrawal Syndrome; NPRS, Numeric Pain Rating Scale; NSSI, nonsuicidal self-injury; OCS−3, Opioid Craving Scale−3; PACS, Pennsylvania Alcohol Craving Scale; PAWSS, Prediction of Alcohol Severity Scale; PCL−5, Post-traumatic Stress Disorder Checklist for DSM−5; PEG−3, Pain, Enjoyment, and General Activity−3; PEP, pre-ejection period; PET, positron emission tomography; PHQ−9, Patient Health Questionnaire−9; PPG, photoplethysmography; PROMIS-A, Patient-Reported Outcomes Measurement Information System-Anxiety; PROMIS-D, Patient-Reported Outcomes Measurement Information System-Anxiety-Depression; PSQI, Pittsburgh Sleep Quality Index; S100B, calcium-binding protein B; SBQ-R, Suicidal Behaviors Questionnaire-Revised; SOCRATES-K, Stages of Change Readiness and Treatment Eagerness Scale-Korean Version; SOWS, Subjective Opiate Withdrawal Scale; SP−2, Sensory Profile 2; STAI-S, State-Trait Anxiety Inventory-State; SURE, Substance Use Recovery Evaluator; tAN, transcutaneous auricular neurostimulation; TAQ, Treatment Acceptability Questionnaire; tcVNS, transcutaneous cervical vagus nerve stimulation; TEAEs, Treatment Emergent Adverse Events; VAS, Visual Analog Scale; WHOQOL-BREF, World Health Organization Quality of Life Assessment; XR-NTX, extended-release naltrexone

Table 5
Methodological quality and bias of published trials using Down and Black Bias Checklist.

Author (Year)	Percentage	Methodological Quality
Miranda et al. (2018)	66.6	Good
Jenkins et al. (2021)	75.7	Good
Tirado et al. (2022)	87.8	Excellent
Gazi et al. (2022)	90.9	Excellent
Rahman et al. (2025)	84.8	Excellent
Wang et al. (2021)	87.8	Excellent
Treiber et al. (2024)	72.7	Good
Klaming et al. (2025)	84.8	Excellent

opioid withdrawal. Strengths of the study include its randomized, double-blind design and multimodal outcome assessment; however, limitations include the small sample size, uncertainty regarding exact timing of last opioid use, and reliance on self-reported withdrawal rather than clinician-administered ratings. Notably, the sham condition delivered low-level stimulation, raising the possibility of partial vagal engagement.

This same cohort is described in two subsequent publications (described below) which appeared in the review search, however, the paper described above represents the original report. Given that heart rate reductions were seen, but there was no significant change in craving, the authors propose that the autonomic system is more prone to modulation than the executive function system and the two subsequent reports offer support by expanding on analyses of the collected data using objective biomarkers. A positive correlation between respiration and pain and a negative correlation between heart rate variability and pain are demonstrated (Gazi et al., 2022b), and reductions in perceived pain are re-reported from the original study. This paper offers further detail and shows that ~50% of participants report no change in pain with either Active (4/9) or Sham (5/11) stimulation. This could reflect the need for further replication in a larger study or potentially raises questions about whether there may be sub-groups of responders and non-responders to tcVNS. The final publication from this cohort is a conference paper reporting a reduction in respiratory variation with tcVNS over sham, providing further support of alleviating withdrawal-related distress and autonomic dysregulation (Gazi et al., 2022c). Collectively, publications from this group suggest tcVNS may be effective for downregulating stress responses in withdrawal from opioids.

The final VNS opioid publication (Rahman et al., 2025) is a neuroimaging positron emission tomography (PET) study from the same investigative group. Unlike the acute withdrawal study, participants were on stable medication for OUD, had been abstinent from opioids for at least 10 days, and underwent stimulation after daily medication dosing; therefore, during a treatment phase with substantially reduced withdrawal burden. The study employed a double-blind, sham-controlled design using left-sided tcVNS during the same cue-reactivity paradigms but now within the PET scanner. Despite the extremely low sample size (n=7 active, n=4 sham, with fewer completing all scans), active tcVNS was associated with increases in activation within prefrontal and control-related regions, including the anterior cingulate cortex and inferior frontal gyrus. There were no significant changes in subjective withdrawal, craving or distress.

The sham condition delivered low-level electrical stimulation, which may have had physiological or expectancy effects. While measures of withdrawal did not show a significant difference between groups, this study was carried out when participants had completed detox, and after medication for OUD had been administered, and is consistent with participants being beyond the withdrawal window, limiting the relevance of these findings. VAS craving scores showed slight increases in both groups. However, statistical analyses relied on frequentist methods despite extremely low participant numbers, and stimulation was titrated to tolerance, introducing additional inter-subject variability. Given the low sample sizes and limitations mentioned, the findings from this study are important but should be regarded as hypothesis-generating observations rather than evidence of clinical efficacy. A conference paper of this cohort appeared within the literature search (Abbaraju et al., 2024), however, as no effect of VNS on craving was found within the study, this reports the associations between short-term heart rate variability and drug cue response across both the active and sham groups.

3.2. Alcohol

In the initial noninvasive VNS for AUD, Wang et al. (2021) conducted a randomized control trial in male inpatients who had completed acute detoxification and were clinically stable. The active group was titrated based on tolerance, using bilateral taVNS of the concha; the sham group received the same device without power. Stimulation occurred three times a day, for 30 minutes, for four weeks with the aim of treating protracted alcohol withdrawal symptoms. Groups did not differ on baseline demographic or clinical measures. Outcomes included validated self-report questionnaires assessing depression, anxiety, sleep quality, and alcohol craving, alongside biomarkers BDNF, TNF-α, IL−6, and leptin. AEs were not listed as an outcome but no AEs were reported in the paper. Results showed both depression and sleep scores were significantly improved in the active group, although anxiety and craving scores showed no significant difference. Biologically, taVNS was associated with a significant increase in BDNF levels, while inflammatory markers (TNF-α, IL−6) and leptin were unchanged. Although significantly different, changes in depression and sleep scores were modest, and it is uncertain if these were clinically, as well as statistically, significant. Notwithstanding, the concordance between improvements in mood and sleep and increased BDNF provides further support for taVNS as an adjunctive intervention for SUD.

Treiber and colleagues (Treiber et al., 2024) conducted an open-label pilot study examining effects of a percutaneous taVNS (AuriStim, Multisana; Vienna, Austria) on autonomic nervous system activity during acute alcohol withdrawal. As pupil size reflects the balance of sympathetic and parasympathetic activity, authors used this as a physiological verification of modulation. VNS was delivered via electrodes that innervated the left cymba concha and delivered stimulation (three hours on/off) for 72 hours during acute alcohol withdrawal. The primary outcome measure was pupillometry under a tropicamide challenge. This challenge involved anticholinergic tropicamide eyedrops administered to induce pupil dilation through blockade of cholinergic receptors. Greater pupil dilation during a tropicamide challenge has previously been observed in individuals with AUD (Grünberger et al., 1998) compared to controls. Therefore, reduced dilation following taVNS was interpreted as a potential indicator of restoration of autonomic imbalance and increased acetylcholine activity. Participants were concurrently receiving standard withdrawal pharmacotherapies, allowing exploratory comparisons between medications. Although participants were in withdrawal, effects of withdrawal were not measured, but craving assessed via VAS was a secondary outcome.

The authors reported significant decreases in the absolute change of pupil diameter from baseline following VNS in the tropicamide challenge, and differences in pupil diameters across multiple time points, suggesting modulation of autonomic responsivity. No differences were observed between the two pharmacological treatment groups. These findings support the use of pupil size as a psychophysiological marker of VNS and authors suggest that pupillometry may provide a low-cost physiological measure for future neuromodulation studies. The findings are preliminary, and further work is required in a larger sham-controlled, randomized study; however, biological markers, such as pupil size, may be less susceptible to placebo than subjective effects. Alcohol craving was also significantly reduced following stimulation, which in spite of the recognized limitations is an interesting finding as, while other studies in OUD have reported reduced craving, this has not been consistent across publications nor reached statistical significance.

Klaming et al. (2025) conducted a double-blind, randomized, sham-controlled pilot study using tcVNS in male Veterans with AUD. The study was a feasibility pilot to test treatment adherence of at-home delivery, and to position the intervention as a means to improve functional outcomes rather than focusing on abstinence or withdrawal. Participants were randomized to active (n=9) or sham (n=10) stimulation and were permitted to continue drinking ad libitum throughout the study. Stimulation was delivered bilaterally with participants self-administering and adjusting stimulation intensity to individual tolerability. Primary outcomes emphasized functional impairment and psychosocial functioning, assessed using the Drinker Inventory of Consequences (DrInC−2R) and the Brief Inventory of Psychosocial Functioning (BIPF), alongside measures of depression and anxiety symptoms.

Both functional outcome measures demonstrated robust improvements with active stimulation. Participants in the tcVNS group exhibited significantly greater reductions in alcohol-related consequences (DrInC−2R) and psychosocial impairment (BIPF) compared with sham, both results with large effect sizes. Treatment adherence was high across both groups, though the at-home administration design limited objective verification of stimulation delivery.

Active tcVNS was associated with significantly greater reductions in depressive symptoms compared with sham, with participants receiving tcVNS showing a shift from 'moderate' to 'mild' depression severity, while the sham group remained in the 'moderate' range. This was reflected by a significant group-by-time interaction on Patient Health Questionnaire−8 (PHQ−8) scores with a large effect size. No significant group differences were observed for anxiety symptoms, percentage of drinking days, or heavy drinking days. Percentage of drinking days showed a numerical trend favoring active stimulation but did not reach statistical significance; given the small sample size, a Bayesian analytic framework may have provided additional information regarding the strength of this effect. Collectively, these findings suggest that tcVNS may improve depressive symptoms and alcohol-related functional outcomes in individuals with AUD, even in the absence of significant changes in drinking behavior.

3.3. Clinical trials

As of February 2026, there were 21 studies listed on clinicaltrials.gov investigating VNS neuromodulation for addiction; ten were designated complete, six were currently recruiting, three were in the pre-recruiting phase, and two were withdrawn (Table 4). Of the studies listed, the primary substances under investigation were alcohol (n=9) and opioids (n=12). Devices being utilized include gammaCore (n=2), ADTPM1 (n=1), Spark Biomedical Roo (n=1), BRIDGE (n=1), Sparrow Link (n=2), AuriStim (n=1), Sparrow Ascent Therapy System (n=4), Sparrow Fledging Therapy System (n=1), Sparrow Therapy System (unspecified) (n=1), unspecified taVNS (n=5), and unspecified tcVNS (n=2). Four devices target the VN cervically and 17 via the auricular branch. Primary outcomes focus on changes in substance-related behaviors (e.g., alcohol/drug use, withdrawal severity, craving); treatment durability and acceptability; physiological and autonomic responses (e.g., heart rate, pupil size, inflammatory biomarkers); and neurobiological markers including PET or functional MRI. Secondary outcomes include broader assessments of cognition, emotion, pain, quality of life, biomarkers of inflammation and neuroplasticity, sleep, device feasibility, and clinical functioning. Primary outcome assessment end points ranged from two minutes to three months post-VNS, with one trial conducting an additional 12-month follow-up as an exploratory time point.

4. Discussion

Clinical research examining non-invasive VNS in addiction remains limited, especially for studies with randomized, sham-controlled designs. Across the studies reviewed, only AUD and OUD were found to have been investigated, and the majority of OUD studies targeted withdrawal rather than longer-term outcomes such as craving, mood, or DUR. In alcohol, two of three studies targeted longer-term effects or functional outcomes, such as reduced drinking days. Despite this narrow focus, the emergence of multiple pilots and early-phase clinical trials reflects a growing interest in VNS as a potential adjunctive intervention for SUD. Collectively, the literature suggests that non-invasive VNS is safe, well tolerated, and capable of modulating some clinically relevant symptoms of acute withdrawal, such as pain, and symptoms of low mood or distress. However, the evidence base remains preliminary, and for other symptoms of SUD, such as craving, the field cannot yet draw definitive conclusions.

Primary outcome measures varied substantially, and therefore consistency cannot be found across every domain, with the exception of safety. However, there is a notable convergence in the direction of effects across the studies, with VNS demonstrating beneficial modulation to autonomic markers, mood-related outcomes, and symptoms of withdrawal. Given the independence of these studies and cohorts, this strengthens the plausibility of non-invasive VNS as an adjunctive treatment in SUD, especially when considered alongside numerous VNS studies on depression and stress regulation (Aaronson et al., 2017; Bremner et al., 2020). However, it remains to be determined if non-invasive VNS impacts craving in a meaningful way. For example, reductions in craving following VNS, compared to sham, were found (Wang et al., 2021; Gazi et al., 2022a), however, these only reached significance in one study (Treiber et al., 2024). Given the neural targets of VNS, it may be that VNS does not directly attenuate craving (Gazi et al., 2022a), but that primary effects are through modulation of the parasympathetic nervous system. Therefore, VNS may affect craving in a downstream manner, possibly with increasing effects over repeated exposure or different stimulation parameters. Thus, effects in the reviewed studies are subtle and while not always statistically different may be clinically important. Alternatively, if with further studies craving is demonstrated not to be affected by VNS, this does not limit its potential to reduce other motives for drug use such as, stress, pain, and negative affect.

While effects on craving were inconsistent, there was convergent evidence for modulation of withdrawal-related distress, affective, autonomic, and functional domains. Critically, these domains may map directly onto meaningful harm-reduction outcomes which does not concentrate on a primary goal of abstinence, and allows for more flexibility, with a focus on improving well-being, mood, and long-term behavioral changes (Pridgen et al., 2025). These changes in turn lead to outcomes that include, but are not limited to, improved medication adherence, fewer heavy-use days, reduced overdose risk, and fewer emergency department visits (Lambdin et al., 2022; Amin-Esmaeili et al., 2024; Logan and Marlatt, 2010). Changes in the domains captured across the reviewed studies may therefore support downstream harm-reduction benefits, even without immediate drug abstinence or reduction in cravings (Schwebel et al., 2026). This reframing is important, if non-invasive VNS, and other neuromodulation techniques, are evaluated solely against traditional endpoints such as craving or abstinence, their therapeutic value for harm-reduction goals may be systematically underestimated (Pridgen et al., 2025).

There is only one brain imaging study in the current review (Rahman et al., 2025), and more neuroimaging research is needed; however, the results are informative. Following short-term neuromodulation with VNS, increased activation in prefrontal regions was noted, which converges with fluorodeoxyglucose-PET evidence of increased glucose metabolism in the prefrontal cortex after 12 weeks of neuromodulation with deep brain stimulation in participants with OUD (Rezai et al., 2024; Mahoney et al., 2021). Taken together, these findings suggest both forms of neurostimulation may engage prefrontal circuitry through subcortical modulation, supporting higher level functions of affect and cognitive control. More broadly, resting state fMRI studies following VNS in both depression (Zhang et al., 2022) and in healthy controls (Mao et al., 2022) support enhanced functional connectivity between limbic and

prefrontal regions.

Other physiological markers suggest that non-invasive VNS may influence autonomic systems in SUD via the vagal afferent and locus coeruleus-norepinephrine mechanisms previously outlined. Cardiovascular and respiratory systems are known to be dysregulated in SUD populations (Zarei et al., 2025) Non-invasive VNS was associated with reductions in heart rate (Gazi et al., 2022b) and respiratory variability (Gazi et al., 2022c), consistent with a shift towards increased parasympathetic engagement. Pupillometry changes implicate the norepinephrine system, which drives arousal, craving, and stress-induced DUR (Treiber et al., 2024), and increased BDNF (Wang et al., 2021) may support mesolimbic plasticity (Ghitza et al., 2010), and contribute to improvements in sleep and depressive symptoms (Wang et al., 2021). All of which may indirectly promote harm-reduction outcomes. However, it is important to note that given the limited literature in VNS in SUD there is no replication of these biomarker findings.

The outcomes reported within this review cannot be directly compared across studies, either within a given modality (auricular versus cervical) or between modalities, precluding a formal meta-analysis. Across studies there is a substantial variability in device type, but also in parameters, such as stimulation frequency, amplitude, duty cycle, and total dose. These differences are not trivial; variations in stimulation thresholds can recruit distinct vagal fiber populations (A, B, and C fibers) (Groves and Brown, 2005), which in turn mediate different neurochemical and autonomic effects. Similarly, differences in duty cycle and total dose may influence the degree and consistency of neuromodulatory effects on brainstem nuclei. Furthermore, some studies apply fixed stimulation intensities, while others titrate to individual tolerability, likely influencing the degree of vagal engagement and consequently, outcomes. As a result, studies reporting similar outcome domains may nonetheless reflect fundamentally different physiological interventions, limiting the interpretability of null or inconsistent findings. Future trials should prioritize transparent and standardized reporting of all parameters to facilitate cross-study comparisons and the development of evidence-based dosing frameworks.

Additionally, variability was seen in characteristics of drug use, such as years of use or co-occurring SUD; laterality (four studies stimulated the left, two the right, two used bilateral stimulation and one was unspecified), session number (1–84 sessions), session length (2 min−120 h) and outcomes. In some studies, the device electrodes were placed in clinic and remained in the same location, while others used a handheld tcVNS device, which could lead to inconsistencies in the location of nerve stimulation.

Since many of the reviewed studies were smaller, pilot trials, the sample sizes leave unanswered questions pertaining to possible sex-differences in responses to VNS. Preclinical literature shows that following VNS females show long-term cardiovascular effects, such as heart rate and heart rate variability, while males demonstrated short-term effects (Yaghouby et al., 2020). Another pre-clinical study found cardiac changes differed in a frequency specific manner across sex, where female rats respond to taVNS at higher frequencies than males (Barbetti et al., 2025). It is also reported clinically that vagally mediated heart rate may be dependent in a sex-specific manner (Koenig and Thayer, 2016).

This review is limited in that it only included wearable or handheld VNS devices and has not included reports of acupuncture or acupressure on relieving SUD symptoms or enhancing abstinence attempts. Meta-analyses of acupuncture describe no differences between sham or active acupressure for cocaine use disorder, however, all were of low methodological quality (Gates et al., 2006) and the evidence was inconclusive given the heterogenous methodology. A review of auricular acupuncture in OUD found just four studies (Baker and Chang, 2016), which was again confounded by methodological issues. Results suggested that craving may not be targeted by acupuncture, but that it may address other causes of DUR, medication assistance treatment, or treatment retention.

4.1. Future directions

There is currently limited evidence of planned trials extending beyond AUD or OUD. This represents a significant gap in the literature, particularly given the high clinical need for effective non-pharmacological interventions across methamphetamine and cocaine populations. Moreover, co-occurring SUD is becoming ubiquitous (Crummy et al., 2020; Rough and Nader, 2026) and future studies should consider testing reductions in use and craving across all substances. Additionally, while the reviewed studies include measures of depression, mood, and craving, the focus lays heavily on the alleviation of withdrawal symptoms with VNS, for which a VNS device (BRIDGE) is already FDA-approved. Instead, investigating whether VNS can produce improved functional harm-reduction outcomes, such as quality of life, cognitive functioning, and distress tolerance, could help demonstrate the use of VNS as an adjunctive treatment alongside medication and behavioral therapy. Increasing the sample size of future studies, reporting on sex-differences, and including randomized-sham controlled designs will be critical to moving the field forward. Non-invasive VNS has the benefit of potential self-administration by the patient, or to be worn for days after professional placement, making it more appealing than other forms of neuromodulation for many conditions. However, as with other neuromodulation techniques, there is an undeniable amount of heterogeneity that exists pertaining to optimal dosing, target engagement, device parameters, laterality and parameter reporting (Farmer et al., 2020). All of which are critical to the development of a standard of care and interpretability of results across studies.

4.2. Conclusions

The evidence for the utility of VNS for alleviating withdrawal symptoms was recognized by the FDA before the publication of the first study (Miranda and Taca, 2018). Later studies provide converging evidence for the safety and tolerability of VNS alongside evidence of possible modulation of acute withdrawal and autonomic responses. Non-invasive VNS seems to provide benefit for a range of symptoms observed in other conditions, including disturbances in sleep and low mood, and now the SUD research field must determine how, or if, VNS can best support those with addiction.

While the studies within this review did not show overwhelming support for reduced craving, there are many reasons why sustaining abstinence becomes challenging, such as poor sleep, depression, and low distress tolerance, to name a few. By targeting these symptoms, outcomes may still improve even if craving itself is not directly affected. If VNS can effectively reduce other co-occurring symptoms of SUD, then combinations of neuromodulation may be beneficial, such as using VNS to reduce stress in combination with focused ultrasound or transcranial magnetic stimulation to target craving.

CRediT authorship contribution statement

Thompson-Lake Daisy: Writing – original draft, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization**. Snetkov Gabriella:** Writing – review & editing, Visualization, Methodology, Data curation. **Johnson Lucas :** Writing – review & editing, Data curation. **Ait-Daoud Nassima :** Writing – review & editing, Resources. **Mahoney James:** Writing – review & editing, Resources.

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Declaration of Competing Interest

The authors declare no conflicts of interest related to the information contained within this manuscript.

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