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Noninvasive Vagal Nerve Stimulation for Opioid Use Disorder

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Abstract

Background: Opioid Use Disorder (OUD) is an escalating public health problem with over 100,000 drug overdose-related deaths last year most of them related to opioid overdose, yet treatment options remain limited. Non-invasive Vagal Nerve Stimulation (nVNS) can be delivered via the ear or the neck and is a non-medication alternative to treatment of opioid withdrawal and OUD with potentially widespread applications.

Methods: This paper reviews the neurobiology of opioid withdrawal and OUD and the emerging literature of nVNS for the application of OUD. Literature databases for Pubmed, Psychinfo, and Medline were queried for these topics for 1982-present.

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Results: Opioid withdrawal in the context of OUD is associated with activation of peripheral sympathetic and inflammatory systems as well as alterations in central brain regions including anterior cingulate, basal ganglia, and amygdala. NVNS has the potential to reduce sympathetic and inflammatory activation and counter the effects of opioid withdrawal in initial pilot studies. Preliminary studies show that it is potentially effective at acting through sympathetic pathways to reduce the effects of opioid withdrawal, in addition to reducing pain and distress.

Conclusions: NVNS shows promise as a non-medication approach to OUD, both in terms of its known effect on neurobiology as well as pilot data showing a reduction in withdrawal symptoms as well as physiological manifestations of opioid withdrawal.

Introduction

Opioid Use Disorder (OUD) is a national epidemic with devastating consequences. Deaths from opioid overdose, including prescription opiates like OxyContin and Percocet, as well as heroin and other illegal opiates, increased five-fold from 1999 to 2016 [1]. Opioid overdose is now the leading cause of accidental death in the United States [2]. In 2021, there were over 100,000 drug overdose-related deaths, most of which were due to opioids [3]. The standard of care for treating Opioid Use Disorder (OUD) are Medications for Opioid Use Disorder (MOUD), which includes opioid receptor agonists and antagonists; however, the barriers to MOUD care are high, including lack of access to MOUDs with proven benefit, like opioid agonists, methadone and buprenorphine [4–9]. Most OUD patients will relapse without medication, and about half relapse even after treatment with the gold standard opioid-agonist, methadone [10]. Many patients don't want to take opioid agonists, but treatment with naltrexone, an opioid receptor antagonist, requires an extended period of detoxification during which the risk of relapse and overdose-related death is high [11–13]. During this period of detoxification there is an increase in both the probability of relapse (due to withdrawal symptoms) and the risk of overdose-related death due to a loss of tolerance [4,14,15]. Management of withdrawal during the treatment of OUD is crucial when initiating OUD treatment protocols that will maintain long-term efficacy in prevention of relapse. Non-pharmacological methods that treat withdrawal could provide a bridge to facilitate effective implementation and continuation of opioid antagonist pharmacological therapies. Additionally, the initial induction period when opioid agonist dose adjustment occurs is often associated with symptoms of opioid withdrawal that can increase the risk of relapse and/overdose. Additional interventions to use as adjuncts to FDA-approved treatments of opioid withdrawal, such as lofexidine [16–18], will also be useful. This paper describes the use of a form of neuromodulation called Non-invasive Vagal Nerve Stimulation (nVNS), and outlines its potential usefulness for the treatment of OUDs in the context of its effects on neurobiology and how this may intersect with the neurobiology of OUD and opioid withdrawal.

Changes in Neurobiological Systems in OUD

OUD is characterized by alterations in multiple neurobiological systems [19]. Opioid withdrawal is associated with uncomfortable symptoms including headache, nausea and vomiting, diarrhea, sweating, fatigue, anxiety, and sleep disturbance. These symptoms

are driven by activation of the sympathetic nervous system with release of inflammatory biomarkers and alterations in dopaminergic reward systems that play a critical role in both addiction and relapse risk [20]. Mesocortical and mesolimbic dopaminergic pathways from the ventral tegmentum area to the medial prefrontal cortex and ventral striatum (nucleus accumbens) play an important role in OUD, and stress and substance use have similar effects on these systems [21–30]. Repeated exposure to opioids, both prescription and illicit, among individuals living with OUD are linked to increased risks for developing pain sensitivity and centralization due, in part to, increased activation of NMDA receptors leading to sensitization of spinal neurons [31]. Compared to controls, persons with OUD show increased cortisol, heart rate and blood pressure response to both drug cues [32] and to a laboratory-based stress task involving public speaking [33]. Persons with OUD have also shown increased drug craving after exposure to drug cues compared to controls [32] although laboratory-based mental stress did not potentiate drug craving over exposure to drug cues alone [33]. Women with OUD showed a pattern of lower cortisol response and experienced more subjective stress during public speaking than men with OUD [34]. Patients with PTSD and either cocaine or alcohol substance use disorders showed increased drug craving following both trauma and drug-related cues [35]. Patients with PTSD experience higher pain levels and have increased instance of substance use disorders than non-PTSD patients, although pain is not a mediator of the increased substance use rates in these patients [36]. These studies show that drug cues activate neurobiological systems that underlie craving, and that responses to this activation differ by gender.

Treatment of OUD with MOUDs

Standard treatments for OUD are medications that act on opioid receptor, including buprenorphine, methadone, and naltrexone. Methadone is a long-acting full opioid agonist of the mu opioid receptor. Buprenorphine is a partial agonist of the mu opioid receptor and an antagonist of the kappa opioid receptor. Methadone must be administered in a specialized clinic, and access to buprenorphine, although it is effective in reducing the risk of relapse and overdose and can be taken at home, is limited. A recent “secret shoppers” study in which volunteers called medical clinics seeking treatment for an OUD showed that only 27% of individuals were able to be seen in a clinic and obtain a buprenorphine prescription if they were not willing to pay cash for treatment [7]. Fifty percent of clinics listed as available for buprenorphine treatment either did not have a working phone number or a physician or practitioner with the necessary specialized certifications to prescribe, and of those, 30% outright refused to treat non-cash paying patients [7]. Thus, buprenorphine treatment, with costs upwards of $350, is cost prohibitive for most people, further precluding access for OUD patients in need of care [9].

Naltrexone is an antagonist of the opioid receptor that is an alternative to opioid agonist therapy that is also effective for OUD [5,11,15,37,38]. Long--acting naltrexone is superior to treatment as usual including non-pharmacological counseling for relapse prevention [12]. Once safely initiated, long-acting naltrexone has equivalent or increased efficacy in relapse prevention as compared to buprenorphine [13]. Naltrexone is an effective long-term treatment for OUD, but the required opioid abstinence and subsequent withdrawal period prior to initiation represents a key barrier to treatment [39]. Interventions during the period

of opioid withdrawal to reduce symptoms and prevent relapse, allowing patients to complete the period of abstinence required before the initiation of long-acting naltrexone treatment may both benefit patients with OUD in recovery maintenance and reduce overdose-related deaths during this critical period [39].

Neuroimaging and Neurobiology of OUD

Advancements in neuroimaging have allowed for identification of brain regions and specific neural circuits that are implicated in OUD [40]. The major pathways that play an important role in addiction and relapse are dopaminergic mesolimbic and mesocortical pathways from the ventral tegmentum to the ventral striatum (nucleus accumbens) and medial prefrontal cortex (anterior cingulate) [20,41] and the amygdala [40,42,43]. Release of dopamine in the nucleus accumbens (ventral striatum) is associated with pleasure and reward and is accepted as playing a role in addiction [19,20,44–47]. The medial prefrontal cortex plays an important role in modulation of emotion that is relevant to relapse and addiction [40,42,43] as well as drug craving. The amygdala mediates anxiety and fear reactions and plays a key role in OUD [40,42,43].

The maintenance of addiction and relapse is often related to craving precipitated by conditioned responses to exposure to drug cues in patients with OUD [48]. These neural circuits allow for the development and maintenance of such conditioned responses in patients with OUD [40,42,43]. The amygdala likely plays a role in symptoms of anxiety associated with opioid addiction and withdrawal [49]. The medial prefrontal cortex is implicated in the appraisal and regulation of emotions. By inhibiting amygdala activity through extinction mechanisms [50] the medial prefrontal cortex plays a critical role in the acquisition of fear memories as shown in both animal studies [51,52] and brain imaging studies in humans [53–63], highlighting its role in anxiety which is a part of the opioid withdrawal response [19]. Changes in these brain areas are reversible with treatment in patients with OUD [46].

The Locus Coeruleus (LC), located in the pons, is the major source of noradrenergic cell bodies in the brain [64]. Noradrenergic neurons project to multiple areas in the brain, including amygdala, medial prefrontal cortex, hippocampus, ventral striatum, and other areas of the cerebral cortex [64]. Release of norepinephrine, which occurs under both stress and opioid withdrawal, causes an increase in attention and vigilance behaviors, and activates the cardiovascular system [23,24,64]. Inputs to the LC come from the nucleus paragigantocellularis and nucleus prepositus hypoglossi, and endogenous opiates in this brain area are inhibitory to LC neurons [65,66]. Withdrawal of opioids in animals addicted to methadone causes a rebound increase in LC activity, resulting in increased norepinephrine release in the amygdala that subsequently activates the cardiovascular system and drives symptoms of withdrawal [65]. Opioids in the LC initially inhibit of production of adenylyl cyclase and Cyclic Adenosine Monophosphate (cAMP) [67,68]. With prolonged dependence there is eventually an increase in adenylyl cyclase and cAMP resulting in increased cAMP dependent response element binding protein (CREB). This upregulation likely represents a compensatory mechanism for the initial inhibitory effects of opioids [67,68]. Upregulation in the cAMP cascade in the LC is hypothesized to represent a component of tolerance, as

well as the mechanism of opioid dependence and withdrawal [67,68]. Norepinephrine and the LC therefore play a central role in opioid addiction and symptoms of withdrawal due to rebound sympathetic activation.

Positron Emission Tomography (PET) studies in patients with OUD implicate similar neurobiological systems and circuits as seen in animal models [46,69]. Morphine acutely reduces brain metabolic activity in the superior frontal gyrus, paracentral lobule, supramarginal gyrus, anterior cingulate, caudate (striatum), gyrus rectus, and middle temporal gyrus [70]. Functional Magnetic Resonance Imaging (fMRI) studies showed abnormal connectivity in OUD in ventral striatum, medial prefrontal cortex (anterior cingulate), amygdala and insula [71]. Functional imaging studies of brain blood flow and metabolism using PET showed increased activation of ventral striatum and medial prefrontal cortex (anterior cingulate) during opioid [46] and nicotine [72,73] craving. Patients with OUD who are exposed to emotional pictures during heroin abstinence had increased connectivity as measured with resting state fMRI between left amygdala and left fusiform gyrus and right amygdala and right orbitofrontal cortex, this normalized after administration of heroin [74].

Chronic opioid use is associated with a decrease in binding of the Dopamine Transporter (DAT) [75] and D-2 receptor binding measured with PET and the radiolig and [C-11] raclopride [40,69,76]. This may reflect a decrease in endogenous dopamine release following chronic overstimulation with opioids and/or decreased transporter and/or receptor binding [40]. DAT uptake was not associated with heroin craving in abstinent OUD patients [75]. These findings implicate dopaminergic pathways in the ventral striatum and medial prefrontal cortex in OUD.

Effects of Early Trauma on Vulnerability to OUD

Early life trauma plays a critical role in the development and maintenance of OUD in many patients [77–83]. Individuals with a high number of Adverse Childhood Experiences (ACEs) have a 10-fold increase in risk for the use of injected drugs, mostly opioids [77,84,85], and there are important links between OUD and Posttraumatic Stress Disorder (PTSD) [36,79,80,86–93]. Recurrent stressors and exposure to triggers of traumatic memories in everyday life is a common precipitator of relapse in patients with OUD [22,89,94], especially for women using prescription opioids [95]. There is a great deal of overlap in brain circuits mediating OUD and PTSD (Figure 1). The fact that nVNS modulates many of these brain regions suggests that it could be useful for both disorders as well as the complex co-morbid conditions that are often seen in patients with OUD.

Vagal Nerve Stimulation for OUD

Neuromodulation represents a new paradigm in the field of mental and substance use disorders [96,97]. Vagal Nerve Stimulation (VNS), is an electrical stimulation treatment that may be useful in the treatment of OUD given its demonstrated effects on brain circuits and systems implicated in OUD and opioid withdrawal and its demonstrated positive effects on related symptom areas like pain and anxiety [96–103]. Currently, implantable VNS devices

are FDA-approved to treat medically refractory epilepsy and treatment-resistant depression [104,105]. Neuromodulation using VNS can reduce symptoms of pain [106,107] and anxiety [108,109] both of which contribute to the development of OUD and/or precipitate relapse. VNS is also beneficial in the treatment of headaches [110–113], epilepsy [114–119] and major depression [104,105,120–131]. The effects of VNS on neuroplasticity and learning suggest it may be useful in extinction of the conditioned stimulus and reinforcement processes that underlie addictions [132–138] possibly through enhancement of Long Term Potentiation (LTP) in the hippocampus [139]. VNS reduces autonomic tone and sympathetic function [140–145] immune function [146–153] and fear circuits that likely play a role in symptoms of anxiety associated with OUD [108,154–159], all of which indicate its potential to play a beneficial role in OUD and withdrawal. Animal studies show that VNS enhances neuroplasticity in the frontal cortex and reduces cocaine seeking behaviors [160]. In animal models of schizophrenia, VNS enhances mesofrontal dopamine transmission [161]. Recent studies have also applied VNS to the treatment of schizophrenia [162,163], obsessive-compulsive disorder [164], PTSD [165–167] and Mild Traumatic Brain Injury (mTBI) [165], all with promising results. The first generation of VNS devices had to be surgically implanted, reducing their feasibility in treatment of mental disorders [102]. Clinical trials testing efficacy of these devices were limited by cost, inconvenience, potential complications, the inability to do placebo comparisons related to ethical considerations [102], and the lack of insurance reimbursement [168,169]. The failure of Medicare and therefore other insurance agencies to reimburse for either VNS implantation or necessary followup care has been a major limitation to its wide-spread use [169].

However, a new generation of non-invasive devices holds potential for wide-spread implementation and is more amenable to rigorous placebo-controlled research studies [97,102]. GammaCore, a Non-invasive VNS (nVNS) that delivers electrical stimulation to the vagus nerve via the neck, was recently approved by the Food and Drug Administration (FDA) for the treatment of intermittent cluster headache [113] and shows promise for wide-spread implementation in psychiatry due to low cost and convenience [102]. We have shown that Transcutaneous Cervical VNS (tcVNS) using the gammaCore blocks sympathetic responses to stress in traumatized persons with and without PTSD [170–177], and blocks inflammatory (IL-6, IFN-γ) [(178] and neuropeptide (Pituitary Adenylate Cyclase Activating Peptide, PACAP) [179] responses to stress in PTSD. It also modulates brain areas involved in emotion in traumatized persons with [180] and without [181] PTSD and reduces PTSD symptoms [182]. Based on our findings of reduction in PTSD symptoms with tcVNS versus sham stimulation after three months of twice daily treatment [182] the FDA granted Breakthrough Device Designation for the gammaCore for PTSD on January 11, 2022. VNS blocks the sympathetic, cardiovascular, and inflammatory activation associated with opioid withdrawal and modulates central brain regions involved in anxiety and reward systems, has the potential to facilitate conversion to long-term therapies such as opioid receptor antagonists and prevent relapse during the critical, potentially lethal, withdrawal period [47,183].

Physiological Correlates of Vagal Nerve Stimulation

The vagus nerve originates in the brain stem and has fibers that travel to both central brain areas as well as peripheral organs [184,185]. Mostly afferent projections of myelinated A fibers of the vagus, relay sensory activity of the visceral organs to the brain through the Nucleus Tractus Solitarius (NTS) in the medulla oblongata. Efferent branches of mostly unmyelinated C fibers of the vagus nerve modulate autonomic and inflammatory function [152] through peripheral anti-sympathetic, pro-parasympathetic, and anti-inflammatory effects [185–187]. These effects may benefit patients with OUD [147,188].

The effects of nVNS, however, are likely mediated through the brain [189]. Projections of the vagus to the brain through the Nucleus Tractus Solitarius (NTS) extend to the locus ceoruleus and hypothalamus [187], key areas involved in sympathetic hyperarousal during opioid withdrawal, as well as to brain areas such as the amygdala and anterior cingulate that mediate emotion and anxiety [187]. Afferent vagal nerve fibers travel through the carotid sheath in the neck (cervical) just medial to the sternocleidomastoid muscle [190] as well as in the ear (auricular), and devices have been developed to non-invasively stimulate the vagus nerve at either branch.

VNS has effects on a number of neurotransmitters that mediate symptoms of mental disorders including OUD [191]. The NTS has direct projections to the Locus Coeruleus (LC), which is located in the pons and is the major site of Norepinephrine (NE) cell bodies in the brain [187]. One of the primary effects of VNS on the brain is activation of norepinephrine in the LC. VNS acts through the LC to increase norepinephrine release in the medial prefrontal cortex, amygdala and hippocampus [192–195], an effect mediated by vagal afferent fibers [193]. Increased NE has a secondary effect on the serotonin (5HT) system through excitatory alpha-1 adrenoreceptors that increase 5HT in the dorsal raphe [192,196–198]. Chronic VNS treatment increases the firing rates of norepinephrine neurons in the LC, hippocampus, and prefrontal cortex and of serotonergic neurons in the dorsal raphe but not in the hippocampus or prefrontal cortex [197,199]. VNS increases both the firing rate and burst pattern of NE neurons [192], an effect which can be blocked by the muscarinic acetylcholine antagonist scopolamine [200]. Chronic VNS decreases dopamine neuronal firing in the ventral tegmental area but leads to increases in extracellular dopamine in the nucleus accumbens and prefrontal cortex [161,197]. Two months of VNS treatment raises levels of dopamine and serotonin metabolites in the Cerebrospinal Fluid (CSF) of patients with epilepsy [142]. Thus, VNS has similar effects to antidepressants [192] without the autoreceptor desensitization seen with chronic use of these medications [192,197].

VNS also has effects on learning and memory systems that may be relevant to stimulus reinforcement and stress diathesis theories of addiction [19,154,201]. Hormones and neurotransmitters released during stress, including cortisol and epinephrine, have effects on learning and memory [198,202–207] even though they don’t cross the blood-brain barrier [208]. One possible explanation for this phenomenon is that the vagus nerve transmits this information to the brain [209]; in fact, lesions of the vagus nerve block the effects of peripheral hormones and neurotransmitters on memory [208,209]. VNS enhances memory retention in a U-shaped curve, with maximum effect at 0.4 mA in rat models [210], an

effect mediated through afferent vagus pathways and not efferent pathways [211]. VNS acts through the LC to increase NE in the basolateral nucleus of the amygdala (BLA) to concentrations capable of modulating emotional memory [193]. Its enhancement of synaptic transmission [212,213], Long-Term Potentiation (LTP) [139], and neurogenesis [214] in the hippocampus likely accounts for its effects on learning and memory as well as its anti-depressant effects (215–217). When paired with conditioned cues, VNS also facilitates extinction in animal models of classic fear conditioning [156–158,218] and reduces fear-like behaviors [156,218]. This effect is mediated through enhancement of the infralimbic (medial prefrontal) amygdala (basal nucleus of the amygdala) pathway [158].

VNS plays a role in neural plasticity and autonomic nervous system function that are relevant to production and maintenance of addictions as well as reinforcement and reinstatement of drug use [159,191,219,220]. Evidence for the role of VNS in neural plasticity comes from animal models showing beneficial effects in treatment of tinnitus when paired with an auditory tone [132–135], recovery of cognitive function after stroke [136], and motor movement when paired with training [221–224]. Animal studies show that VNS reduces ventricular arrhythmia in the setting of myocardial ischemia [225] and promotes recovery from cerebral hemorrhage [226] congestive heart failure [227] and other cardiovascular events [219,228]. VNS promotes learning and memory in patients with Alzheimer's Disease [229,230] and acts through the LC in animal models of TBI to enhance new learning and memory, synaptic plasticity and motor recovery [231,232]. In summary, VNS has a broad range of effects on neural circuits and symptoms that likely are beneficial for patients with OUD, including opioid withdrawal.

The anti-inflammatory and anti-stress hormone effects of VNS may be beneficial for alleviating symptoms of opioid withdrawal. Opioids activate the Hypothalamic-Pituitary-Adrenal (HPA) axis (which through cortisol plays a critical role in stress) and inflammatory systems, and dysregulation of these systems during opioid withdrawal likely plays a key role in the symptoms of withdrawal in OUD patients [233]. VNS has modulatory effects on the HPA axis which may benefit symptoms of withdrawal [47,234–236]. Repeated administration of opioids, including morphine, in animal models activates inflammasomes [237] including p38 Mitogen-Activated Protein Kinase (MAPK), nuclear factor-κB (NF-κB) p65 and Nod-like Receptor Protein (NLRP3) [237]. Opioids also lead to increases in the inflammatory factors interleukin-6 (IL-6) [183,233,238] and Tissue Necrosis Factor- α (TNF- α) [239], as well as corticosterone (cortisol in humans) [233]. Opioid dependence is associated with increases in IL-1β, IL-2, and IL-8 [183]. Stress, which is often linked to OUD, is associated with increases in IL-1B, IL-6, TNF-α, Interferon Gamma (IFNγ) and C Reactive Protein (CRP) in animal models [240,241], and we have shown an increase in mental stress-induced IL-6 and IFNγ in PTSD patients [178,182,242]. Opioid-addicted animals show greater increases in IFNγ [243] and TNF-α when under stress than non-addicted animals [239], and post-mortem studies show increased TNF-α in the LC of patients with OUD [244,245]. These inflammatory markers interacting with the HPA axis may mediate, in part, symptoms of withdrawal in OUD and contribute to the development and maintenance of addictions [240,241,246]. VNS counters these inflammatory responses to opioids, through a reduction of high mobility group protein B 1 (HMGB1) [237,247,248], TNF-α production [249], RANTES (CCL5) (250), Macrophage Inhibition Factor (MIF)

[214,251,252], and kynurenines [153,245,249,253,254]. Emerging evidence indicates the anti-inflammatory effects of VNS seen in response to opioids may also benefit individuals living with co-occurring chronic pain [255]. These studies demonstrate the potential for VNS to have utility in opioid withdrawal symptom reduction through its modification of immune, neuropeptidal and neurohormonal systems. Some key questions remain to be addressed by future research, including why VNS acts through the locus coeruleus to stimulate release of norepinephrine in the hippocampus while simultaneously reducing sympathetic function in the periphery.

Effects of Vagal Nerve Stimulation on Brain Function: Relevance to Mental Disorders and Addictions

Studies have begun to map neural correlates of VNS, improving understanding of potential mechanisms of action in OUD [256–258]. Functional imaging studies in human subjects show that VNS, as predicted from animal models, results in effects on brain regions connected to the Nucleus Tractus Solitarius (NTS), including the medial prefrontal cortex (anterior cingulate) and amygdala [259–261]. Successful treatment of depression with VNS also results in changes to brain regions implicated in that disorder [262–265] as well as beneficial effects on cardiovascular function [266] and cognition [131]. These findings from studies of implanted VNS devices have been replicated in functional imaging studies of healthy human subjects with non-invasive vagal nerve stimulation applied both through the ear [267] and the neck [268,269]. We have shown that tcVNS blocks insula response to stress and enhances anterior cingulate function in PTSD [180,181].

In 2017, the FDA approved a percutaneous form of VNS for the treatment of opioid withdrawal [270]. This was based on the results of an open label trial of 73 patients with OUD, where significant reductions in opioid withdrawal symptoms were observed within one hour of VNS treatment initiation [271]. This study did not use a sham control or obtain objective physiological measurements of sympathetic nervous system activity. Other studies have shown that transcutaneous auricular VNS (taVNS, applied to the ear) is beneficial in promoting oral feeding in infants with brain damage [272] and in withdrawal from opioids in infants born addicted to opioids [273].

Transcutaneous Cervical Vagal Nerve Stimulation for Acute Opioid Withdrawal

To further evaluate the clinical uses of VNS, we assessed the effects of tcVNS on opioid withdrawal in 21 patients with OUD. Patients were randomized to a double-blind administration of active tcVNS (N=10), or sham stimulation (N=11) paired with viewing of neutral and opioid use videos designed to elicit opioid craving (Figure 2). Participants stopped using opioids the night before experimentation and were studied prior to initiation of medication for their OUD. Each administration of vagal nerve stimulation occurred two minutes. There were a total of six stimulations per subject. Subjective opioid withdrawal and craving as well as pain and anxiety were measured using numerical rating scales with a range of 0 to 10 with 10 being most severe. Perceived distress was measured due

its role in craving and relapse [88,274–276] using the Subjective Units of Distress Scale (SUDS) which rates subjective distress on a scale of 0 to 100 [277]. Peripheral autonomic activity was measured using wearable sensing devices [278]. Active tcVNS compared to sham stimulation resulted in significant reductions in withdrawal (−1.9±3.7 versus 0.4±1.0, p=.047) [279] and pain [280] (−0.8±2.4 versus 0.9±1.0, p=.045) as well lower opioid craving which reached trend significance (−2.2±3.6 versus 0.1±2.7, p=0.1) [279] (Table 1). tcVNS also resulted in significant decreases in subjective distress measured with the SUDS compared to sham stimulation (−17.5±26.5 versus 2.2±5.9, p=.004). Active tcVNS also had an effect on peripheral autonomic function measured with a significant reduction in heart rate measured with wearable sensing devices (−5.5±3.5 bpm versus −1.4±4.6 bpm, p=.035) [279] as well as a reduction in breathing irregularity (i.e., respiratory variability) (−368.5±514.1 ms versus 74.2±253.1 ms, p=.02) [281]. Another finding of this study was that opioid withdrawal was associated with an increase in sinusoidal movements in the peripheral extremities that were associated with increased severity of subjective opioid withdrawal [282]. These findings support adjunctive use of tcVNS in mitigating acute opioid withdrawal symptoms, especially during detoxification and transitional periods (e.g., prior to MOUD) – periods of increased vulnerability [4] when opioid withdrawal symptoms can be highly uncomfortable and precipitate relapse in patients with OUD [283–287].

Avoidance of withdrawal symptoms, with associated in increases in pain and anxiety, is often cited as a primary factor in continuing opioid use [283]. Pain intensification during opioid withdrawal has been independently associated with relapse risk [288,289]. For many patients, opioid treatment of a primary pain disorder represents an entry phase into opioid addiction. The return of pain either from the primary pain disorder that was previously masked by opioid use or a new injury in a patient recovering from OUD with an increased pain sensitivity due to the withdrawal state can motivate opioid use, thus perpetuating the addictive cycle [290,291]. Even mild pain can catalyze the learned associations between pain and drug relief among individuals with chronic pain and OUD [292]. Further, increased pain sensitivity and undermanaged pain are associated with worst treatment outcomes, including relapse, for patients with co-occurring chronic pain and OUD [293]. Anxiety and distress can also trigger relapse [88,274,275,287]. Patients with OUD will often continue to use opioids to avoid negative affective states [283,287], which as outlined above are often linked to a history of trauma [79,80]. Affective distress can trigger relapse, even after lengthy periods of abstinence [276,294]. Continued use of VNS into the period of recovery when withdrawal symptoms are reduced but still present in diminished form may reduce the risk of relapse in OUD patients.

Opioid craving and withdrawal are mediated by complex interaction of brain and peripheral autonomic and inflammatory processes in response to the withdrawal of opioids [19,285,294]. The extended amygdala, prefrontal, hypothalamic, and brainstem regions are postulated to mediate dysphoria and autonomic imbalance associated with opioid withdrawal [19,285,294], brain regions which are also implicated in PTSD and other stress-related disorders [295,296].

The effects of tcVNS on signs of opioid withdrawal were greatest for heart rate. Heart rate is mediated by both the parasympathetic and sympathetic branches of the autonomic

nervous system, where decreases in sympathetic arousal and/or increases in parasympathetic activity cause heart rate to decrease [65,297]. Subjective withdrawal is also driven by factors including overdrive of the locus coeruleus/noradrenergic/sympathetic nervous system [65]. Symptoms of withdrawal including increased heart rate, sweating, and respiration, and pupil constriction, are driven by increased sympathetic arousal and/or decreased parasympathetic activity [65,68], a similar physiology and presentation to that of patients with stress-related psychiatric disorders [23,24,298,299]. Successful interventions with tcVNS would be expected to reduce both autonomic signs as well as behavioral symptoms in both disorders by intervening at the level of the autonomic nervous system.

Conclusions

Acute opioid withdrawal in the context of opioid addiction in patients with OUD is related to a complex interaction of central brain regions involved in emotion and peripheral autonomic and inflammatory processes. Non-invasive Vagal Nerve Stimulation (nVNS) non-pharmacological intervention that offers a promising new tool in the treatment of opioid withdrawal. Safety is demonstrated by successful administration in thousands of patients with a range of disorders from mTBI to depression, PTSD and OUD without adverse effects. Adjunctive use of nVNS and medication management of opioid withdrawal may be useful when establishing long-term treatment for OUD with opioid agonists including methadone and buprenorphine, or during the abstinence period before the initiation of treatment with opioid antagonists like naltrexone treatment, reducing symptoms and enhancing the potential for a successful recovery [284]. The non-invasive, non-pharmacological nature of nVNS as well as its ease of use in the home and ability to self-administer during periods of vulnerability make it a useful tool to reduce the risk of opioid relapse by decreasing withdrawal symptoms, pain, and distress. NVNS may be in particular be a useful tool in the window of heightened vulnerability to relapse during the initial period of abstinence [38]. NVNS poses minimal risk, requires minimal training for self-administration and has the potential to be a widely-applied, effective treatment for patients with OUD due to lower cost and enhanced convenience [300].

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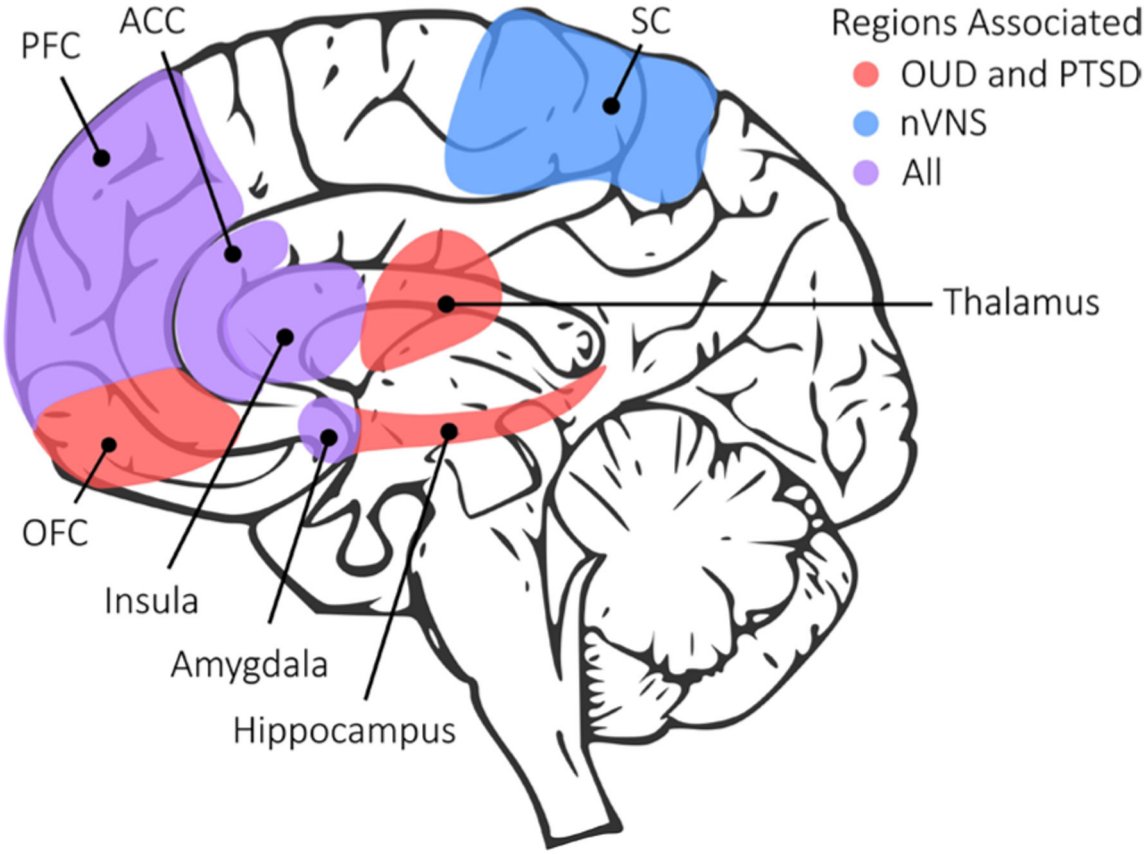

Figure 1:

Neural circuits in Opioid Use Disorder (OUD) and Post-traumatic Stress Disorder (PTSD) and effects of Non-invasive Vagal Nerve Stimulation (nVNS). OUD and PTSD share overlapping brain circuits (hence the association of trauma with OUD) including Orbitofrontal Cortex (OFC), thalamus and hippocampus (red colored regions in diagram) as well as areas also impacted by nVNS like Prefrontal Cortex (PFC), Anterior Cingulate Cortex (ACC), insula and amygdala. nVNS additionally has effects on Somatosensory Cortex (SC).

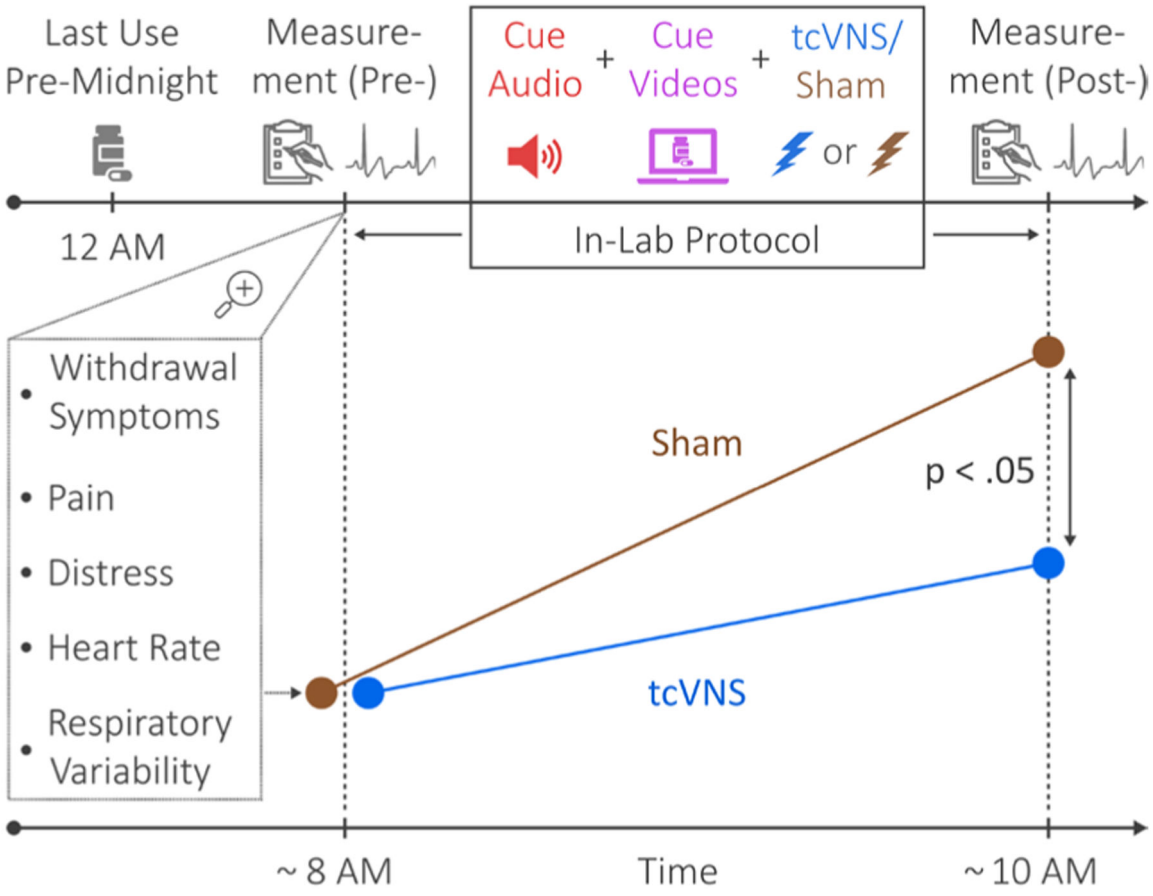

Figure 2:

Study protocol for Transcutaneous Cervical Vagus Nerve Stimulation (tcVNS) in Opioid Use Disorder (OUD). Patients with OUD discontinued use of opioids by midnight of the night before the protocol. They presented early in the morning before initiation of Medication for Opioid Use Disorder (MOUD) initiation and underwent measurement of physiological variables with wearable sending devices (heart rate, respiratory variability) and behavioral variables with rating scales (withdrawal, pain, distress). tcVNS or sham was paired with opioid use cues (videos) in a double blind randomized fashion. There were significant increases in behavioral and physiological measures of withdrawal in the sham versus tcVNS group (i.e. tcVNS blocked measures of opioid withdrawal both subjective and objective related to sympathetic nervous system function).

Table 1:

Active tcVNS and Sham Group Behavioral Measures Before and After Stimulation in Patients with OUD in active Opioid Withdrawal.

Outcome	Timepoint	Active (n=10)	Sham (n=11)
VAS-Withdrawal	Pre	5.8±3.1	5.3±2.5
	Post	3.9±3.1*	6.3±2.5
VAS-Craving	Pre	7.4±2.7	6.8±2.5
	Post	5.2±3.4	6.9±3.5
VAS-Anxiety	Pre	5.6±3.6	6.4±2.3
	Post	3.7±3.0*	6.3±2.6
SUDS	Pre	43.1±32.3	45.1±24.5
	Post	25.6±30.4*	47.6±28.5
NRS-Pain	Pre	3.5±2.6	4.4±1.7
	Post[1]	2.4±2.5*	5.3±2.3
COWS Total	Pre	7.6±3.4	8.5±3.1
	Post	8.2±4.6	10.3±4.2

Abbreviations: VAS, Visual Analog Scale; SUDS, Subjective Units of Distress Scale; NRS, Numerical Rating Scale; COWS, Clinical Opiate Withdrawal Scale.

*$p<0.05$ for reduction post treatment in the active but not the sham stimulation group.

[1]Missing data for one participant in the active group. Adapted from Gazi et al 2022 [279,280].